Differential effects of morphine on central mechanisms of reward as assessed by intracranial self-stimulation

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Abstract

DIFFERENTIAL EFFECTS OF MORPHINE ON CENTRAL MECHANISMS OF REWARD AS ASSESSED BY INTRACRANIAL SELF-STIMULATION

by

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The present study examined two hypotheses: (1) that morphine, a high-abuse-liability drug, has a facilitative effect on central "reward" mechanisms and (2) that morphine has differential effects within the reward system(s). The study consisted of two experiments. Each of the hypotheses was confirmed.

In the first experiment, rats implanted with dorsal brainstem (DB) and hypothalamic (HYP) electrodes bar-pressed for ICSS at two current intensities at each electrode placement eight hours a day during six days each of pre-drug saline, morphine (2.5, 5.0, 7.5 or 10.0 mg/kg) and post-drug saline conditions. Based upon Duncan a posteriori tests for site x drug condition x day x hour interactions, the data for each electrode were classified as displaying "primarily" depressant effects, "primarily"

facilitative effects, a biphasic pattern or "negligible" effects. Thirteen electrodes were classified as displaying a biphasic pattern and one electrode was classified as displaying "primarily" facilitative effects; these results support the hypothesis that morphine has facilitative effects on central reward system(s). Each electrode within eight of the fourteen animals received differential classifications of morphine effect; in fact, during the initial hours post-injection two animals tested at the 2.5 mg/kg dose displayed significant facilitations at the HYP electrode while the DB electrode displayed significant depressant effects. These results are in support of the hypothesis that morphine has differential effects within central reward system(s). In addition, most animals showed differences in patterns in the time-course of effects at the two electrodes. In several animals, the DB electrode seemed to react as though it had received a functionally higher morphine dose than the corresponding HYP electrode; the DB electrode appeared comparatively more likely to show significant depressant effects and less likely to display facilitative effects.

There were several general trends as a result of hour and day. Depressions tended to occur most often during the first two hours post-injection while facilitations tended to occur most often two to five hours post-injection. In general, at those electrodes displaying a biphasic pattern of effects, facilitations initially appeared during the second or third day of morphine administration. Repeated morphine administration appeared to modify the temporal patterning of these effects: the duration of depressions shortened and facilitations had an earlier hour of onset. Tolerance to the depressant effects was observed frequently and seemed to occur occasionally to the facilitative effects. Similar morphine effects were generally seen at both current intensity values within each electrode. The highest morphine dose (10.0 mg/kg) tended to elicit more depressant effects and the lower morphine doses (particularly 5.0 mg/kg) tended to elicit more signficant facilitations.

There appeared to be a tendency toward a depression in ICSS rates during post-drug saline testing; this occurred primarily on the first day of post-drug saline testing. By the fifth day of

post-drug saline testing, most electrodes displayed rates which were not significantly different from pre-drug saline testing. The drug effects on ICSS rates were dissociated from those observed on other behavioral measures and thus were not artifacts of concomitant changes in activity levels.

Experiment 2 investigated the effects of 2.5, 5.0 and 10.0 mg/kg morphine on rate-intensity functions from DB and HYP electrodes. ICSS testing began three hours post-injection to maximize the likelihood of eliciting facilitations at the 10.0 mg/kg dose. The results indicated monophasic effects within electrode placements; depressant effects were somewhat more likely to be displayed at the higher current intensity values tested within an electrode. The highest morphine dose (10.0 mg/kg) elicited only depressant effects. Facilitations occurred at one electrode tested at the 5.0 mg/kg dose. Although it was not analyzed statistically, it appeared that DB electrodes showed more signficant effects than corresponding HYP electrodes.

Acknowlegments

I would like to dedicate this dissertation to the memory of Darlene Hinkin, my cousin. She had no doubts that I had the ability to finish this work. I am sorry that she was not given the time to fulfill her own goals.

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The underlying physiological mechanisms by which opiates alter mood states have been a source of inquiry over many years. The opiates are well known for their analgesic properties as well as for their psychological effects (Beaver, Wallenstein, Houde & Rogers, 1969; Beecher, 1959). Opiate users report that the drug produces a euphoria, a high, a feeling of well-being (Haertzen, 1966; Kolb, 1925); this is believed to be a reason why opiates are abused. These subjective reports suggest that opiates have some influence on limbic system structures, specifically those involved in reinforcement. Studies on the physiology of motivation and emotion (e.g., hunger, thirst, sex, rage) and subsequently on reinforcement have indicated that the physical substrates of these behaviors are limbic system pathways (Olds, 1977; Papez, 1937). Several studies, which have been published since the present study was first designed, have demonstrated the existence in the central nervous system of opiate receptors, the locations of which parallel brain areas involved in the reinforcement system(s) (Pert & Snyder, 1973; Simon & Hiller, 1976; Stein & Belluzzi, 1978; Unl, Childers & Snyder, 1978). The present series of experiments tested the

hypotheses that opiates affect the functioning of the reinforcement system(s) and that the actions of opiates are site-specific.

With the discovery that rats will work to deliver electrical stimulation to their brains (Olds & Milner, 1954) a technique emerged which allowed direct examination of pharmacologically induced alterations in the reinforcement value of stimulating specific neural sites. The method of intracranial self-stimulation (ICSS) has been used to study the so-called reward or pleasure center(s) (Olds & Olds, 1965). ICSS is a method that directly, although artificially, stimulates brain pathways. The response of the animal (bar press) leads to a direct stimulation of the area under the electrode (Ranck, 1975). The animal controls the rate of stimulation (reinforcement) for any given stimulation parameter (e.g., wave form, electrode placement, current intensity) set by the experimenter; in addition, in certain experimental designs the response of the animal can modify the parameters of stimulation (e.g., threshold titration: Marcus & Kornetsky, 1974; Stein & Ray, 1960; Poschel & Ninteman, 1966). Also, an advantage of ICSS is that the investigator can adjust

parameters judiciously to elicit stable behavior (i.e., self-stimulation at a specified rate from different sites and/or at a range of rates at several current intensities within a site) and then to superimpose one or more drugs to assess the effects on this stable behavior.

ICSS has been used to test directly the reinforcing properties of psychoactive drugs (amphetamine: Ellman, Ackermann, Bodnar, Jackler & Steiner, 1976; Phillips & Fibiger, 1973; Stein, 1964; Wauquier & Niemegeers, 1974; barbiturates: Olds & Travis, 1960; neuroleptics: Phillips, Brooke & Fibiger, 1975; Stark, Turk, Redman & Henderson, 1969; minor tranquilizers: Olds & Travis, 1960; Olds, M., 1966; Stark et al., 1969). If the opiates also affect reinforcement behavior as measured by ICSS, then ICSS may be a suitable animal test model. Several psychoactive drugs have produced differential effects at different neuroanatomical sites within the reinforcement system(s) as measured by ICSS. For example, the d-isomer of amphetamine is more active than the l-isomer of amphetamine at noradrenergic sites, whereas the d- and l-isomers are equally potent at dopaminergic sites (Phillips & Fibiger, 1973;

Ellman et al., 1976). The differential effects are indicative of different neurotransmitters present at each site. Thus, opiates might also be expected to have site-specific actions within the reinforcement system(s) as measured by ICSS.

Morphine, the opiate analgesic often administered in clinical situations, is also the drug most studied in determining the mechanisms of action of the opiates. Although heroin is the opiate most often abused, it exerts its pharmacologic actions in the brain in the form of morphine, following hydrolysis of the heroin molecule. The blood brain barrier tends to impede the entry of morphine into the brain, while the barrier is considerably less effective against heroin. Thus, the rate of entry to the brain and subsequently the time to onset of action in the brain of injected heroin is earlier than that of injected morphine. As a result, the effective dose of heroin is less than that needed for morphine (Jaffe & Martin, 1975). Thus, a probable cause of the high abuse of heroin rather than morphine is the more rapid onset and increased magnitude of effects upon injection of heroin. To study more efficiently the mechanisms of action of opiates, it is of interest to study the actions of morphine directly.

The dual action hypothesis of morphine physical dependence was proposed by Tatum, Seevers and Collins (1929) and states that (1) direct pharmacological action of morphine produces both depression and stimulation in the central nervous system, (2) the depression is dominant, and even masks the stimulant effects, during the early phases of drug action and (3) the stimulant effects are of longer duration than the depressive effects and therefore, the later stages of drug action are characterized by hyperexcitability. These depressant and stimulant actions may be indicative of differential mechanisms as well as neuroanatomical sites of action of morphine. If the behavioral biphasic nature of morphine is a reflection of these suggested dual effects of the drug within the reinforcement system(s), then changes that occur in ICSS response rates might be a sensitive reflection of the drug's effects. Therefore, the ICSS technique might serve as a tool with which to begin to identify and differentiate among neuroanatomical mechanisms and sites of action.

When the present study was initiated, there were three studies in which the effects of morphine on ICSS were tested. The results of two studies suggested

site-specificity (Olds, 1959; Olds & Travis, 1960) and the results of the third study (Adams, Lorens & Mitchell, 1972) demonstrated the time-dependent and facilitative effects that were proposed by the dual action hypothesis. As of January 1979, more than twenty additional studies have appeared in the literature. Acute administration of high morphine doses (greater than or equal to 20.0 mg/kg) produced depressions in hypothalamic (HYP) ICSS rates which co-varied with hypoactivity (Glick, Marsanico, Zimmerberg & Charap, 1973; Lorens & Mitchell, 1973; Marcus & Kornetsky, 1974; Schaefer & Holtzman, 1977; van der Kooy, Schiff & Steele, 1978; Wauquier & Niemegeers, 1976; Wauquier, Niemegeers & Lal, 1974; Zvartau, 1977). In contrast, acute administration of lower morphine doses (0.3-15.0 mg/kg) produced biphasic effects: initial ICSS rate depressions followed by facilitations (Adams, Lorens & Mitchell, 1972; Bozarth & Reid, 1977; Bush, Bush, Miller & Reid, 1976; Glick & Rapaport, 1974; Holtzman, 1976; Kelley & Reid, 1977; Liebman & Segal, 1977; Lorens, 1972, 1976; Lorens & Mitchell, 1973; Maroli, Tsang & Stutz, 1978; Marcus & Kornetsky, 1974; Olds, M. 1976; Olds & Travis, 1960; Ornstein & Huston, 1977; Pert &

Hulsebus, 1975; Schaefer & Holtzman, 1977; Wauquier & Niemegeers, 1976). Tolerance developed to morphine's depressant effects upon ICSS responding, since repeated administration of the same morphine dose shortened the duration of ICSS depressions, while facilitating ICSS rates sooner (Bush et al., 1976; Glick & Rapaport, 1974; Lorens, 1976; Lorens & Mitchell, 1973; Schaefer & Holtzman, 1977). Withdrawal from morphine generally produced a return to pre-drug HYP ICSS rates (Bush et al., 1976; Glick & Rapaport, 1974; Lorens, 1976), although withdrawal from higher morphine doses (100-200 mg/kg) facilitated ICSS rates (Glick et al., 1973).

Another feature of morphine-induced changes in ICSS responding is that these effects are site-specific. Following morphine administration septal placements produced facilitations (Olds & Travis, 1960). Medial prefrontal cortex ICSS placements supported earlier response rate facilitations than did HYP ICSS placements (Lorens, 1976). Larger ICSS response rate facilitations occurred following morphine injections at electrode placements more than 0.3 mm dorsal to the substantia nigra, pars compacta or more than 0.2 mm lateral to

the midline of central gray than at placements directly impinging upon these respective structures (Liebman & Segal, 1977). The results of this latter study parallel the differential effects that d- and l-amphetamine exert upon these placements (Ackermann, Steiner, Bodnar, Spielman, Halperin & Ellman, in press; Ellman, Ackermann, Bodnar, Jackler & Steiner, 1975, 1976; Phillips & Fibiger, 1973). A study using intracerebral morphine injections reported that ventral tegmental and HYP ICSS rates either increased following posterior HYP micro-injections or exhibited biphasic effects following micro-injection in intermediately-located areas (Broekkamp, van den Bogaard, Heijnen, Rops, Cools & van Rossum, 1976).

Thus, several studies have reported differential effects of morphine on ICSS that seem to indicate dose- and site-specificity of action. Since both fibers and neurons are activated during stimulation of a brain area, one cannot specifically infer whether the drug is acting directly on those fibers and/or neurons, or whether the effects are indirect. There are several lines of information, such as labelling of neurotransmitters and mapping of receptor sites, which can be correlated with the location of electrode tips

and the corresponding ICSS data to enable predictions to be made about site-specificity of drug action. However, even if opiate receptors are located in the area of an electrode placement, the effects observed cannot automatically be assumed to be due to direct activation of those receptors because behavior does not reside within a particular neuroanatomical structure. We are dealing with a whole animal; there appear to be several systems of pathways within the brain, and systems interact with one another. However, the law of parsimony would suggest that if differences in drug effect on ICSS are noted among different electrode placements, then drug actions are directly or indirectly affecting those sites and subsequently one or more neuroanatomical systems, differently.

The results of several studies testing the effects of psychoactive drugs on ICSS suggest a neurochemical basis of action, i.e., drugs affect neurohumoral transmitter substances (Olds, J., 1961; Poschel & Finteman, 1963; Stein, 1964). Certain drugs clearly exhibit differential effects on self-stimulation at different loci. For example, the d- and l-isomers of amphetamine are approximately

equally potent in facilitating response rates from the substantia nigra, while d-amphetamine is 7 to 10 times more potent than l-amphetamine in facilitating hypothalamic self-stimulation (Phillips & Fibiger, 1973; Ellman et al., 1976). This pharmacological differentiation has been correlated with the distribution of catecholaminergic neurotransmitters. Ungerstedt (1971) has found the substantia nigra to be primarily dopaminergic and the lateral hypothalamus to be innervated by noradrenergic fibers.

At the time this study was begun numerous attempts were being made to correlate the pharmacological effects of morphine with several known neurotransmitter substances, particularly norepinephrine, dopamine, serotonin and acetylcholine. Shortly thereafter Pert & Snyder (1973) reported that there are opiate receptors in the brain and that these receptors appear to parallel the distribution of acetylcholine receptors. Two years later Hughes (1975) demonstrated the existence of an endogenous opiate-like substance. It is now clear that there are several endogenous opiate systems within the brain and pituitary and that morphine exerts many of its primary effects within these systems; however, recent evidence

still suggests that some behavioral effects noted are due to interactions of the endogenous opiate-like system(s) with one or more other neurotransmitter systems.

In the present study, dorsal brainstem (DB) and HYP ICSS sites were selected because of their suggested involvement in opiate-mediated behavior. Both sites support stimulation-produced analgesia (Balagura & Ralph, 1973; Mayer & Liebeskind, 1974; Mayer, Wolfle, Akil, Carder & Liebeskind, 1971; Rose, 1974; Segal & Sandberg, 1977), but differ in other respects. DB ICSS sites possess high densities of opiate receptors while HYP ICSS sites possess moderate densities of opiate receptors (Atweh & Kuhar, 1977b; Hiller, Pearson & Simon, 1973; Kuhar, Pert & Snyder, 1973; Pert, Kuhar & Snyder, 1976). Differences in the sensitivity to the opiate antagonist naloxone have been demonstrated between these sites. In a study using a separate groups design, electrodes in the DB (locus coeruleus) were more sensitive to naloxone's suppressant effect on ICSS rates than those in the HYP (Stein & Belluzzi, 1978). The present study enables us to determine whether these sites also react differentially to morphine. In addition, our

multiple-implant design enables us to examine the issue of whether any morphine effects are a result of site-specificity of opiate action as opposed to individual differences among animals in their sensitivities to the drug.

The primary purpose of the proposed series of experiments was to study the question of whether morphine differentially affects the positive reinforcement systems. Morphine may have a facilitative as well as a depressant effect on ICSS response rates. These two effects may reflect the time course of action of morphine; i.e., morphine may initially cause a depression on the central nervous system, which is then followed by a 'rebound' facilitation. On the other hand, these effects may reflect site specific actions of morphine on the central nervous system; i.e., morphine may differentially affect discrete neuroanatomical sites, facilitating the actions of certain areas of the central nervous system while depressing the actions of others. It is also possible that morphine might act on the central nervous system by a combination of these two mechanisms; i.e., morphine may exhibit differences in time course of its depressant and/or

facilitative effects within discrete neuroanatomical sites.

The main experiment (Experiment 1) investigated both the possibility of neuroanatomical specificity as well as time course of action of morphine within the 'reward' system(s) as measured by intracranial self-stimulation (ICSS). Two bipolar electrodes were implanted within each animal; each electrode was aimed at a discrete and distant neuroanatomical site. The time course of the effects of morphine on ICSS rates of responding at each of the two electrode sites within an animal was examined for eight hours following injection.

Experiment 2 was designed to ascertain the effects of morphine on ICSS rate-intensity functions obtained from two different electrode sites within each animal and serves as an adjunct to the first experiment. The first experiment was designed to ascertain time course effects of morphine, and therefore repeatedly measured the effects of morphine on ICSS elicited by a limited number of current intensities from each electrode site. The effects on ICSS of many drugs, however, are often best detected by a range of stimulation parameters. Manipulating

current level yields a 'rate-intensity' function. The effects of the drug on response rates are compared to saline at each of the current intensity values.

Experiment 1: The effects of morphine on ICSS

Rationale

This experiment examines two hypotheses: (1) Does morphine, a high-abuse-liability drug, have a facilitative effect on central "reward" mechanisms? and (2) Does morphine, as other high-abuse-liability drugs, affect some "reward" areas in a manner different from the way it affects other "reward" areas? In other words, does morphine have site-specific effects within the reward system?

There is evidence which suggested that different electrode sites yielding similar behavioral effects upon stimulation may have differential drug sensitivities (Ellman et al., 1976; Phillips & Pibiger, 1973). Reports of the acute effects of morphine on self-stimulation suggested that the effects differ as a function of site of stimulation (Olds & Travis, 1960). However, reports of the chronic effects of morphine on self-stimulation suggested that the variability within a subject at an electrode site may be due to initial depressant effects of morphine to which tolerance may develop (Adams et al., 1972).

It was decided that the effects of repeated administration of morphine on self-stimulation tested for several hours daily at two different electrode placements within an animal would be studied. This testing procedure allowed for a time course of the effects of a single administration of the drug to be assessed each day at each electrode placement.

As an additional index of the drug's effects, observations of general activity were made both during saline baseline tests as well as during morphine tests. Morphine is known to have general depressant effects on behavior, e.g., increased pain threshold and respiratory depression (Jaffe & Martin, 1975). In cats and rats, stimulant effects have been reported, e.g., increases in stereotyped behavior (Blasig, et al., 1973). Reports of human opiate addicts suggested that there are effects opposite to the depressant effects: these effects are commonly referred to as a "rush", or a "euphoria" (Jaffe, 1975). Facilitative effects of morphine on ICSS behavior have been reported in the rat (Adams et al., 1972; Liebman & Segal, 1977; Lorens, 1976). These facilitative effects on ICSS behavior may be accounted for by either a general stimulant effect on behavior or may

be a result of specific actions of morphine within reward sites. Therefore, in an effort to determine whether a facilitation in ICSS behavior correlated with an increase in general activity levels (i.e., increased motor output), observations of general activity levels were made (see below).

Examining ICSS behavior obtained from two distant and discrete central reward sites within an animal provides a control in the determination of the specificity of facilitative effects of morphine. If the facilitative effects were nonspecific, both sites within an animal would evidence a facilitation in response rates. The behavioral watches allowed me to answer the question: Do individual rats show facilitations in all behaviors, including ICSS behavior, or is a facilitation evidenced in ICSS behavior specific within the reward system(s)?

Another advantage of multiple implantations within an animal is that of greatly reducing subject-specific variability in comparisons between different electrode placements. Each animal was tested at both electrode placements; general behavior was observed during pre-drug saline, morphine and post-drug saline conditions. In effect, each animal

served as its own control in the experiment; the treatment of each additional animal served as a replication of the experiment.

Method

Subjects. Twenty-six male albino rats (Holtzman Sprague-Dawley) weighing 350-515 grams at the time of operation were used. All animals were housed individually and maintained on an ad libitum food and water schedule.

Surgery. Animals were anesthetized with Equithesin (Jensen, 2 ml/kg, i.p.). Bipolar stainless steel electrodes (Plastic Products, MS-303-.018-.312-SS-.010), completely insulated except at the tips, were implanted using a Kopf stereotaxic instrument. All animals were implanted with two bipolar pairs of electrodes; one electrode pair was aimed at the lateral hypothalamus (HYP), the other was aimed at the dorsal brainstem (DB) in the area of the rostral locus coeruleus. The coordinates for the stereotaxic placements of these electrodes were modifications of those of Zeman & Innes (1963), De Groot (1959) and Konio and Klippel (1963). In these modifications, the lambda and bregma suture lines served as points of reference for the derivation of

stereotaxic coordinates. Setting the incisor bar at -5.0 mm lowered the angle of the rat's head in the stereotaxic instrument and thereby allowed parallel implantation of both bipolar electrode pairs, while avoiding the puncture of the transverse sinus during the implantation of the locus coeruleus electrode. The coordinates for the lateral hypothalamus implants were: 0.3 mm anterior to the midpoint between lambda point and bregma, 1.5 mm lateral to the mid-sagittal suture, and 8.7 mm ventral to the surface of the skull. The locus coeruleus coordinates were 0.3 mm posterior to lambda line, 1.0 mm lateral to the mid-sagittal suture, and 7.0 mm ventral to the surface of the skull. Lambda line was a hypothetical transverse line determined in relation to lambda point (see Figure 1). Lambda point was that point where the occipital bones meet the mid-sagittal suture. Three stainless steel cortical screws were attached to the skull. These screws serve as anchors to hold a cap of dental acrylic to the skull. The dental acrylic formed a solid, immobile bond with the plastic caps of the electrodes.

Apparatus. Animals were trained to press a bar for electrical stimulation delivered to each electrode

site. Intracranial self-stimulation (ICSS) tests were run in a plexiglass operant chamber (20 cm x 20 cm x 22 cm). A retractable bar (4 cm x 2 cm, Scientific Prototype), located 4 cm above a grid floor, protruded into the chamber. Depression of this bar activated a microswitch. The number of bar presses per minute was automatically recorded by solid state and electro-mechanical programming equipment; rate of response was the dependent variable. Each response was reinforced with a 250 msec train of 60 Hz, sinusoidal wave stimulation to one bipolar electrode placement on a continuous reinforcement schedule. Stimulus intensity, measured in microamperes, was under the control of the experimenter and varied according to the demands of the experiment. Current applied to the tip of the electrode served as the reinforcing stimulus (Hanck, 1975). Wave form and stimulus intensity were continuously monitored by observing the voltage drop across a 100 ohm resistor in series with each bipolar elctrode on a differential input Hewlitt Packard #1200-E cathode ray oscilloscope. Each pair of the animal's bipolar electrodes was separately isolated from both ground and from the other electrode pair.

Preliminary testing. Fourteen days after surgery each animal was tested to determine if electrical stimulation of the two electrode sites would serve as a reinforcer for the bar-press response. Animals were shaped by the method of successive approximations at several intensities from 15-280 microamperes (uA) during daily ninety-minute sessions. Training began with the HYP electrode. The process was then repeated for the DB electrode. Animals were shaped at several current intensities at each electrode placement for a minimum of 15 days. A stringent criterion for inclusion was employed in this study. Rates produced from both electrode placements had to exceed ten responses per minute on three consecutive daily testing sessions. Twenty of the 28 rats tested met this criterion. The eight animals not meeting this criterion were sacrificed.

Procedure. Two current intensities were chosen for each electrode placement and were tested daily for eight consecutive hourly sessions. Initially there were to be six hours of testing each day; however, the data of the first animal (37E) indicated that a longer daily testing schedule was required to optimize the likelihood of eliciting facilitations in ICSS rates,

especially following the high dose (10.0 mg/kg). Therefore, all other animals were tested for eight hourly testing sessions per day. Each hourly session consisted of four 7-min ICSS periods in which the data from the last five minutes constituted the dependent variable. To minimize stimulus carry-over effects, the first two minutes of each seven-minute period were not included in the data analysis. Changes in current intensity occurred during one-minute periods between successive seven-minute periods. During an hourly test the bar was available to the animal for 28-minutes: four seven-minute periods, each period separated by one minute during which the bar was retracted while site and stimulus current values were changed. During the remainder of the hour, the bar was retracted. Thus the bar was unavailable 32 minutes of each hour. Animals were given priming stimulation if they did not initiate responding during the first minute of each seven-minute period.

The basic design of the study presupposed that saline baseline response rates at an electrode placement remained stable throughout the experiment. Negative contrast effects are particularly evident in paradigms that sample ICSS response rates at more than

one stimulus intensity (Trowill, Panksepp & Gandelman, 1969), particularly when drug effects interact with current effects (Maroli, Tsang & Stutz, 1978; Steiner & Stokely, 1973). Four procedures were implemented to control for these effects: (1) treating the first two minutes of each seven minute period separately, (2) using a low current intensity which elicited supra-threshold, rather than threshold, response rates, (3) presenting the two current intensities in ascending order, and (4) presenting the electrode placement which supported lower peak ICSS rates first.

Pilot data demonstrated that if the low intensity value was that which elicited threshold rates of responding, that the animal extinguished ICSS behavior both within and across days at this intensity value; i.e., the animal would self-stimulate only at the higher intensity value. However, when the animal was given an intensity value which elicited response rates between threshold and peak, the animal would consistently respond at both intensity values. Therefore, although it may have been desirable to obtain information specifically about morphine effects on threshold ICSS behavior, a compromise was necessitated because of the experimental design since

the animals were each tested for long periods of time. Thus, one current intensity within each electrode placement supported ICSS rates which were above operant levels but below peak rates (the low intensity value) and the second current intensity yielded peak ICSS rates (the high intensity value).

Related to this, results of pilot experiments indicated that more consistent ICSS rates within and across days were obtained within each test session when the low intensity values were presented prior to the high intensity values, particularly when the "less preferred" site (i.e., the site which elicited lower response rates at the high intensity) started the session. In addition to preliminary testing sessions, each animal was tested with a particular sequence of site and current intensities at least 144 times (six days each of pre-drug saline, drug and post-drug saline for eight sessions per day). Within a few days animals were not only observed to position themselves at the bar just prior to its return following the one-minute time-outs, but also at the beginning of each test session, i.e., following a 28-minute time-out. Animals approached the "bar" before any electro-mechanical switches were activated and,

therefore, without any external visible or audible signals. Thus, the animals, due to the regularity of the testing procedure, "learned" when the bar would enter the box and, apparently, the order of presentation of site/intensity stimuli. During the pilot study when presentation of low and high intensities were alternated within a site, e.g., DB-low, DB-high, HYP-low, HYP-high, animals would not approach the bar, nor once activated could they be shaped to the bar. In anthropomorphic terms, the animals compared the "reward values" of the stimuli and, once the presentation sequence was "learned", would "choose" when to work. This frequently occurs in a descending rate-intensity function and is called the "little-pig" effect. Thus, due to the apparent learning of the testing sequence, the "little-pig" effect necessitated, not only the use of an above-threshold current intensity for the low intensity value, but also necessitated the order of presentation of intensities and sites within each animal. Thus for each animal, the electrode placement which supported lower peak ICSS rates was tested during the first and third periods, while the electrode placement which supported higher peak ICSS

rates was tested during the second and fourth periods. The lower current intensity selected for each electrode placement was tested during the first two periods, while the higher current intensity for each electrode placement was tested during the second two periods of each hourly session. For example, if an animal responded less for stimulation at the peak intensity value at the DB electrode than at the HYP electrode, then each hourly test for this animal was as follows: DB-low intensity; HYP-low intensity; DB-high intensity; HYP-high intensity.

Six animals were eliminated from the experiment during the preliminary 6-hr testing sessions. Four animals either lost their electrode assemblies or died. One animal extinguished ICSS responding for both electrode placements by the fourth session of each day. One animal became too active to handle. Fourteen animals entered the drug testing procedure.

When ICSS responding over daily and hourly sessions stabilized, each animal entered an eighteen day testing sequence, consisting of six days of saline baseline, six days of morphine administration, and six days of saline withdrawal. Each day, five minutes prior to the second ICSS test session, either saline

or morphine was injected (1 ml/kg, s.c.). Each animal was then tested over the seven subsequent consecutive hours (post-injection hours 1-7). The first test session of the day corresponded to twenty-four hours following an injection administered on the previous day (post-injection hour 24). Four different doses of morphine, solubilized in 0.9% normal saline, were utilized in the study: 2.5, 5.0, 7.5 and 10.0 mg/kg (measured as the salt). Each animal was tested with one and only one dose during the six drug days. The 2.5, 5.0 and 10.0 mg/kg morphine doses were each tested in four rats; the 7.5 mg/kg morphine dose was tested in two rats.

To monitor drug effects upon other opiate-related behaviors, three daily behavioral watches, each of 5-min duration, were conducted immediately prior to the pre-injection (24th-hr), 1st-hr post-injection and 5th-hr post-injection ICSS sessions. Locomotor activity (determined by the number of traverses across the grid floor subdivided into 5 cm x 5 cm squares), wet shakes, shudders, and rearings were counted for the 5-min period, while instances of general behavior, such as grooming/sniffing, masticating, and stereotyped biting/licking of the grid floor were also

noted. In addition, a 1-min observation was made immediately prior to the other ICSS sessions to observe whether stereotyped biting/licking behavior occurred.

The behavioral watches also served as an additional measure to verify that a drug had been administered properly. Occasionally the full dose and/or volume of a drug was not given. The experimenter noted this at the time of injection, e.g., "the rat struggled when injected and an indeterminate amount of drug entered the animal." Morphine's effects on general behavior are consistent (Blasio et al., 1973). Of tje experimenter believed, at the time of injection, that an incorrect dose of morphine had been given to an animal and if the behavioral data were aberrant and, therefore, corroborated this belief, then, and only then, were a day's data (plus the data for the following drug day) not included in the data analysis.

Histology. Following completion of the experiment(s), each animal was overdosed with Equithesin (2 ml, i.p.) and perfused intracardially with a .9% saline solution followed by a 10% formalin solution. The animal was then decapitated, and its

brain removed and stored in a 10% formalin solution. The brain was frozen and sectioned at 40 microns on a Spencer 860 microtome. The sections containing electrode tracts were collected and stored in 10% formalin for at least three days, before being mounted on glass slides and stained with luxol fast blue and cresylviolet according to the method of Kluver and Barrera (1953). Electrode locus was determined by microscopic examination of the sections by two raters uninformed as to the behavioral results.

Data analysis of ICSS response rates. Data for each animal were analyzed independently by means of an analysis of variance, repeated measures design, on five factors (5-way ANOVA). The dependent variable was the number of responses per minute (R). To normalize the distribution of the data, 0.5 was added to each value of the dependent variable and a square-root transform was performed (sq. rt. (R + 0.5)). The factor "minute" (number of responses/minute) served as the error term for testing the five main effects and their interactions. The five main factors were site, drug condition, intensity, day and hour. Site consisted of two groups (Db and MFB); drug condition (drugcond) consisted of

three groups (pre-drug saline, morphine and post-drug saline); intensity (intensty) consisted of two groups (low current intensity and high current intensity); day consisted of six groups (six days/drug condition); hour consisted of eight groups (eight hourly test sessions daily, with the exception of animal 37E, which was tested six hourly test sessions daily).

Duncan a posteriori tests were performed on the main effect of site, the site x drugcond interaction, the site x drugcond x intensity interaction, as well as on the site x drugcond x day x hour interaction (α level = .01). The a posteriori comparison of the main effect of site shows whether, collapsed over all factors, response rates elicited at each electrode placement within an animal differed significantly. It was felt that the contribution of the main effects of drug condition, intensity, day and hour would be best explored via the Duncan a posteriori tests of the site x drugcond, site x drugcond x intensity and site x drugcond x day x hour interactions.

The Duncan a posteriori test of the site x drugcond interactions enabled us to classify each electrode placement into an overall pattern of morphine effect. This would indicate whether morphine

differentially affected each electrode within an animal (collapsing over intensity, day and hour).

The Duncan *a posteriori* tests of the site x drugcond x intensity interactions enabled us to determine if morphine significantly affected each intensity similarly within a site, collapsing across days and hours.

The Duncan *a posteriori* tests of the site x drugcond x day x hour interactions enabled us to (1) study the time course of drug effects, both within a day as well as across days of each electrode placement and (2) make descriptive comparisons of the time course of morphine's effects on ICSS rates at each electrode placement within an animal.

Results

Figures 3 and 4 are schematic representations of the electrode placements for the rats which completed Experiment 1. Table 1 presents the histological location of each electrode placement. The 2.5, 5.0 and 10.0 m/kg morphine doses were each tested in four doubly-implanted rats; the 7.5 mg/kg morphine dose was tested in two doubly-implanted rats. Each rat received repeated administration of one morphine dose.

The HYP electrode placements were localized primarily in the area of the lateral hypothalamus, with some electrode placements impinging laterally on the crus cerebri and other electrode placements bordering medially on the medial hypothalamic nuclei. One HYP electrode (37E) was localized in the posterior hypothalamic nucleus. Most of the DB electrodes were localized in or near the locus coeruleus nucleus or anteriorlly along its major efferent, the dorsal noradrenergic bundle (DNB). One DB electrode (4G) was localized as impinging upon the mesencephalic V nucleus and another DB electrode (54F) was localized as impinging upon the medial longitudinal fasciculus (MLF).

Table 2 presents a summary of the results of the overall 5-way ANOVA procedure. For each animal, the significance level of the overall F-statistic was .0001. R-square source is an expression of the variance accounted for by the five factors and the interaction terms. The lowest R-square value was 0.57 and the highest value was 0.94. Thus, for each animal the factors site, drugcond, intensity, day, hour and their interactions accounted for more than 50 percent of the variation in the dependent variable.

Tables 3-16 present the results of the complete 5-way ANOVA procedure for each individual animal. Table 17 presents the R-square value for the five factors and the interaction terms for each animal. The main effect of site was significant at the .0001 level in thirteen of fourteen animals; the p-level of the fourteenth animal (86F) was .0762. Table 18 presents the results of the Duncan a posteriori tests for the main effect of site, collapsing over all other factors. In 10 animals, the DB electrode elicited significantly lower rates than the HYP electrode, while in three animals, the DB electrode elicited significantly higher rates (animals 37F, 54F, 21C); in the fourteenth animal (86F) the DB electrode elicited

rates higher than the HYP electrode, however the difference failed to reach significance. Although the P-value of the main effect of site is independent of all other factors and interactions, the a posteriori test of the main effect of site collapse the data across all other factors, and presents somewhat different results than if pre-drug saline rates are looked at independently. Table 19 presents the data for pre-drug saline, collapsing over intensity, day and hour. Although the differences were not measured statistically, the mean response rate for the DB electrode was lower than for the corresponding HYP electrode in 12 animals (exceptions: 37E and 54F); the maximal response rate for the DB electrode was lower than for the corresponding HYP electrode in 13 animals (exception: 37E); and the standard error of the mean was smaller for the DB than for the corresponding HYP electrode in all fourteen animals. A point of possible importance when interpreting the results is that the HYP electrode of animal 37E, unlike any of the other thirteen animals, was localized within the posterior hypothalamic nucleus.

Thus, when the data are collapsed across intensity, it appears that during the pre-drug saline

condition DB electrodes generally elicited lower mean and maximal response rates and a smaller degree of variability than the corresponding HYP electrodes. To further explore this, Duncan a posteriori tests were performed comparing the mean response rate for pre-drug saline elicited by the high current intensity values at each site for every animal (see Tables 20-21). The difference between rates elicited at each site was significant for all fourteen animals; twelve animals had a significantly greater mean response rate for the HYP electrode than for the corresponding DB electrode and in two animals (37E and 86F) the DB electrode elicited a significantly higher mean response rate.

The main effect of intensity was significant at the .0001 level in 13 of the 14 animals; the p-level for the 14th animal (37E) was .0744. Tables 20 and 21 are summaries of the response rates of each intensity at each site during pre-drug saline condition for each animal. Although not statistically tested, several other within-animal trends may be noted. Animal 37E, the only animal in which the main effect of intensity is not significant, had similar mean and maximal response rates at both the low and high current

intensities within each site during pre-drug saline. As can be seen in Tables 20 and 21, other animals also displayed similar pre-drug saline response rates (mean or maximal) at both the intensity values within an electrode; however, such instances generally occurred at only one site within an animal, and more often at the DB electrode. Also, in several instances, a higher maximal response rate (but not mean response rate), as well as a larger standard error of the mean, were displayed from the lower current value tested within an electrode placement.

The main effect of drug condition was significant at the .0001 level in all animals. The main effect of day had a significant F-value, at p-level < .01 in 13 of the 14 animals (exception: 86F). The main effect of hour was significant at the .0001 level for all fourteen animals.

The Duncan a posteriori tests were performed on the site x drugcond interactions and the results are summarized in Table 22. The F-value of the site x drugcond interaction was significant in 12 of the 14 animals at p-level < .0001. In agreement with the initial hypotheses that morphine has interactive effects within sites of reinforcement, the site x drug

condition interaction reached significance (α = .01) in twelve of 14 animals; two animals almost reached significance (animal 54F, p=.05; animal 76F, p=.10).

The results of the Duncan tests of the site x drugcond interaction, which collapses the data over day, hour and intensity, indicated that both electrode placements within nine animals showed similar drug effects: seven animals had a significant depressant effect of morphine at both electrode placements, one animal (21G) had a significant facilitative effect of morphine at both electrode placements and one animal (9G) failed to show a significant site x drugcond interactive effect at either the DB or HYP electrode. Five animals showed differences in the site x drugcond interactions. One animal (74E) showed a significant depressant effect at the DB electrode, while the site x drugcond interaction for the HYP electrode failed to reach significance. Two animals showed a significant facilitative effect at one electrode placement (4G - DB, 3G - HYP) while the site x drugcond interaction effect for pre-drug saline and morphine failed to reach significance at the second electrode placement. The two other animals (84F and 86F, both tested at 2.5 mg/kg morphine) had a

significant depressant DB x morphine interaction effect with a concomitant significant facilitative HYP x morphine interaction. Although the comparisons of morphine effect at each site cannot be tested directly statistically within the context of the present experiment, the data of animals 84F and 86F most clearly support the initial hypothesis that morphine differentially affects brain reinforcement sites.

The nature of the similarities and differences in drug effect between electrode placements within each animal is explored in greater detail via Duncan *a posteriori* tests on the site x drugcond x day x hour interactions (see below).

To test statistically the interactive effects of electrode placement, morphine and current intensity, Duncan *a posteriori* tests were performed on the site x drugcond x intensity interactions. Table 23 presents the results of these tests. The F-value of the site x drugcond x intensity interaction was significast in 11 of the 14 animals at p-level < .01; animal 74F had p-level < .02 and animals 66F and 84F had p-level < .05. The Duncan *a posteriori* tests (α = .01) indicated that within the DB electrodes, 11 of 14 animals showed effects in the same direction at both

intensities; nine animals showed depressions and two animals showed facilitations in rates. The DB electrodes of the other three animals (3G, 18G and 9G) showed significant depressions at the low intensity value, while the high intensity value failed to show a significant difference in ICSS rates. Within the HYP electrode placements, eight of the fourteen animals showed effects in the same direction at both intensities; four animals showed significant depressions, two animals (at 2.5 mg/kg morphine) showed significant facilitations and two animals (75P-7.5 mg/kg; 21G-5.0 mg/kg morphine) failed to show an overall significant effect of drug at either intensity. Of the six HYP electrodes which showed differences in morphine effect in the drug x site x intensity interaction, three showed significant effects at only one intensity value; three animals (94P, 18G and 9G) showed a significant depressant effect at one intensity value and a significant facilitative effect at the second intensity value.

In summary, based upon the Duncan tests on the site x drugcond x intensity interactions, 19 of 28 electrode placements displayed similar morphine effects at both the low and high current intensity

values tested. Only three of the remaining nine electrode placements had significant site x morphine interactions in opposite directions at each intensity value. These apparent discrepancies in morphine effect at the two intensities within an electrode placement are discussed later in more detail. However, at this point I would like to mention that certain effects may tend to cancel out when collapsing data across factors in performing the Duncan a posteriori tests. For instance, the HYP electrode of animal 74F failed to show a significant effect on the site x drugcond x intensity interaction Duncan a posteriori tests; however, if the data are examined by hour, it can be seen that both intensities responded similarly to morphine administration: response rates initially below and then above the s.e.m. of morphine, i.e., a biphasic effect. The site x drugcond x day x hour interaction a posteriori tests confirm that morphine had a biphasic effect by hour across days (see Table 33; Figures 23-24). Thus, the Duncan tests of the site x drugcond x intensity interactions indicate that generally morphine affects both intensities in a similar fashion, while Duncan tests of the site x drugcond x day x hour elaborate further on the effects within and across days.

Tables 24-51 present the results of the Duncan *a posteriori* tests (α = .01) for the site x drugcond x day x hour interaction effects. The results of these tests are discussed in conjunction with Figures 5-130. The site x drugcond x day x hour Duncan *a posteriori* tests do not directly test differences in magnitude of morphine effects across days or hours, since all comparisons are made between pairwise means of saline and morphine response rates. However, certain trends magnitude of effects are discernible from the graphed data. Figures 5-60 present the ICSS data for pre-drug saline, morphine and post-drug saline expressed as the mean of the six days per drug condition. Figures 61-116 present the ICSS data for pre-drug saline expressed as the mean response rate over the six days; and for morphine, expressed as the (1) mean of days 1-2, (2) mean of days 3-4 and (3) mean of days 5-6.

Figures 117-130 present, for each animal, the data for locomotor activity (as measured by the number of box crossings for pre-drug saline, morphine and post-drug saline) expressed as the mean of the six days per drug condition. As previously noted for

animals 84F and 86F, there was evidence for specificity of morphine action within the brain reinforcement system(s), as evidenced by differential drug effects on ICSS rates at the two electrode placements within an animal. However, locomotor activity served as an additional indicator of whether morphine's effects on ICSS behavior can be dissociated from those on general behavior. At this point, comparisons based upon visual inspection of the graphed data will be made. The data for locomotor behavior were analyzed statistically by grouping animals together by dose. The results of the grouped analysis are presented later.

Based upon the pattern of significant site x drug x day x hour interactions during hours 1-7 and days 1-6 (i.e., 42 comparisons), each electrode placement was given a classification for pattern of morphine effects. The four possible patterns were (1) "primarily" depressant, (2) "primarily" facilitative, (3) biphasic, i.e., both depressions and facilitations in ICSS rates, and (4) "negligible" effects. If significant depressions and/or significant

facilitations occurred in only two or fewer of the 42 possible comparisons (5% chance), then that effect was regarded as negligible and the data were classified as though the two or fewer significant effects did not occur. For example, Table 25 presents the results of the Duncan tests for the site x drugcond x day x hour interaction for the HYP electrode of animal 37E. This electrode meets the criteria for a classification of showing a "primarily" depressant effect since there were more than two significant depressions, but only two significant facilitations. Table 52 presents a summary of the pattern classifications for each electrode placement based on the site x drugcond x day x hour Duncan tests. Table 53 presents a comparison of the morphine effect based on the results of the site x drugcond Duncan tests with the classification received based on the site x drugcond x day x hour Duncan tests.

The results of the analysis of the site x drugcond x day x hour interactions for each animal are presented for each rat, beginning with those animals which received the highest morphine dose (10.0 mg/kg).

Following repeated administration of 10.0 mg/kg morphine, animal 37E displayed depressions in ICSS rates from both intensities at both electrode placements (see Tables 24-25; Figures 5-8 and 61-64). In this animal, a "bad" shot was administered on what was to be the fifth day of morphine administration. Therefore, the data from that day as well as the following day were not included within the analysis and days labeled 5 and 6 were actually drug administration days 7 and 8 (see Methods section). Although the Duncan tests for site x drug x day x hour indicated two instances of significant facilitations, visual inspection oP Figures 63-64 suggest that the magnitude of the facilitations were not large. Both the DB and HYP electrodes of this animal met the classification criteria of a "primarily" depressant pattern of morphine effects on ICSS rates. The site x drugcond Duncan tests had also indicated a depressant effect of morphine at each electrode placement. Locomotor activity was within the range of the s.e.m. of pre-drug saline immediately after morphine injection and 24-hours post-morphine injection; however, at 5-hours post-morphine injection locomotor activity was above the s.e.m. of pre-drug saline.

Although not tested statistically, the effects of morphine on ICSS rates appear dissociated from those on locomotor activity.

Animal 54F received repeated administration of 10.0 mg/kg morphine and displayed significant depressions from each electrode placement (see Tables 26-27; Figures 9-12 and 65-68). This animal also received a "bad" shot. This occurred on what was to be the fourth day of morphine administration; therefore, the data from that and the following day were not included within the analysis and days labeled 4,5 and 6 were actually drug administration days 6,7 and 8 (see Methods section; animals 37E and 54F received the only known instances of "bad" shots). The Duncan tests for the site x drugcond x interaction had indicated that both electrode placements of these animals had depressant effects on ICSS. Both the DB and HYP electrodes of animals 54F also met the criteria for the "primarily" depressant pattern of morphine effects based upon the site x drugcond x day x hour Duncan tests. The mean response rate for morphine days 1-2 was somewhat below those for the later days during the first few hours post-injection at both intensities of each electrode placement. The

measure for locomotor activity during morphine administration was within the s.e.m. of pre-drug saline for each behavioral watch post-injection. Thus, it appears again that the effects of morphine on general behavior did not reflect the effects of morphine on ICSS behavior.

Animal 76P also received repeated administration of the 10.0 mg/kg dose of morphine. The site x drugcond Duncan tests indicated that both electrode placements had depressed ICSS rates during morphine administration; however, visual inspection of the graphed data indicate, and the site x drugcond x day x hour Duncan tests confirm, that both electrode placements displayed significant facilitations as well as significant depressions over the eight hours sampled (see Tables 28-29; Figures 13-16 and 69-72). The facilitations occurred primarily on the fourth-hour post-injection, with the first occurrence on the second day of morphine administration for both sites. Figures 69-72 indicate that the magnitude of the depressions was larger and the durations were longer for morphine days 1-2 than for days 3-4 and 5-6. Both electrode placements, therefore, met the criteria for a biphasic pattern classification. The

site x drugcond interactions indicated that the overall effects within each site were depressant. The site x drugcond x day x hour interactions indicated that there was a complex interaction of morphine with day and hour. Somewhat fewer significant depressions occurred over the six days. Both electrode placements displayed instances of significant facilitations in ICSS rates during morphine administration in the later hours of most days. The graph of locomotor activity (Figure 119) shows that during morphine administration, the animal moved slightly less immediately following injection and moved slightly more during the fifth-hour post-injection. Thus, the initial depression in ICSS rates may be correlated with the depression in locomotor activity immediately post-injection. Locomotor activity was not measured during the fourth-hour post-injection, when most of the significant facilitations in ICSS rates occurred. During the fifth-hour post-injection, however, locomotor activity was slightly above the s.e.m. of pre-drug saline, at which time ICSS behavior was generally depressed or not significantly different from pre-drug saline. Therefore, it is difficult to determine to what extent the facilitations in ICSS

behavior correlate with morphine's effects on general behavior in this animal.

Animal 94F received repeated administration of 10.0 mg/kg morphine. The Duncan tests on the site x drugcond interactions showed that both electrode placements had significant overall depressant effects. The results of the site x drugcond x day x hour interaction Duncan a posteriori tests are presented in Tables 30-31. In the Duncan tests of the site x drugcond x day x hour interactions, the DB electrode had several significant depressions in ICSS rates, but only two significant facilitations. Both Figures 17-18 and 73-74 indicate that ICSS rates during morphine administration were generally above the s.e.m. of pre-drug saline, primarily during the third-hour post-injection, although these reached statistical significance for only a total of two instances within the context of the site x drugcond x day x hour Duncan tests. Thus, based upon the criteria described earlier, this electrode is classified as having displayed a "primarily" depressant pattern of morphine effects. Although the site x drugcond interaction for the HYP electrode indicated that this electrode placement had an overall

depressant morphine effect, the site x drugcond x day x hour Duncan tests showed many instances of facilitations as well as depressions in ICSS rates during morphine administration (see Table 31). This electrode, therefore, meets the criteria for the classification of a biphasic pattern of morphine effects. Figures 19-20 and 75-76 indicate that the facilitations occurred primarily at the low intensity value, as was also indicated statistically in the Duncan a posteriori tests of the site x drugcond x intensity interactions. The data for the HYP electrode of this animal present a good example of the importance of parceling out orthogonal interaction effects. When the data are collapsed over intensity and day and hour (the site x drugcond interaction), the a posteriori tests indicated a depressant effect of morphine. When the data are collapsed across day and hour (the site x drugcond x intensity interaction), each intensity showed opposite morphine effects on ICSS response rates. When the day x hour interactive effects are combined with these factors (the site x drugcond x day x hour interaction) thereby collapsing across intensity, the facilitative effects of the low intensity value are so strong that the

Duncan tests showed many instances of significant facilitations. As with the other animals that received 10.0 mg/kg morphine, the first two days of morphine administration elicited somewhat lower response rates than did days 3-4 or 5-6 during the first few hours post-injection. This morphine-induced depression waned during days 3-6, indicating tolerance. The measures for locomotor activity during morphine administration were below the s.e.m. of pre-drug saline immediately following injection, but were within the s.e.m. thereafter (see Figure 120). Thus, there is some indication of correlation of depressant action on ICSS and general behavior immediately following injection in this animal; however, the facilitations in ICSS rates seen 5-hours post-injection appear to be dissociated from the effects of morphine on general behavior at that time.

Animal 74E received repeated administration of 7.5 mg/kg morphine. The site x drugcond interaction Duncan tests indicated that both electrode placements had significant depressant effects during morphine administration. The DB electrode had several significant depressions, but only two significant facilitations in the site x drugcond x day x hour

interaction Duncan tests (see Table 32). The data for this electrode placement, therefore, met the criteria for "primarily" depressant effects on ICSS rates. As with animal 94F, graphs of the data (see Figures 21-22 and 77-78) indicate that there were instances in which ICSS rates during morphine administration were above the s.e.m. of pre-drug saline, primarily during the fifth-hour post-injection for the low intensity value but during the fourth-hour post-injection for the high intensity value. Thus, probably due to slight difference in time-course of the facilitative effects of morphine being reflected at both intensity values the site x drugcond x day x hour interaction tests, (which collapse across intensity) indicated only two instances of significant facilitations. Although displaying an overall depressant effect on the Duncan tests of the site x drugcond interaction, the HYP electrode met the criteria for a biphasic pattern of morphine effects based on the Duncan tests for the site x drugcond x day x hour interaction (see Table 33). Most of the facilitations occurred during the fourth- and fifth-hours post-injection (see Figures 23-24 and 79-80). The depressant effects were slightly greater for the first two days of morphine

for the low intensity value at both electrode placements. Locomotor activity during morphine administration fell within the s.e.m. of pre-drug saline for all three behavioral watches, indicating a dissociation between morphine's effects on ICSS and locomotor activity (see Figure 121).

Animal 4G also received repeated administration of 7.5 mg/kg morphine. The DB electrode displayed a facilitative effect on the site x drugcond Duncan tests and met the criteria for "primarily" facilitative morphine effects based upon the site x drugcond x day x hour interaction Duncan tests (see Table 34). The high intensity, however, did consistently display rates below the s.e.m. of pre-drug saline on the first-hour post-injection (see Figures 25-26 and 81-82); however, only the Duncan test for the first-hour on the first day of of the site x drugcond x day x hour interaction yielded a significant depression in ICSS rates. Facilitations. occurred mostly two to four hours post-injection. The HYP electrode had failed to show a significant site x drugcond interaction; however, the site x drugcond x day x hour interaction Duncan tests indicated several instances of both depressant and facilitative effects

of morphine and met the criteria for a classification of a biphasic pattern of morphine effects (see Table 35). This is another good example of the importance of studying the interactions of the time-course of the drug's effects. Facilitations occurred primarily during the fifth-hour post-injection (see Figures 27-28 and 83-84). The facilitations at the DB electrode were of a smaller magnitude and the depressions at the HYP electrode were of a larger magnitude for the first few hours post-injection on the first two days of morphine administration than on subsequent pairs of drug-days (see Figures 81-84). Thus, the drug's effects were more depressant the first two days at both sites. Locomotor activity during morphine administration was below the s.e.m. of pre-drug saline immedaitely post-injection and slightly above the s.e.m. at the fifth-hour post-injection (see Figure 122). Thus, there may be a correlation between morphine's effects on ICSS behavior and locomotor activity in this animal.

Animal 75P received repeated administration of 5.0 mg/kg morphine. Both electrode placements displayed a significant site x drugcond depressant effect and also met the criteria for "primarily"

depressant pattern of morphine effect on ICSS (see Tables 36-37; Figures 29-32 and 85-88). The depressant effects were of a larger magnitude the first two days of drug administration than drug days 3-4 or 5-6. Locomotor activity was within the s.e.m. of pre-drug saline during the first- and fifth-hours post-injection but was slightly below 24-hours post-injection (see Figure 123). Since ICSS rates were depressed during the first- and fifth-hours post-injection and generally not significantly different 24-hours post-injection, morphine's effects on these behaviors appear to be dissociated.

Animal 66F received repeated administration of 5.0 mg/kg morphine. Both electrode placements displayed depressant effects on the site x drugcond interaction Duncan tests. The DB electrode showed several instances of significant depressions for the first two hours of most days on the site x drugcond x day x hour Duncan tests; there was only one instance of significant facilitation in rates (see Table 38). Thus, this electrode met the criteria for "primarily" depressant morptine effects based upon tte site x drugcond x day x hour Duncan tests. Visual inspection of the graphed data indicate that there was a trend

toward facilitations following the first two days of morphine administration (see Figures 33-34 and 89-90). For the HYP electrode, the site x drugcond x day x hour interaction Duncan tests and the graphed data indicated that morphine elicited both depressions and facilitations in ICSS rates and met the criteria for a biphasic pattern of morphine effects (see Figures 35-36 and 91-92, Table 39). Facilitations occurred mostly on the fourth-hour post-injection. The first two days for each intensity at both electrode placements had larger depressions for longer durations post-injection than on subsequent pairs of days. Locomotor activity was below the s.e.m. during the first-hour post-injection but within the s.e.m. of pre-drug saline during the 5th- and 24th-hours post-injection (see Figure 124). Thus, although there may be a correlation immediately following injection between ICSS and locomotor activity, the effects were dissociated during the fifth-hour post-injection.

Animal 3G received repeated administration of 5.0 mg/kg morphine. The DB electrode failed to show a significant difference during morphine administration and the HYP electrode showed a significant overall facilitative effect on the site x drugcond interaction

Duncan tests. Both the DB and the HYP electrodes met the criteria for biphasic effects based on the site x drugcond x day x hour interaction Duncan tests (see Tables 40-41; Figures 37-40). Unlike the data for most other electrode placements, the depressions in this rat tended to occur during the later hours post-injection. The facilitations occurred primarily during the third hour post-injection at both electrode placements. ICSS rates were somewhat lower immediately following morphine injection on days 1-2 than 3-4 or 5-6 for both intensities at each electrode placement. Locomotor behavior was within the s.e.m. for pre-drug saline for all three behavioral watches. Since there were significant facilitations in ICSS rates immediately following injections in ICSS rates and significant depressions during the fifth-hour, it appears as though there was a dissociation of morphine effect between ICSS an general locomotor behavior (see Figure 125).

Animal 21G received repeated injection of 5.0 mg/kg morphine. Both electrode placements showed a facilitative effects on the site x drugcond interaction Duncan tests, but met the criteria for a biphasic pattern of morphine effects based upon the

site x drugcond x day x hour interaction Duncan tests (see Tables 42-43; Figures 41-44 and 97-100). Facilitations occurred primarily during the third-hour post-injection in both intensities at both electrode placements. The comparative magnitude of the facilitations appeared larger and occurred more often than depressions (see Figures 41-44 and 97-100), and this may be what is being reflected in the apparent differences between the results of the site x drugcond interaction and site x drugcond x day x hour interaction Duncan tests. Locomotor activity was below the s.e.m. of pre-drug saline during the 1st- and 24th-hours post-injection but within the s.e.m. during the 5th-hour post-injection (see Figure 126). Since ICSS rates were often facilitated during the first-hour post-injection, the correlation, between morphine's effects on ICSS and locomotor activity, although not tested statistically, would apparently be low.

Animal 84F received repeated administration of 2.5 mg/kg morphine. The Duncan a posteriori tests of both the site x drugcond, as well as the site x drugcond x day x hour interactions indicated that morphine depressed ICSS rates at the DB electrode

while morphine facilitated ICSS rates at the HYP electrode (see Tables 44-45; Figures 45-48 and 101-104). Thus, this animal showed a clear dissociation of morphine effects at each electrode placement. Visual inspection of the graphed data also indicate that morphine had depressant effects at the DB electrode and facilitative effects at the HYP electrode. The dissociation is most obvious during the second-hour post-injection during which the facilitations occurred most often and the magnitude of facilitations was most consistently the largest. There appeared to be an effect of day, in that the mean response rates were comparatively lower for both intensities at both electrode placements immediately post-injection for days 1-2 of morphine administration than for days 3-4 or 5-6. The data for this animal clearly confirms the initial hypothesis that morphine has facilitative effects on central reward system(s) and that these effects may be site-specific. Locomotor activity was below the s.e.m. of pre-drug saline for the fist-hour and above the s.e.m. for the fifth-hour post-injection (see Figure 127). Since morphine's effects on ICSS rates elicited at both electrode placements were in opposite directions

during the first-hour post-injection, the correlation of morphine's effects on ICSS behavior and locomotor activity would apparently be low.

Animal 86P received repeated administration of 2.5 mg/kg morphine. The DB electrode had a depressant effect and the HYP electrode had a facilitative effect on the site x drugcond interaction Duncan Tests. Based on the results of the site x drugcond x day x hour interaction Duncan tests, the DB electrode met the criteria for a "primarily" depressant pattern of effects; however, the HYP electrode met the criteria for a biphasic pattern of morphine effects (see Tables 46-47; Figures 49-52 and 105-108). The magnitude of effects for the first two days of morphine administration was in the direction of slightly more depressant effects at the high intensity of the DB electrode and slightly less facilitative effects at the HYP electrode. As in the case of animal 3G, the depressions at the HYP electrode of 86P occurred at the later hours of the day. The first two hours post-injection showed only significant depressant effects at the DB electrode while the HYP electrode showed only significant facilitative effects. Thus, for the first two hours post-injection, animal 86P

also showed a clear dissociation of morphine effects at the DB and HYP electrodes. As in the case of animal 84F, which also received repeated administration of the lowest morphine dose tested in the present study (2.5 mg/kg), the DB electrode displayed significant depressions while the corresponding HYP electrode displayed significant facilitations. Locomotor activity was below the s.e.m. of pre-drug saline for the first-hour post-injection and within the s.e.m. thereafter. Again, since morphine's effects were dissociated at each electrode placement during the first-hour post-injection, any correlation of morphine effects on general behavior and ICSS behavior would of necessity be low.

Animal 18G received repeated administration of 2.5 mg/kg morphine. Both the DB and HYP electrodes had an overall depressant effect based upon the site x drugcond interaction Duncan tests. The DB electrode met the criteria for a biphasic pattern of morphine effects based on the site x drugcond x day x hour interaction Duncan tests. (see Table 48; Figures 53-54 and 109-110). The figures indicate that the facilitations occurred primarily at the high

intensity; in fact the magnitude of the facilitations was larger on the first two days of morphine administration, i.e., the mean of days 1-2 was not only above the s.e.m. of pre-drug saline, but also the s.e.m. of morphine days 3-4 and 5-6, especially at the fourth- and fifth-hours post-injection. The HYP electrode had only two significant depressions in the site x drugcond x day x hour interactions for the seven consecutive hours post-injection and therefore met the criteria for "negligible" morphine effects (see Table 49; Figures 55-56 and 111-112). Both of the significant depressions in ICSS rates at the HYP electrode occurred during the first day of morphine administration. The site x drugcond x intensity interaction Duncan tests had indicated that the low intensity displayed depressant effects while the high intensity displayed facilitative effects. The graphs of the data show that, particularly for the first three-hours post-injection, the mean response rates during morphine administration for the low intensity were lower than those for pre-drug saline while rates for the high intensity were above those for pre-drug saline (see Figures 55-56 and 111-112). Thus, this electrode placement consistently displayed opposite

effects at each intensity value during morphine administration. Of the 28 electrode placements tested, only this electrode placement consistently showed differential drug effects at each intensity. It should also be pointed out, that for the HYP electrode of animal 18G, the mean response rate during pre-drug saline at the high intensity was 191.3 with an s.e.m. of 1.05, and that during morphine administration rates of over 240 responses per minute were elicited, while the low intensity had a mean response rate of 19.6 with an s.e.m. of 2.16 during pre-drug saline and responded, on the average, less than ten responses per minute during morphine administration (see Table 21). Thus, each intensity value tested the extreme ends of this animal's "rate-intensity" function. The relatively negligible effects indicated by the site x drugcond x day x hour interaction Duncan tests, may be reflecting a similar relative magnitude of effects at each intensity value. Thus, although this electrode received a classification of "negligible" pattern of effects based upon the criteria, it does appear as though morphine did affect response rates, but due to the fact that both intensities displayed an opposite

direction of effects, unlike most other electrode placements tested in this study, it is difficult to categorize the effects in a clearcut fashion. As with most other electrode placements, the first two days of drug administration had lower mean response rates for the first-hour post-injection than on days 3-4 or 5-6. Locomotor activity was below the s.e.m. of pre-drug saline immediately post-injection and within the s.e.m. thereafter (see Figure 129). Although not tested directly statistically, the degree of correlation between morphine's effects on ICSS and locomotor behaviors would probably be low, since the HYP electrode displayed differential effects at each intensity value, and since the DB electrode showed some trends toward facilitation during the 5th-hour post-injection.

Animal 9G received repeated administration of 2.5 mg/kg morphine. Both electrodes failed to show a significant morphine effect on the site x drugcond interaction Duncan tests. The DB electrode met the criteria for biphasic effects based on the site x drugcond x day x hour interaction Duncan tests (see Table 50; Figures 57-58 and 113-114). The depressions, as in the case of both electrode

placements of 3G and the HYP electrode of 86P, occurred primarily at the later hours of the day. The facilitations occurred most often on the second-hour post-injection and primarily on the later days of testing. The HYP electrode met the criteria for "negligible" pattern of morphine effects based on the site x drugcond x day x hour interactions Duncan tests (see Table 51; Figures 59-60 and 115-116); within the seven consecutive hours of testing each day, there were two instances of significant depressions on the first day and two instances of significant facilitations on the last day of morphine administration. The site x drugcond x intensity interaction Duncan tests had indicated that the low intensity had displayed an overall depressant effect while the high intensity had displayed an overall facilitative effect. The graphs indicate that the low intensity had response rates below the s.e.m. the first-hour post-injection as well as during the later hours of the daily testing sessions. During the third- and fourth-hours post-injection, the low intensity displayed facilitations. The ICSS rates elicited by the high intensity, however, were generally at or above baseline, with the highest

response rates occurring two- to three-hours post-morphine injection. Thus, both intensities displayed facilitations in rates during the third-hour post-injection (see Figures 59-60 and 115-116). To determine whether the facilitation for the third-hour would reach significance if the data were collapsed across day as well as intensity, since the mean response rates during morphine administration was above the s.e.m. at both intensities the Duncan a posteriori tests (α= .01) were performed on the site (HYP) x drugcond (morphine) x hour interactions for each hour. The Duncan tests indicated that response rates during morphine administration were significantly depressed immediately post-injection and significantly facilitated during the third- and fourth-hours post-morphine injection. Thus, although the site x drugcond and the site x drugcond x day x hour interactions indicated that this electrode had negligible morphine effects on ICSS rates at this electrode placement, there was a trend toward depressions immediately post-injection and facilitations during the third- and fourth-hours post-injection. As with most other animals, the mean for the first two days during morphine administration

displayed somewhat lower response rates than during days 3-4 or 5-6. Locomotor activity was above the s.e.m. for pre-drug saline for all three behavioral watches during morphine administration (see Figure 130). Since the HYP electrode had a tendency toward depressions immediately post-injection and the DB electrode had both depressions and facilitations during the 5th- and 24th-hours post-injection, the correlation with locomotor activity, although not tested statistically, would probably be low.

Table 53 presents a summary of the results for the site x drugcond and site x drugcond x day x hour interactions. The two hypotheses tested in the present experiment were (1) does morphine facilitate the reward system(s) in the brain as measured by intracranial self-stimulation and (2) are there indications that these effects might be site-specific as defined by differences in morphine effect at the two electrode placements within an animal. The site x drugcond interactions indicated that five electrode placements had a significant overall facilitative effect of morphine on ICSS rates; with no instances of a facilitative effect based on the Duncan tests for the site x drugcond interaction occurring at the

highest morphine dose (10.0 mg/kg). Based upon the results of the Duncan tests for the site x drugcond x day x hour interactions, 15 electrode placements were classified as displaying facilitative effects. Thirteen of these electrode placements also had depressant effects which generally occurred prior, within and across days, to the facilitations. Based upon the Duncan tests of both the site x drugcond and site x drugcond x day x hour interactions, one animal, 84F, had a clear dissociation of morphine effect at either electrode placement: depressions at the DB electrode and facilitations at the HYP electrode. Another animal, 86F, also had results that clearly indicated site-specific effects of morphine on ICSS rates: the site x drugcond interaction indicated, as in the case of animal 84F, depressant actions at the DB electrode and facilitative actions at the HYP electrode. The site x drugcond x day x hour interactions met the criteria, which I had set, for a biphasic pattern at the HYP electrode; however, the facilitations occurred immediately post-injection at which time the DB electrode was exhibiting depressant effects. Thus, the data for two animals, each tested at the lowest morphine dose (2.5 mg/kg) indicated that

morphine has differential effects within the reward system(s).

Thus, of the 14 animals tested, 2 animals were classified with opposite patterns of drug effects at each electrode placement, 6 animals received differential, though not opposite classifications of drug effects at each electrode placement and the data for the other six animals were classified with the same pattern of drug effects at both electrode placements, but presented a somewhat different time course of effects at each electrode placement (see Tables 24-52; Figures 61-116). The differences in morphine effect at both electrode placements cannot be tested directly statistically within the context of the 5-way analysis of variance. Visual inspection of the data and the results of the site x drugcond x day x hour interaction Duncan tests, however, seem to indicate a trend regarding differential morphine effects at the two electrode placements within each animal. Six DB placements were classified as either displaying facilitative or biphasic drug effects. Nine HYP electrodes were so classified. Furthermore, four of the nine HYP electrodes showed significant facilitations while the corresponding DB electrodes

met the criteria for "primarily" depressant effects. This may be an indication that the DB is receivng a functionally larger morphine dose than the HYP. This is correlated with the fact that facilitations tended to occur more often at the lower doses and during the later days of drug administration at the higher morphine doses. Two animals (9G and 18G) that received the lowest morphine dose (2.5 mg/kg) met the criteria for biphasic pattern of morphine effects at the DB electrode, while the HYP electrode met the criteria for the classification of "negligible" morphine effects. This represents further evidence that the DB site may be more sensitive to morphine than the HYP site. Based upon the histological localization of the electrode placements, a simple relationship between localization within a particular nuclear group and morphine does not seem possible from the present study. The electrodes were localized within a fairly large area within the hypothalamic and dorsal brainstem areas. This, together with the fact that four doses of morphine were studied, makes difficult a precise loalization of those areas most likely to elicit facilitations in ICSS rates during

morphine administration. However, the present experiment was designed to study the question of whether differences in pattern of drug effects are more likely attributable to differential reactions within the reward system, or whether the differences are attributable to differential reactions of morphine on general behavior among animals. The fact that differences in pattern of morphine effect occurred in the within-animal, multiple implant design in eight animals indicates that morphine acts somewhat differentially on the central reward system(s).

The present study does not permit a direct statistical analysis of the data across animals; therefore, the comparative effects of morphine dose cannot be analyzed directly. If the data had been analyzed across animals, then it would not have been possible to study the effects of drug within each electrode within an animal, the prime focus of the present study. However, some general statements can be made regarding morphine effects across animals, including the comparative effects of dose, based upon visual inspection of the interaction terms of the five main factors.

Table 17 presents a summary of the R-square value of each source in the 5-way ANOVA for each animal. R-square is the percent variance accounted for by each main factor and interaction term with each animal. Visual inspection of the table indicates that for each animal the variance was accounted for by slightly different patterns of effects. The mean R-square for each term serves as an index of the orthogonal amount of variance accounted for by each source. The largest proportions of the variance appear to be accounted for by the main effects of site and intensity and the interaction of site and intensity. This may reflect (1) the lower mean response rates of the DB electrode compared to those of the HYP electrode within an animal; (2) intensities chosen to sample both low and high response rates within the animal's rate-intensity function; and/or (3) a generally smaller difference between the low and high intensity rates of the DB site compared to those of the corresponding HYP site. Although it is not a statistical measure, one can look at the interaction terms in which drug and intensity interact versus those terms in which intensity interacts with other factors. When this was done a trend appeared which supported those seen visually in

the graphed data and statistically in the Duncan post-hoc tests for each intensity value at each site: intensity contributed least to the interactions with drugcond. That is, morphine generally had similar effects at each electrode placement within an animal. The time course of drug within a day contributed the most in relation to drugcond, the time course of drug within a day contributed the most to the variance in the dependent variable; site and day factors (time-course of drug effects over repeated daily administration) contributed toward a somewhat lesser amount of the variance in the dependent variable.

The interactions of morphine with site have already been discussed. A few statements can also be made about the interactions of morphine with day and hour. The time-course of morphine, both within a day and across days, seemed to be influenced by the dose of morphine. Although not directly tested statistically, it appeared that the higher doses were more likely to elicit depressions in ICSS rates. The lower doses, particularly the 5.0 mg/kg dose, seemed more likely to elicit facilitations in ICSS rates. The data show that morphine can elicit facilitative effects without first displaying a depressant effect

on ICSS rates. This indicates that the facilitation is a specific effect and not a "rebound" effect. In nine of thirteen electrode placements which met the criteria for a biphasic pattern of drug effects, the depressant effects occurred prior to the facilitative effects (Tables 24-52; Figures 61-116). At the 10.0 mg/kg dose, in particular, the facilitative effects did not occur consistently until the third or fourth days of drug administration, and occurred most often at the third or fourth hours post-injection. There may be a general depressant effect of the drug to which tolerance develops, since 49 of 56 intensity-electrode combinations displayed more depressions during the first two days of morphine administration than on subsequent days. In general, the depressant effects occurred during the first few hours post-injection and the facilitations occurred primarily two to four hours post-injection; appearing comparatively sooner after injection at the lower morphine doses. Upon repeated morphine administration, facilitations often occurred earlier following injection, and occassionally the data reached significance for fewer hours, i.e., in some electrode placements there was indication of tolerance

occurring to the facilitative effects (see especially Tables 31, 41, 42 and 45).

Twenty-four hours post-injection, ICSS rates were generally not significantly different from baseline. Based on the results of the site x drugcond x day x hour interaction Duncan tests, 12 electrode placements showed no significant differences 24-hours post-injecton and five showed only one significant effect. Of the 16 electrode placements that displayed one or more significant differences in ICSS rates 24-hours post-injection, only four had one or more instances of a facilitation. Thus, it appears that if there is a residual drug effect 24-hours post-injection, it is a depressant effect. Based on a visual inspection of the tables, there does not appear to be a strong correlation between dose or effect of drug during the hours post-injection, and the likelihood of having a significant effect 24-hours post-injection.

Tables 54-58 summarize the results of the statistical analysis of the data obtained during the behavioral obervation periods. Since the data were mostly of an ordinal nature, the data were analyzed by dose to increase the number of cases. Figures 117-130

present graphically the data for locomotor activity for each animal. Figures 131-134 present the data for stereotyped biting behavior by dose.

Immediately after being injected with a dose of 10.0 mg/kg, animals displayed ataxia, exopthalmia and piloerection. The animals became fixed in one position, with their hindlimbs often falling limp through the grid floor of the cage. The animals gradually regained limb support, stood on the grid floor and continuously gnawed the grid floor. Palpating the animals produced no overt responding. Eventually the animals began to ambulate. At this point they could be shaped to press the bar to receive electrical stimulation to an electrode placement. Prior to this time, attempts to shape the animals to bar press were unsuccessful. The dramatic behavioral effects of morphine diminished upon repeated drug administration. Following administration of lower morphine doses somewhat less severe behavioral effects were noted.

In general, the level of spontaneous wet shakes, shudders, rearings and locomotor activity during morphine administration was not significantly different from those during pre-drug saline.

Actually, the data for the highest and lowest morphine doses were not significantly different from baseline on any of these measures; however, the data for the 5.0 mg/kg group were significantly depressed on all but the number of shudders and the 7.5 mg/kg group had fewer rearings. Figures 117-130 indicate that immediately post-injection locomotor activity was below the range of the s.e.m. of pre-drug saline in 9 of the 14 animals. Thus, although the differences were not significant when measured within a dose, there were some indications of a general depressant trend. One factor that may account for for a decrease in locomotor activity, is that stereotyped biting behavior was, in general, significantly facilitated for the first few hours post-injection. Anecdotal reports, particularly for those animals that received 10.0 mg/kg morphine, indicated that often the animals would literally "lift" one end of the operant chamber off the ground with their teeth as they were biting the grid flooring. Table 57 indicates that stereotyped biting behavior was significantly facilitated during the first four hours post-injection following 10.0 and 7.5 mg/kg morphine and during the second- and third-hours post-injection following 5.0

mg/kg morphine; however, following 2.5 mg/kg morphine the difference failed to reach significance. Although not tested directly statistically, there appeared to be a positive correlation between dose of morphine and the number of occurrences of stereotyped biting behavior. Thus, stereotyped biting behavior appears to be a sensitive measure of morphine effect.

General behavioral activity, except for stereotyped biting behavior, was generally not significantly different from morphine. This, together with the fact that often each electrode placement within an animal displayed differential effects, indicate that the correlation between morphine's effect on ICSS and general behavior would be low. Since stereotyped behavior occurred most often at the 10.0 mg/kg morphine dose, which also displayed somewhat more depressant and fewer facilitative effects, might indicate that this is a competing drive and correlate with the depressant effects in ICSS behavior. No behavior measured in the present study appeared to correlate with the facilitations in ICSS. This, together with the fact that during the first few hours post-injection, two animals (84F and 86F) displayed facilitations at the DB electrode placement

while the HYP electrode placement displayed depressions in ICSS rates, indicate that morphine does have specific effects within the reward system(s).

The present study was not designed to fully determine the extent or pattern of withdrawal effects on ICSS or general behavior. Withdrawal was not precipitated, nor were animals tested for an additional time period if the ICSS data looked aberrant upon visual inspection. In general, it can be seen that ICSS rates were not significantly different from baseline during the six days of post-drug testing.

The results of the site x drugcond x days x hour interaction Duncan tests for post-drug saline are presented in Tables 24-51. Figures 5-60 present the data graphically. The data will be presented in general terms, beginning with those animals which had received the 10.0 mg/kg morphine dose.

Animal 37E had a depressant morphine effect at both electrode placements during repeated administration of 10.0 mg/kg morphine. During the first day of post-drug saline testing, both electrode placements displayed a few instances of depressant effects. On subsequent days there were a few

instances of significant effects, but generally the rates were not different from those of pre-drug saline. Animal 54P displayed depressant effects at both electrode placements during repeated administration of 10.0 mg/kg morphine. On the first day of post-drug saline several instances of significant depressions in rates occurred at both electrode placements. Subsequently the DB electrode had only one more significant depression. The HYP electrode had a few instances each of significant depressions and facilitations during the early hours of the next two days of post-drug saline, and then appeared to have rates equivalent to pre-drug saline. Animal 76P displayed a biphasic pattern of effects at both electrode placements during repeated administration of 10.0 mg/kg morphine. During post-drug saline, there were several instances of depressant effects on most days. The graphed data indicate that at both sites, although the mean response rates for both intensities were below those of pre-drug saline, the rates for the low intensity were further from baseline. The rates for the later hours post-injection were generally not significantly different from baseline. Thus, it appears that there

may have been some residual effects during post-drug saline in this animal. It should be pointed out that this animal had several instances of significant facilitations during morphine administration, thus if the depressions reflect a change in baseline, the facilitations seen during drug administration would be reflecting a comparatively larger magnitude of effects. For Animal 94F, the DB electrode data met the criteria for a depressant pattern of effects and the HYP electrode data met the criteria for a biphasic pattern of effects during repeated administration of 10.0 mg/kg morphine. During post-drug saline both electrodes displayed significant depressant effects; the DB electrode rates seemed equivalent to baseline by the fourth day post-morphine administration, whereas the HYP electrode seemed to still have some residual effects during the last three days of withdrawal; however, these occurred mainly during the middle hours of the daily testing sessions.

Animal 74E received repeated administration of 7.5 mg/kg morphine and the data met the criteria for depressant effects at the DB electrode and a biphasic pattern of effects at the HYP electrode. During post-drug saline the DB electrode had a few instances

of depressant effects during the first three days and one instance of a significant facilitation on the fourth day; subsequently the data was not significantly different from pre-drug saline. The HYP electrode had two instances of facilitations and on the last two days of pre-drug saline testing there were no significant differences in rates. Thus, this animal appeared to have only a slight residual drug effect. Animal 4G received repeated administration of 7.5 mg/kg morphine and the data met the criteria for "primarily" facilitative effects at the DB electrode and a biphasic pattern of effects at the HYP electrode. During post-drug saline the DB electrode had three instances of depressions and the HYP electrode had two instances of facilitations and two depressions. Thus, the data for this animal also displayed few residual effects.

Animal 75F had a depressant pattern of effects at both electrode placements during morphine administration (5.0 mg/kg). During post-drug saline both electrode placements had depressant effects on the first three days, and the HYP electrode continued to show significant depressant effects through the sixth day. Visual inspection of Figures 31-32

indicate that during post-drug saline the low intensity elicited rates that were more severely depressed than the high intensity value. Thus, it is possible that some of the depressant effects displayed during post-drug saline, and perhaps even during morphine administration, might reflect a change in threshold. Animal 66F received 5.0 mg/kg morphine and the data for the DB electrode met the criteria for "primarily" depressant effects and for the HYP electrode met the criteria for a biphasic pattern of effects. The DB electrode had only one instance of a significant facilitation during post-drug saline and thus shows little residual effect. The HYP electrode had several significant depressions, but these occurred primarily during the middle hours of the day. Visual inspection of the data seem to indicate that the rates were just below the range of the s.e.m. of pre-drug saline for the early hours of post-drug saline. The data for animal 3G met the criteria for biphasic drug effects at both electrode placements during administration of 5.0 mg/kg morphine. During post-drug saline the DB electrode had four isolated instances of significant effects and generally the data appear equivalent to that of pre-drug saline.

The HYP electrode showed several significant depressions on the first day of post-drug saline, but then appeared to have data equivalent to pre-drug saline. Animal 21G met the criteria for a biphasic pattern of effects at both electrode placements during administration of 5.0 mg/kg morphine. During post-drug saline the DB electrode had a few instances of significant facilitations and the HYP electrode had a few instances of "primarily" depressant effects. Both electrodes appeared to have little residual effect of drug.

For animal 84F the data for the DB electrode met the criteria for "primarily" depressant effects while for the HYP electrode met the criteria for "primarily" facilitative effects. Both electrodes had significant facilitations during post-drug saline; the DB electrode had only two instances while the HYP electrode displayed several through the fourth day of post-drug saline, and none thereafter. Thus both electrode placements apparently had no residual effect by the fourth day. The data for 86F met the criteria for "primarily" depressant effects at the DB electrode and a biphasic pattern at the HYP electrode during administration of 2.5 mg/kg morphine. Both electrode

placements had a few significant depressant effects during post-drug saline, with the HYP electrode showing a somewhat larger number. In general, the data for both electrode placements appeared to be equivalent to that of pre-drug saline. The data for 18G met the criteria for a biphasic effect at the DB electrode and "negligible" effects at the HYP electrode during administration of 2.5 mg/kg morphine. During post-drug saline the DB electrode displayed several significant depressions on the first day post-injection and during the first two hours post-injection on subsequent days. Thus, the data for this electrode placement seemed to indicate residual effects and/or a change in baseline (see Figures 53-54). The HYP electrode showed only a few significant depressions during post-drug saline, mostly during the initial hours post-injection on the first three days. This electrode placement displayed differential effects at each intensity value during morphine administration. Figures 55 and 56 indicate that during post-drug saline ICSS rates for the low intensity were below those of pre-drug saline and the rates for the high intensity were somewhat above those of pre-drug saline although not as high as during

morphine administration. Thus, it is difficult to determine whether the data during morphine administration reflects a change in baseline rates of responding, or whether the effects noted during post-drug saline reflect a residual effect from morphine administration. However, it must again be pointed out, that this was the only electrode placement to show such conflicting effects at each intensity value; apparently this is also the case for the post-drug saline ICSS data. For 9G the data met the criteria for a biphasic pattern of effects at the DB electrode, and "negligible" effects at the HYP electrode (with a trend towards significant facilitations) during administration of 2.5 mg/kg morphine. During post-drug saline, the DB electrode displayed several instances of depressant effects, primarily on the first two days, and two instances of facilitiative effects. Figures 57-58 indicate that the high intensity had generally equivalent rates to those of post-drug saline. The HYP electrode had several instances of depressions during post-drug saline; however these were fairly isolated and these depressions are likely reflecting variability in rates at the low intensity value (see Figures 60-61).

Thus, although a "return to baseline" was not tested directly statistically, visual inspection of the data indicate that of the twenty-eight electrodes, 20 clearly showed little or no residual effects. The data for seven electrode placements had rates fairly comparable to those of pre-drug saline, particularly at the high intensity by the later days of testing. Only one electrode placement (18G-HYP) had data that is difficult to interpret, i.e., whether the effects seen during post-drug saline are reflecting a withdrawal effect and/or a change in baseline responding. Twenty electrode placements showed "mainly" significant depressions, and six "mainly" significant facilitations during post-drug saline. A trend could not be seen, upon visual inspection, between the effects during morphine administration and those seen during post-drug saline. Also, a trend was not evident between electrode locus and effects displayed during post-drug saline. Thus, there appears to be a tendency toward depressions in ICSS rates during post-drug saline, as well as 24-hours post-injection (see above), however the present study does not enable predictions as to the cause or effects of particular results.

During the post-drug saline condition the animals' general behavior was similar to that during pre-drug saline; there were no behavioral signs of morphine withdrawal syndrome (wet shakes, writhing, jumping, etc.). Tables 54-58 present the results for the statistical test on general behavior, analyzed within dose. Figures 117-130 present the data for locomotor activity for each animal and Figures 131-134 present the data for stereotyped biting behavior, grouped by dose. The only significant effects occurred at the 5.0 mg/kg dose; a decrease in locomotor behavior 5- and 24-hours post-injection and a decrease in rearing 24-hours post-injection. Figures 117-130 indicate that during the first-hour post-injection the s.e.m. of pre- and post-drug saline overlapped for twelve of the fourteen animals. As during pre-drug saline, stereotyped biting behavior generally did not occur.

Thus, upon termination of repeated morphine administration, typical withdrawal signs did not appear, although decreases in behavioral levels did occur. The general behavioral effects were dissociated from those on ICSS during withdrawal as was also the case during morphine treatment.

Discussion

The results of Experiment 1 confirmed the hypotheses that acute administration of morphine exerts (1) facilitative effects upon ICSS response rates and (2) differential effects within the central reward system(s). Repeated morphine administration modifies the temporal patterning of these effects. During post-drug saline, decreases in ICSS rates occur. These effects are generally dissociated from those on general behavior.

Neuroanatomical specificity to morphine's effects on ICSS has been previously suggested, however all of these studies employed separate groups designs (Leibman & Segal, 1977; Lorens, 1976; Olds & Travis, 1960). Experiment 1 demonstrated that morphine differentially affects ICSS rates elicited at neuroanatomically discrete brain sites within an animal. Based upon the results of the statistical analyses, the data for each electrode placement were classified as displaying "primarily" depressant effects, "primarily" facilitative effects, a biphasic pattern or "negligible" effects. Eleven electrode placements were classified as displaying "primarily" depressant effects, 13 electrode placements were

classified as displaying a biphasic pattern, two electrodes were classified as displaying "primarily" facilitative effects and two electrode placements were classified as displaying "negligible" effects. Thus, 15 of the 28 electrode placements displayed facilitations in ICSS rates. Of the 14 animals tested, five animals clearly showed differential results at each electrode placement. For the initial hours post-injection, two of these animals displayed only depressant effects at the DB electrodes while the HYP electrodes showed only facilitative effects. Thus, both facilitative effects of morphine as well as differential effects of morphine within the central reward system(s) were demonstrated in the present study. Although not tested directly statistically, there appeared to be a correlation with dose: the higher morphine doses tended to display more depressant effects and the lower morphine doses appeared more likely to display facilitative effects on ICSS rates. With slight exceptions, both intensities within a given electrode placement showed the same drug effect. The pattern of effect seems to be related to the discrete neuroanatomical sites being stimulated; however not enough placements were tested at each dose to draw conclusions about the precise

neuroanatomical structures responsible for the morphine effects. Often the two tips of an electrode placement impinged upon two different neuroanatomical areas, thus possibly obscuring a drug effect correlated with only one of them. Further work investigating morphine's effects upon ICSS site-specificty with the HYP and DB has been reported by my laboratory (Nelson, Brutus, Wilson, Farrell, Ocheret, Ellman & Steiner, 1977). Since the inception of this experiment, other studies have reported differences in morphine's chronic effects upon ICSS from distant, discrete brain sites including: facilitations in the cingulate and medial frontal cortices (Lorens, 1972, 1976), a biphasic pattern in the lateral hypothalamus (Adams et al., 1972; Bush et al., 1976; Lorens, 1976; Lorens & Mitchell, 1973) and depressions in circumscribed areas of the midbrain central gray and substantia nigra, pars compacta (Liebman & Segal, 1977). The present study is the first to have demonstrated differential effects within each of two electrode placements within an animal.

The data of Experiment 1 indicated that DB electrodes tended to display more instances of

significant effects, which were most often rate depressions, than did corresponding HYP electrodes. Five DB electrodes displayed a depressant pattern of effects while the corresponding HYP electrodes displayed biphasic patterns of effect. In addition, two DB electrodes displayed biphasic patterns of effect while the corresponding HYP electrodes had "negligible" effects. The DB area may receive a functionally larger morphine dose than the HYP area since more depressions were found from this area; higher morphine doses generally produce more depressions in ICSS rates (Bush et al., 1976; Lorens, 1976; Lorens & Mitchell, 1973; the present study). If the DB receives a functionally higher morphine dose, then the depressant effects might mask some of the facilitative effects. The locus coeruleus might be more strongly affected by systemic morphine than the lateral hypothalamus because there is a higher density of opiate receptor sites (Atweh & Kuhar, 1977c; Miller et al., 1973; Kuhar et al., 1973; Pert et al., 1976). In addition, the DB is more sensitive than the HYP to systemic injections of the opiate antagonist naloxone as measured by ICSS rates (Stein & Belluzzi, 1978). The area of the fourth ventricle has been found to be

more sensitive than the area around the lateral ventricle to microinjections of opiate antagonists as measured by withdrawal signs elicited (Laschka, Teschemacher, Mehraein & Herz, 1976). Thus the difference in pattern and duration of effects on ICSS rates demonstrated in Experiment 1 may reflect differences in the amount of morphine delivered to the two neuroanatomical sites and their sensitivities to the drug.

The mechanisms underlying depressions in ICSS appear to be both dose- and site-dependent. The depressions may be either a direct effect on the reward system(s) or a nonspecific incapacitation, although these effects need not be mutually exclusive. Tatum, Seevers & Collins (1929) hypothesized that morphine had two effects, a generalized depressant effect which masks a more specific facilitative effect. The tolerance observed to the depressions in ICSS response rates supports this hypothesis. The dose-response characteristics of the depressions coupled with the data from the lowest dose (2.5 mg/kg) in which facilitations with no initial depressions appeared, also support this hypothesis.

In addition to a nonspecific incapacitation hypothesis, there is evidence in the data that supports a specific depressant action on some reward sites. Eleven electrode placements exhibited "primarily" depressant effects in ICSS rates. Five of these occurred following administration of 10.0 mg/kg morphine; however, these "pure" depressions cannot be explained on the sole basis of a high dose effect for the following reasons: 1) similar "pure" depressions followed the administration of the lowest dose of morphine (2.5 mg/kg) at electrode placements in two animals; 2) while showing "primarily" depressant effects at one electrode site, these animals (84F & 86F) simultaneously showed facilitations at the other electrode site; 3) other electrodes at the highest dose (10.0 mg/kg) exhibited facilitations; and 4) any late-appearing facilitation as part of a biphasic pattern would very likely have been detected, since ICSS was sampled as long within a day as any study in the literature which reported "pure" facilitations or a biphasic pattern of effects following administration of even higher doses of morphine (Adams et al., 1972; Bush et al., 1976; Lorens, 1972, 1976). The existence

of site-specific "pure" depressions has been reported by others as well (Liebman & Siegel, 1977). Thus, the sites at which electrodes exhibit "pure" depressions show a fundamental difference (lack of a facilitation) from sites that exhibit a biphasic pattern or "pure" facilitations. Therefore, while nonspecific incapacitation certainly plays a role in determining ICSS rates following morphine, it cannot account for all response rate depressions.

One factor which may account for the relatively large number of electrodes exhibiting "pure" depressions in this study compared to others is differences in stimulation parameters, particularly with respect to the relative duration in which current is "flowing" within each stimulus train. In studies using biphasic square waves (Adams et al., 1972; Lorens, 1972, 1976; Lorens & Mitchell, 1973) facilitations were noted upon the first day of drug administration following a morphine dose of up to 20.0 mg/kg. In studies utilizing sine waves, as in Experiment 1, "pure" depressions were noted following administration of up to 15 mg/kg morphine for at least four days (Bush et al., 1976; Liebman & Segal, 1977; van der Kooy et al., 1978). During sine wave

stimulation current is continuously flowing within each stimulus train. In studies employing square wave stimulation, however, there are discrete periods during which current is not flowing. Perhaps techniques employing continuous current flow are less sensitive to the facilitative effects of morphine than are intermittent stimulation techniques. If one of morphine's effects is to potentiate the excitability characteristics of some reward neurons, then an intermittent form of stimulation would be more sensitive to morphine's facilitative effects by allowing many opportunities within a stimulus train for the increased excitability to be apparent. Conversely, a continuous stimulation technique, which would drive "reward" neurons both in the saline and morphine conditions, would only allow the increased excitability to become apparent at the end of each stimulus train. A direct comparison of both techniques on morphine's effects on ICSS rates at circumscribed brain sites has not been reported in the literature. There are other factors, including grouped vs. individual subject analysis, which may contribute to the relative differences in results reported among studies.

In Experiment 1, three electrodes displayed facilitations with no prior depressions in ICSS rates. In addition, five other electrodes displaying a biphasic pattern showed facilitations immediately post-injection on at least one drug day. "Pure" facilitations observed in ICSS rates support the hypothesis that morphine potentiates the reinforcement value of ICSS and is not dependent upon a prior depression. The facilitative effects of morphine as measured by ICSS bar-press rates are similar to those obtained using other dependent measures, such as shuttle box (Levitt, Baltzer, Evers, Stilwell & Furby, 1977) and threshold titration (Esposito & Kornetsky, 1977). The results of Experiment 1, showing morphine-induced facilitations, are congruent with the hypothesis that: all drugs of abuse that have been studied with ICSS have the common property of showing facilitations at some sites (Steiner, 1976).

Tolerance to the depressant effects of morphine on ICSS rates clearly occurred as other studies have reported (Adams et al., 1972, Bush et al., 1976; Lorens, 1976; Lorens & Mitchell, 1973). Experiment 1 suggests tolerance to the facilitative effects in some rats but not in others. Only one other study has

reported clear evidence of tolerance to morphine's facilitative effects (Glick et al., 1974). Several studies, however, claim to have found no evidence of the development of tolerance to the facilitative effects of morphine on reinforcing brain stimulation (Bush et al., 1976; Esposito & Kornetsky, 1977; Lorens, 1976; Ornstein & Huston, 1977). Site-specific differences in the development of tolerance to the facilitative effects of d-amphetamine have been reported (Anderson, Leith & Barrett, 1978). Thus, site may play a role in the observed tolerance to the morphine facilitation of ICSS, since there is a precedent of site-specificity in the development of tolerance to the facilitative effects of d-amphetamine, which is also a drug of abuse, on the reward system.

Upon termination of morphine injection, typical withdrawal signs as described by others (Buckett, 1964; Martin, Wikler, Eades & Pescor, 1963) did not appear. This was expected since the morphine doses were low and an opiate antagonist was not used to precipitate withdrawal. ICSS may even be a more sensitive measure of withdrawal than general behavioral activity, since depressions were seen 24

hours post-injection in the morphine condition as well as for several days during post-drug saline.

Several studies, all of which used a single-implant design, have indicated that the effects of opiates on ICSS are dissociated from those on general activity levels (Koob, Spector & Meyerhoff, 1975; Lorens & Mitchell, 1973; Ornstein & Huston, 1977; Shizgal, Bellisle, Winer & Amit, 1978). In Experiment 1, differences in the morphine effects at both electrode placements often occurred within test sessions. Therefore, differences in morphine's effects on ICSS rates are not artifacts of concomitant changes in activity levels.

Thus, the effects observed were a result of a complex interaction of drug condition (including dose), time post-injection, site, number of days of drug administration, and stimulation current intensity.

Experiment 2: Effects of morphine on rate-intensity functions.

Rationale

The eight-hour daily testing procedure precludes an assessment of the effects of morphine on a full rate intensity function. Since a drug may exhibit different effects along the rate-intensity function (Steiner & Stokely, 1973), it would be important for the interpretation of the results of Experiment 1 to show whether morphine has differential effects at different current intensities. This experiment was designed to determine the effects of several doses of morphine on ICSS rate-intensity functions.

Method

Subjects. Twelve male albino rats (Holtzman Sprague Dawley) weighing 250-315 grams at the time of operation were used. All animals were maintained on an ad libitum food and water schedule and were housed within each site individually.

Surgery, Apparatus, Preliminary Testing and Histology. The details of these methods are the same as described in Experiment 1. Six of the twelve rats tested met the criteria to be included in this

experiment; i.e., rates produced from both electrode placements had to exceed ten responses per minute on three consecutive daily testing sessions. The six animals not meeting this criterion either did not press from one electrode or had variable rates.

Procedure. Each day an animal was allowed to self-stimulate for a 96-minute session which was divided into twelve seven-minute periods, separated by one-minute time-outs. The data for the last five minutes of each seven-minute period served as the dependent variable (as in Experiment 1). To control for the order effects, stimulation was counterbalanced with each site tested first in an A-B-B-A sequence (Site A-intensity 1, Site B-intensity 1, Site B-intensity 2, Site A-intensity 2.....Site B-intensity 6, Site A-intensity 60. During the first two seven-minute periods for each electrode placement, stimulation intensities were sufficiently low so that the animals' response rates over the last five minutes of the period were below an arbitrarily-defined response threshold of ten responses per minute. For each electrode placement, the third, fourth and fifth intensities, presented in ascending order, sustained

self-stimulation behavior at rates which approached or reached optimal responding. The sixth intensity elicited either peak rates or a decrement in response rate, characteristic of an inverted U rate-intensity function. The HYP electrode was tested first in each daily testing procedure, except for two rats (19P and 15G), which extinguished pressing when the DB electrode was tested first. In these instances it was necessary to begin each daily testing session with the DB electrode (see Method, Experiment 1).

Animals were given priming stimulation if they did not initiate responding during the first minute of each seven-minute period; rats were never primed during the last five minutes.

When rate-intensity functions stabilized, each animal entered a nine day testing sequence, consisting of three days of pre-drug saline, three days of morphine and three days of post-drug saline. Each day, three hours prior to the daily ICSS test session, either saline or morphine was administered; this time period was selected, based upon pilot data from Experiment 1, to increase the likelihood of sampling facilitative effects of morphine on ICSS, particularly

following administration of the highest morphine dose (10.0 mg/kg). Each animal was tested with one and only one dose of morphine during the three drug days. Three doses of morphine were tested in the third experiment: 2.5, 5.0 and 10.0 mg/kg.

Five minutes prior to ICSS testing, the rat's general behavior was monitored in a five-minute behavioral watch, as described in Experiment 1.

Statistics. Since rate-intensity functions were sampled only once per day and changes in time-course of drug effects were not being measured, the data were analyzed with a series of two-way analyses of variance with repeated measures on all factors. The drug conditions analyzed in this fashion were pre-drug saline (3 days), morphine (3 days) and post-drug saline (3 days). The experimental design is day nested within drug condition by current intensity, the data for each electrode placement analyzed separately. Duncan *a posteriori* tests were performed on both the overall morphine effect (collapsing over all current intensities) as well as the interaction of drug condition x current intensity (within intensity) for each electrode placement ($\alpha = .01$).

Results

A schematic representation of the electrode placements for the animals which completed Experiment 2 appear in Figures 135 and 136 and is detailed in Table 59. Six animals completed the experiment. Two animals were tested per morphine dose: 41E and 19P at 10.0 mg/kg, 15G and 10G at 5.0 mg/kg and 8G and 7G at 2.5 mg/kg. The rate-intensity functions for each electrode placement are graphed in Figures 137-148. Although it was not tested directly statistically, there appeared to be a site-specific difference in pre-drug saline rate-intensity functions: DB electrodes more often had "inverted-U" shaped functions, while HYP electrodes more often had "ogive" shaped functions.

Individual ANOVA tables for each electrode placement arranged by site appear in Tables 60-61. All electrode placements had a significant main effect of current intensity. Morphine effects appeared either as significant main effects of drug condition, drug condition x current intensity or both the main and interaction effects. Duncan a posteriori tests (α

<.01) were performed on the interaction of drug condition x current intensity within each electrode placement (see Tables 62-63). Two such comparisons were made: pre-drug saline vs. morphine and pre-drug saline vs. post-drug saline. The electrode placements displayed ICSS rates that were either significantly depressed or significantly facilitated or else no instances in which the p-level was < .01; no electrode placement had a significant depression at one intensity and a significant facilitation at another intensity. Each electrode placement received a pattern classification for morphine effects on ICSS rate-intensity functions that was based upon the direction of effect obtained on the Duncan a posteriori test (α = .01). Only five of the 12 electrode placements displayed significant morphine effects on the site x drugcond x intensity interactions.

Following administration of 10.0 mg/kg morphine, significant depressions occurred at the DB electrodes of the animals 41E and 19F for both the third and fourth current intensity values. ICSS rates at the

HYP electrodes in both animals did not differ significantly from pre-drug saline at a p-level of < .01.

Following administration of 5.0 mg/kg morphine, the DB electrode of animal 15G had a significant depression in ICSS rates at the fourth current intensity value. The DB electrode of animal 10G had significant facilitations in ICSS rates for the first three intensity values as well as a facilitative effect in the overall site x drugcond interaction. As at the 10.0 mg/kg dose, ICSS rates at the HYP electrodes in both animals did not differ significantly from pre-drug saline at a p-level of < .01.

Following administration of 2.5 mg/kg morphine, the HYP electrode of animal 8G displayed a significant depression in ICSS rates for the third current intensity value. ICSS rates at the DB electrode of 8G and both electrode placements of 7G were not significantly different from pre-drug saline at a p-level of < .01.

Although differences in drug effect across sites cannot be directly tested statistically within the

context of a two-way analysis of variance, the DB electrode appeared to be more affected than the corresponding HYP electrode within the animals tested in the present experiment. In fact, four of the five electrode placements which displayed significant morphine effects were those aimed at the DB area. Only one electrode placement (10G-DB) displayed significant facilitations in ICSS rates and this was following the 5.0 mg/kg morphine dose. These facilitations occurred at the lower current intensity values while the depressions displayed at electrode placements in the other animals occurred at intensities higher within their rate-intensity functions; however, within the context of the present data analysis, it cannot be determined whether there is a statistically significant trend toward facilitations in ICSS rates occurring at lower current intensity values than depressions.

The Duncan a posteriori tests of the overall effects of drug condition (collapsed across current intensity) for each electrode placement indicated that ICSS rates returned to baseline during post-drug saline condition ($p<.01$). The results of the Duncan

tests on the drugcond x intensity interactions for each electrode placement are summarized in Tables 62-63. ICSS rates during post-drug saline following administration of 10.0 mg/kg morphine dose, were not significantly different from those of pre-drug saline for any current intensity value at any electrode placement. During post-drug saline following the lower morphine doses, five electrodes displayed rates significantly different from pre-drug saline; in general, the effect was displayed at only one of the six current intensity values tested per electrode placement (see Tables 62-63).

Behavioral observations of general activity were made five minutes prior to ICSS testing; i.e., the third-hour post-injection. Tables 64-65 present the results of these statistical tests. When the data are combined across dose, no significant differences in behavior were noted at a p-level of $< .01$. Thus, as in Experiment 1, the morphine effects on ICSS rates appear to be dissociated from those on general behavior.

Discussion

The effects of morphine on ICSS rate-intensity functions were studied, as a supplement to Experiment 1, to more fully determine whether or not morphine differentially affects behavior at the lower and higher current intensity values within an electrode placement. The results indicated that all electrode placements displayed monophasic effects of morphine: no electrode placements displayed both significant depressions and faciltations.

The effects of morphine on ICSS rate-intensity functions were studied three hours post-injection to maximize the likelihood of eliciting morphine's facilitative effects following the highest (10.0 mg/kg) morphine dose. However, following this dose, no significant facilitations in ICSS rates ($p<.01$) were noted; although significant depressions occurred at the DB electrodes of both animals. Following the 5.0 mg/kg dose, significant facilitations were displayed at the DB electrode of one animal. No other facilitations were noted.

Only five of the 12 electrode placements tested displayed significant effects, and only at a maximum

of three of the six current intensities tested per electrode placement. The apparent lack of effects at most current intensities within each electrode placement may be related to the fact that ICSS was only sampled during a single time interval post-injection. Although not tested statistically, each morphine dose, as noted in Experiment 1, appeared to have a different time course of effect: the lower the dose the shorter the duration of depressions and the earlier the onset of facilitations. Thus, in Experiment 2, by keeping the time of testing ICSS following drug administration constant across dose conditions, as is desirable in a parametric study, the primary facilitative effects following administration of 5.0 and 2.5 mg/kg morphine doses may have passed but may not yet have occurred for the 10.0 mg/kg morphine dose. The first experiment did not study the effects of morphine on complete rate-intensity functions because of the nature of the experimental design. Since the purpose of this third experiment was to supplement the first experiment, it did not include all categories of groups (e.g., parametrically studying the influence of interval

post-injection to rate-intensity ICSS testing) which may have enabled stronger statements on the effects of morphine on rate-intensity functions.

Also of note is that of the five animals in which significant morphine effects on ICSS rates were detected, four displayed these effects only at the DB electrode while the data at the corresponding HYP electrode was not significantly different from baseline. Thus, although not tested statistically, the DB electrodes appeared more likely to show significant effects than the corresponding HYP electrodes. This supports the hypothesis that DB may receive a functionally higher morphine dose than the HYP area.

The effects of morphine were not directly compared across intensities, however the results of Experiment 2 indicated a greater likelihood of noting facilitations than depressions at the lower intensity values. Changes in threshold following morphine administration have been reported in studies utilizing threshold determination (Esposito & Kornetsky, 1977; Kelley & Reid, 1977; Marcus & Kornetsky, 1974; Ornstein & Huston, 1977), baseline threshold value (Lorens, 1976) and rate-intensity functions (Maroli et

al., 1978; Olds, 1959). In these studies, thresholds were generally lowered, however raised and unchanged thresholds were also reported which appeared to be dependent upon site, dose, time post-injection, tolerance and stimulus parameters. The methods used and the comparative results obtained within these and the present study provide additional support for the hypothesis that continuous stimulation techniques may be less sensitive than intermittent stimulation techniques for studying morphine-induced facilitations on the reward system(s) (see Discussion, Experiment 1).

Experiment 1 demonstrated that within an electrode placement, morphine generally has depressant effects followed by facilitative effects within, as well as across days. When the results of Experiment 2 are viewed in this light, it appears that a chronic study such as Experiment 1 in which ICSS rates at particular current intensity values tested over several sessions per day is a more efficient model for observing morphine's effects on multiple electrode sites within an animal; especially when the effects of several drug doses are to be studied. Although not directly tested statistically, the results of

Experiment 2 support the dose- and site-specific depressant and facilitative trends suggested by the data obtained in Experiment 1 and further suggests that morphine may differentially affect response rates at different current intensities and that these factors may contribute to the apparent discrepancies in results reported among studies.

General Discussion

The present series of experiments demonstrated that morphine has facilitative as well as depressant effects on ICSS behavior. In fact, most electrode placements displayed depressions followed, within and/or across days, by facilitations in ICSS rates. In general, higher morphine doses elicited more instances of depressions and lower morphine doses elicited more facilitations of ICSS rates. The two electrode placements within each animal often had significant effects that were opposite in direction during particular test sessions; in general, the DB electrodes had more depressions within a day and upon repeated drug administration than the corresponding HYP electrodes. The rate-intensity data also indicated similar dose and site trends. Thus, morphine does appear to have direct effects on central reward system(s). The present data are in support with the "dual action" hypothesis of morphine (Tatum Seevers & Collins, 1929), which suggests that there is a general depressant effect of morphine that masks a specific facilitative effect on the central nervous system. This hypothesis would predict that with administration of lower doses of morphine it would be

more likely to observe the facilitative effects. The general differences observed between electrode sites within animals support previous studies that report site-specific differences when using separate-groups design (Liebman & Segal, 1976; Lorens, 1976).

Since opiate receptor sites have now been extensively mapped (Simon & Hiller, 1978; Uhl, Childers & Snyder, 1978), it would be beneficial to investigate the differences in ICSS rates upon administration of morphine and enkephalins at sites possessing high vs. low receptor densities. This might also begin to answer whether the trend for DB electrode placements to appear as though it received a functionally larger morphine dose than HYP electrodes is due to differences in the amount of drug passing though the blood-brain-barrier and subsequently arriving at these brain sites, or due to the differences in the relative amount of receptor sites at each of these brain areas. Also, as more specific biochemical techniques become available, chemical manipulation of the endogenous opiate-like substances, together with the ICSS techniques, might further indicate the mechanisms responsible for morphine's effects on central reward mechanisms. It would also

be of interest to study the effects of larger doses of morphine administered over longer time periods to determine whether (1) facilitative effects occur upon the development of tolerance to the depressant effects and (2) there are more obvious withdrawal effects, as measured by ICSS rates, in an animal "addicted" to morphine and, if so, whether these effects are site-specific within the central reward system(s)?

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Table 1 Histological localization of electrode placements.

Dose mg/kg	Rat	Electrode Placement
10.0	37E	DB: ventral-lateral to LC HYP: post. hyp. nuc.
	54F	DB: MLF HYP: betw. LH & VMN
	76F	DB: lateral to LC HYP: post. LH-crus cerebri
	94F	DB: DNB in post. midbrain HYP: fornix
7.5	74E	DB: LC in transitional area HYP: Dorsal to MFB
	4G	DB: ventral to mesen. V HYP: medial LH-fornix
5.0	66F	DB: ventral LC in trans. area HYP: between LH & fornix
	75F	DB: ventral LC in midbrain HYP: lateral MFB
	3G	DB: ventral LC in trans. area HYP: LH
	21G	DB: dorsal in midbrain LC HYP: ventral lateral to MFB
2.5	84F	DB: ventral LC in post. pons HYP: LH
	86F	DB: post. midbrain DNB HYP: dorso-medial LH
	18G	DB: trans. area/midbrain DNB HYP: LH
	9G	DB: ventral LC/DNB HYP: ventral-lateral to LH

Table 2

SUMMARY TABLE : 5-way ANOVA (pre-drug saline vs. morphine and post-drug saline)

(mg/kg) DOSE	Rat #	df	mean square (error)	F-value	p	r-square (source)
10.0	37E	1728[a]	1.7236	25.77	.0001	0.87
	54F	2304	7.4826	5.34	.0001	0.57
	76F	2304	1.7941	20.40	.0001	0.84
	94F	2304	6.6173	15.25	.0001	0.79
7.5	74E	2304	4.2756	7.58	.0001	0.65
	4G	2304	5.4063	28.01	.0001	0.87
5.0	75F	2304	2.6933	44.90	.0001	0.92
	66F	2304	6.0906	7.60	.0001	0.65
	3G	2304	5.3477	11.71	.0001	0.75
	21G	2304	1.8808	29.24	.0001	0.88
2.5	84F	2304	1.6012	7.82	.0001	0.66
	86F	2304	11.4238	6.09	.0001	0.60
	18G	2304	2.3387	89.92	.0001	0.94
	9G	2304	0.9907	21.97	.0001	0.85

Dependent Variable = sq. rt. (resp/min + 0.5)

[a] tested six sessions/day

TABLE 3 . 5-WAY ANOVA: 37E (MORPHINE-10.0 MG/KG)

ANALYSIS OF VARIANCE PROCEDURE

DEPENDENT VARIABLE:R-SQ. RT. (R + 0.5)

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	P	R-SQUARE	C.V.
MODEL	431	19147.03765979	44.42653749	25.77	0.0001	0.865389	20.4643
ERROR	1728	2978.43344670	1.72363047		STD DEV		R MEAN
CORRECTED TOTAL	2159	22126.27110649			1.31287108		6.41543022

SOURCE	DF	ANOVA SS	F VALUE	P
SITE	1	9096.60834865	5277.59	0.0001
DRUGCOND	2	2108.15101748	611.54	0.0001
INTENSTY	1	5.49489963	3.19	0.0744
DAY	5	375.11851790	43.53	0.0001
HOUR	5	979.14798460	113.61	0.0001
SITE*DRUGCOND	2	138.73434171	40.24	0.0001
SITE*INTENSTY	1	38.30013898	22.22	0.0001
SITE*DAY	5	52.00268737	6.04	0.0001
SITE*HOUR	5	182.69973861	21.20	0.0001
DRUGCOND*INTENSTY	2	1.31627666	0.38	0.6827
DRUGCOND*DAY	10	403.09506433	23.43	0.0001
DRUGCOND*HOUR	10	2561.19511842	148.59	0.0001
INTENSTY*DAY	5	18.56038125	2.15	0.0581
INTENSTY*HOUR	5	50.37167667	5.84	0.0001
DAY*HOUR	25	450.58656486	10.46	0.0001
SITE*DRUGCON*INTENST	2	18.61932983	5.40	0.0046
SITE*DRUGCOND*DAY	10	174.27812697	10.11	0.0001
SITE*DRUGCOND*HOUR	10	193.63612777	11.23	0.0001
SITE*INTENSTY*DAY	5	43.04007285	4.99	0.0002
SITE*INTENSTY*HOUR	5	33.48490554	3.89	0.0018
SITE*DAY*HOUR	25	179.87836690	4.17	0.0001
DRUGCOND*DAY*HOUR	50	670.49709673	7.78	0.0001
DRUGCOND*INTENST*DAY	10	120.26005140	6.98	0.0001
DRUGCON*INTENST*HOUR	10	54.30868412	3.15	0.0005
INTENSTY*DAY*HOUR	25	147.76382559	3.43	0.0001
SITE*DRUGCO*DAY*HOUR	50	337.91457662	3.92	0.0001
SITE*DRUGC*INTEN*DAY	10	45.24257716	2.62	0.0036
SITE*DRUGC*INTE*HOUR	10	47.64461259	2.76	0.0022
SITE*INTENS*DAY*HOUR	25	161.66371639	3.75	0.0001
DRUGC*INTEN*DAY*HOUR	50	240.04495623	2.79	0.0001
SITE*DRU*INT*DAY*HOU	50	217.29787599	2.52	0.0001

TABLE 4 . 5-WAY ANOVA: 54F (MORPHINE-10.0 MG/KG)

ANALYSIS OF VARIANCE PROCEDURE

DEPENDENT VARIABLE: R SQ. RT. (R + 0.5)

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	P	R-SQUARE	C.V.
MODEL	575	22985.80932452	39.97532056	5.34	0.0001	0.571422	55.9032
ERROR	2304	17239.80096594	7.48255250		STD DEV		R MEAN
CORRECTED TOTAL	2879	40225.61029046			2.73542547		4.89314251

SOURCE	DF	ANOVA SS	F VALUE	P
SITE	1	2361.39368414	315.59	0.0001
DRUGCOND	2	3757.57008053	251.09	0.0001
INTENSITY	1	2145.29265300	286.71	0.0001
DAY	5	313.99392420	8.39	0.0001
HOUR	7	2530.49356777	48.31	0.0001
SITE*DRUGCOND	2	44.38335809	2.97	0.0517
SITE*INTENSITY	1	121.56795005	16.25	0.0001
SITE*DAY	5	346.56220340	9.26	0.0001
SITE*HOUR	7	392.01639473	7.48	0.0001
DRUGCOND*INTENSITY	2	179.99530109	12.03	0.0001
DRUGCOND*DAY	10	938.15463116	12.54	0.0001
DRUGCOND*HOUR	14	2014.98196196	19.24	0.0001
INTENSITY*DAY	5	27.00155592	0.72	0.6095
INTENSITY*HOUR	7	374.29591797	7.15	0.0001
DAY*HOUR	35	625.62011018	2.39	0.0001
SITE*DRUGCON*INTENST	2	153.49365738	10.26	0.0001
SITE*DRUGCOND*DAY	10	318.49245468	4.26	0.0001
SITE*DRUGCOND*HOUR	14	413.51271365	3.95	0.0001
SITE*INTENSITY*DAY	5	85.68222922	2.29	0.0431
SITE*INTENSITY*HOUR	7	185.67470915	3.54	0.0009
SITE*DAY*HOUR	35	325.76230985	1.24	0.1547
DRUGCOND*DAY*HOUR	70	1527.45797617	2.92	0.0001
DRUGCOND*INTENST*DAY	10	105.87938989	1.42	0.1671
DRUGCON*INTENST*HOUR	14	199.61888871	1.91	0.0217
INTENSITY*DAY*HOUR	35	406.11336759	1.55	0.0210
SITE*DRUGCO*DAY*HOUR	70	943.37088495	1.80	0.0001
SITE*DRUGC*INTEN*DAY	10	60.52951541	0.81	0.6201
SITE*DRUGC*INTE*HOUR	14	473.85716523	4.52	0.0001
SITE*INTENS*DAY*HOUR	35	319.57848408	1.22	0.1750
DRUGC*INTEN*DAY*HOUR	70	583.37725903	1.11	0.2443
SITE*DRU*INT*DAY*HOU	70	710.06886452	1.36	0.0278

TABLE 5 . 5-WAY ANOVA: 76F (MORPHINE-10.0 MG/KG)

ANALYSIS OF VARIANCE PROCEDURE

DEPENDENT VARIABLE: R' SQ. RT. (R + 0.5)

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	P	R-SQUARE	C.V.
MODEL	575	21048.41674395	36.60594216	20.40	0.0001	0.835854	35.2633
ERROR	2304	4133.50171316	1.79405456		STD DEV		R MEAN
CORRECTED TOTAL	2879	25181.91845711			1.33942322		3.79834949

SOURCE	DF	ANOVA SS	F VALUE	P
SITE	1	907.12797659	505.63	0.0001
DRUGCOND	2	1251.47413775	348.78	0.0001
INTENSITY	1	8789.62646910	4899.31	0.0001
DAY	5	26.65223150	2.97	0.0113
HOUR	7	710.09406316	56.54	0.0001
SITE*DRUGCOND	2	8.15969090	2.27	0.1031
SITE*INTENSITY	1	898.46630977	500.80	0.0001
SITE*DAY	5	113.90770182	12.70	0.0001
SITE*HOUR	7	83.64617822	6.66	0.0001
DRUGCOND*INTENSITY	2	525.81292192	146.54	0.0001
DRUGCOND*DAY	10	217.28136774	12.11	0.0001
DRUGCOND*HOUR	14	1726.33760047	68.73	0.0001
INTENSITY*DAY	5	95.96505278	10.70	0.0001
INTENSITY*HOUR	7	501.53700234	39.94	0.0001
DAY*HOUR	35	444.30328591	7.08	0.0001
SITE*DRUGCON*INTENST	2	93.19199658	25.97	0.0001
SITE*DRUGCOND*DAY	10	114.96161397	6.41	0.0001
SITE*DRUGCOND*HOUR	14	174.75123887	6.96	0.0001
SITE*INTENSITY*DAY	5	49.57231634	5.53	0.0001
SITE*INTENSITY*HOUR	7	57.29042037	4.56	0.0001
SITE*DAY*HOUR	35	179.65724038	2.85	0.0001
DRUGCOND*DAY*HOUR	70	939.91636154	7.48	0.0001
DRUGCOND*INTENST*DAY	10	82.23092225	4.58	0.0001
DRUGCON*INTENST*HOUR	14	367.22055137	14.62	0.0001
INTENSITY*DAY*HOUR	35	375.05930826	5.97	0.0001
SITE*DRUGCO*DAY*HOUR	70	616.16301281	4.91	0.0001
SITE*DRUGC*INTEN*DAY	10	39.80357229	2.22	0.0145
SITE*DRUGC*INTE*HOUR	14	281.25019541	11.20	0.0001
SITE*INTENS*DAY*HOUR	35	234.49248813	3.73	0.0001
DRUGC*INTEN*DAY*HOUR	70	665.49846935	5.30	0.0001
SITE*DRU*INT*DAY*HOU	70	477.56504606	3.80	0.0001

TABLE 6 . 5-WAY ANOVA: 94F (MORPHINE-10.0 MG/KG)

ANALYSIS OF VARIANCE PROCEDURE

DEPENDENT VARIABLE: R- SQ. RT. (R + 0.5)

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	P	R-SQUARE	C.V.
MODEL	575	58022.23991447	100.90824333	15.25	0.0001	0.791912	35.5896
ERROR	2304	15246.30477478	6.61731978		STD DEV		R MEAN
CORRECTED TOTAL	2879	73268.54468925			2.57241516		7.22799475

SOURCE	DF	ANOVA SS	F VALUE	P
SITE	1	8108.55949442	1225.35	0.0001
DRUGCOND	2	3263.69950840	246.60	0.0001
INTENSITY	1	9050.32611946	1367.67	0.0001
DAY	5	495.88417954	14.99	0.0001
HOUR	7	1017.21937357	21.96	0.0001
SITE*DRUGCOND	2	380.61528867	28.76	0.0001
SITE*INTENSITY	1	6370.58361106	962.71	0.0001
SITE*DAY	5	343.60932297	10.39	0.0001
SITE*HOUR	7	946.61507214	20.44	0.0001
DRUGCOND*INTENSITY	2	785.68794473	59.37	0.0001
DRUGCOND*DAY	10	1838.43198762	27.78	0.0001
DRUGCOND*HOUR	14	2801.74556249	30.24	0.0001
INTENSITY*DAY	5	285.14596826	8.62	0.0001
INTENSITY*HOUR	7	376.81191478	8.13	0.0001
DAY*HOUR	35	1870.08548443	8.07	0.0001
SITE*DRUGCON*INTENSI	2	620.05345455	46.85	0.0001
SITE*DRUGCOND*DAY	10	375.36303627	5.67	0.0001
SITE*DRUGCOND*HOUR	14	1478.36163183	15.96	0.0001
SITE*INTENSTY*DAY	5	507.20800420	15.33	0.0001
SITE*INTENSTY*HOUR	7	219.56390310	4.74	0.0001
SITE*DAY*HOUR	35	1112.09491815	4.80	0.0001
DRUGCOND*DAY*HOUR	70	2726.38756619	5.89	0.0001
DRUGCOND*INTENST*DAY	10	299.87619403	4.53	0.0001
DRUGCON*INTENST*HOUR	14	547.20246581	5.91	0.0001
INTENSTY*DAY*HOUR	35	1451.49232311	6.27	0.0001
SITE*DRUGCO*DAY*HOUR	70	2539.21828081	5.48	0.0001
SITE*DRUGC*INTEN*DAY	10	244.44629349	3.69	0.0001
SITE*DRUGC*INTE*HOUR	14	773.14439144	8.35	0.0001
SITE*INTENS*DAY*HOUR	35	1630.64518565	7.04	0.0001
DRUGC*INTEN*DAY*HOUR	70	3174.98185012	6.85	0.0001
SITE*DRU*INT*DAY*HOU	70	2387.17958318	5.15	0.0001

TABLE 7 . 5-WAY ANOVA: 74E (MORPHINE- 7.5 MG/KG)

ANALYSIS OF VARIANCE PROCEDURE

DEPENDENT VARIABLE: R. SQ. RT. (R + 0.5)

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	P	R-SQUARE	C.V.
MODEL	575	18632.95806504	32.40514446	7.58	0.0001	0.654159	46.5425
ERROR	2304	9850.87043030	4.27555140		STD DEV		R MEAN
CORRECTED TOTAL	2879	28483.82849534			2.06774065		4.44269733

SOURCE	DF	ANOVA SS	F VALUE	P
SITE	1	260.15856541	60.85	0.0001
DRUGCOND	2	255.22116369	29.85	0.0001
INTENSTY	1	4975.83960179	1163.79	0.0001
DAY	5	74.80241356	3.50	0.0039
HOUR	7	449.94195150	15.03	0.0001
SITE*DRUGCOND	2	483.23379785	56.51	0.0001
SITE*INTENSTY	1	1647.73066164	385.38	0.0001
SITE*DAY	5	142.17215050	6.65	0.0001
SITE*HOUR	7	420.74084999	14.06	0.0001
DRUGCOND*INTENSTY	2	0.89311438	0.10	0.9008
DRUGCOND*DAY	10	445.72552488	10.42	0.0001
DRUGCOND*HOUR	14	2384.40213868	39.83	0.0001
INTENSTY*DAY	5	59.18589541	2.77	0.0169
INTENSTY*HOUR	7	66.66174290	2.23	0.0294
DAY*HOUR	35	482.85752799	3.23	0.0001
SITE*DRUGCON*INTENST	2	33.90353437	3.96	0.0191
SITE*DRUGCOND*DAY	10	257.62241457	6.03	0.0001
SITE*DRUGCOND*HOUR	14	690.81168909	11.54	0.0001
SITE*INTENSTY*DAY	5	61.25059599	2.87	0.0139
SITE*INTENSTY*HOUR	7	266.83277458	8.92	0.0001
SITE*DAY*HOUR	35	360.14074045	2.41	0.0001
DRUGCOND*DAY*HOUR	70	733.79722363	2.45	0.0001
DRUGCOND*INTENST*DAY	10	178.85090479	4.18	0.0001
DRUGCON*INTENST*HOUR	14	619.42295324	10.35	0.0001
INTENSTY*DAY*HOUR	35	368.65989110	2.46	0.0001
SITE*DRUGCO*DAY*HOUR	70	746.18889837	2.49	0.0001
SITE*DRUGC*INTEN*DAY	10	45.69376200	1.07	0.3829
SITE*DRUGC*INTE*HOUR	14	285.40667343	4.77	0.0001
SITE*INTENS*DAY*HOUR	35	361.15142001	2.41	0.0001
DRUGC*INTEN*DAY*HOUR	70	726.61726515	2.43	0.0001
SITE*DRU*INT*DAY*HOU	70	747.04022411	2.50	0.0001

TABLE 8 . 5-WAY ANOVA: 4G (MORPHINE- 7.5 MG/KG)

ANALYSIS OF VARIANCE PROCEDURE

DEPENDENT VARIABLE: R-SQ. RT. (R + 0.5)

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	P	R-SQUARE	C.V.
MODEL	575	87056.68620921	151.40293254	28.01	0.0001	0.874830	28.7286
ERROR	2304	12456.03437008	5.40626492		STD DEV		R MEAN
CORRECTED TOTAL	2879	99512.72057929			2.32513761		8.09344898

SOURCE	DF	ANOVA SS	F VALUE	P
SITE	1	69375.90006784	12832.50	0.0001
DRUGCOND	2	804.58984388	74.41	0.0001
INTENSTY	1	988.89831176	182.92	0.0001
DAY	5	180.20909303	6.67	0.0001
HOUR	7	872.97442964	23.07	0.0001
SITE*DRUGCOND	2	1053.48314711	97.43	0.0001
SITE*INTENSTY	1	843.63160863	156.05	0.0001
SITE*DAY	5	442.57132431	16.37	0.0001
SITE*HOUR	7	409.76635993	10.83	0.0001
DRUGCOND*INTENSTY	2	163.56036664	15.13	0.0001
DRUGCOND*DAY	10	523.99065423	9.69	0.0001
DRUGCOND*HOUR	14	1518.23846535	20.06	0.0001
INTENSTY*DAY	5	44.71594775	1.65	0.1412
INTENSTY*HOUR	7	308.32485995	8.15	0.0001
DAY*HOUR	35	726.72181481	3.84	0.0001
SITE*DRUGCON*INTENST	2	77.68030212	7.18	0.0008
SITE*DRUGCOND*DAY	10	427.54890405	7.91	0.0001
SITE*DRUGCOND*HOUR	14	1579.66541338	20.87	0.0001
SITE*INTENSTY*DAY	5	45.25987830	1.67	0.1362
SITE*INTENSTY*HOUR	7	236.95260890	6.26	0.0001
SITE*DAY*HOUR	35	334.79609563	1.77	0.0037
DRUGCOND*DAY*HOUR	70	1843.00162467	4.87	0.0001
DRUGCOND*INTENST*DAY	10	203.97010892	3.77	0.0001
DRUGCON*INTENST*HOUR	14	503.00787184	6.65	0.0001
INTENSTY*DAY*HOUR	35	374.73327181	1.98	0.0006
SITE*DRUGCO*DAY*HOUR	70	803.07668086	2.12	0.0001
SITE*DRUGC*INTEN*DAY	10	150.58998019	2.79	0.0020
SITE*DRUGC*INTE*HOUR	14	245.17232226	3.24	0.0001
SITE*INTENS*DAY*HOUR	35	410.30762649	2.17	0.0001
DRUGC*INTEN*DAY*HOUR	70	814.95216717	2.15	0.0001
SITE*DRU*INT*DAY*HOU	70	748.38705776	1.98	0.0001

TABLE 9 . 5-WAY ANOVA: 75F (MORPHINE- 5.0 MG/KG)

ANALYSIS OF VARIANCE PROCEDURE

DEPENDENT VARIABLE: R: SQ. RT. (R + 0.5)

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	P	R-SQUARE	C.V.
MODEL	575	69537.25847493	120.93436257	44.96	0.0001	0.918072	20.3255
ERROR	2304	6205.47814958	2.69334989		STD DEV		R MEAN
CORRECTED TOTAL	2879	75742.73662451			1.64114286		8.07431334

SOURCE	DF	ANOVA SS	F VALUE	P
SITE	1	19946.37517697	7405.79	0.0001
DRUGCOND	2	4732.07959694	878.47	0.0001
INTENSTY	1	7569.22724974	2810.34	0.0001
DAY	5	1860.07470261	138.12	0.0001
HOUR	7	1278.89334214	67.83	0.0001
SITE*DRUGCOND	2	1525.96422397	283.28	0.0001
SITE*INTENSTY	1	4632.63200644	1720.03	0.0001
SITE*DAY	5	1102.47319047	81.87	0.0001
SITE*HOUR	7	745.77970156	39.56	0.0001
DRUGCOND*INTENSTY	2	1345.40215613	249.76	0.0001
DRUGCOND*DAY	10	3131.20094742	116.26	0.0001
DRUGCOND*HOUR	14	1036.86771969	27.50	0.0001
INTENSTY*DAY	5	816.82957378	60.66	0.0001
INTENSTY*HOUR	7	490.28626341	26.01	0.0001
DAY*HOUR	35	1419.77753021	15.06	0.0001
SITE*DRUGCON*INTENST	2	760.17760064	141.12	0.0001
SITE*DRUGCOND*DAY	10	1578.01343180	58.59	0.0001
SITE*DRUGCOND*HOUR	14	1238.87647477	32.86	0.0001
SITE*INTENSTY*DAY	5	686.16679206	50.95	0.0001
SITE*INTENSTY*HOUR	7	335.23817500	17.78	0.0001
SITE*DAY*HOUR	35	947.20798701	10.05	0.0001
DRUGCOND*DAY*HOUR	70	2657.23567423	14.09	0.0001
DRUGCOND*INTENST*DAY	10	1527.81732539	56.73	0.0001
DRUGCON*INTENST*HOUR	14	1284.78790412	34.07	0.0001
INTENSTY*DAY*HOUR	35	985.37269684	10.45	0.0001
SITE*DRUGCO*DAY*HOUR	70	1660.38399186	8.81	0.0001
SITE*DRUGC*INTEN*DAY	10	692.68197253	25.72	0.0001
SITE*DRUGC*INTE*HOUR	14	555.21298720	14.72	0.0001
SITE*INTENS*DAY*HOUR	35	615.93556737	6.53	0.0001
DRUGC*INTEN*DAY*HOUR	70	1080.73069058	5.73	0.0001
SITE*DRU*INT*DAY*HOU	70	1297.55574206	6.88	0.0001

TABLE 10. 5-WAY ANOVA: 66F (MORPHINE- 5.0 MG/KG)

ANALYSIS OF VARIANCE PROCEDURE

DEPENDENT VARIABLE: R= SQ. RT. (R + 0.5)

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	P	R-SQUARE	C.V.
MODEL	575	26631.60971101	46.31584298	7.60	0.0001	0.654911	32.6702
ERROR	2304	14032.84393172	6.09064407		STD DEV		R MEAN
CORRECTED TOTAL	2879	40664.45364273			2.46792303		7.55405397

SOURCE	DF	ANOVA SS	F VALUE	P
SITE	1	1399.48927896	229.78	0.0001
DRUGCOND	2	352.15195281	28.91	0.0001
INTENSTY	1	7414.56992339	1217.37	0.0001
DAY	5	218.80521199	7.18	0.0001
HOUR	7	1475.82855588	34.62	0.0001
SITE*DRUGCOND	2	624.65828164	51.28	0.0001
SITE*INTENSTY	1	5203.14701312	854.29	0.0001
SITE*DAY	5	167.29125194	5.49	0.0001
SITE*HOUR	7	176.68176481	4.14	0.0002
DRUGCOND*INTENSTY	2	1.75842480	0.14	0.8656
DRUGCOND*DAY	10	338.87693375	5.56	0.0001
DRUGCOND*HOUR	14	3148.97428544	36.93	0.0001
INTENSTY*DAY	5	32.23053628	1.06	0.3819
INTENSTY*HOUR	7	226.35748956	5.31	0.0001
DAY*HOUR	35	574.29840511	2.69	0.0001
SITE*DRUGCON*INTENST	2	10.44032297	0.86	0.4245
SITE*DRUGCOND*DAY	10	326.99965680	5.37	0.0001
SITE*DRUGCOND*HOUR	14	332.94635571	3.90	0.0001
SITE*INTENSTY*DAY	5	39.13526288	1.29	0.2666
SITE*INTENSTY*HOUR	7	103.59303728	2.43	0.0177
SITE*DAY*HOUR	35	165.12349925	0.77	0.8263
DRUGCOND*DAY*HOUR	70	847.49870045	1.99	0.0001
DRUGCOND*INTENST*DAY	10	85.23732073	1.40	0.1741
DRUGCOND*INTENST*HOUR	14	117.30531954	1.38	0.1564
INTENSTY*DAY*HOUR	35	393.22085111	1.84	0.0019
SITE*DRUGCO*DAY*HOUR	70	674.46157642	1.58	0.0017
SITE*DRUGC*INTEN*DAY	10	90.31654182	1.48	0.1393
SITE*DRUGC*INTE*HOUR	14	89.85997900	1.05	0.3958
SITE*INTENS*DAY*HOUR	35	350.05166210	1.64	0.0104
DRUGC*INTEN*DAY*HOUR	70	928.93246829	2.18	0.0001
SITE*DRU*INT*DAY*HOU	70	721.36784738	1.69	0.0004

TABLE // . 5-WAY ANOVA: 3G (MORPHINE- 5.0 MG/KG)

ANALYSIS OF VARIANCE PROCEDURE

DEPENDENT VARIABLE: R- SQ. RT. (R + 0.5)

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	P	R-SQUARE	C.V.
MODEL	575	35999.84599629	62.60842782	11.71	0.0001	0.745015	24.2564
ERROR	2304	12321.12414107	5.34771013		STD DEV		R MEAN
CORRECTED TOTAL	2879	48320.97013736			2.31251165		9.53362161

SOURCE	DF	ANOVA SS	F VALUE	P
SITE	1	850.77876894	159.09	0.0001
DRUGCOND	2	185.42833224	17.34	0.0001
INTENSITY	1	13502.26101691	2524.87	0.0001
DAY	5	81.99792142	3.07	0.0093
HOUR	7	1998.48094107	53.39	0.0001
SITE*DRUGCOND	2	216.22482170	20.22	0.0001
SITE*INTENSTY	1	5897.63695450	1102.83	0.0001
SITE*DAY	5	176.76668799	6.61	0.0001
SITE*HOUR	7	110.33594680	2.95	0.0046
DRUGCOND*INTENSTY	2	189.87217153	17.75	0.0001
DRUGCOND*DAY	10	443.63992444	8.30	0.0001
DRUGCOND*HOUR	14	2324.36438534	31.05	0.0001
INTENSTY*DAY	5	109.03653636	4.08	0.0012
INTENSTY*HOUR	7	1181.28136448	31.56	0.0001
DAY*HOUR	35	540.48338962	2.89	0.0001
SITE*DRUGCON*INTENST	2	628.61502957	58.77	0.0001
SITE*DRUGCOND*DAY	10	855.02869574	15.99	0.0001
SITE*DRUGCOND*HOUR	14	91.40403059	1.22	0.2515
SITE*INTENSTY*DAY	5	239.07413458	8.94	0.0001
SITE*INTENSITY*HOUR	7	205.38579477	5.49	0.0001
SITE*DAY*HOUR	35	337.42983519	1.80	0.0028
DRUGCOND*DAY*HOUR	70	759.61852906	2.03	0.0001
DRUGCOND*INTENST*DAY	10	288.58414119	5.40	0.0001
DRUGCON*INTENST*HOUR	14	1211.78686934	16.19	0.0001
INTENSTY*DAY*HOUR	35	311.60498032	1.66	0.0087
SITE*DRUGCO*DAY*HOUR	70	419.02724767	1.12	0.2349
SITE*DRUGC*INTEN*DAY	10	1032.85483173	19.31	0.0001
SITE*DRUGC*INTE*HOUR	14	322.93320070	4.31	0.0001
SITE*INTENS*DAY*HOUR	35	393.23987758	2.10	0.0002
DRUGC*INTEN*DAY*HOUR	70	466.19656883	1.25	0.0842
SITE*DRU*INT*DAY*HOU	70	628.39306611	1.68	0.0004

TABLE 12. 5-WAY ANOVA: 21G (MORPHINE- 5.0 MG/KG)

ANALYSIS OF VARIANCE PROCEDURE

DEPENDENT VARIABLE: R= SQ. RT. (R + 0.5)

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	P	R-SQUARE	C.V.
MODEL	575	31616.95203256	54.98600353	29.24	0.0001	0.879464	19.4588
ERROR	2304	4333.29016450	1.88076830		STD DEV		R MEAN
CORRECTED TOTAL	2879	35950.24219706			1.37141106		7.04777245

SOURCE	DF	ANOVA SS	F VALUE	P
SITE	1	291.76113983	155.13	0.0001
DRUGCOND	2	319.50943867	84.94	0.0001
INTENSITY	1	10155.51623728	5399.66	0.0001
DAY	5	311.47511484	33.12	0.0001
HOUR	7	504.81376594	38.34	0.0001
SITE*DRUGCOND	2	98.20547649	26.11	0.0001
SITE*INTENSITY	1	12142.96953554	6456.39	0.0001
SITE*DAY	5	44.48521733	4.73	0.0003
SITE*HOUR	7	459.63810866	34.91	0.0001
DRUGCOND*INTENSITY	2	48.80976837	12.98	0.0001
DRUGCOND*DAY	10	173.12553884	9.21	0.0001
DRUGCOND*HOUR	14	761.25868992	28.91	0.0001
INTENSITY*DAY	5	24.27906776	2.58	0.0244
INTENSITY*HOUR	7	156.88464470	11.92	0.0001
DAY*HOUR	35	681.68048233	10.36	0.0001
SITE*DRUGCON*INTENST	2	118.21280705	31.43	0.0001
SITE*DRUGCOND*DAY	10	120.68135578	6.42	0.0001
SITE*DRUGCOND*HOUR	14	150.46984686	5.71	0.0001
SITE*INTENSITY*DAY	5	61.98236928	6.59	0.0001
SITE*INTENSITY*HOUR	7	146.35453291	11.12	0.0001
SITE*DAY*HOUR	35	320.64943958	4.87	0.0001
DRUGCOND*DAY*HOUR	70	1140.88352900	8.67	0.0001
DRUGCOND*INTENST*DAY	10	197.99756241	10.53	0.0001
DRUGCON*INTENST*HOUR	14	436.71653010	16.59	0.0001
INTENSITY*DAY*HOUR	35	327.13190958	4.97	0.0001
SITE*DRUGCO*DAY*HOUR	70	517.17527024	3.93	0.0001
SITE*DRUGC*INTEN*DAY	10	132.51015718	7.05	0.0001
SITE*DRUGC*INTE*HOUR	14	130.04742418	4.94	0.0001
SITE*INTENS*DAY*HOUR	35	352.22128933	5.35	0.0001
DRUGC*INTEN*DAY*HOUR	70	635.68345308	4.83	0.0001
SITE*DRU*INT*DAY*HOU	70	653.82232871	4.97	0.0001

TABLE 13 . 5-WAY ANOVA: 84F (MORPHINE- 2.5 MG/KG)

ANALYSIS OF VARIANCE PROCEDURE

DEPENDENT VARIABLE: R² SQ. RT. (R + 0.5)

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	P	R-SQUARE	C.V.
MODEL	575	7197.11268083	12.51671771	7.82	0.0001	0.661111	19.6016
ERROR	2304	3689.27055442	1.60124590		STD DEV		R MEAN
CORRECTED TOTAL	2879	10886.38323524			1.26540345		6.45560740

SOURCE	DF	ANOVA SS	F VALUE	P
SITE	1	2100.74389552	1311.94	0.0001
DRUGCOND	2	185.34026572	57.87	0.0001
INTENSTY	1	352.09983858	219.89	0.0001
DAY	5	254.00924743	31.73	0.0001
HOUR	7	91.35460405	8.15	0.0001
SITE*DRUGCOND	2	379.88549088	118.62	0.0001
SITE*INTENSTY	1	586.00100193	365.97	0.0001
SITE*DAY	5	178.26896684	22.27	0.0001
SITE*HOUR	7	457.92853420	40.85	0.0001
DRUGCOND*INTENSTY	2	13.85777701	4.33	0.0133
DRUGCOND*DAY	10	162.58749746	10.15	0.0001
DRUGCOND*HOUR	14	209.26029870	9.33	0.0001
INTENSTY*DAY	5	10.01135135	1.25	0.2821
INTENSTY*HOUR	7	11.89607400	1.06	0.3861
DAY*HOUR	35	199.76445389	3.56	0.0001
SITE*DRUGCON*INTENST	2	1.48796130	0.46	0.6284
SITE*DRUGCOND*DAY	10	247.32478953	15.45	0.0001
SITE*DRUGCOND*HOUR	14	489.38132655	21.83	0.0001
SITE*INTENSTY*DAY	5	16.56897549	2.07	0.0657
SITE*INTENSTY*HOUR	7	29.23560430	2.61	0.0112
SITE*DAY*HOUR	35	135.87167468	2.42	0.0001
DRUGCOND*DAY*HOUR	70	184.96713974	1.65	0.0007
DRUGCOND*INTENST*DAY	10	52.40576689	3.27	0.0003
DRUGCON*INTENST*HOUR	14	52.23397208	2.33	0.0034
INTENSTY*DAY*HOUR	35	122.75554340	2.19	0.0001
SITE*DRUGCO*DAY*HOUR	70	108.99611099	1.69	0.0004
SITE*DRUGC*INTEN*DAY	10	45.51292752	2.84	0.0016
SITE*DRUGC*INTE*HOUR	14	50.67375101	2.26	0.0047
SITE*INTENS*DAY*HOUR	35	81.49150536	1.45	0.0419
DRUGC*INTEN*DAY*HOUR	70	171.20515228	1.53	0.0035
SITE*DRU*INT*DAY*HOU	70	133.91117413	1.19	0.1314

TABLE 14 . 5-WAY ANOVA: 86F (MORPHINE- 2.5 MG/KG)

ANALYSIS OF VARIANCE PROCEDURE

DEPENDENT VARIABLE: R= SQ. RT. (R + 0.5)

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	P	R-SQUARE	C.V.
MODEL	575	39982.36905534	69.53455488	6.09	0.0001	0.603027	62.9160
ERROR	2304	26320.39790339	11.42378381		STD DEV		R MEAN
CORRECTED TOTAL	2879	66302.76695873			3.37990885		5.37209977

SOURCE	DF	ANOVA SS	F VALUE	P
SITE	1	35.94670034	3.15	0.0762
DRUGCOND	2	1576.97886267	69.02	0.0001
INTENSTY	1	5229.04776414	457.80	0.0001
DAY	5	64.47020041	1.13	0.3427
HOUR	7	2258.94206060	28.25	0.0001
SITE*DRUGCOND	2	2652.07220008	116.08	0.0001
SITE*INTENSTY	1	4101.92841705	359.07	0.0001
SITE*DAY	5	51.16770272	0.90	0.4842
SITE*HOUR	7	4192.44644091	52.43	0.0001
DRUGCOND*INTENSTY	2	259.66152255	11.36	0.0001
DRUGCOND*DAY	10	143.16926459	1.25	0.2517
DRUGCOND*HOUR	14	1009.39581309	6.31	0.0001
INTENSTY*DAY	5	37.20798278	0.65	0.6630
INTENSTY*HOUR	7	256.29837215	3.21	0.0023
DAY*HOUR	35	680.46216565	1.70	0.0065
SITE*DRUGCON*INTENST	2	735.58574420	32.20	0.0001
SITE*DRUGCOND*DAY	10	355.16152847	3.11	0.0006
SITE*DRUGCOND*HOUR	14	6005.72063719	37.55	0.0001
SITE*INTENSTY*DAY	5	135.09692528	2.37	0.0373
SITE*INTENSTY*HOUR	7	1109.13200278	13.87	0.0001
SITE*DAY*HOUR	35	721.71276730	1.81	0.0027
DRUGCOND*DAY*HOUR	70	1571.07722301	1.96	0.0001
DRUGCOND*INTENST*DAY	10	311.30143197	2.73	0.0025
DRUGCON*INTENST*HOUR	14	430.56116650	2.69	0.0006
INTENSTY*DAY*HOUR	35	568.84262773	1.42	0.0518
SITE*DRUGCO*DAY*HOUR	70	2005.74059722	2.51	0.0001
SITE*DRUGC*INTEN*DAY	10	169.08637839	1.48	0.1403
SITE*DRUGC*INTE*HOUR	14	400.76142932	2.51	0.0015
SITE*INTENS*DAY*HOUR	35	586.32352439	1.47	0.0384
DRUGC*INTEN*DAY*HOUR	70	1089.69589445	1.36	0.0258
SITE*DRU*INT*DAY*HOU	70	1236.57290743	1.55	0.0026

TABLE 15. 5-WAY ANOVA: 18G (MORPHINE- 2.5 MG/KG)

ANALYSIS OF VARIANCE PROCEDURE

DEPENDENT VARIABLE: R-SQ. RT. (R + 0.5)

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	P	R-SQUARE	C.V.
MODEL	575	80574.01425769	140.12872045	59.92	0.0001	0.937317	24.8807
ERROR	2304	5388.39388293	2.33871262		STD DEV		R MEAN
CORRECTED TOTAL	2879	85962.40814062			1.52928500		6.14646443

SOURCE	DF	ANOVA SS	F VALUE	P
SITE	1	11487.21202182	4911.77	0.0001
DRUGCOND	2	408.53565715	87.34	0.0001
INTENSITY	1	50480.62045271	21584.79	0.0001
DAY	5	60.17033666	5.15	0.0001
HOUR	7	1403.65581352	85.74	0.0001
SITE*DRUGCOND	2	131.36277871	28.08	0.0001
SITE*INTENSTY	1	11839.93830446	5062.59	0.0001
SITE*DAY	5	21.03073477	1.80	0.1087
SITE*HOUR	7	24.24061345	1.48	0.1685
DRUGCOND*INTENSTY	2	495.26897704	105.68	0.0001
DRUGCOND*DAY	10	324.55154272	13.88	0.0001
DRUGCOND*HOUR	14	183.15797523	5.59	0.0001
INTENSTY*DAY	5	149.10141773	12.75	0.0001
INTENSTY*HOUR	7	584.15817840	35.68	0.0001
DAY*HOUR	35	264.93592230	3.24	0.0001
SITE*DRUGCON*INTENST	2	71.57596961	15.30	0.0001
SITE*DRUGCOND*DAY	10	96.62497235	4.13	0.0001
SITE*DRUGCOND*HOUR	14	91.60681789	2.80	0.0004
SITE*INTENSTY*DAY	5	27.00256402	2.31	0.0415
SITE*INTENSTY*HOUR	7	42.24407909	2.58	0.0120
SITE*DAY*HOUR	35	98.89631545	1.21	0.1874
DRUGCOND*DAY*HOUR	70	398.83433254	2.44	0.0001
DRUGCOND*INTENST*DAY	10	194.04165610	8.30	0.0001
DRUGCON*INTENST*HOUR	14	238.50134298	7.28	0.0001
INTENSTY*DAY*HOUR	35	168.29242280	2.06	0.0003
SITE*DRUGCO*DAY*HOUR	70	402.00262562	2.46	0.0001
SITE*DRUGC*INTEN*DAY	10	112.02516030	4.79	0.0001
SITE*DRUGC*INTE*HOUR	14	108.96024816	3.33	0.0001
SITE*INTENS*DAY*HOUR	35	152.95753254	1.87	0.0016
DRUGC*INTEN*DAY*HOUR	70	229.63075540	1.40	0.0164
SITE*DRU*INT*DAY*HOU	70	282.07672818	1.72	0.0002

TABLE /6 . 5-WAY ANOVA: 9G (MORPHINE- 2.5 MG/KG)

ANALYSIS OF VARIANCE PROCEDURE

DEPENDENT VARIABLE: SQ. RT. (R + 0.5)

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	P	R-SQUARE	C.V.
MODEL	575	12515.81158709	21.76662885	21.97	0.0001	0.845754	11.1764
ERROR	2304	2282.60123852	0.99071234		STD DEV		R MEAN
CORRECTED TOTAL	2879	14798.41282561			0.99534534		8.90574852

SOURCE	DF	ANOVA SS	F VALUE	P
SITE	1	5332.93562245	5382.93	0.0001
DRUGCOND	2	491.65477057	248.13	0.0001
INTENSTY	1	191.27384023	193.07	0.0001
DAY	5	292.34794520	59.02	0.0001
HOUR	7	116.11513941	16.74	0.0001
SITE*DRUGCOND	2	19.41095311	9.80	0.0001
SITE*INTENSTY	1	25.77225848	26.01	0.0001
SITE*DAY	5	59.70592847	12.05	0.0001
SITE*HOUR	7	147.00402816	21.20	0.0001
DRUGCOND*INTENSTY	2	110.07955801	55.56	0.0001
DRUGCOND*DAY	10	621.08070701	62.69	0.0001
DRUGCOND*HOUR	14	627.81727863	45.26	0.0001
INTENSTY*DAY	5	68.28128108	13.78	0.0001
INTENSTY*HOUR	7	35.32416916	5.09	0.0001
DAY*HOUR	35	770.04943738	22.21	0.0001
SITE*DRUGCON*INTENST	2	40.36805891	20.37	0.0001
SITE*DRUGCOND*DAY	10	151.84164635	15.33	0.0001
SITE*DRUGCOND*HOUR	14	227.57908624	16.41	0.0001
SITE*INTENSTY*DAY	5	30.49060463	6.16	0.0001
SITE*INTENSTY*HOUR	7	76.83781043	11.08	0.0001
SITE*DAY*HOUR	35	139.90000793	4.03	0.0001
DRUGCOND*DAY*HOUR	70	1626.86802971	23.46	0.0001
DRUGCOND*INTENST*DAY	10	73.76618909	7.45	0.0001
DRUGCON*INTENST*HOUR	14	85.89667414	6.19	0.0001
INTENSTY*DAY*HOUR	35	126.26693010	3.64	0.0001
SITE*DRUGCO*DAY*HOUR	70	435.63824939	6.28	0.0001
SITE*DRUGC*INTEN*DAY	10	22.79503082	2.30	0.0110
SITE*DRUGC*INTE*HOUR	14	93.62624932	6.75	0.0001
SITE*INTENS*DAY*HOUR	35	58.32376574	1.68	0.0076
DRUGC*INTEN*DAY*HOUR	70	177.45118934	2.56	0.0001
SITE*DRU*INT*DAY*HOU	70	239.30913961	3.45	0.0001

TABLE 17.

R-SQUARE VALUE OF EACH SOURCE IN THE 5-WAY ANOVA FOR EACH ANIMAL

SOURCE	37E	54F	76F	94F	74E	4G	75F	66F	3G	21G	84F	86F	18G	9G	MEAN
SITE	.41	.06	.04	.11	.01	.70	.26	.03	.02	.01	.19	.00	.13	.36	16.6
DRUGCOND	.10	.09	.05	.04	.01	.01	.06	.01	.00	.01	.02	.02	.00	.03	3.1
INTENSTY	.00	.05	.35	.12	.17	.01	.10	.18	.28	.28	.03	.08	.59	.01	16.1
DAY	.02	.01	.00	.01	.00	.00	.02	.01	.00	.01	.02	.00	.00	.02	1.5
HOUR	.04	.06	.03	.01	.02	.01	.02	.04	.04	.01	.01	.03	.02	.01	2.5
SITE*DRUGCOND	.00	.00	.00	.01	.02	.01	.02	.02	.00	.00	.03	.04	.00	.00	1.1
SITE*INTENSTY	.00	.00	.04	.09	.06	.01	.06	.13	.12	.34	.05	.06	.14	.00	7.9
SITE*DAY	.00	.01	.00	.00	.00	.00	.01	.00	.00	.00	.02	.00	.00	.00	0.3
SITE*HOUR	.01	.01	.00	.01	.01	.00	.01	.00	.00	.01	.04	.06	.00	.01	1.2
DRUGCOND*INTENSTY	.00	.00	.02	.01	.00	.00	.02	.00	.00	.00	.00	.00	.01	.01	0.5
DRUGCOND*DAY	.02	.02	.01	.03	.02	.01	.04	.01	.01	.00	.01	.00	.00	.04	1.6
DRUGCOND*HOUR	.12	.05	.07	.04	.08	.02	.01	.08	.05	.02	.02	.02	.00	.04	4.4
INTENSTY*DAY	.00	.00	.00	.00	.00	.00	.01	.00	.00	.00	.00	.00	.00	.00	0.1
INTENSTY*HOUR	.00	.01	.02	.01	.00	.00	.01	.01	.02	.00	.00	.00	.01	.00	0.6
DAY*HOUR	.02	.02	.02	.03	.02	.01	.02	.01	.01	.02	.02	.01	.00	.05	1.9
SITE*DRUGCON*INTENST	.00	.00	.00	.01	.00	.00	.01	.00	.01	.00	.00	.01	.00	.00	0.3
SITE*DRUGCOND*DAY	.01	.01	.00	.01	.01	.00	.02	.01	.02	.00	.02	.01	.00	.01	0.9
SITE*DRUGCOND*HOUR	.01	.01	.01	.02	.02	.02	.02	.01	.00	.00	.04	.09	.00	.02	1.9
SITE*INTENSTY*DAY	.00	.00	.00	.01	.00	.00	.01	.00	.00	.00	.00	.00	.00	.00	0.1
SITE*INTENSTY*HOUR	.00	.00	.00	.00	.01	.00	.00	.00	.00	.00	.00	.02	.00	.01	0.3
SITE*DAY*HOUR	.01	.01	.01	.02	.01	.00	.01	.00	.01	.01	.01	.01	.00	.01	0.9
DRUGCOND*DAY*HOUR	.03	.04	.04	.04	.03	.02	.04	.02	.02	.03	.02	.02	.00	.11	3.3
DRUGCOND*INTENST*DAY	.01	.00	.00	.00	.01	.00	.02	.00	.01	.01	.00	.00	.00	.01	0.5
DRUGCON*INTENST*HOUR	.00	.00	.01	.01	.02	.01	.02	.00	.03	.01	.00	.01	.00	.00	0.9
INTENSTY*DAY*HOUR	.01	.01	.01	.02	.01	.00	.01	.01	.01	.01	.01	.01	.00	.01	0.9
SITE*DRUGCO*DAY*HOUR	.02	.02	.02	.03	.03	.01	.02	.02	.01	.01	.02	.03	.00	.03	1.9
SITE*DRUGC*INTEN*DAY	.00	.00	.00	.00	.00	.00	.01	.00	.02	.00	.00	.00	.00	.00	0.2
SITE*DRUGC*INTE*HOUR	.00	.01	.01	.01	.01	.00	.01	.00	.01	.00	.00	.01	.00	.01	0.6
SITE*INTENS*DAY*HOUR	.01	.01	.01	.02	.01	.00	.01	.01	.01	.01	.01	.01	.00	.00	0.9
DRUGC*INTEN*DAY*HOUR	.01	.01	.03	.04	.03	.01	.01	.02	.01	.02	.02	.02	.00	.01	1.7
SITE*DRU*INT*DAY*HOU	.01	.02	.02	.03	.03	.01	.02	.02	.01	.02	.01	.02	.00	.02	1.7

Table 18
Duncan a posteriori tests ($\alpha = .01$):

Dose (mg/kg)	Rat #	Site: DB vs. HYP
10.0	37E	+
	54F	+
	76F	-
	94F	-
7.5	74E	-
	4G	-
5.0	75F	-
	66F	-
	3G	-
	21G	+
2.5	84F	-
	86F	=
	18G	-
	9G	-

- = response rate, collapsing across all factors, less at DB than HYP electrode
+ = response rate, collapsing across all factors, greater at DB than HYP electrode
= = $p > .01$

Table 19

RESPONSES/MIN DURING PRE-DRUG SALINE COLLAPSING ACROSS INTENSITY

	DB			HYP			
Rat #	$\bar{X}$	Maximum Value	Std. Err.	$\bar{X}$	Maximum Value	Std. Err.	Site Tested First Per Hourly Session
37E	92.4	120	0.63	28.9	62	0.76	HYP
54F	46.2	79	0.95	43.6	194	2.53	DB
76F	22.7	80	0.75	38.2	117	1.43	HYP
94F	48.3	96	1.07	140.6	258	4.46	HYP
74E	30.2	97	0.99	31.8	316	1.60	DB
4G	17.7	75	1.11	181.3	333	2.49	HYP
75F	38.8	67	0.51	192.2	290	2.61	DB
66F	50.3	94	0.78	98.8	205	2.95	DB
3G	89.5	173	1.66	125.9	224	3.85	DB
21G	49.9	93	0.79	65.1	169	2.51	HYP
94F	32.4	57	0.41	47.9	104	1.12	DB
86F	54.9	110	1.52	87.3	224	3.36	DB
18G	31.0	69	1.05	108.4	238	4.10	DB
9G	64.2	114	0.91	111.9	143	0.60	HYP

Table 20

RESPONSES/MIN DURING PRE-DRUG SALINE: DB

	LOW INTENSITY				HIGH INTENSITY			
Rat #	Current (uA)	$\bar{x}$	Maximum Value	Std. Err.	Current (uA)	$\bar{x}$	Maximum Value	Std. Err.
37E	49	94.0	120	1.00	57	90.8	119	0.74
54F	46	38.8	79	1.63	64	53.6	74	0.68
76F	106	15.5	80	1.22	127	29.8	56	0.60
94F	42	44.6	84	1.82	49	52.0	86	1.08
74E	53	25.4	81	1.45	60	35.0	97	1.28
4G	170	18.9	75	1.61	198	16.4	66	1.52
75F	64	38.5	67	0.67	78	39.1	61	0.53
66F	99	46.6	83	1.02	113	54.1	94	1.12
3G	64	78.8	173	2.94	85	100.3	141	1.22
21G	21	48.6	90	1.48	35	51.2	93	0.64
84F	177	33.8	57	0.64	199	31.0	50	0.50
86F	18	34.6	110	2.04	21	75.8	106	1.29
18G	71	16.1	89	1.30	99	46.0	69	0.92
9G	57	64.9	114	1.62	71	83.6	98	0.84

Table 21

RESPONSES/MIN DURING PRE-DRUG SALINE: HYP

	LOW INTENSITY				HIGH INTENSITY			
Rat #	Current (uA)	$\bar{x}$	Maximum Value	Std. Err.	Current (uA)	$\bar{x}$	Maximum Value	Std. Err.
37E	35	28.4	62	1.12	42	29.4	60	1.01
54F	25	24.2	160	2.60	28	63.0	194	3.98
76F	35	13.2	99	1.41	49	63.2	117	0.97
94F	42	79.0	233	5.60	57	202.1	256	4.09
74E	42	14.9	316	2.16	60	46.8	115	1.78
4G	49	152.7	224	4.10	57	210.5	233	1.06
75F	57	167.1	290	4.58	85	217.2	251	0.98
66F	28	53.5	173	3.53	39	144.1	205	2.28
3G	42	54.8	216	3.85	57	197.0	224	1.53
21G	49	14.7	86	1.24	92	115.4	169	1.80
84F	35	37.6	96	1.46	49	58.2	104	1.41
86F	32	47.0	205	4.27	35	67.6	224	5.11
18G	25	19.6	173	2.16	42	191.3	238	1.05
9G	28	112.7	143	1.08	42	111.0	134	0.52

Table 22 Duncan a posteriori Tests (α = .01):

Site x Drug:cond

dose (mg/kg)		DB	HYP
10.0	37E	M < S	M < S
	54F	M < S	M < S
	76F	M < S	M < S
	94F	M < S	M < S
7.5	74E	M < S	M = S
	4G	M > S	M = S
5.0	75F	M < S	M < S
	66F	M < S	M < S
	3G	M = S	M > S
	21G	M > S	M > S
2.5	84F	M < S	M > S
	86F	M < S	M > S
	18G	M < S	M < S
	9G	M = S	M = S

S = pre-drug saline
M = morphine

Table 23.
Duncan a posteriori Tests (α = .01):

Site x Drugcond x Intensity

Dose (mg/kg)	Rat #	DB electrode Intensity Low	DB electrode Intensity High	HYP electrode Intensity Low	HYP electrode Intensity High
10.0	37E	M<S	M<S	M<S	M<S
	54P	M<S	M<S	M<S	M<S
	76P	M<S	M<S	M<S	M<S
	94P	M<S	M<S	M>S	M<S
7.5	74E	M<S	M<S	M=S	M=S
	4G	M>S	M>S	M=S	M<S
5.0	75P	M<S	M<S	M<S	M<S
	66P	M<S	M<S	M=S	M<S
	3G	M<S	M=S	M>S	M=S
	21G	M>S	M>S	M=S	M=S
2.5	84P	M<S	M<S	M>S	M>S
	86P	M<S	M<S	M>S	M>S
	18G	M<S	M=S	M<S	M>S
	9G	M<S	M=S	M<S	M>S

M<S = morphine < pre-drug saline
M>S = morphine > pre-drug saline
M=S = p > .01

Table 24. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

SITE - DB

PRE-DRUG SALINE vs. MORPHINE (10.0 mg/kg)

	HOUR POST-INJECTION							
DAY	1	2	3	4	5	6	7	24
1	-	-	-					
2	-	-	-					
3	-							
4	-	-			-			
5	-	-	-					
6	-							

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
DAY	1	2	3	4	5	6	7	24
1		-	-	-	-			
2								
3								
4								-
5				-				
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 25. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

SITE - HYP

PRE-DRUG SALINE vs. MORPHINE (10.0 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-	-					
2	-	-	-		+			
3	-	-						
4	-	-		+				
5	-	-	-	-				
6	-	-						

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-	-		-			
2	+							
3								
4								
5								
6			-	-				

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 26. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

5HF - DB

PRE-DRUG SALINE vs. MORPHINE (10.0 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-	-	-				
2	-	-	-					
3	-	-				-		
4	-	-						
5	-	-	-					
6	-	-	-				-	

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-	-	-				
2							+	
3								
4								
5								
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 27. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

SAP - HYP

PRE-DRUG SALINE vs. MORPHINE (10.0 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-	-	-				-
2		-						
3	-	-	-	-	-			
4	-	-	-					
5	-		-					
6	-	-						

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-	-					
2			+					
3	-		+	-				
4								
5								
6					+			

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 28. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

76F - DB

PRE-DRUG SALINE vs. MORPHINE (10.0 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-	-	-			-	
2	-	-	-	-	-		+	-
3	-	-	-		-			-
4	-	-		+			+	
5	-	-	-	+	-			
6	-		+	+	+			-

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-	-	-			-	-
2				-				-
3	-	-	-	-	-			-
4	-	-						
5			-					-
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 29. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

76P - HYP

PRE-DRUG SALINE vs. MORPHINE (10.0 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-	-	-			+	
2	-	-		+				
3	-	-		+				+
4	-	-	-	+				-
5	-	-	+					
6	-			+		-	-	+

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-	-	-				
2		-						
3	-							
4		-	-					-
5		-	+					-
6	-			-				

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 30. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

94P - DB

PRE-DRUG SALINE vs. MORPHINE (10.0 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-						
2	-	-				-		-
3				-			-	
4	-			+				
5								
6			+					-

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1		-	-				-	
2			-	-	-	-		
3	-			-			-	
4								
5						-		
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 31. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

94F - HYP

PRE-DRUG SALINE vs. MORPHINE (10.0 mg/kg)

	HOUR POST-INJECTION							
DAY	1	2	3	4	5	6	7	24
1	-	-	-			-		-
2	-	-						-
3	-	-	+	+		+		-
4	-			+	+	+	+	
5	-	+			+	+	+	-
6			+	+				-

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
DAY	1	2	3	4	5	6	7	24
1	-	-	-	-	-	-	-	-
2	-			-	-		-	-
3			-				-	
4			-	-				
5				-	-			
6	-							

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 32. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

SITE - DB

PRE-DRUG SALINE vs. MORPHINE (7.5 mg/kg)

DAY	HOUR POST-INJECTION 1	2	3	4	5	6	7	24
1	-	-	-					
2	-	-	-				-	-
3	-	-	-				-	
4	-	-		+		+		
5	-	-	-	-				
6	-	-	-	-			-	

PRE-DRUG SALINE vs. POST-DRUG SALINE

DAY	HOUR POST-INJECTION 1	2	3	4	5	6	7	24
1						-	-	
2		-				-	-	-
3				-				
4						+		
5								
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 33. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

SITE - HYP

PRE-DRUG SALINE vs. MORPHINE (7.5 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-		-	+	+			-
2				+	+			-
3	-	-						-
4				+	+			
5		-			+			
6	-		+	+				

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1								
2				+				
3								
4					+			
5								
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 34. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

4G - DB

PRE-DRUG SALINE vs. MORPHINE (7.5 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-		+	+				
2		+	+	+	+			
3		+	+	+	+			
4		+	+	+				
5		+	+	+				
6		+	+	+				

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1					-			
2								
3								
4					-			
5								
6			-					

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 35. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

4G - HYP

PRE-DRUG SALINE vs. MORPHINE (7.5 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-				+		
2								-
3					+			
4					+	+		
5		-			+			
6		-			+	-		

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1						+		
2							-	
3								
4						+		-
5								
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 36. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

75F - DB

PRE-DRUG SALINE vs. MORPHINE (5.0 mg/kg)

	HOUR POST-INJECTION							
DAY	1	2	3	4	5	6	7	24
1	-	-	-	-	-	-	-	
2	-	-					-	
3	-	-						
4	-	-	-		-	-	-	
5	-	-					-	
6	-					-		

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
DAY	1	2	3	4	5	6	7	24
1		-	-			-		
2				-	-	-		
3				-		-		
4								
5								
6							-	

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 37. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

75F - HYP

PRE-DRUG SALINE vs. MORPHINE (5.0 mg/kg)

DAY	HOUR POST-INJECTION 1	2	3	4	5	6	7	24
1	-	-	-	-	-	-	-	
2	+		-				-	
3	-							
4	-	-	-	-	-	-	-	-
5	-		-	-	-	-	-	+
6	+	-	-	-	-	-	-	

PRE-DRUG SALINE vs. POST-DRUG SALINE

DAY	HOUR POST-INJECTION 1	2	3	4	5	6	7	24
1	-	-	-	-	-	-	-	
2			-			-	-	-
3	-	-	-	-	-	-	-	
4								+
5	-	-	-	-	-	-		+
6		-	-	-	-	-	-	

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 38. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

66F - DB

PRE-DRUG SALINE vs. MORPHINE (5.0 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-						
2	-	-						
3	-	-						
4		-						
5	-				+			
6	-	-						

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1		+						
2								
3								
4								
5								
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 39. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

66F - HYP

PRE-DRUG SALINE vs. MORPHINE (5.0 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-			+			+	
2		-				+		
3	-	-		+				
4	-			+				
5	-							
6	-	+		+		-		

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-					-		
2	-							
3			-		-	-		
4								
5				-				
6				-		-		

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 40. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

3G - DB

PRE-DRUG SALINE vs. MORPHINE (5.0 mg/kg)

DAY	HOUR POST-INJECTION 1	2	3	4	5	6	7	24
1			+	+				
2			+		-	-	-	
3					-	-	-	
4							-	
5						-	-	
6	+	+	+			-		

PRE-DRUG SALINE vs. POST-DRUG SALINE

DAY	HOUR POST-INJECTION 1	2	3	4	5	6	7	24
1								
2			-			-		
3			-					
4								
5								
6							+	

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 41. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

3G - HYP

PRE-DRUG SALINE vs. MORPHINE (5.0 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1					-	-		
2		+	+	+				
3	+	+	+	+				
4	+	-	+				-	
5								
6			+				-	-

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-	-	-	-	-		
2			-					
3								
4						+		
5								
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 42. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

21G - DB

PRE-DRUG SALINE vs. MORPHINE (5.0 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-	+	+				
2	-	+	+					
3	+		+	+	+			+
4		+	+					
5	+	+	+					+
6	+	-	+					

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	+			+				
2								
3	+							+
4								
5								+
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 43. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

21G - HYP

PRE-DRUG SALINE vs. MORPHINE (5.0 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-		+	+		-	
2			+	+	+		+	
3			+					
4	+		+		+			-
5			+					-
6			+			-		-

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-						-	-
2							+	
3								
4								
5			-					
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 44. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (≤= .01)

84P - DB

PRE-DRUG SALINE vs. MORPHINE (2.5 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-						
2	-	-						
3	-	-						
4	-	-						
5	-							
6	-							

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1								
2								
3								
4							+	+
5								
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 45. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

84F - HYP

PRE-DRUG SALINE vs. MORPHINE (2.5 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1		+	+	+		+	+	
2	+	+	+	+	+	+	+	
3	+	+	+					
4		+		+		+	+	
5					+			
6		+			-			

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1								
2	+		+				+	
3	+	+						+
4				+	+	+	+	+
5								
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 46. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

86F - DB

PRE-DRUG SALINE vs. MORPHINE (2.5 mg/kg)

DAY	HOUR POST-INJECTION 1	2	3	4	5	6	7	24
1	-	-		+				
2	-	-	-	-				
3	-	-						
4	-	-						
5	-	-	-					
6	-	-						

PRE-DRUG SALINE vs. POST-DRUG SALINE

DAY	HOUR POST-INJECTION 1	2	3	4	5	6	7	24
1							-	
2								
3								
4							-	
5								
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 47. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

86F - HYP

PRE-DRUG SALINE vs. MORPHINE (2.5 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1		+						-
2	+	+	+	+	+			
3	+	+			-			
4	+	+	+	-				
5	+	+	+					
6	+	+	+			-		-

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-		-					
2		-						
3								-
4	-		-					
5		-						
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 48. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

18G - DB

PRE-DRUG SALINE vs. MORPHINE (2.5 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-	-			-		
2	-	-		+	+			
3	-	+	-			-		
4	-							
5	-							
6							-	

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	-	-	-	-	-	-		-
2	-	-			-			
3	-		-			-		
4	-	-						
5	-							
6	-	-						

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 49. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (∝= .01)

18G - HYP

PRE-DRUG SALINE vs. MORPHINE (2.5 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1		-			-			-
2								-
3								
4								
5								
6								-

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1		-	-					
2			-					-
3	-							
4								
5								+
6								

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 50. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

9G - DB

PRE-DRUG SALINE vs. MORPHINE (2.5 mg/kg)

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	+				-	-	-	-
2				-	-	-	-	-
3	-	+					-	-
4		+	+		+			
5	+	+	+	+		-		
6	+	+	+		+			+

PRE-DRUG SALINE vs. POST-DRUG SALINE

	HOUR POST-INJECTION							
	1	2	3	4	5	6	7	24
DAY								
1	+	-	-	-	-	-	-	
2		-			-	-	-	
3					-			
4		-		-	+			
5				+				
6	-	-						

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

Table 51. SITE x DRUG x DAY x HOUR
DUNCAN a posteriori Tests (α = .01)

9G - HYP

PRE-DRUG SALINE vs. MORPHINE (2.5 mg/kg)

DAY	HOUR POST-INJECTION 1	2	3	4	5	6	7	24
1	-					-		
2								
3								
4								-
5								
6			+	+				-

PRE-DRUG SALINE vs. POST-DRUG SALINE

DAY	HOUR POST-INJECTION 1	2	3	4	5	6	7	24
1			-			-	-	
2				-				
3		-						-
4				-				
5				-				
6	-	-						

Note:
- = Morphine (mean) < Pre-drug Saline (mean) or Post-drug Saline (mean) < Pre-drug Saline (mean), as appropriate.
+ = Morphine (mean) > Pre-drug Saline (mean) or Post-drug Saline (mean) > Pre-drug Saline (mean), as appropriate.

TABLE 52

Classification of pattern of morphine effects: Based upon Duncan a posteriori tests (α = .01) of the site x drug x day x hour interactions

Dose (mg/kg)	Rat #	DB	HYP
10.0	37E	-	-
	54F	-	-
	76F	biphasic	biphasic
	94F	-	biphasic
7.5	74E	-	biphasic
	4G	-	biphasic
5.0	75F	-	-
	86F	-	biphasic
	3G	biphasic	biphasic
	21G	biphasic	biphasic
2.5	84F	-	+
	86F	-	biphasic
	18G	biphasic	n.e.
	9G	biphasic	n.e.

\- = morphine IOSS rates "primarily" depressed
\+ = morphine IOSS rates "primarily" facilitated
biphasic = morphine IOSS rates displayed instances of both depressions and facilitations
n.e. = morphine IOSS rates displayed negligible differences

Note.
1. Criteria for pattern classification:
   a. The classifications were based upon the site x drug x day x hour interactions of hours 1-7 post-injection of days 1-6.
   b. Two instances of significance in either direction were considered negligible (5% chance) and were disregarded for purposes of pattern classification.

Table 53 Comparison of pattern of morphine effects based upon the results of the Duncan a posteriori tests (α = .01)

Site x Drugcond Interactions vs. Site x Drugcond x Day x Hour Interactions

		Site x Drugcond Interactions		Site x Drugcond x Day x Hour Interactions	
Dose (mg/kg)	Rat #	DB	HYP	DB	HYP
10.0	37E	-	-	-	-
	54F	-	-	-	-
	76F	-	-	bi	bi
	94F	-	-	-	bi
7.5	74E	-	-	-	bi
	4G	-	-	-	bi
5.0	75F	-	-	-	-
	56F	-	-	-	bi
	3G	=	-	bi	bi
	21G	+	+	bi	bi
2.5	84F	-	+	-	+
	86F	-	+	-	bi
	19G	-	-	bi	=
	9G	=	=	bi	=

\+ "primarily" facilitations
\- "primarily" depressions
bi biphasic effect
= "negligible" effect

Note. This table is a compilation of the data presented in Table [illegible] and Table [illegible]

TABLE 54.
Wet Shakes
Summary of t-tests (α = .01) for each morphine dose

Pre-drug saline vs. Morphine

Dose (mg/kg)	# Rats (N)	df	Hour Post-injection 1	5	24
			t=		
10.0	4	23	-1.14	1.37	-0.31
7.5	2	11	1.73	2.03	1.22
5.0	4	23	2.93** M<S	1.00	-1.88
2.5	4	23	2.56	-1.14	-1.76

Pre-drug saline vs. Post-drug saline

Dose (mg/kg)	# Rats (N)	df	Hour Post-injection 1	5	24
			t=		
10.0	4	23	-2.13	0.37	-0.76
7.5	2	11	-1.07	0.43	0.71
5.0	4	23	-1.66	1.00	-0.88
2.5	4	23	1.33	-1.45	-0.40

M<S = morphine < pre-drug saline
** = p < .01

TABLE 55.
Shudders
Summary of t-tests (α = .01) for each morphine dose

Pre-drug saline vs. Morphine

Dose (mg/kg)	# Rats (N)	df	Hour Post-injection 1	5	24
			t=		
10.0	4	23	-1.09	-1.25	1.44
7.5	2	11	0.00	-0.52	1.48
5.0	4	23	0.25	0.01	1.82
2.5	4	23	-1.84	0.94	-1.42

Pre-drug saline vs. Post-drug saline

Dose (mg/kg)	# Rats (N)	df	Hour Post-injection 1	5	24
			t=		
10.0	4	23	-1.63	0.59	0.27
7.5	2	11	-0.80	1.02	-1.23
5.0	4	23	-0.26	1.10	-0.12
2.5	4	23	-1.44	-0.96	-2.05

** = $p < .01$

TABLE 56.
Rearings
Summary of t-tests (α = .01) for each morphine dose

Pre-drug saline vs. Morphine

Dose (mg/kg)	# Rats (N)	df	Hour Post-injection 1	5	24
			t=		
10.0	4	23	1.22	-0.34	-0.34
7.5	2	11	3.36** M<S	0.84	0.84
5.0	4	23	3.55** M<S	0.00	0.00
2.5	4	23	1.11	-1.58	-1.58

Pre-drug saline vs. Post-drug saline

Dose (mg/kg)	# Rats (N)	df	Hour Post-injection 1	5	24
			t=		
10.0	4	23	-1.45	0.71	1.40
7.5	2	11	-1.26	1.69	1.28
5.0	4	23	-0.19	2.42	3.96** PS<S
2.5	4	23	1.31	-0.83	1.36

M<S = morphine < pre-drug saline
PS<S = post-drug saline < pre-drug saline
** = p < .01

TABLE 57.
Locomotor Activity
Summary of t-tests (α = .01) for each morphine dose

Pre-drug saline vs. Morphine

Dose (mg/kg)	# Rats (N)	df	Hour Post-injection 1	5	24
			t=		
10.0	4	23	1.55	-0.98	-0.12
7.5	2	11	1.27	-0.72	0.04
5.0	4	23	3.29** M<S	0.25	2.83** M<S
2.5	4	23	1.66	-1.72	-0.09

Pre-drug saline vs. Post-drug saline

Dose (mg/kg)	# Rats (N)	df	Hour Post-injection 1	5	24
			t=		
10.0	4	23	0.72	1.70	2.13
7.5	2	11	-1.30	1.13	-2.02
5.0	4	23	-0.73	3.52** PS<S	4.85** PS<S
2.5	4	23	-0.59	-0.02	1.21

M<S = morphine < pre-drug saline
PS<S = post-drug saline < pre-drug saline
** = p < .01

TABLE 58.
Stereotyped Biting Behavior
Summary of McNemar tests (α = .01) for each morphine dose

Pre-drug saline vs. Morphine

Dose (mg/kg)	# Rats (N)	df	Hour Post-injection 1	2	3	4	5	6	7	24
10.0	4	23	+	+	+	+				
7.5	2	11	+	+	+	+				
5.0	4	23		+	+					
2.5	4	23								

Pre-drug saline vs. Post-drug saline

Dose (mg/kg)	# Rats (N)	df	Hour Post-injection 1	2	3	4	5	6	7	24
10.0	4	23								
7.5	2	11								
5.0	4	23								
2.5	4	23								

+ = morphine > pre-drug saline

Table 59 Histological localization of electrode placements.

Dose mg/kg	Rat	Electrode Placement
10.0	41E	DB: betw. LC and dorsal tegmental nucleus HYP: dorso-lateral to LH
	19F	DB: medial to dorsal tegmental nucleus HYP: dorsal to fornix
5.0	15G	DB: ventral-lateral to LC HYP: dorso-medial to LH
	10G	DB: ventral in pontine LC HYP: lateral to LH
2.5	8G	DB: locus coeruleus in trans. area HYP: dorso-medial to LH
	7G	DB: brachium conjuntivum in trans. area HYP: lateral hypothalamus

Table 60

Summary of two-way analysis of variance of morphine effect; DB

Dose (mg/kg)	Animal	"Pattern"	Drug Cond. (df 2, 42)	Intensity (df 5, 210)	Drug x Intensity (df 10, 210)
10.0	41E	-	F=3.183	F=42.242***	F=2.361*
	19F	-	20.478***	244.108***	3.930***
5.0	15G	N.E.	2.841	47.652***	2.453**
	10G	+	25.636***	37.754***	1.957*
2.5	8G	N.E.	3.589*	280.767***	7.613***
	7G	+	2.746	37.669***	1.588

\- =depression(s)
\+ =facilitation(s)
N.E. =no effects
* $\alpha < .05$
** $\alpha < .01$
*** $\alpha < .001$

Table 67

Summary of two-way analysis of variance of morphine effect: HYP

Dose (mg/kg)	Animal	"Pattern"	Drug Cond. (df 2, 42)	Intensity (df 5, 210)	Drug x Intensity (df 10, 210)
10.0	41E	+	F=0.067	F=197.223***	F=2.072*
	19F	-	1.224	350.835***	2.263*
5.0	15G	+	2.816	139.793***	1.312
	10G	+	2.857	147.459***	1.963*
2.5	8G	N.E.	4.969*	273.165***	1.700
	7G	+	0.220	576.346***	0.904

\- = depression(s)
\+ = facilitation(s)
N.E. = no effects
* $\alpha < .05$
** $\alpha < .01$
*** $\alpha < .001$

TABLE 62.
Duncan a posteriori tests: Experiment 2,
Drugcond x Intensity - DB
(α = .01)

Pre-drug saline vs. Morphine

Dose (mg/kg)	Rat #	Intensity 1	2	3	4	5	6
10.0	41E				-	-	
	19F				-	-	
5.0	15G				-		
	10G	+	+	+			
		10G-DB overall: +					
2.5	8G						
	7G						

Pre-drug saline vs. Post-drug saline

Dose (mg/kg)	Rat #	Intensity 1	2	3	4	5	6
10.0	41E						
	19F						
5.0	15G				-	-	
	10G		+				
2.5	8G		+				
	7G			-			

- = morphine < pre-drug saline or post-drug saline < pre-drug saline, as appropriate
+ = morphine > pre-drug saline or post-drug saline > pre-drug saline, as appropriate

TABLE 63.
Duncan a posteriori tests: Experiment 2,
Drugcond x Intensity - HYP
(α = .01)

Pre-drug saline vs. Morphine

Dose (mg/kg)	Rat #	Intensity 1	2	3	4	5	6
10.0	41E						
	19F						
5.0	15G						
	10G						
2.5	8G			-			
	7G						

Pre-drug saline vs. Post-drug saline

Dose (mg/kg)	Rat #	Intensity 1	2	3	4	5	6
10.0	41E						
	19F						
5.0	15G						
	10G				-		
2.5	8G			-	-		
	7G						

- = morphine < pre-drug saline or post-drug saline < pre-drug saline, as appropriate
+ = morphine > pre-drug saline or post-drug saline > pre-drug saline, as appropriate

TABLE 64.
Behavioral Watch
Summary of t-tests (α = .01) for each morphine dose
Experiment 2

Pre-drug saline vs. Morphine

Dose (mg/kg)	# Rats (N)	df	Wet Shakes t=	Shudders	Rearings	Locomotor Activity
10.0	2	5	1.00	1.00	2.19	-0.93
5.0	2	5	1.00	1.00	3.11	1.36
2.5	2	5	1.00	1.00	-0.14	-0.05

Pre-drug saline vs. Post-drug saline

Dose (mg/kg)	# Rats (N)	df	Wet Shakes t=	Shudders	Rearings	Locomotor Activity
10.0	2	5	-1.66	0.00	-0.91	-1.05
5.0	2	5	0.42	0.70	-0.10	1.05
2.5	2	5	-0.35	1.00	0.20	-0.37

** = $p < .01$

TABLE 65.
Stereotyped Biting Behavior
Summary of McNemar tests (α = .01) for each morphine dose
Experiment 2

Pre-drug saline vs. Morphine

Dose (mg/kg)	# Rats (N)	df	
10.0	2	6	NS
5.0	2	6	NS
2.5	2	6	NS

Pre-drug saline vs. Post-drug saline

Dose (mg/kg)	# Rats (N)	df	
10.0	2	6	NS
5.0	2	6	NS
2.5	2	6	NS

NS = $p > .01$

FIGURE LEGENDS

FIGURE 1 Operative field. Indicates the measurements used in defining lambda line: x = the distance measured from a line extending 2 mm. lateral of lambda point to the intersection with the parietal-occipital suture.

FIGURE 2 Schematic diagram of testing procedure: Experiment 1.

FIGURE 3 Location of DB electrode tips. Symbols represent the classification of morphine effects; based upon the Duncan a posteriori tests on the interactions of Site x Drugcond x Day x Hour. ○ = "primarily" depressant; △ = "primarily" facilitative; ● = a biphasic pattern; □ = "negligible" effects. The two sections on the right are adapted from Konig & Klippel (1963).

FIGURE 4 Location of HYP electrode tips. Symbols represent the classification of morphine effects; based upon the Duncan a posteriori tests on the interactions of

Site x Drugcond x Day x Hour. ○ = "primarily" depressant; △ = "primarily" facilitative; ● = a biphasic pattern; □ = "negligible" effects. The sections are adapted from Konig & Klippel (1963).

FIGURE 5 Graph of ICSS response rate by hour: 37E - morphine (10.0 mg/kg) - DB electrode - low intensity (49 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 6 Graph of ICSS response rate by hour: 37E - morphine (10.0 mg/kg) - DB electrode - high intensity (57 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 7 Graph of ICSS response rate by hour: 37E - morphine (10.0 mg/kg) - HYP electrode - low intensity (35 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 8 Graph of ICSS response rate by hour: 37E - morphine (10.0 mg/kg) - HYP electrode - high intensity (42 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 9 Graph of ICSS response rate by hour: 54F - morphine (10.0 mg/kg) - DB electrode - low intensity (46 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 10 Graph of ICSS response rate by hour: 54F - morphine (10.0 mg/kg) - DB electrode - high intensity (64 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 11 Graph of ICSS response rate by hour: 54F - morphine (10.0 mg/kg) - HYP electrode - low intensity (25 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 12 Graph of ICSS response rate by hour: 54F - morphine (10.0 mg/kg) - HYP electrode - high intensity (28 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 13 Graph of ICSS response rate by hour: 76F - morphine (10.0 mg/kg) - DB electrode - low intensity (106 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 14 Graph of ICSS response rate by hour: 76F - morphine (10.0 mg/kg) - DB electrode - high intensity (127 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 15 Graph of ICSS response rate by hour: 76F - morphine (10.0 mg/kg) - HYP electrode - low intensity (35 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 16 Graph of ICSS response rate by hour: 76F - morphine (10.0 mg/kg) - HYP electrode - high intensity (49 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 17 Graph of ICSS response rate by hour: 94F - morphine (10.0 mg/kg) - DB electrode - low intensity (42 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 18 Graph of ICSS response rate by hour: 94F - morphine (10.0 mg/kg) - DB electrode - high intensity (49 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 19 Graph of ICSS response rate by hour: 94F - morphine (10.0 mg/kg) - HYP electrode - low intensity (42 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 20 Graph of ICSS response rate by hour: 94F - morphine (10.0 mg/kg) - HYP electrode - high intensity (57 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 21 Graph of ICSS response rate by hour: 74E - morphine (7.5 mg/kg) - DB electrode - low intensity (53 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 22 Graph of ICSS response rate by hour: 74E - morphine (7.5 mg/kg) - DB electrode - high intensity (60 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 23 Graph of ICSS response rate by hour: 74E - morphine (7.5 mg/kg) - HYP electrode - low intensity (42 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 24 Graph of ICSS response rate by hour: 74E - morphine (7.5 mg/kg) - HYP electrode - high intensity (60 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 25 Graph of ICSS response rate by hour: 4G - morphine (7.5 mg/kg) - DB electrode - low intensity (170 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 26 Graph of ICSS response rate by hour: 4G - morphine (7.5 mg/kg) - DB electrode - high intensity (198 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 27 Graph of ICSS response rate by hour: 4G - morphine (7.5 mg/kg) - HYP electrode - low intensity (49 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 28 Graph of ICSS response rate by hour: 4G - morphine (7.5 mg/kg) - HYP electrode - high intensity (57 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 29 Graph of ICSS response rate by hour: 75F - morphine (5.0 mg/kg) - DB electrode - low intensity (64 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 30 Graph of ICSS response rate by hour: 75F - morphine (5.0 mg/kg) - DB electrode - high intensity (78 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 31 Graph of ICSS response rate by hour: 75F - morphine (5.0 mg/kg) - HYP electrode - low intensity (57 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 32 Graph of ICSS response rate by hour: 75F - morphine (5.0 mg/kg) - HYP electrode - high intensity (85 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 33 Graph of ICSS response rate by hour: 66F - morphine (5.0 mg/kg) - DB electrode - low intensity (99 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 34 Graph of ICSS response rate by hour: 66F - morphine (5.0 mg/kg) - DB electrode - high intensity (113 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 35 Graph of ICSS response rate by hour: 66F - morphine (5.0 mg/kg) - HYP electrode - low intensity (28 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 36 Graph of ICSS response rate by hour: 66P - morphine (5.0 mg/kg) - HYP electrode - high intensity (39 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 37 Graph of ICSS response rate by hour: 3G - morphine (5.0 mg/kg) - DB electrode - low intensity (64 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 38 Graph of ICSS response rate by hour: 3G - morphine (5.0 mg/kg) - DB electrode - high intensity (85 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 39 Graph of ICSS response rate by hour: 3G - morphine (5.0 mg/kg) - HYP electrode - low intensity (42 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 40 Graph of ICSS response rate by hour: 3G - morphine (5.0 mg/kg) - HYP electrode - high intensity (57 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 41 Graph of ICSS response rate by hour: 21G - morphine (5.0 mg/kg) - DB electrode - low intensity (21 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 42 Graph of ICSS response rate by hour: 21G - morphine (5.0 mg/kg) - DB electrode - high intensity (35 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 43 Graph of ICSS response rate by hour: 21G - morphine (5.0 mg/kg) - HYP electrode - low intensity (49 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 44 Graph of ICSS response rate by hour: 21G - morphine (5.0 mg/kg) - HYP electrode - high intensity (92 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 45 Graph of ICSS response rate by hour: 84F - morphine (2.5 mg/kg) - DB electrode - low intensity (177 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 46 Graph of ICSS response rate by hour: 84F - morphine (2.5 mg/kg) - DB electrode - high intensity (199 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 47 Graph of ICSS response rate by hour: 84F - morphine (2.5 mg/kg) - HYP electrode - low intensity (35 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 48 Graph of ICSS response rate by hour: 84F - morphine (2.5 mg/kg) - HYP electrode - high intensity (49 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 49 Graph of ICSS response rate by hour: 86F - morphine (2.5 mg/kg) - DB electrode - low intensity (18 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 50 Graph of ICSS response rate by hour: 86F - morphine (2.5 mg/kg) - DB electrode - high intensity (21 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 51 Graph of ICSS response rate by hour: 86F - morphine (2.5 mg/kg) - HYP electrode - low intensity (32 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 52 Graph of ICSS response rate by hour: 86F - morphine (2.5 mg/kg) - HYP electrode - high intensity (35 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 53 Graph of ICSS response rate by hour: 18G - morphine (2.5 mg/kg) - DB electrode - low intensity (71 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 54 Graph of ICSS response rate by hour: 18G - morphine (2.5 mg/kg) - DB electrode - high intensity (99 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 55 Graph of ICSS response rate by hour: 18G - morphine (2.5 mg/kg) - HYP electrode - low intensity (25 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 56 Graph of ICSS response rate by hour: 18G - morphine (2.5 mg/kg) - HYP electrode - high intensity (42 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 57 Graph of ICSS response rate by hour: 9G - morphine (2.5 mg/kg) - DB electrode - low intensity (57 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 58 Graph of ICSS response rate by hour: 9G - morphine (2.5 mg/kg) - DB electrode - high intensity (71 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 59 Graph of ICSS response rate by hour: 9G - morphine (2.5 mg/kg) - HYP electrode - low intensity (28 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 60 Graph of ICSS response rate by hour: 9G - morphine (2.5 mg/kg) - HYP electrode - high intensity (42 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 61 Graph of ICSS response rate by day by hour: 37E - morphine (10.0 mg/kg) - DB electrode - low intensity (49 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 62 Graph of ICSS response rate by day by hour: 37E - morphine (10.0 mg/kg) - DB electrode - high intensity (57 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 63 Graph of ICSS response rate by day by hour: 37E - morphine (10.0 mg/kg) - HYP electrode - low intensity (35 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 64 Graph of ICSS response rate by day by hour: 37E - morphine (10.0 mg/kg) - HYP electrode - high intensity (42 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 65 Graph of ICSS response rate by day by hour: 54F - morphine (10.0 mg/kg) - DB electrode - low intensity (46 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 66 Graph of ICSS response rate by day by hour: 54F - morphine (10.0 mg/kg) - DB electrode - high intensity (64 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 67 Graph of ICSS response rate by day by hour: 54F - morphine (10.0 mg/kg) - HYP electrode - low intensity (25 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 68 Graph of ICSS response rate by day by hour: 54F - morphine (10.0 mg/kg) - HYP electrode - high intensity (28 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 69 Graph of ICSS response rate by day by hour: 76F - morphine (10.0 mg/kg) - DB electrode - low intensity (106 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 70 Graph of ICSS response rate by day by hour: 76F - morphine (10.0 mg/kg) - DB electrode - high intensity (127 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 71 Graph of ICSS response rate by day by hour: 76F - morphine (10.0 mg/kg) - HYP electrode - low intensity (35 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 72 Graph of ICSS response rate by day by hour: 76P - morphine (10.0 mg/kg) - HYP electrode - high intensity (49 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 73 Graph of ICSS response rate by day by hour: 94P - morphine (10.0 mg/kg) - DB electrode - low intensity (42 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 74 Graph of ICSS response rate by day by hour: 94P - morphine (10.0 mg/kg) - DB electrode - high intensity (49 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 75 Graph of ICSS response rate by day by hour: 94P - morphine (10.0 mg/kg) - HYP electrode - low intensity (42 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 76 Graph of ICSS response rate by day by hour: 94F - morphine (10.0 mg/kg) - HYP electrode - high intensity (57 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 77 Graph of ICSS response rate by day by hour: 74E - morphine (7.5 mg/kg) - DB electrode - low intensity (53 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 78 Graph of ICSS response rate by day by hour: 74E - morphine (7.5 mg/kg) - DB electrode - high intensity (60 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 79 Graph of ICSS response rate by day by hour: 74E - morphine (7.5 mg/kg) - HYP electrode - low intensity (42 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 80 Graph of ICSS response rate by day by hour: 74E - morphine (7.5 mg/kg) - HYP electrode - high intensity (60 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 81 Graph of ICSS response rate by day by hour: 4G - morphine (7.5 mg/kg) - DB electrode - low intensity (170 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 82 Graph of ICSS response rate by day by hour: 4G - morphine (7.5 mg/kg) - DB electrode - high intensity (198 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 83 Graph of ICSS response rate by day by hour: 4G - morphine (7.5 mg/kg) - HYP electrode - low intensity (49 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 84 Graph of ICSS response rate by day by hour: 4G - morphine (7.5 mg/kg) - HYP electrode - high intensity (57 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 85 Graph of ICSS response rate by day by hour: 75F - morphine (5.0 mg/kg) - DB electrode - low intensity (64 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 86 Graph of ICSS response rate by day by hour: 75F - morphine (5.0 mg/kg) - DB electrode - high intensity (78 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 87 Graph of ICSS response rate by day by hour: 75F - morphine (5.0 mg/kg) - HYP electrode - low intensity (57 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 88 Graph of ICSS response rate by day by hour: 75F - morphine (5.0 mg/kg) - HYP electrode - high intensity (85 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 89 Graph of ICSS response rate by day by hour: 66F - morphine (5.0 mg/kg) - DB electrode - low intensity (99 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 90 Graph of ICSS response rate by day by hour: 66F - morphine (5.0 mg/kg) - DB electrode - high intensity (113 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 91 Graph of ICSS response rate by day by hour: 66F - morphine (5.0 mg/kg) - HYP electrode - low intensity (28 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 92 Graph of ICSS response rate by day by hour: 66F - morphine (5.0 mg/kg) - HYP electrode - high intensity (39 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 93 Graph of ICSS response rate by day by hour: 3G - morphine (5.0 mg/kg) - DB electrode - low intensity (64 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 94 Graph of ICSS response rate by day by hour: 3G - morphine (5.0 mg/kg) - DB electrode - high intensity (85 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 95 Graph of ICSS response rate by day by hour: 3G - morphine (5.0 mg/kg) - HYP electrode - low intensity (42 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 96 Graph of ICSS response rate by day by hour: 3G - morphine (5.0 mg/kg) - HYP electrode - high intensity (57 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 97 Graph of ICSS response rate by day by hour: 21G - morphine (5.0 mg/kg) - DB electrode - low intensity (21 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 98 Graph of ICSS response rate by day by hour: 21G - morphine (5.0 mg/kg) - DB electrode - high intensity (35 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 99 Graph of ICSS response rate by day by hour: 21G - morphine (5.0 mg/kg) - HYP electrode - low intensity (49 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 100 Graph of ICSS response rate by day by hour: 21G - morphine (5.0 mg/kg) - HYP electrode - high intensity (92 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 101 Graph of ICSS response rate by day by hour: 84F - morphine (2.5 mg/kg) - DB electrode - low intensity (177 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 102 Graph of ICSS response rate by day by hour: 84F - morphine (2.5 mg/kg) - DB electrode - high intensity (199 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 103 Graph of ICSS response rate by day by hour: 84F - morphine (2.5 mg/kg) - HYP electrode - low intensity (35 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 104 Graph of ICSS response rate by day by hour: 84F - morphine (2.5 mg/kg) - HYP electrode - high intensity (49 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 105 Graph of ICSS response rate by day by hour: 86F - morphine (2.5 mg/kg) - DB electrode - low intensity (18 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 106 Graph of ICSS response rate by day by hour: 86F - morphine (2.5 mg/kg) - DB electrode - high intensity (21 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 107 Graph of ICSS response rate by day by hour: 86F - morphine (2.5 mg/kg) - HYP electrode - low intensity (32 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 108 Graph of ICSS response rate by day by hour: 86F - morphine (2.5 mg/kg) - HYP electrode - high intensity (35 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 109 Graph of ICSS response rate by day by hour: 18G - morphine (2.5 mg/kg) - DB electrode - low intensity (71 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 110 Graph of ICSS response rate by day by hour: 18G - morphine (2.5 mg/kg) - DB electrode - high intensity (99 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 111 Graph of ICSS response rate by day by hour: 18G - morphine (2.5 mg/kg) - HYP electrode - low intensity (25 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 112 Graph of ICSS response rate by day by hour: 18G - morphine (2.5 mg/kg) - HYP electrode - high intensity (42 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 113 Graph of ICSS response rate by day by hour: 9G - morphine (2.5 mg/kg) - DB electrode - low intensity (57 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 114 Graph of ICSS response rate by day by hour: 9G - morphine (2.5 mg/kg) - DB electrode - high intensity (71 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 115 Graph of ICSS response rate by day by hour: 9G - morphine (2.5 mg/kg) - HYP electrode - low intensity (28 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 116 Graph of ICSS response rate by day by hour: 9G - morphine (2.5 mg/kg) - HYP electrode - high intensity (42 uA). Data expressed as mean (+ and - the s.e.m.) response rate/five minutes for the six days of each drug condition.

FIGURE 117 Graph of locomotor activity by hour: 37E - morphine (10.0 mg/kg). Data expressed as the mean (+ and - s.e.m.) number of observed box crossings/five minute behavioral watches for the six days of each drug condition.

FIGURE 118 Graph of locomotor activity by hour: 54P - morphine (10.0 mg/kg). Data expressed as the mean (+ and - s.e.m.) number of observed box crossings/five minute behavioral watches for the six days of each drug condition.

FIGURE 119 Graph of locomotor activity by hour: 76P - morphine (10.0 mg/kg). Data expressed as the mean (+ and - s.e.m.) number of observed box crossings/five minute behavioral watches for the six days of each drug condition.

FIGURE 120 Graph of locomotor activity by hour: 94P - morphine (10.0 mg/kg). Data expressed as the mean (+ and - s.e.m.) number of observed

box crossings/five minute behavioral watches for the six days of each drug condition.

FIGURE 121 Graph of locomotor activity by hour: 74E - morphine (7.5 mg/kg). Data expressed as the mean (+ and - s.e.m.) number of observed box crossings/five minute behavioral watches for the six days of each drug condition.

FIGURE 122 Graph of locomotor activity by hour: 4G - morphine (7.5 mg/kg). Data expressed as the mean (+ and - s.e.m.) number of observed box crossings/five minute behavioral watches for the six days of each drug condition.

FIGURE 123 Graph of locomotor activity by hour: 75F - morphine (5.0 mg/kg). Data expressed as the mean (+ and - s.e.m.) number of observed box crossings/five minute behavioral watches for the six days of each drug condition.

FIGURE 124 Graph of locomotor activity by hour: 66F - morphine (5.0 mg/kg). Data expressed as the mean (+ and - s.e.m.) number of observed box crossings/five minute behavioral watches for the six days of each drug condition.

FIGURE 125 Graph of locomotor activity by hour: 3G - morphine (5.0 mg/kg). Data expressed as the mean (+ and - s.e.m.) number of observed box crossings/five minute behavioral watches

for the six days of each drug condition.

FIGURE 126 Graph of locomotor activity by hour: 21G - morphine (5.0 mg/kg). Data expressed as the mean (+ and - s.e.m.) number of observed box crossings/five minute behavioral watches for the six days of each drug condition.

FIGURE 127 Graph of locomotor activity by hour: 84P - morphine (2.5 mg/kg). Data expressed as the mean (+ and - s.e.m.) number of observed box crossings/five minute behavioral watches for the six days of each drug condition.

FIGURE 128 Graph of locomotor activity by hour: 86P - morphine (2.5 mg/kg). Data expressed as the mean (+ and - s.e.m.) number of observed box crossings/five minute behavioral watches for the six days of each drug condition.

FIGURE 129 Graph of locomotor activity by hour: 18G - morphine (2.5 mg/kg). Data expressed as the mean (+ and - s.e.m.) number of observed box crossings/five minute behavioral watches for the six days of each drug condition.

FIGURE 130 Graph of locomotor activity by hour: 9G - morphine (2.5 mg/kg). Data expressed as the mean (+ and - s.e.m.) number of observed

box crossings/five minute behavioral watches for the six days of each drug condition.

FIGURE 131 Graph of stereotyped biting behavior by hour: Morphine - 10.0 mg/kg. N = 4 animals. Data expressed as the mean (+ and - s.e.m.) number of sessions in which biting behavior was observed for the six days of each drug condition.

FIGURE 132 Graph of stereotyped biting behavior by hour: Morphine - 7.5 mg/kg. N = 2 animals. Data expressed as the mean (+ and - s.e.m.) number of sessions in which biting behavior was observed for the six days of each drug condition.

FIGURE 133 Graph of stereotyped biting behavior by hour: Morphine - 5.0 mg/kg. N = 4 animals. Data expressed as the mean (+ and - s.e.m.) number of sessions in which biting behavior was observed for the six days of each drug condition.

FIGURE 134 Graph of stereotyped biting behavior by hour: Morphine - 2.5 mg/kg. N = 4 animals. Data expressed as the mean (+ and - s.e.m.) number of sessions in which

biting behavior was observed for the six days of each drug condition.

FIGURE 135 Location of DB electrode tips. Symbols represent the classification of morphine effects; based upon the Duncan a posteriori tests on the interactions of Site x Drugcond x Day x Hour. ○ = "primarily" depressant; △ = "primarily" facilitative; ● = a biphasic pattern; □ = "negligible" effects. The two sections on the right are adapted from Konig & Klippel (1963).

FIGURE 136 Location of HYP electrode tips. Symbols represent the classification of morphine effects; based upon the Duncan a posteriori tests on the interactions of Site x Drugcond x Day x Hour. ○ = "primarily" depressant; △ = "primarily" facilitative; ● = a biphasic pattern; □ = "negligible" effects. The sections are adapted from Konig & Klippel (1963).

FIGURE 137 Graph of rate intensity function: 41E - morphine (10.0 mg/kg) - DB electrode. Data expressed as mean (+ and - s.e.m.) response rate/five

minutes for the three days of each drug condition.

FIGURE 138 Graph of rate intensity function: 41E - morphine (10.0 mg/kg) - HYP electrode. Data expressed as mean (+ and - s.e.m.) response rate/five minutes for the three days of each drug condition.

FIGURE 139 Graph of rate intensity function: 19F - morphine (10.0 mg/kg) - DB electrode. Data expressed as mean (+ and - s.e.m.) response rate/five minutes for the three days of each drug condition.

FIGURE 140 Graph of rate intensity function: 19F - morphine (10.0 mg/kg) - HYP electrode. Data expressed as mean (+ and - s.e.m.) response rate/five minutes for the three days of each drug condition.

FIGURE 141 Graph of rate intensity function: 15G - morphine (10.0 mg/kg) - DB

electrode. Data expressed as mean (+ and - s.e.m.) response rate/five minutes for the three days of each drug condition.

FIGURE 142 Graph of rate intensity function: 15G - morphine (10.0 mg/kg) - HYP electrode. Data expressed as mean (+ and - s.e.m.) response rate/five minutes for the three days of each drug condition.

FIGURE 143 Graph of rate intensity function: 10G - morphine (10.0 mg/kg) - DB electrode. Data expressed as mean (+ and - s.e.m.) response rate/five minutes for the three days of each drug condition.

FIGURE 144 Graph of rate intensity function: 10G - morphine (10.0 mg/kg) - HYP electrode. Data expressed as mean (+ and - s.e.m.) response rate/five minutes for the three days of each drug condition.

FIGURE 145 Graph of rate intensity function: 8G - morphine (10.0 mg/kg) - DB electrode. Data expressed as mean

(+ and - s.e.m.) response rate/five minutes for the three days of each drug condition.

FIGURE 146 Graph of rate intensity function: 8G - morphine (10.0 mg/kg) - HYP electrode. Data expressed as mean (+ and - s.e.m.) response rate/five minutes for the three days of each drug condition.

FIGURE 147 Graph of rate intensity function: 7G - morphine (10.0 mg/kg) - DB electrode. Data expressed as mean (+ and - s.e.m.) response rate/five minutes for the three days of each drug condition.

FIGURE 148 Graph of rate intensity function: 7G - morphine (10.0 mg/kg) - HYP electrode. Data expressed as mean (+ and - s.e.m.) response rate/five minutes for the three days of each drug condition.

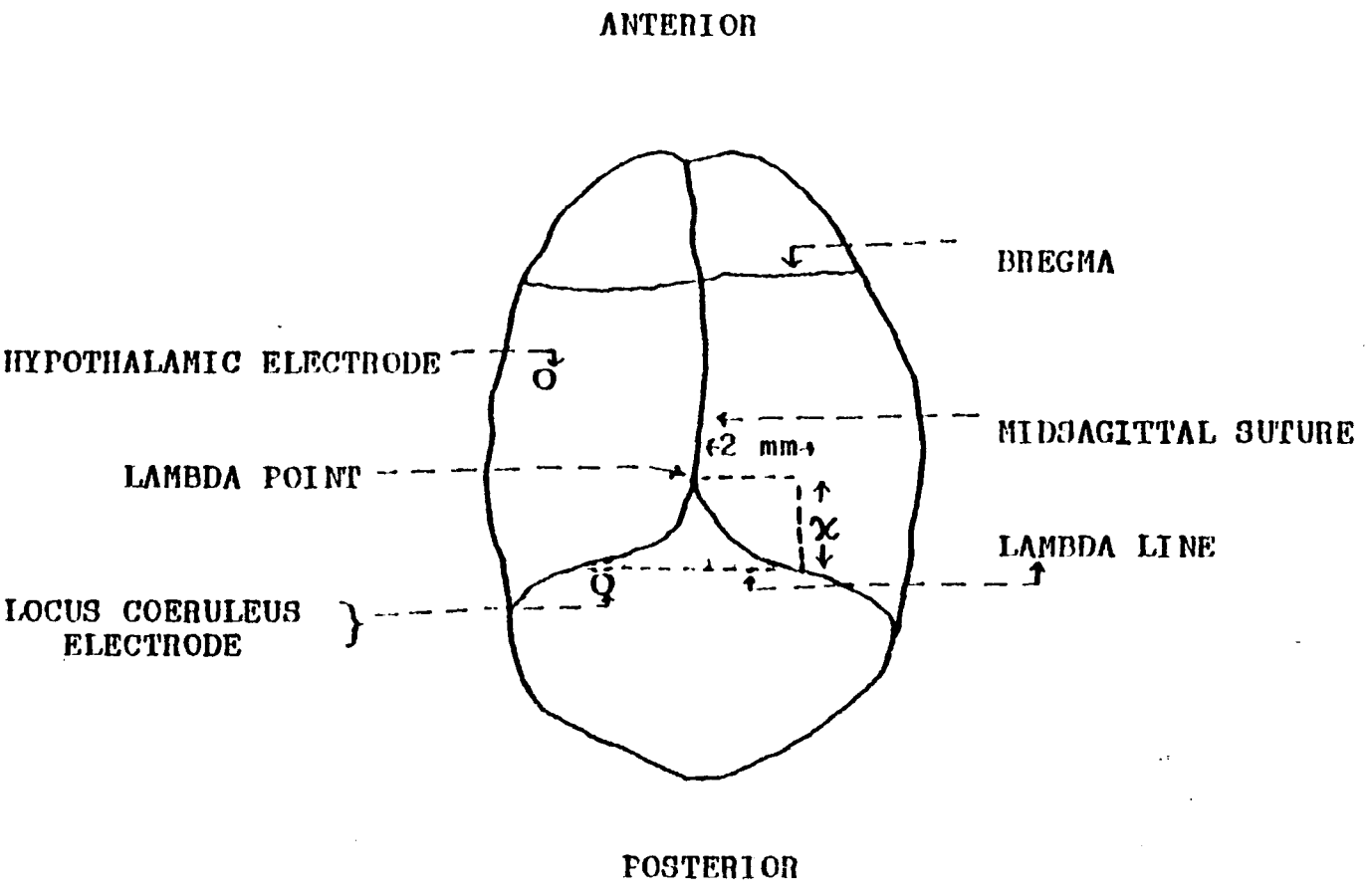

ANTERIOR
BREGMA
HYPOTHALAMIC ELECTRODE
MIDSAGITTAL SUTURE
2 mm
LAMBDA POINT
LAMBDA LINE
LOCUS COERULEUS ELECTRODE
POSTERIOR

Figure 1

FIGURE 2 TESTING PROCEDURE

HOURLY SESSION:

7 min. Site A Low Intensity	1 m i n	7 min. Site B Low Intensity	1 m i n	7 min. Site A High Intensity	1 m i n	7 min. Site B High Intensity	29 min. timeout (Bar retracted)

injection[a]

DAILY TESTING PROCEDURE:

B W III	ICSS session pre-injection hour 1 = post injection hour 24 of previous day	B W I	ICSS session: post injection hour 1	G C 1	ICSS session: post-injection hour 2	G C 2	ICSS session post-injection hour 3

G C 3	ICSS session post-injection hour 4	B W II	ICSS session: post-injection hour 5	G C 4	ICSS sessions: post-injection hour 6	G C 5	ICSS session: post-injection hour 7

DRUG TEST PROCEDURE Experiment 1:

6 days saline	6 days morphine	6 days saline

BW = 5 min Behavioral Watch
GC = 1 min behavioral observation

[a] morphine or saline administered 5 minutes prior to testing when appropriate

Figure 2

Figure 3

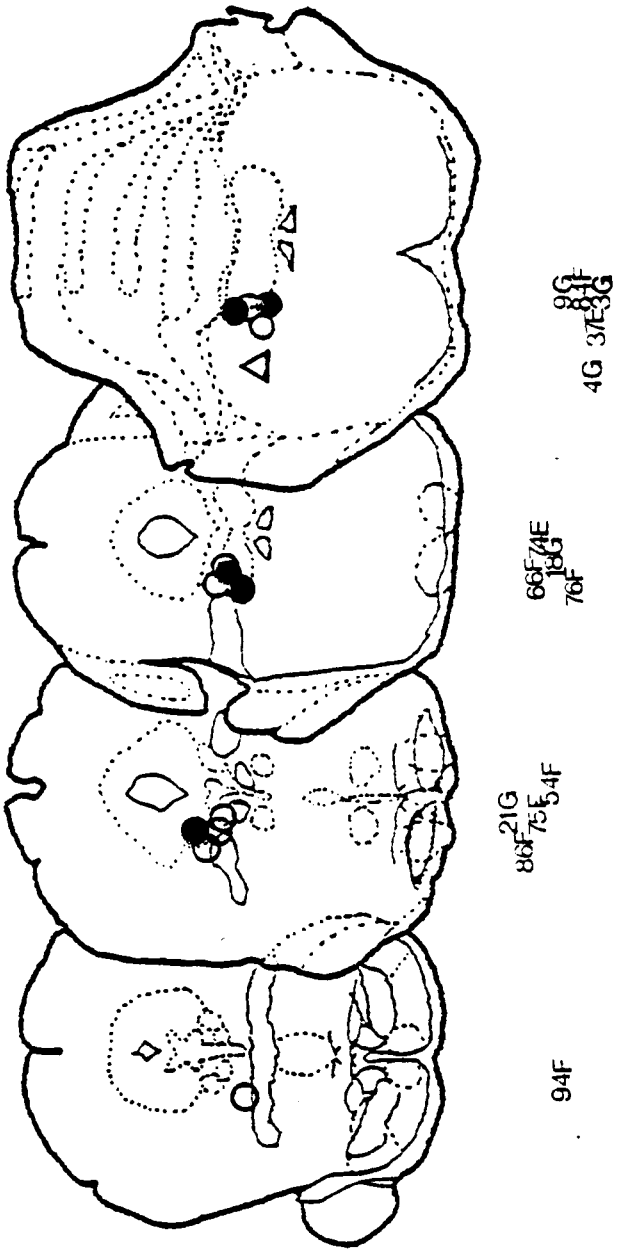
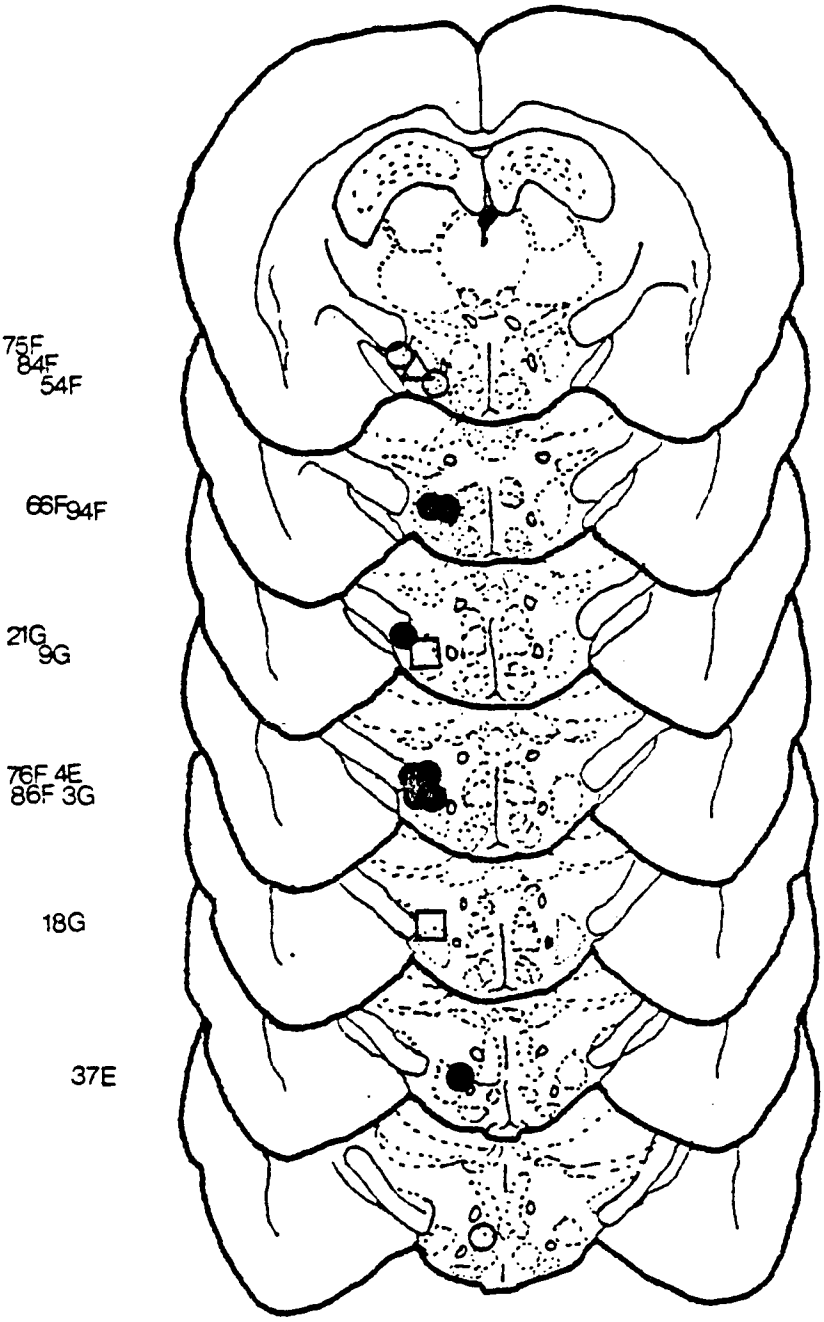


Figure 4



37E - DB, low intensity (49 uA)

pre-drug saline = 1 = —·——·—
morphine (10.0 mg/kg) = 2 = ————
post-drug saline = 3 = ·———·——

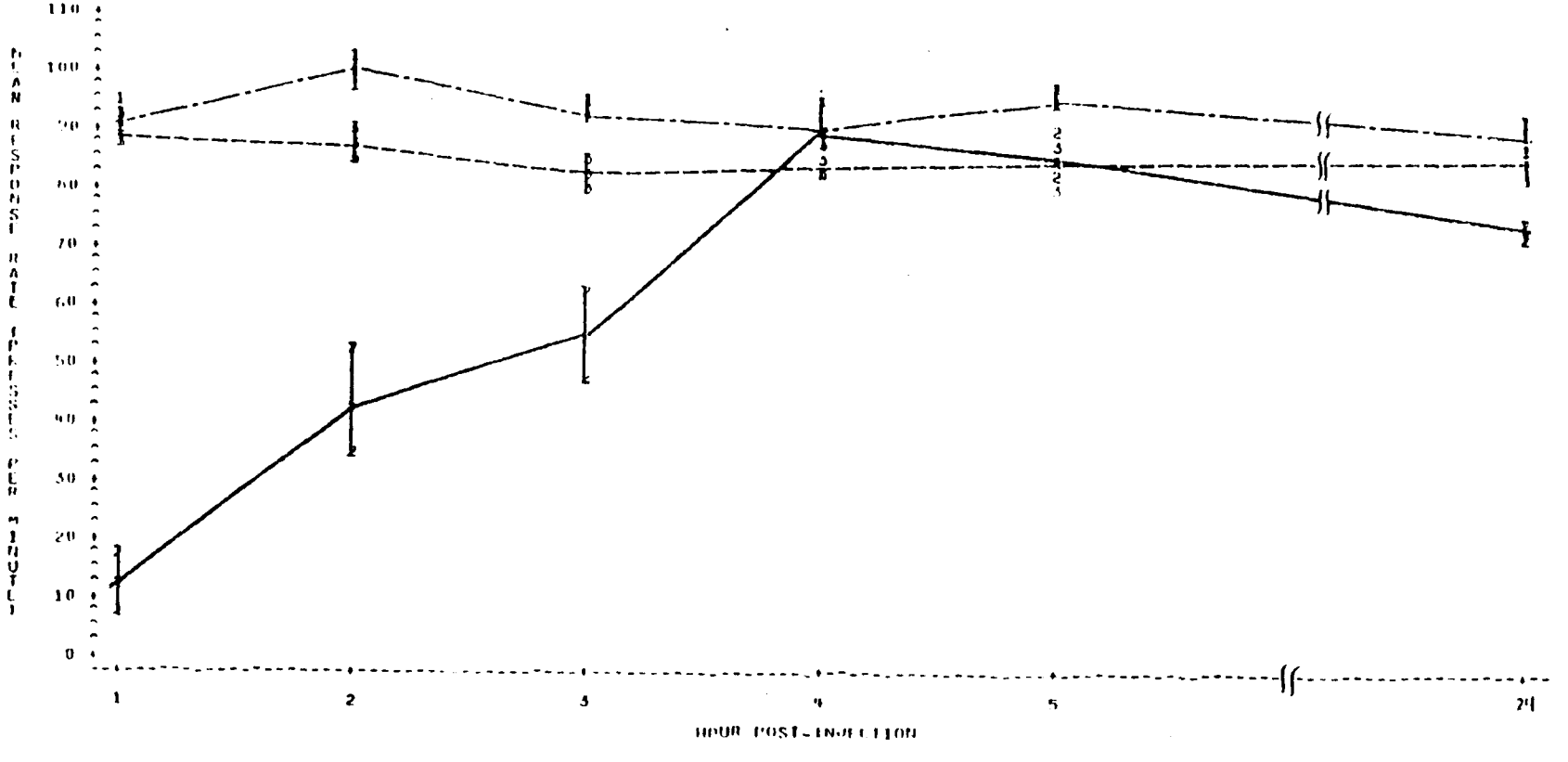


Figure 5

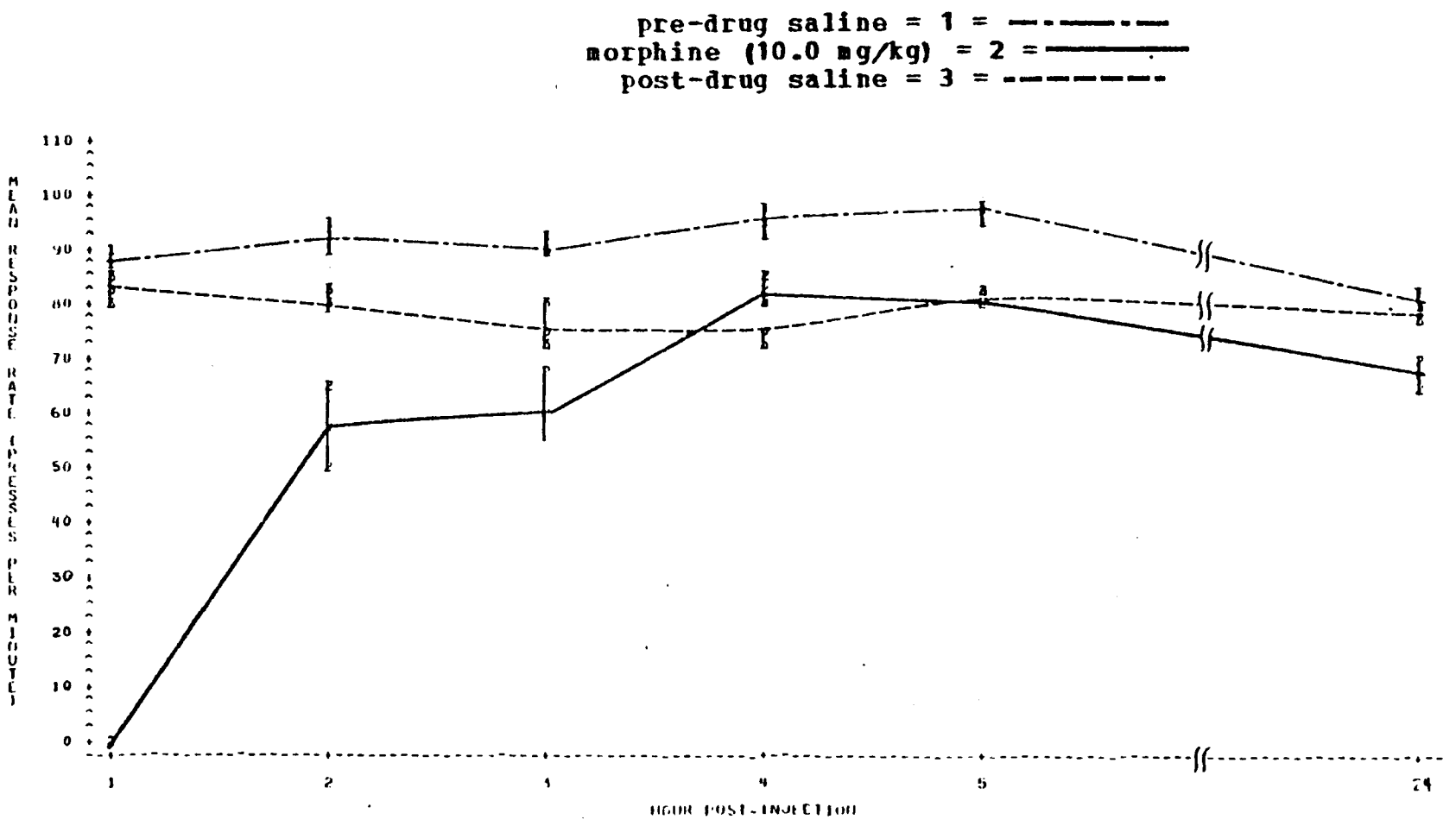

37E - DB, high intensity (57 uA)
pre-drug saline = 1 =
morphine (10.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
110
100
90
80
70
60
50
40
30
20
10
0
1
2
4
5
24
HOUR POST-INJECTION

Figure 6

37E - HYP, low intensity (35 uA)

pre-drug saline = 1 = -·-·-·-
morphine (10.0 mg/kg) = 2 = ———
post-drug saline = 3 = - - - - -

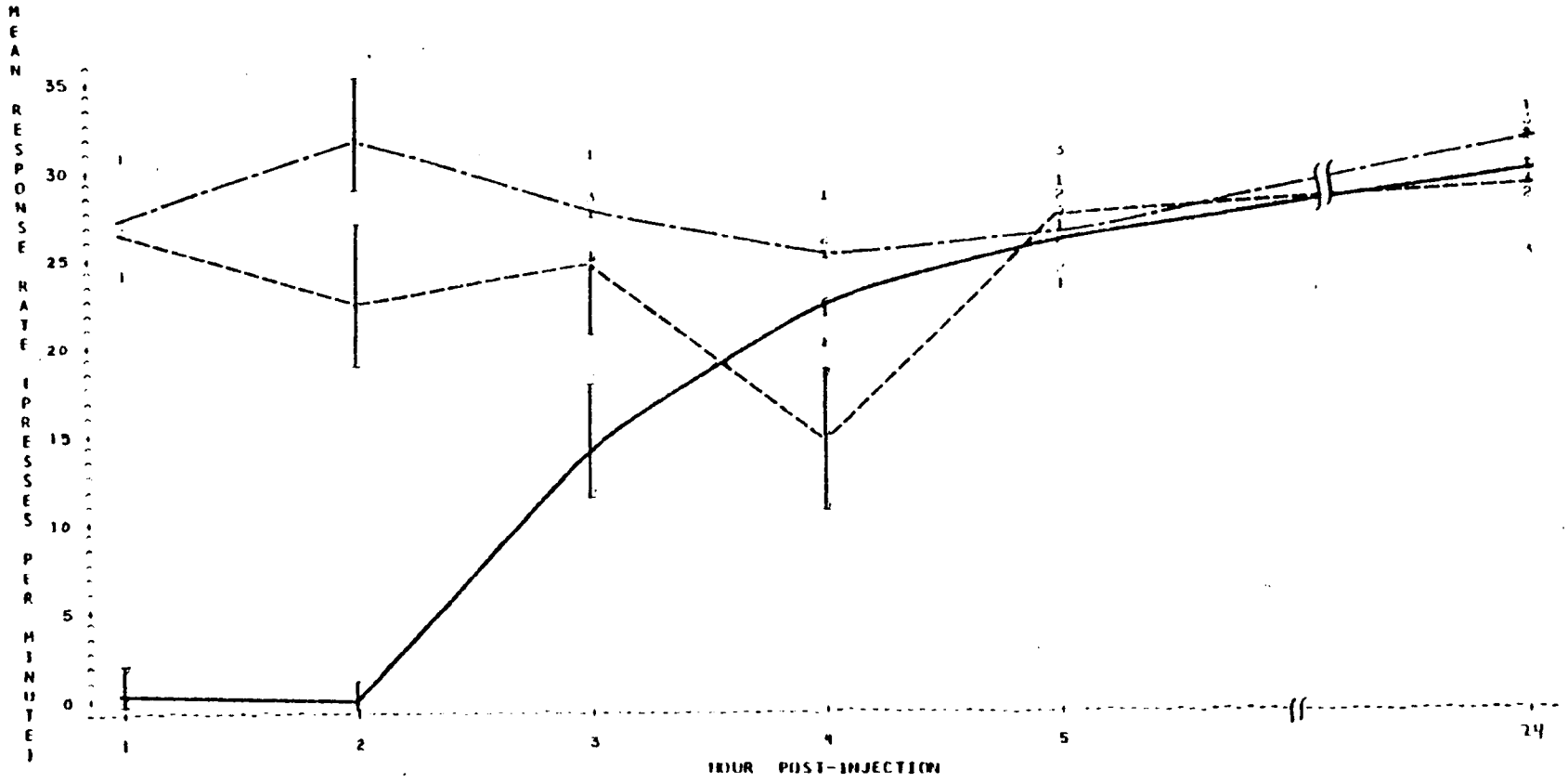


Figure 7

37E - HYP, high intensity (42 uA)

pre-drug saline = 1 = —·—·—·—
morphine (10.0 mg/kg) = 2 = ————
post-drug saline = 3 = ·——·——·

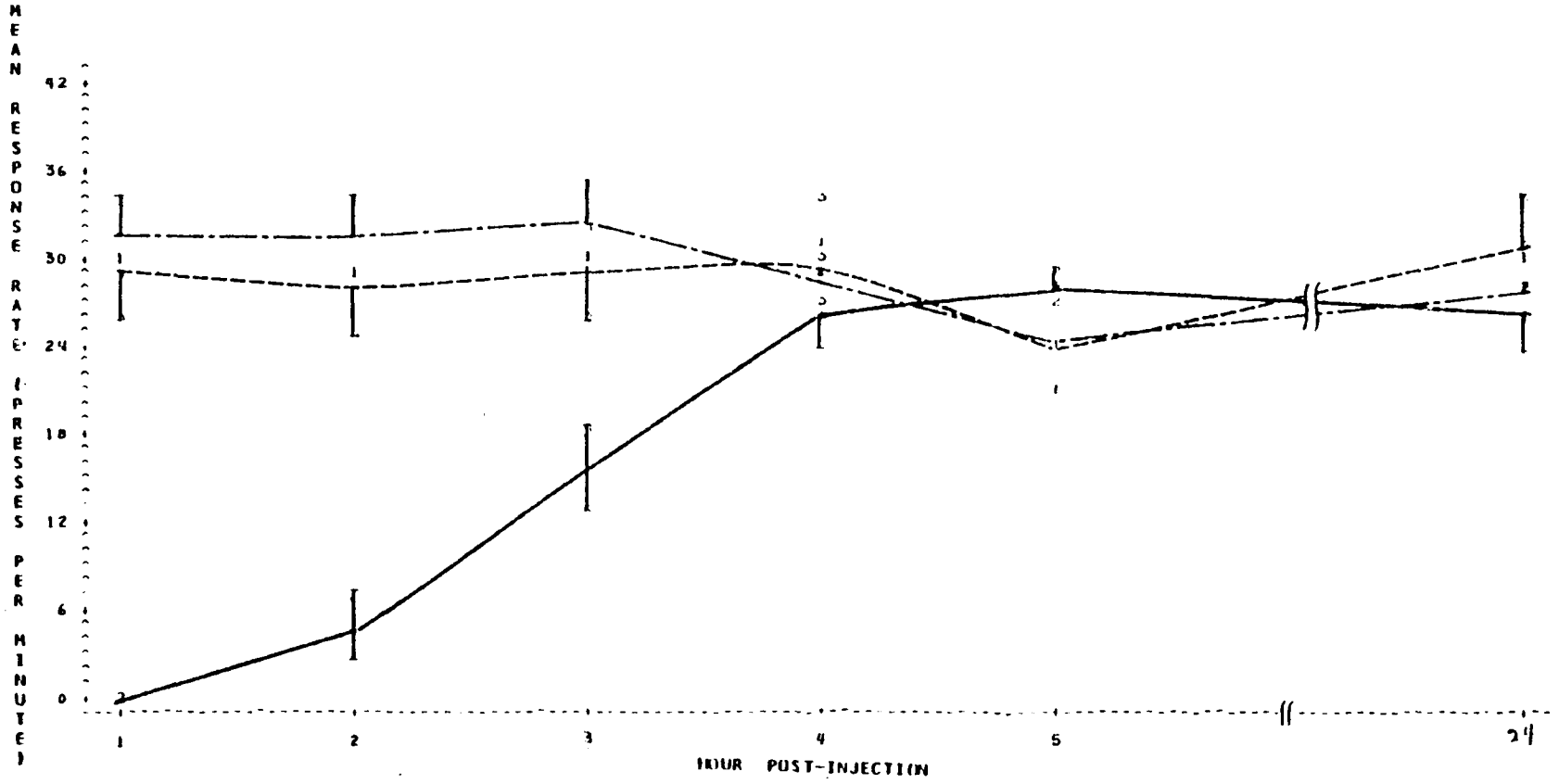


Figure 8

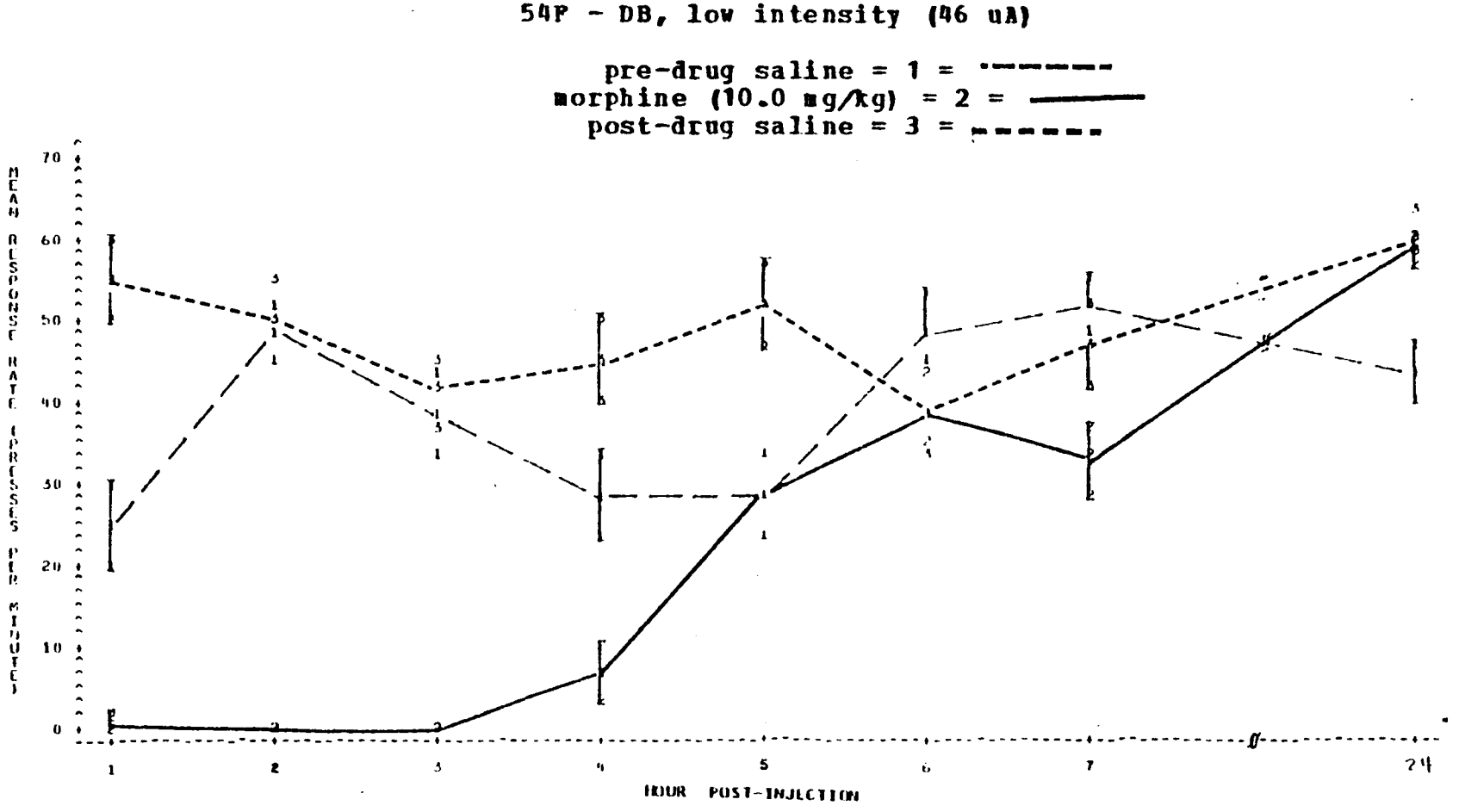

54P - DB, low intensity (46 uA)
pre-drug saline = 1 =
morphine (10.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 9

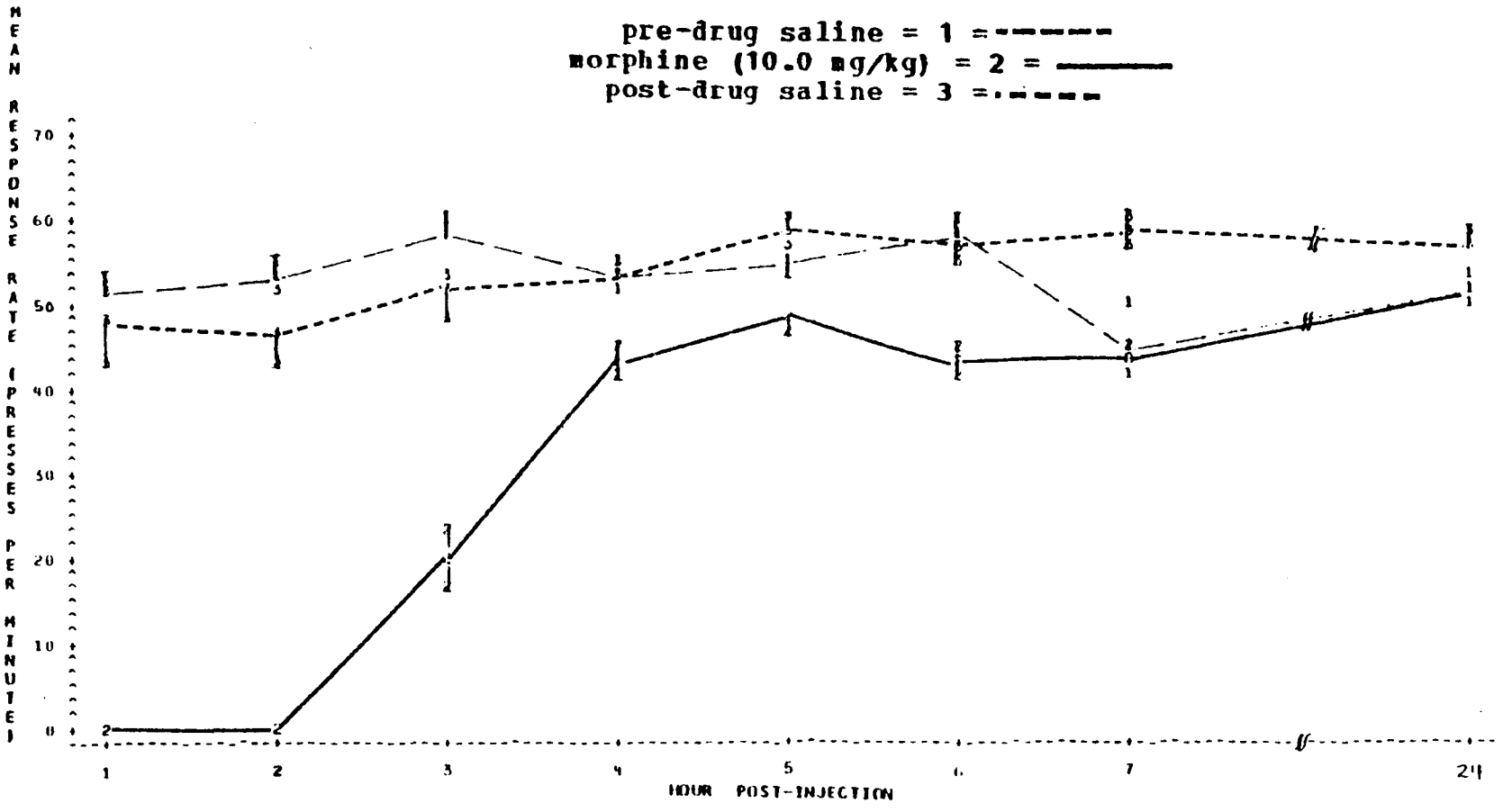

54P - DB, high intensity (64 uA)
pre-drug saline = 1 =
morphine (10.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
0
10
20
30
40
50
60
70
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 10

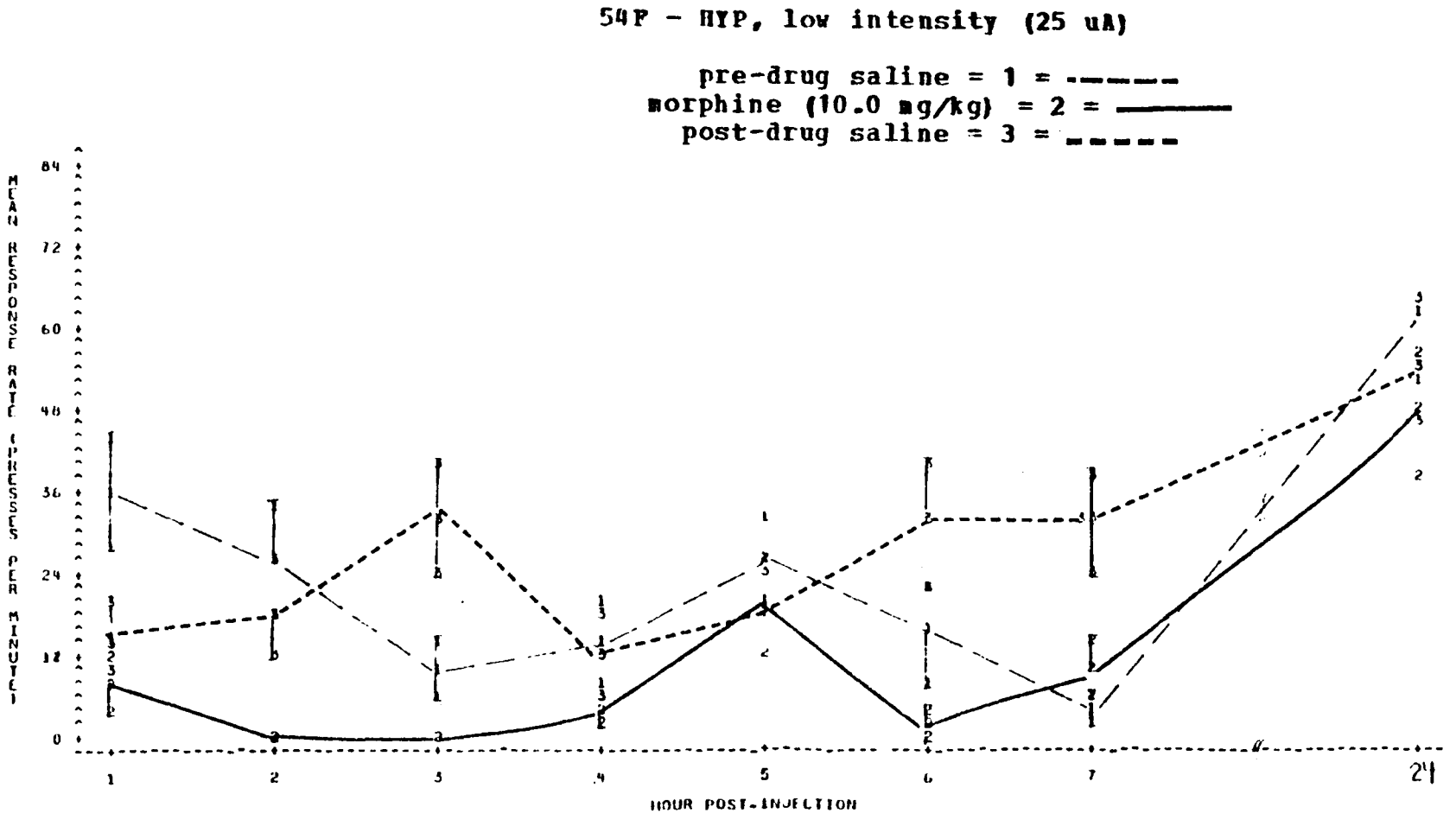

54P - HYP, low intensity (25 uA)
pre-drug saline = 1 = -----
morphine (10.0 mg/kg) = 2 = ———
post-drug saline = 3 = - - - - -
MEAN RESPONSE RATE (PRESSES PER MINUTE)
84
72
60
48
36
24
12
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 11

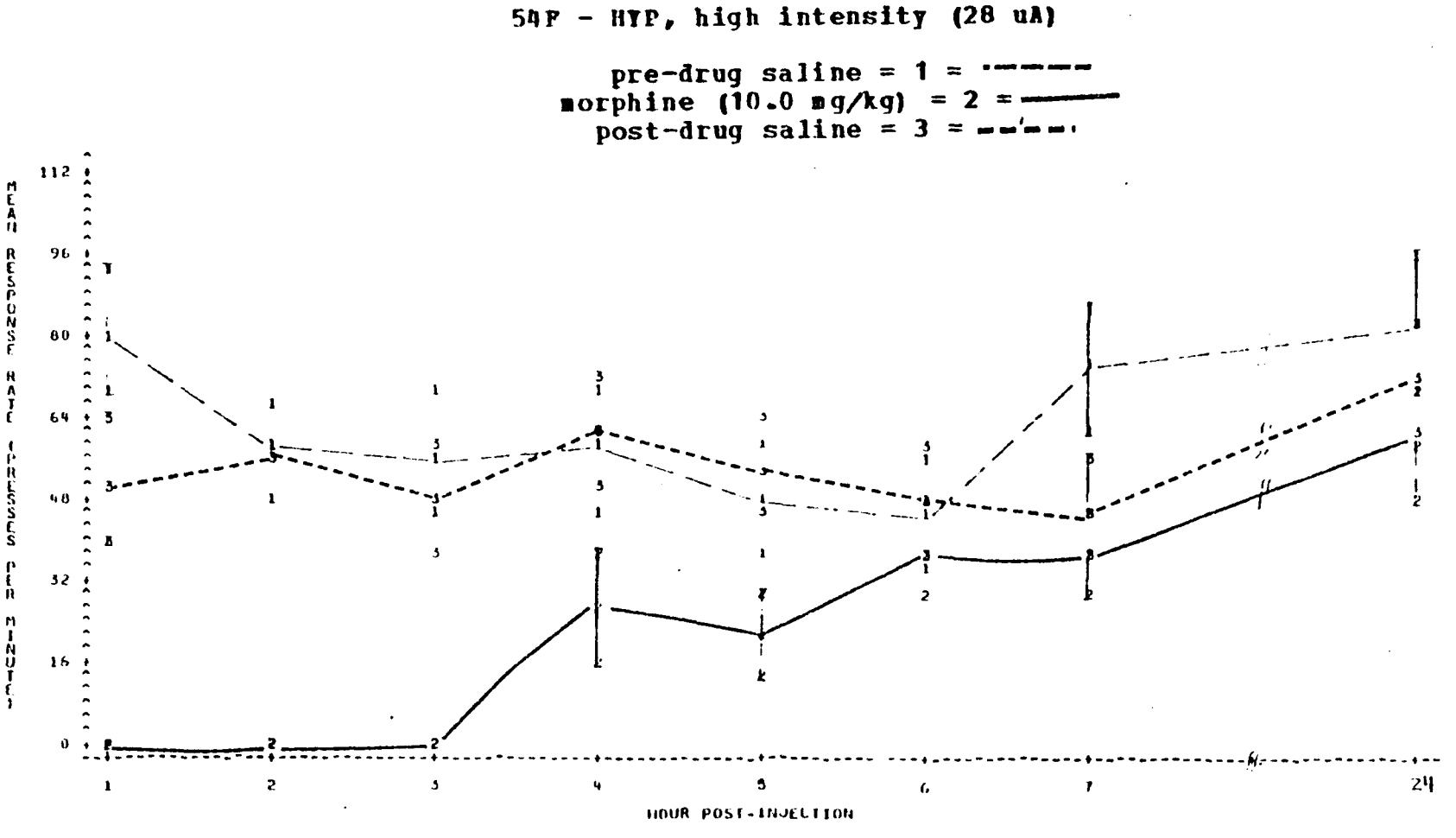

54F - HYP, high intensity (28 uA)
pre-drug saline = 1 =
morphine (10.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
112
96
80
64
48
32
16
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 12

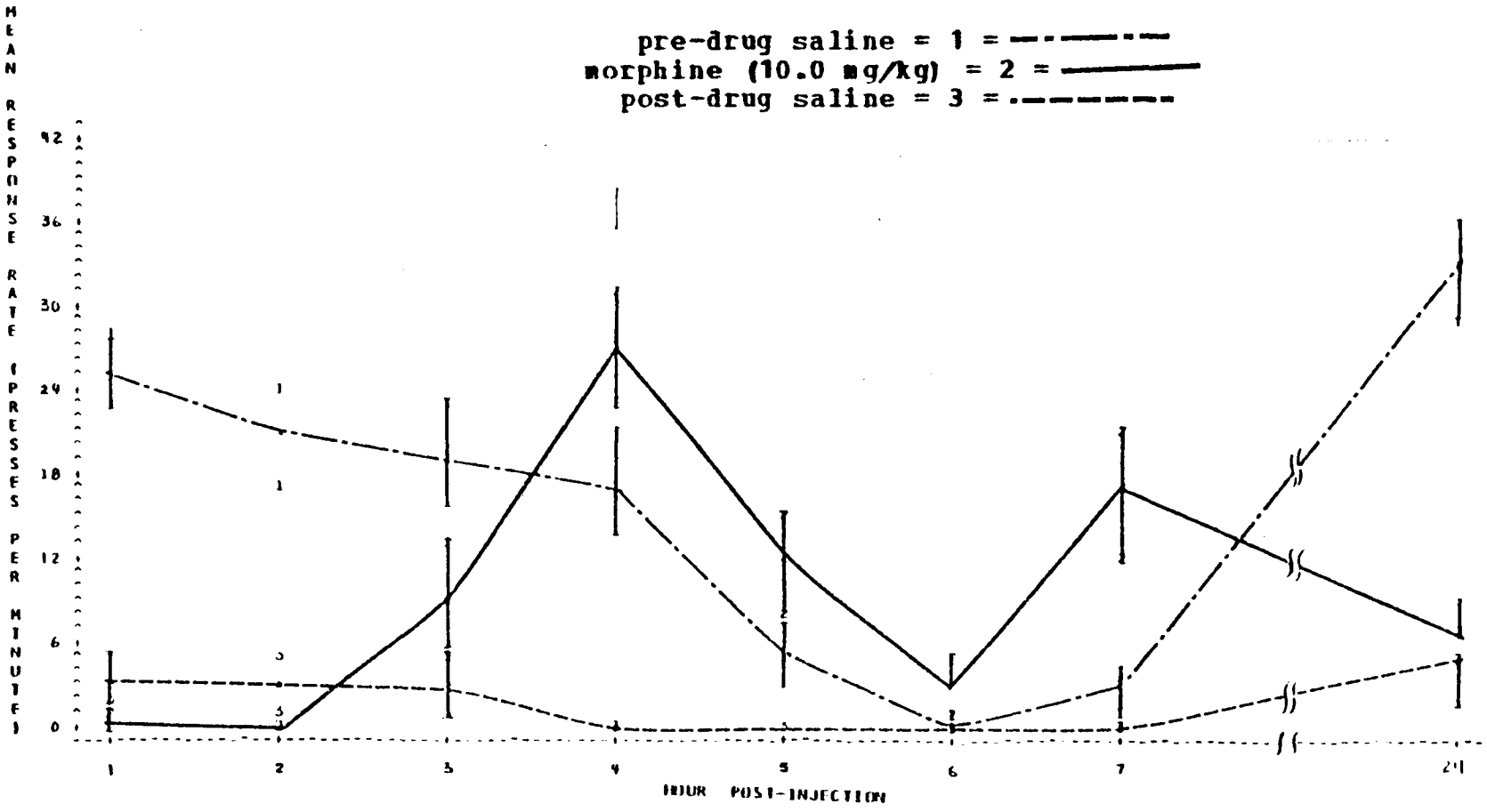

76F - DB, low intensity (106 uA)
pre-drug saline = 1 =
morphine (10.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
42
36
30
24
18
12
6
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 13

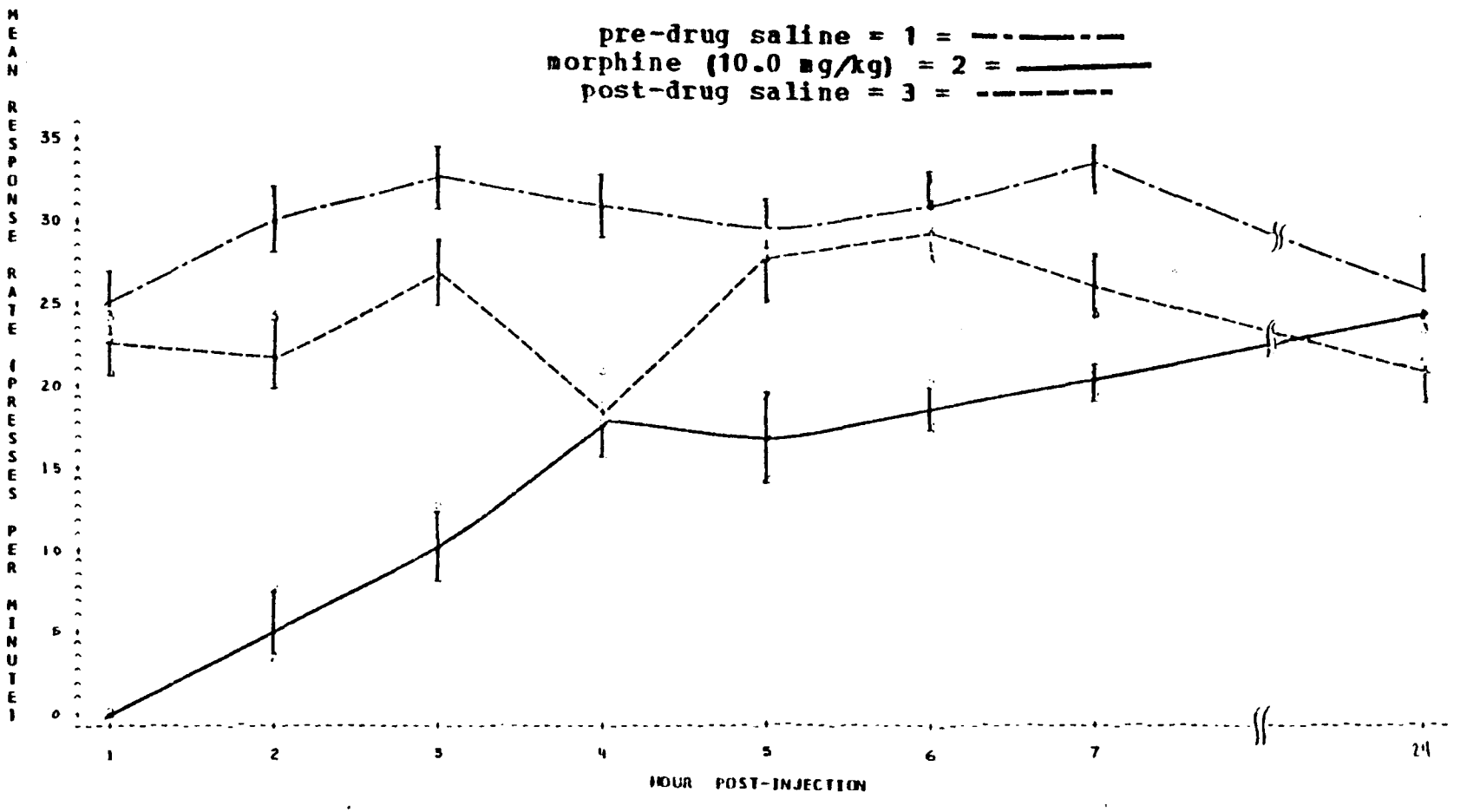

76F - DB, high intensity (127 uA)
pre-drug saline = 1 =
morphine (10.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
0
5
10
15
20
25
30
35
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 14

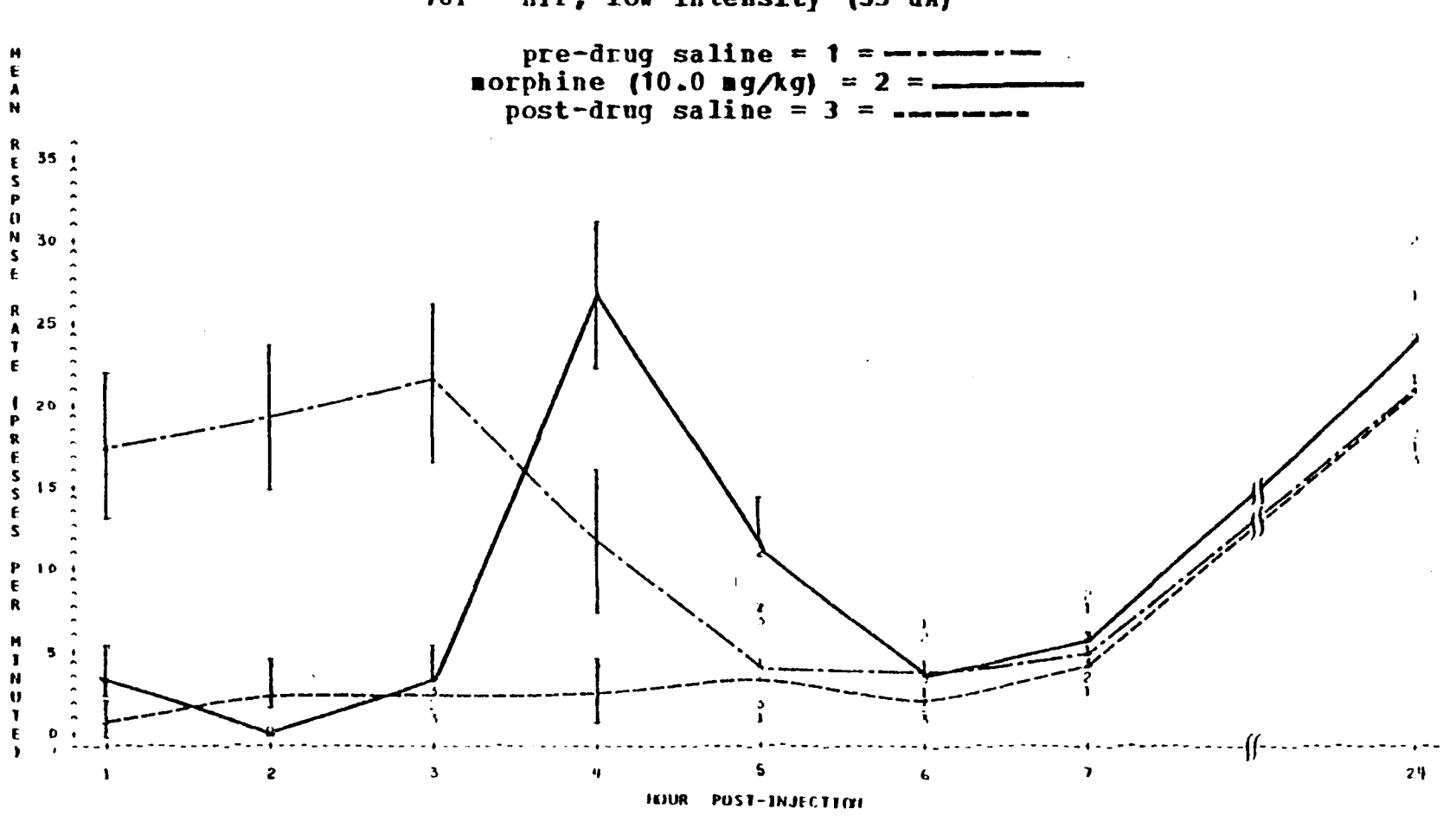

76F - HYP, low intensity (35 uA)
pre-drug saline = 1 =
morphine (10.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
0
5
10
15
20
25
30
35
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 15

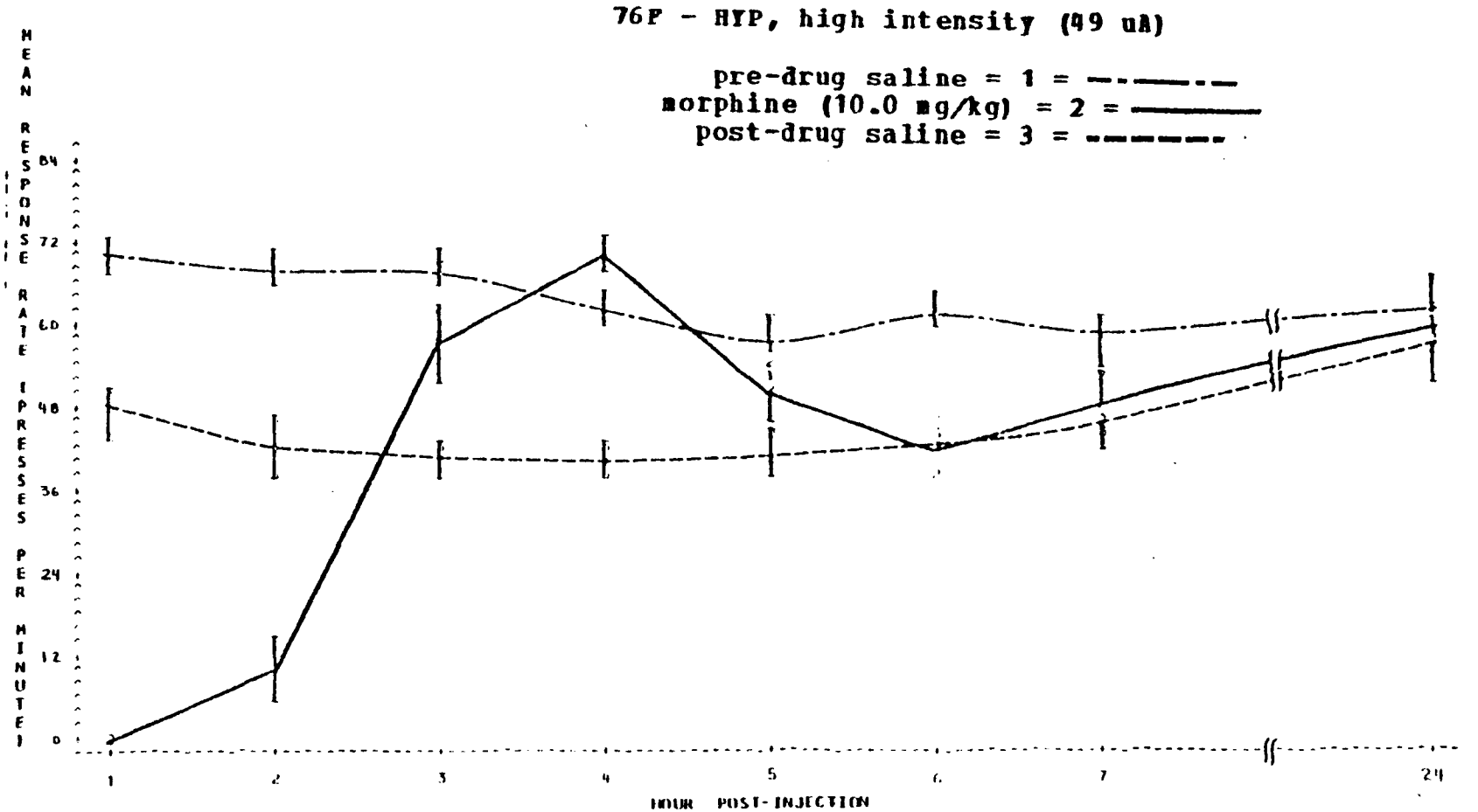

76P - HYP, high intensity (99 uA)
pre-drug saline = 1 =
morphine (10.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
84
72
60
48
36
24
12
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 16

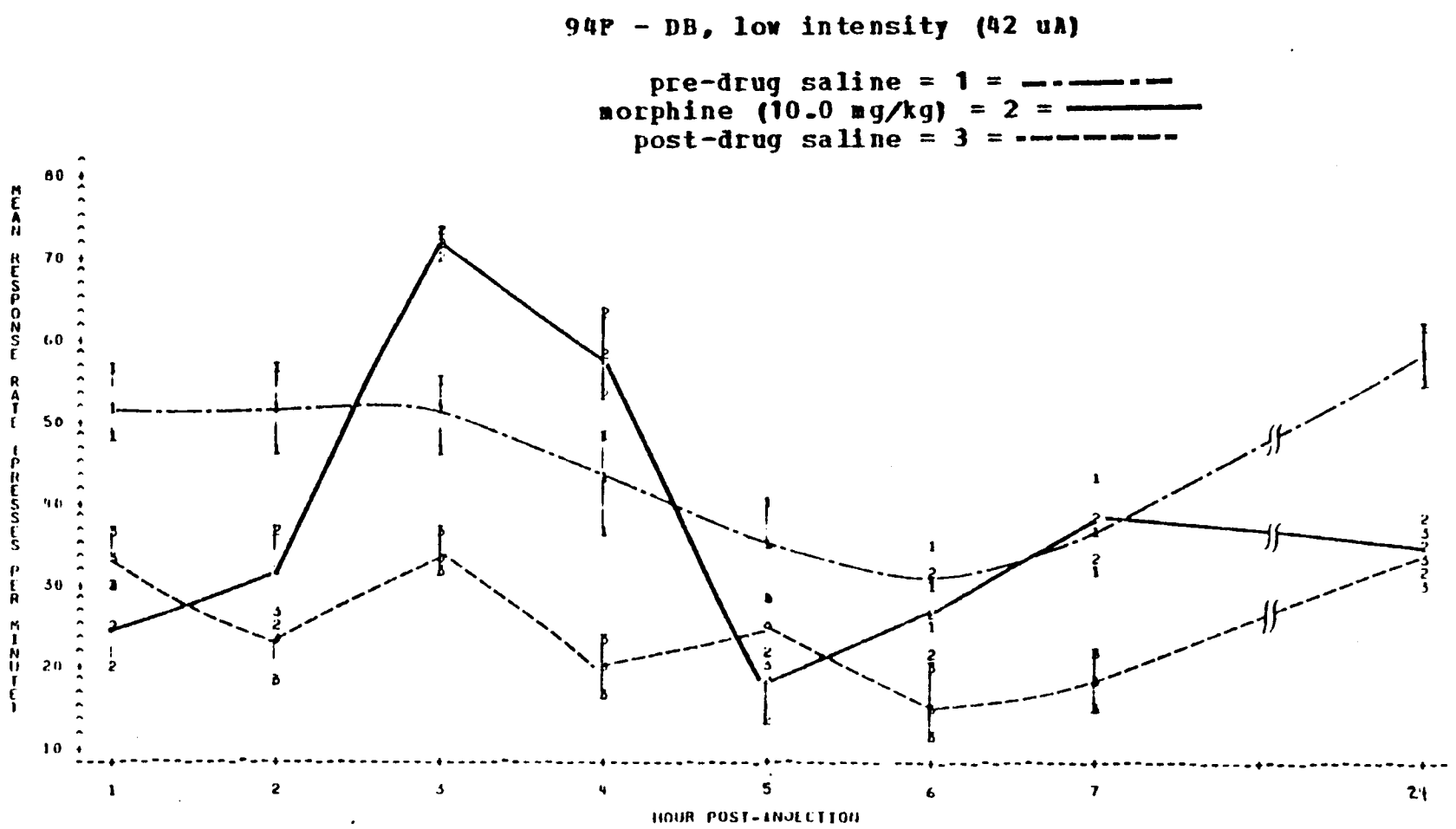

94P - DB, low intensity (42 uA)
pre-drug saline = 1 =
morphine (10.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
80
70
60
50
40
30
20
10
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 17

94F - DB, high intensity (49 uA)

pre-drug saline = 1 = —·——·—
morphine (10.0 mg/kg) = 2 = ————
post-drug saline = 3 = – – – –

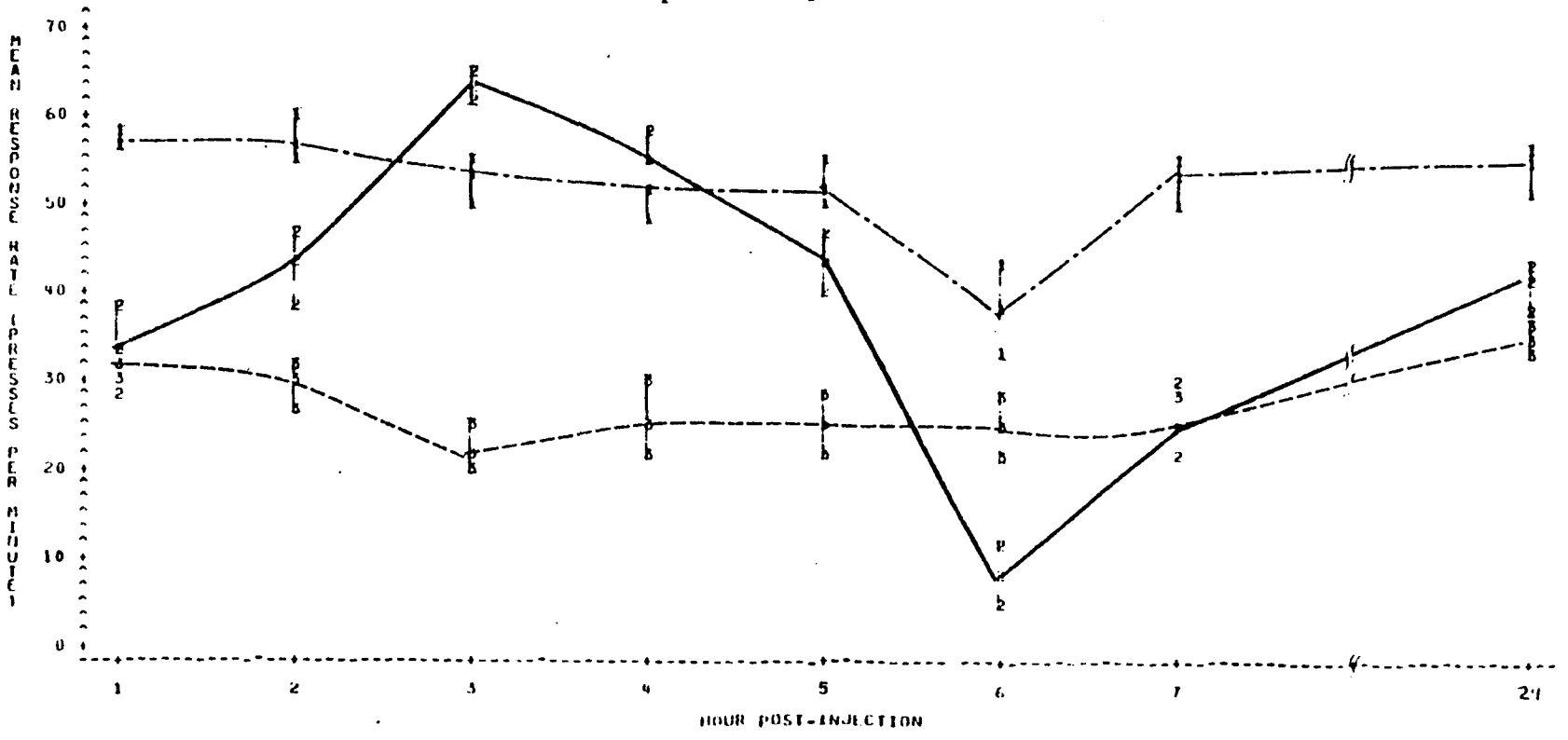


Figure 18

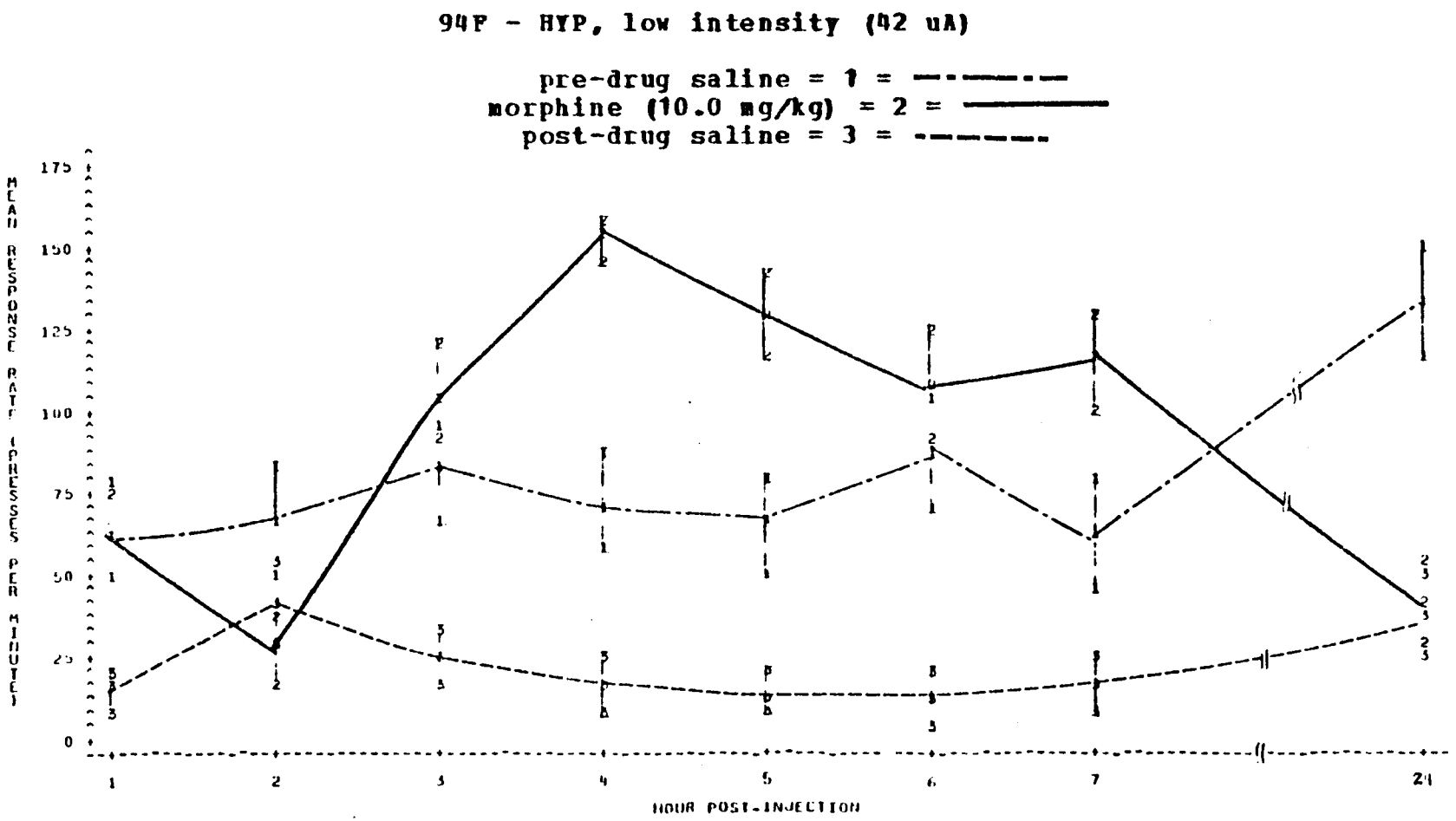

94P - HYP, low intensity (42 uA)
pre-drug saline = 1 =
morphine (10.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
175
150
125
100
75
50
25
0
1
2
3
4
5
6
7
21
HOUR POST-INJECTION

Figure 19

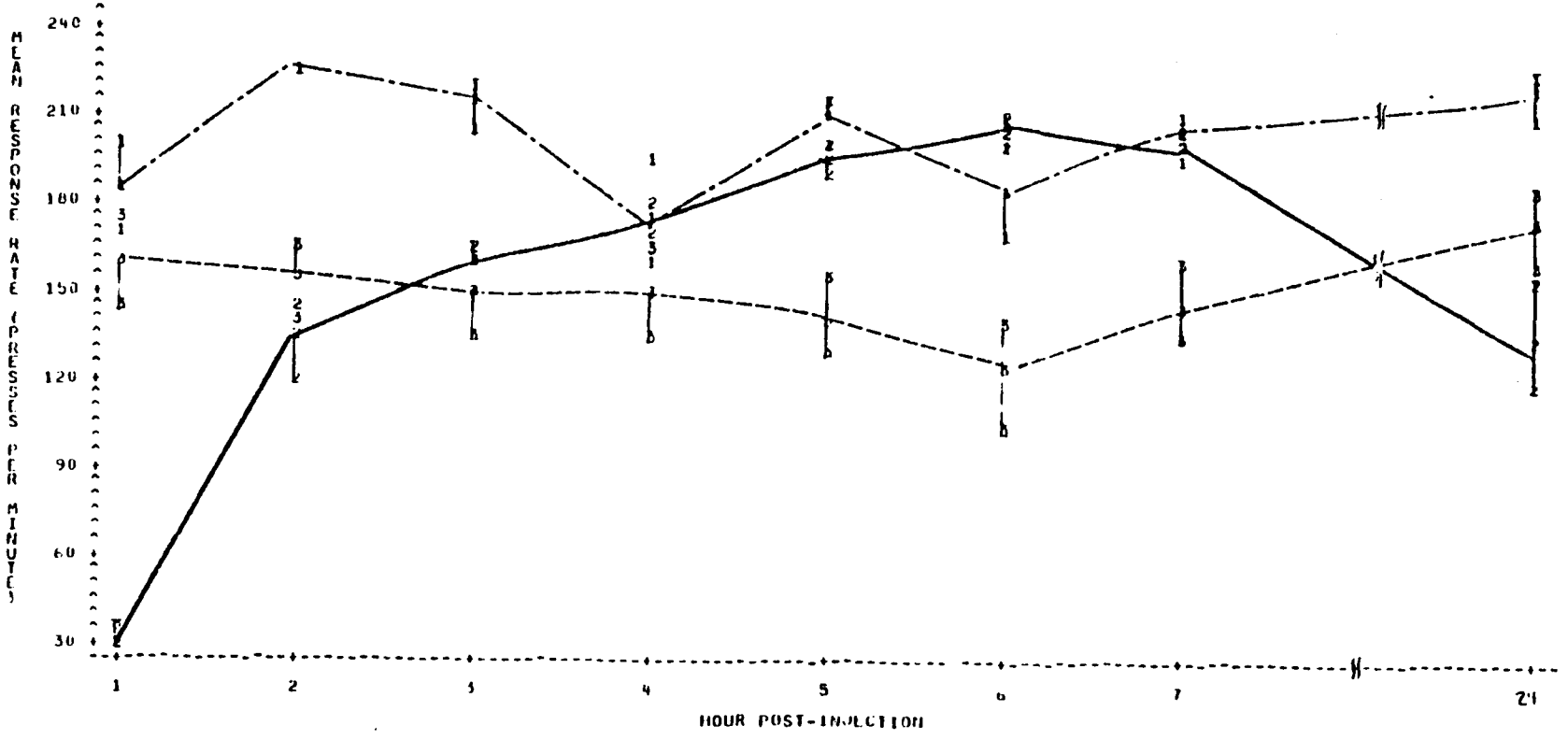

94P - HYP, high intensity (57 uA)
pre-drug saline = 1 =
morphine (10.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
240
210
180
150
120
90
60
30
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 20

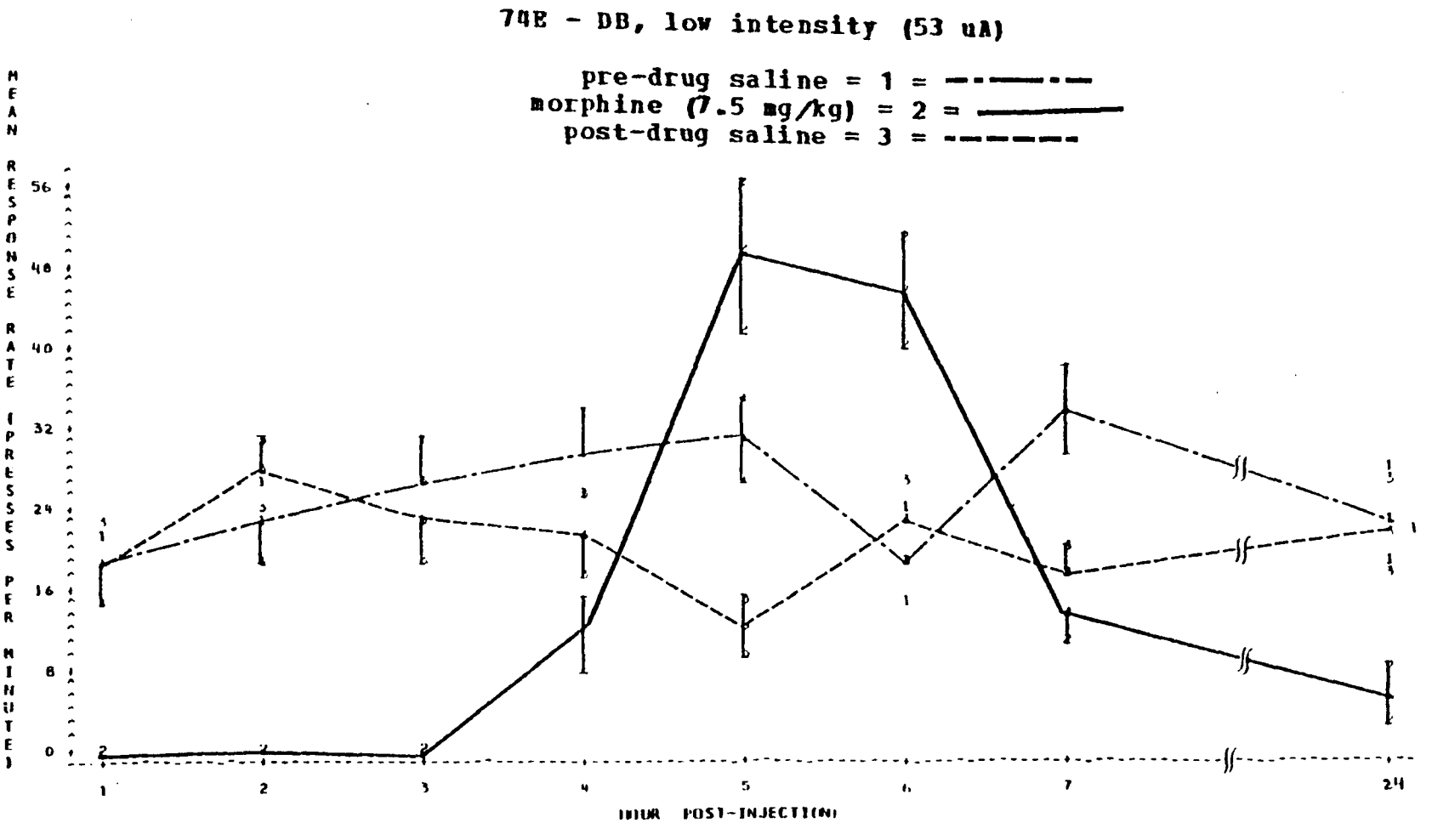

74E - DB, low intensity (53 uA)
pre-drug saline = 1 =
morphine (7.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
0
8
16
24
32
40
48
56
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 21

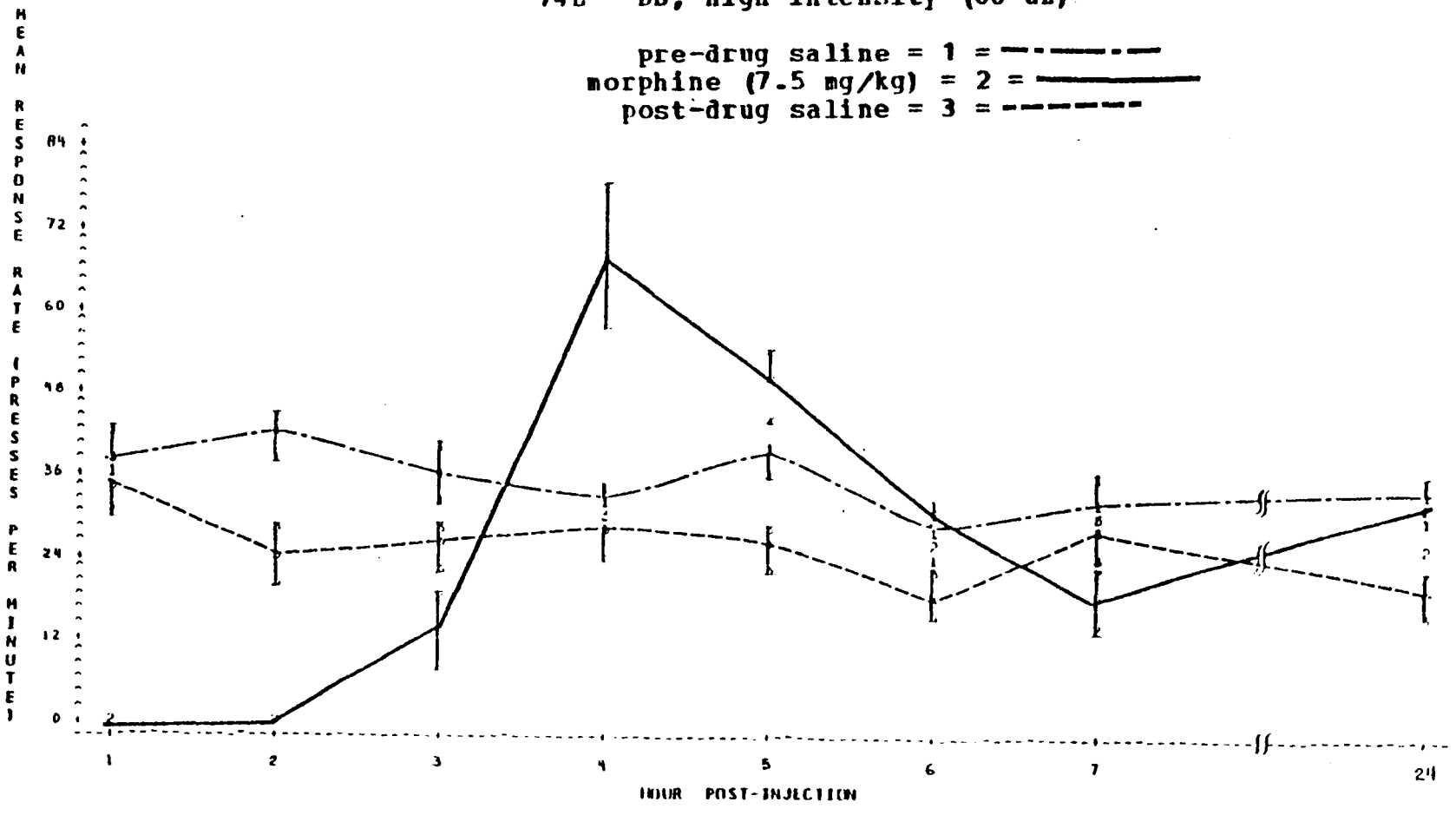

74E - DB, high intensity (60 uA)
pre-drug saline = 1 =
morphine (7.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
84
72
60
48
36
24
12
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 22

74E - HYP, low intensity (42 uA)

pre-drug saline = 1 = —·——·—
morphine (7.5 mg/kg) = 2 = ———
post-drug saline = 3 = – – – –

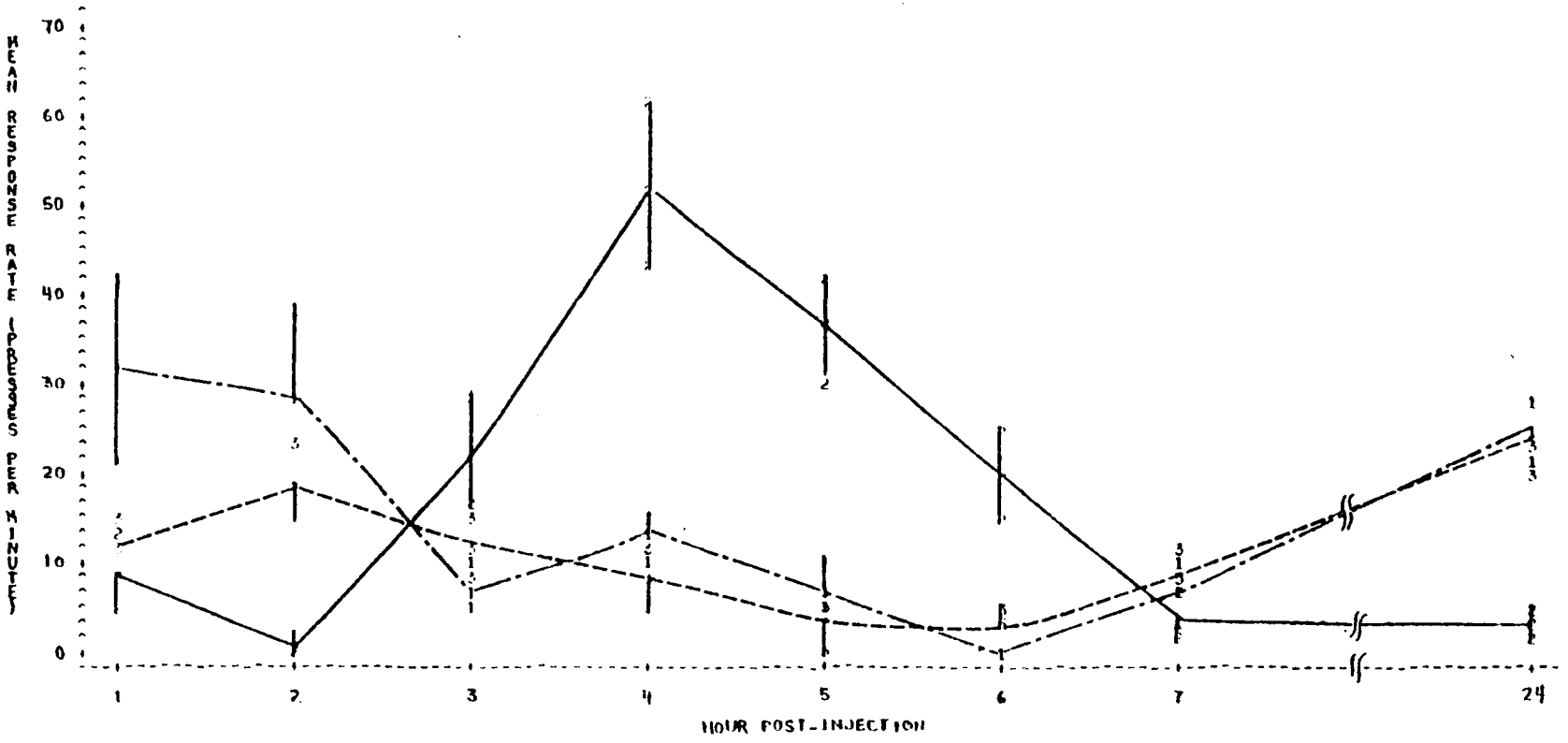


Figure 23

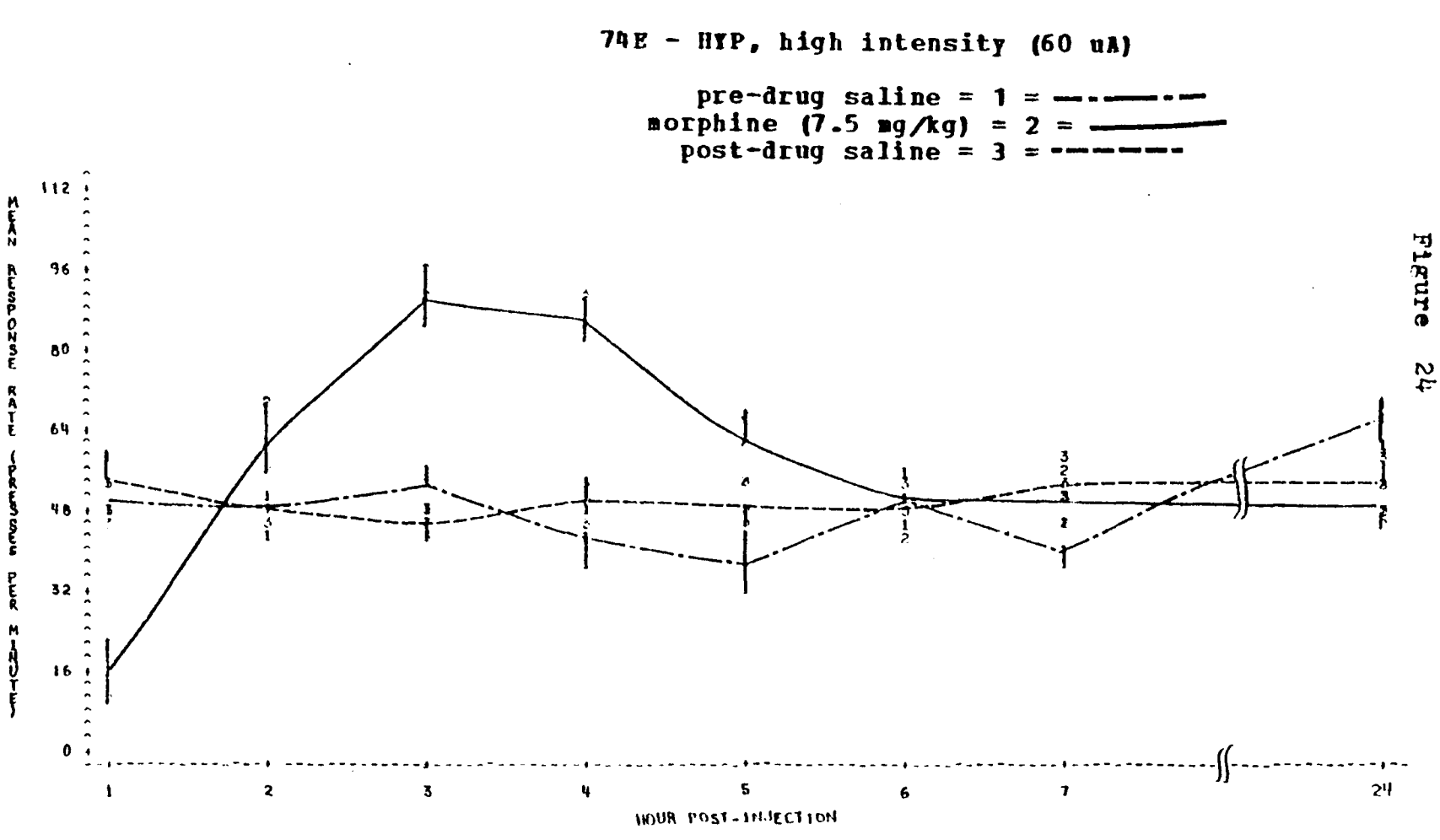

74E - HYP, high intensity (60 uA)
pre-drug saline = 1 =
morphine (7.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
112
96
80
64
48
32
16
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 24

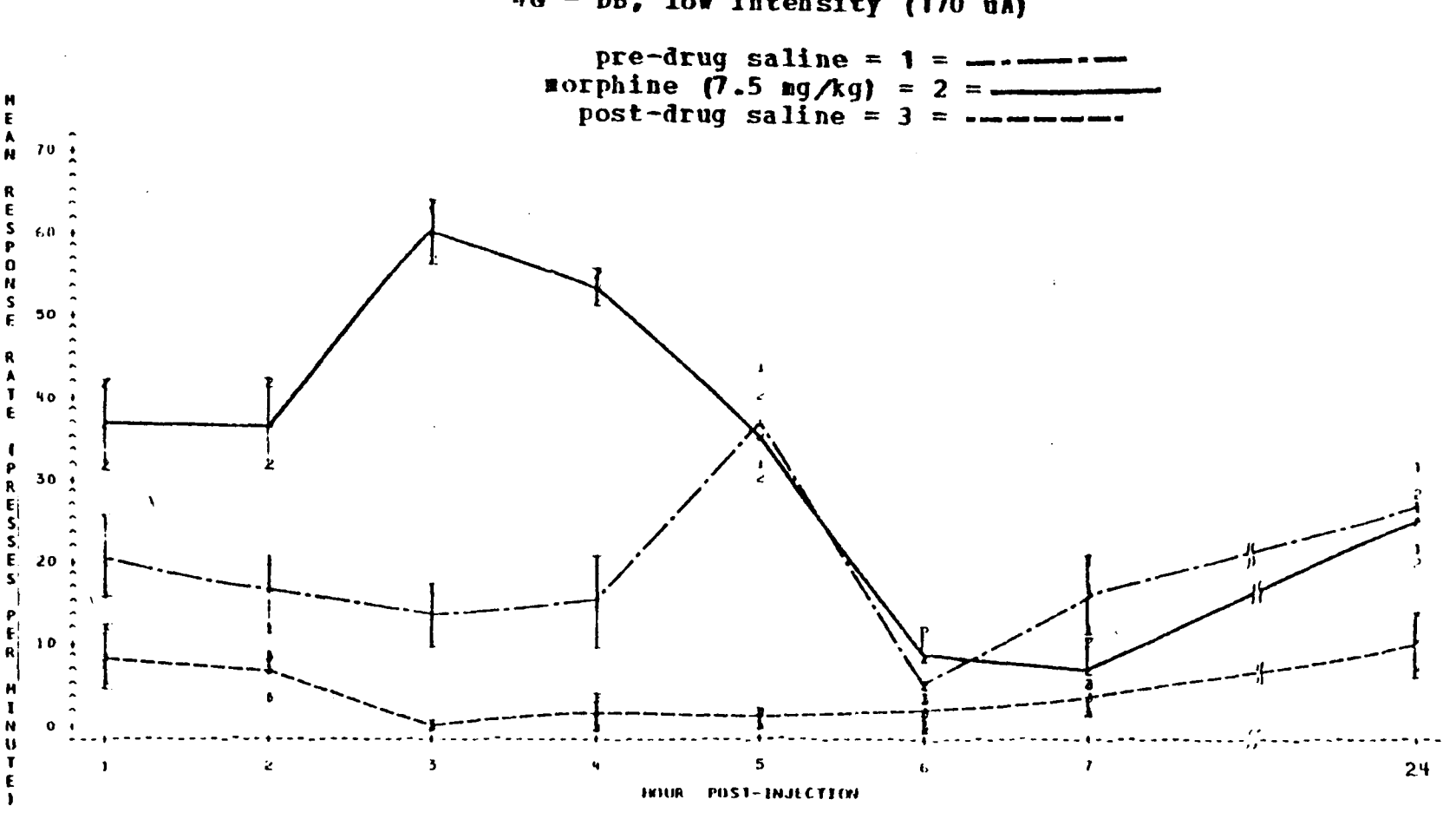

4G - DB, low intensity (170 uA)
pre-drug saline = 1 =
morphine (7.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 25

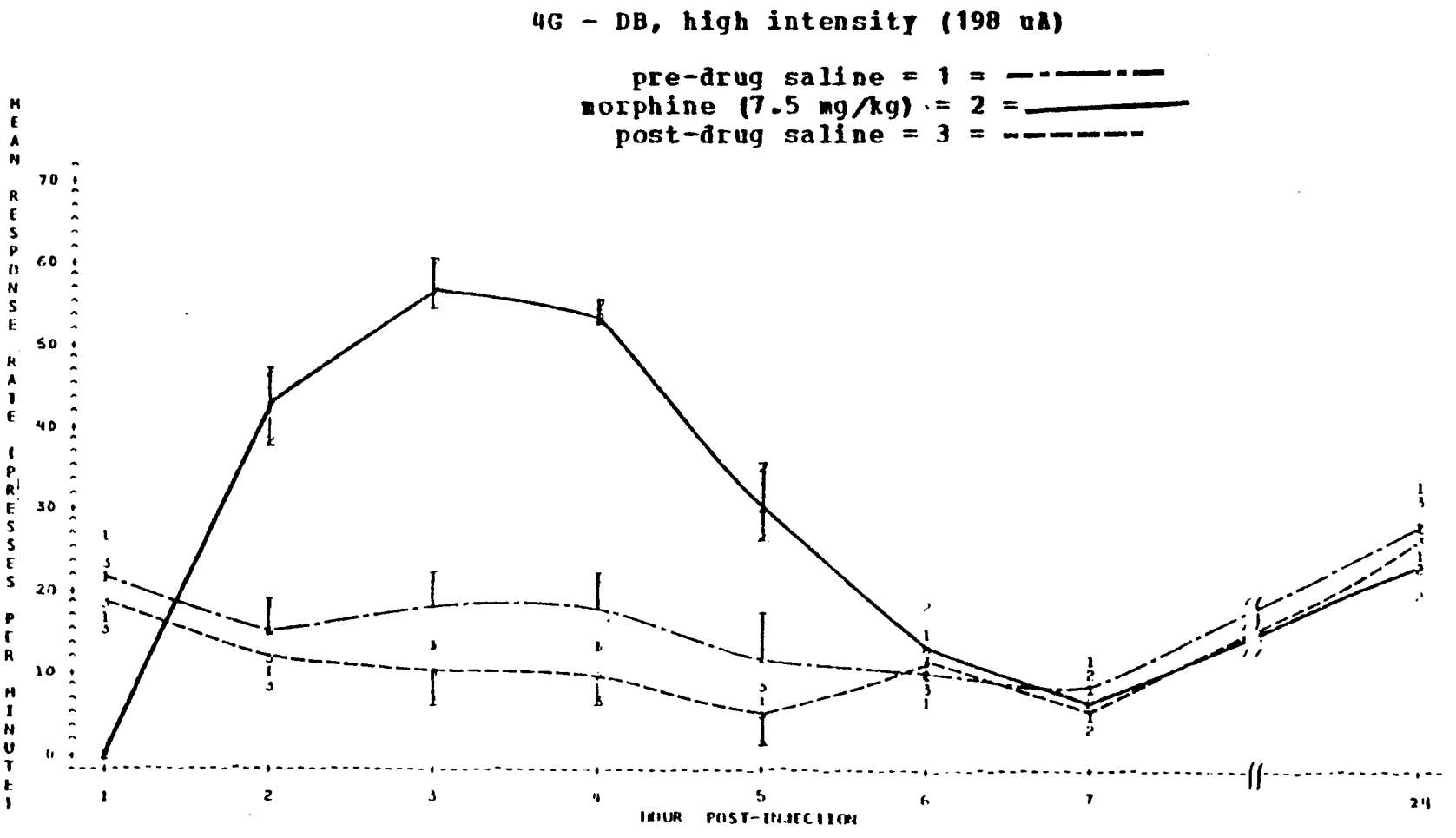

4G - DB, high intensity (198 uA)
pre-drug saline = 1 =
morphine (7.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
0
10
20
30
40
50
60
70
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 26

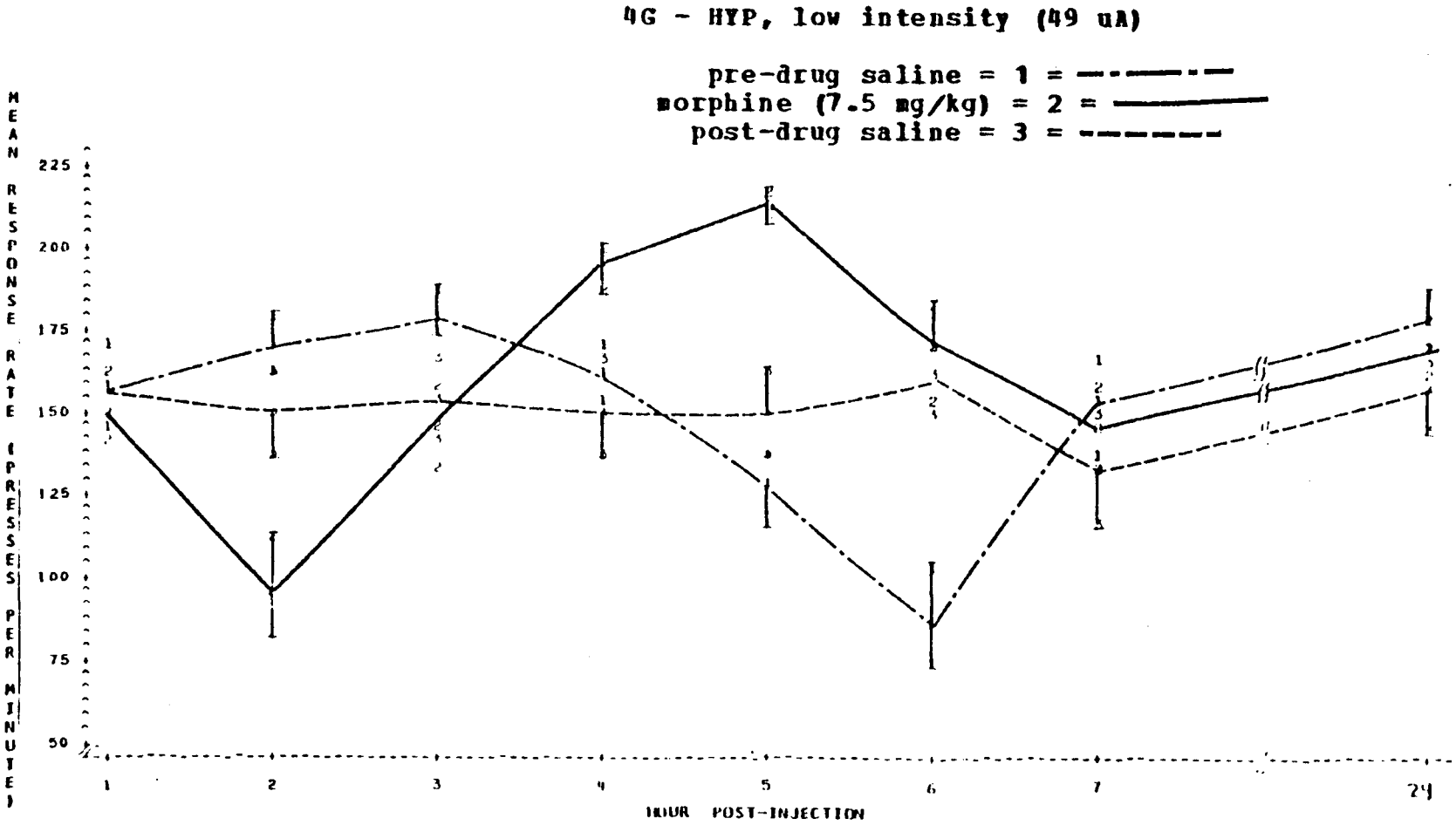

4G - HYP, low intensity (49 uA)
pre-drug saline = 1 =
morphine (7.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
225
200
175
150
125
100
75
50
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 27

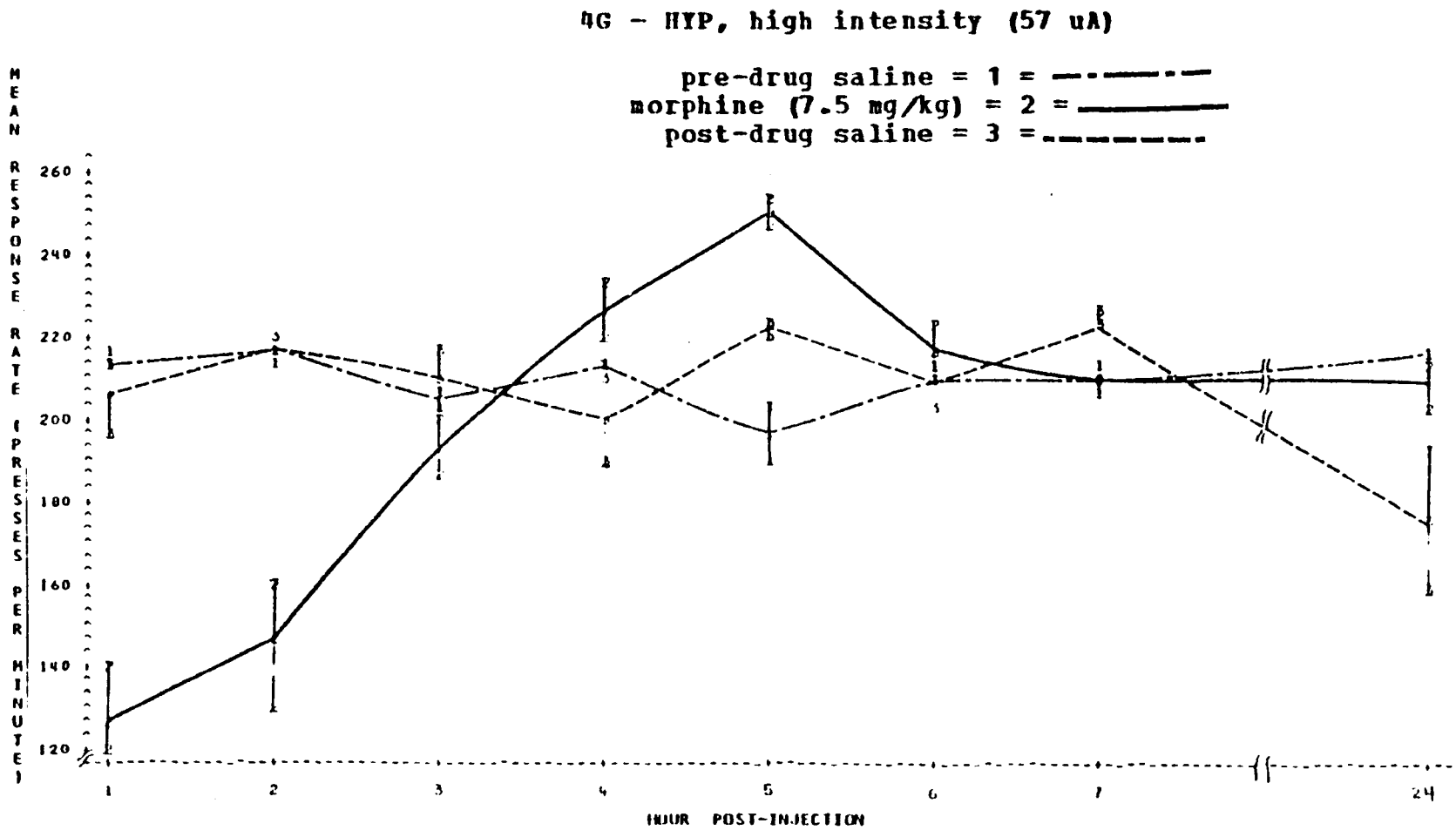

4G - HYP, high intensity (57 uA)
pre-drug saline = 1 =
morphine (7.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
260
240
220
200
180
160
140
120
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 28

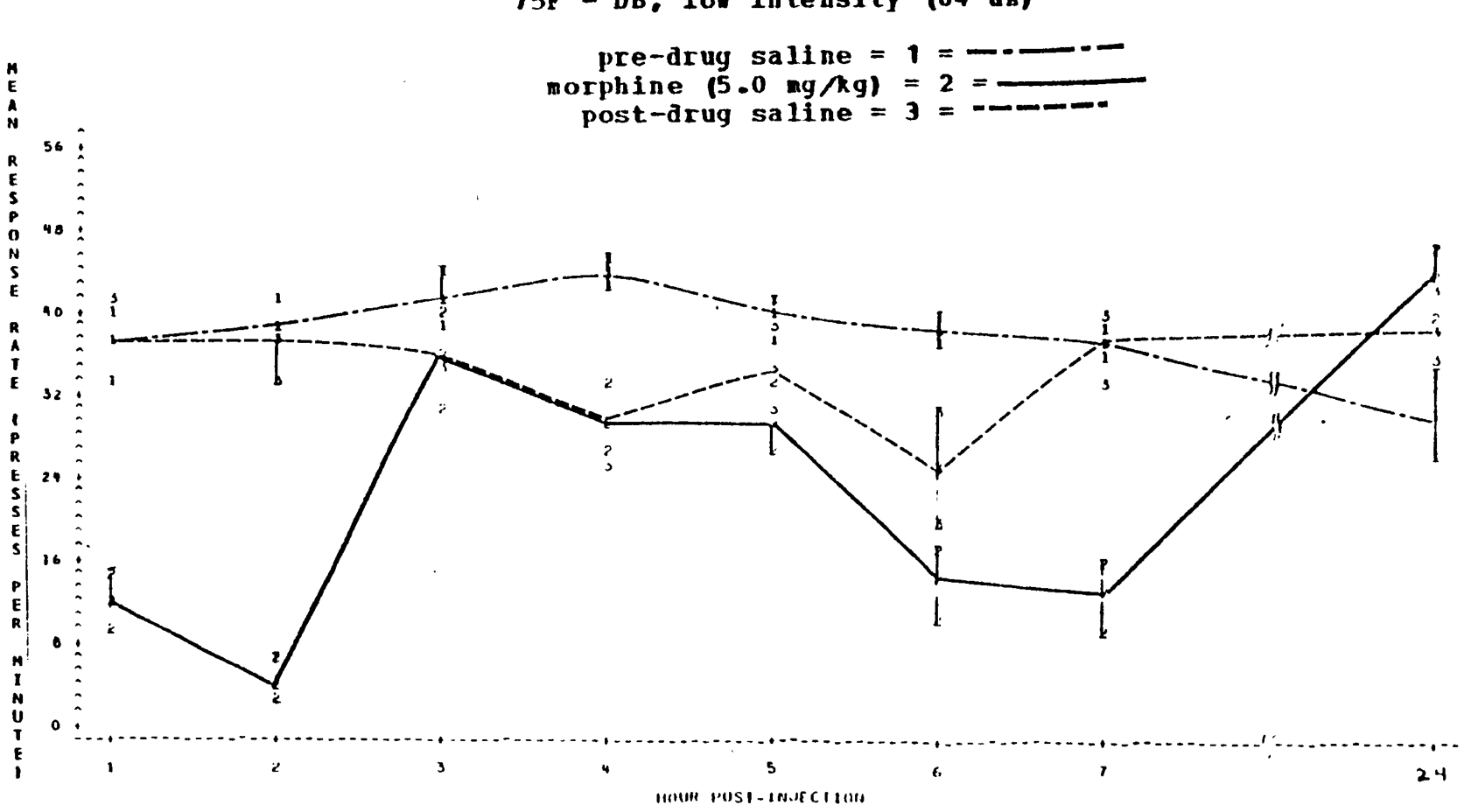

75F - DB, low intensity (64 uA)
pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
56
48
40
32
24
16
8
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 29

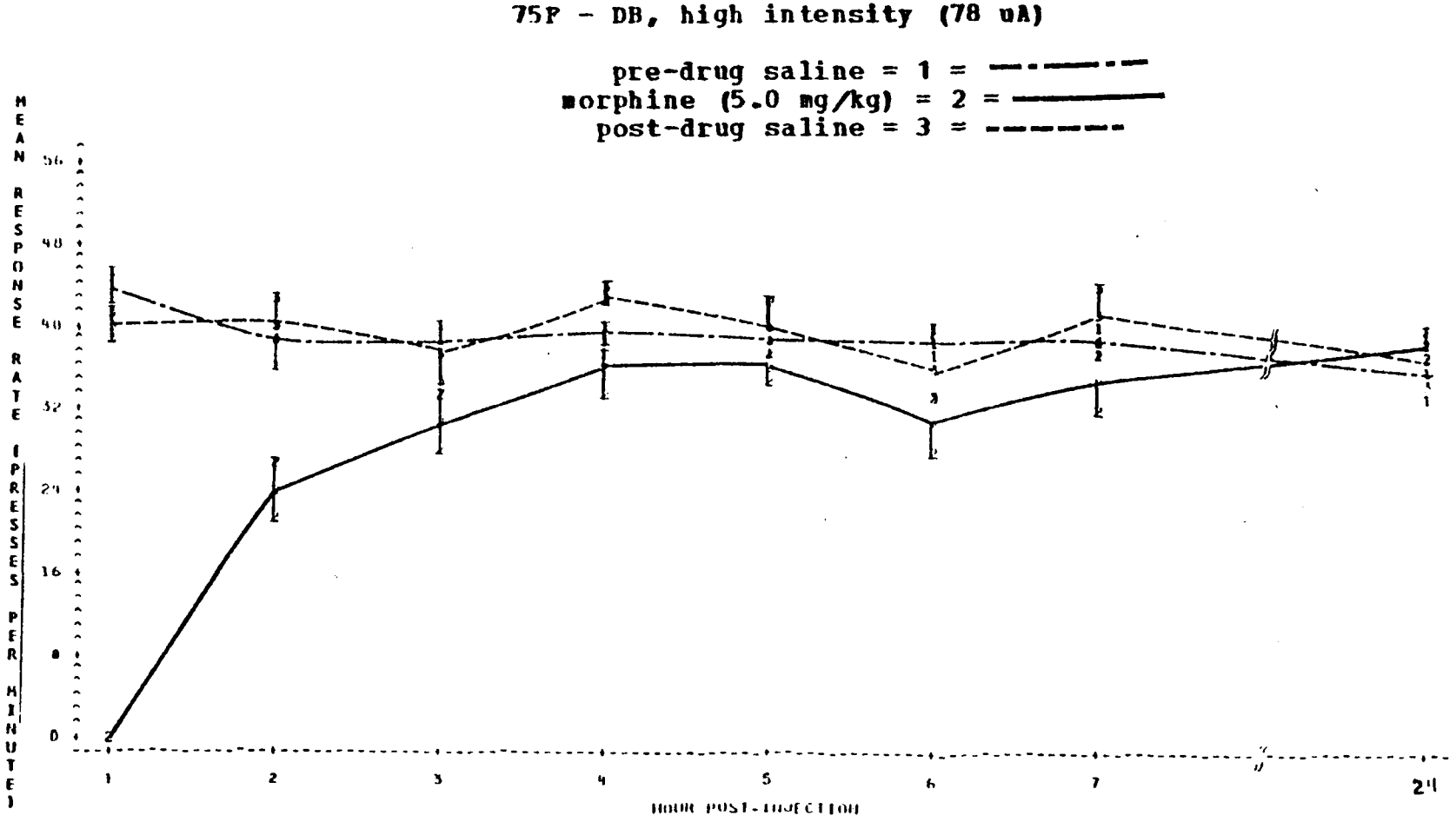

75P - DB, high intensity (78 uA)
pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
56
48
40
32
24
16
8
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 30

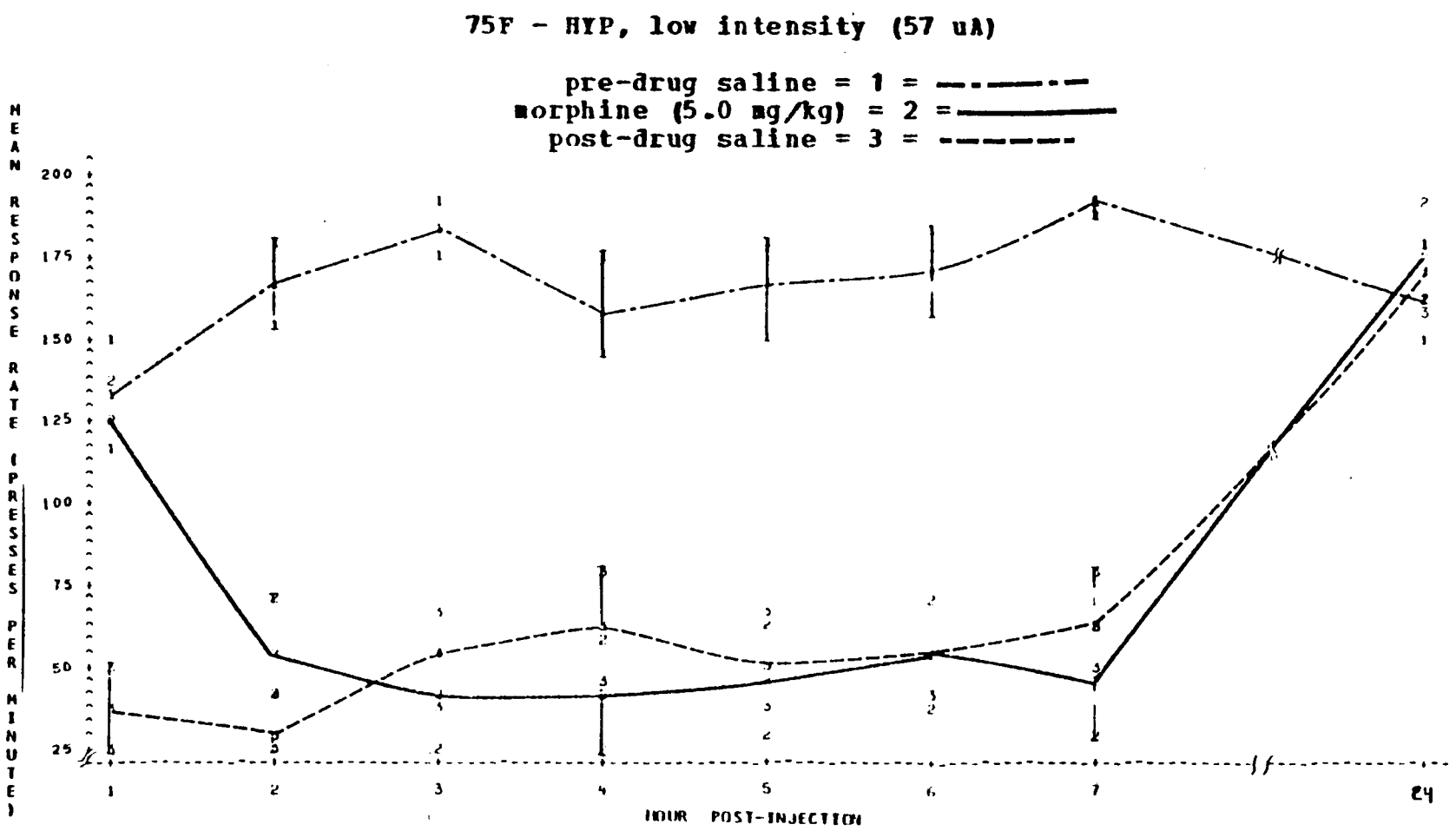

75F - HYP, low intensity (57 uA)
pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
200
175
150
125
100
75
50
25
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 31

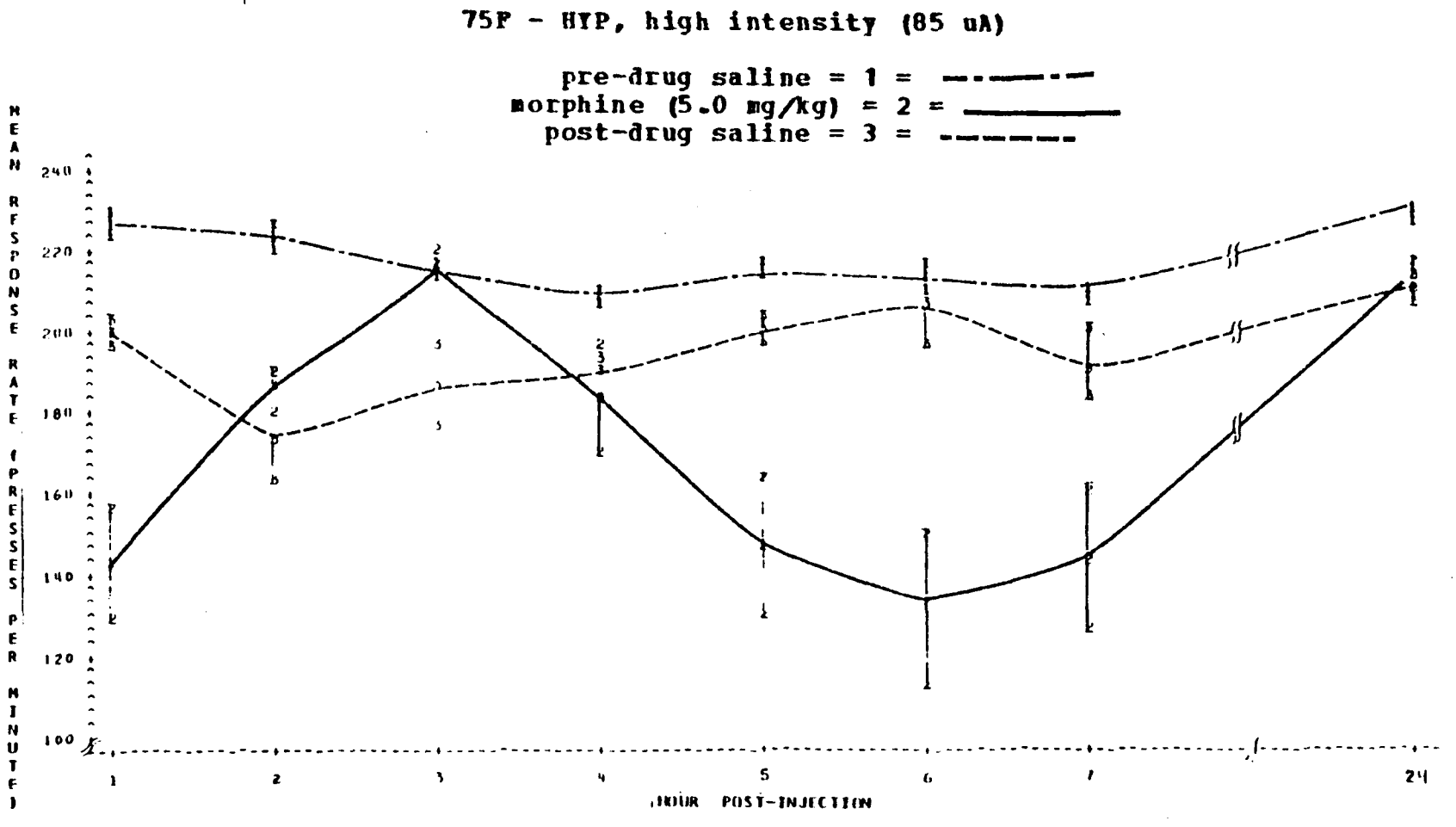

75P - HYP, high intensity (85 uA)
pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
240
220
200
180
160
140
120
100
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 32

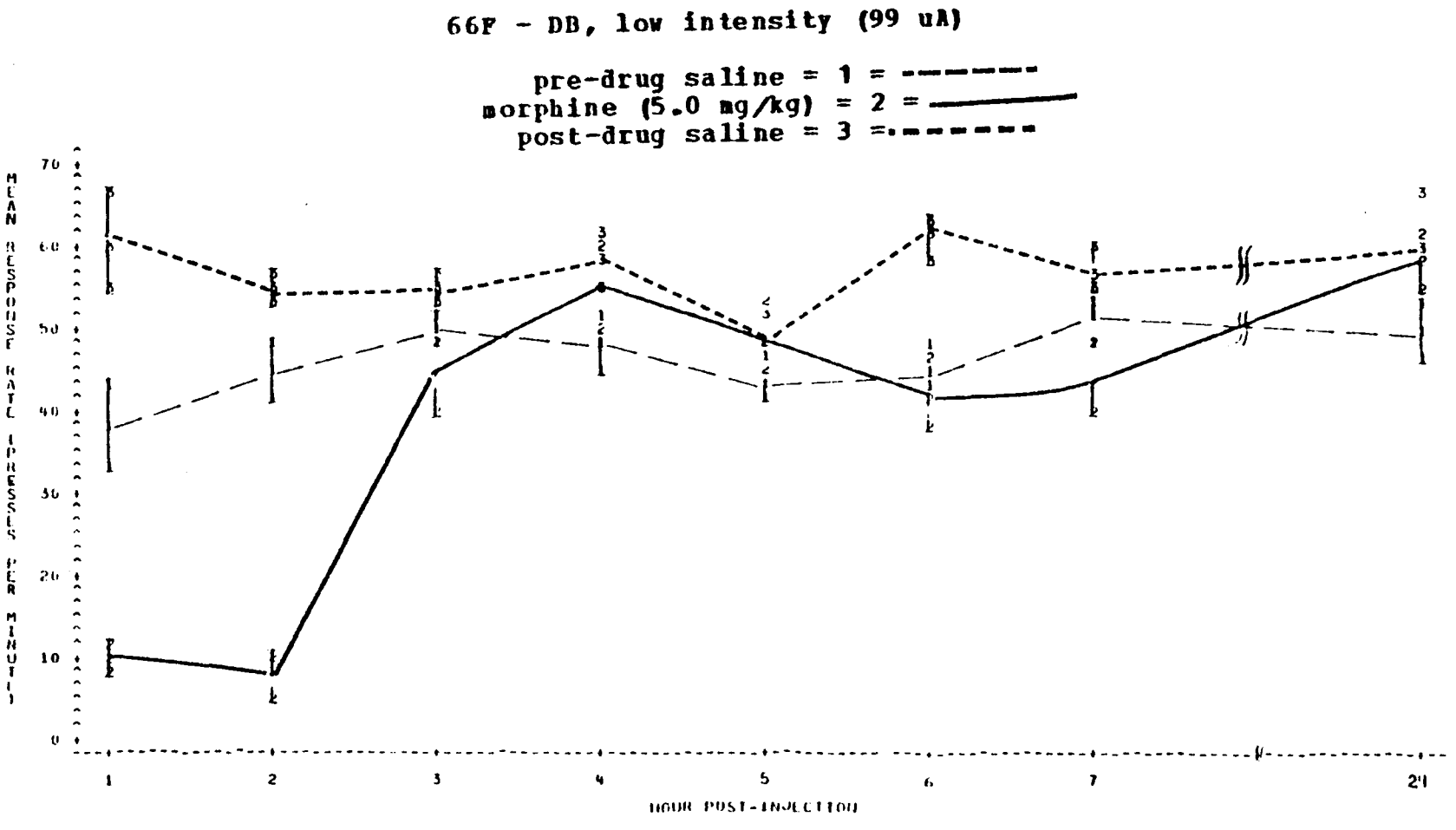

66F - DB, low intensity (99 uA)
pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
0
10
20
30
40
50
60
70
1
2
3
4
5
6
7
21
HOUR POST-INJECTION

Figure 33

66F - DB, high intensity (113 uA)

pre-drug saline = 1 = - - - - - -
morphine (5.0 mg/kg) = 2 = ——————
post-drug saline = 3 = - - - - - -

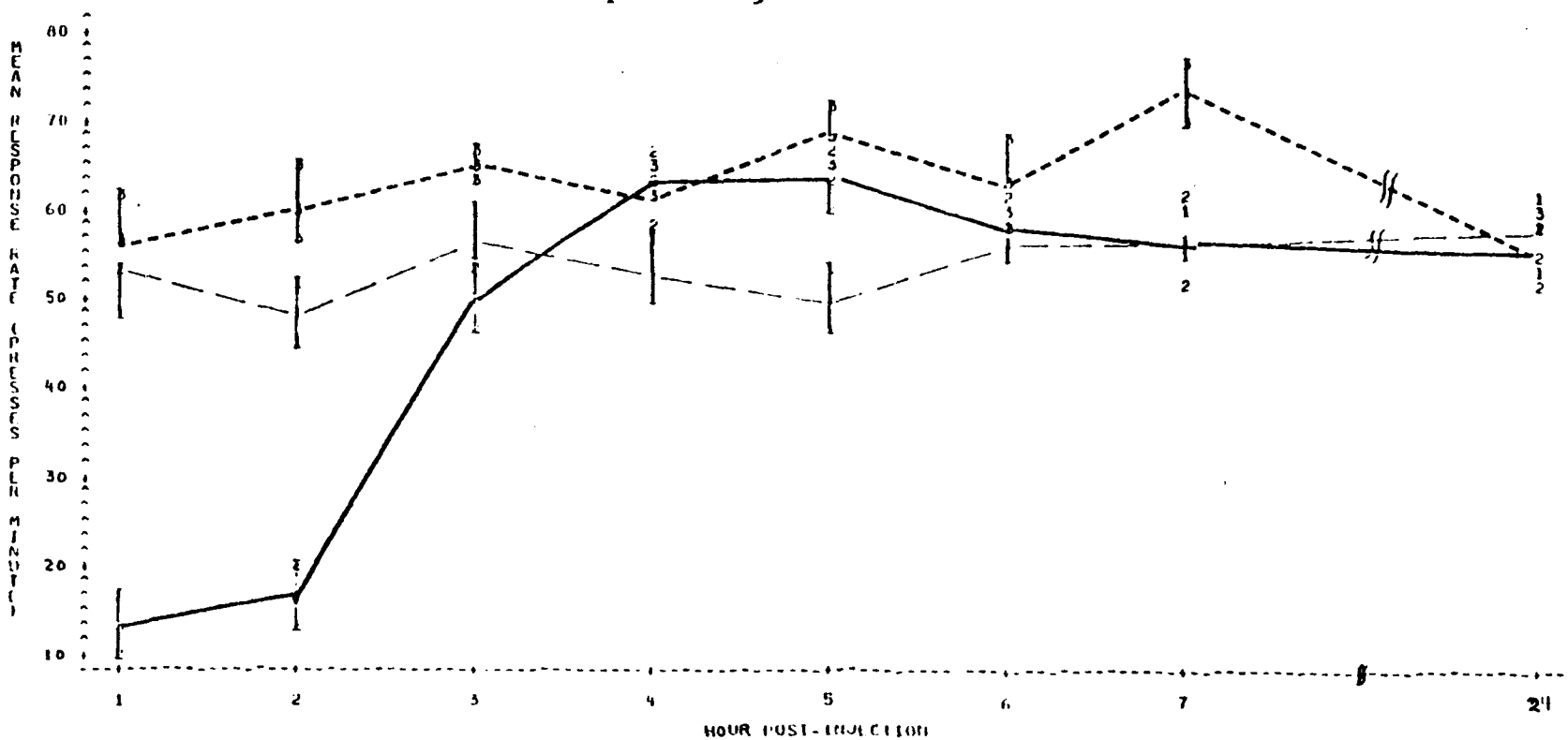


Figure 34

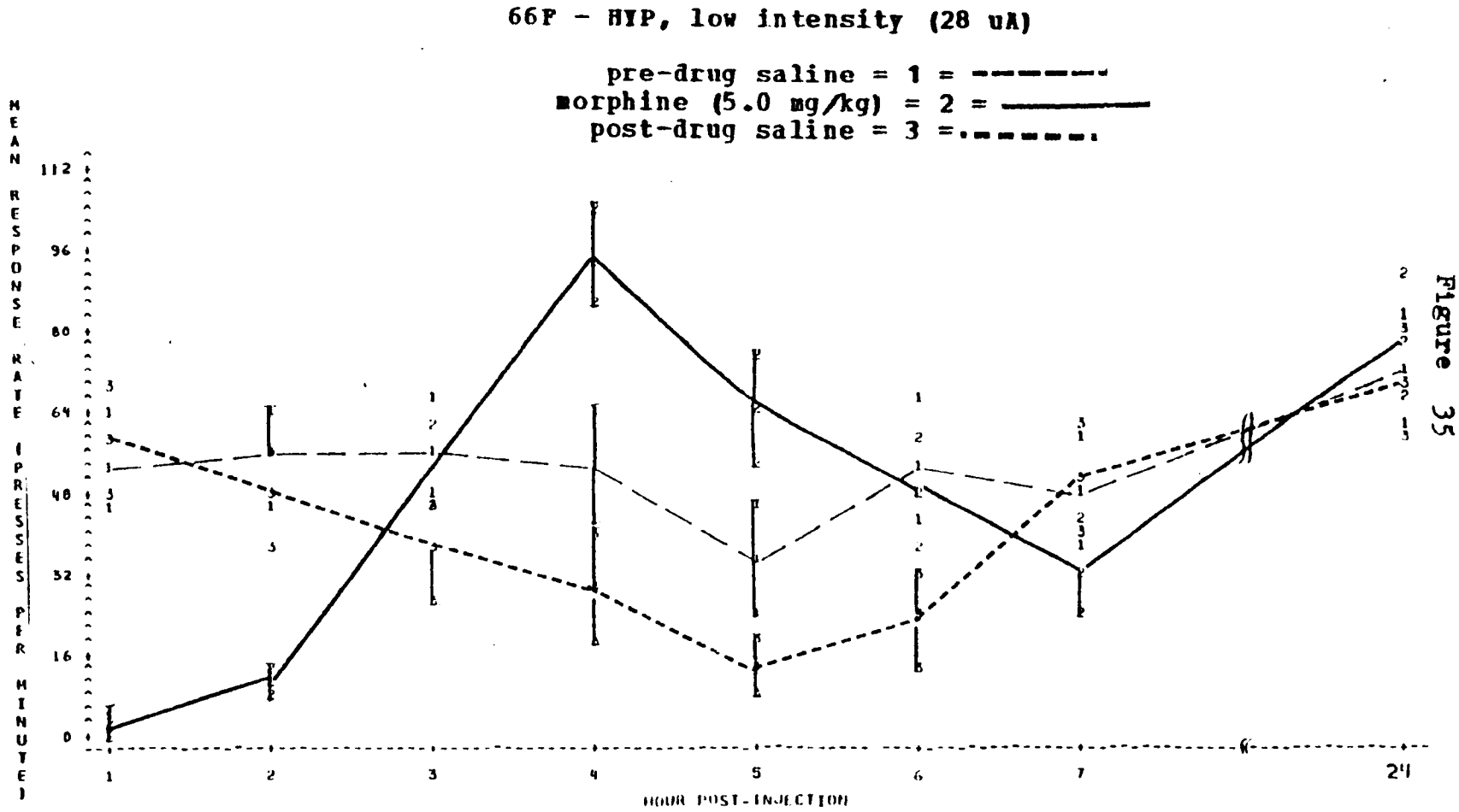

66F - HYP, low intensity (28 uA)
pre-drug saline = 1 = ------
morphine (5.0 mg/kg) = 2 = ——————
post-drug saline = 3 =.-.-.-.
MEAN RESPONSE RATE (PRESSES PER MINUTE)
112
96
80
64
48
32
16
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 35

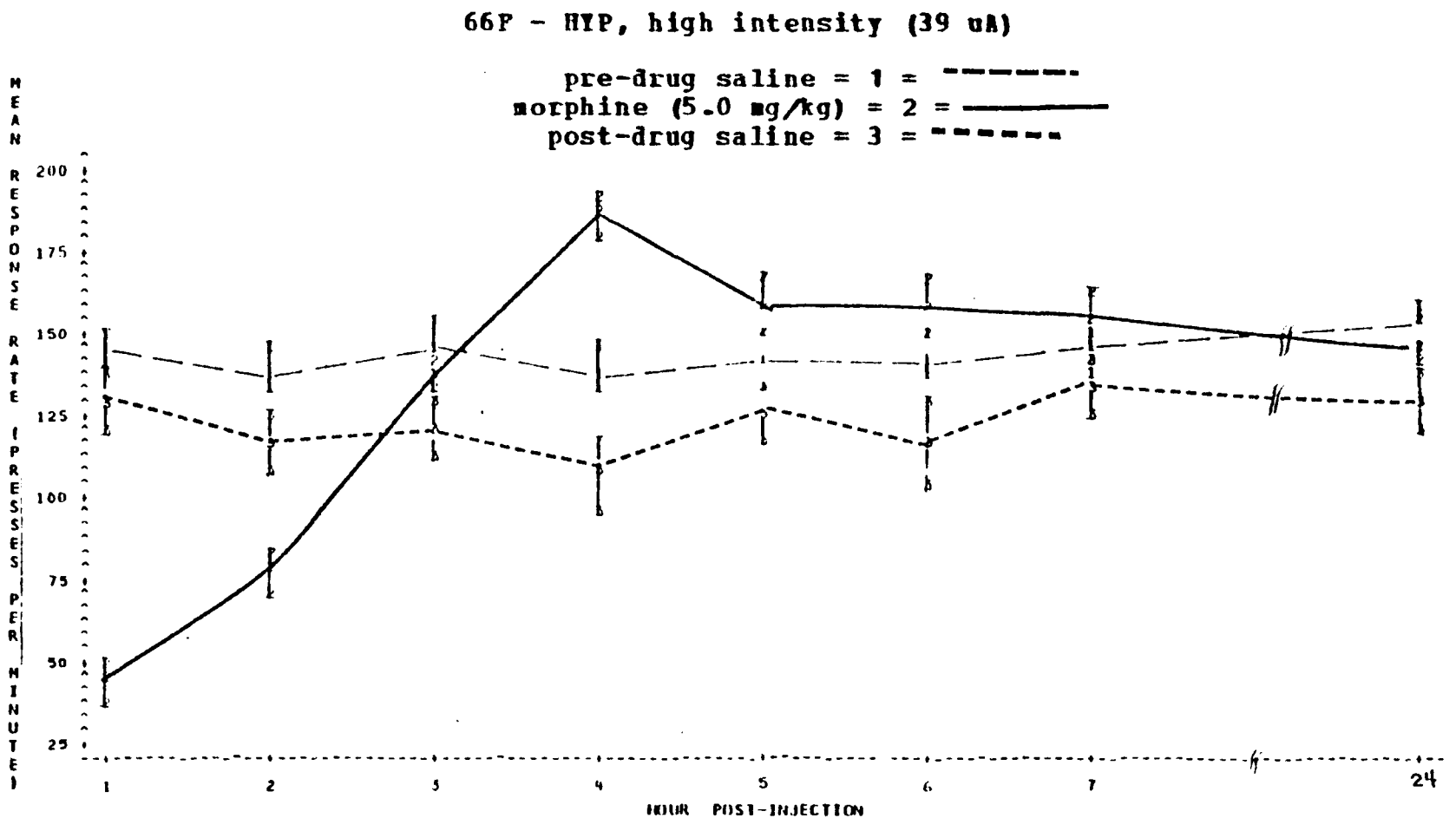

66P - HYP, high intensity (39 uA)
pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
200
175
150
125
100
75
50
25
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 36

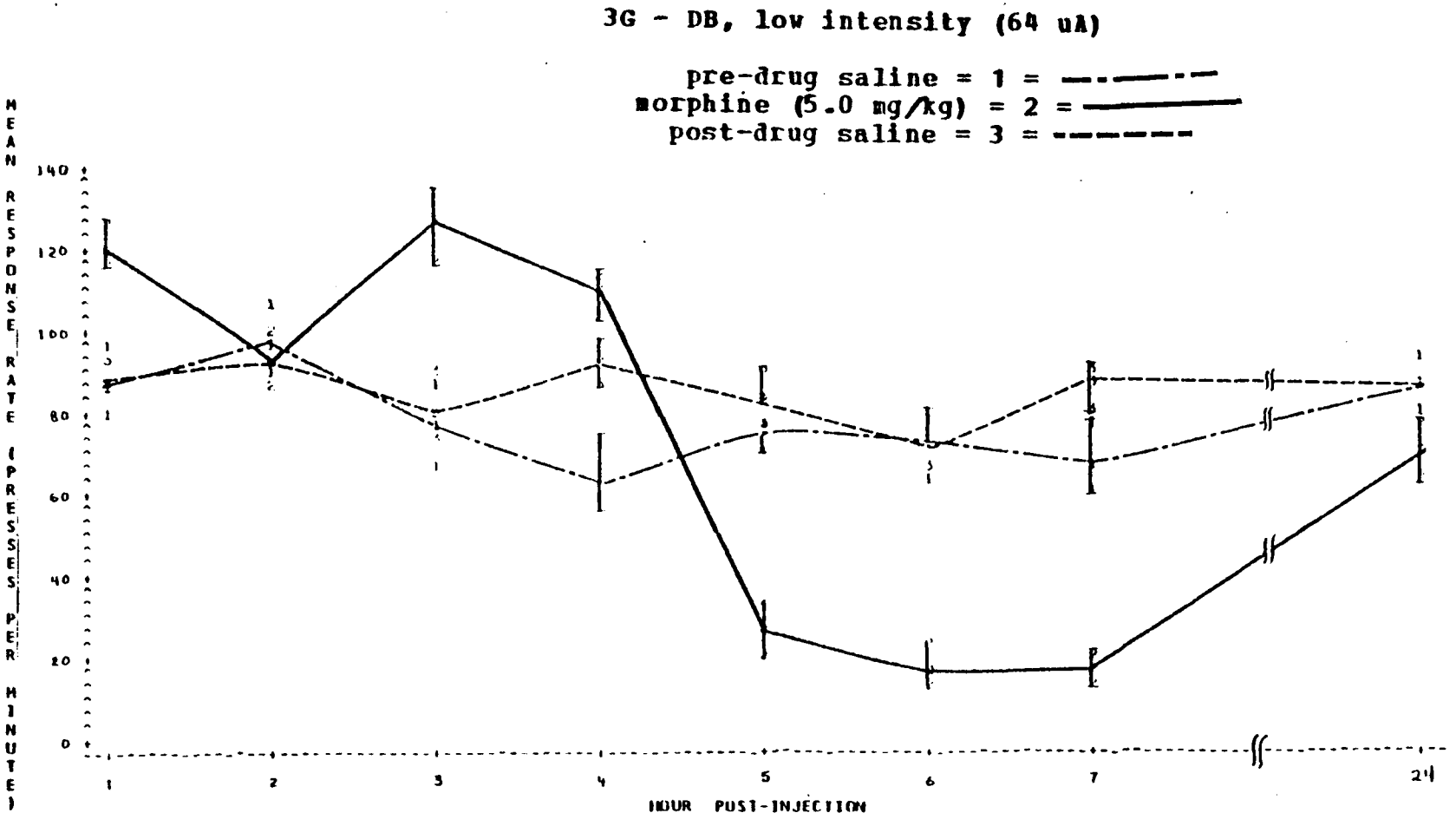

3G - DB, low intensity (64 uA)
pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
140
120
100
80
60
40
20
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 37

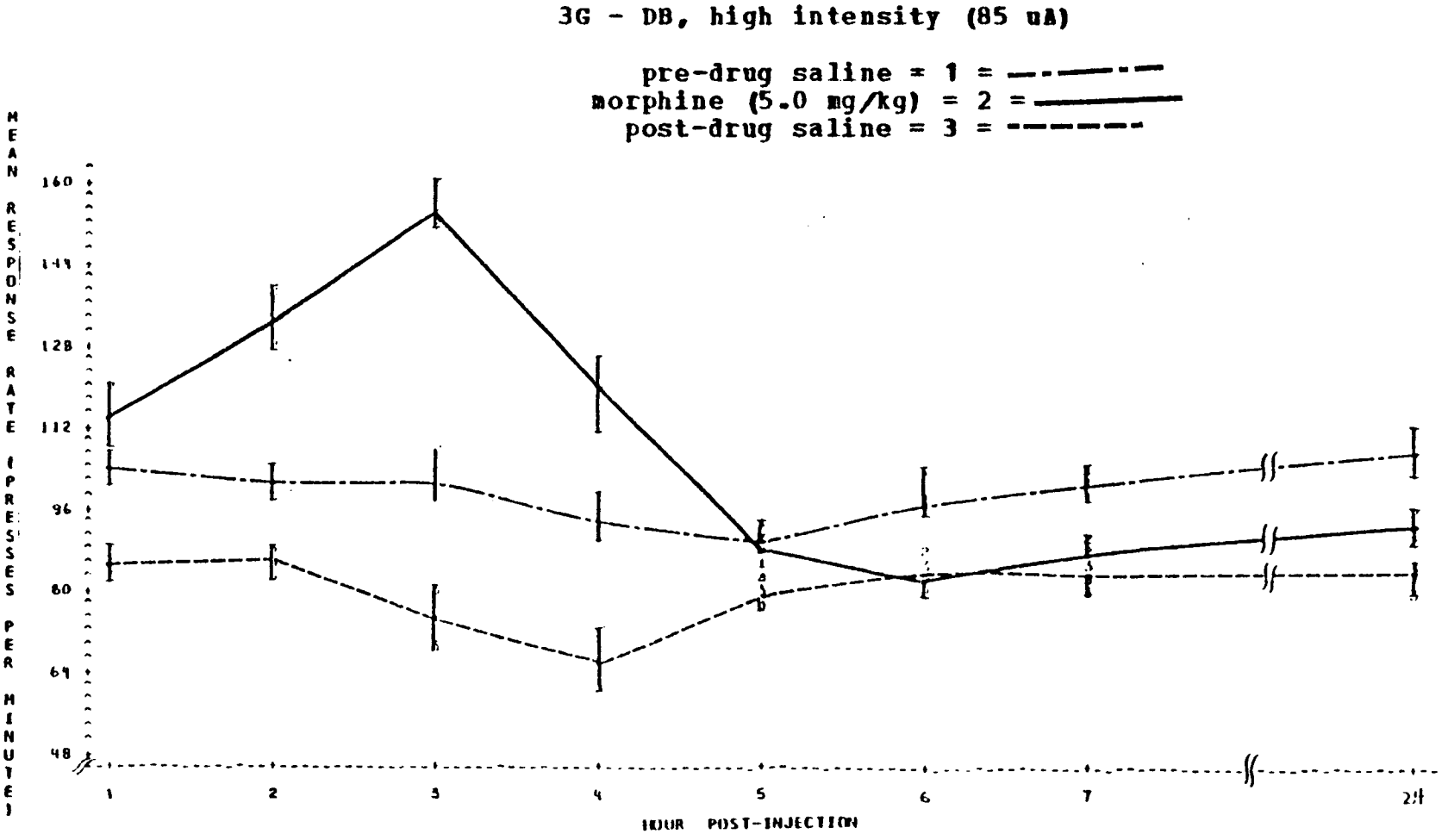

3G - DB, high intensity (85 uA)
pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
160
144
128
112
96
80
64
48
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 38

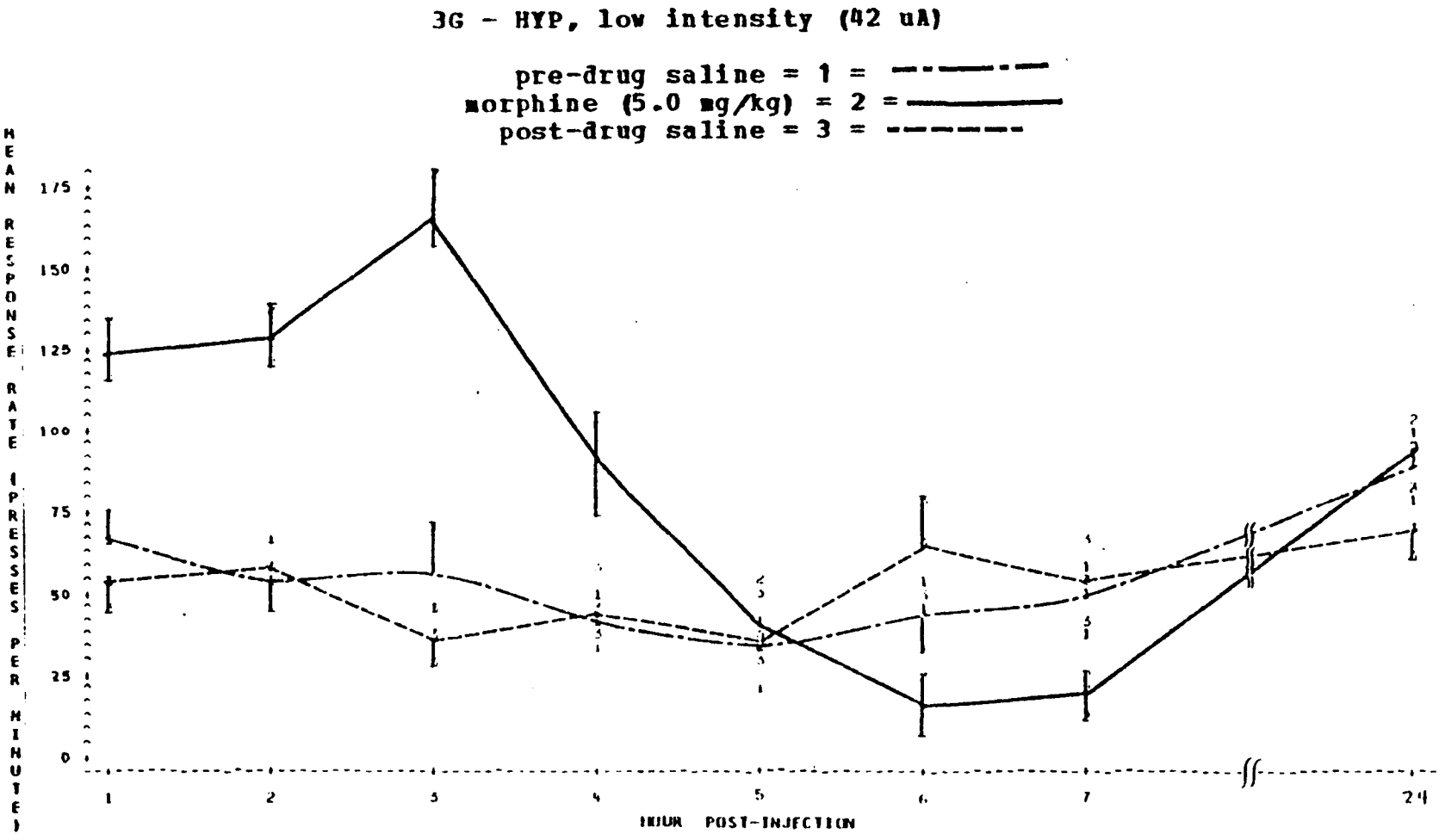

3G - HYP, low intensity (42 uA)
pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
175
150
125
100
75
50
25
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 39

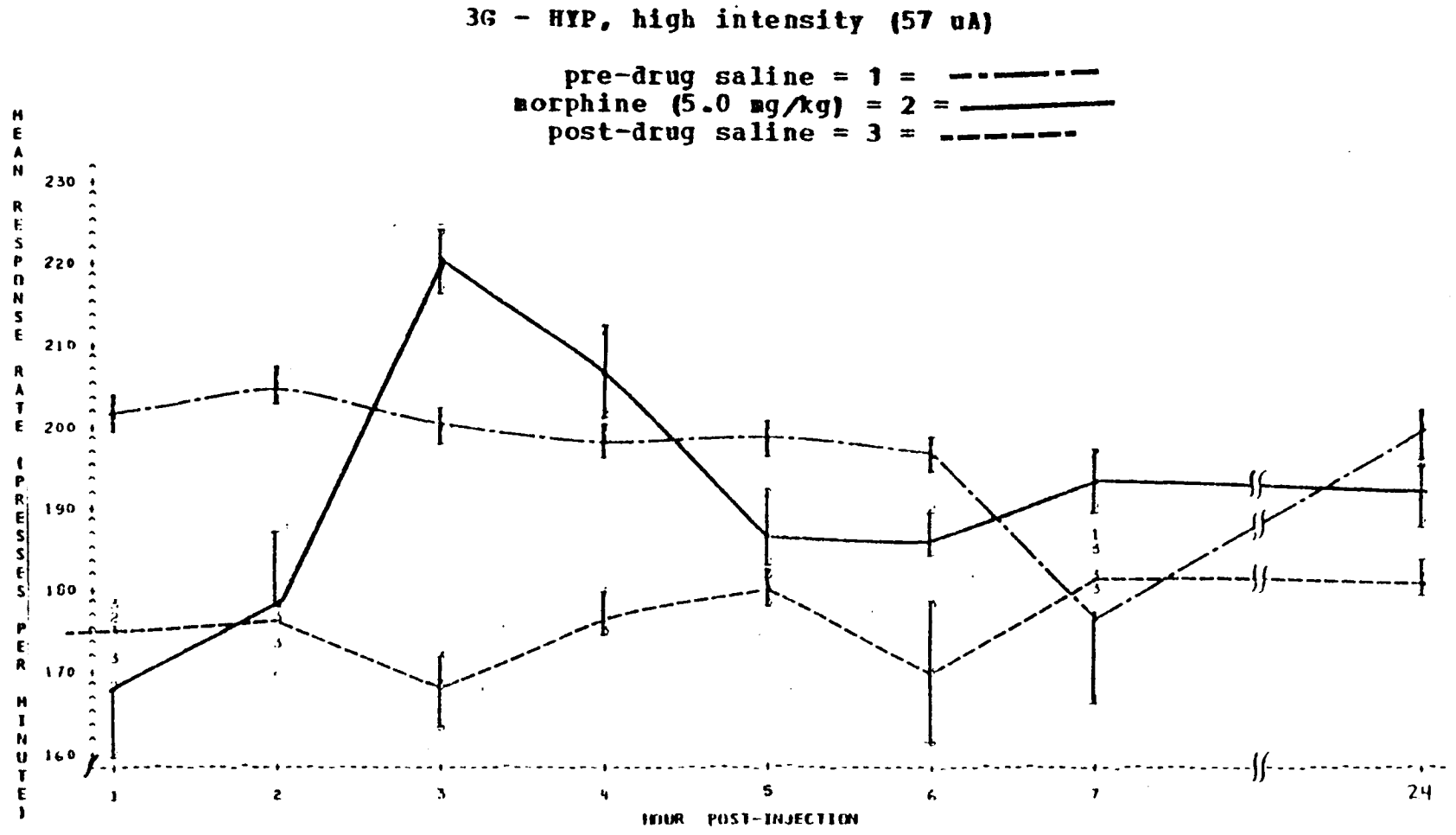

3G - HYP, high intensity (57 uA)
pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
230
220
210
200
190
180
170
160
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 40

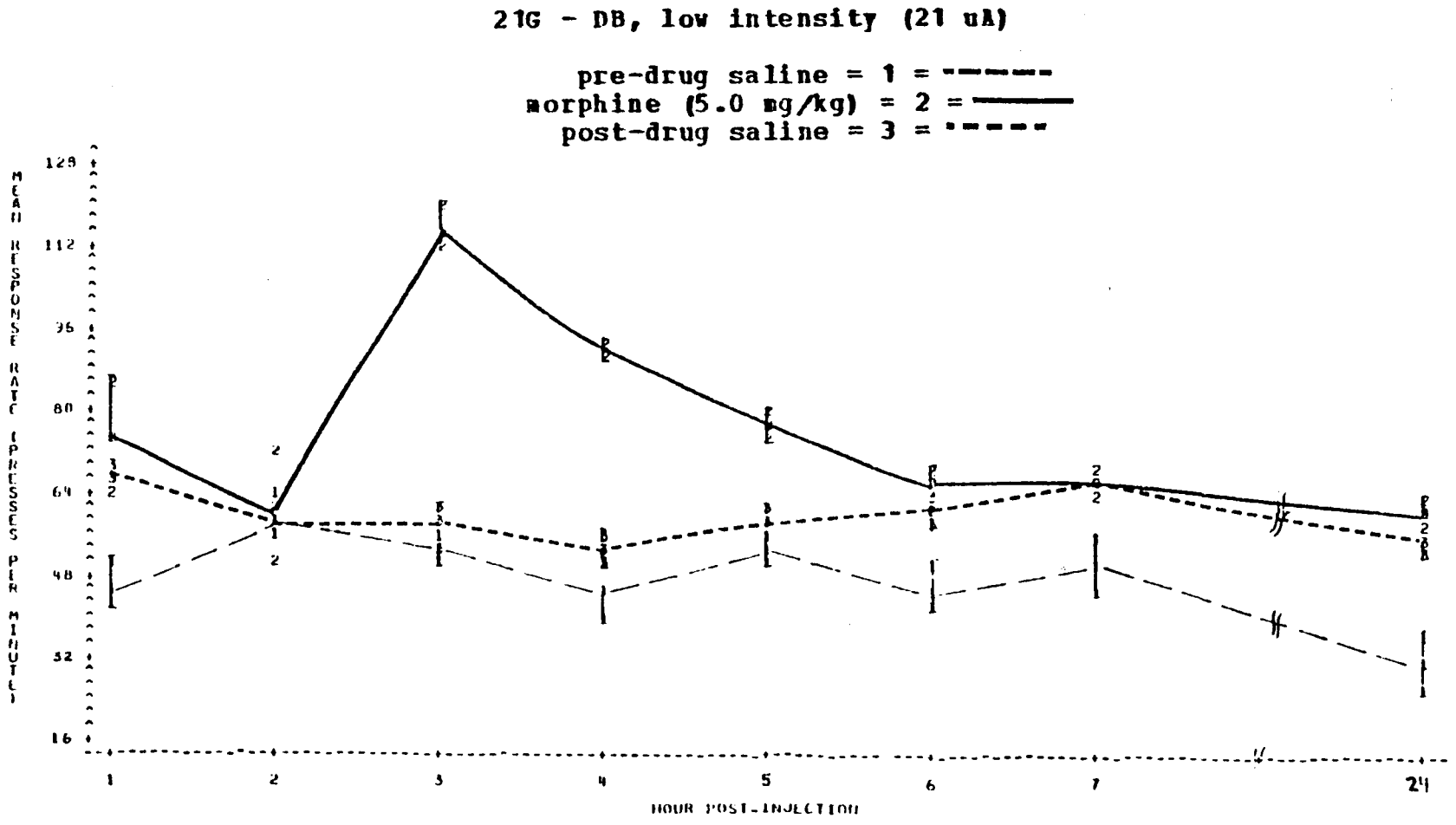

21G - DB, low intensity (21 uA)
pre-drug saline = 1 = ----
morphine (5.0 mg/kg) = 2 = ——
post-drug saline = 3 = •----
MEAN RESPONSE RATE (PRESSES PER MINUTE)
128
112
96
80
64
48
32
16
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 41

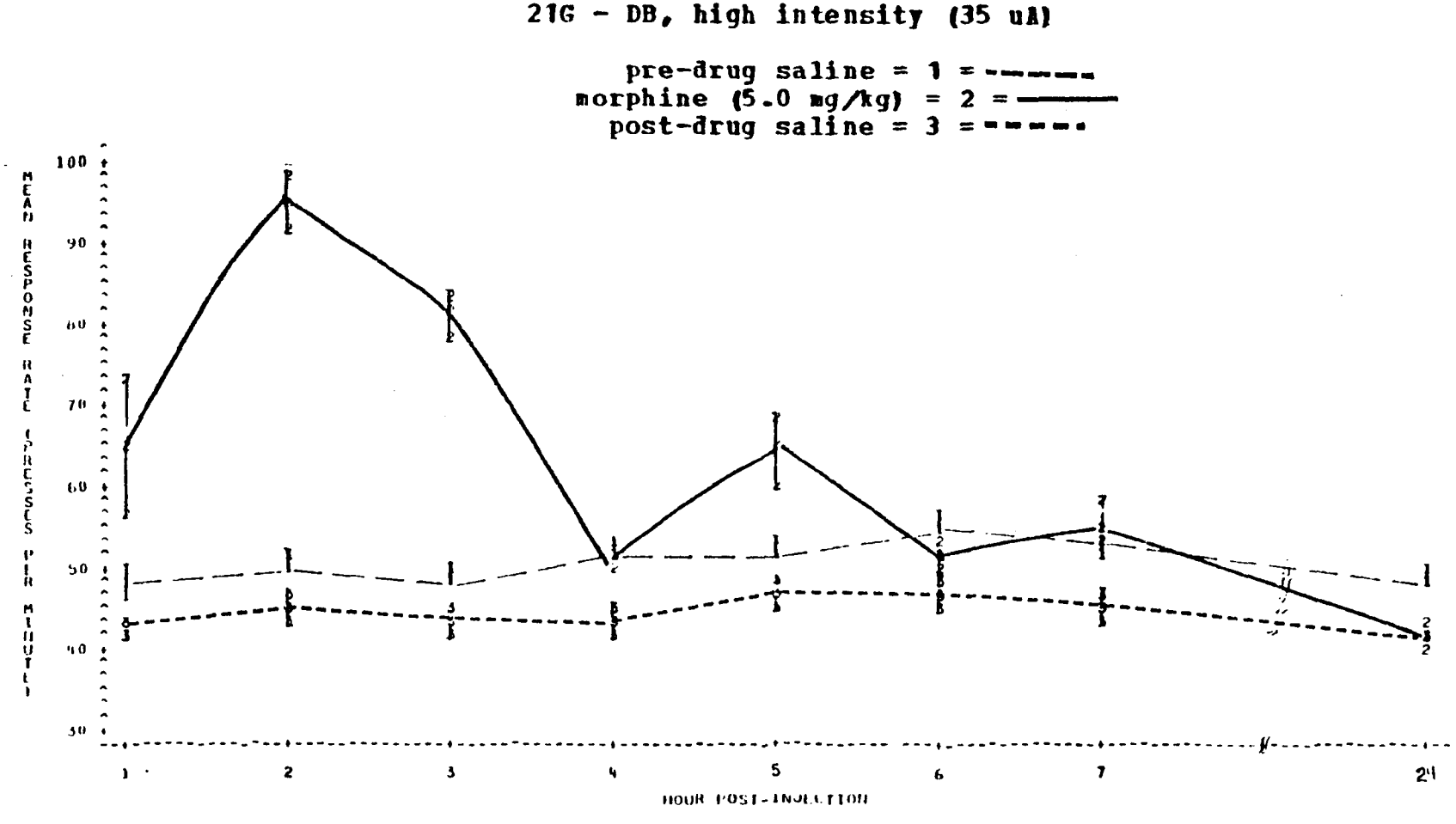

21G - DB, high intensity (35 uA)
pre-drug saline = 1 = - - - - -
morphine (5.0 mg/kg) = 2 = ———
post-drug saline = 3 = - - - - -
MEAN RESPONSE RATE (PRESSES PER MINUTE)
100
90
80
70
60
50
40
30
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 42

21G - HYP, low intensity (49 uA)

pre-drug saline = 1 = - - - - -
morphine (5.0 mg/kg) = 2 = ———
post-drug saline = 3 = - - - - -

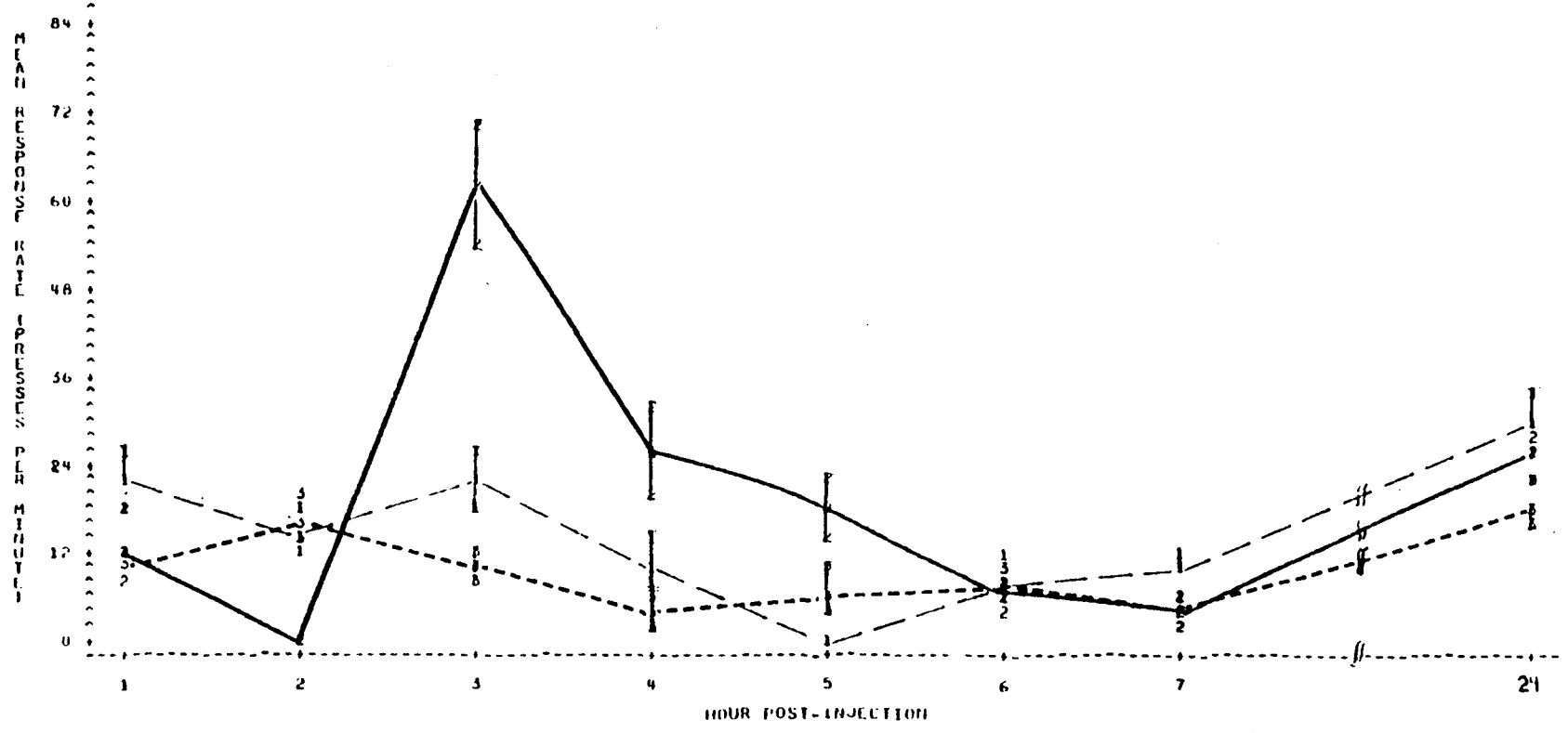


Figure 43

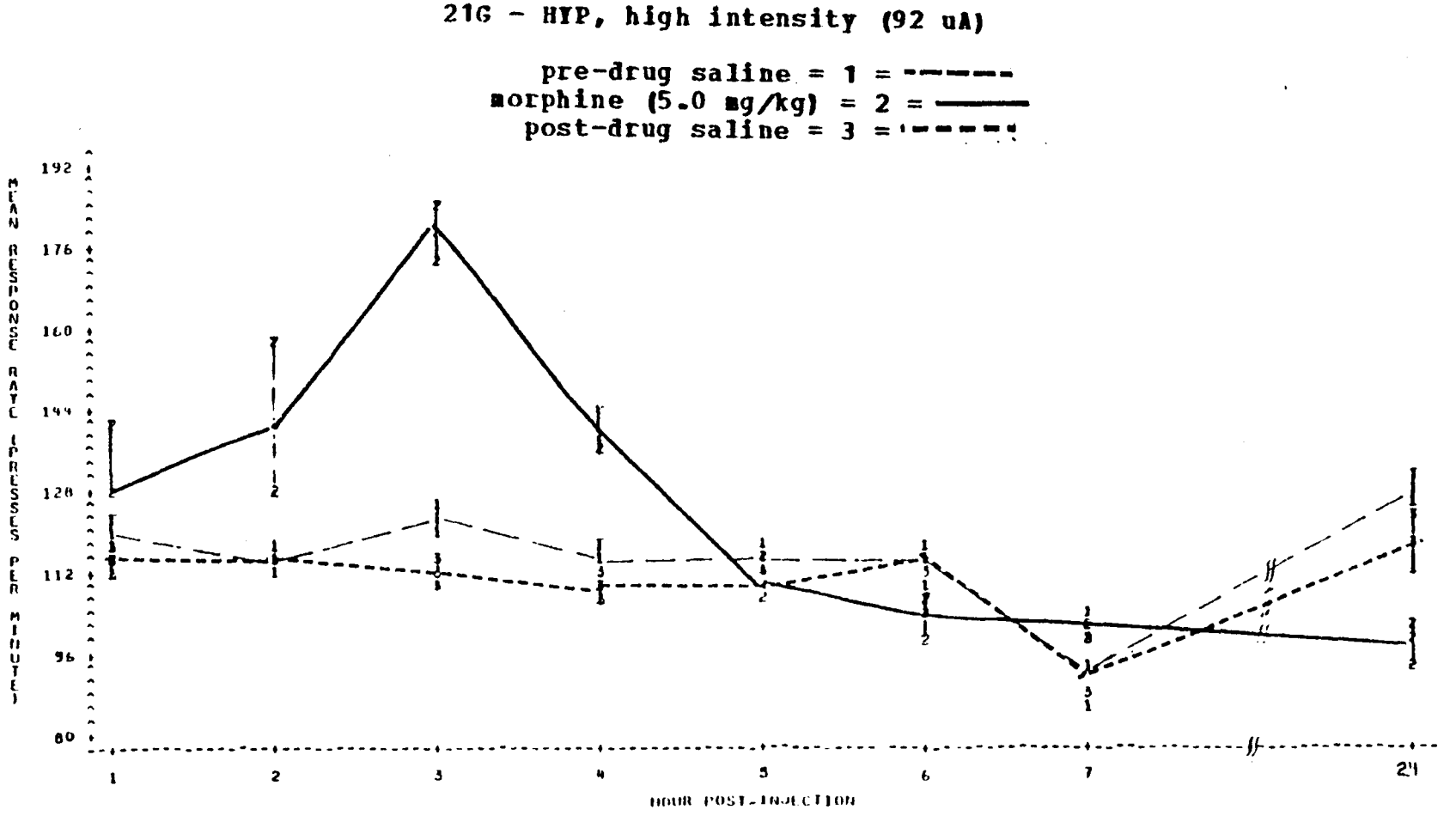
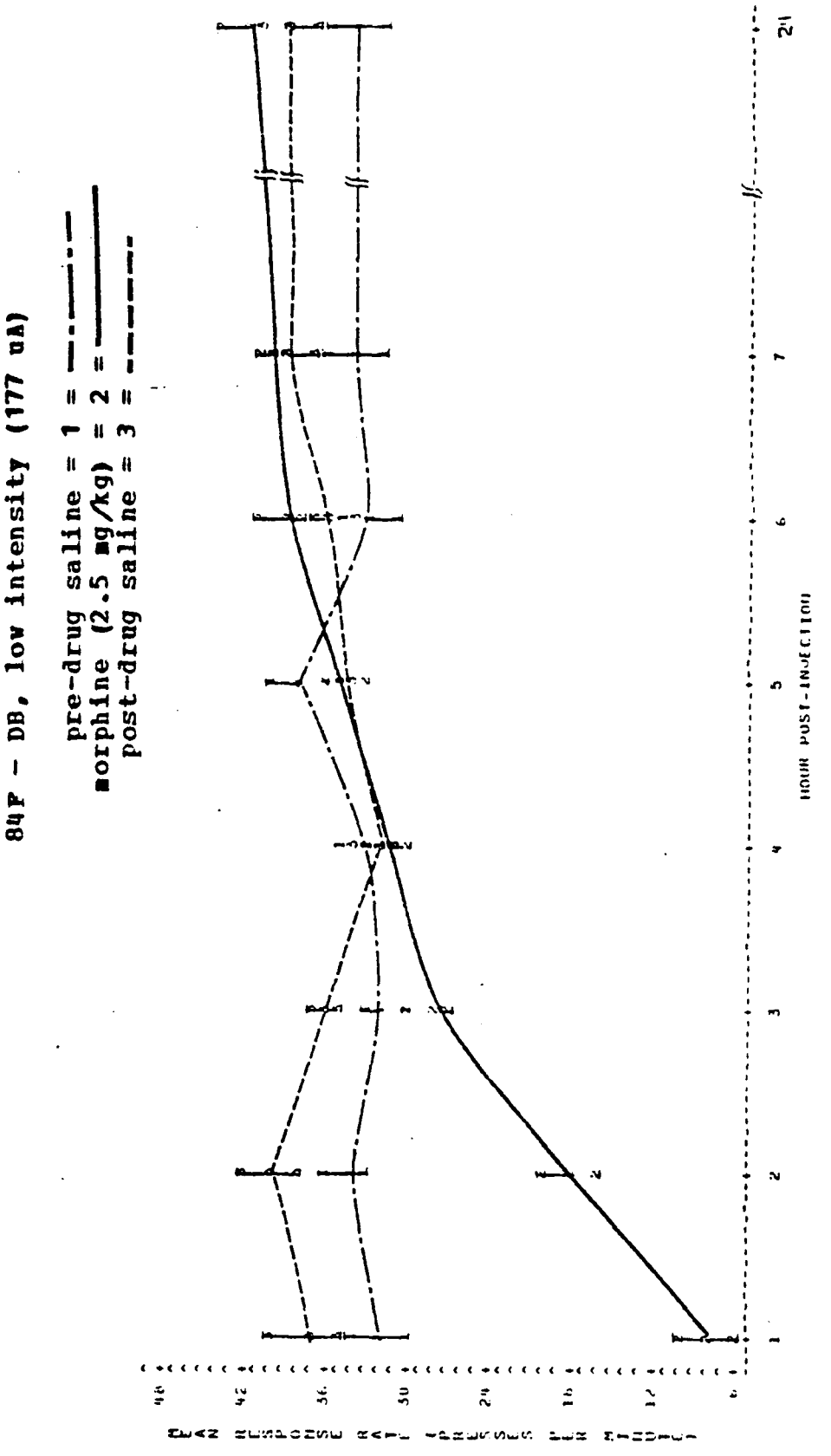

216 - HYP, high intensity (92 uA)
pre-drug saline = 1 = - - - -
morphine (5.0 mg/kg) = 2 = ———
post-drug saline = 3 = - - - -
MEAN RESPONSE RATE (PRESSES PER MINUTE)
192
176
160
144
128
112
96
80
1
2
3
4
5
6
7
21
HOUR POST-INJECTION

Figure 44

Figure 45


84P - DB, low intensity (177 uA)
pre-drug saline = 1 = —·—·—
morphine (2.5 mg/kg) = 2 = ————
post-drug saline = 3 = - - - -
HOUR POST-INJECTION

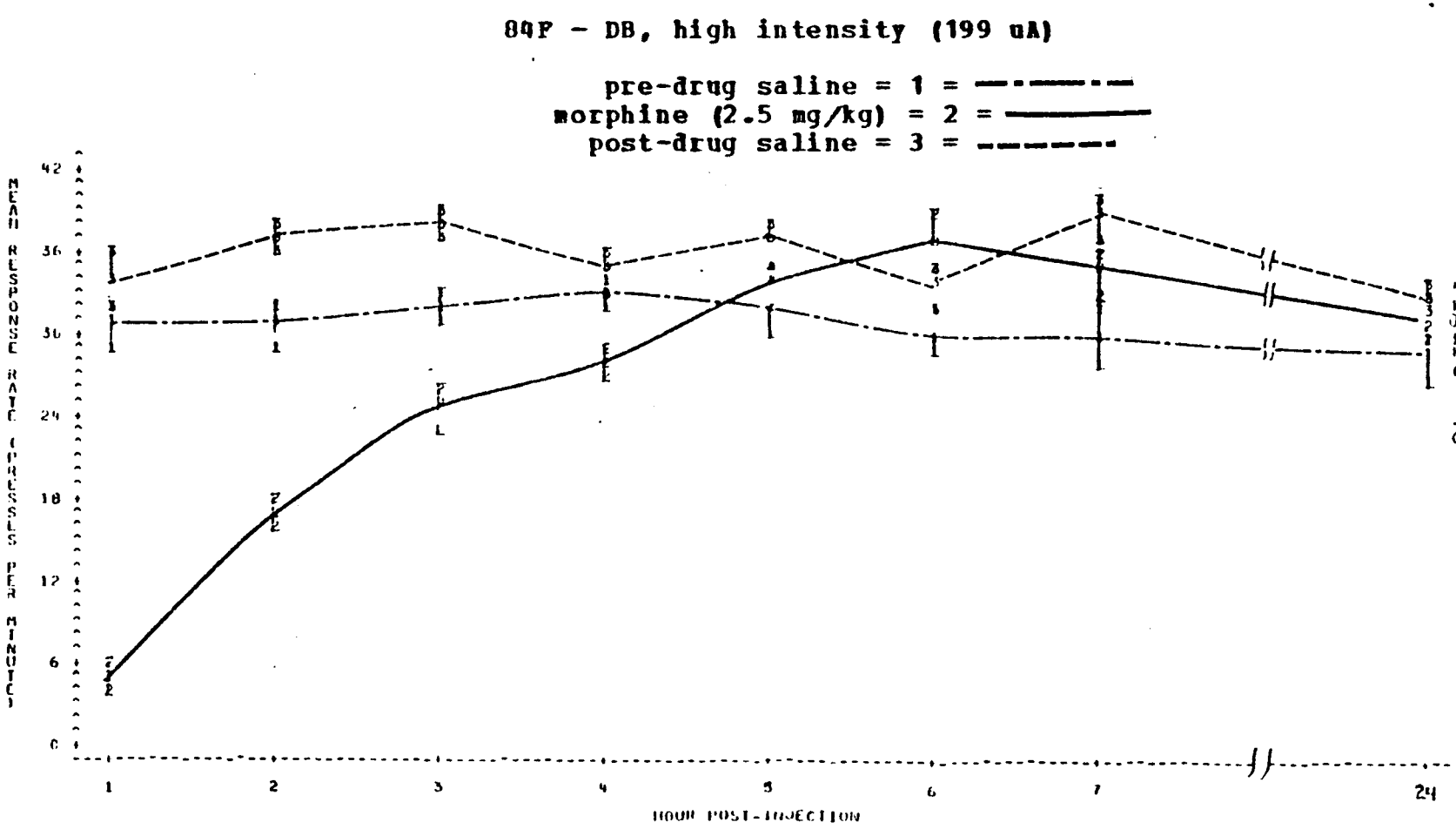

84P - DB, high intensity (199 uA)
pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
42
36
30
24
18
12
6
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 46

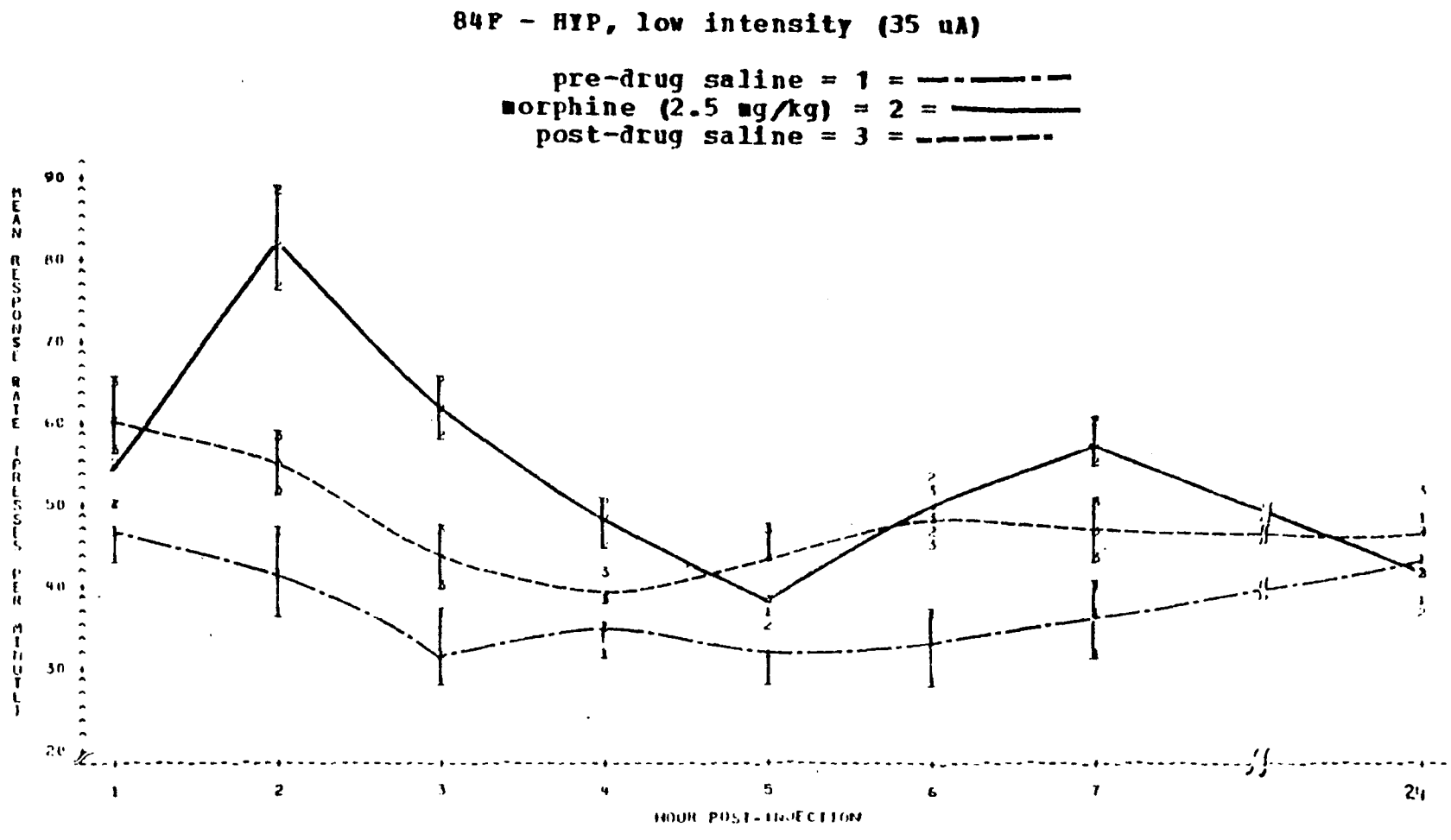

84P - HYP, low intensity (35 uA)
pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
90
80
70
60
50
40
30
20
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 47

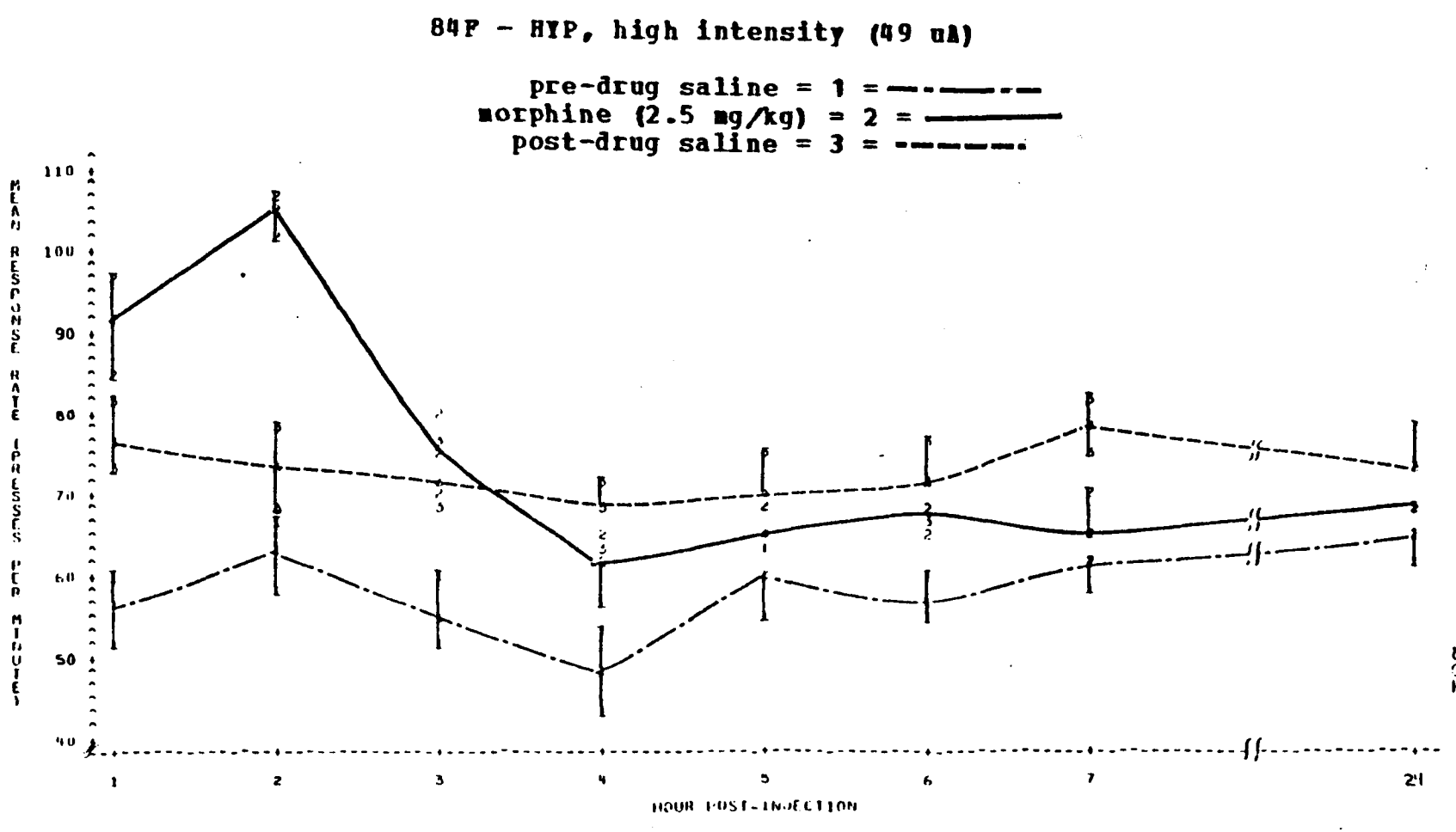

84P - HYP, high intensity (49 uA)
pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
110
100
90
80
70
60
50
40
1
2
3
4
5
6
7
21
HOUR POST-INJECTION

Figure 48

86P - DB, low intensity (18 uA)

pre-drug saline = 1 = —·——·—
morphine (2.5 mg/kg) = 2 = ————
post-drug saline = 3 = – – – –

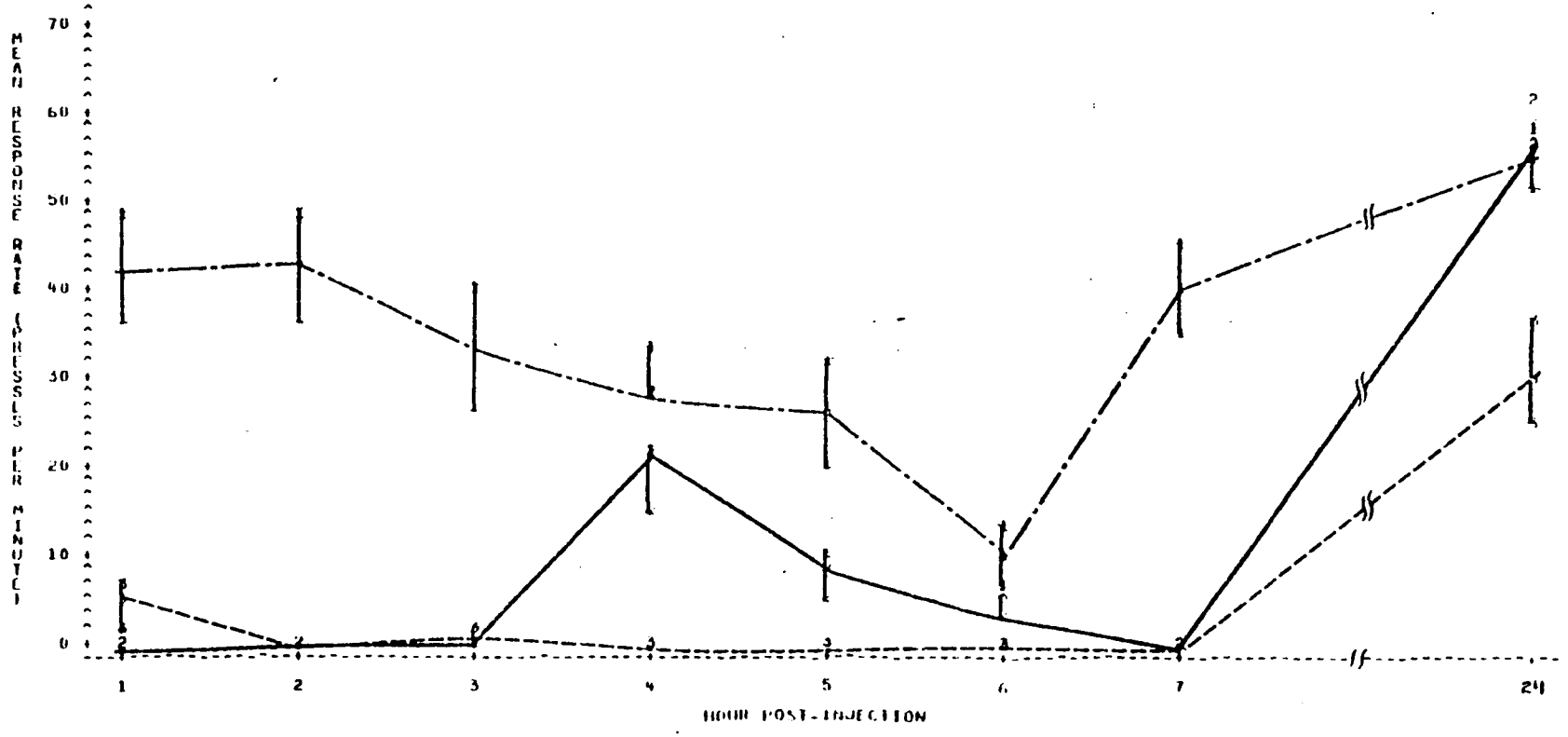


Figure 49

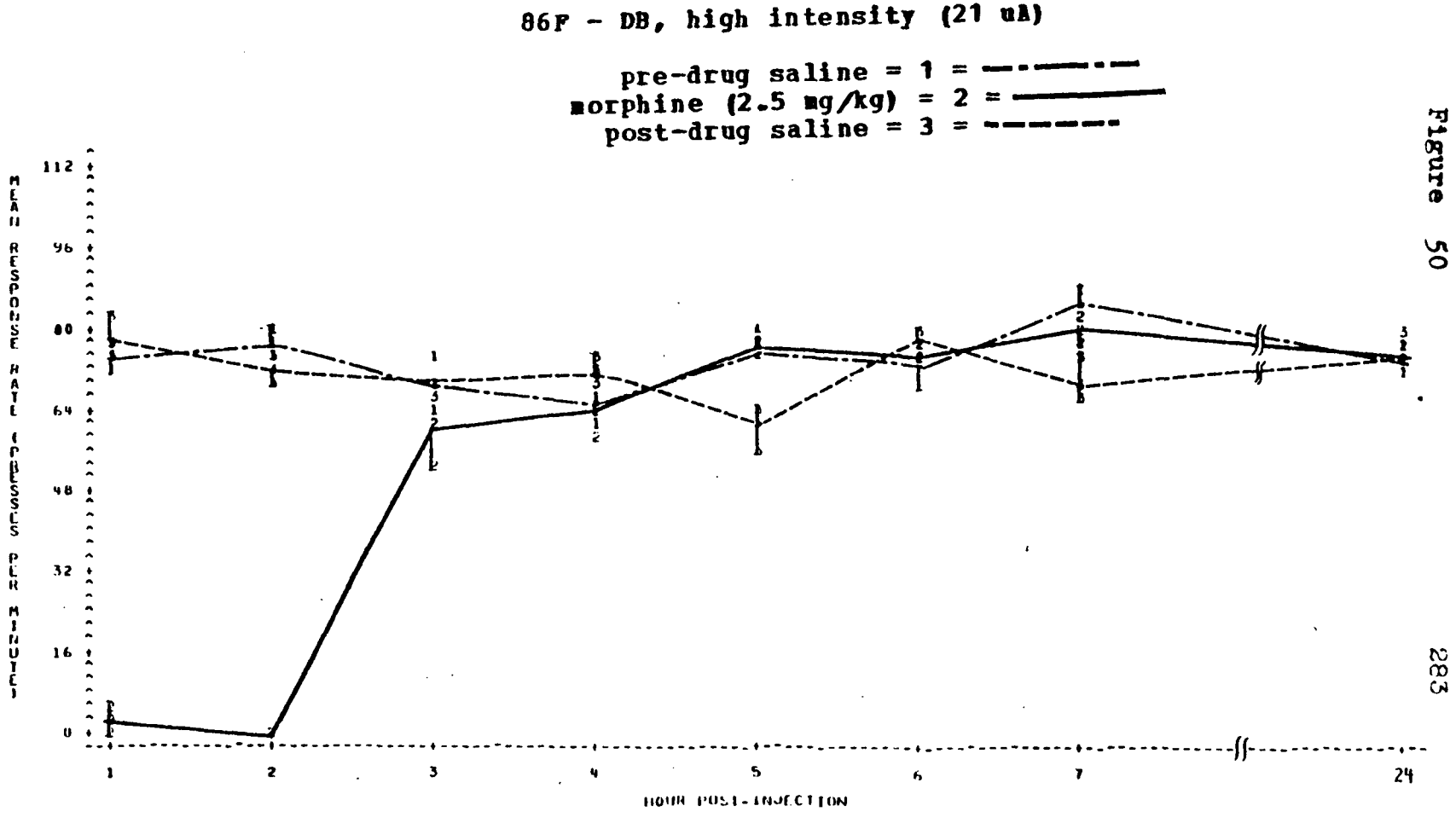

86F - DB, high intensity (21 uA)
pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
112
96
80
64
48
32
16
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 50

86P - HYP, low intensity (32 uA)

pre-drug saline = 1 = —·——·—

morphine (2.5 mg/kg) = 2 = ————

post-drug saline = 3 = – – – –

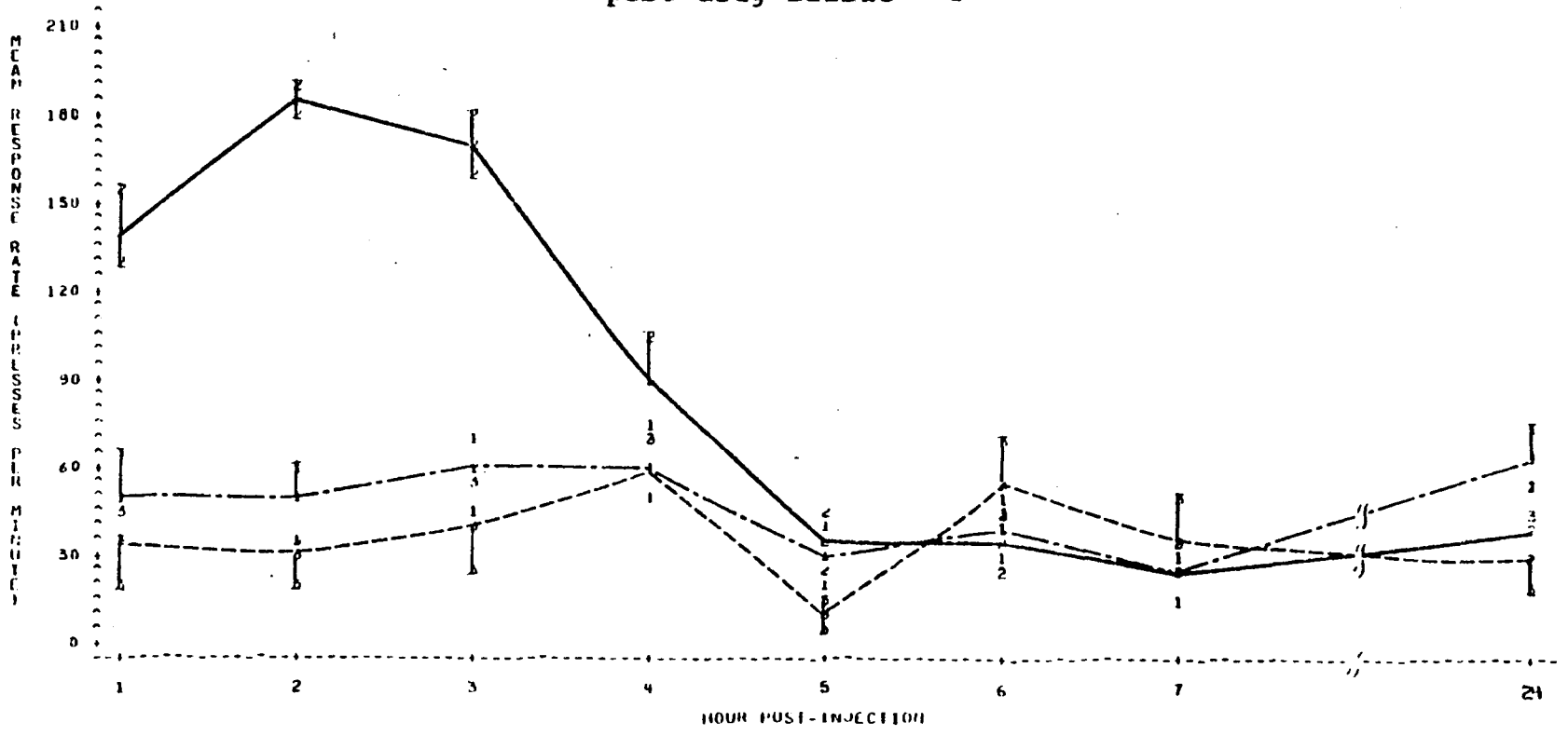


Figure 51

86F - HYP, high intensity (35 uA)

pre-drug saline = 1 = -·——·-
morphine (2.5 mg/kg) = 2 = ——
post-drug saline = 3 = - - - -

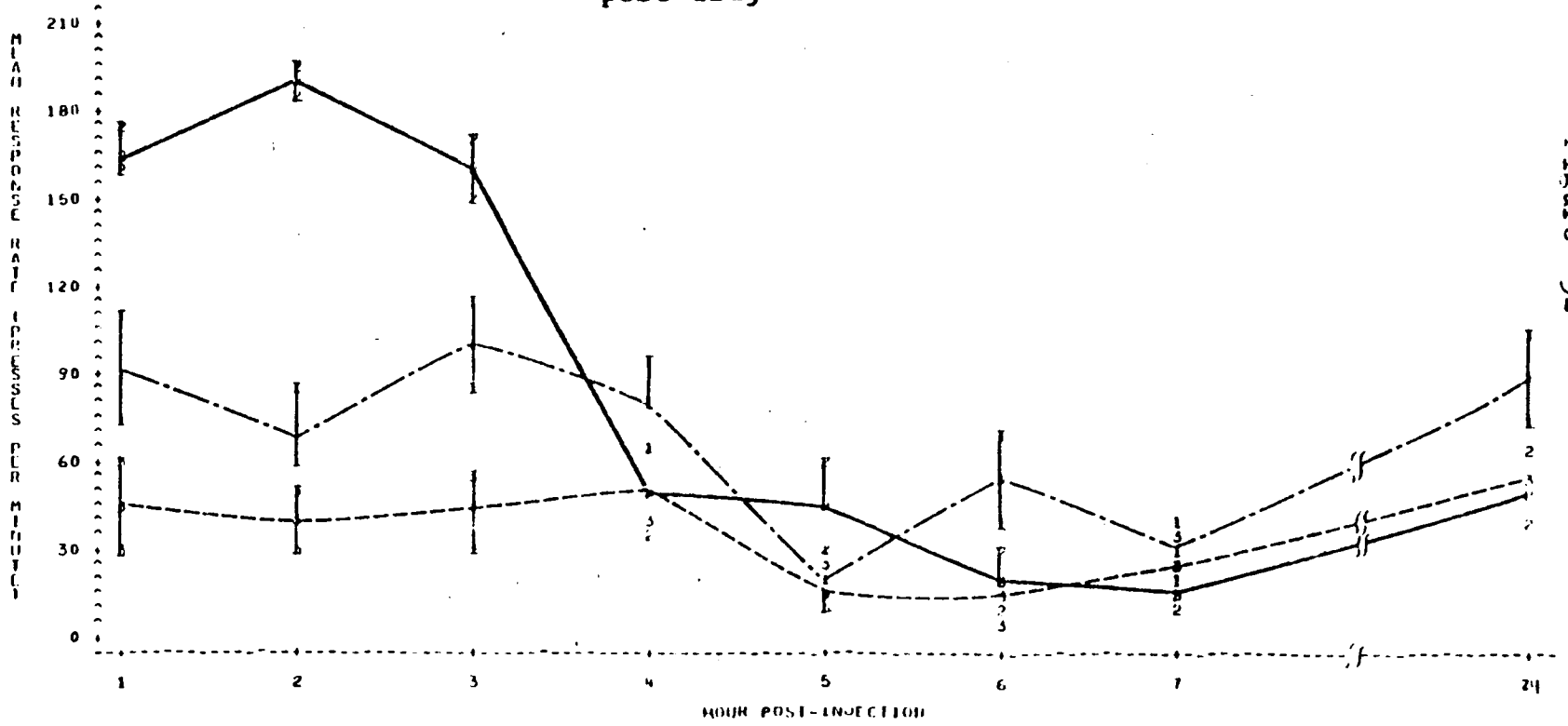


Figure 52

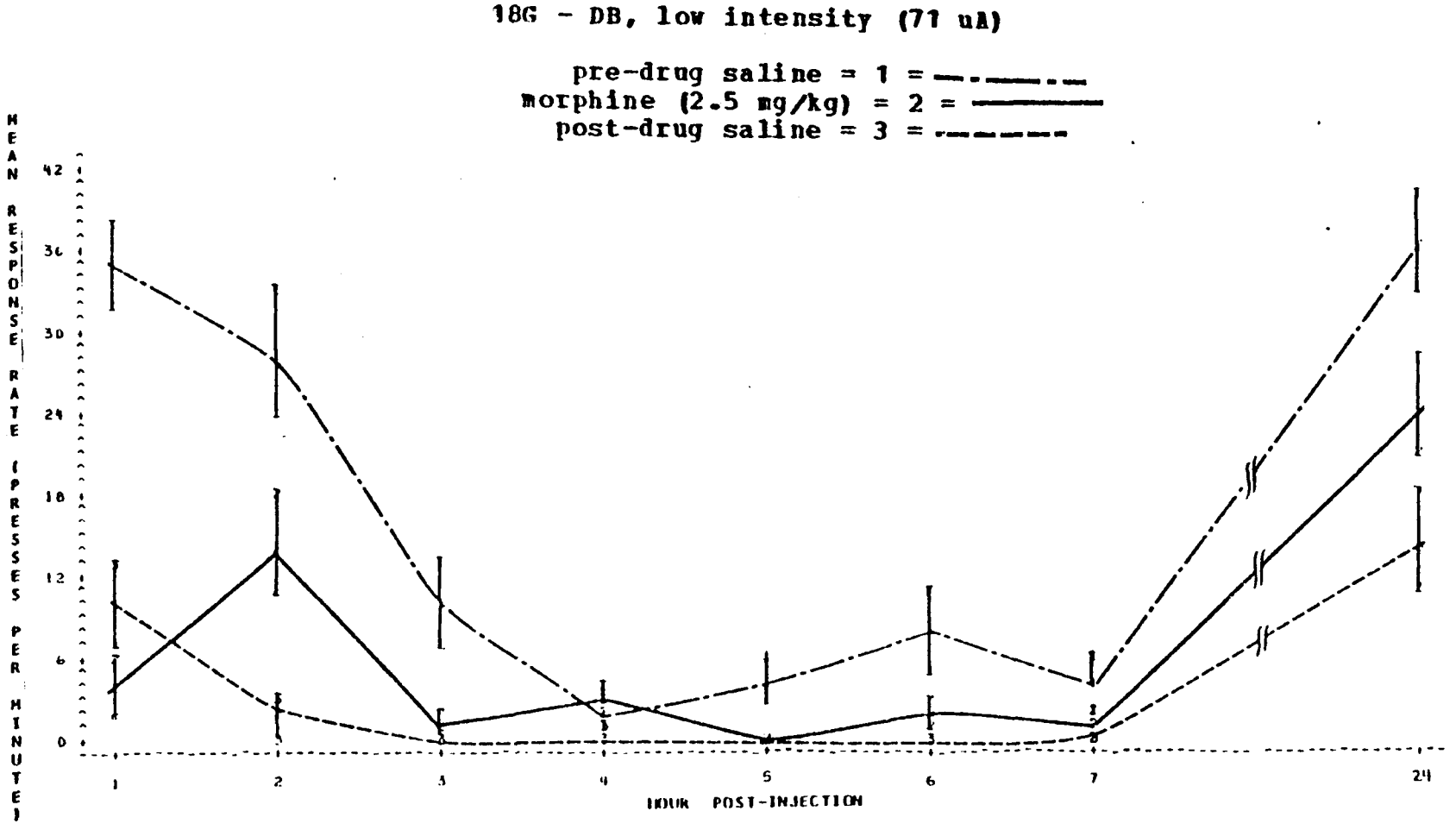

18G - DB, low intensity (71 uA)
pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
42
36
30
24
18
12
6
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 53

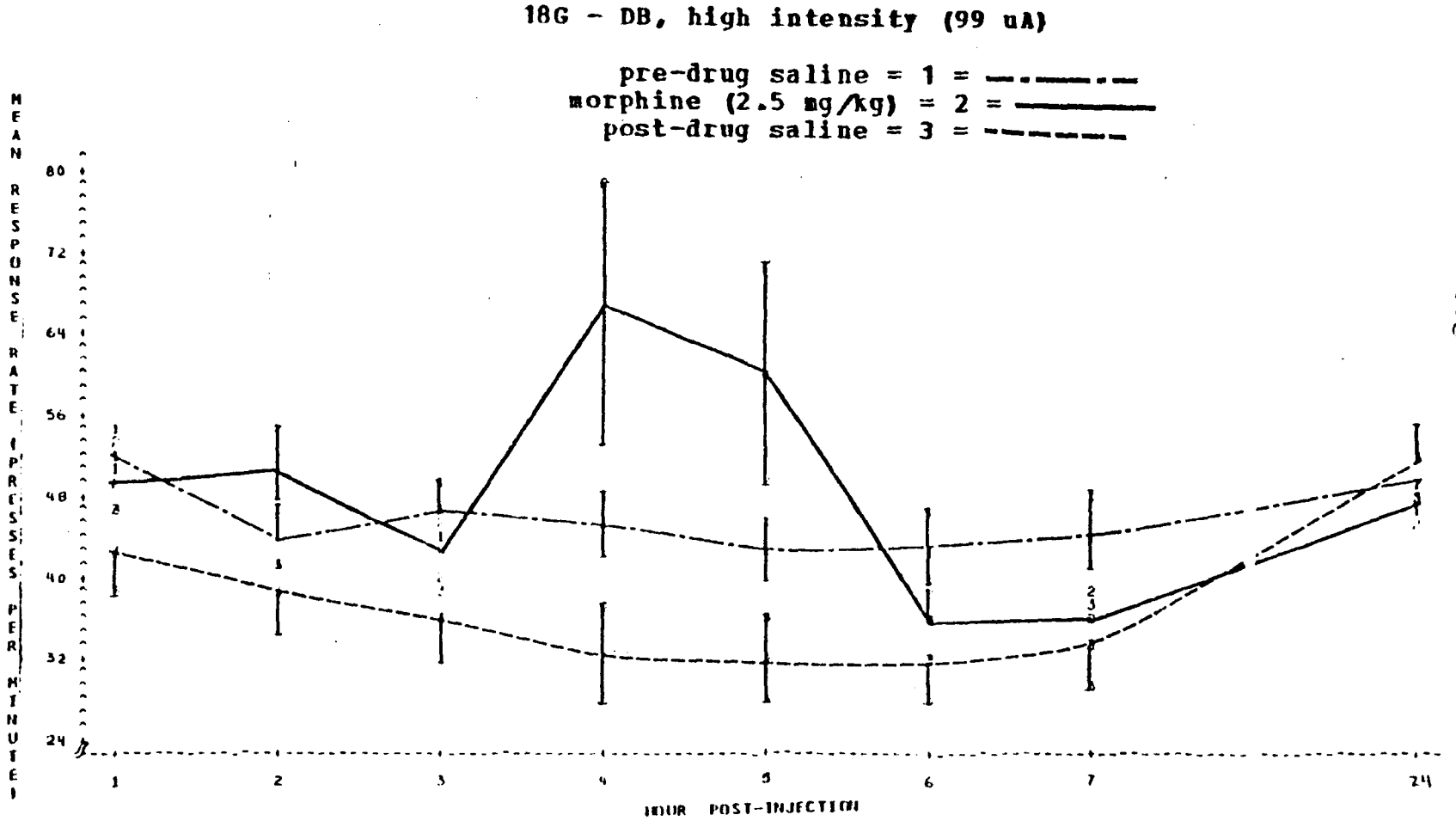

18G - DB, high intensity (99 uA)
pre-drug saline = 1 = -·-·-·-
morphine (2.5 mg/kg) = 2 = ——
post-drug saline = 3 = - - -
MEAN RESPONSE RATE (PRESSES PER MINUTE)
80
72
64
56
48
40
32
24
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 54

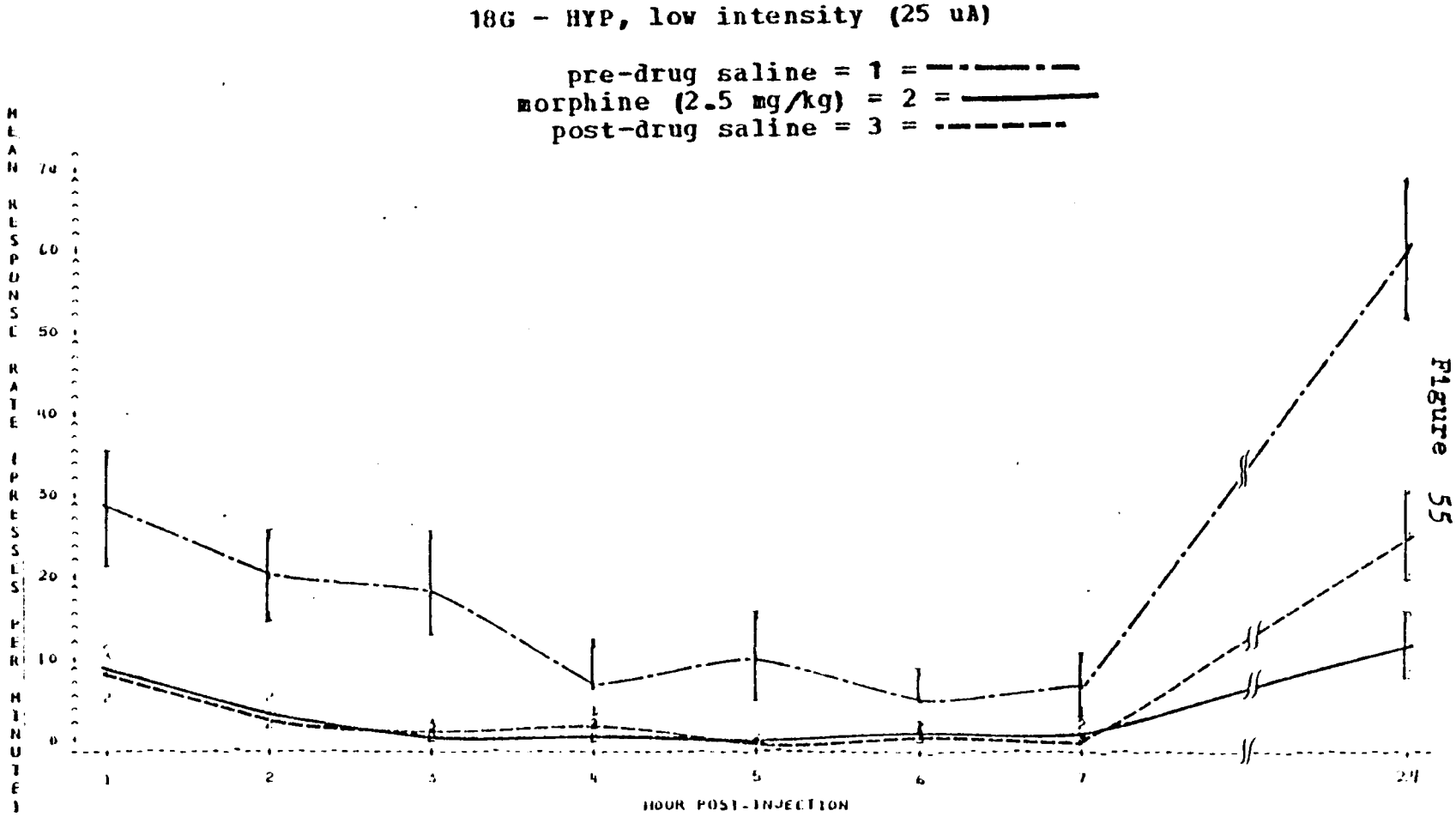

18G - HYP, low intensity (25 uA)
pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 55

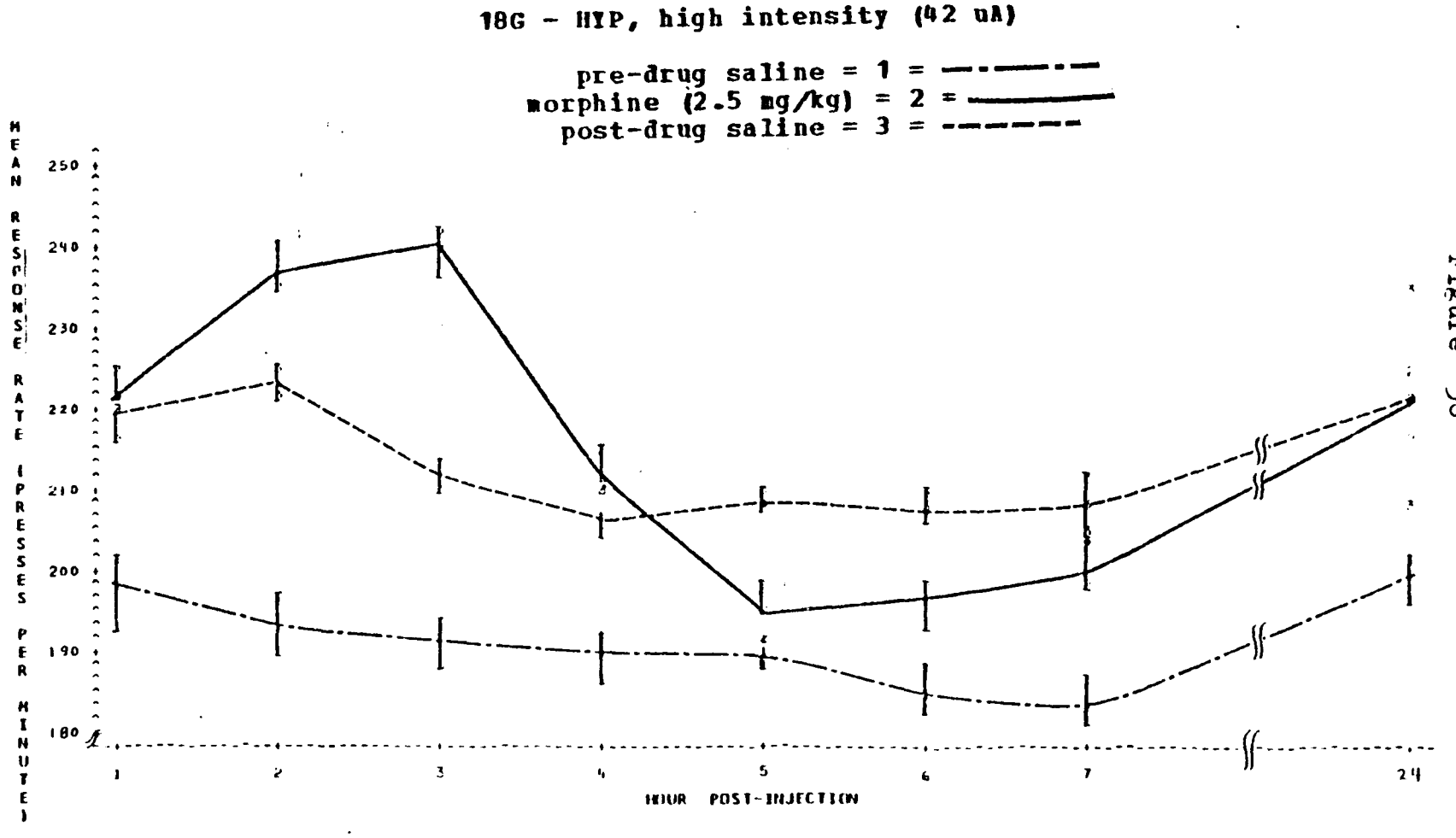

18G - HYP, high intensity (42 uA)
pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
250
240
230
220
210
200
190
180
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 56

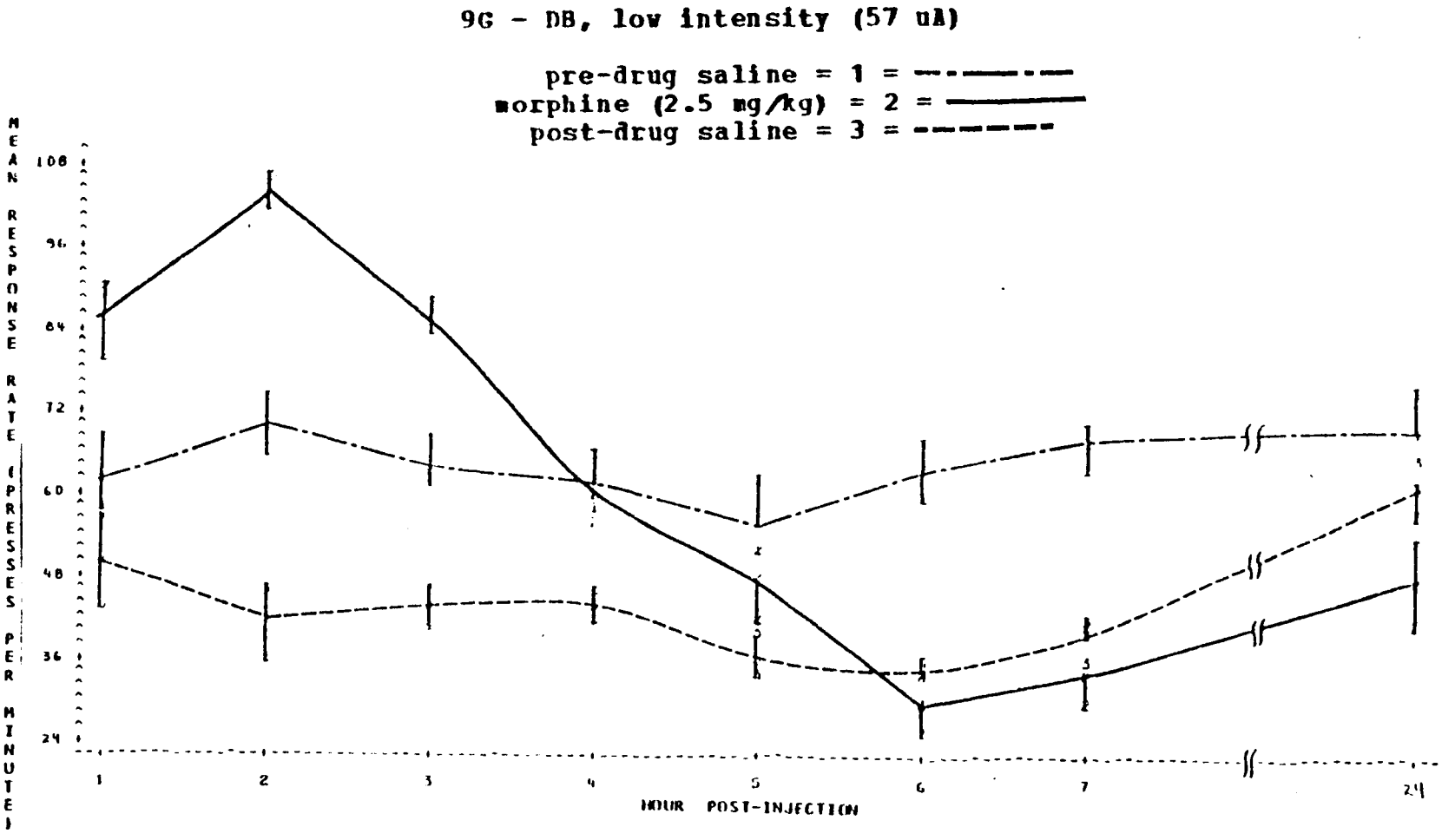

9G - DB, low intensity (57 uA)
pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
108
96
84
72
60
48
36
24
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 57

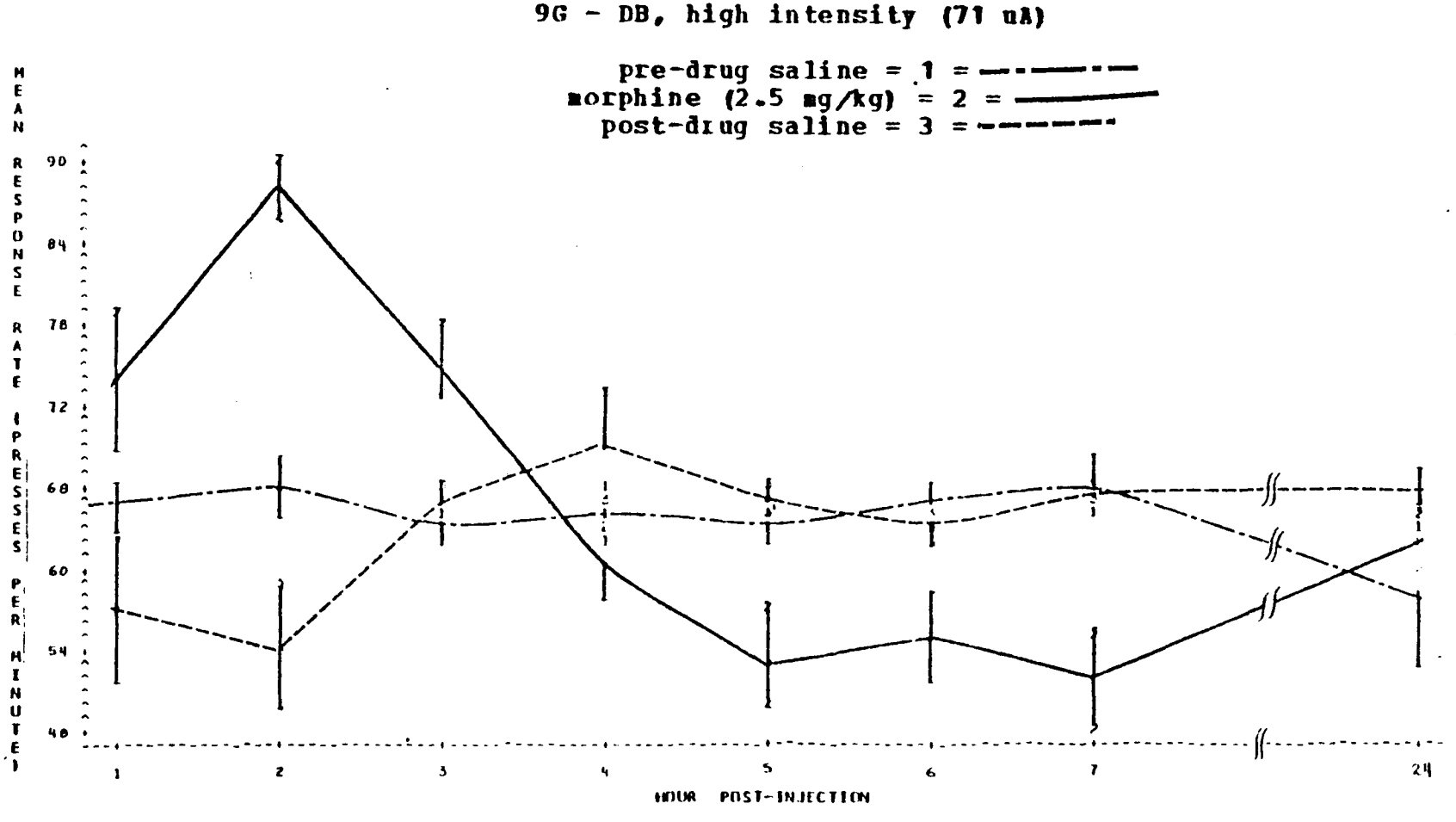

9G - DB, high intensity (71 uA)
pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
90
84
78
72
66
60
54
48
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 58

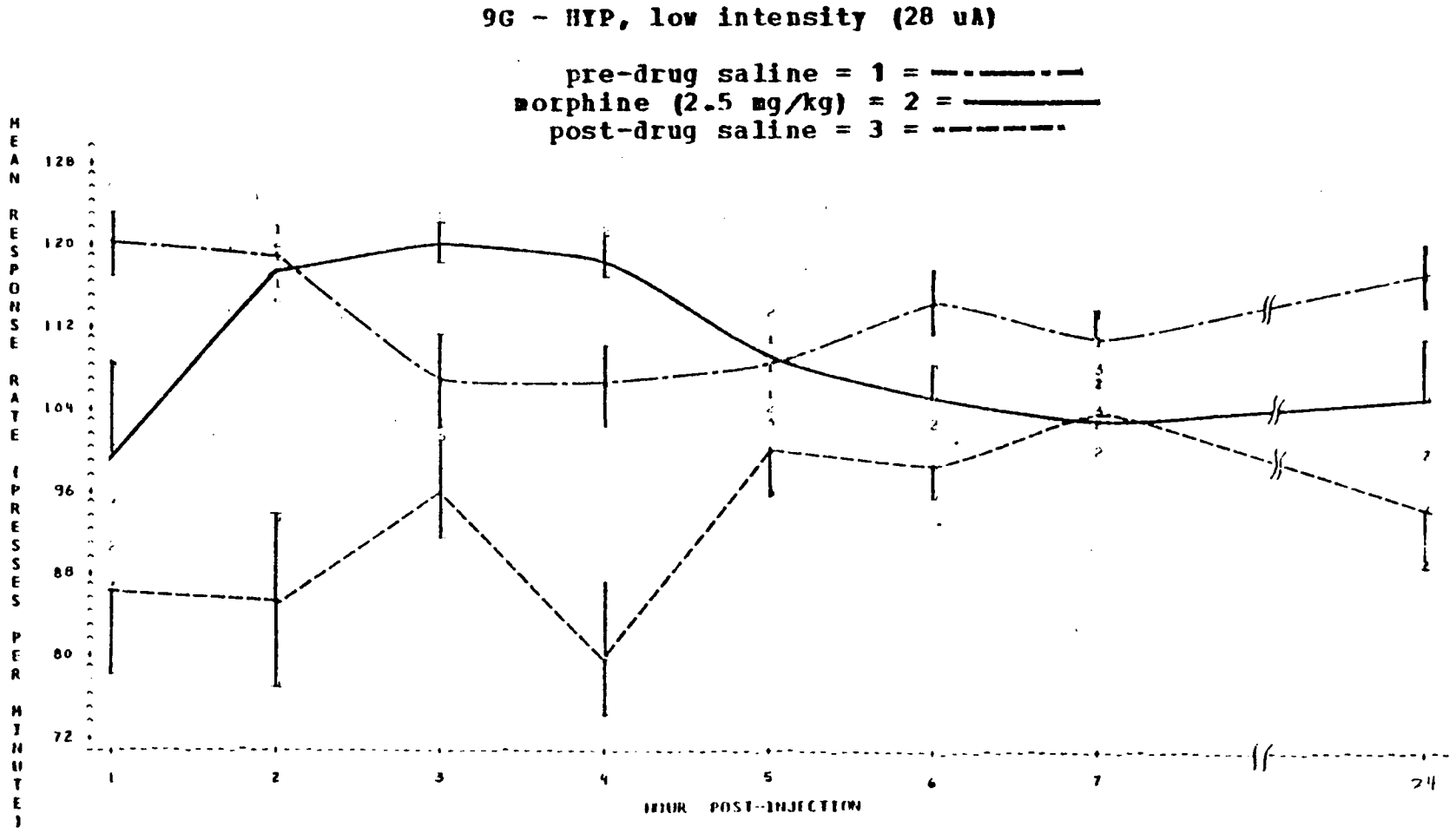

9G - HYP, low intensity (28 uA)
pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
128
120
112
104
96
88
80
72
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 59

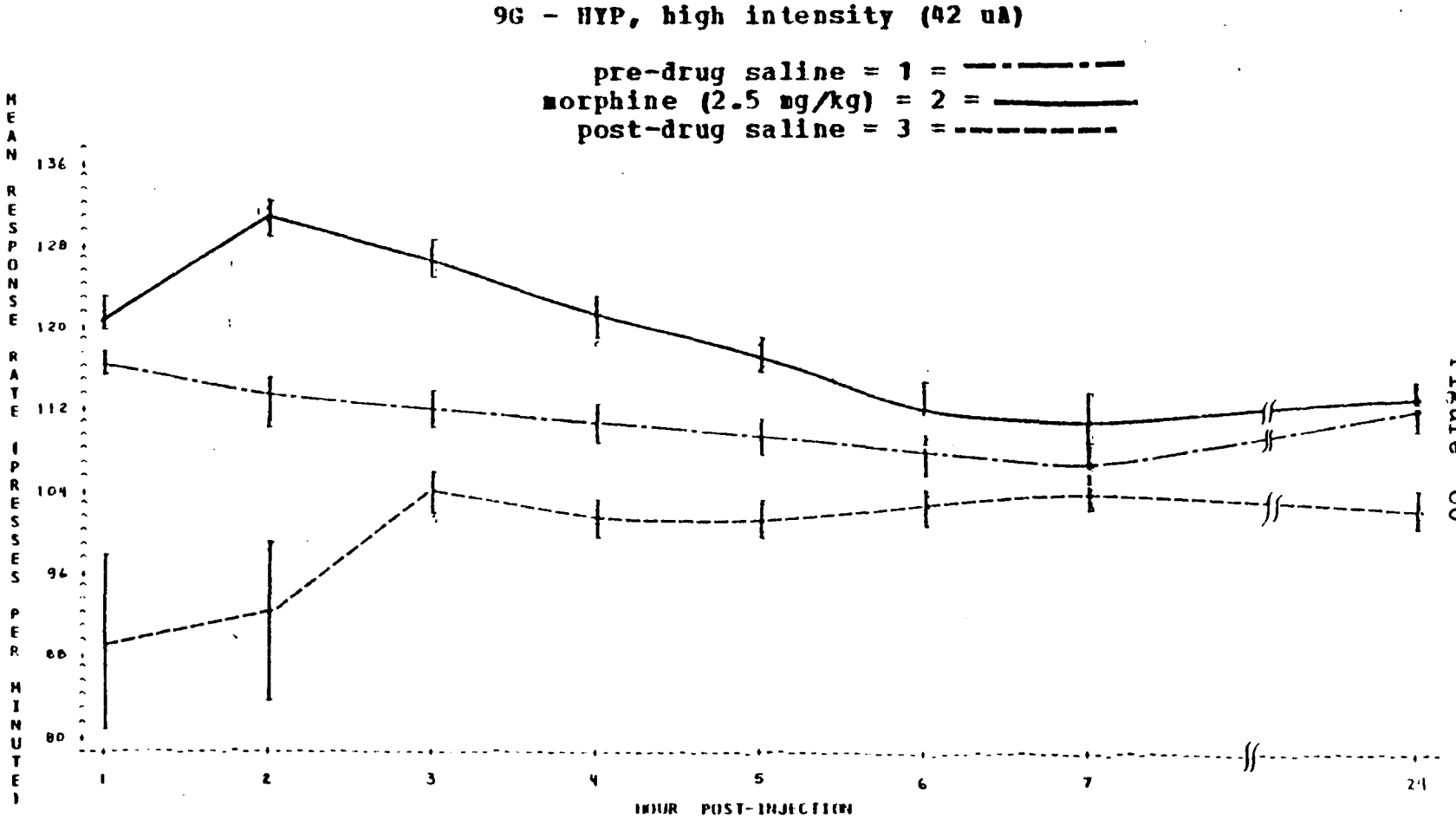

9G - HYP, high intensity (42 uA)
pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
136
128
120
112
104
96
88
80
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 60

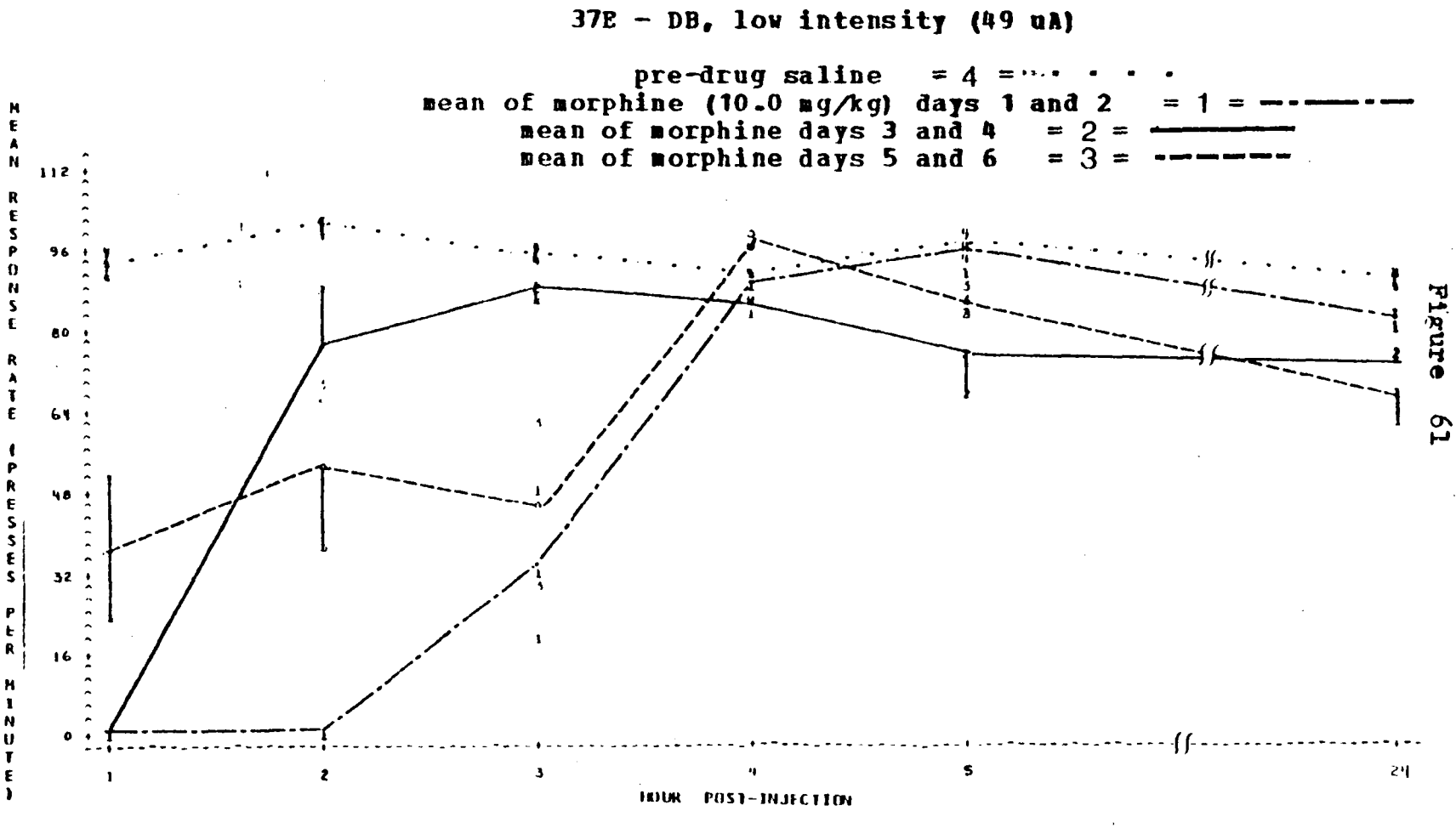

37E - DB, low intensity (49 uA)
pre-drug saline = 4 =
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 =
mean of morphine days 3 and 4 = 2 =
mean of morphine days 5 and 6 = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
112
96
80
64
48
32
16
0
1
2
3
4
5
24
HOUR POST-INJECTION

Figure 61

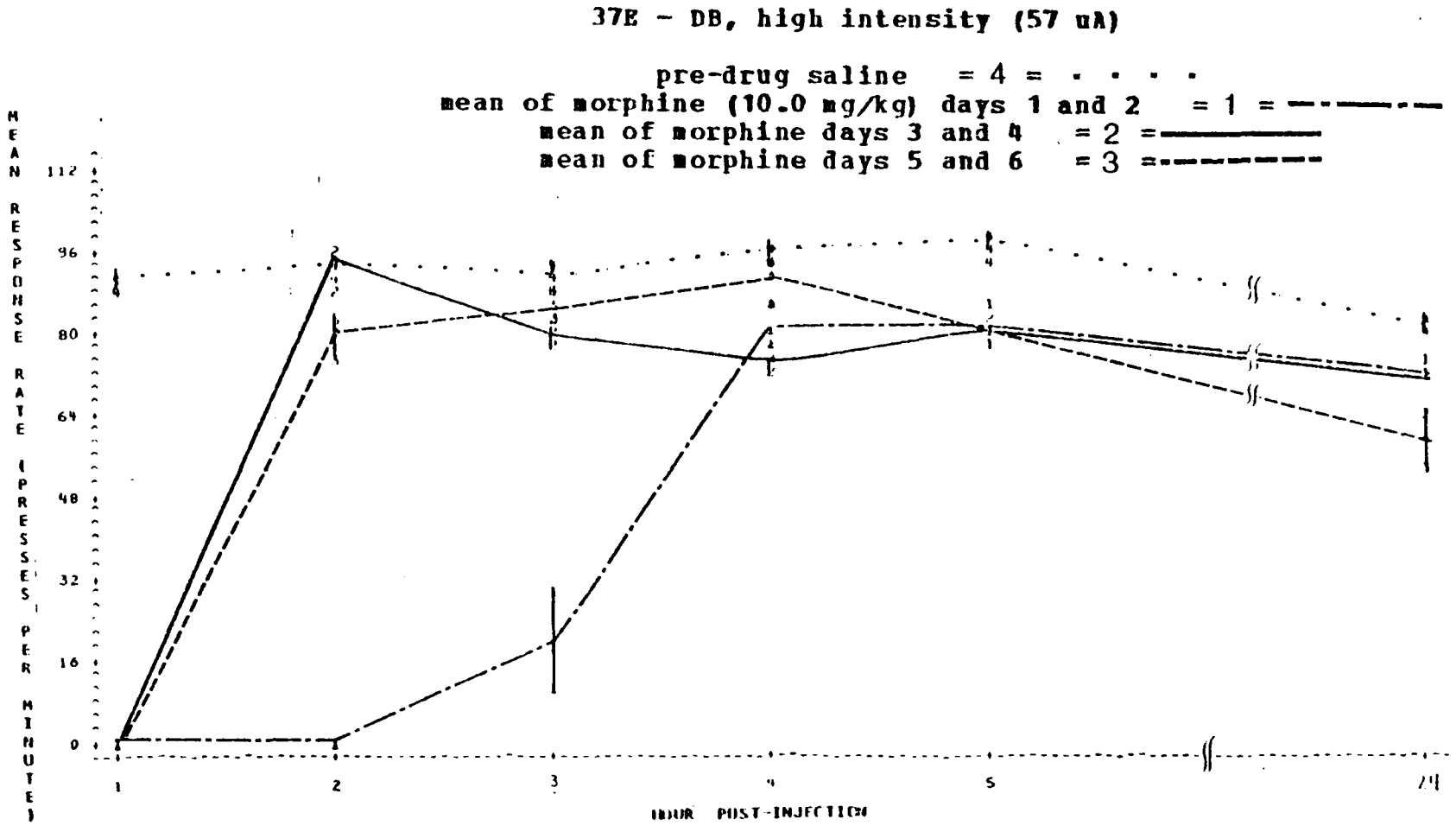

37E - DB, high intensity (57 uA)
pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 =————
mean of morphine days 5 and 6 = 3 =·——·——
MEAN RESPONSE RATE (PRESSES PER MINUTE)
112
96
80
64
48
32
16
0
1
2
3
4
5
24
HOUR POST-INJECTION

Figure 62

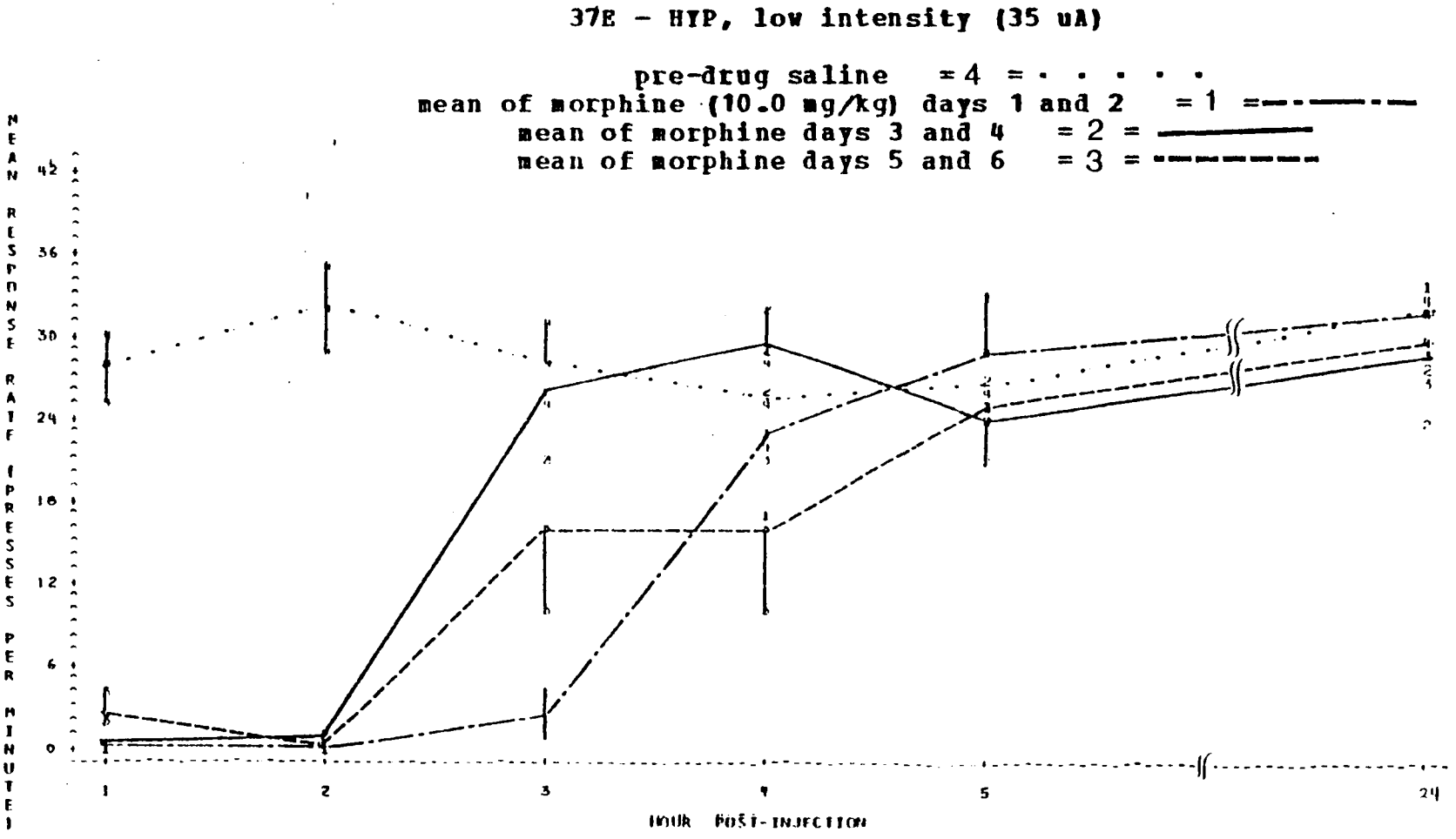

37E - HYP, low intensity (35 uA)
pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 =
mean of morphine days 3 and 4 = 2 =
mean of morphine days 5 and 6 = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
42
36
30
24
18
12
6
0
1
2
3
4
5
24
HOUR POST-INJECTION

Figure 63

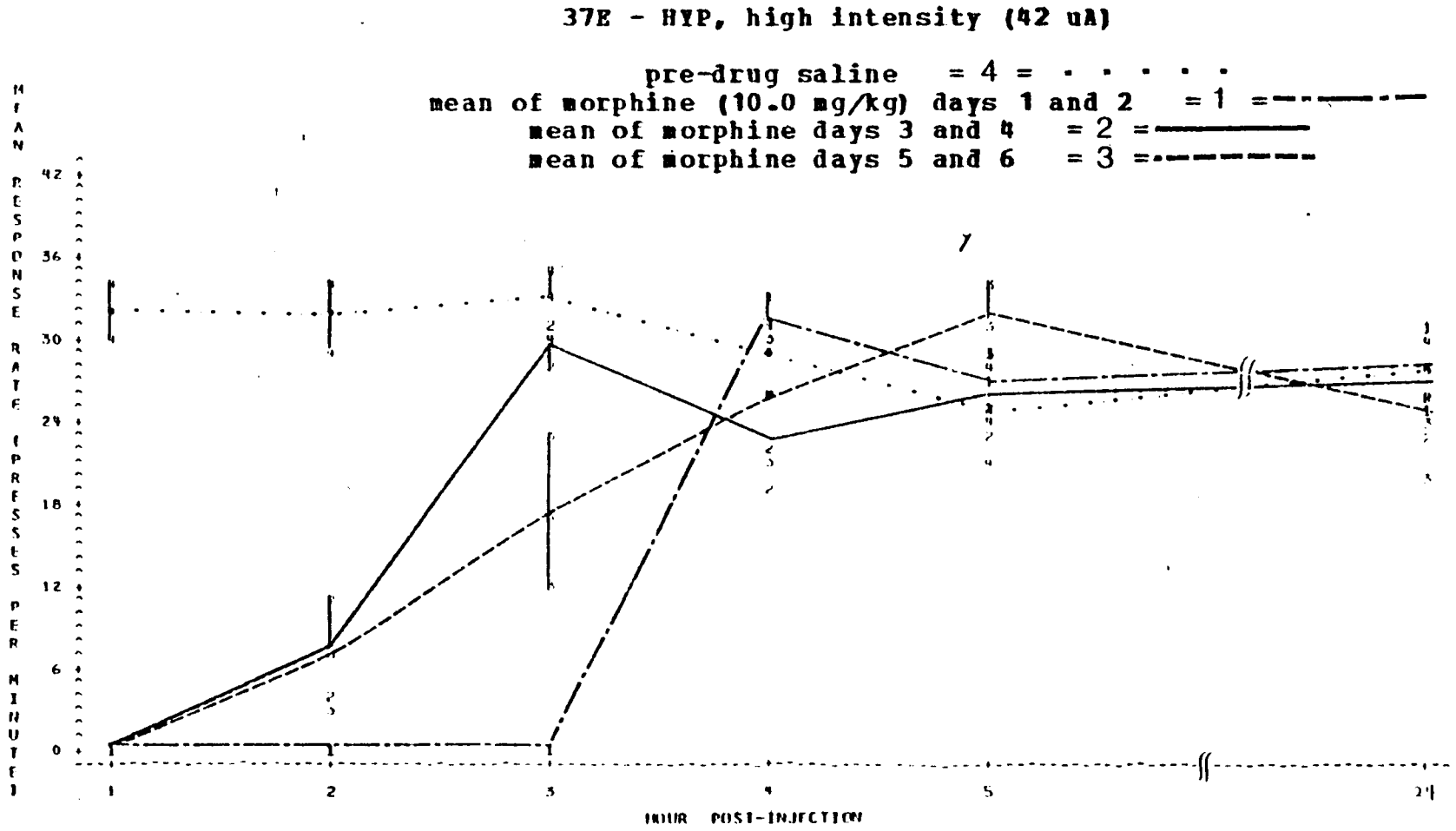

37E - HYP, high intensity (42 uA)
pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 =
mean of morphine days 3 and 4 = 2 =
mean of morphine days 5 and 6 = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
42
36
30
24
18
12
6
0
1
2
3
4
5
24
HOUR POST-INJECTION

Figure 64

54F - DB, low intensity (46 uA)

pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = — — —

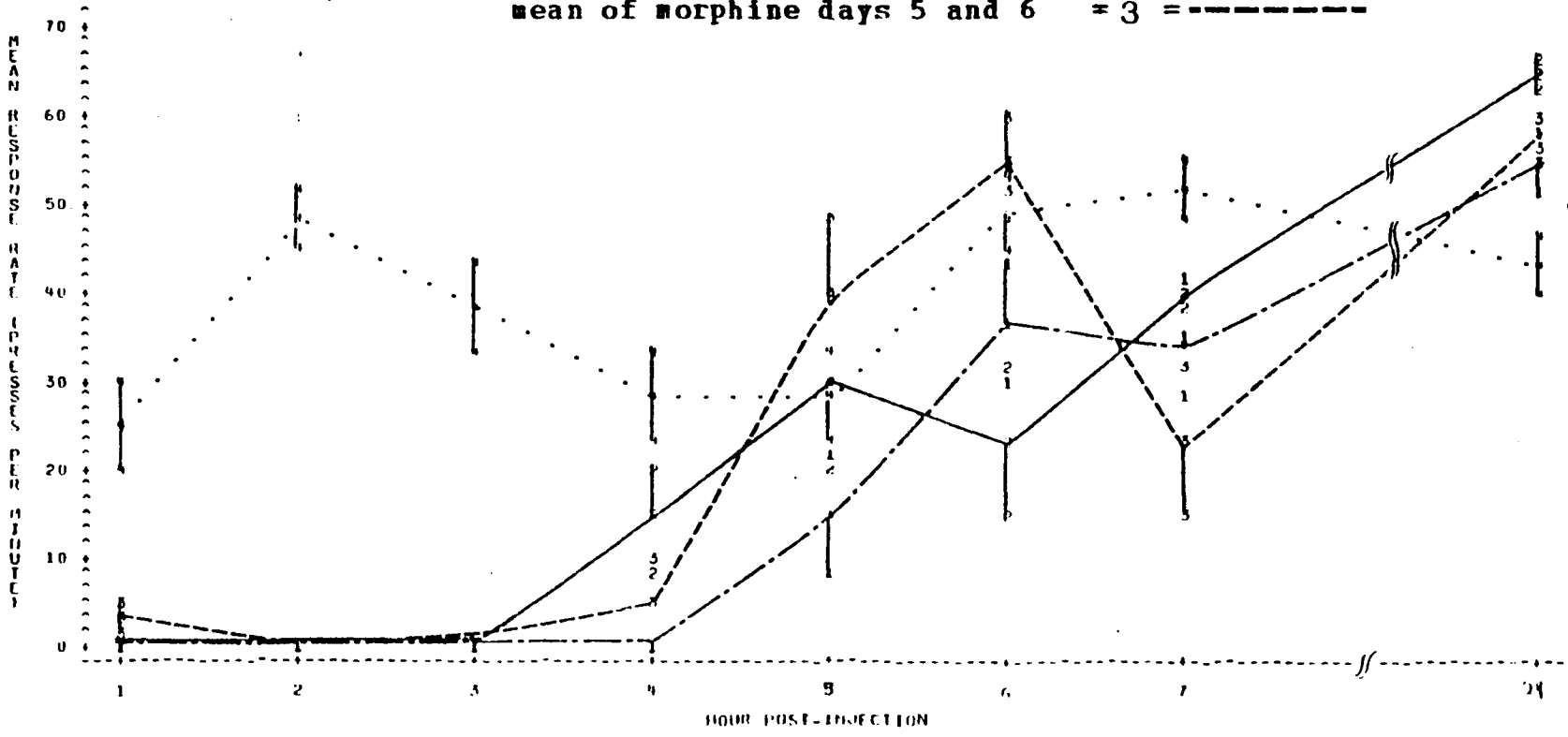


Figure 65

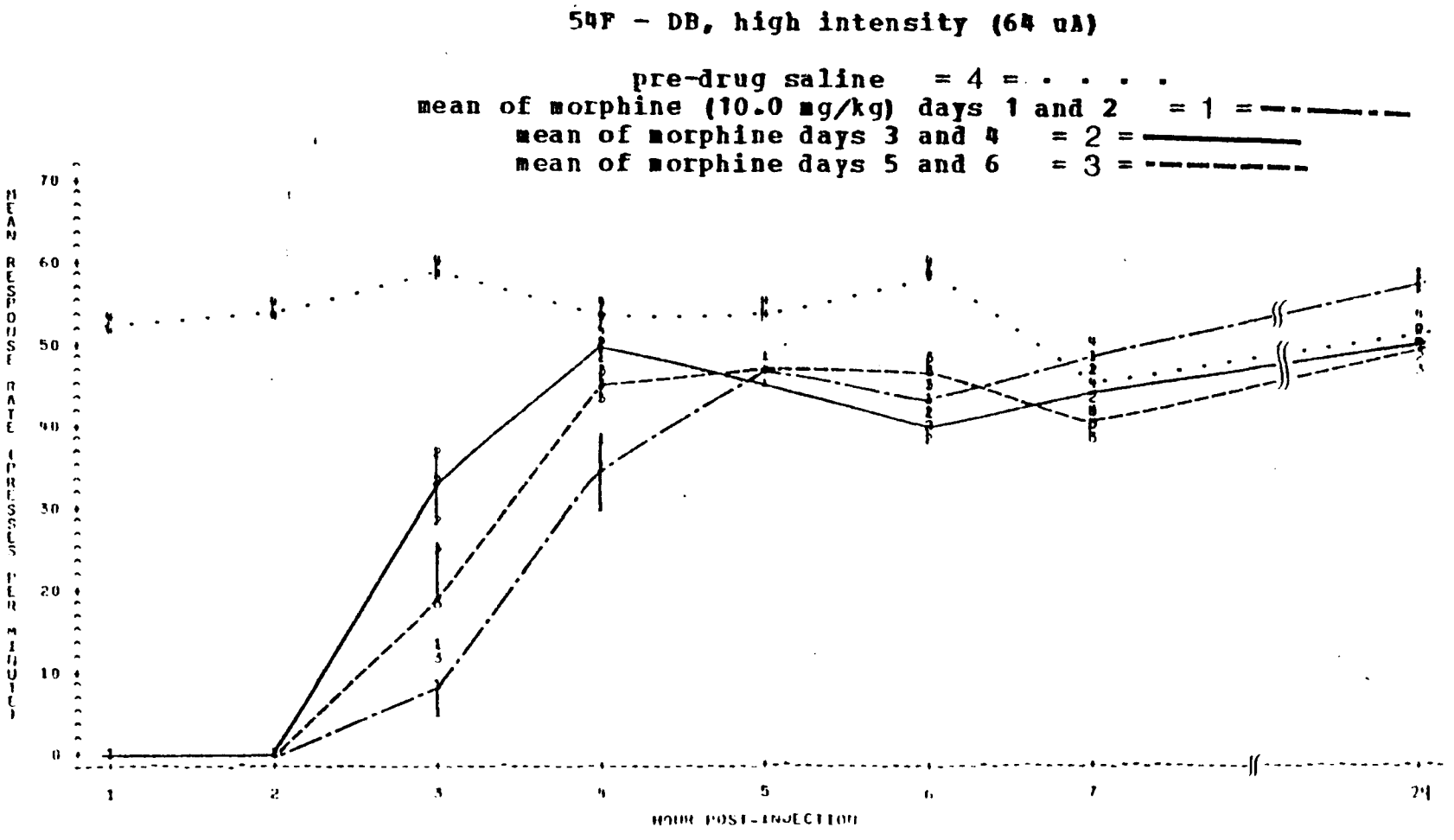

54F - DB, high intensity (64 uA)
pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 = -·-·-·-
mean of morphine days 3 and 4 = 2 = ——————
mean of morphine days 5 and 6 = 3 = - - - - - -
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 66

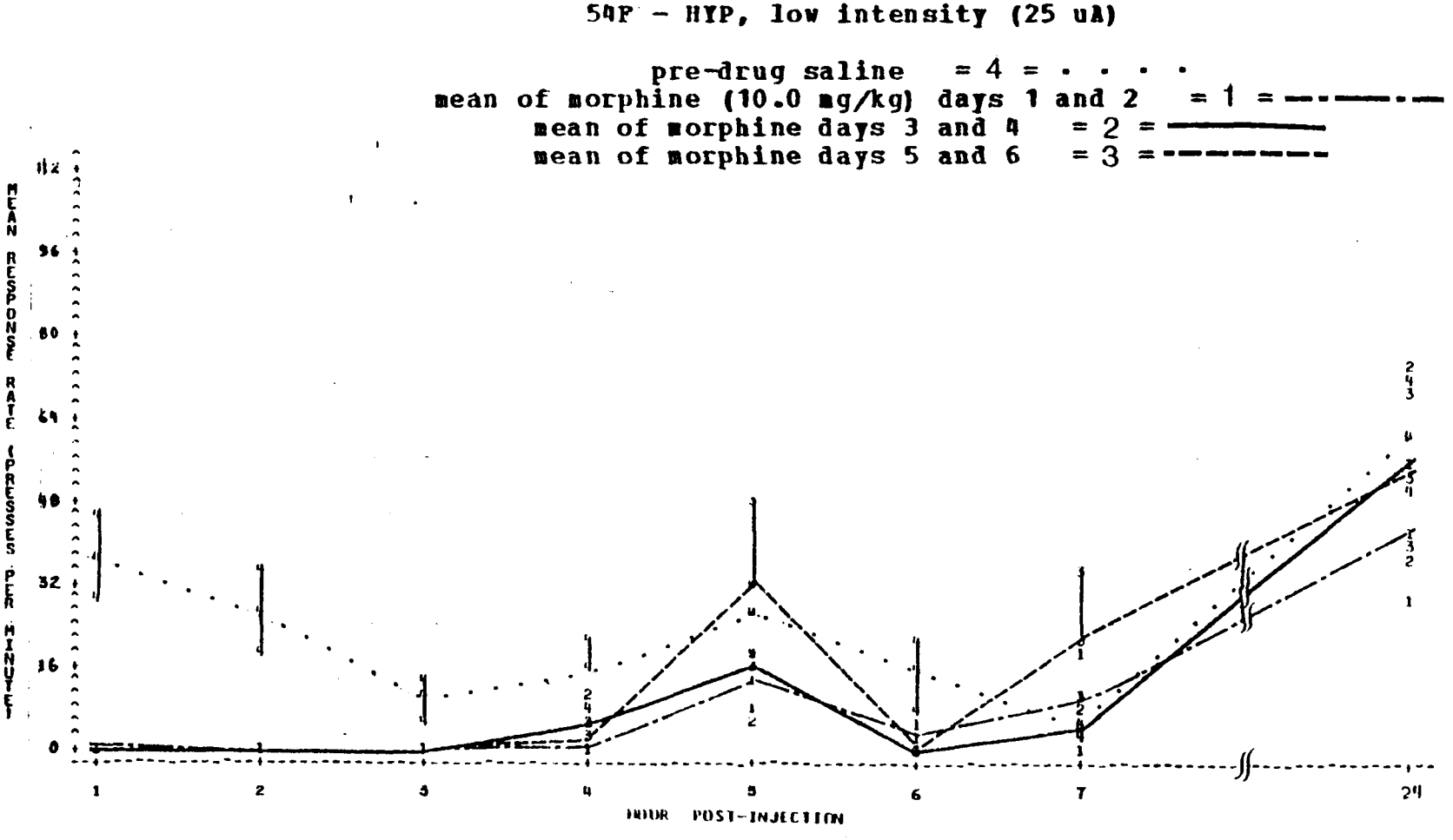

SQP - HYP, low intensity (25 uA)
pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = ————
MEAN RESPONSE RATE (PRESSES PER MINUTE)
112
96
80
64
48
32
16
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 67

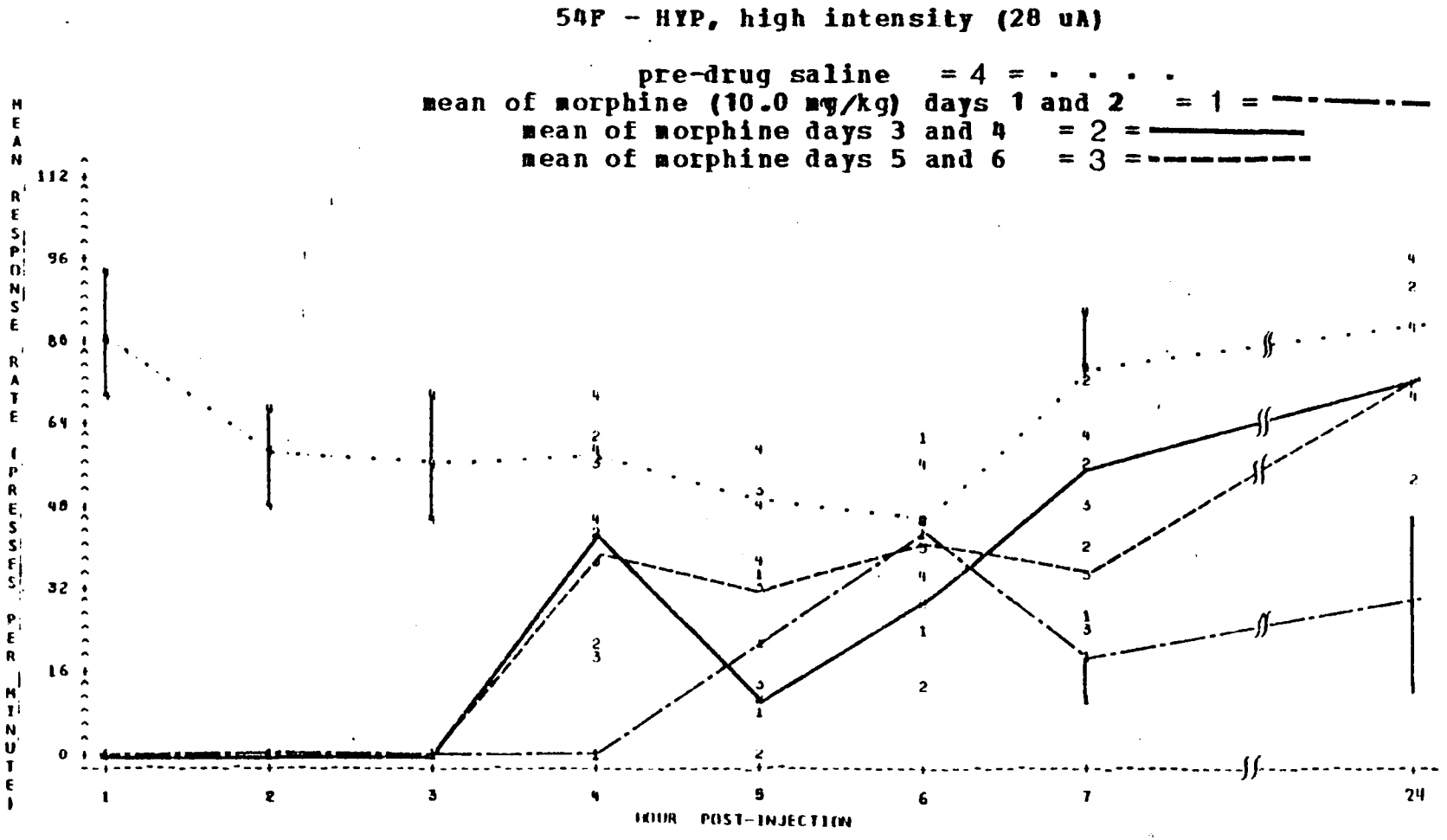

54P - HYP, high intensity (28 uA)
pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = ——————
MEAN RESPONSE RATE (PRESSES PER MINUTE)
112
96
80
64
48
32
16
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 68

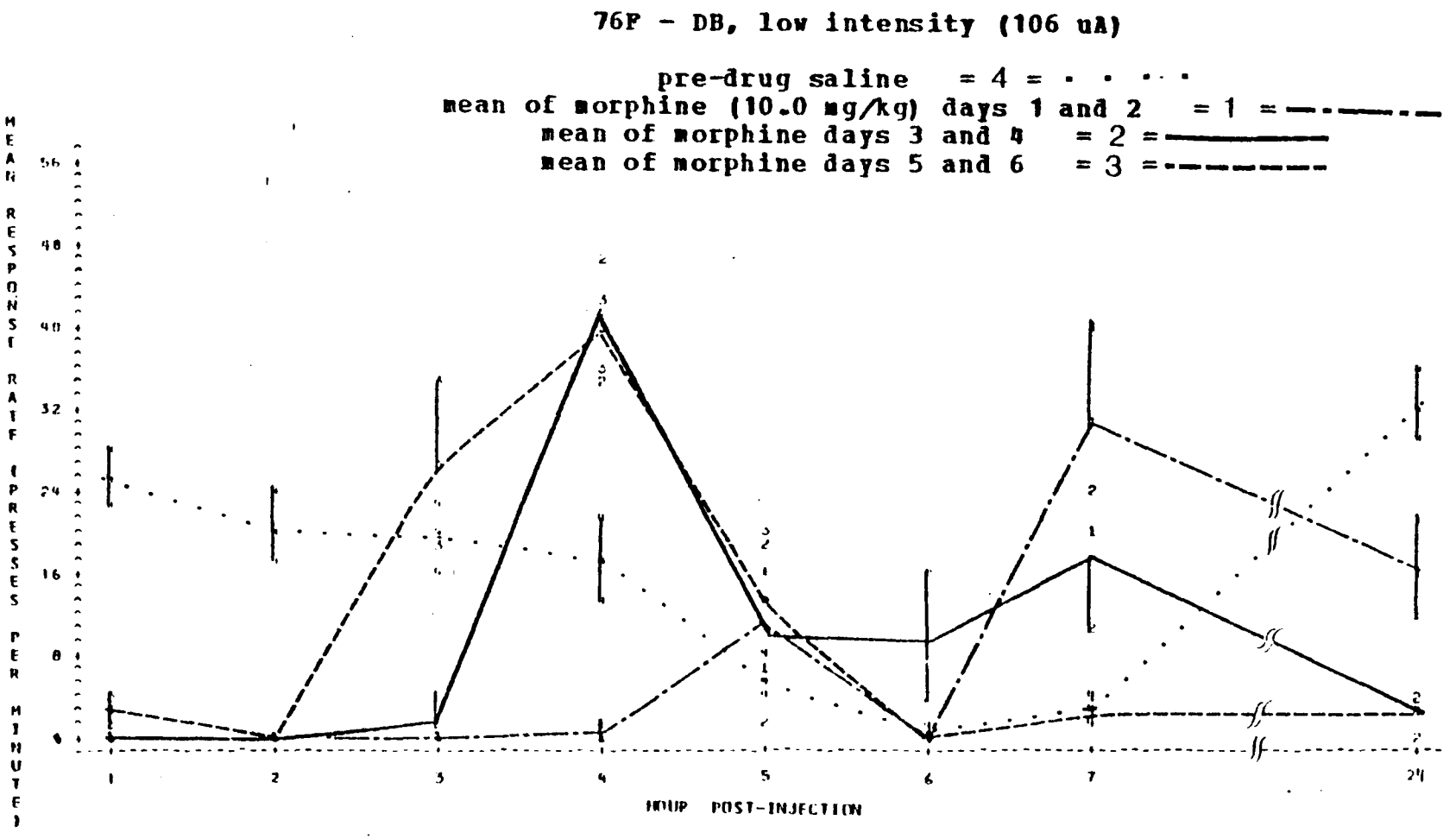

76F - DB, low intensity (106 uA)
pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 = —·——·——
mean of morphine days 3 and 4 = 2 = ————————
mean of morphine days 5 and 6 = 3 = ·——·——·——
MEAN RESPONSE RATE (PRESSES PER MINUTE)
56
48
40
32
24
16
8
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 69

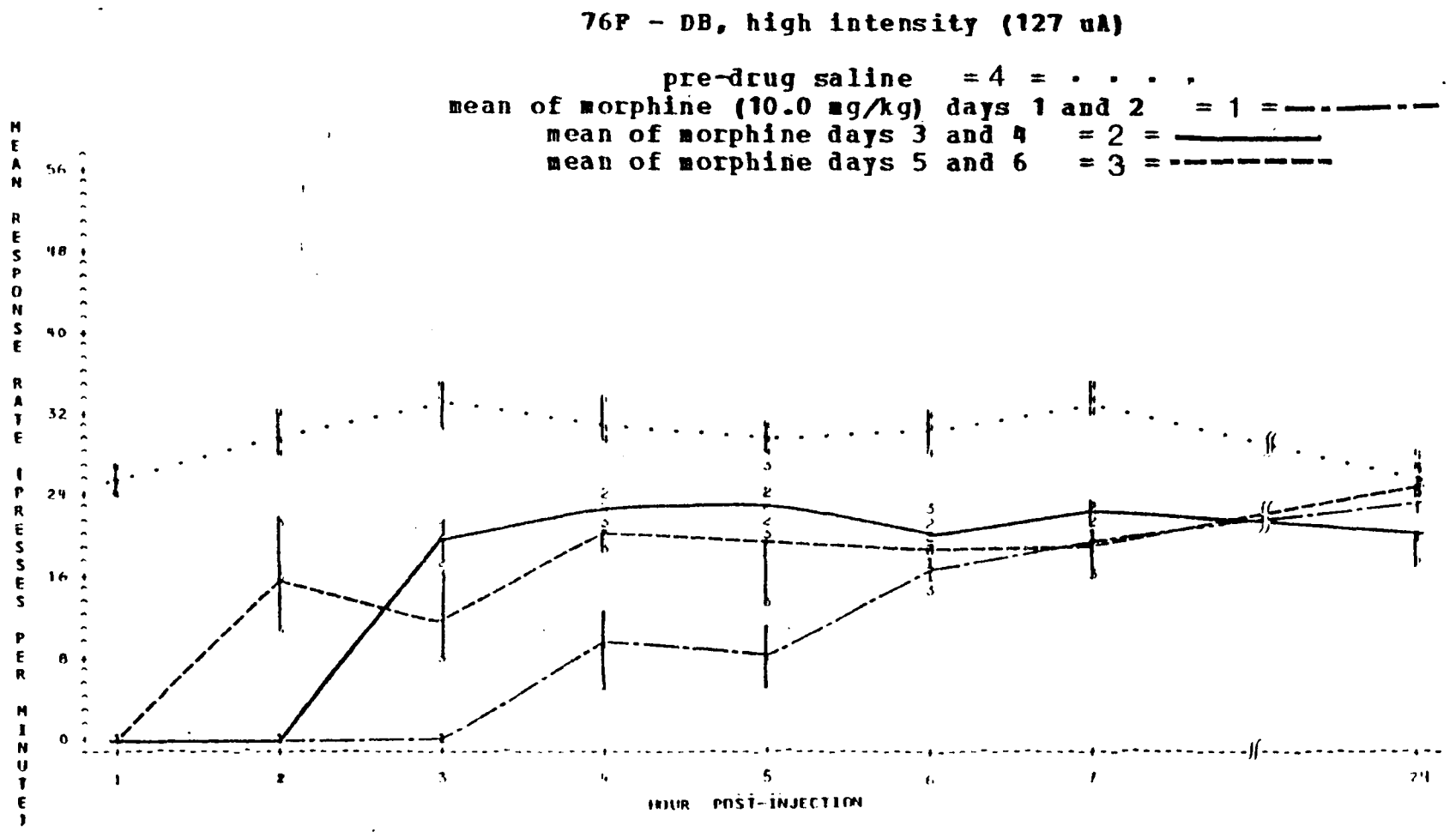
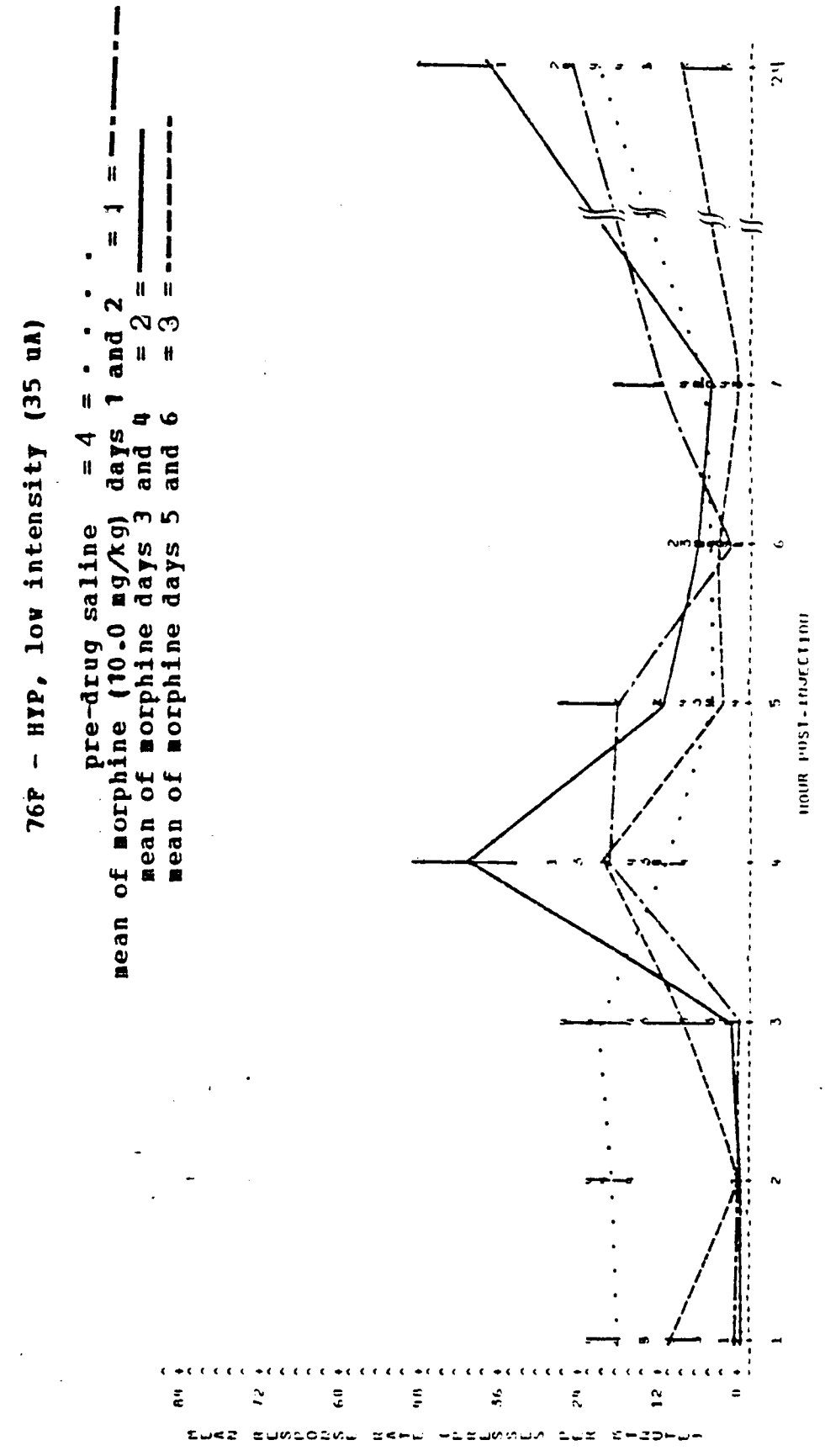

76P - DB, high intensity (127 uA)
pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = ———
MEAN RESPONSE RATE (PRESSES PER MINUTE)
56
48
40
32
24
16
8
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 70

Figure 71


76P - HYP, low intensity (35 uA)
pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 = —·—·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = - - - - -
HOUR POST-INJECTION

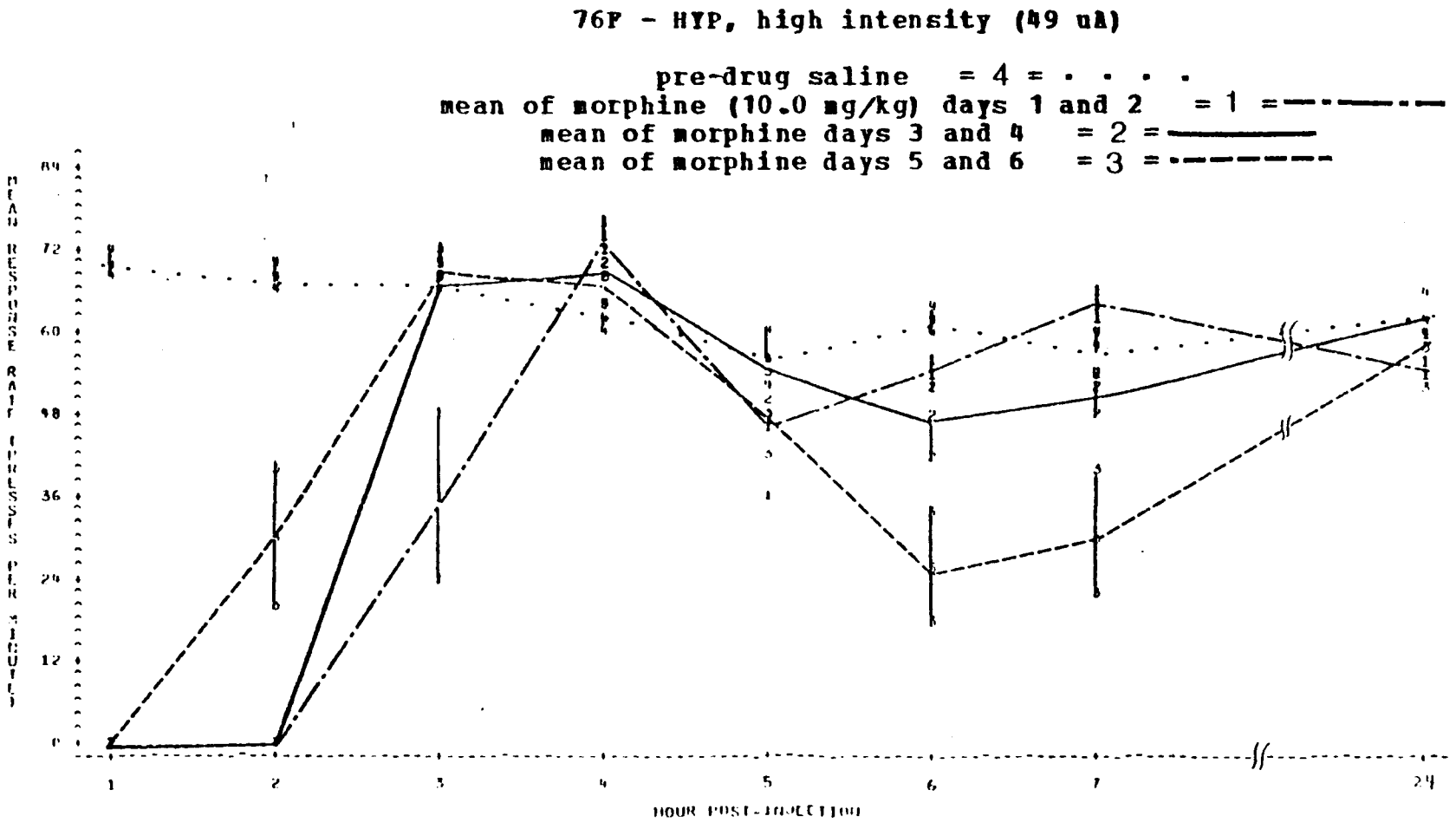

76P - HYP, high intensity (49 uA)
pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 =
mean of morphine days 3 and 4 = 2 =
mean of morphine days 5 and 6 = 3 =
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
84
72
60
48
36
24
12
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 72

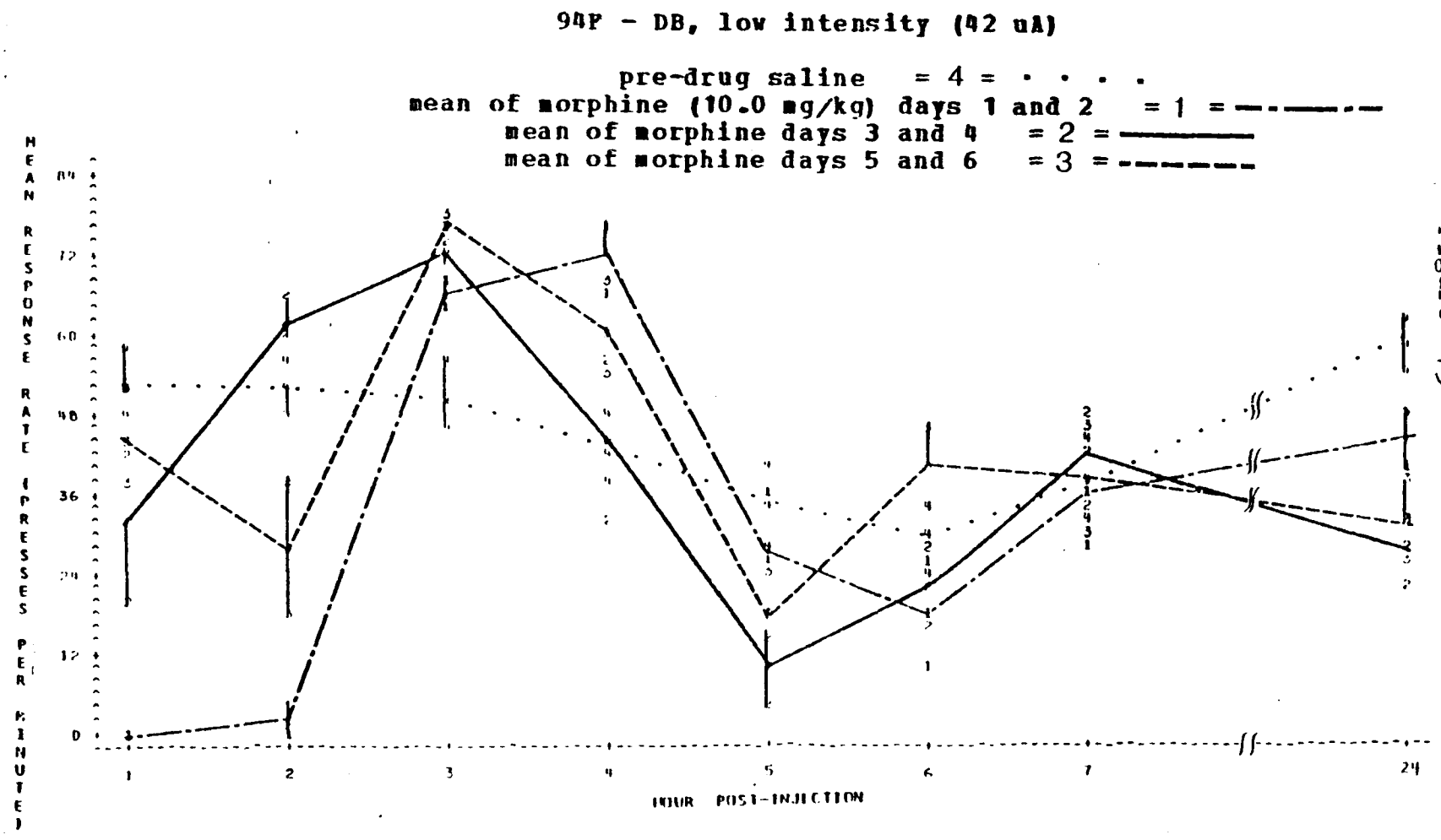

94P - DB, low intensity (42 uA)
pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = – – – –
MEAN RESPONSE RATE (PRESSES PER MINUTE)
84
72
60
48
36
24
12
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 73

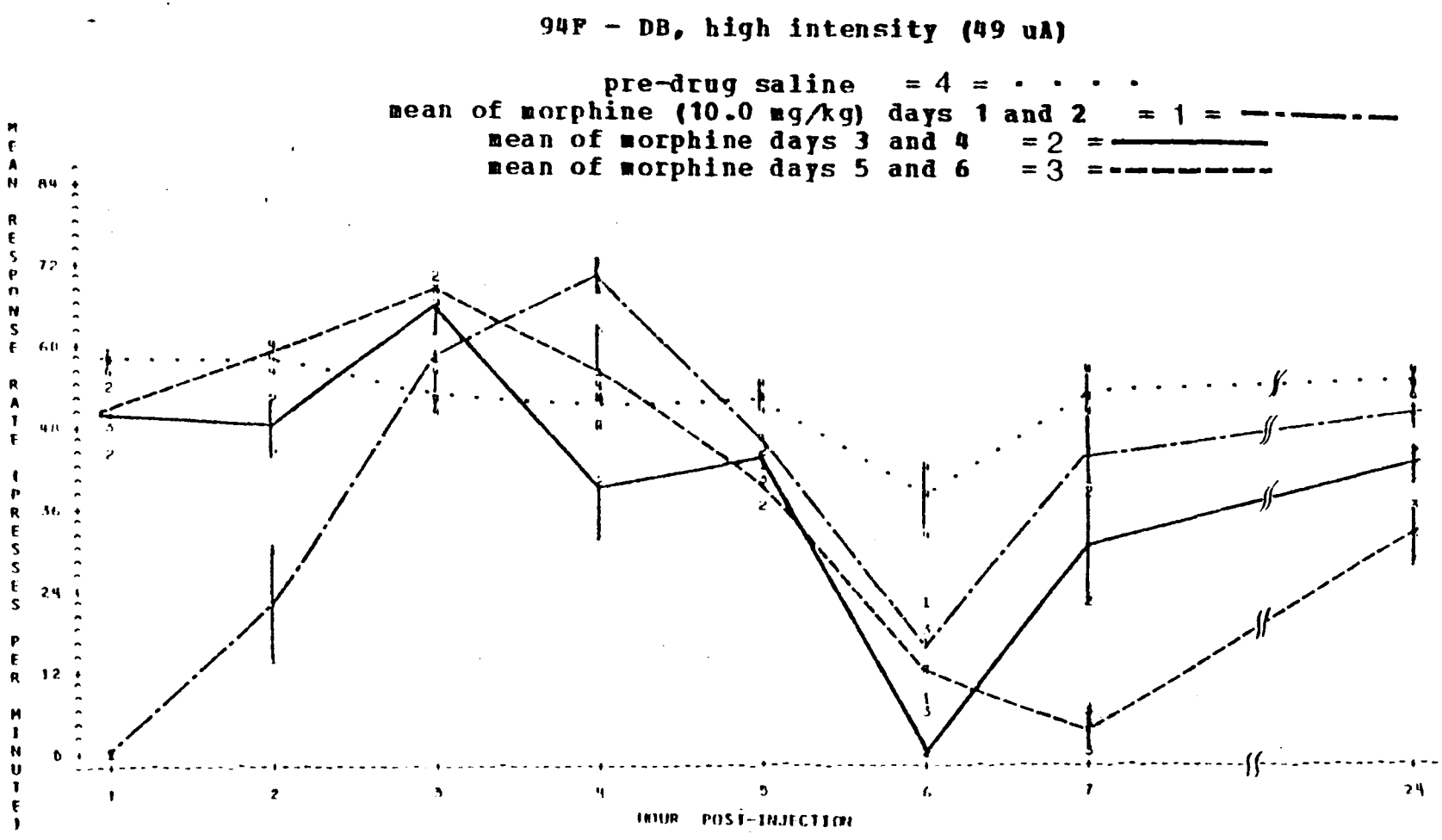
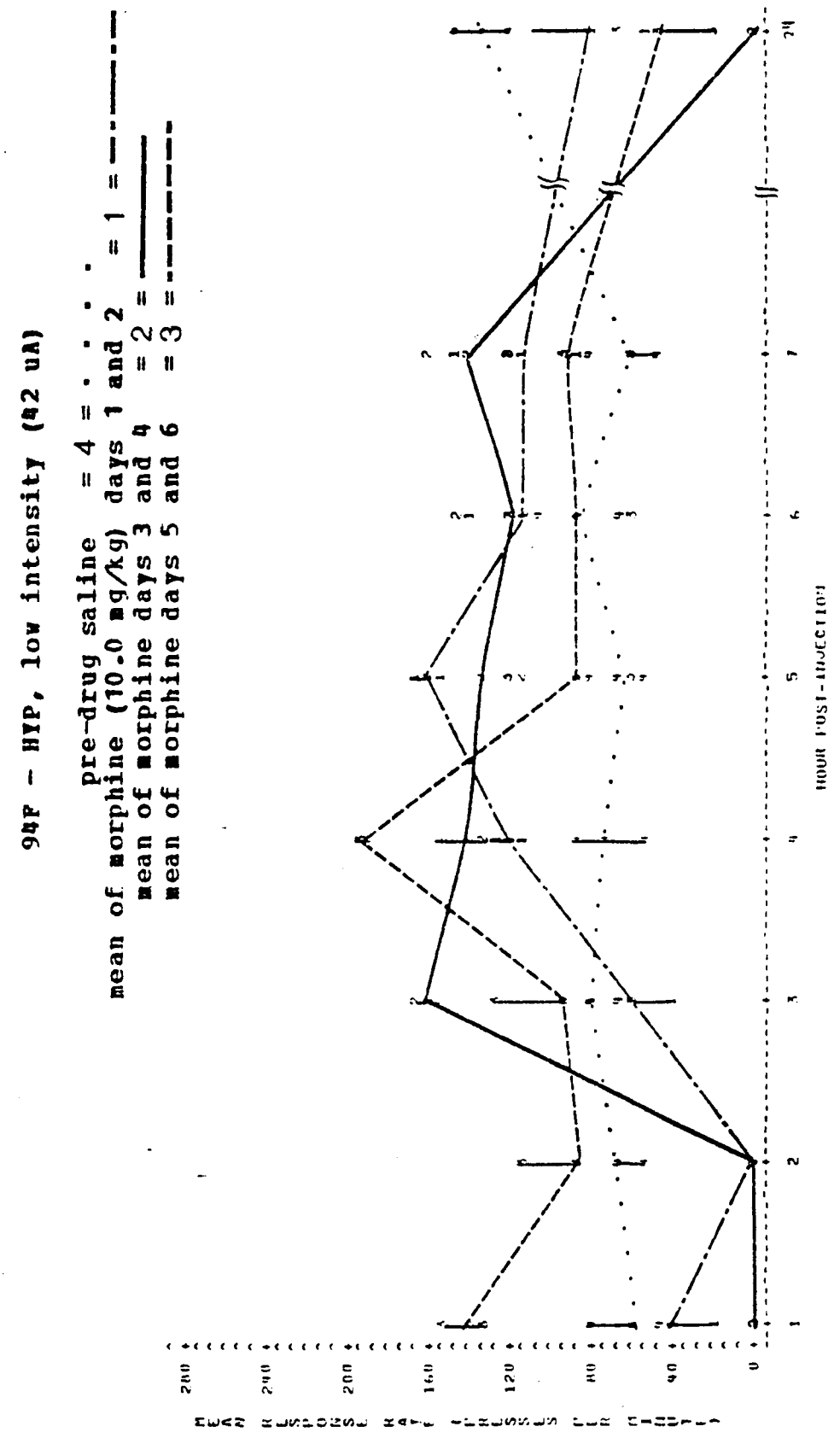

94F - DB, high intensity (49 uA)
pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = ——————
MEAN RESPONSE RATE (PRESSES PER MINUTE)
84
72
60
48
36
24
12
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 74

Figure 75


94F - HYP, low intensity (42 uA)
pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 = —·—·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = — — — —
HOUR POST-INJECTION

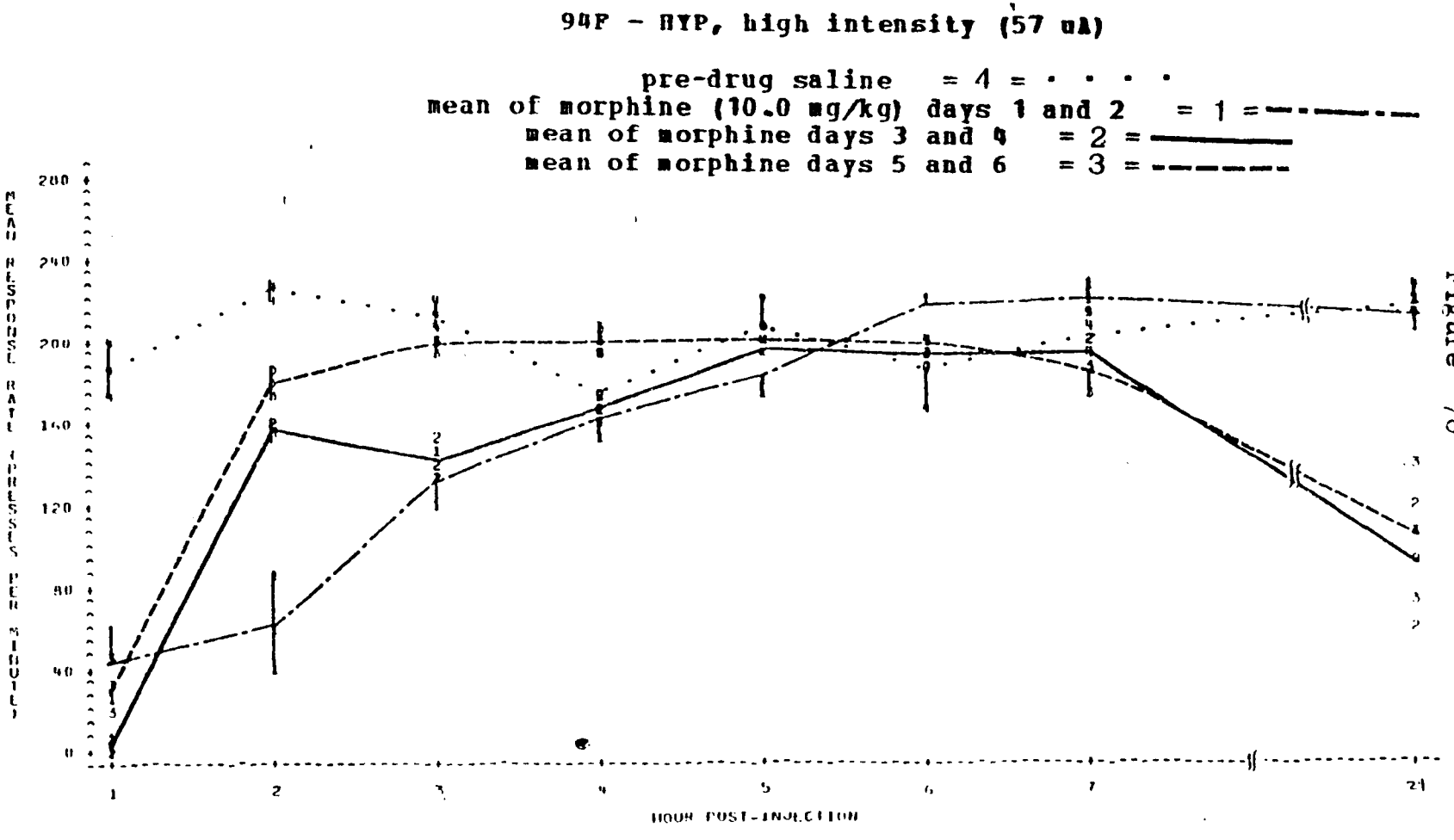

94F - HYP, high intensity (57 mA)
pre-drug saline = 4 = ...
mean of morphine (10.0 mg/kg) days 1 and 2 = 1 = —·—·—
mean of morphine days 3 and 4 = 2 = ——————
mean of morphine days 5 and 6 = 3 = — — — —
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
200
240
200
160
120
80
40
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 76

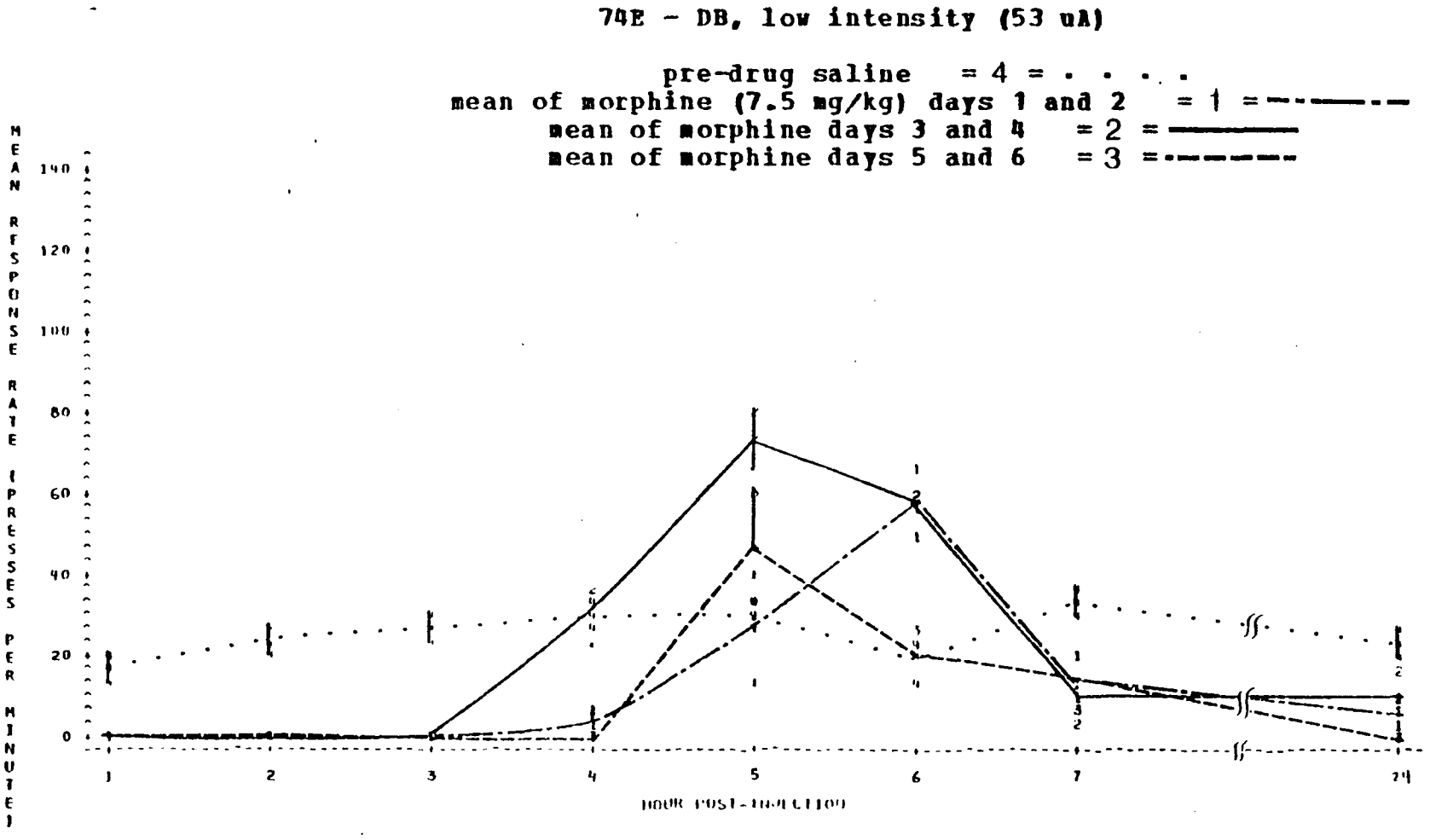

74E - DB, low intensity (53 uA)
pre-drug saline = 4
mean of morphine (7.5 mg/kg) days 1 and 2 = 1
mean of morphine days 3 and 4 = 2
mean of morphine days 5 and 6 = 3
MEAN RESPONSE RATE (PRESSES PER MINUTE)
140
120
100
80
60
40
20
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 77

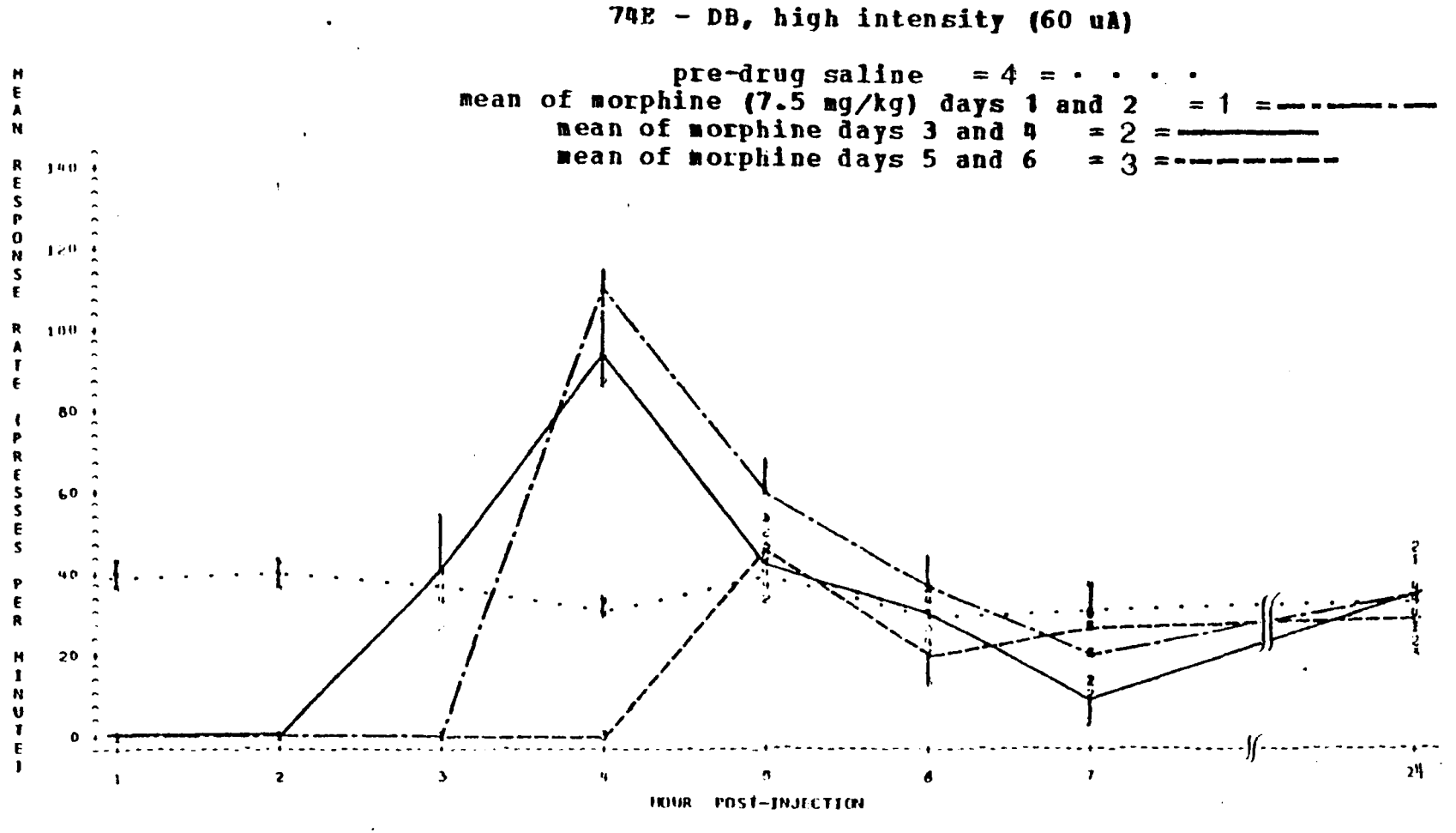

78E - DB, high intensity (60 uA)
pre-drug saline = 4 = ...
mean of morphine (7.5 mg/kg) days 1 and 2 = 1 =
mean of morphine days 3 and 4 = 2 =
mean of morphine days 5 and 6 = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
140
120
100
80
60
40
20
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 78

74E - HYP, low intensity (42 uA)

pre-drug saline = 4 = ...
mean of morphine (7.5 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = — — —

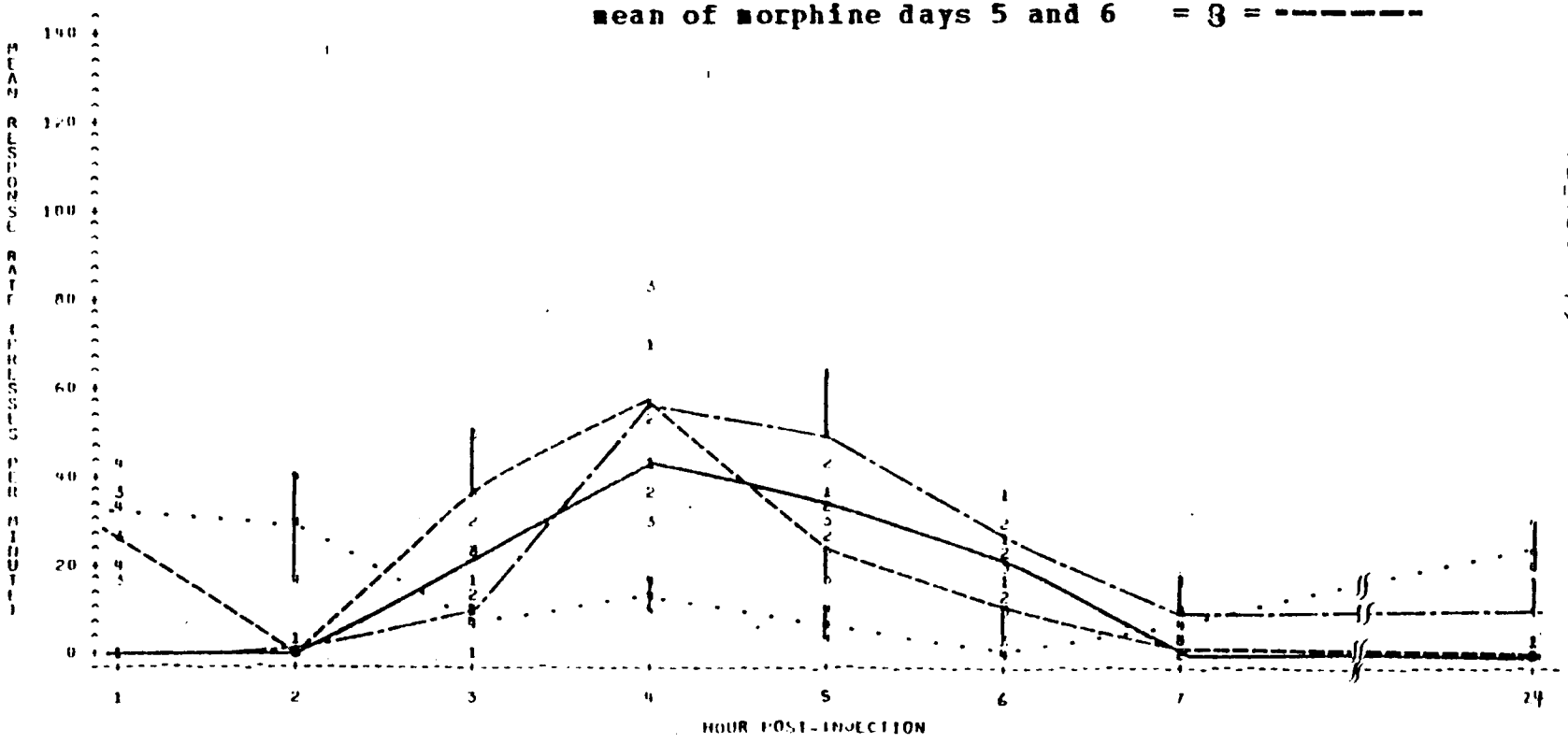


Figure 79

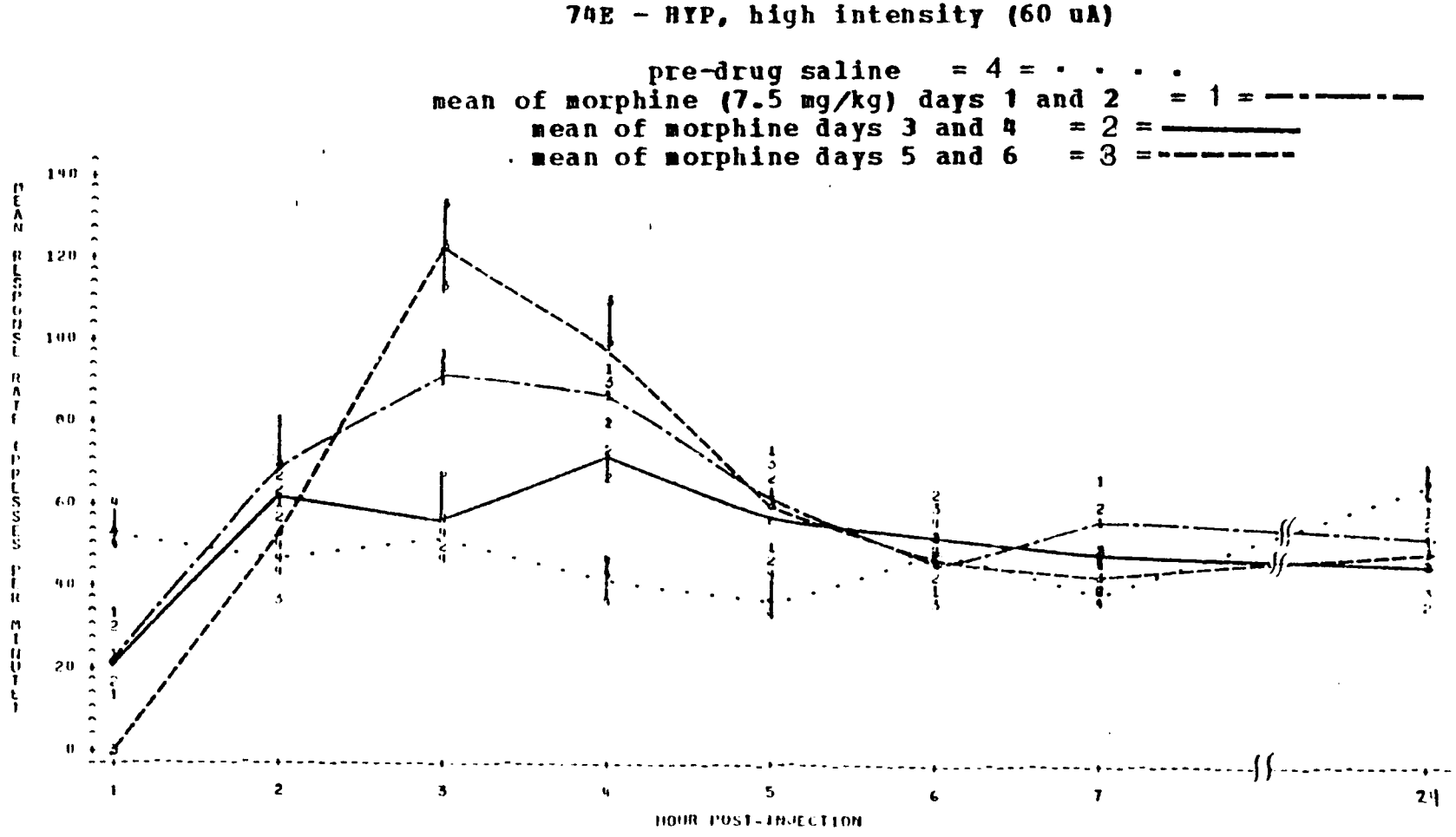

74E - HYP, high intensity (60 uA)
pre-drug saline = 4 = ...
mean of morphine (7.5 mg/kg) days 1 and 2 = 1 = —·—·—·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = — — — —
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
0
20
40
60
80
100
120
140
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 80

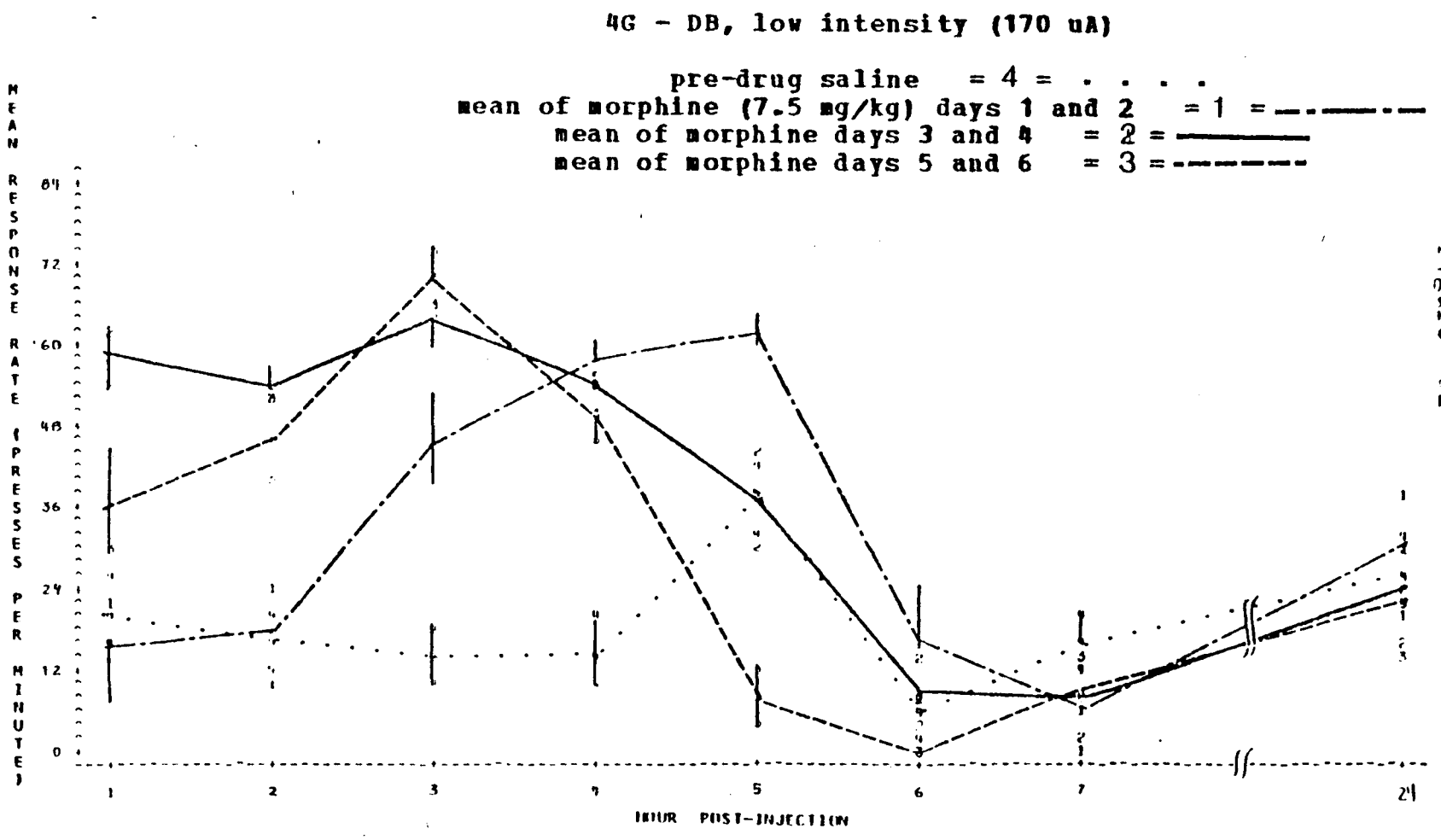

4G - DB, low intensity (170 uA)
pre-drug saline = 4 = ...
mean of morphine (7.5 mg/kg) days 1 and 2 = 1 = _ . _ _ _ . _
mean of morphine days 3 and 4 = 2 = _____
mean of morphine days 5 and 6 = 3 = _ _ _ _ _
MEAN RESPONSE RATE (PRESSES PER MINUTE)
84
72
60
48
36
24
12
0
1
2
3
4
5
6
7
21
HOUR POST-INJECTION

Figure 81

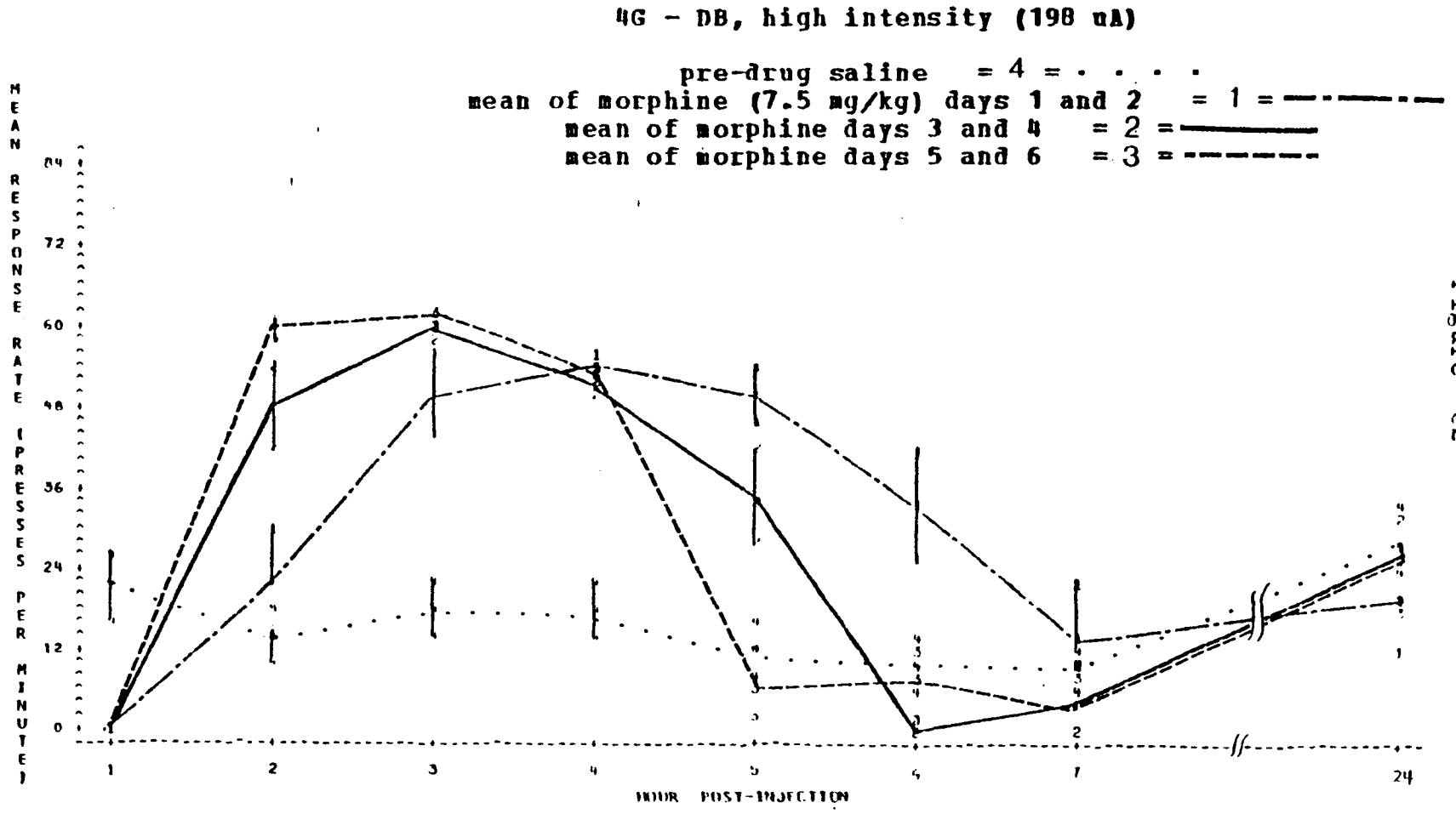

4G - DB, high intensity (198 uA)
pre-drug saline = 4 = ...
mean of morphine (7.5 mg/kg) days 1 and 2 = 1 = —·—·—
mean of morphine days 3 and 4 = 2 = ——
mean of morphine days 5 and 6 = 3 = – – –
MEAN RESPONSE RATE (PRESSES PER MINUTE)
84
72
60
48
36
24
12
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 82

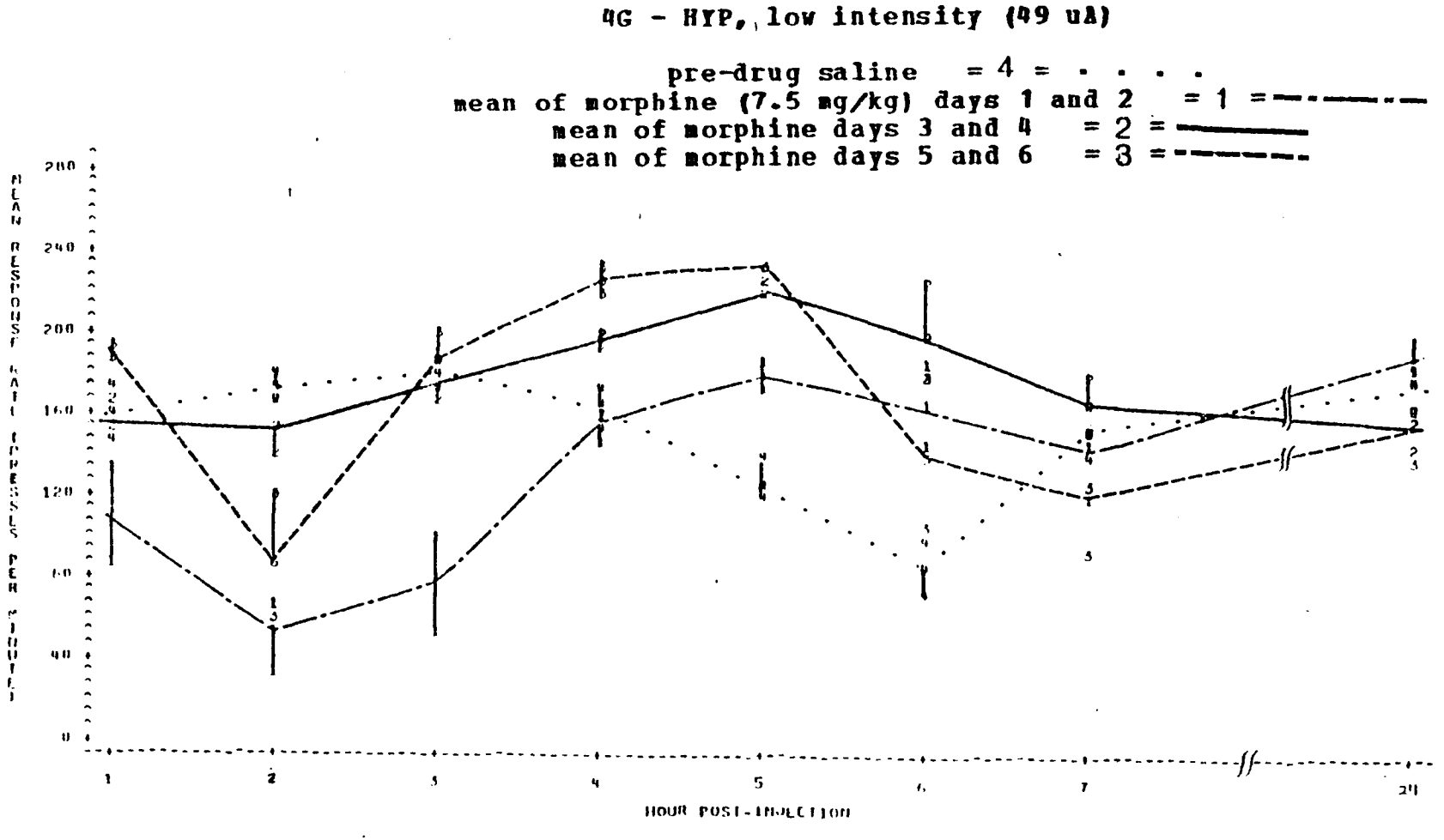

4G - HYP, low intensity (49 uA)
pre-drug saline = 4 = ...
mean of morphine (7.5 mg/kg) days 1 and 2 = 1 =
mean of morphine days 3 and 4 = 2 =
mean of morphine days 5 and 6 = 3 =
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
200
240
200
160
120
80
40
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 83

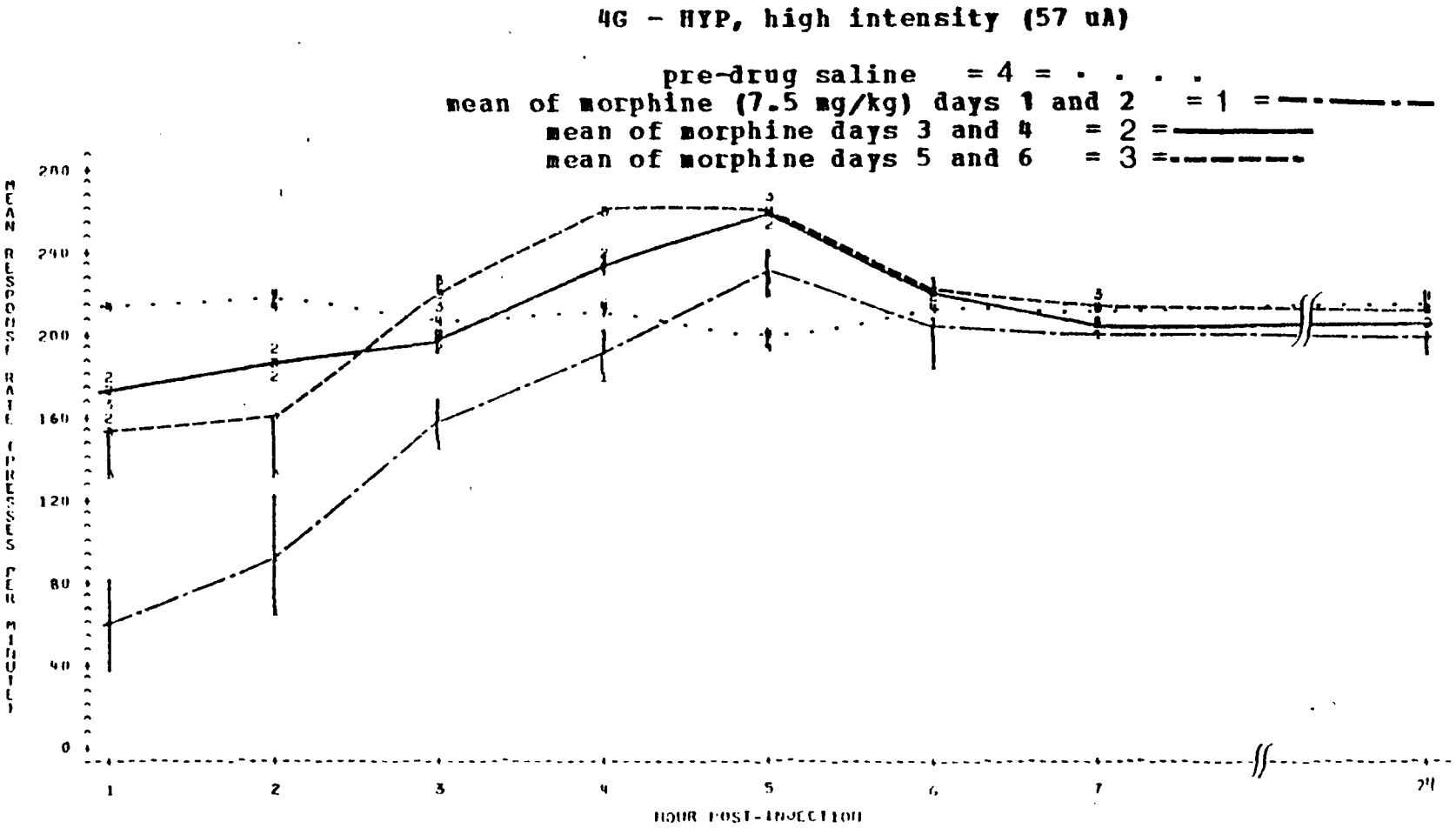

4G - HYP, high intensity (57 uA)
pre-drug saline = 4 = ...
mean of morphine (7.5 mg/kg) days 1 and 2 = 1 =
mean of morphine days 3 and 4 = 2 =
mean of morphine days 5 and 6 = 3 =
MEAN RESPONSE RATE (PRESSES PER MINUTE)
0
40
80
120
160
200
240
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 84

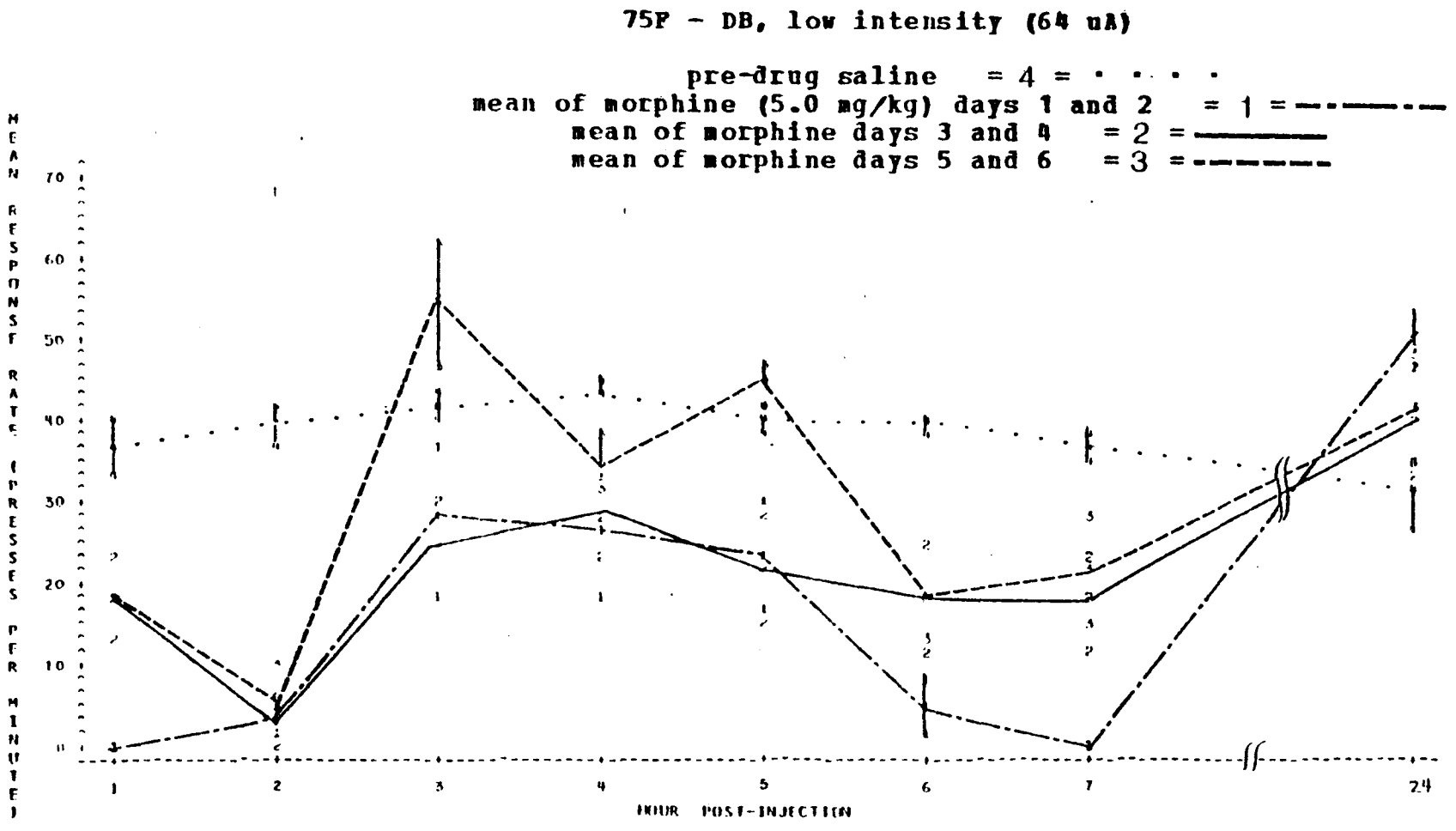

75P - DB, low intensity (64 uA)
pre-drug saline = 4 = • • • • •
mean of morphine (5.0 mg/kg) days 1 and 2 = 1 = — • — — • —
mean of morphine days 3 and 4 = 2 = ——————
mean of morphine days 5 and 6 = 3 = — — — — —
MEAN RESPONSE RATE (PRESSES PER MINUTE)
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 85

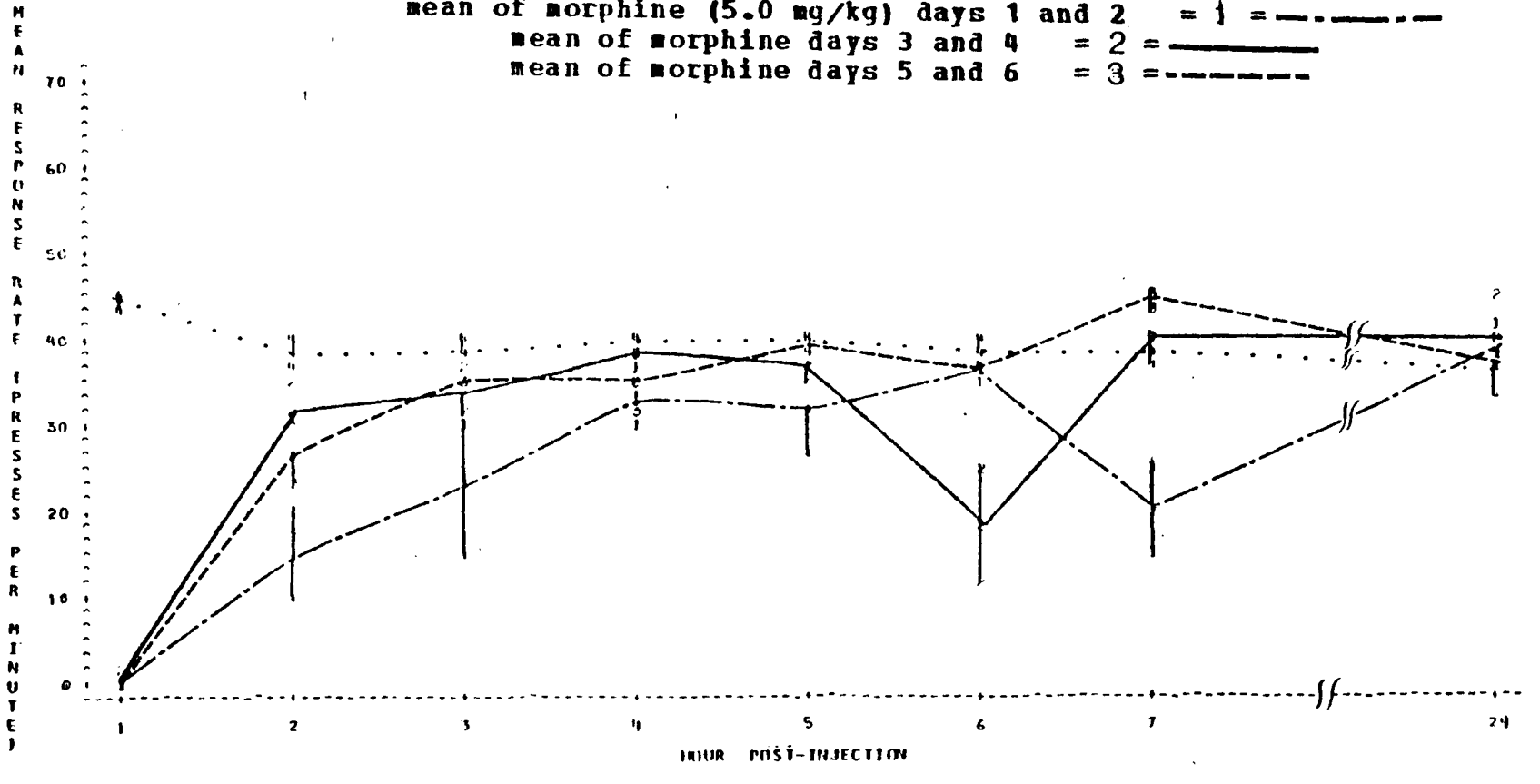

75P - DB, high intensity (78 uA)
pre-drug saline = 4 = ...
mean of morphine (5.0 mg/kg) days 1 and 2 = 1 = —.——.—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 =-——-——
MEAN RESPONSE RATE (PRESSES PER MINUTE)
0
10
20
30
40
50
60
70
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 86

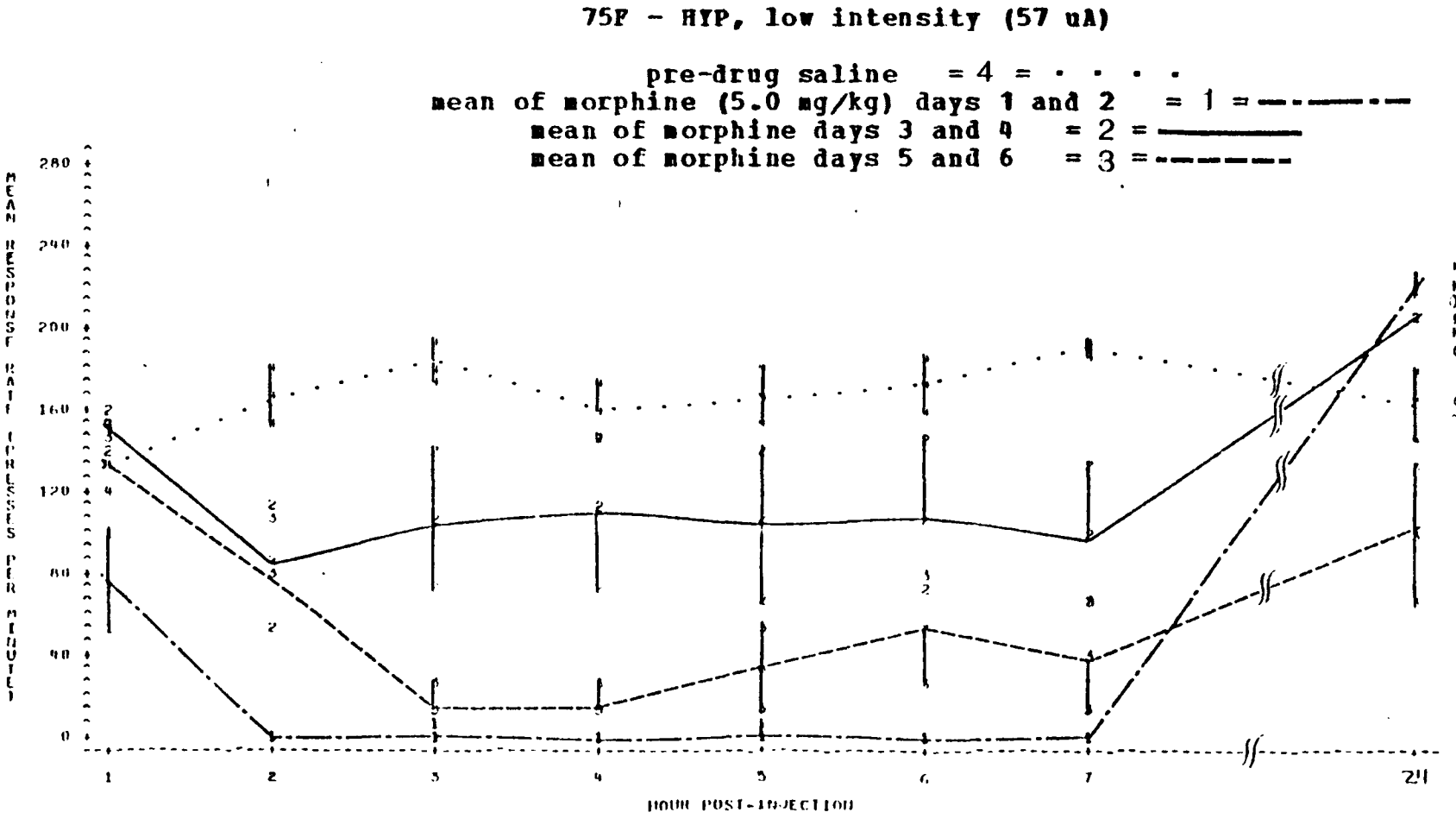

75F - HYP, low intensity (57 uA)
pre-drug saline = 4
mean of morphine (5.0 mg/kg) days 1 and 2 = 1
mean of morphine days 3 and 4 = 2
mean of morphine days 5 and 6 = 3
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
280
240
200
160
120
80
40
0
1
2
3
4
5
6
7
21
HOUR POST-INJECTION

Figure 87

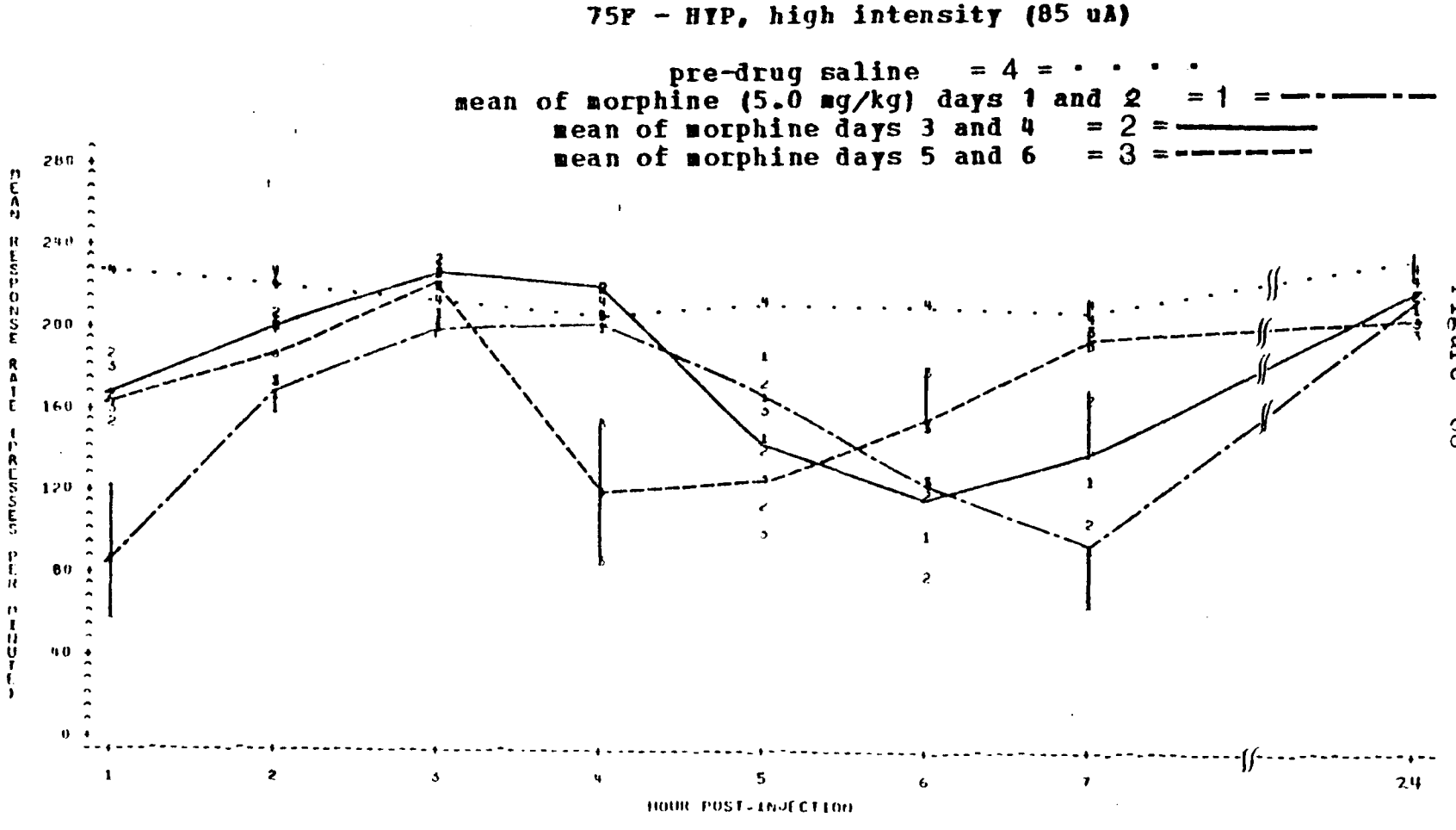

75P - HYP, high intensity (85 uA)
pre-drug saline = 4
mean of morphine (5.0 mg/kg) days 1 and 2 = 1
mean of morphine days 3 and 4 = 2
mean of morphine days 5 and 6 = 3
MEAN RESPONSE RATE (RESSES PER MINUTE)
280
240
200
160
120
80
40
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 88

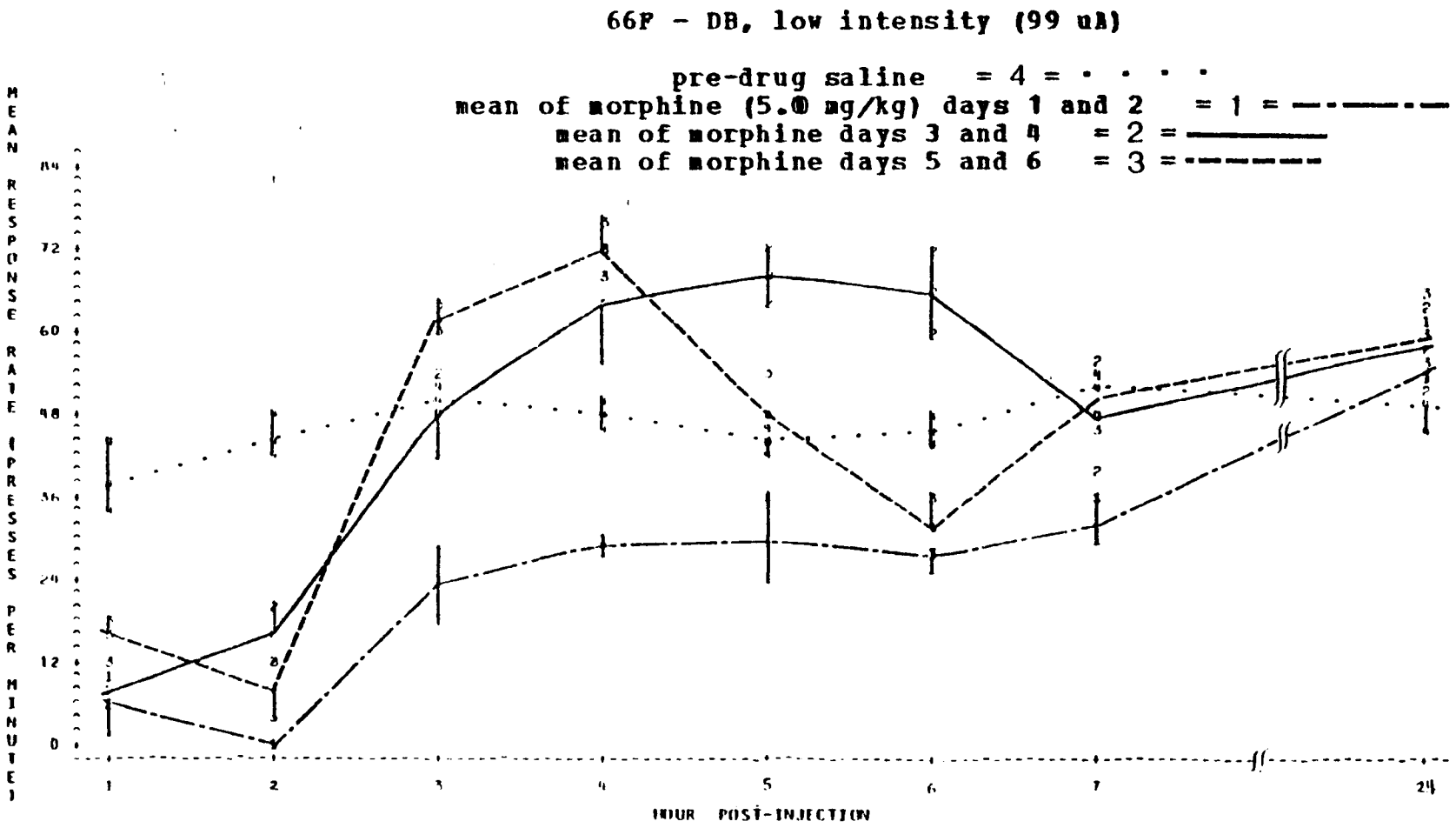

66P - DB, low intensity (99 uA)
pre-drug saline = 4 = ...
mean of morphine (5.0 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = ·——·——
MEAN RESPONSE RATE (PRESSES PER MINUTE)
0
12
24
36
48
60
72
84
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 89

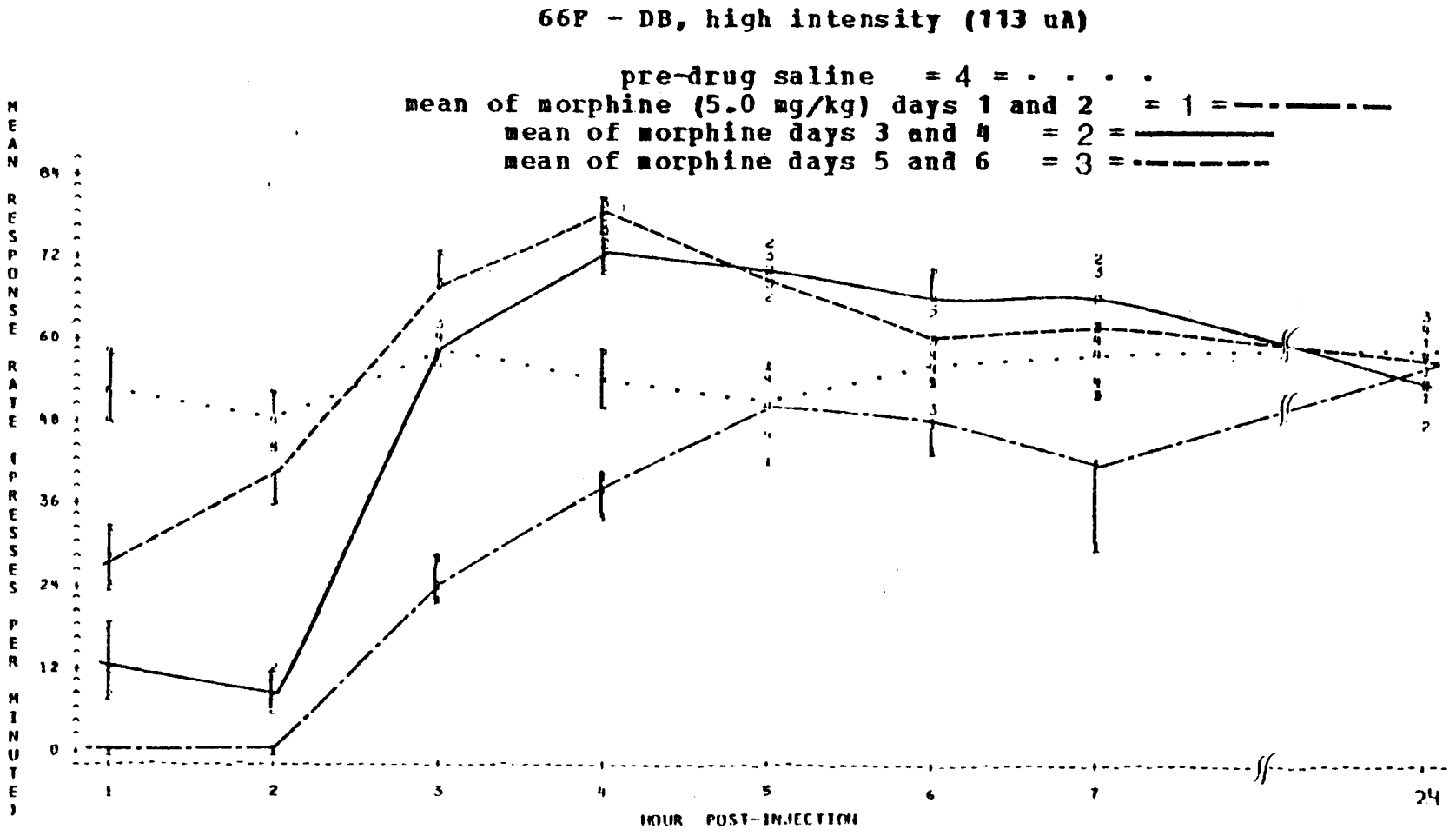

66F - DB, high intensity (113 uA)
pre-drug saline = 4
mean of morphine (5.0 mg/kg) days 1 and 2 = 1
mean of morphine days 3 and 4 = 2
mean of morphine days 5 and 6 = 3
MEAN RESPONSE RATE (PRESSES PER MINUTE)
84
72
60
48
36
24
12
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 90

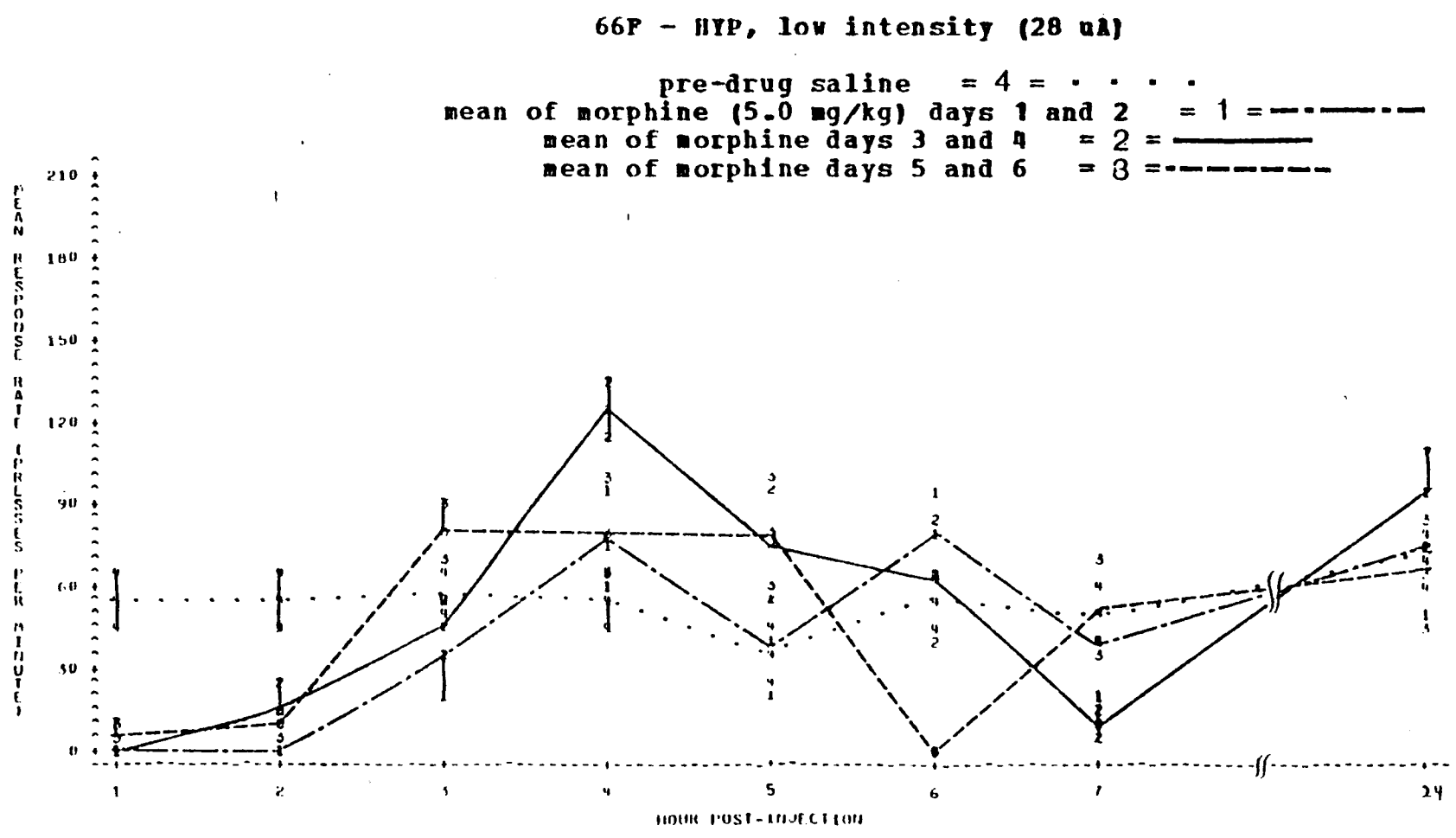

66P - HYP, low intensity (28 uA)
pre-drug saline = 4
mean of morphine (5.0 mg/kg) days 1 and 2 = 1
mean of morphine days 3 and 4 = 2
mean of morphine days 5 and 6 = 3
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
210
180
150
120
90
60
30
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 91

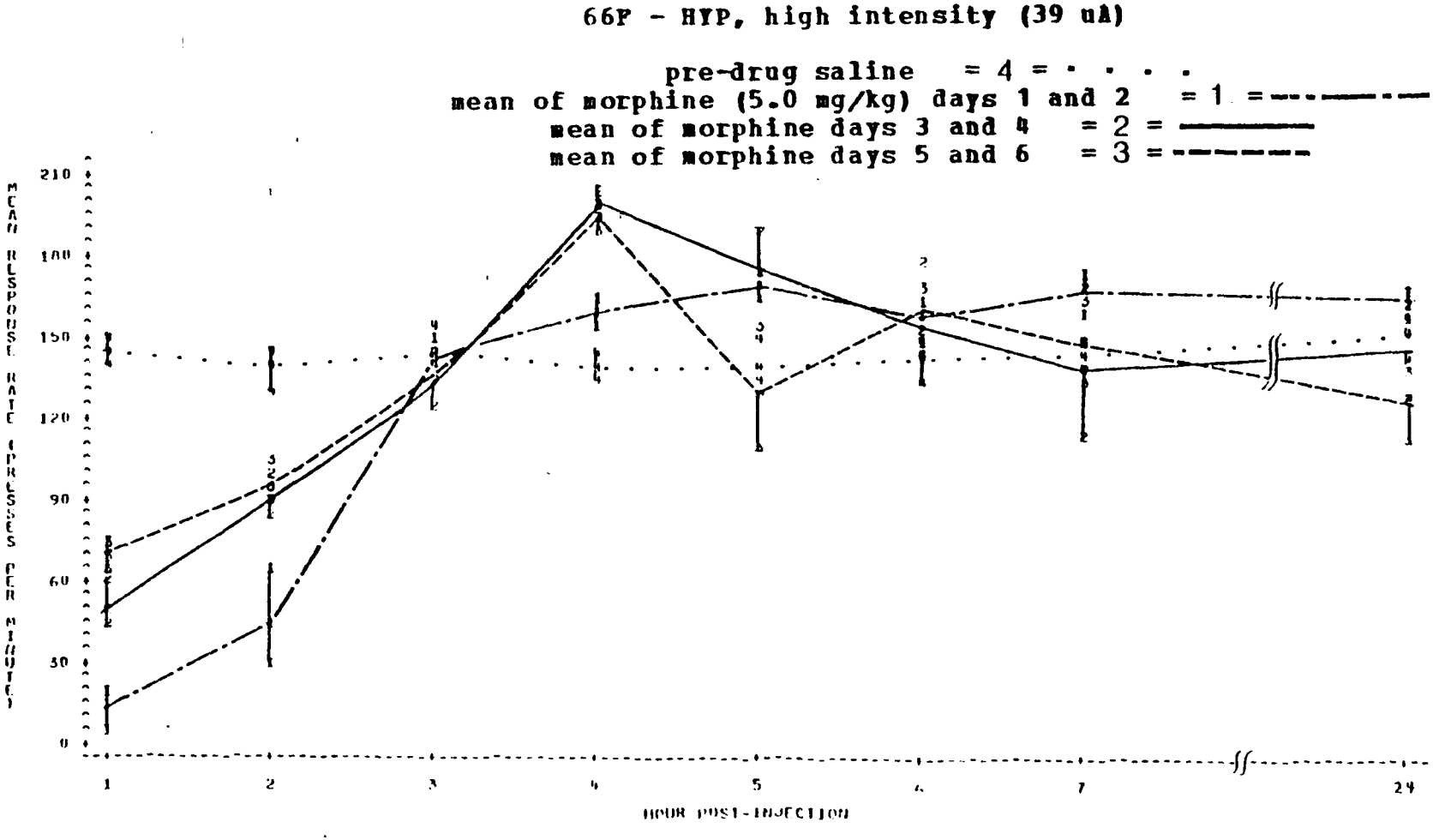

66P - HYP, high intensity (39 uA)
pre-drug saline = 4 = ...
mean of morphine (5.0 mg/kg) days 1 and 2 = 1 = ---.---.---
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = - - - -
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
210
180
150
120
90
60
30
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 92

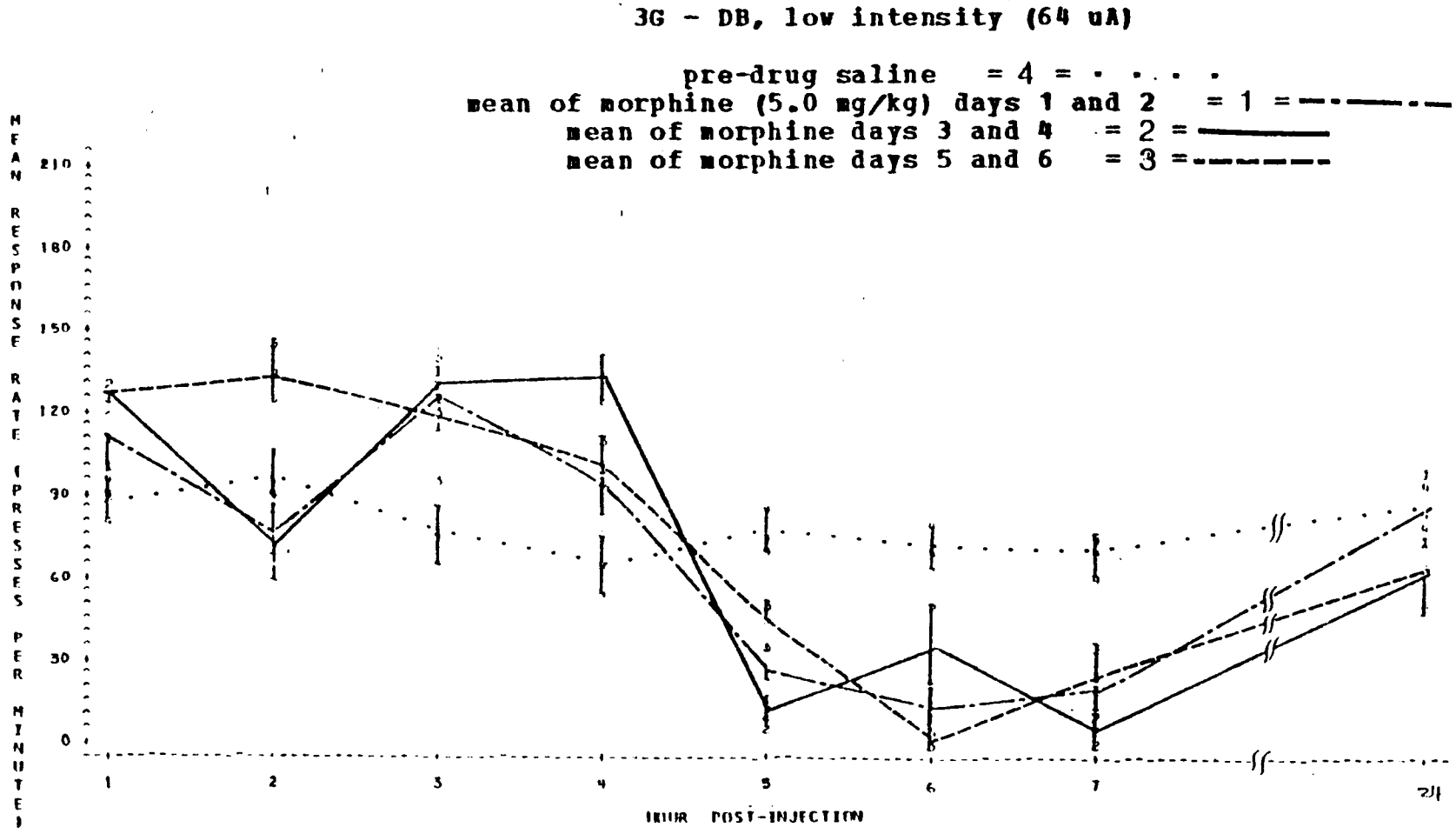

3G - DB, low intensity (64 uA)
pre-drug saline = 4
mean of morphine (5.0 mg/kg) days 1 and 2 = 1
mean of morphine days 3 and 4 = 2
mean of morphine days 5 and 6 = 3
MEAN RESPONSE RATE (PRESSES PER MINUTE)
210
180
150
120
90
60
30
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 93

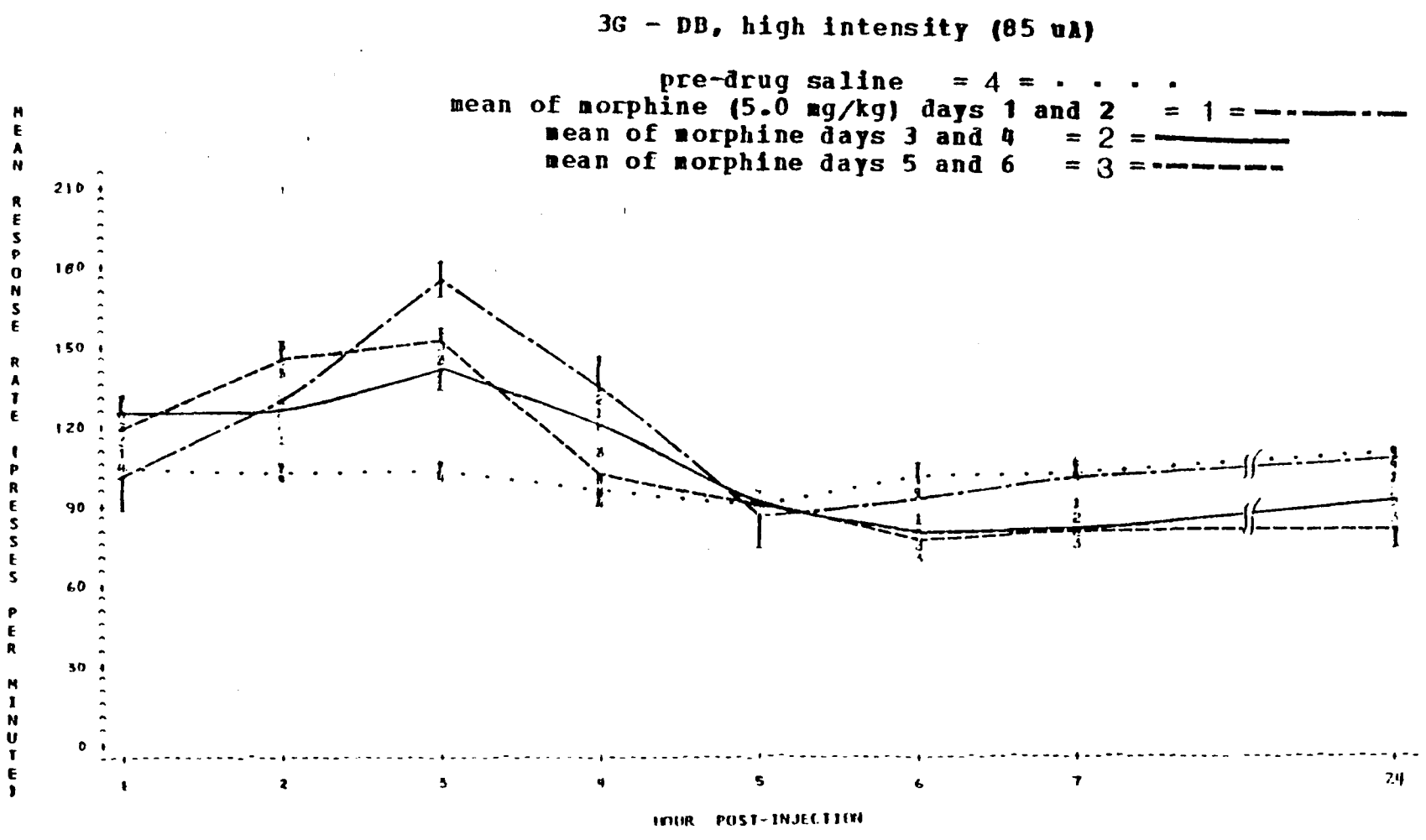

3G - DB, high intensity (85 uA)
pre-drug saline = 4 = ...
mean of morphine (5.0 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ——————
mean of morphine days 5 and 6 = 3 = — — — —
MEAN RESPONSE RATE (PRESSES PER MINUTE)
210
180
150
120
90
60
30
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 94

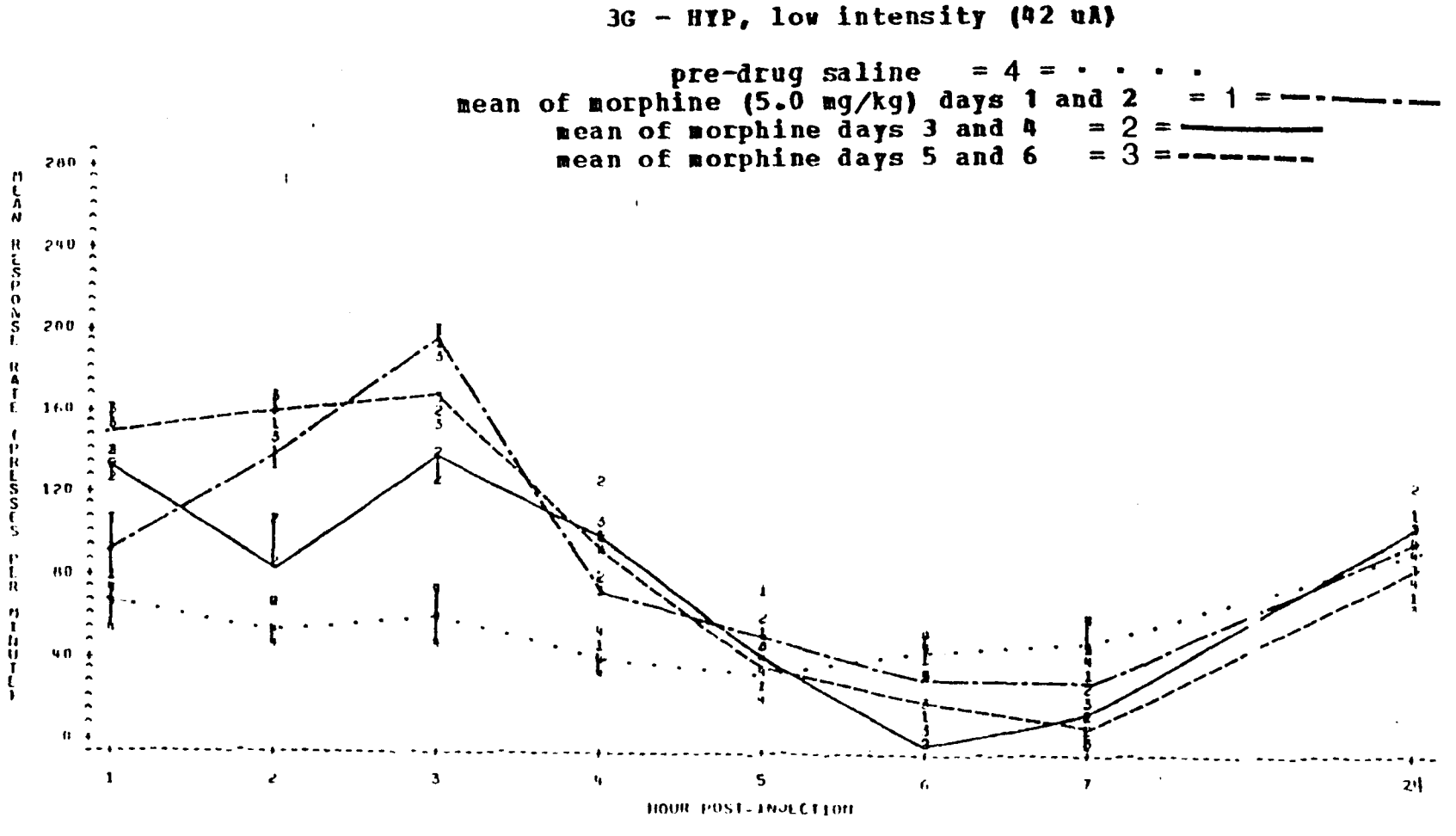

3G - HYP, low intensity (92 uA)
pre-drug saline = 4 = ...
mean of morphine (5.0 mg/kg) days 1 and 2 = 1 = —·—·—·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = - - - - -
MEAN RESPONSE RATE (PRESSES PER MINUTE)
0
40
80
120
160
200
240
280
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 95

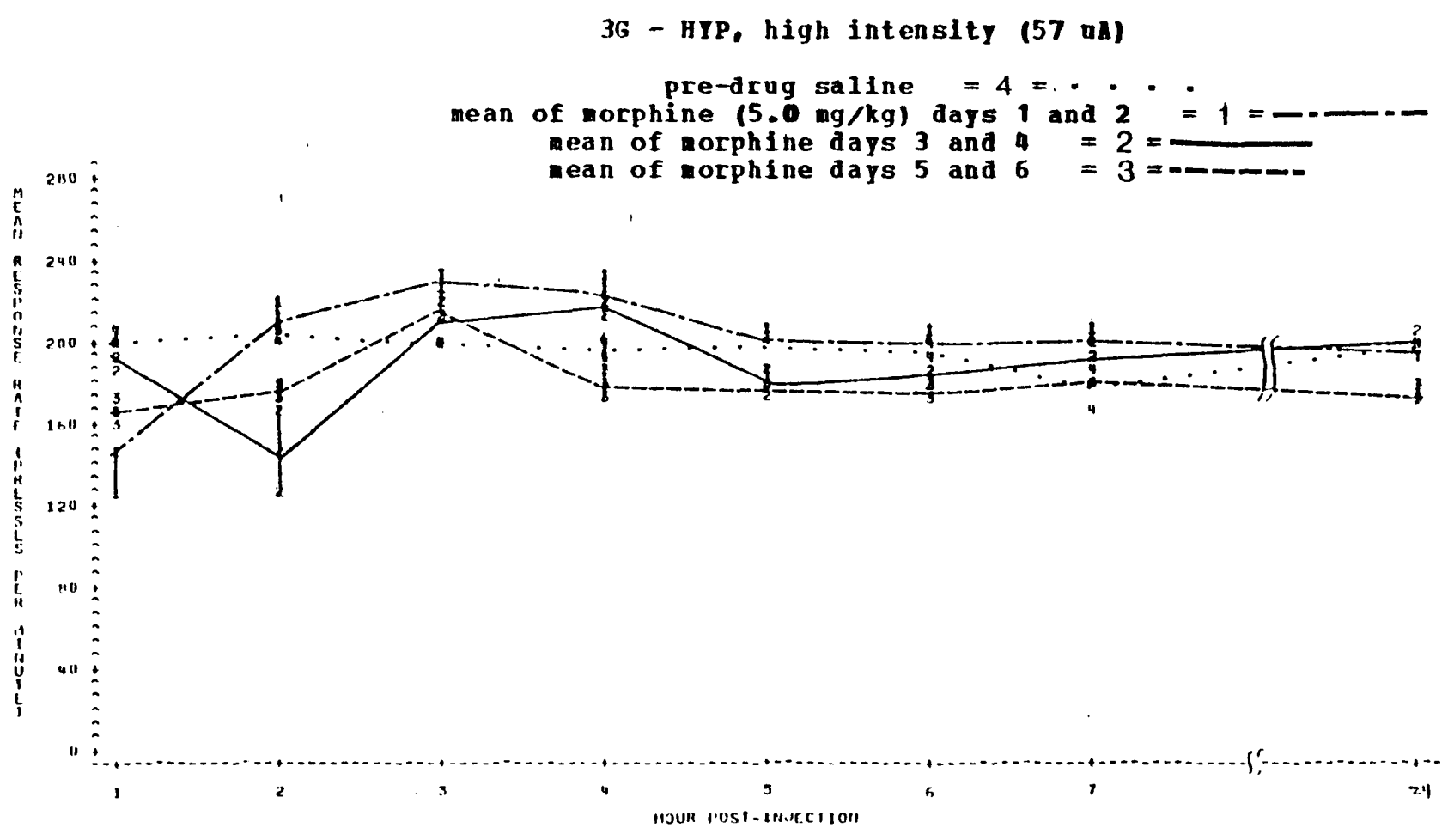

3G - HYP, high intensity (57 uA)
pre-drug saline = 4 = ...
mean of morphine (5.0 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = — — —
MEAN RESPONSE RATE (PRESSES PER MINUTE)
280
240
200
160
120
80
40
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 96

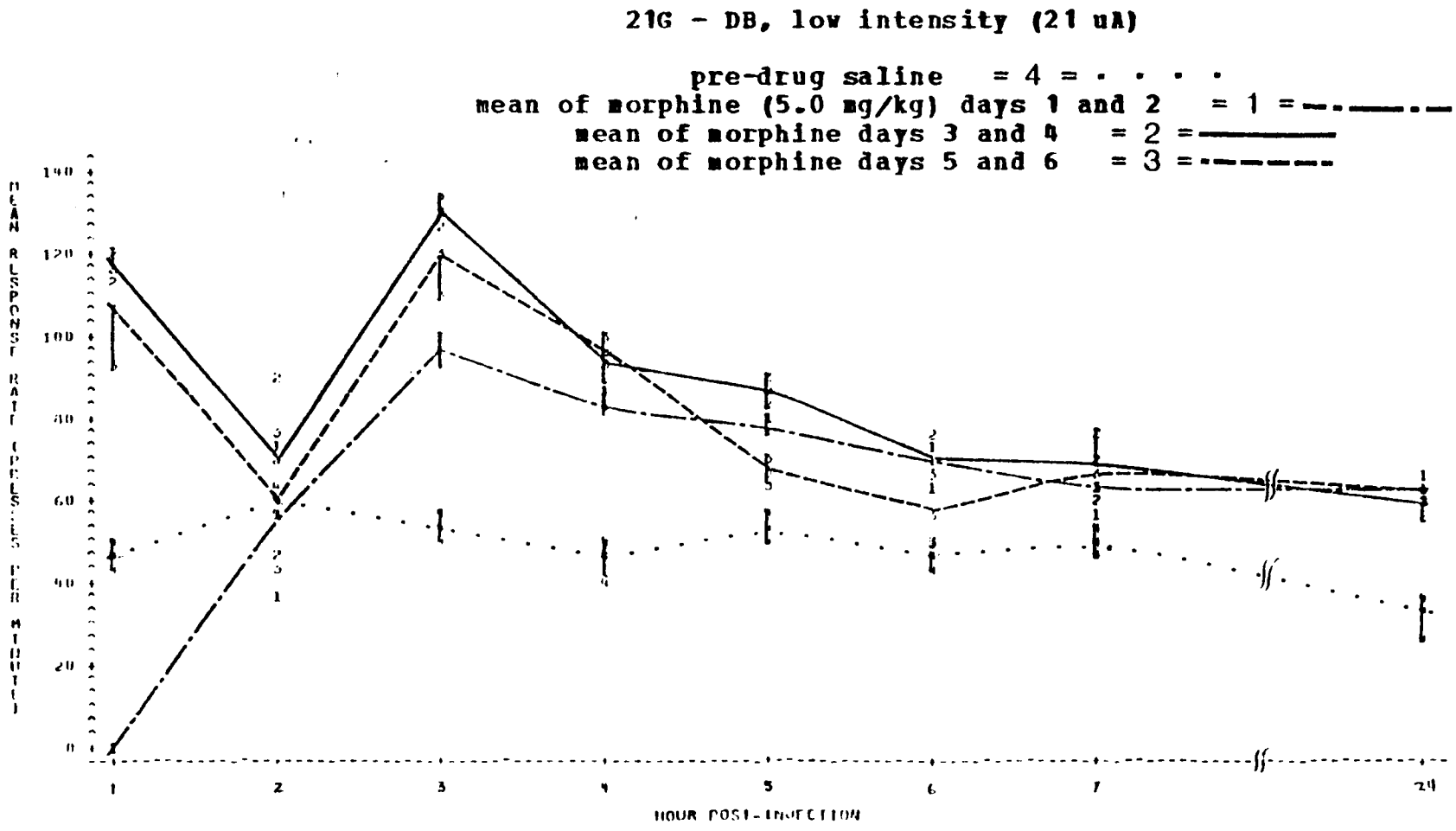

21G - DB, low intensity (21 uA)
pre-drug saline = 4
mean of morphine (5.0 mg/kg) days 1 and 2 = 1
mean of morphine days 3 and 4 = 2
mean of morphine days 5 and 6 = 3
HOUR POST-INJECTION

Figure 97

21G - DB, high intensity (35 uA)

pre-drug saline = 4 = ...
mean of morphine (5.0 mg/kg) days 1 and 2 = 1 = —·—·—·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = -——-——

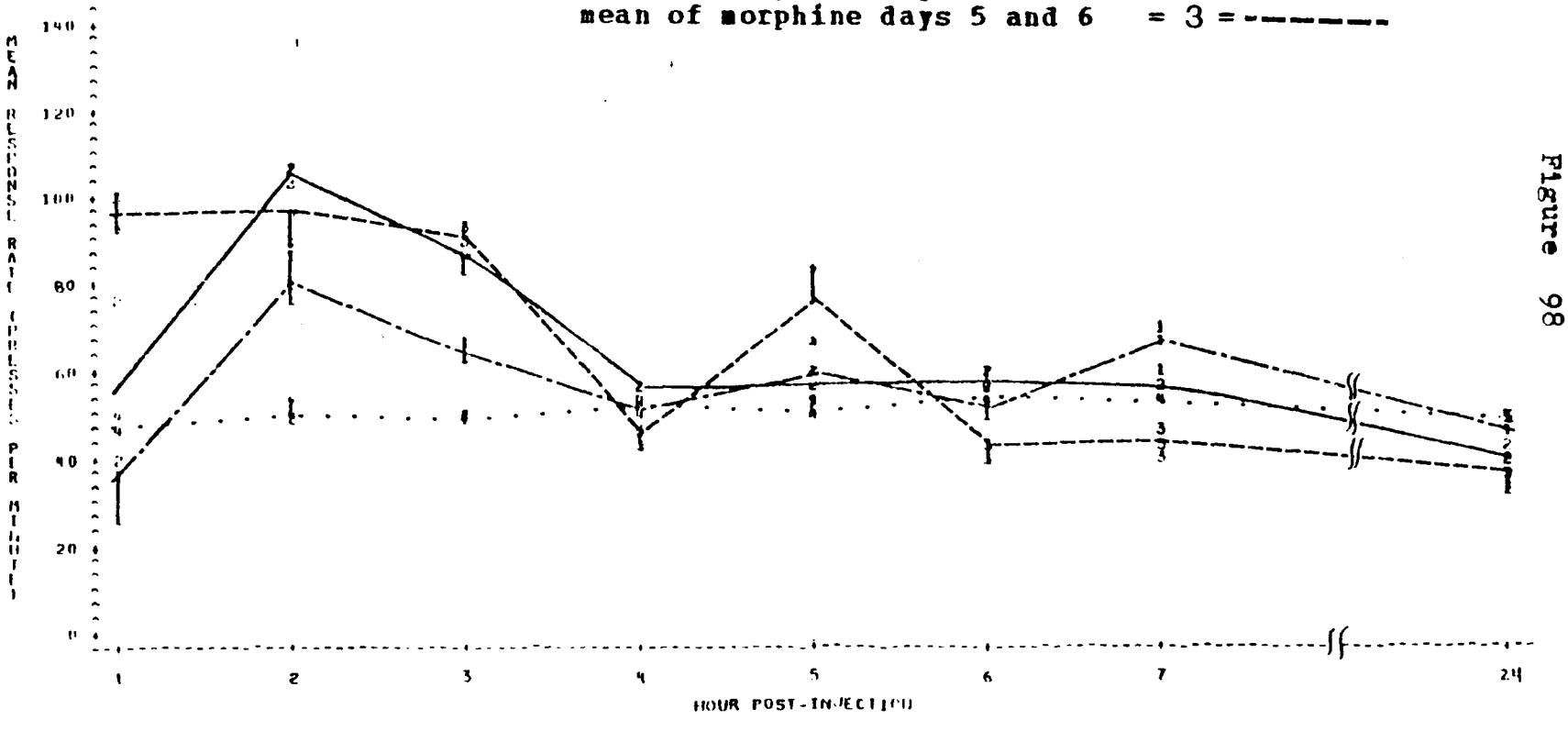


Figure 98

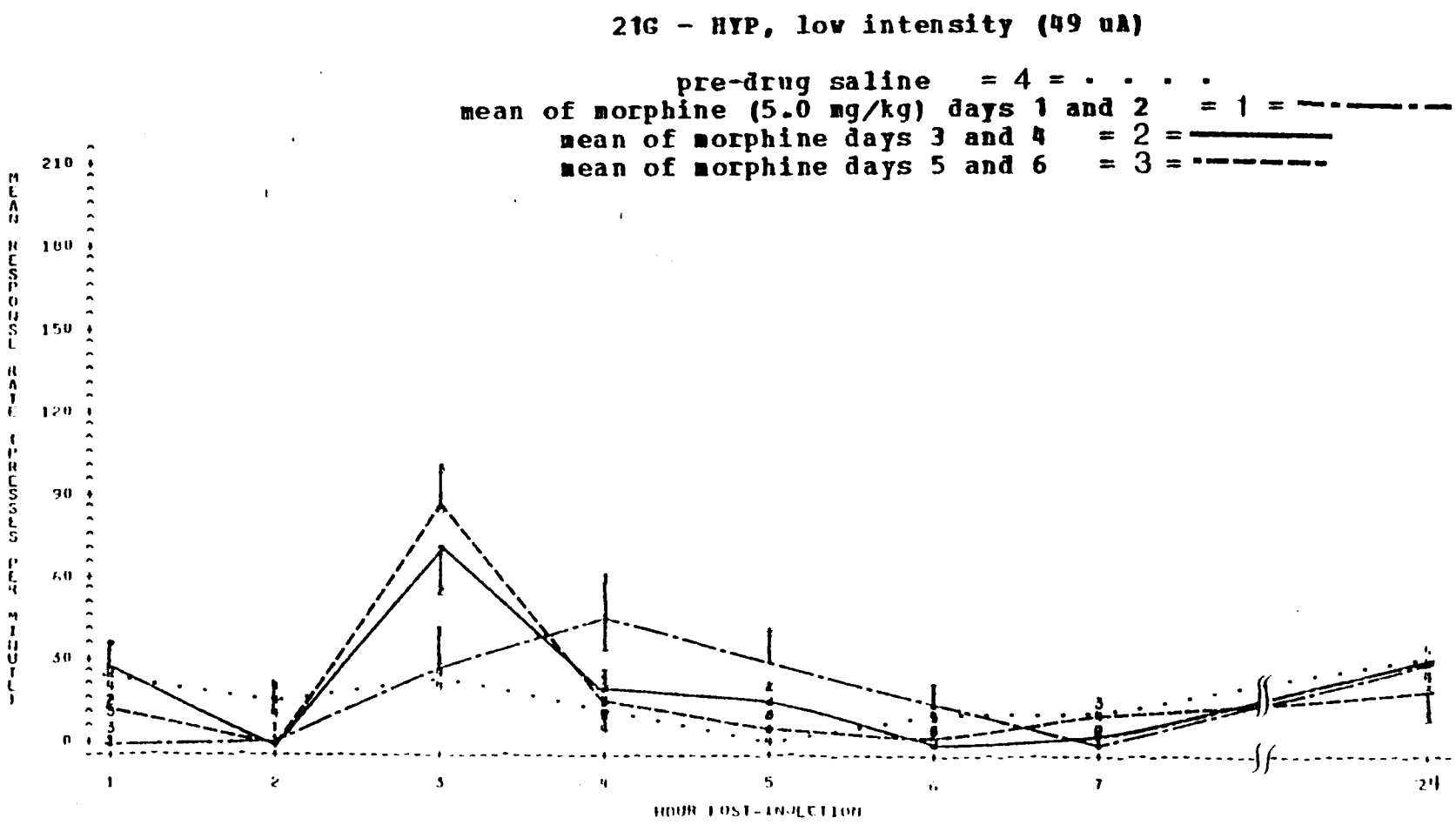

21G - HYP, low intensity (49 uA)
pre-drug saline = 4 = ...
mean of morphine (5.0 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = ·——·——
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
210
180
150
120
90
60
30
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 99

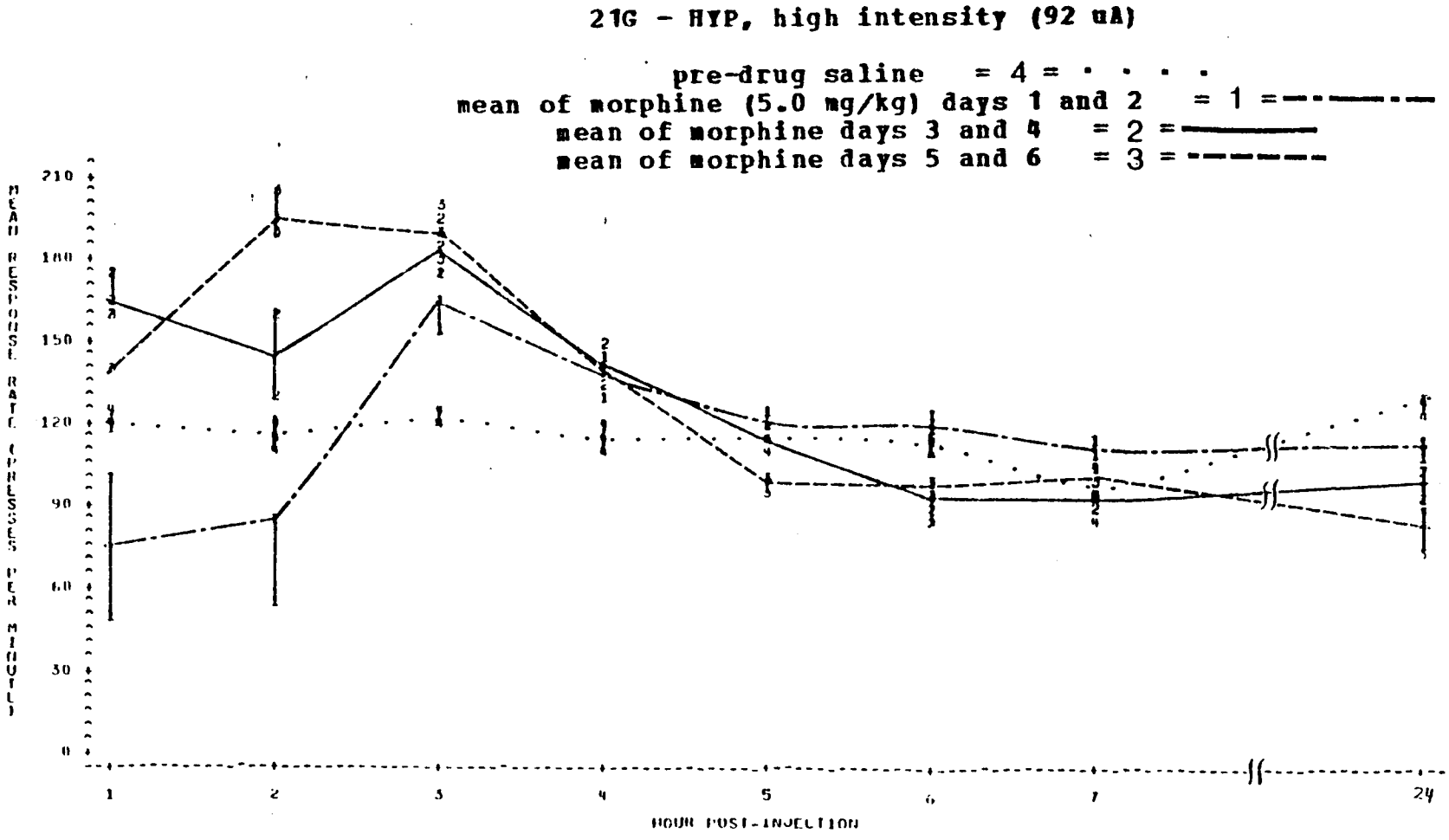
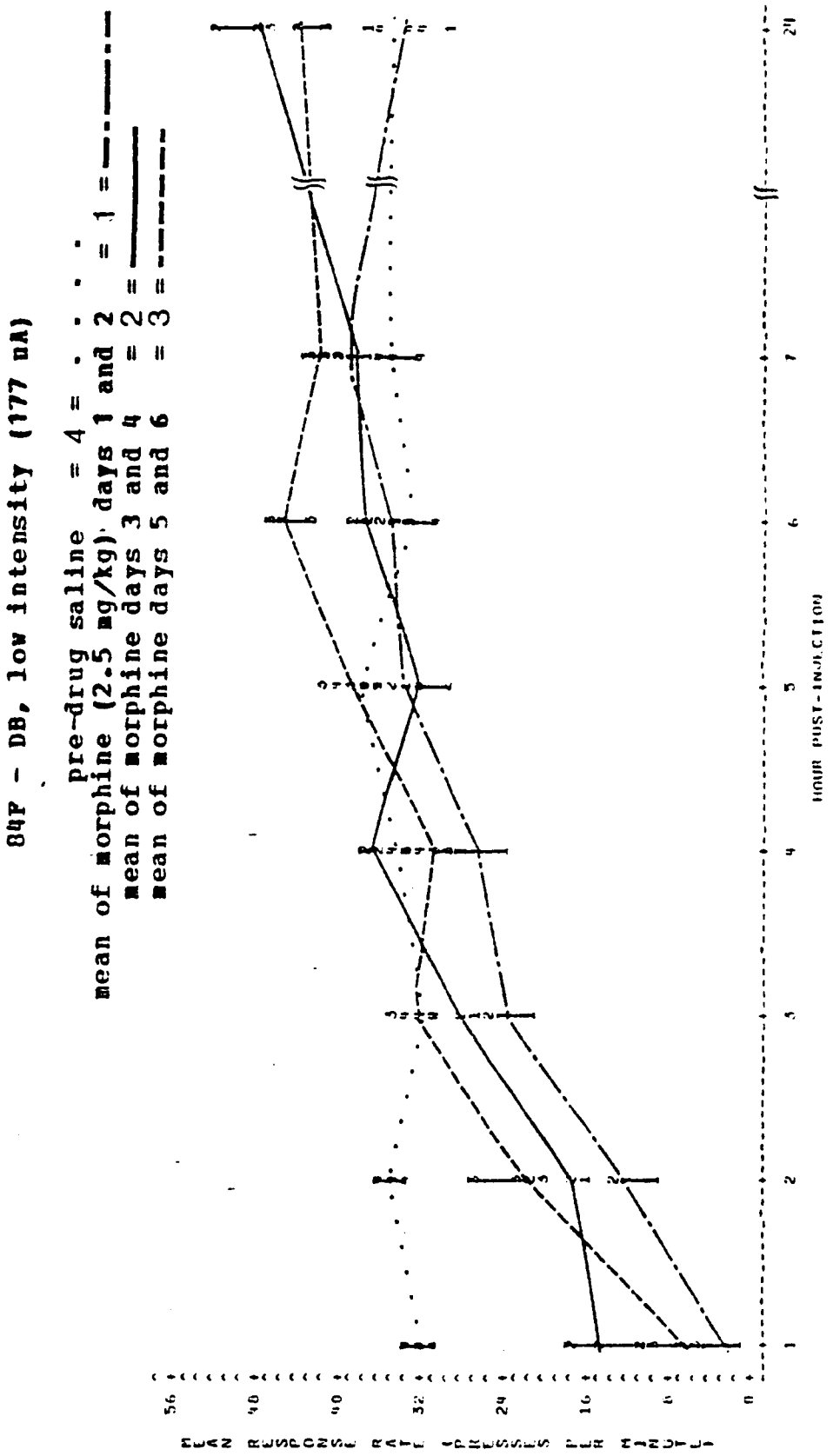

21G - HYP, high intensity (92 uA)
pre-drug saline = 4
mean of morphine (5.0 mg/kg) days 1 and 2 = 1
mean of morphine days 3 and 4 = 2
mean of morphine days 5 and 6 = 3
MEAN RESPONSE RATE (RESPONSES PER MINUTE)
210
180
150
120
90
60
30
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 100

Figure 101


84P - DB, low intensity (177 nA)
pre-drug saline = 4 = ...
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = —·—·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = - - - - -
HOUR POST-INJECTION

84P - DB, high intensity (199 uA)

pre-drug saline = 4 = ...
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = —·—·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = - - - -

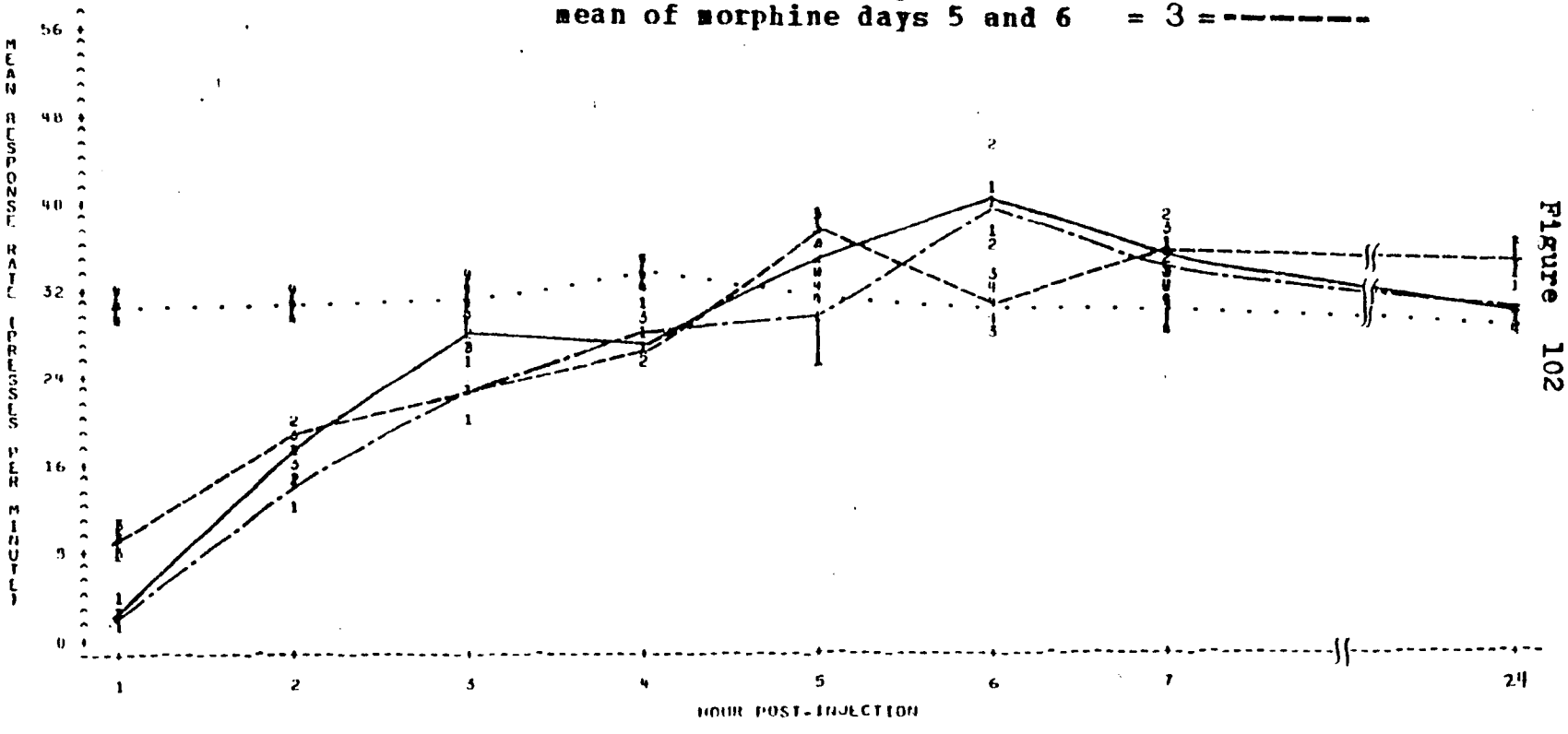


Figure 102

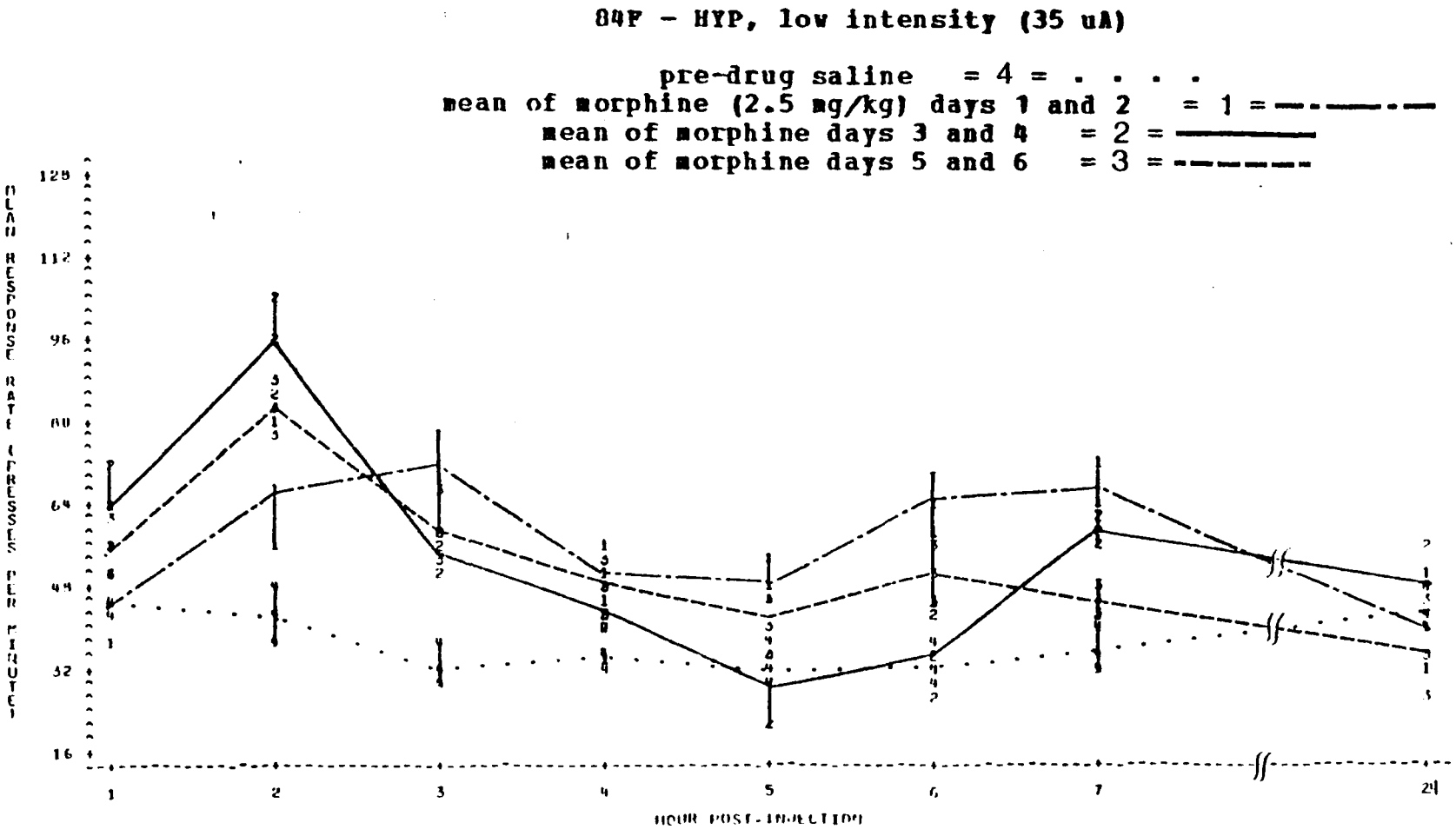

84F - HYP, low intensity (35 uA)
pre-drug saline = 4 = ...
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = — — —
128
112
96
80
64
48
32
16
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 103

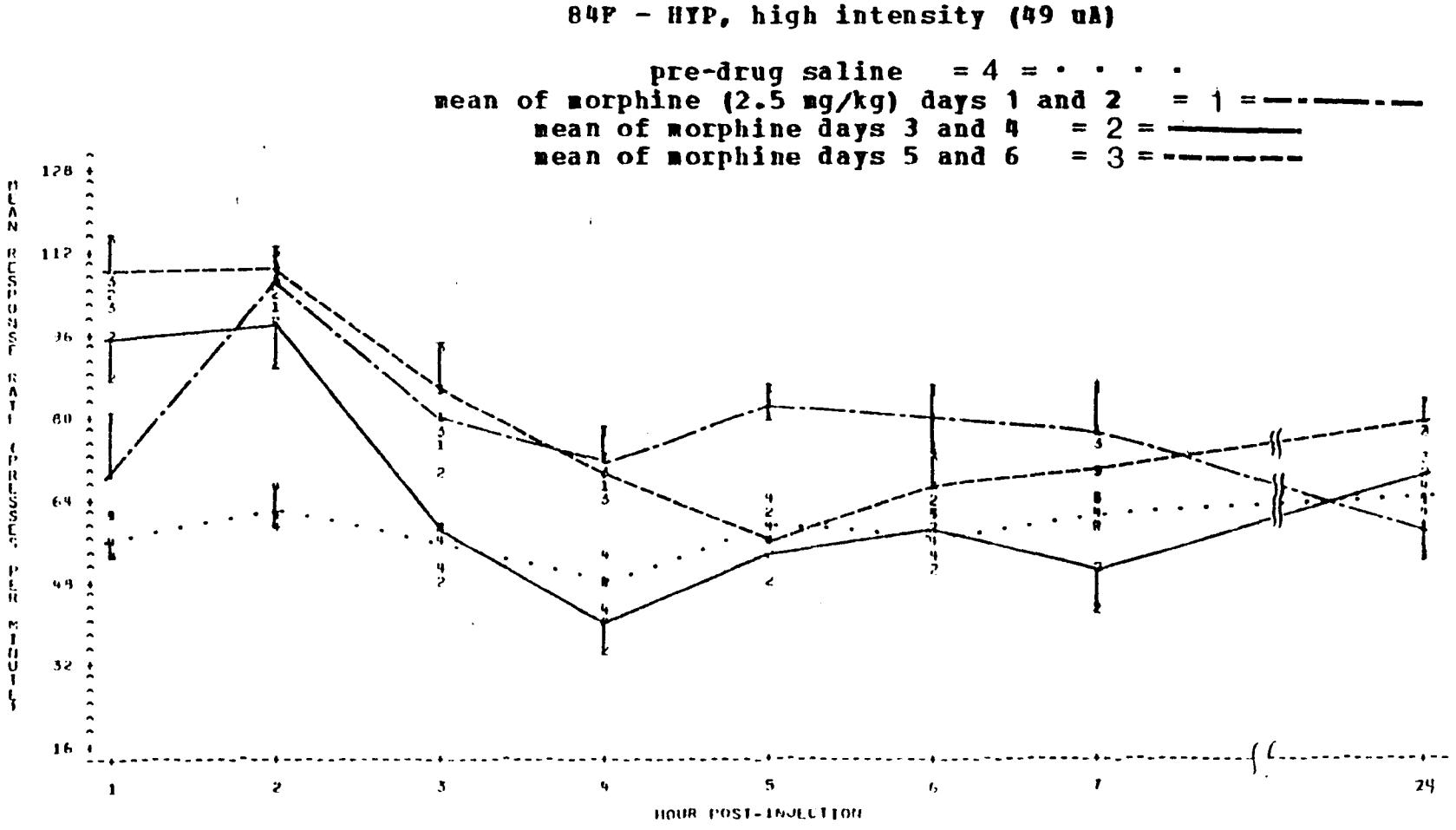

84P - HYP, high intensity (49 uA)
pre-drug saline = 4 = • • • •
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = -——-——
128
112
96
80
64
48
32
16
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 104

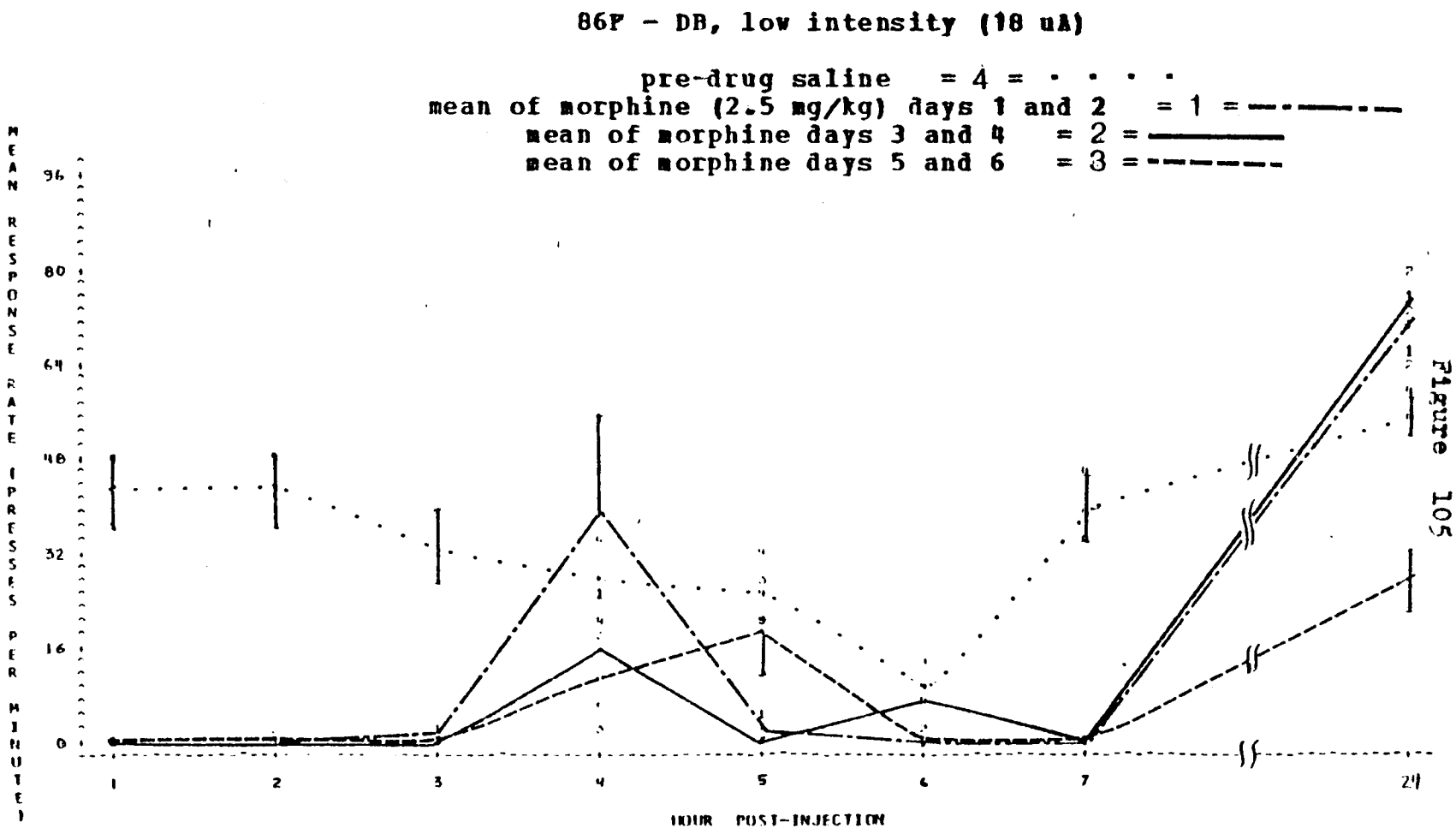

86P - DB, low intensity (18 uA)
pre-drug saline = 4 = ...
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = —·—·—·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = - - - - - -
MEAN RESPONSE RATE (PRESSES PER MINUTE)
96
80
64
48
32
16
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 105

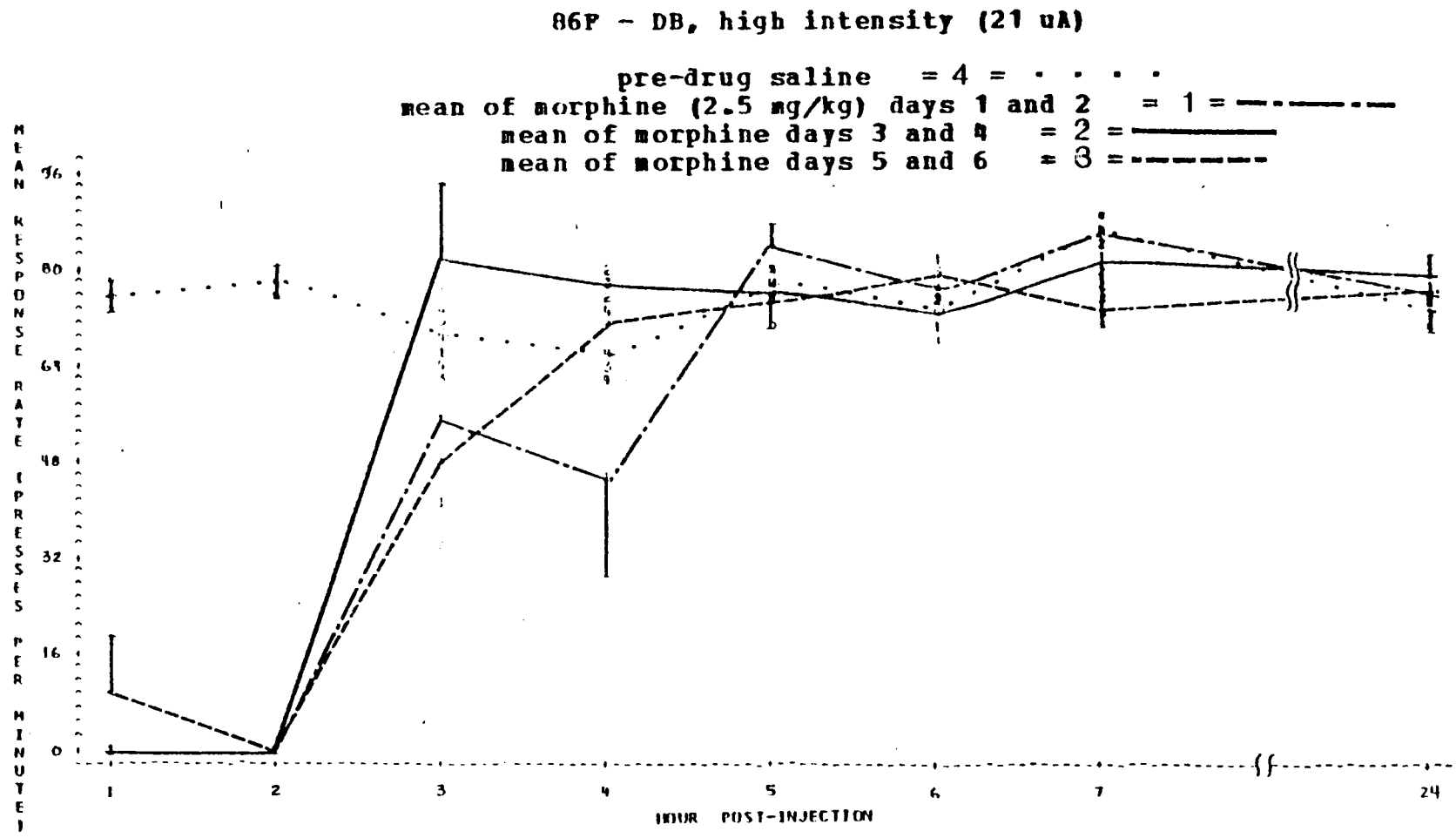

86P - DB, high intensity (21 uA)
pre-drug saline = 4 = ...
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = — — —
MEAN RESPONSE RATE (PRESSES PER MINUTE)
96
80
64
48
32
16
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 106

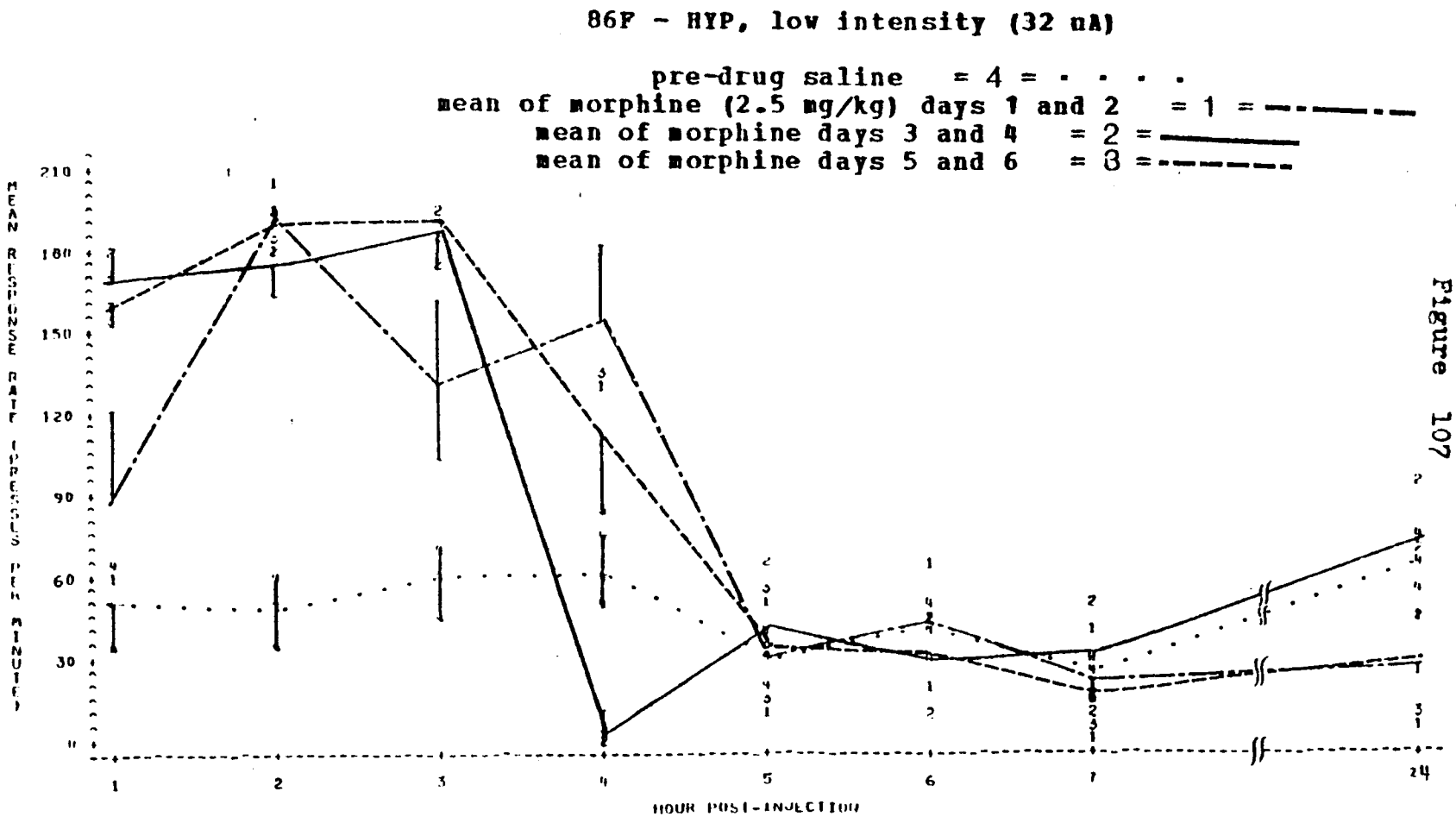

86F - HYP, low intensity (32 uA)
pre-drug saline = 4 = ...
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = -.-.-.-
mean of morphine days 3 and 4 = 2 = ——————
mean of morphine days 5 and 6 = 3 = - - - - -
MEAN RESPONSE RATE (PRESSES PER MINUTE)
210
180
150
120
90
60
30
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 107

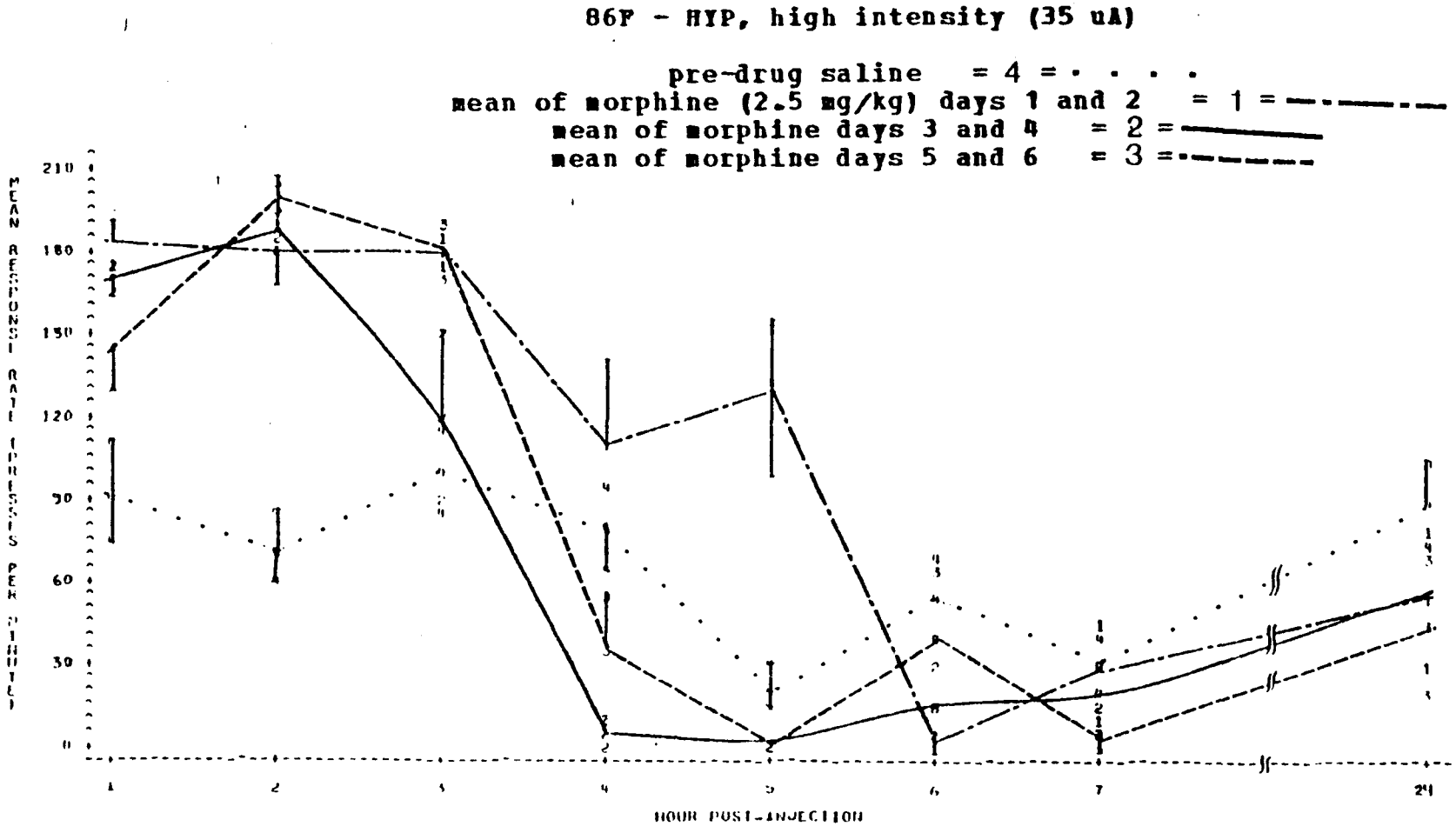

86F - HYP, high intensity (35 uA)
pre-drug saline = 4 = ...
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ——————
mean of morphine days 5 and 6 = 3 = ·——·——
210
180
150
120
90
60
30
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 108

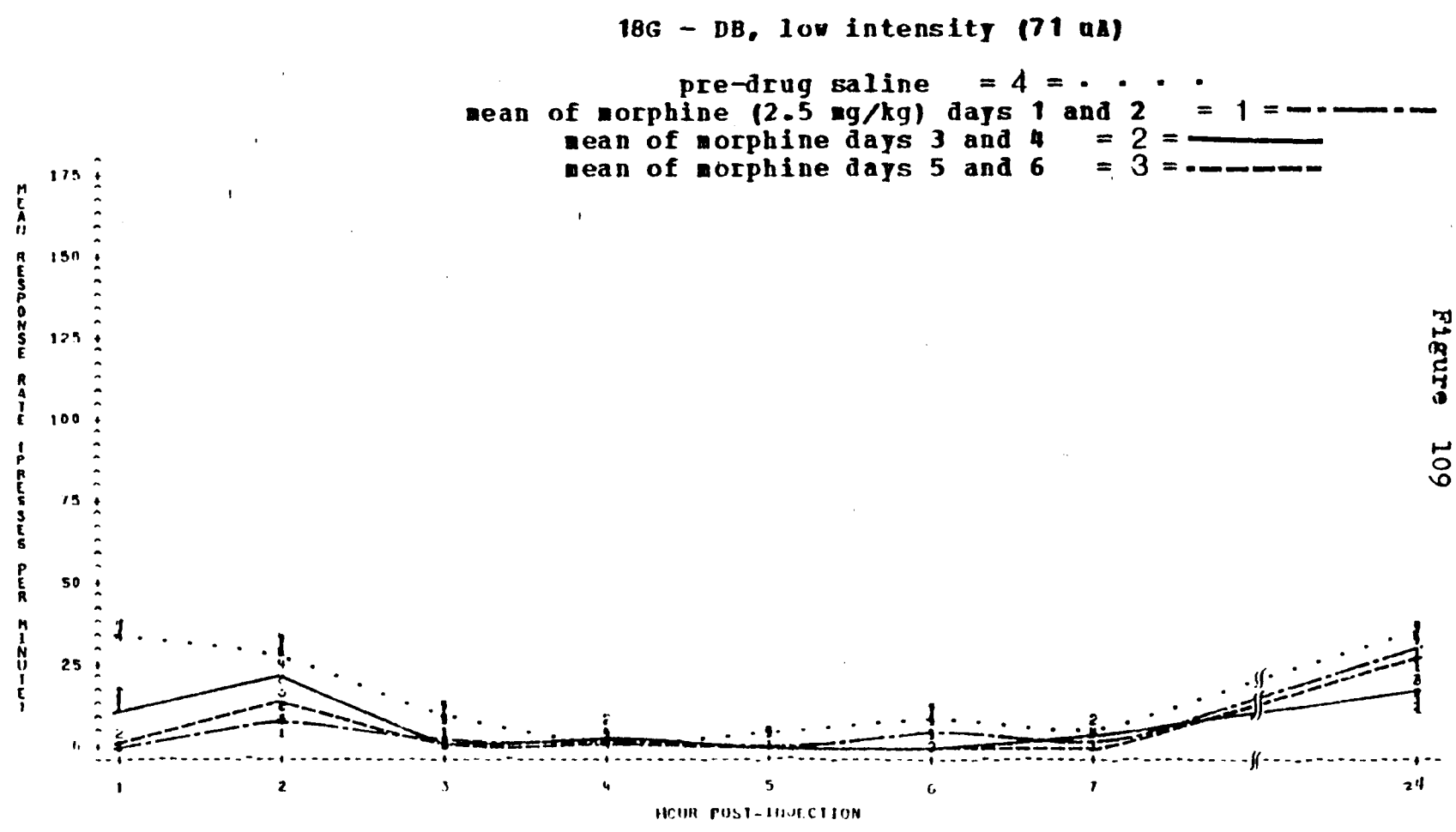

18G - DB, low intensity (71 uA)
pre-drug saline = 4 = ...
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = ·———
MEAN RESPONSE RATE (PRESSES PER MINUTE)
175
150
125
100
75
50
25
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 109

18G - DB, high intensity (99 uA)

pre-drug saline = 4 = ...
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = -.-.-.-
mean of morphine days 3 and 4 = 2 = ——————
mean of morphine days 5 and 6 = 3 = - - - - - -

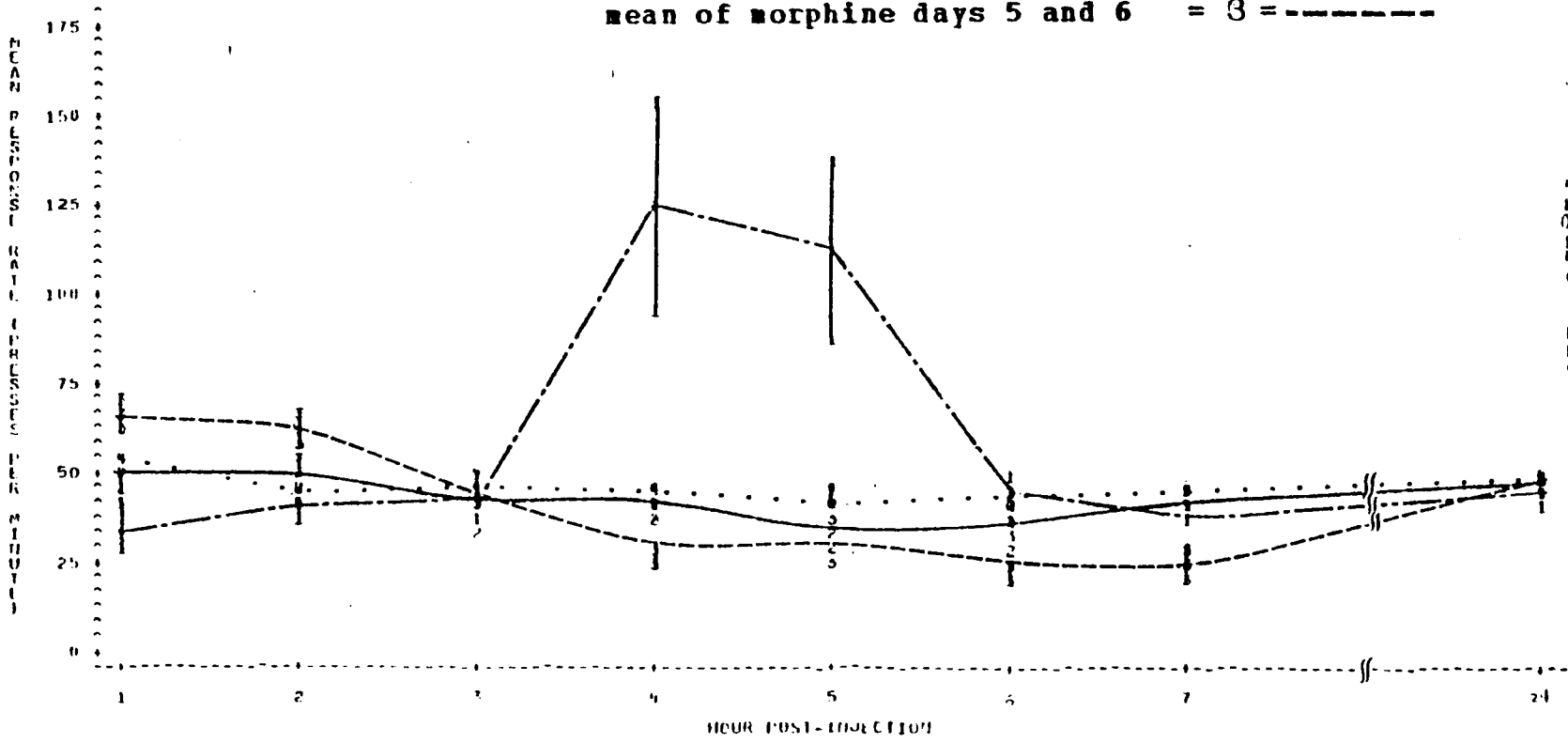


Figure 110

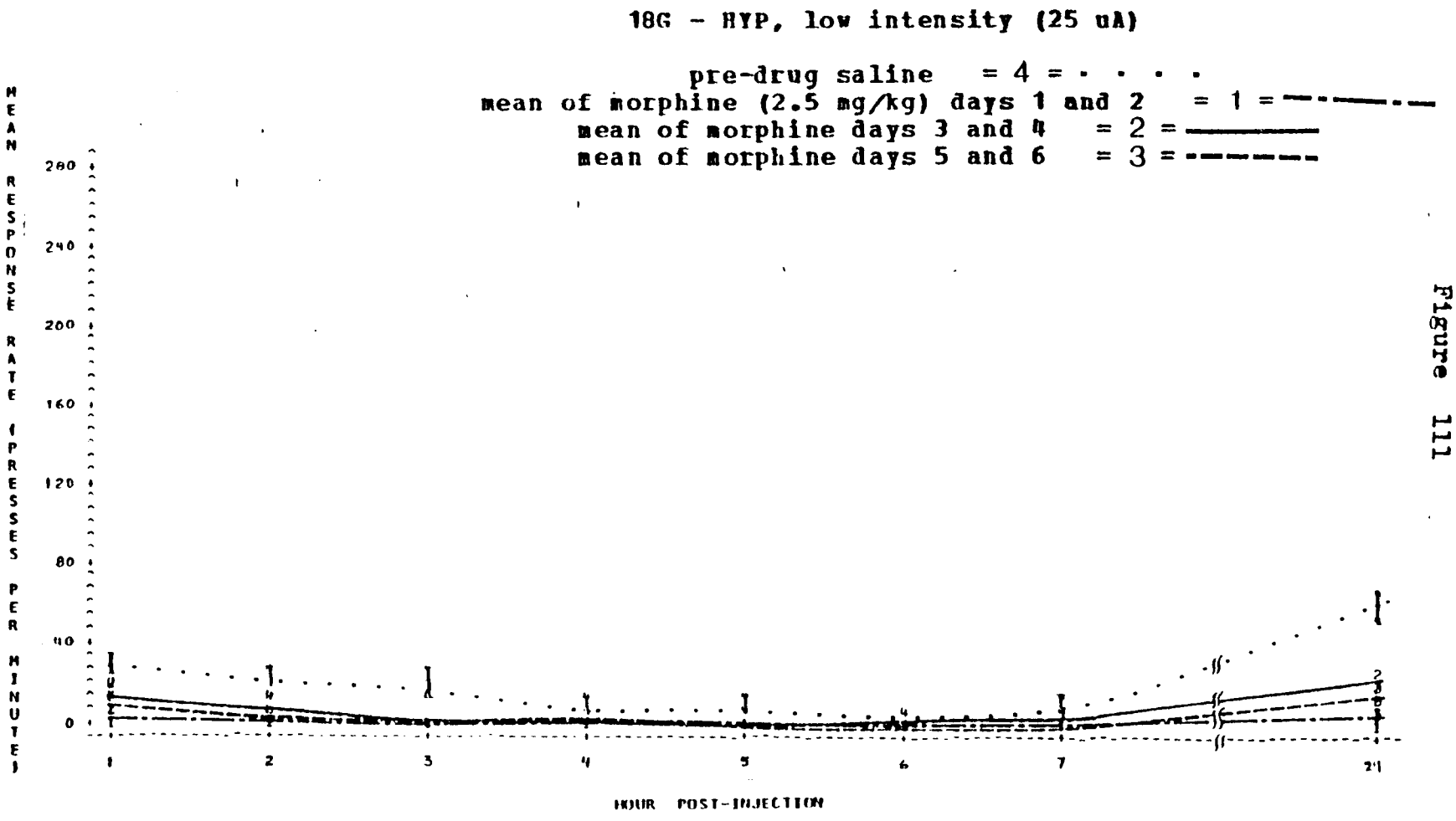

18G - HYP, low intensity (25 uA)
pre-drug saline = 4
mean of morphine (2.5 mg/kg) days 1 and 2 = 1
mean of morphine days 3 and 4 = 2
mean of morphine days 5 and 6 = 3
MEAN RESPONSE RATE (PRESSES PER MINUTE)
280
240
200
160
120
80
40
0
1
2
3
4
5
6
7
21
HOUR POST-INJECTION

Figure 111

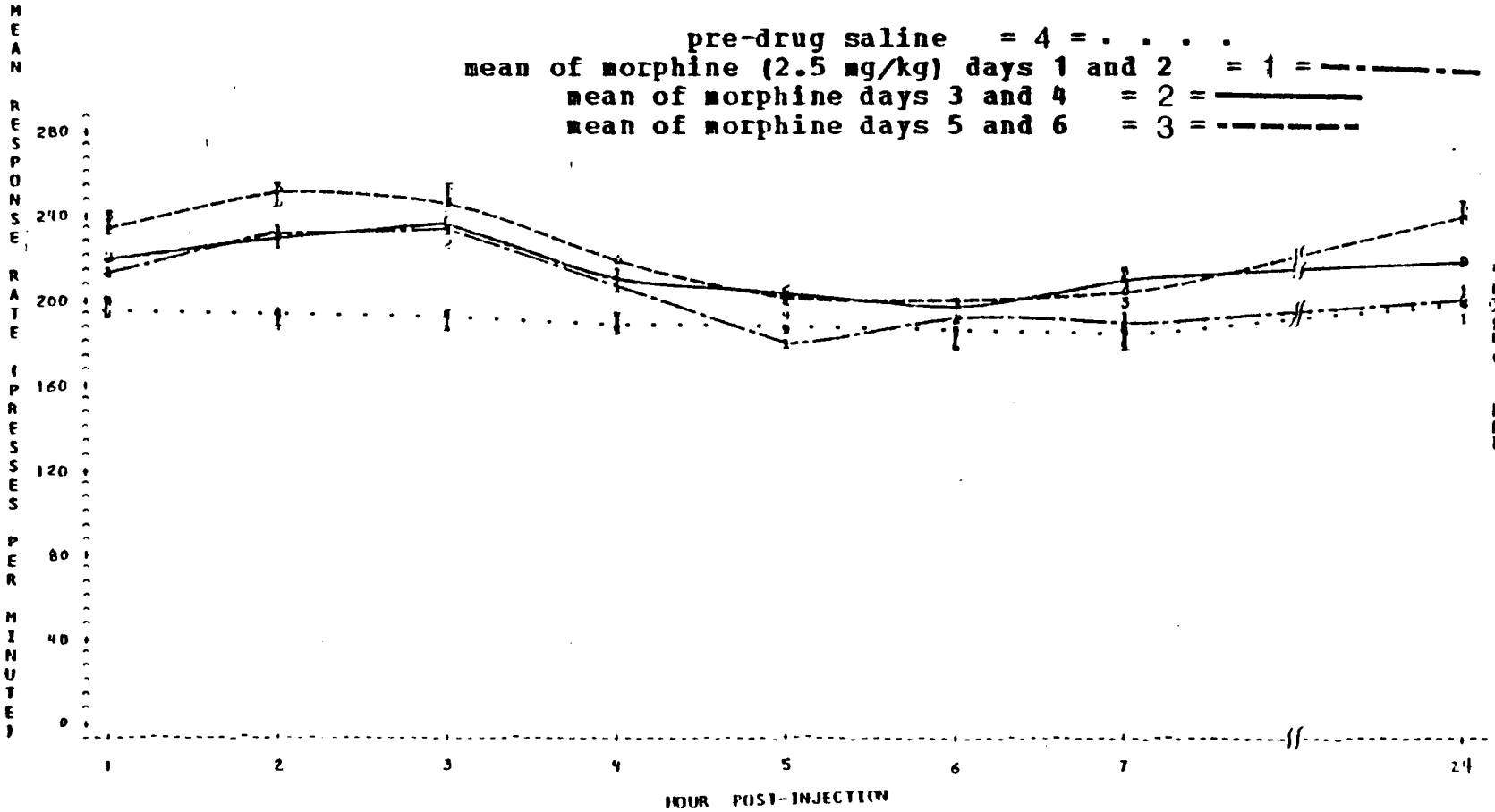

18G - HYP, high intensity (42 uA)
pre-drug saline = 4 = ...
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = -·-·-·-
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = - - - -
MEAN RESPONSE RATE (PRESSES PER MINUTE)
280
240
200
160
120
80
40
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 112

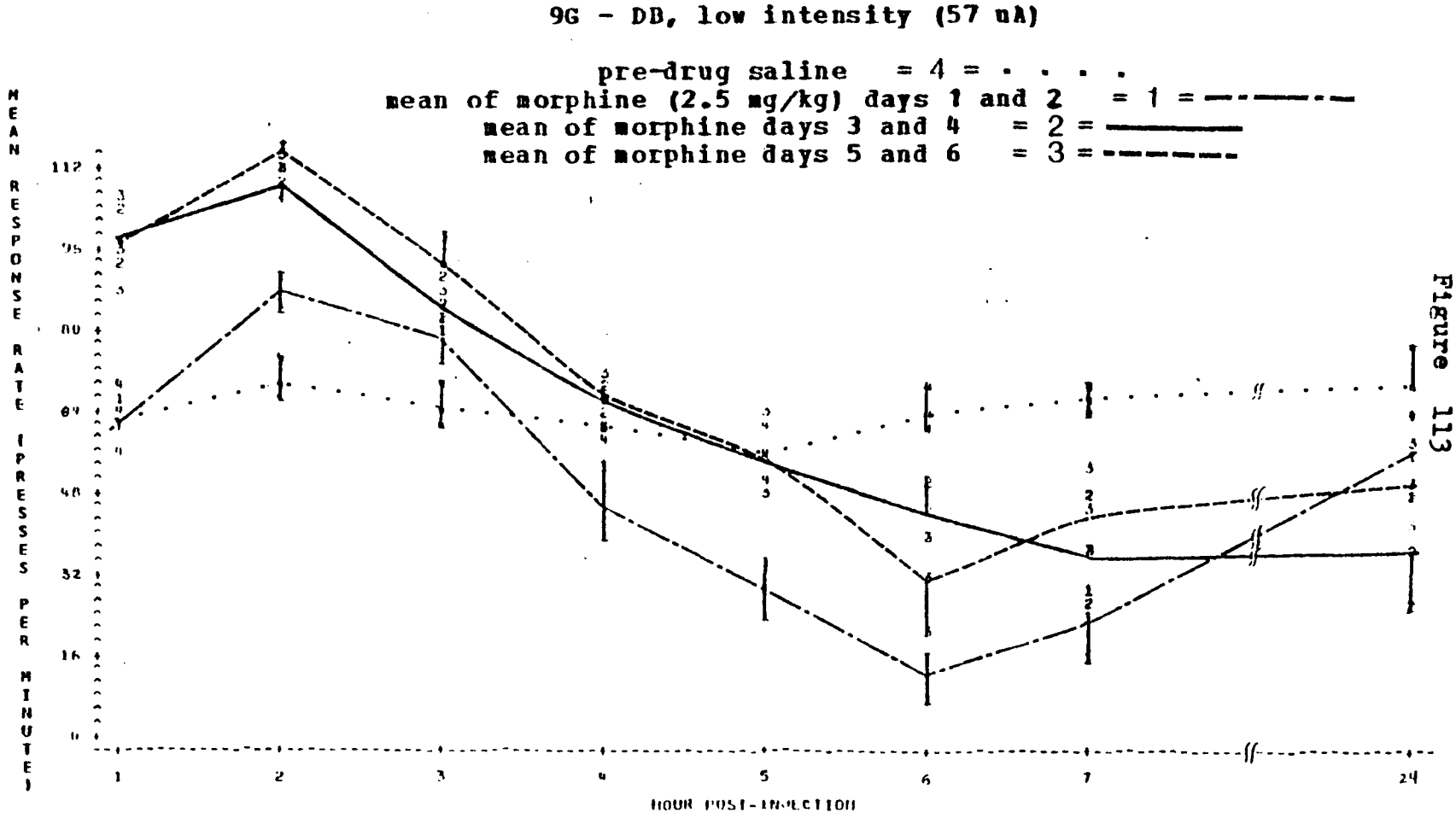

9G - DB, low intensity (57 uA)
pre-drug saline = 4 = ...
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = — · — · —
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = — — —
MEAN RESPONSE RATE (PRESSES PER MINUTE)
112
96
80
64
48
32
16
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 113

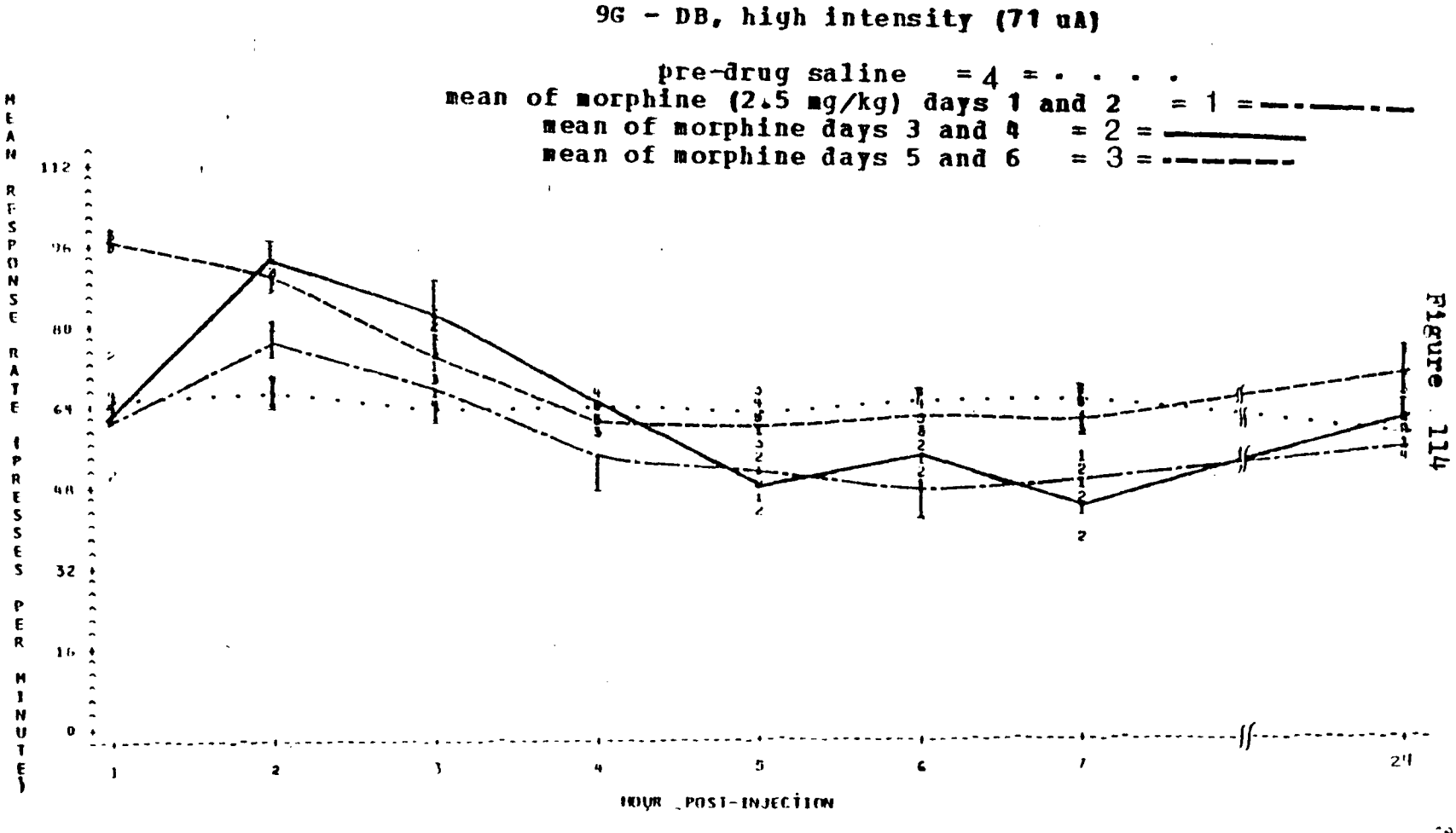

9G - DB, high intensity (71 uA)
pre-drug saline = 4 = ...
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = -.-.-.-
mean of morphine days 3 and 4 = 2 = ——————
mean of morphine days 5 and 6 = 3 = - - - - - -
MEAN RESPONSE RATE (PRESSES PER MINUTE)
112
96
80
64
48
32
16
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 114

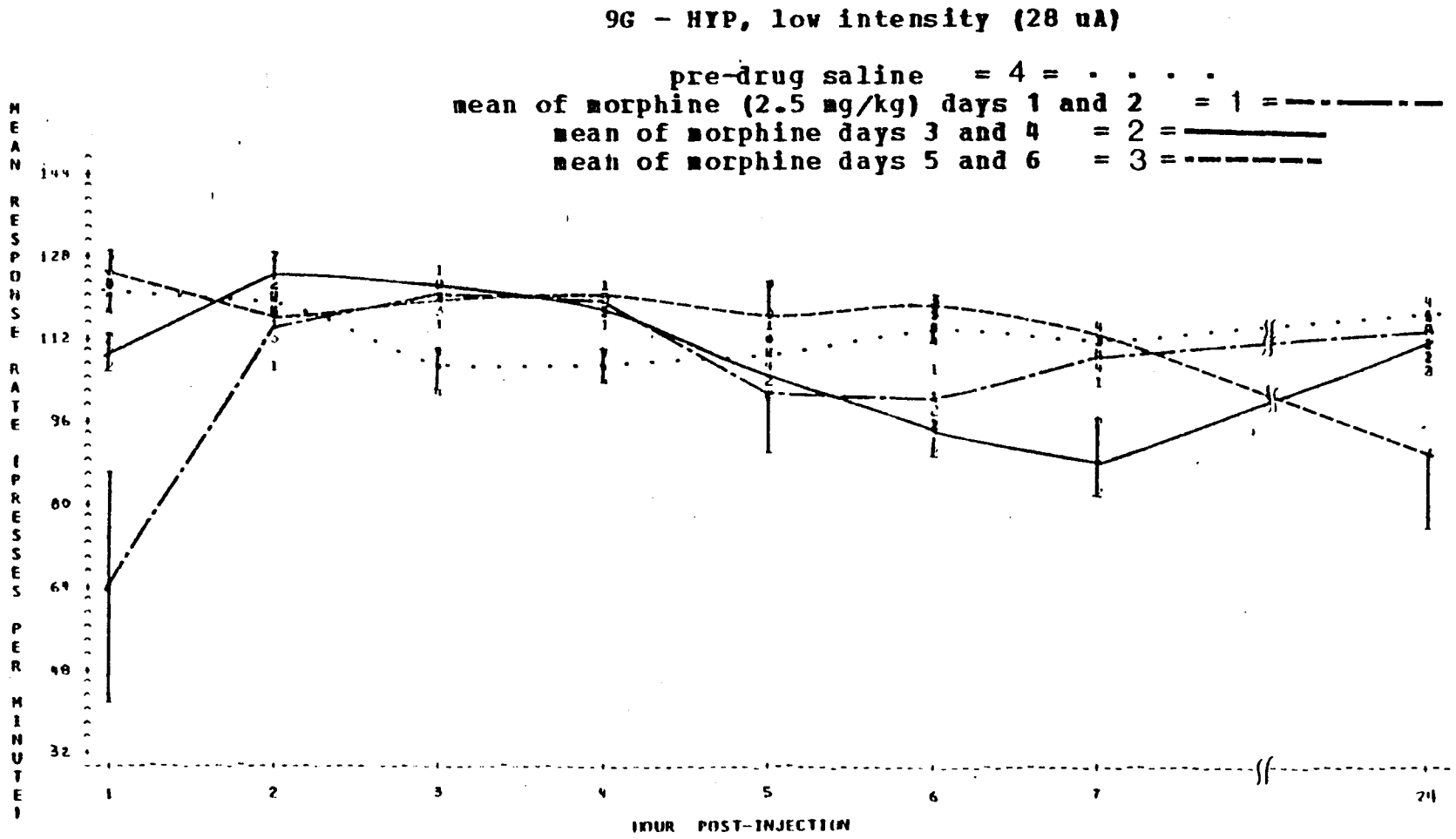

9G - HYP, low intensity (28 uA)
pre-drug saline = 4 = ...
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ————
mean of morphine days 5 and 6 = 3 = ·——·——
MEAN RESPONSE RATE (PRESSES PER MINUTE)
144
128
112
96
80
64
48
32
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 115

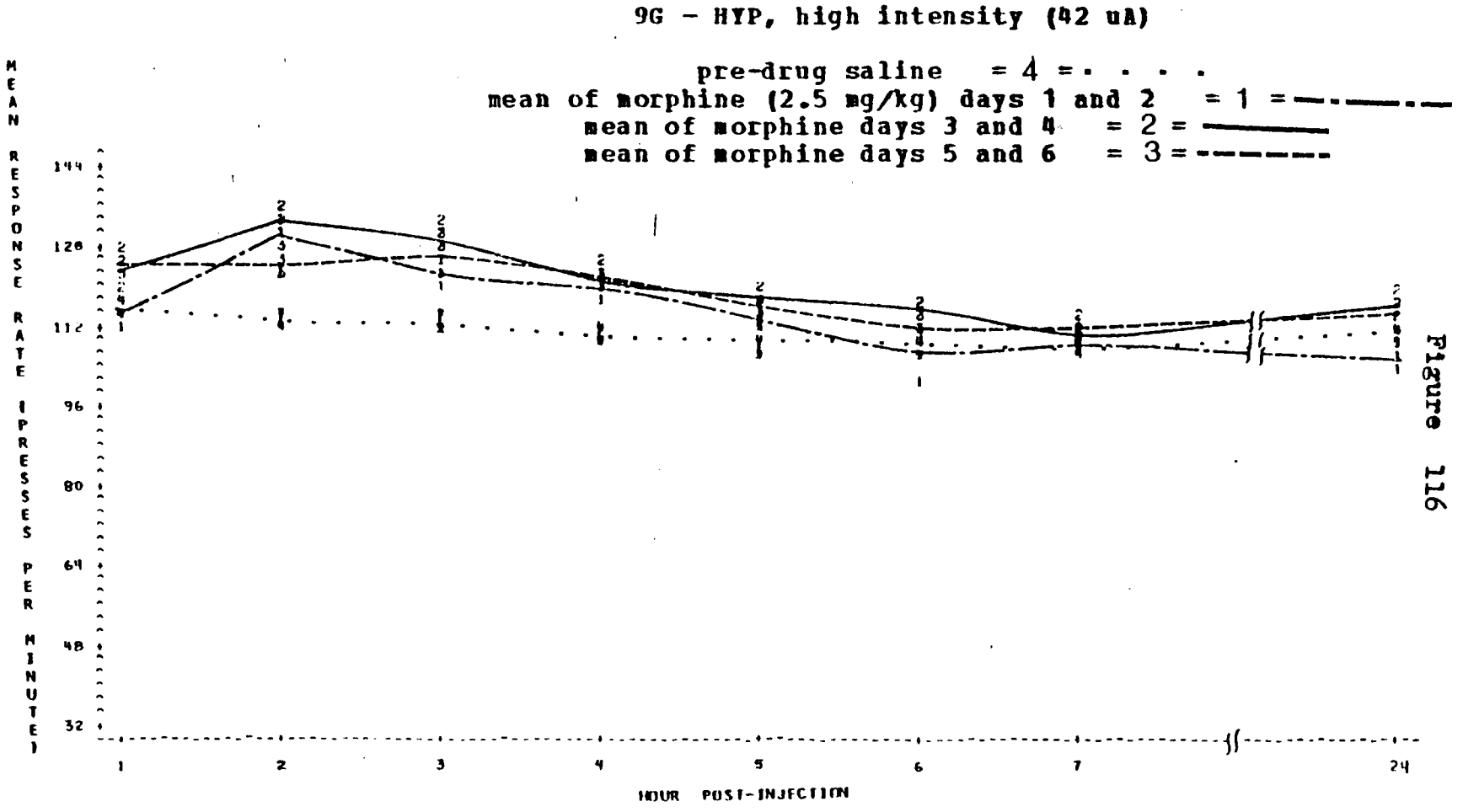

9G - HYP, high intensity (42 uA)
pre-drug saline = 4 = ...
mean of morphine (2.5 mg/kg) days 1 and 2 = 1 = —·——·—
mean of morphine days 3 and 4 = 2 = ——————
mean of morphine days 5 and 6 = 3 = — — — —
MEAN RESPONSE RATE (PRESSES PER MINUTE)
144
128
112
96
80
64
48
32
1
2
3
4
5
6
7
24
HOUR POST-INJECTION

Figure 116

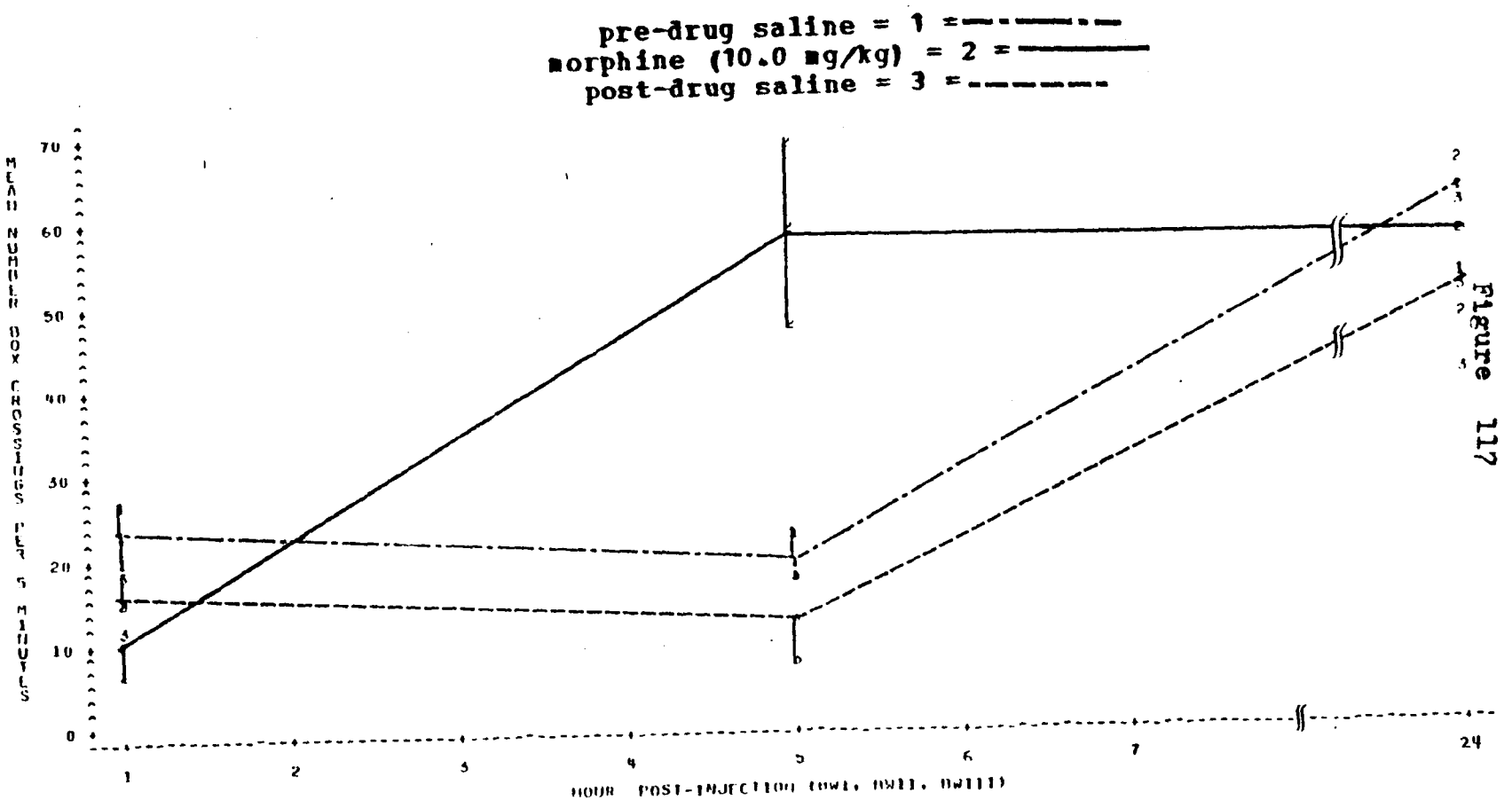

pre-drug saline = 1 =
morphine (10.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN NUMBER BOX CROSSINGS PER 5 MINUTES
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION (HR1, HR11, HR111)

Figure 117

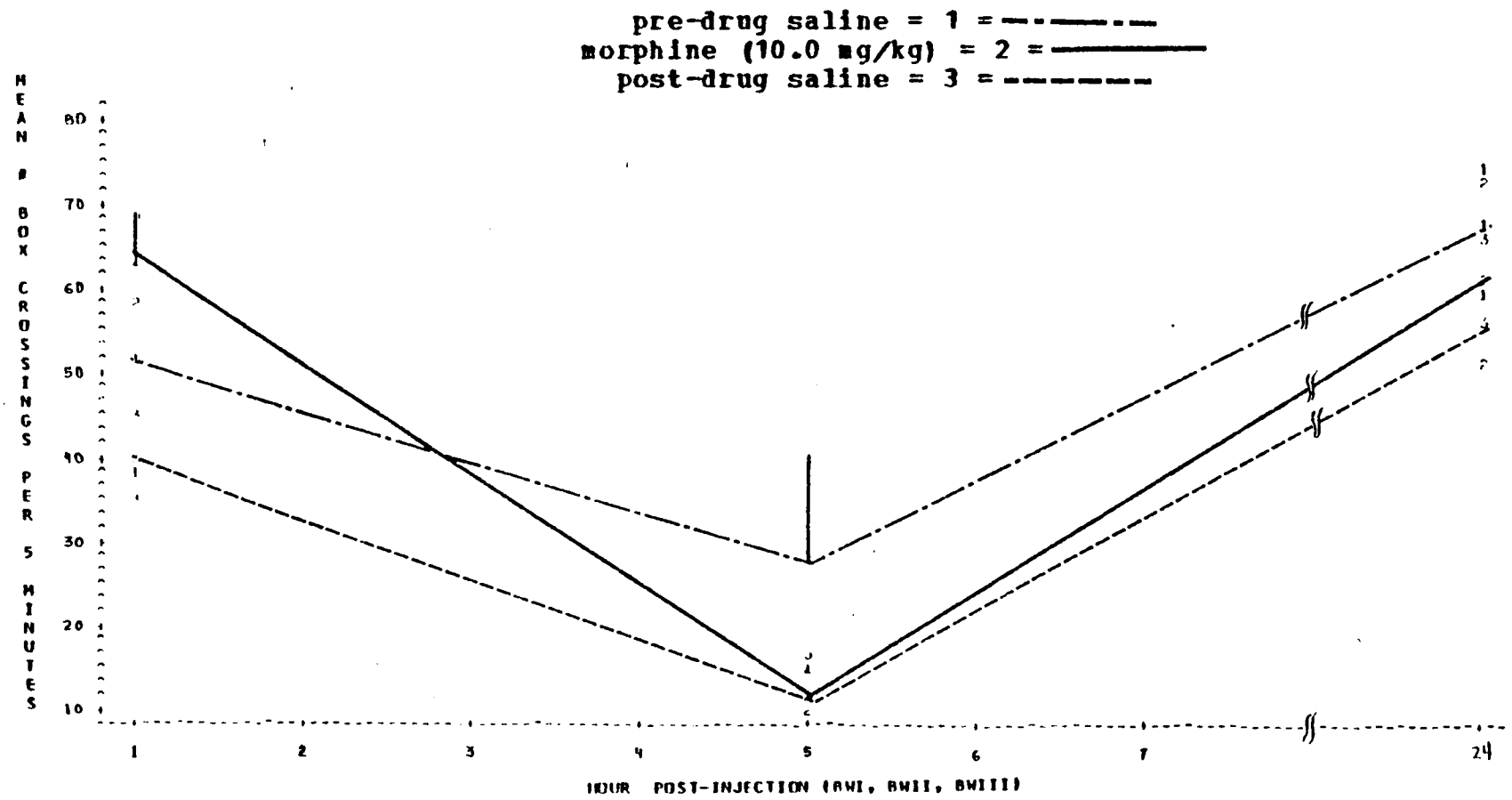

pre-drug saline = 1 =
morphine (10.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN # BOX CROSSINGS PER 5 MINUTES
80
70
60
50
40
30
20
10
1
2
3
4
5
6
7
24
HOUR POST-INJECTION (BWI, BWII, BWIII)

Figure 118

pre-drug saline = 1 = —·——·—
morphine (10.0 mg/kg) = 2 = ————
post-drug saline = 3 = — — — —

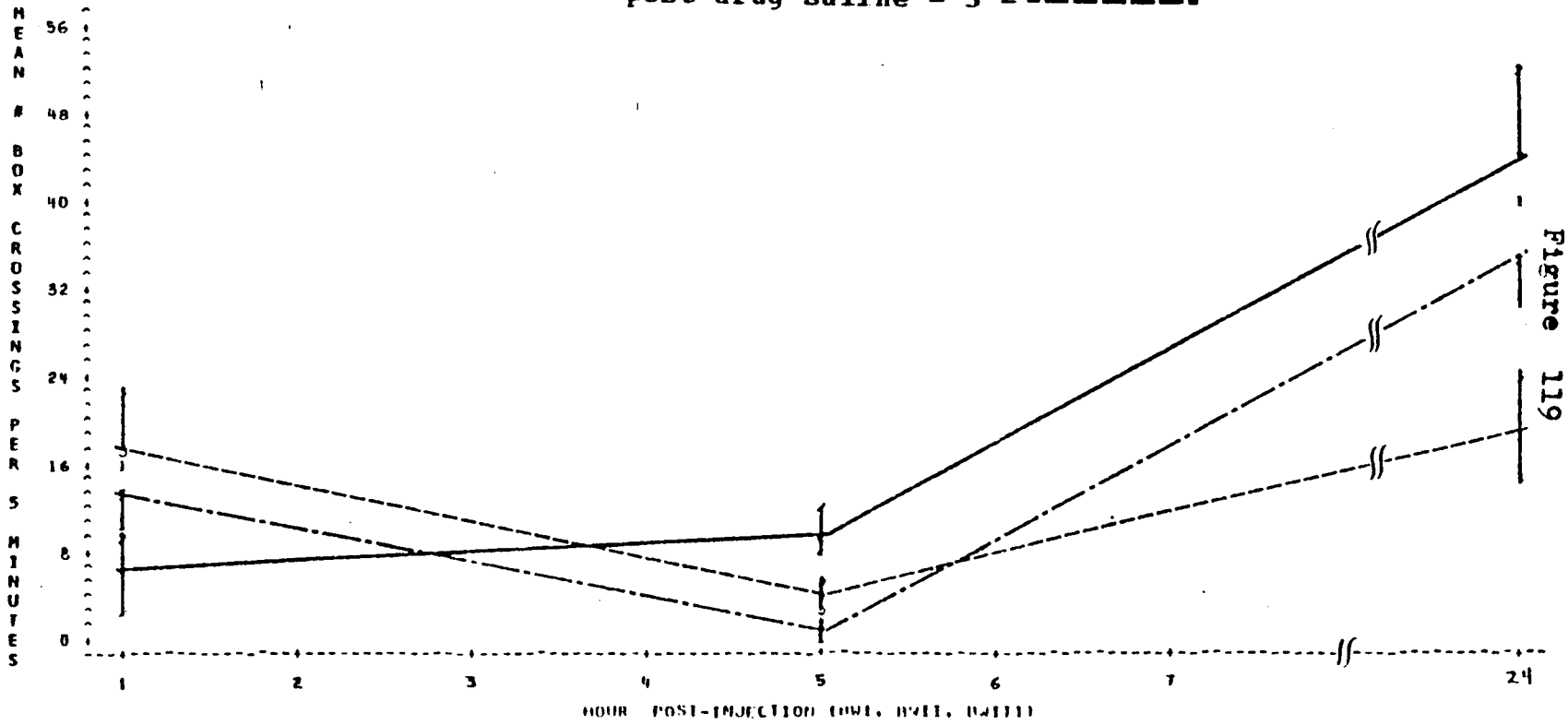


Figure 119

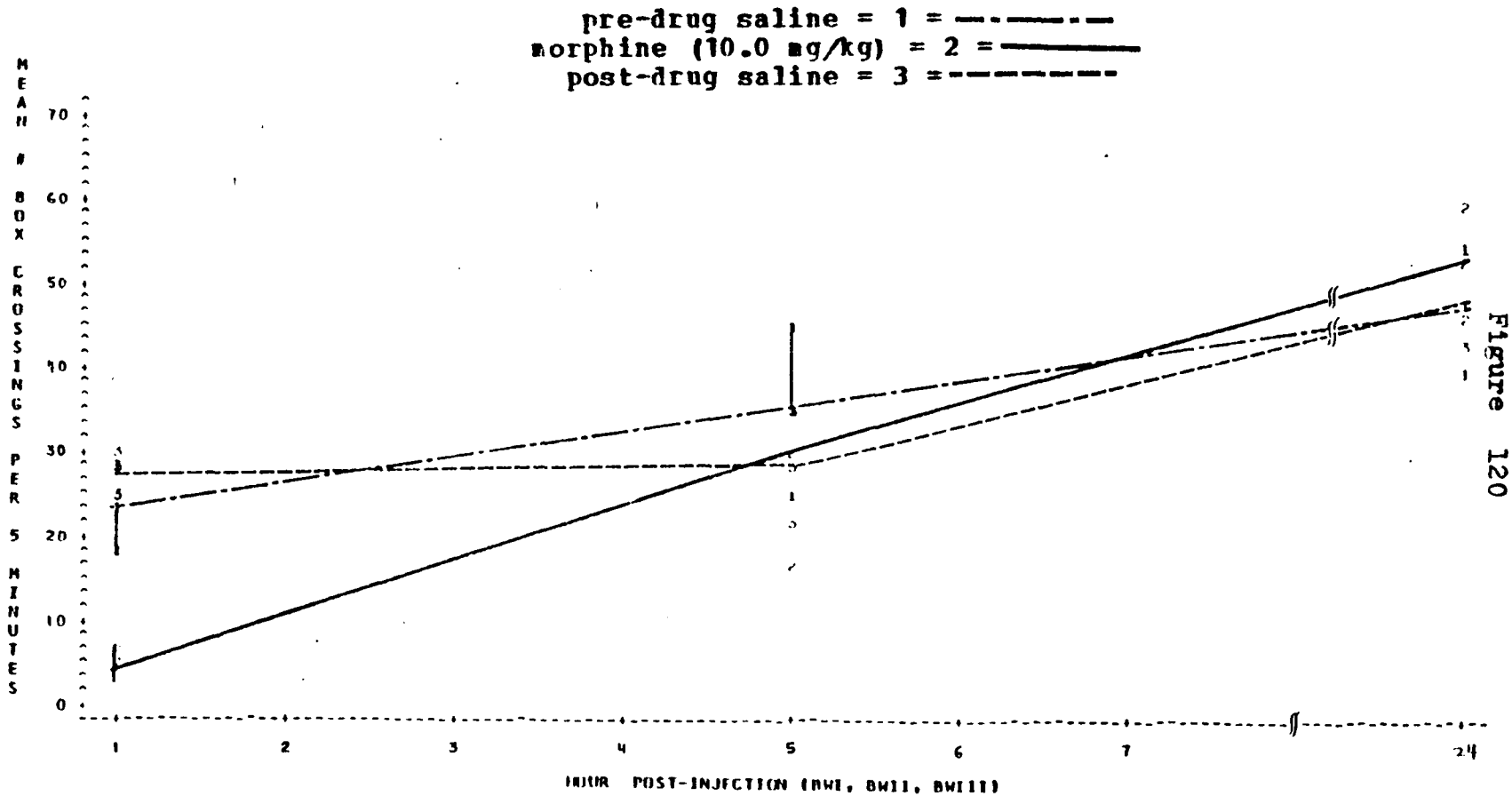

pre-drug saline = 1 = —·——·—
morphine (10.0 mg/kg) = 2 = ————
post-drug saline = 3 = - - - - - -
MEAN # BOX CROSSINGS PER 5 MINUTES
0
10
20
30
40
50
60
70
1
2
3
4
5
6
7
24
HOUR POST-INJECTION (BWI, BWII, BWIII)

Figure 120

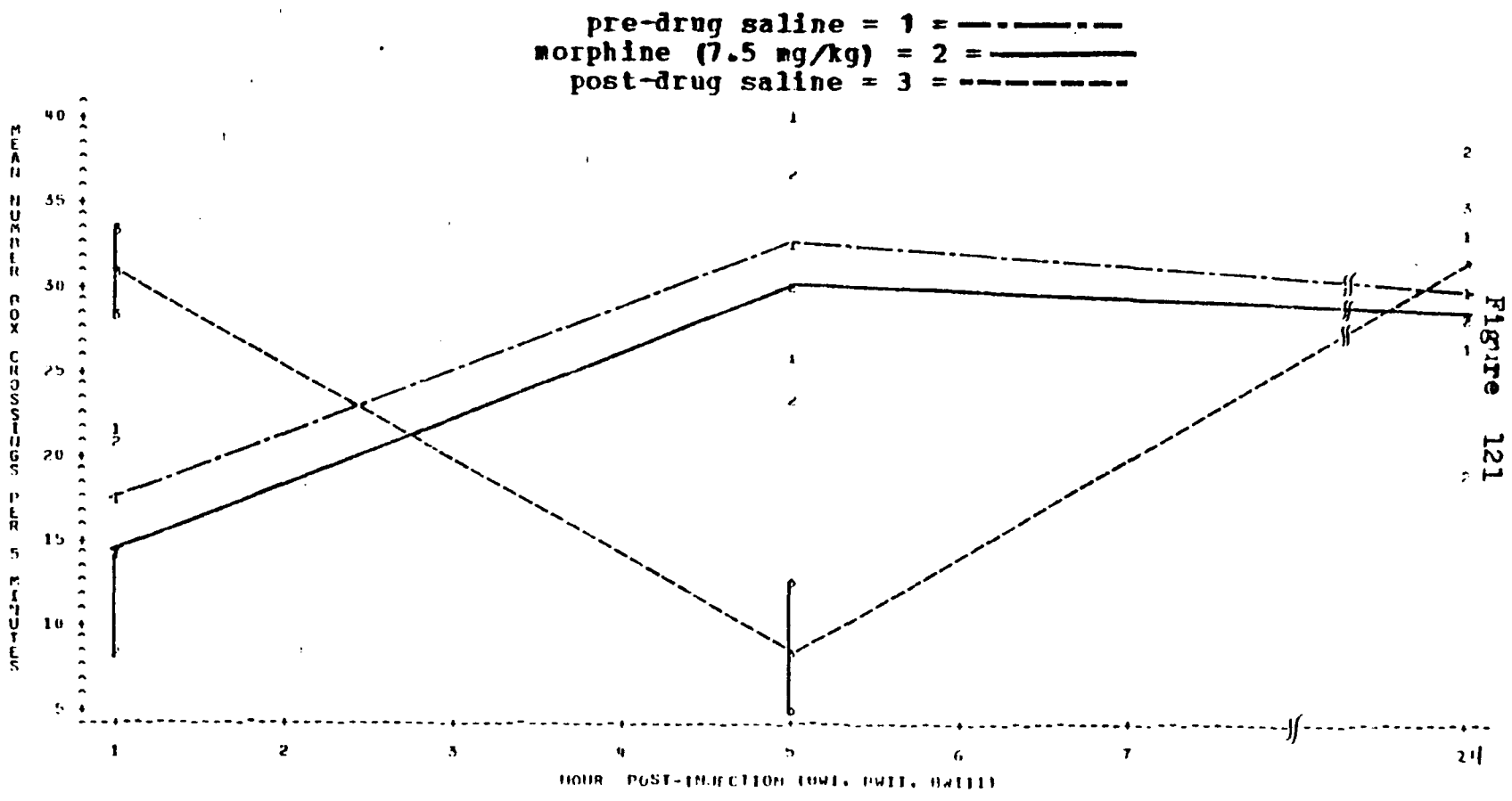

pre-drug saline = 1 =
morphine (7.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN NUMBER OF CROSSINGS PER 5 MINUTES
HOUR POST-INJECTION (0WI, 0WII, 0WIII)

Figure 121

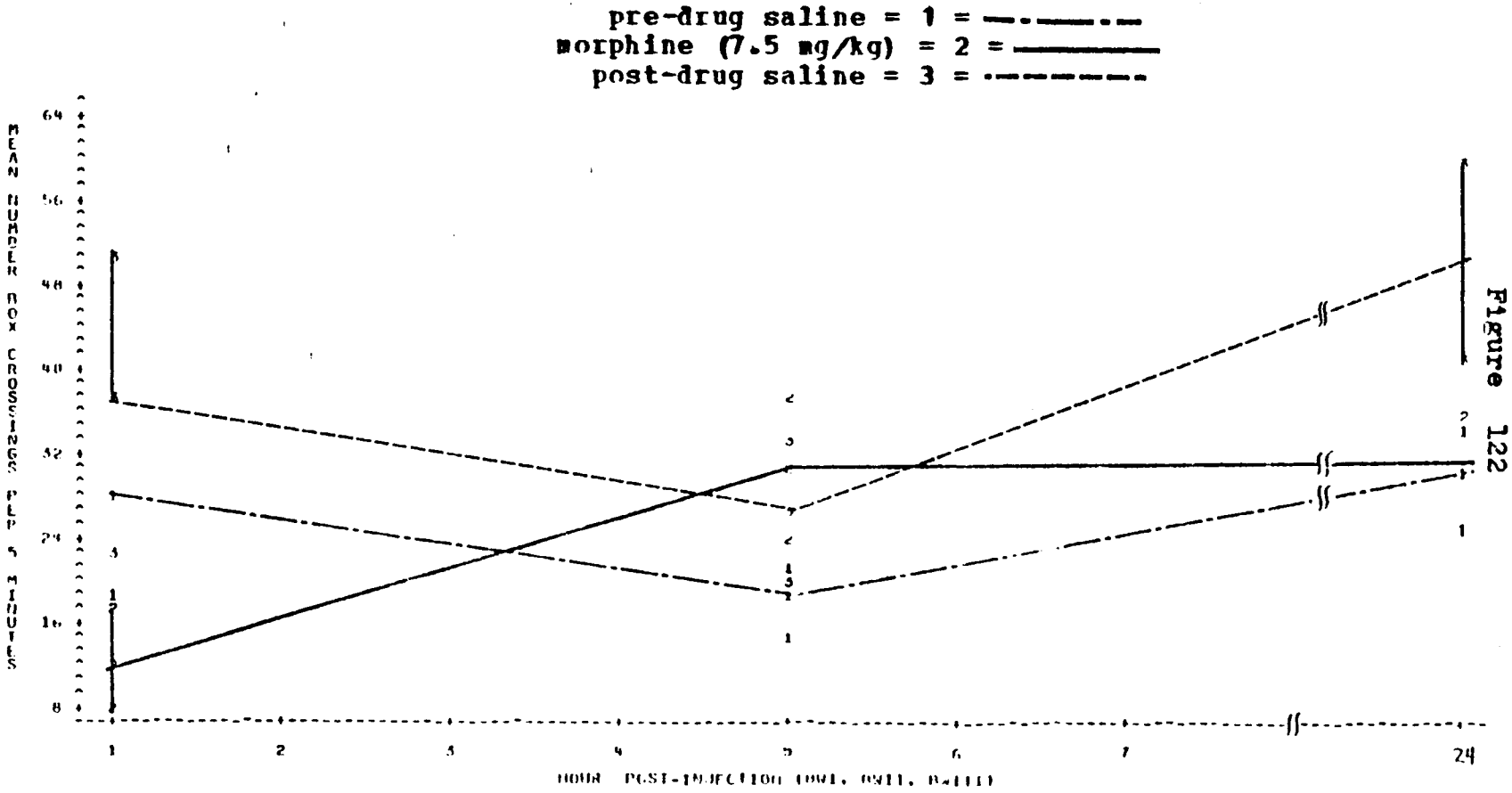

pre-drug saline = 1 =
morphine (7.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN NUMBER BOX CROSSINGS PER 5 MINUTES
64
56
48
40
32
24
16
8
1
2
3
4
5
6
7
24
HOUR POST-INJECTION (DAY1, DAY2, DAY3)

Figure 122

pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =

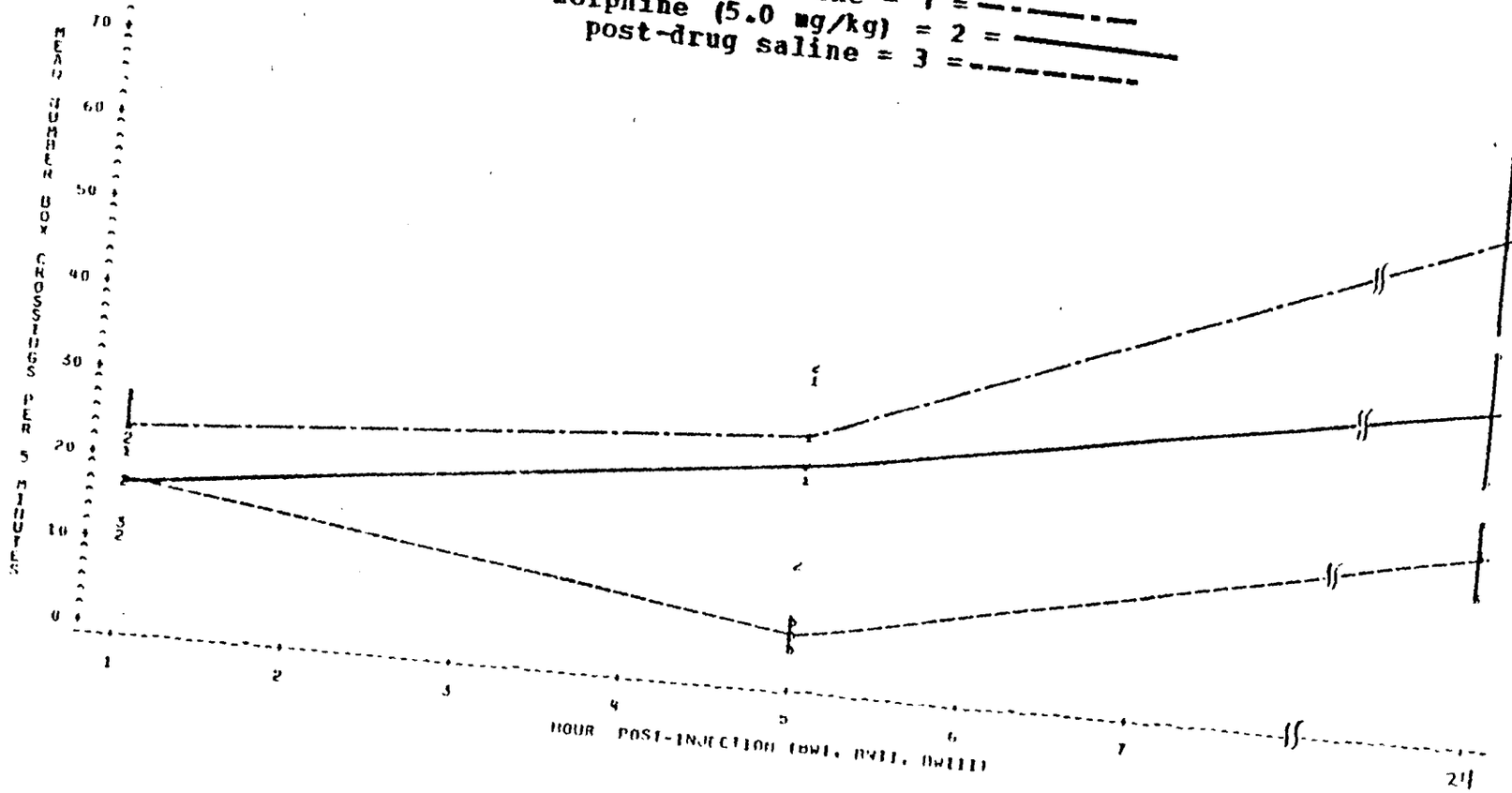


Figure 123

pre-drug saline = 1 = ——·——·——
morphine (5.0 mg/kg) = 2 = ————————
post-drug saline = 3 = — — — — —

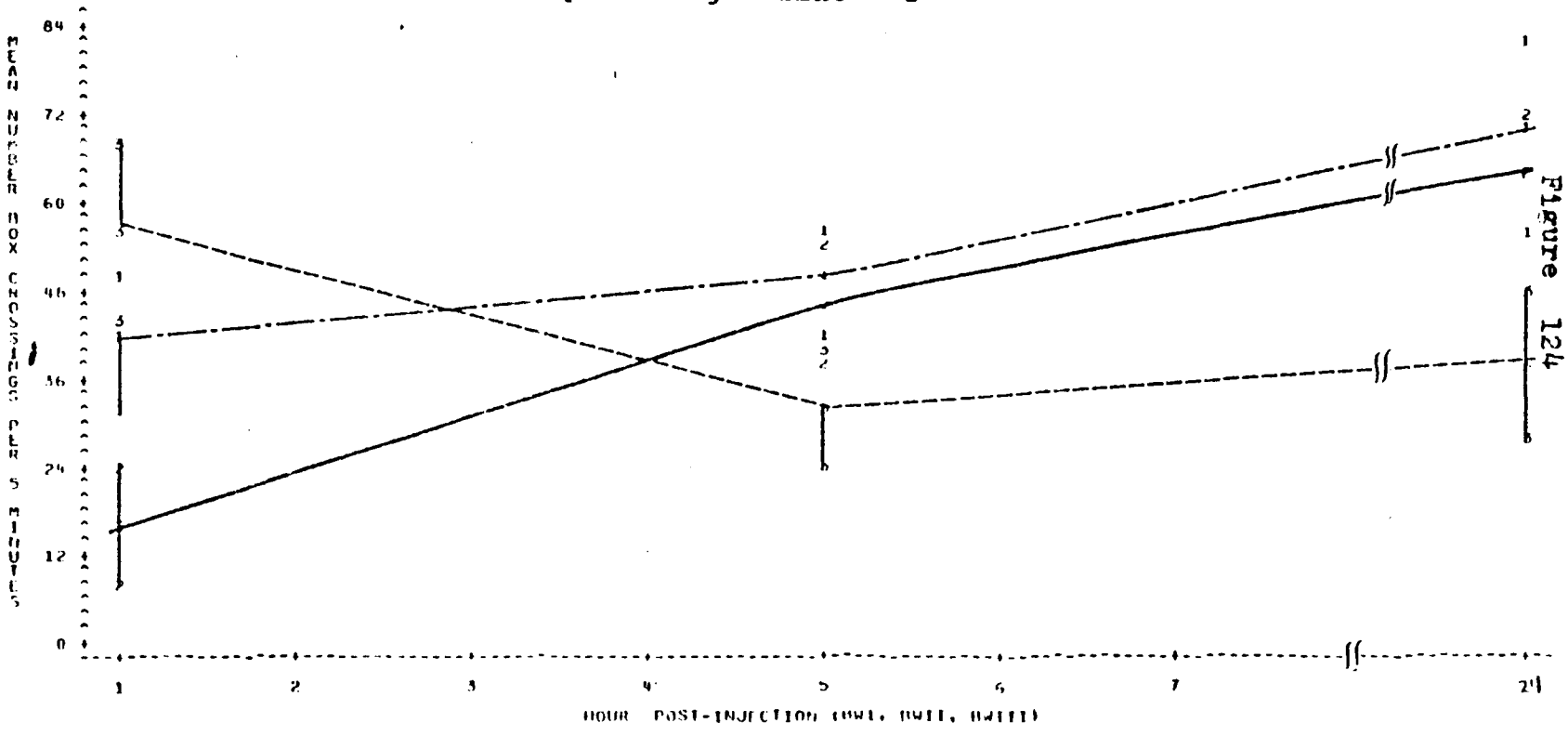


Figure 124

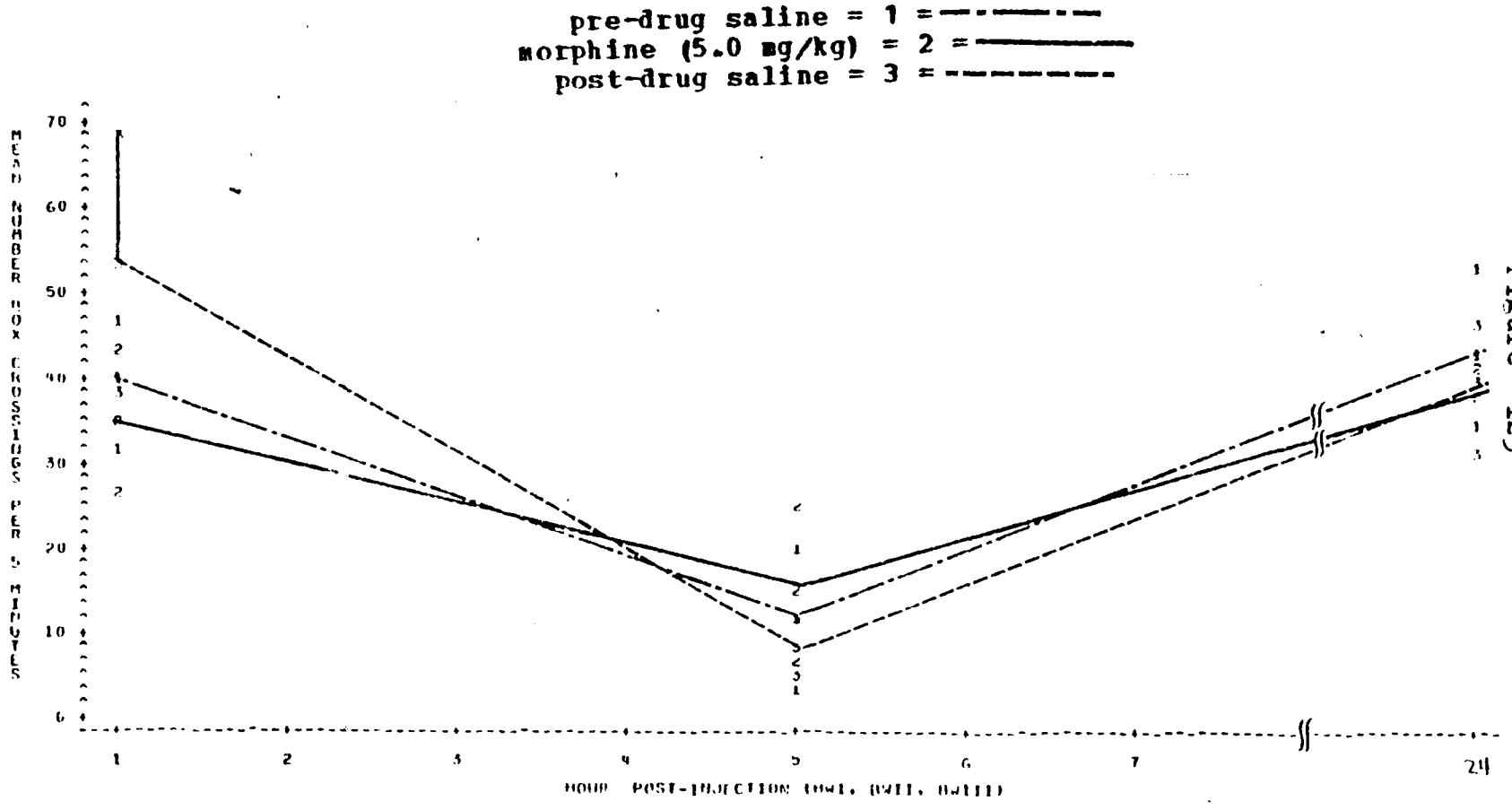

pre-drug saline = 1
morphine (5.0 mg/kg) = 2
post-drug saline = 3
MEAN NUMBER BOX CROSSINGS PER 5 MINUTES
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION (DAY1, DAY2, DAY3)

Figure 125

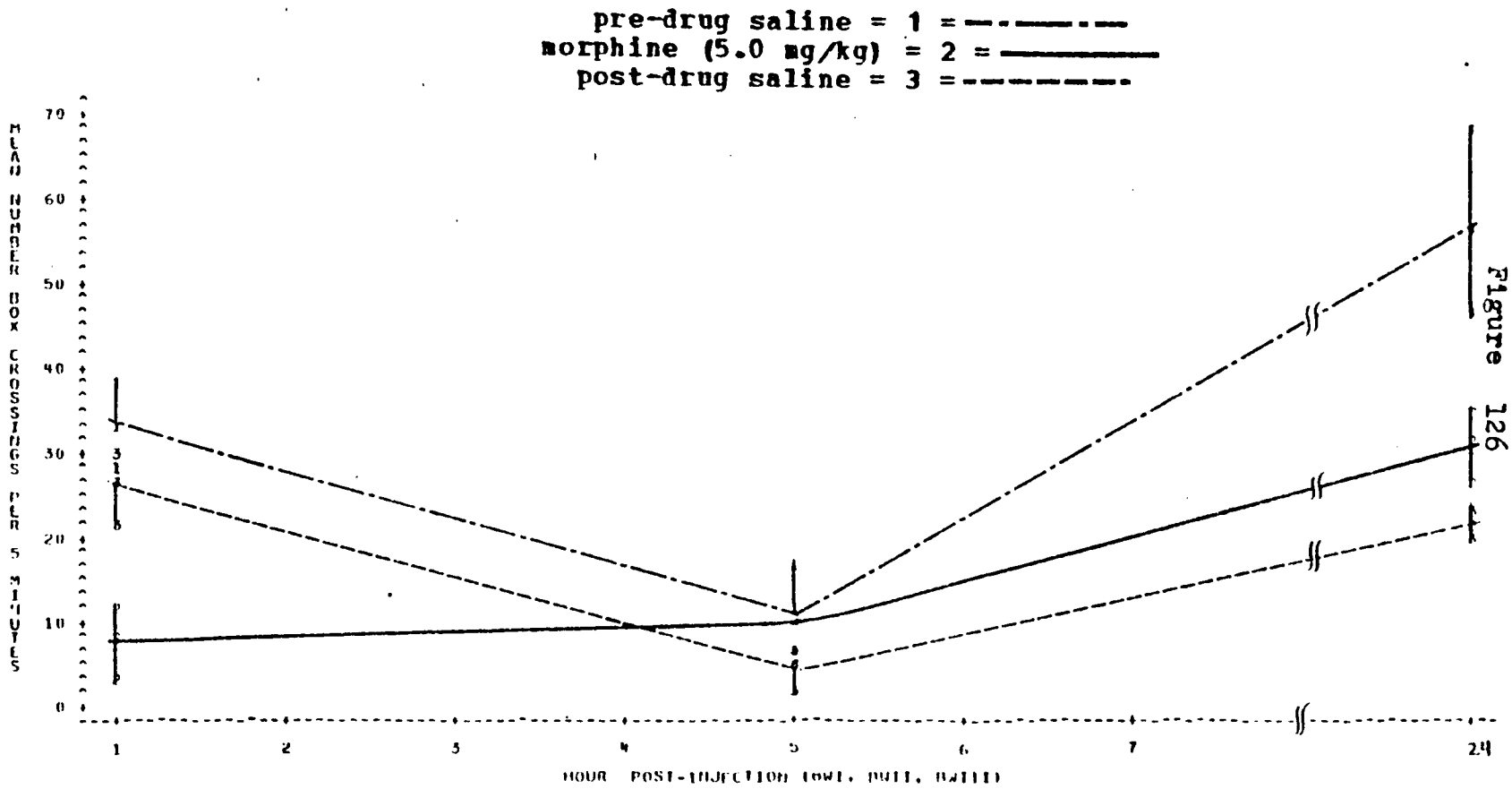

pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN NUMBER BOX CROSSINGS PER 5 MINUTES
0
10
20
30
40
50
60
70
1
2
3
4
5
6
7
24
HOUR POST-INJECTION (WHI, DUIT, DAIIII)

Figure 126

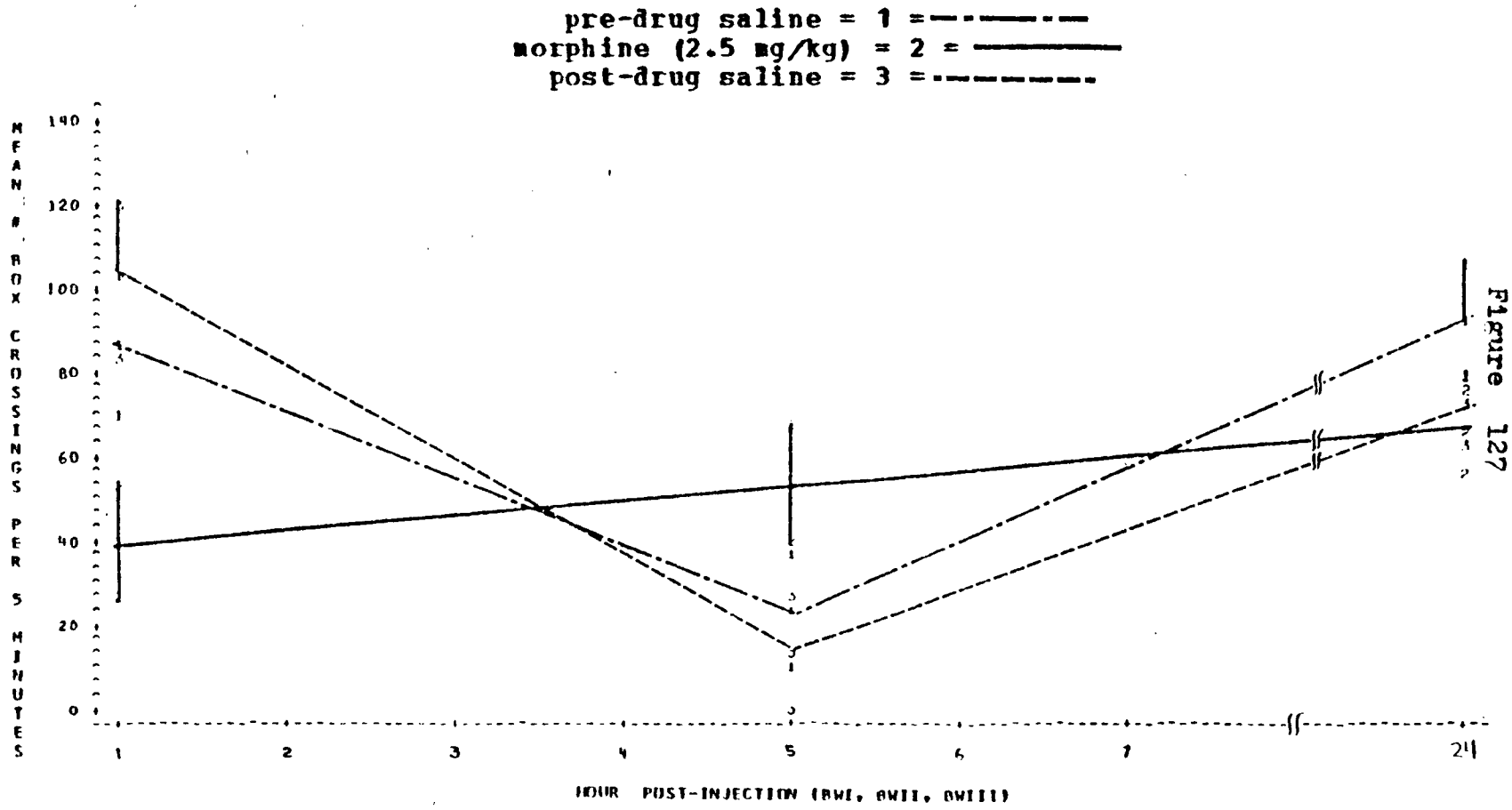

pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN # BOX CROSSINGS PER 5 MINUTES
140
120
100
80
60
40
20
0
1
2
3
4
5
6
7
24
HOUR POST-INJECTION (BWI, BWII, BWIII)

Figure 127

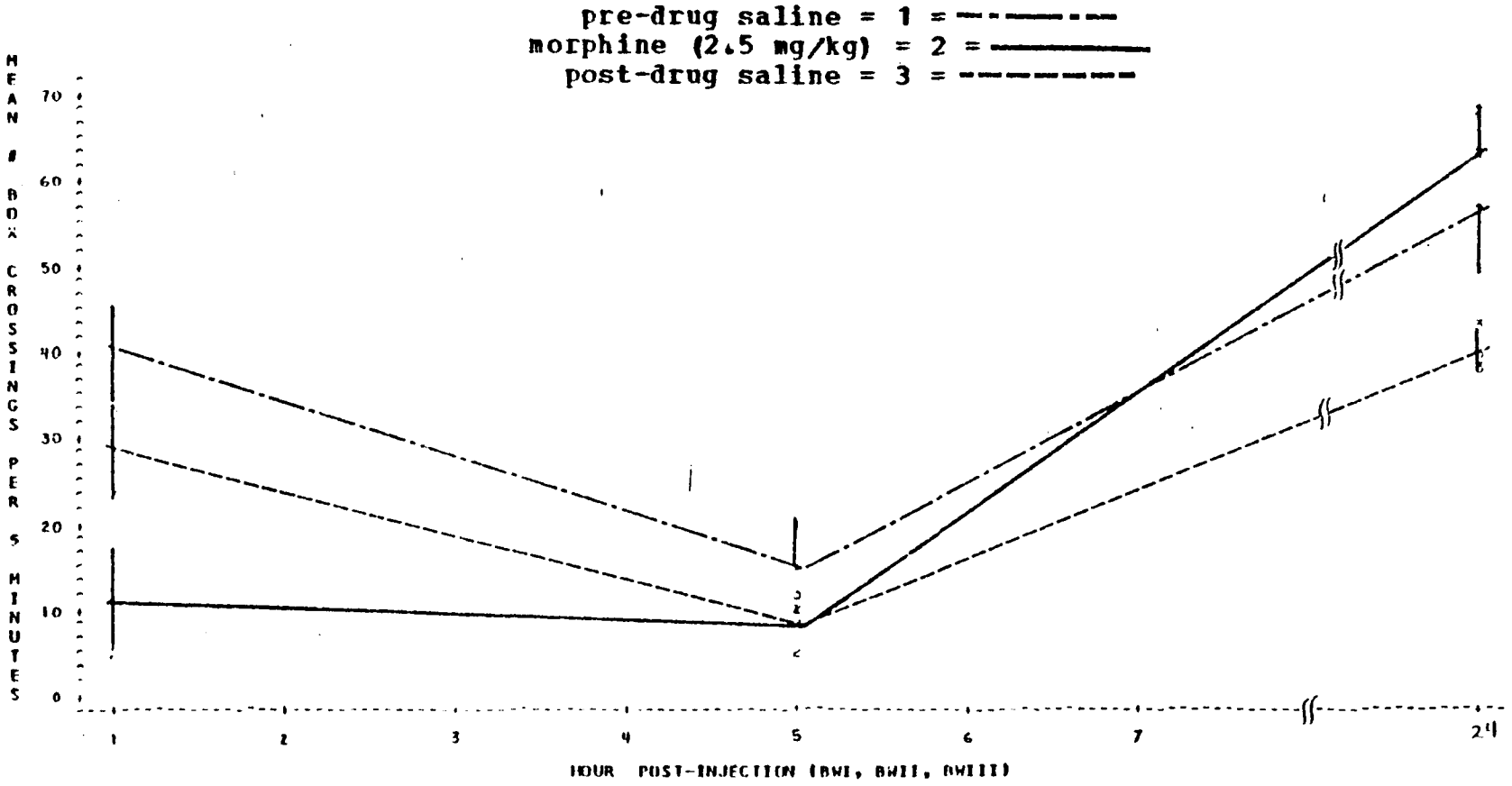

pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN # BOX CROSSINGS PER 5 MINUTES
0
10
20
30
40
50
60
70
1
2
3
4
5
6
7
24
HOUR POST-INJECTION (BWI, BWII, BWIII)

Figure 12B

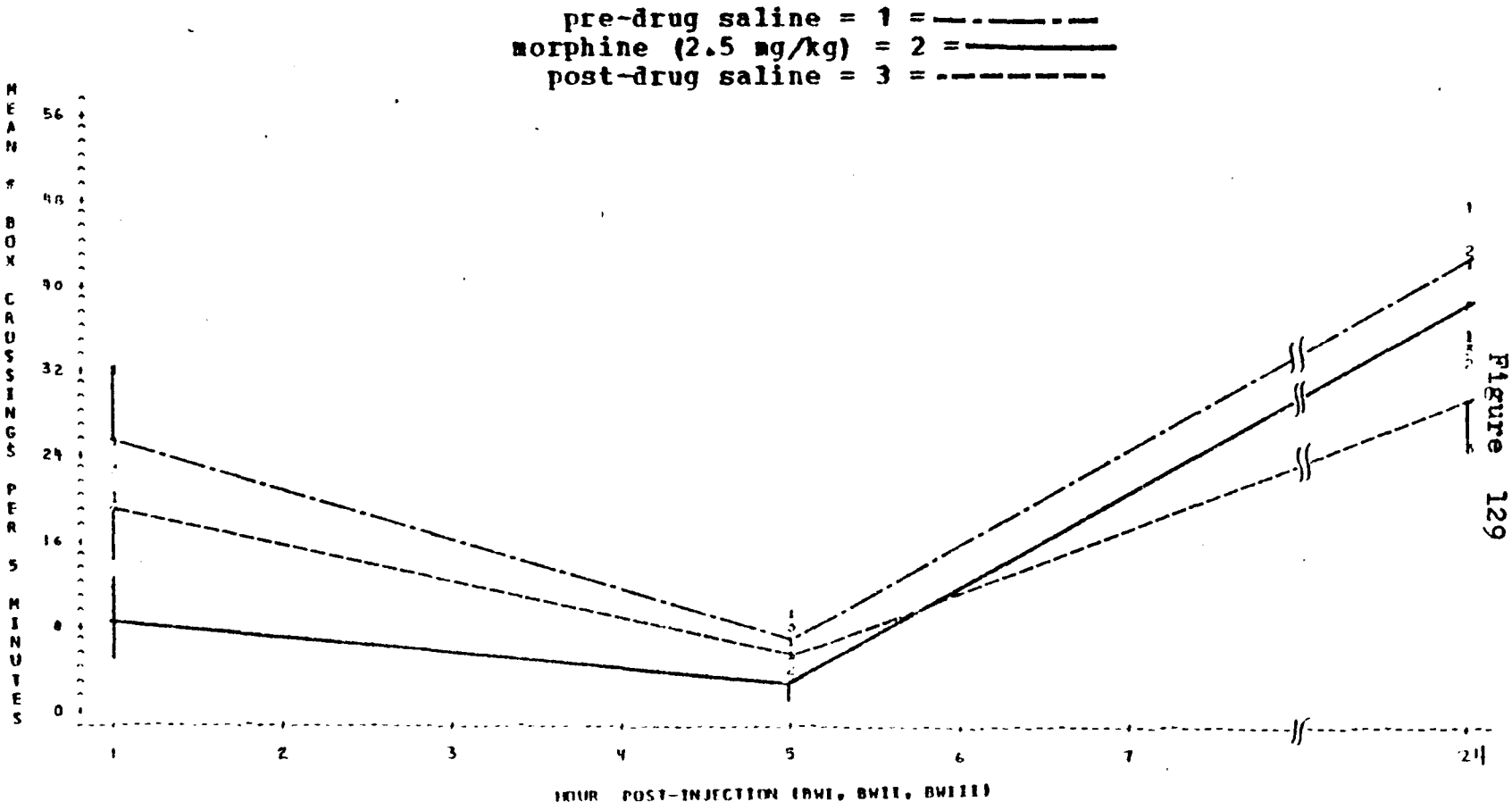

pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN # BOX CROSSINGS PER 5 MINUTES
56
48
40
32
24
16
8
0
1
2
3
4
5
6
7
21
HOUR POST-INJECTION (BWI, BWII, BWIII)

Figure 129

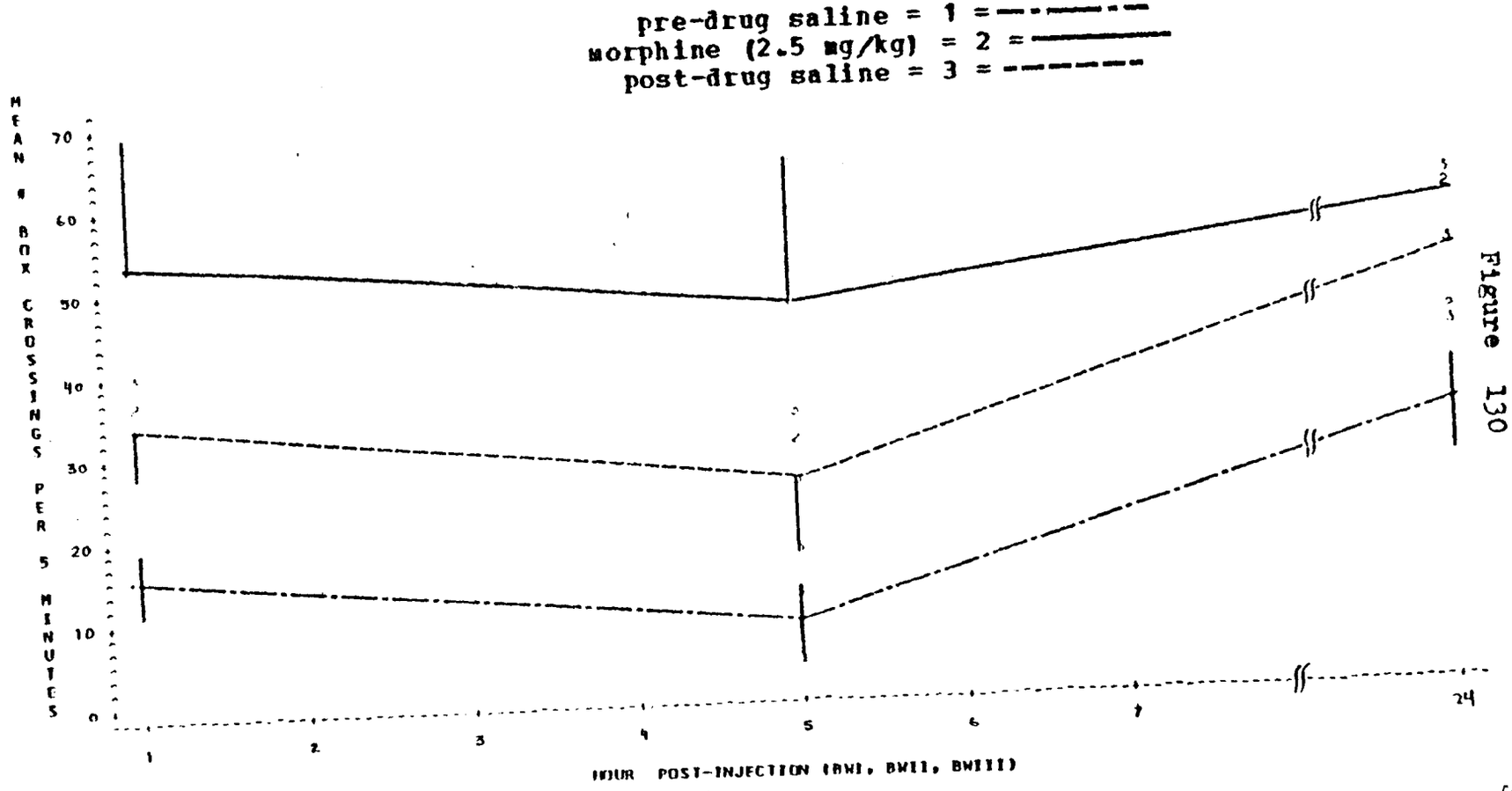

pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN # BOX CROSSINGS PER 5 MINUTES
0
10
20
30
40
50
60
70
1
2
3
4
5
6
7
24
HOUR POST-INJECTION (BWI, BWII, BWIII)

Figure 130

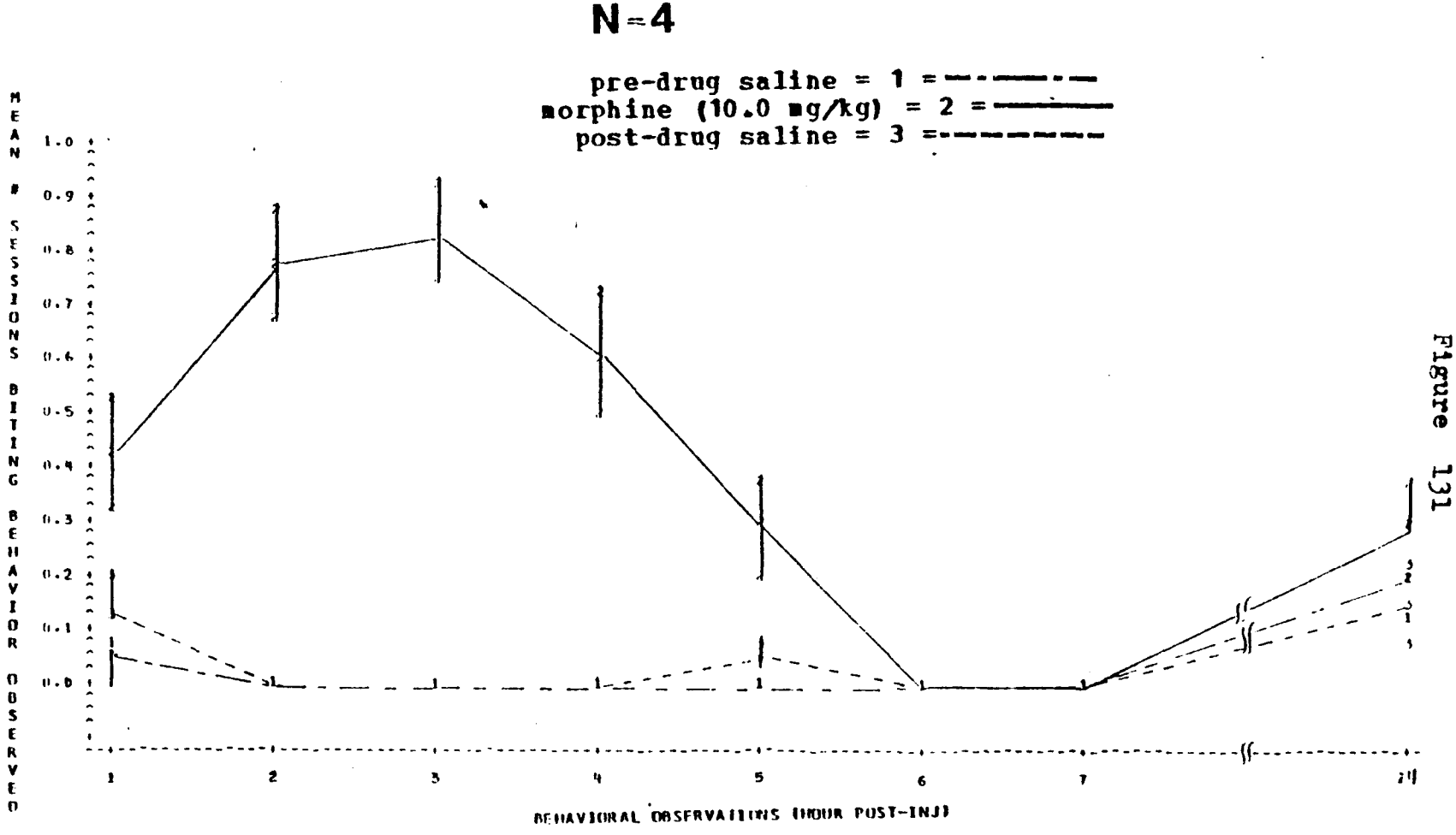

N=4
pre-drug saline = 1 =
morphine (10.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN # SESSIONS BITING BEHAVIOR OBSERVED
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
1
2
3
4
5
6
7
24
BEHAVIORAL OBSERVATIONS (HOUR POST-INJ)

Figure 131

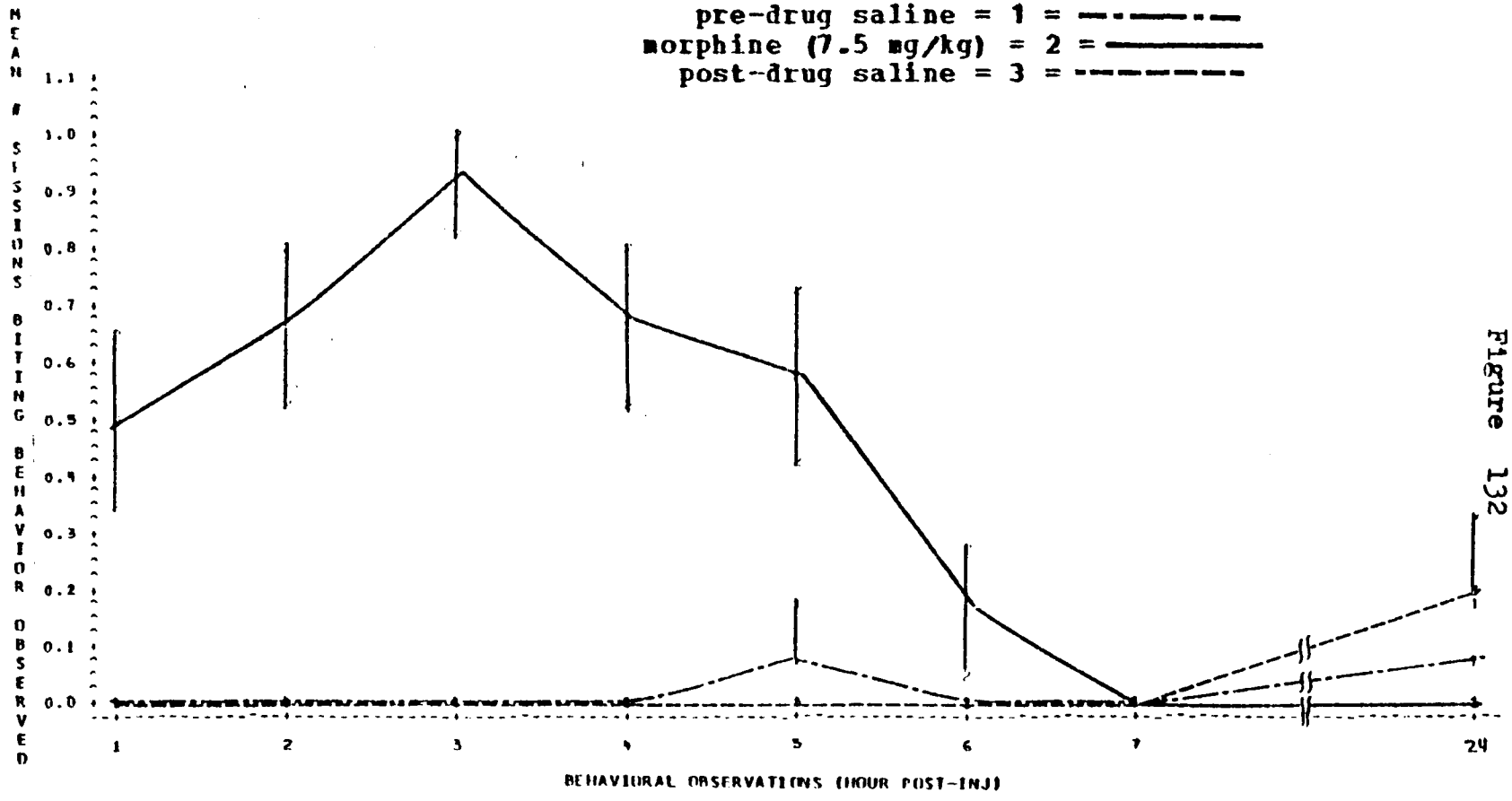

N = 2
pre-drug saline = 1 =
morphine (7.5 mg/kg) = 2 =
post-drug saline = 3 =
MEAN # SESSIONS BITING BEHAVIOR OBSERVED
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
1
2
3
4
5
6
7
24
BEHAVIORAL OBSERVATIONS (HOUR POST-INJ)

Figure 132

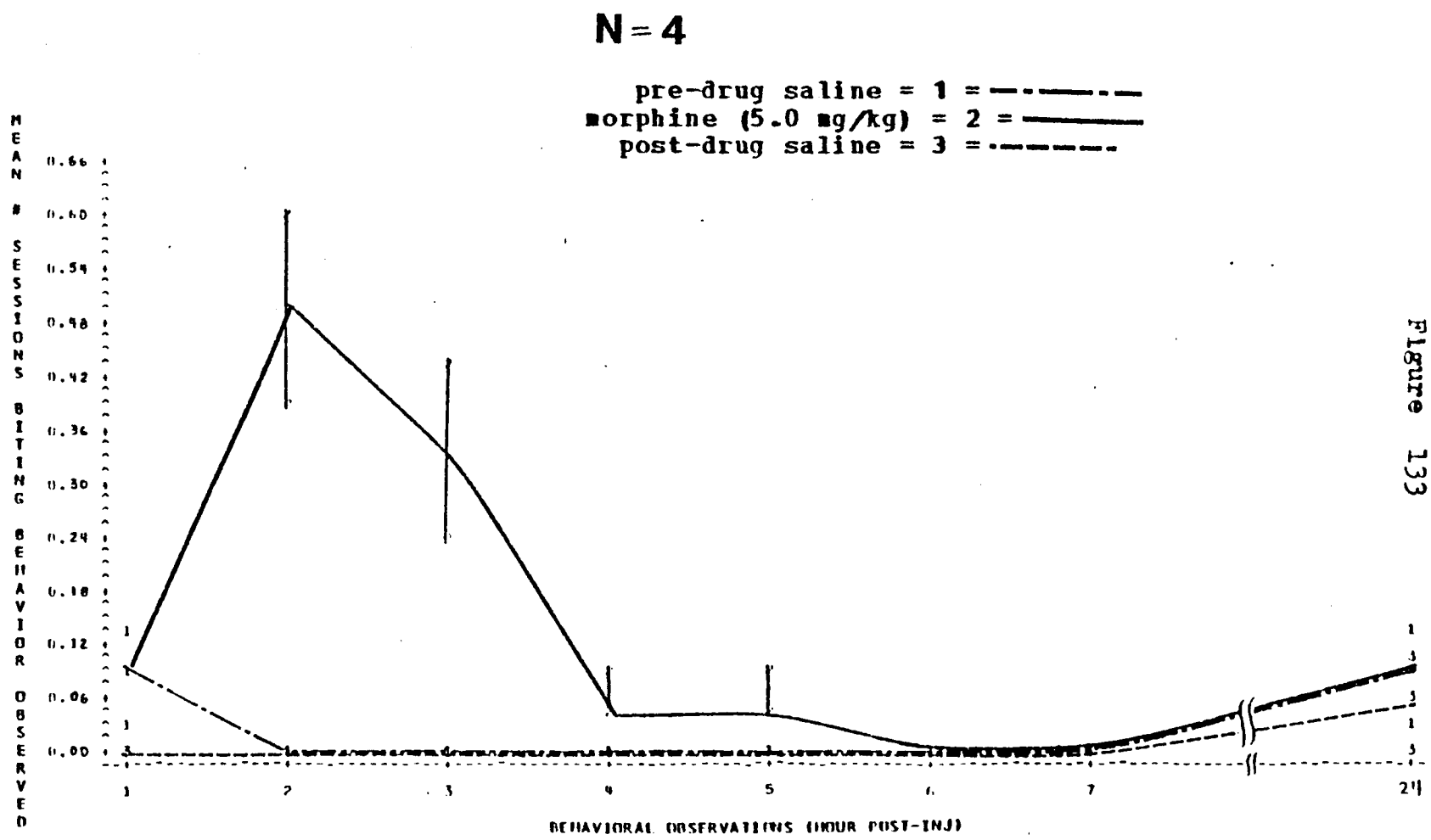

N = 4
pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =
MEAN # SESSIONS BITING BEHAVIOR OBSERVED
0.66
0.60
0.54
0.48
0.42
0.36
0.30
0.24
0.18
0.12
0.06
0.00
1
2
3
4
5
6
7
24
BEHAVIORAL OBSERVATIONS (HOUR POST-INJ)

Figure 133

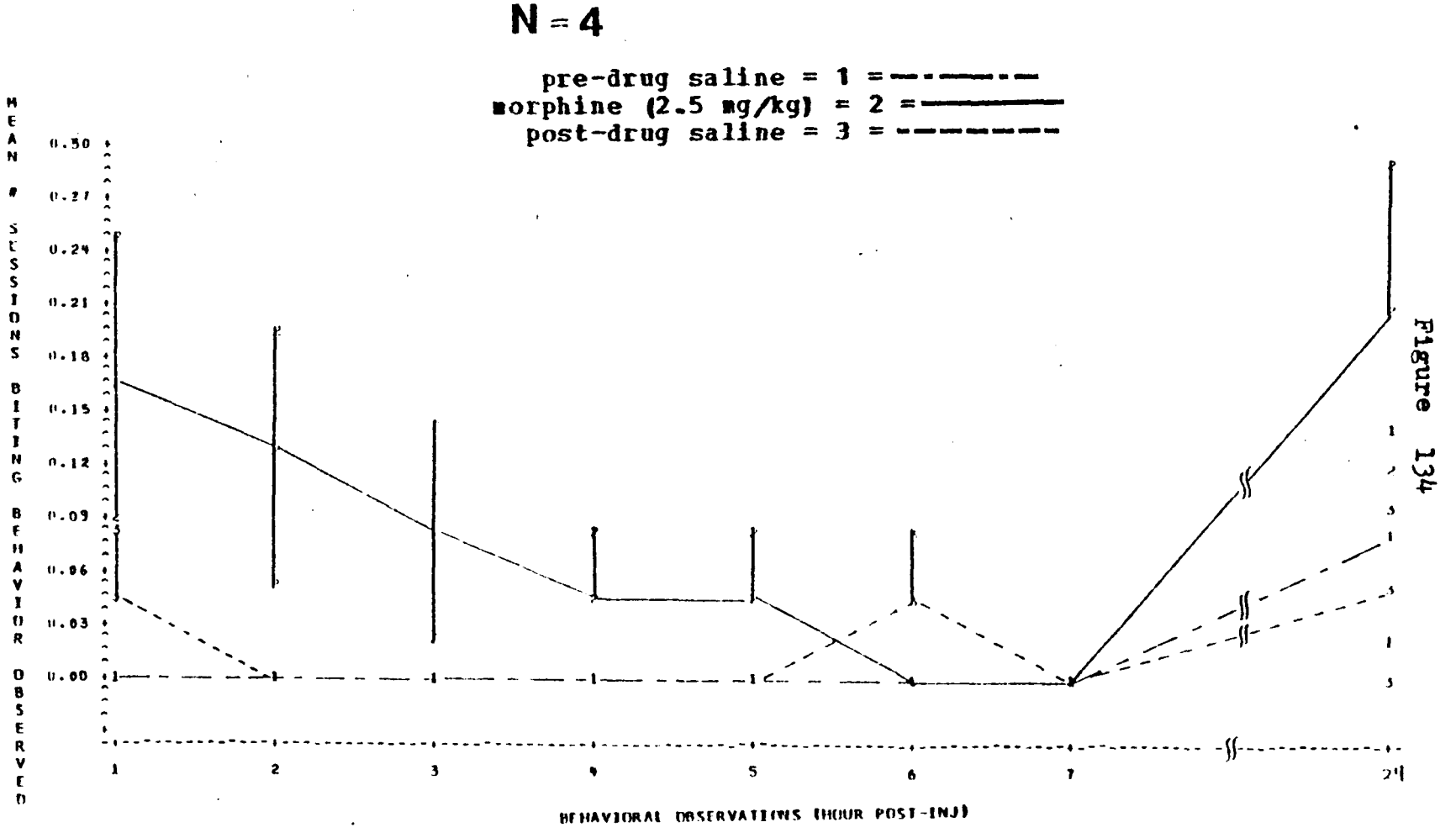

N = 4
pre-drug saline = 1
morphine (2.5 mg/kg) = 2
post-drug saline = 3
MEAN # SESSIONS BITING BEHAVIOUR OBSERVED
0.30
0.27
0.24
0.21
0.18
0.15
0.12
0.09
0.06
0.03
0.00
1
2
3
4
5
6
7
24
BEHAVIORAL OBSERVATIONS (HOUR POST-INJ)

Figure 134

Figure 135

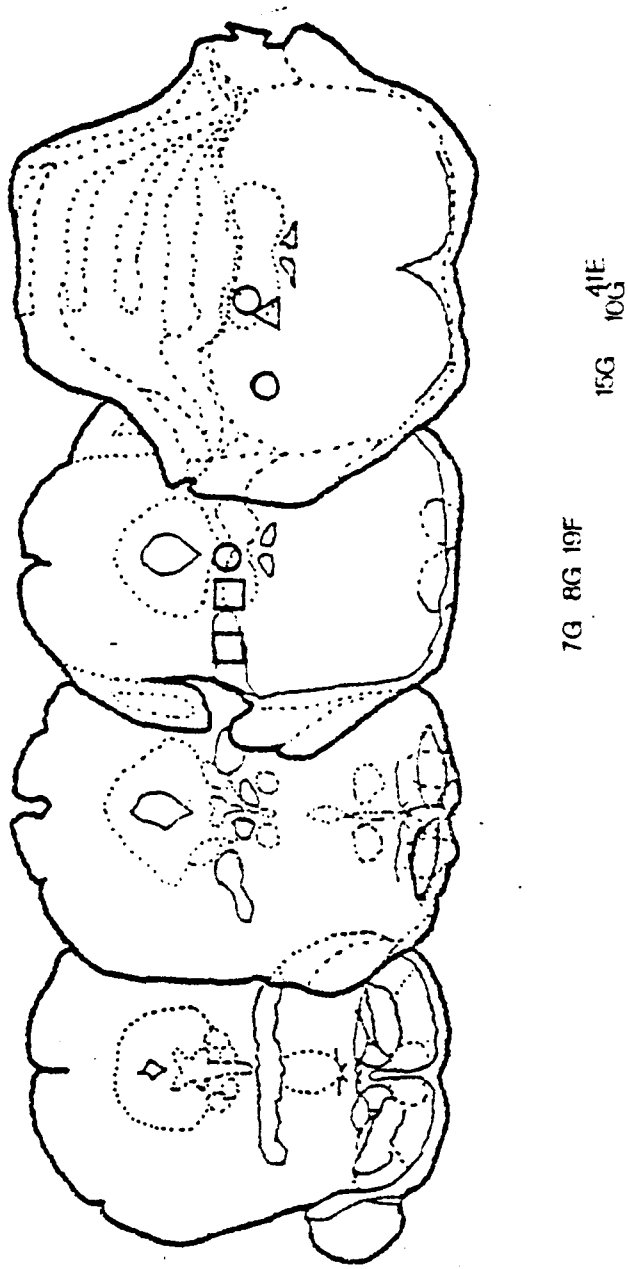
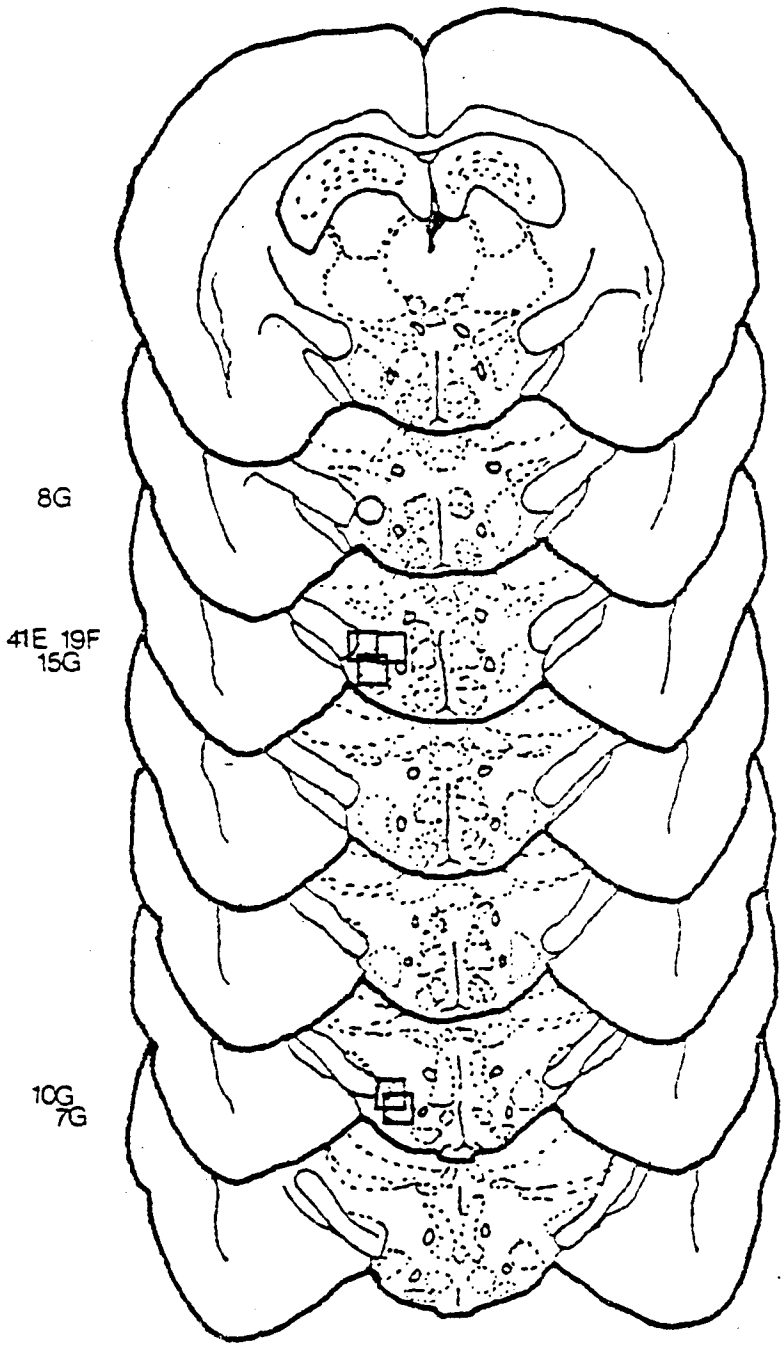


Figure 136



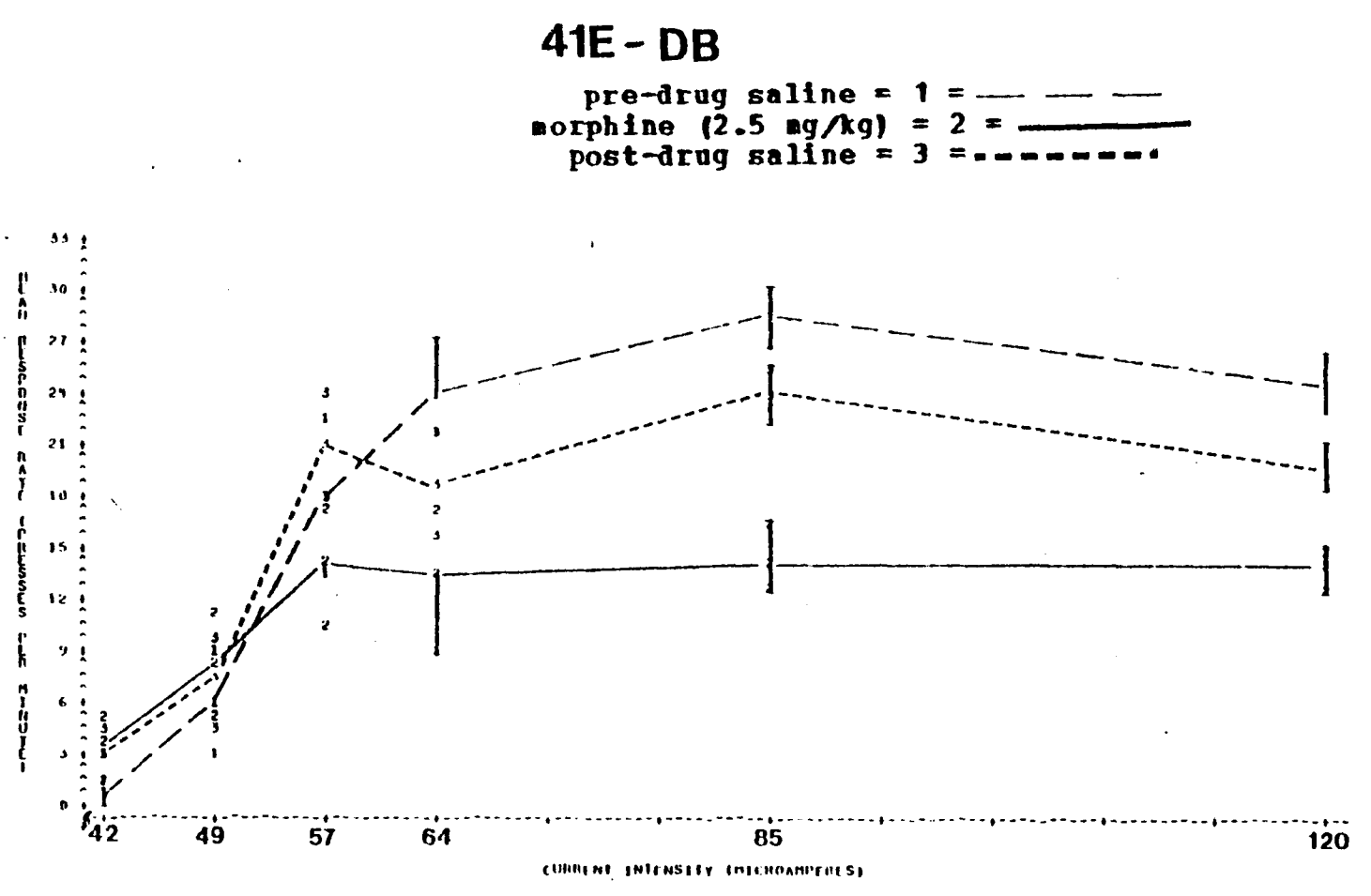

41E - DB
pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
42
49
57
64
85
120
CURRENT INTENSITY (MICROAMPERES)

Figure 137

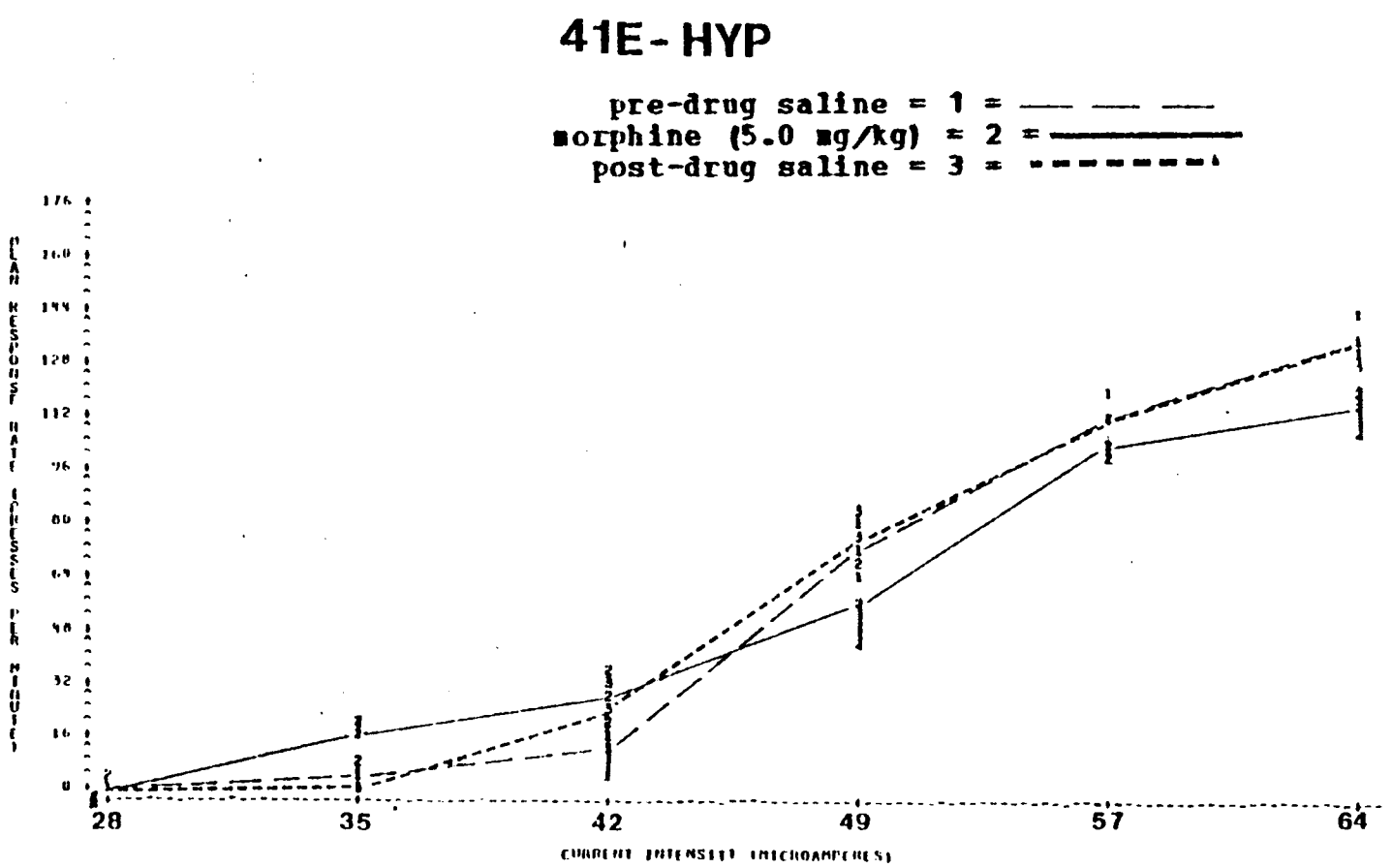

41E-HYP
pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =
28
35
42
49
57
64

Figure 138

19F - DB

pre-drug saline = 1 = — — —
morphine (10.0 mg/kg) = 2 = ————
post-drug saline = 3 = ·—·—·—·—·

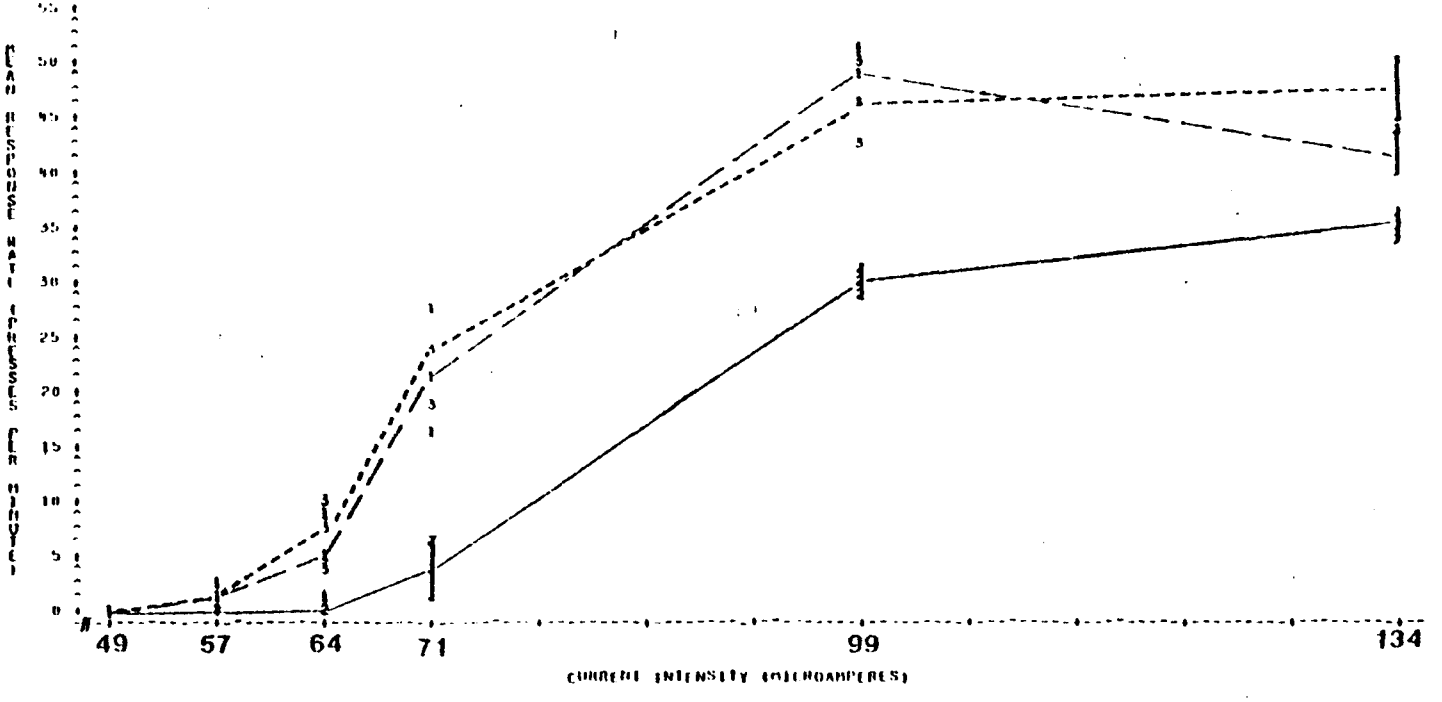


Figure 139

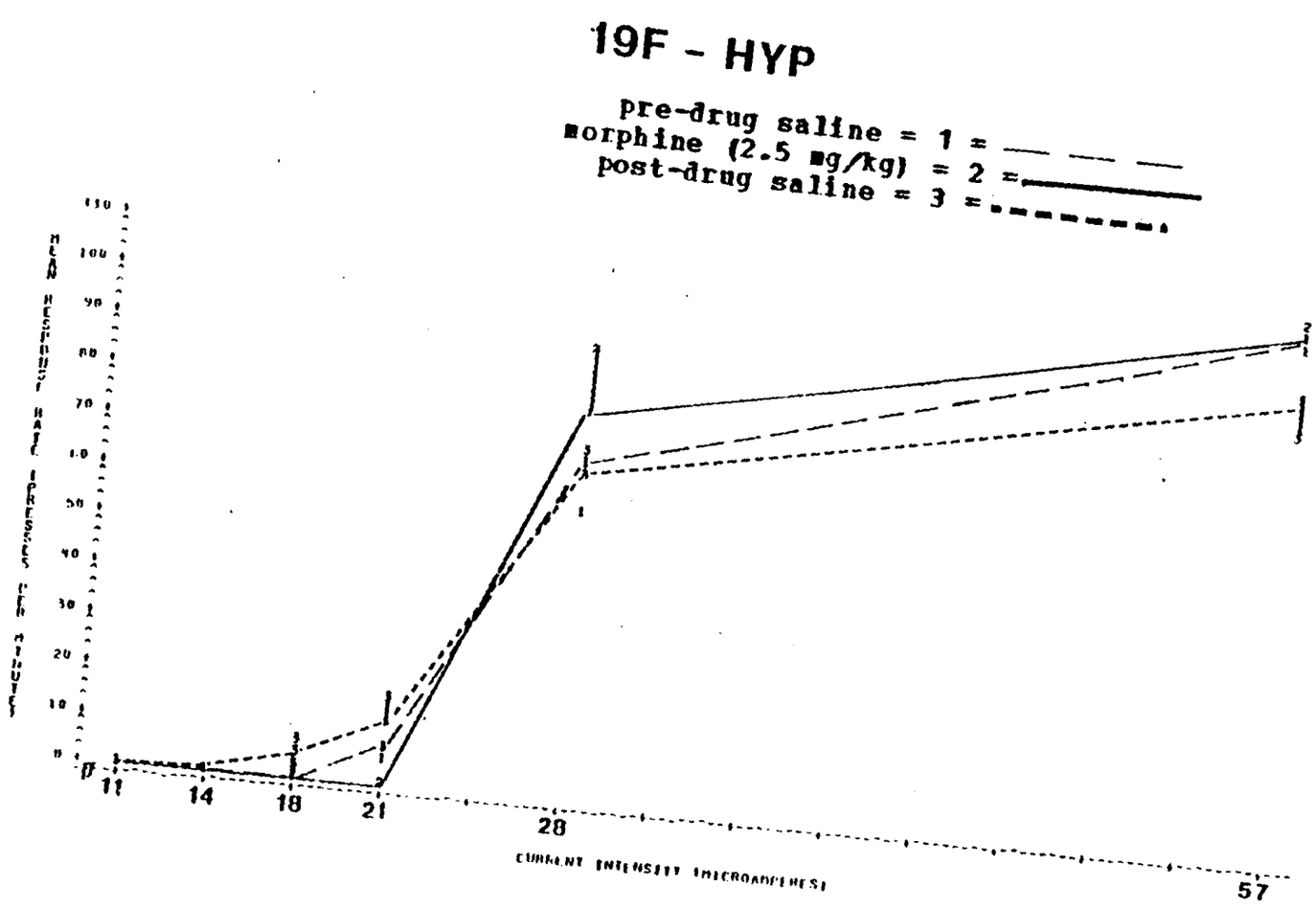

19F - HYP
pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
11
14
18
21
28
57

Figure 140

15G - DB

pre-drug saline = 1 = — — —
morphine (5.0 mg/kg) = 2 = ————
post-drug saline = 3 = •••••••

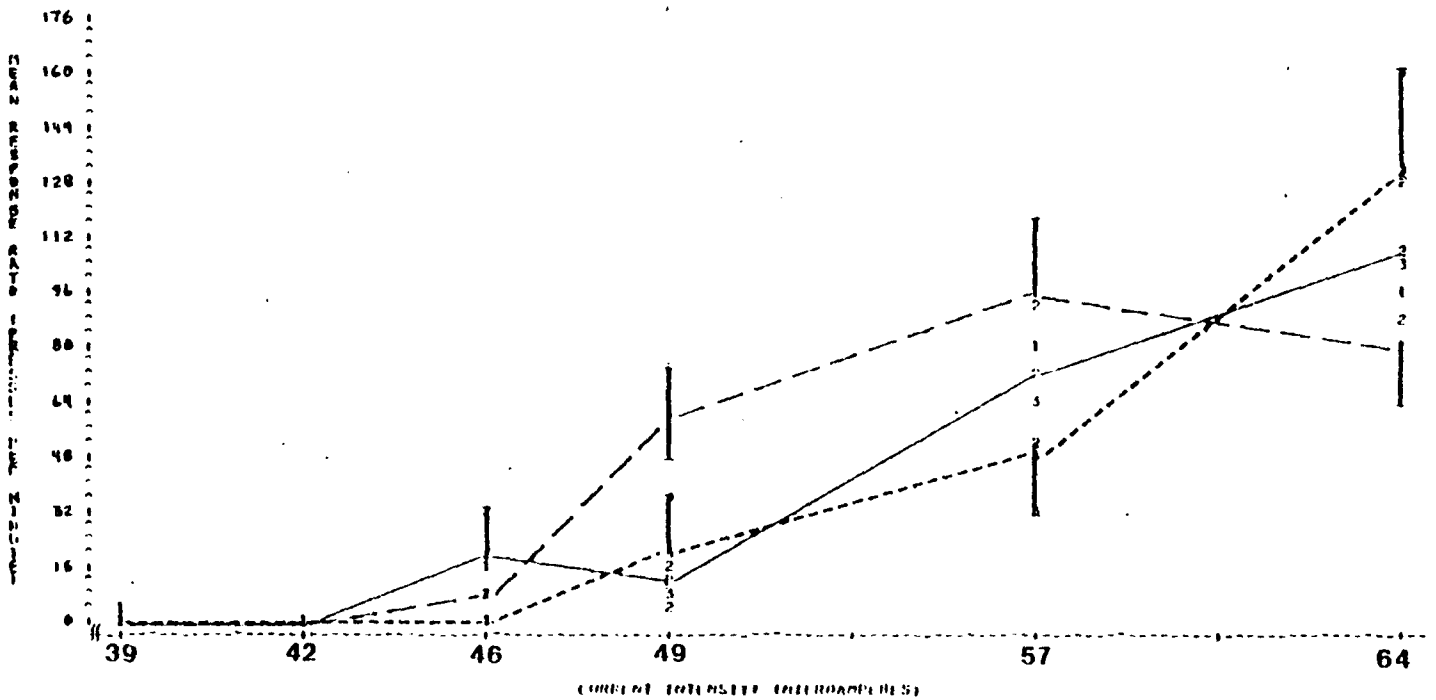


Figure 141

15G - HYP

pre-drug saline = 1 = — — —
morphine (7.5 mg/kg) = 2 = ————
post-drug saline = 3 = - - - - - -

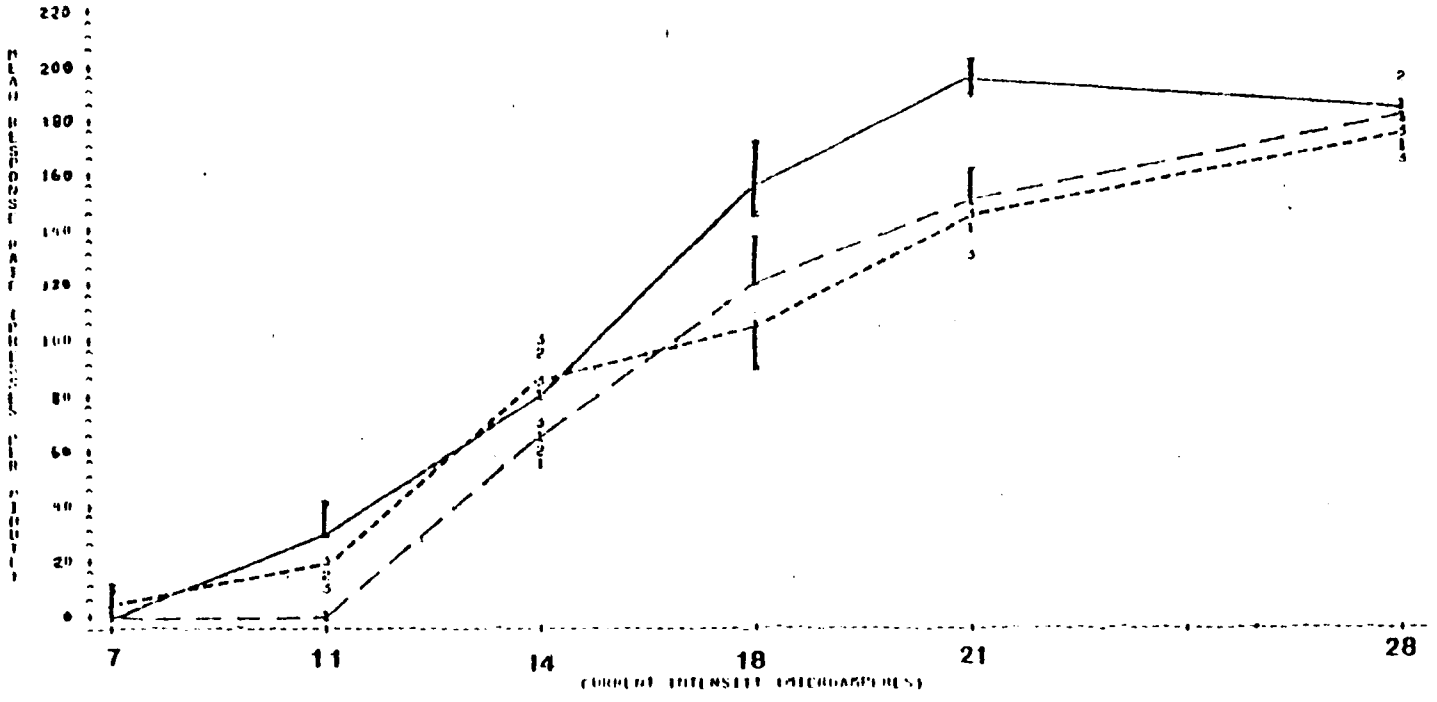


Figure 142

10G - DB

pre-drug saline = 1 = — — —
morphine (2.5 mg/kg) = 2 = ————
post-drug saline = 3 = ·—·—·—·

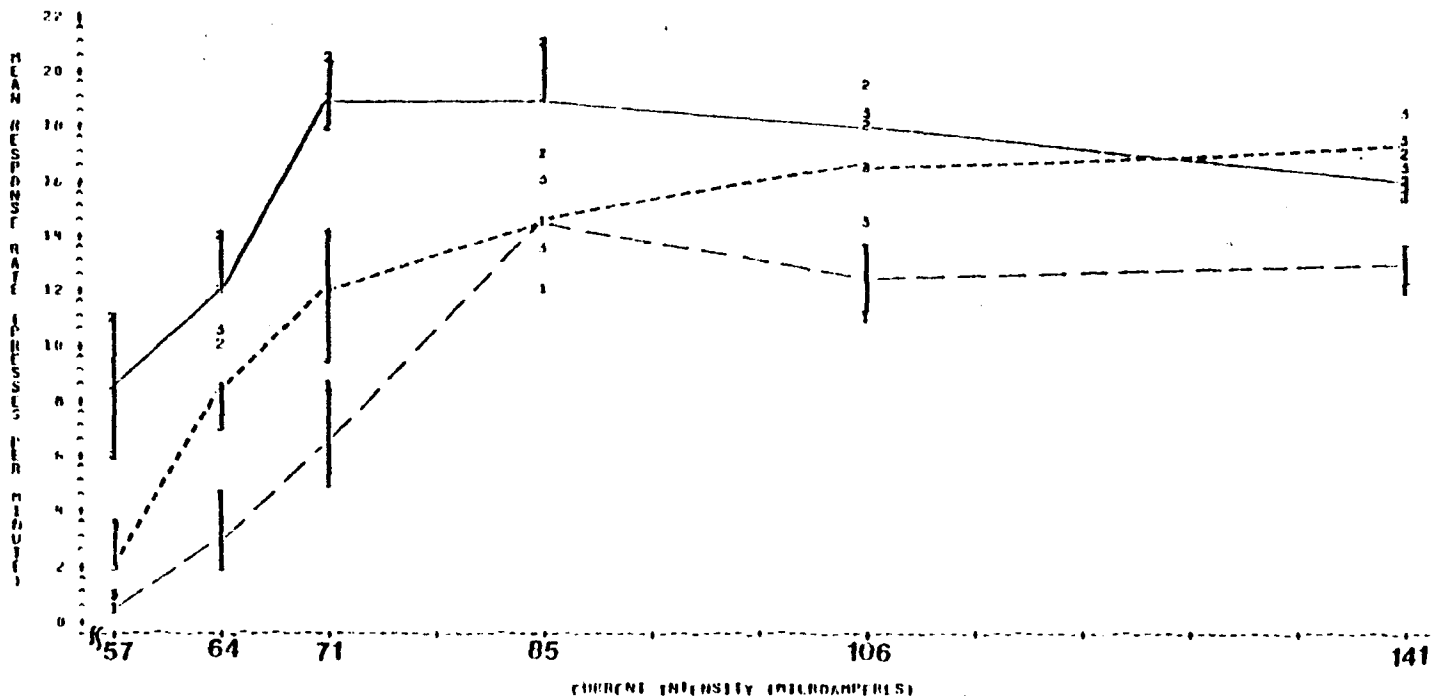


Figure 143

10G - HYP

pre-drug saline = 1 = — — —
morphine (10.0 mg/kg) = 2 = ————
post-drug saline = 3 = - - - - - -

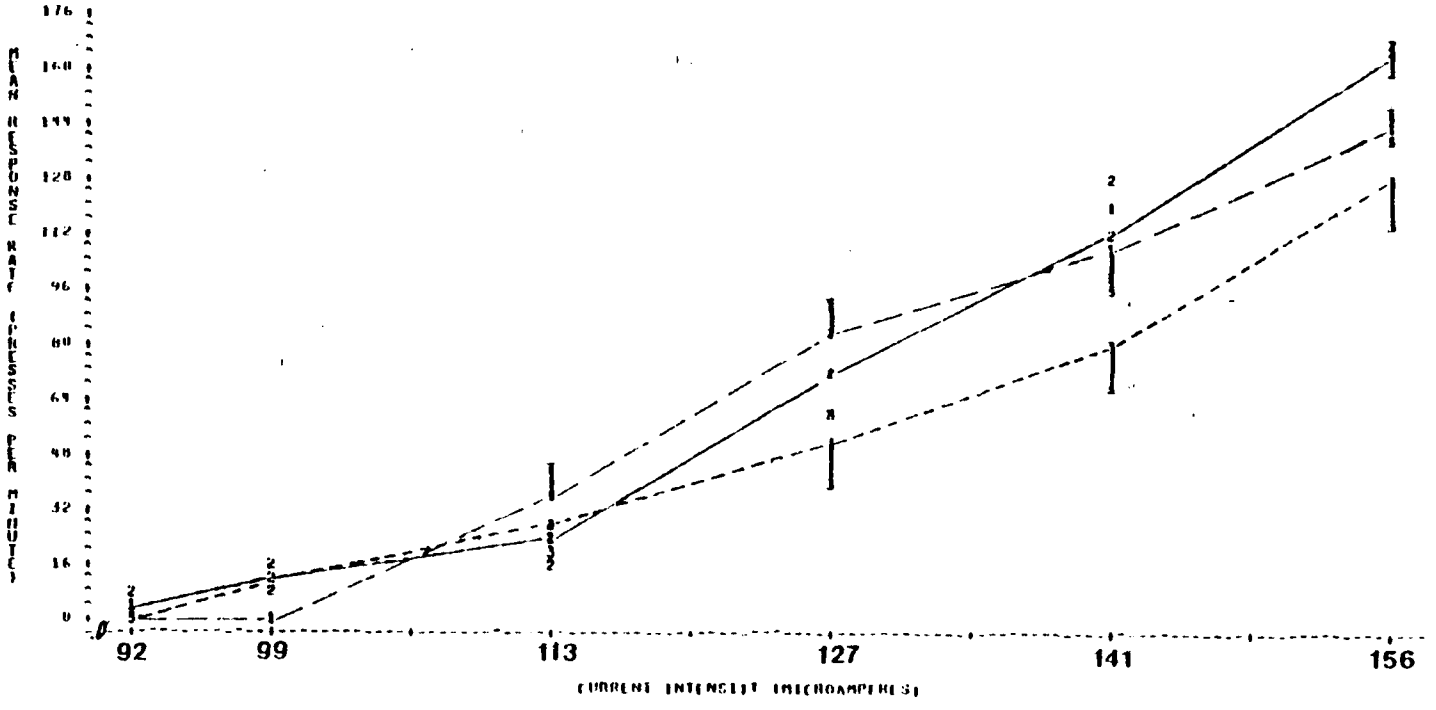
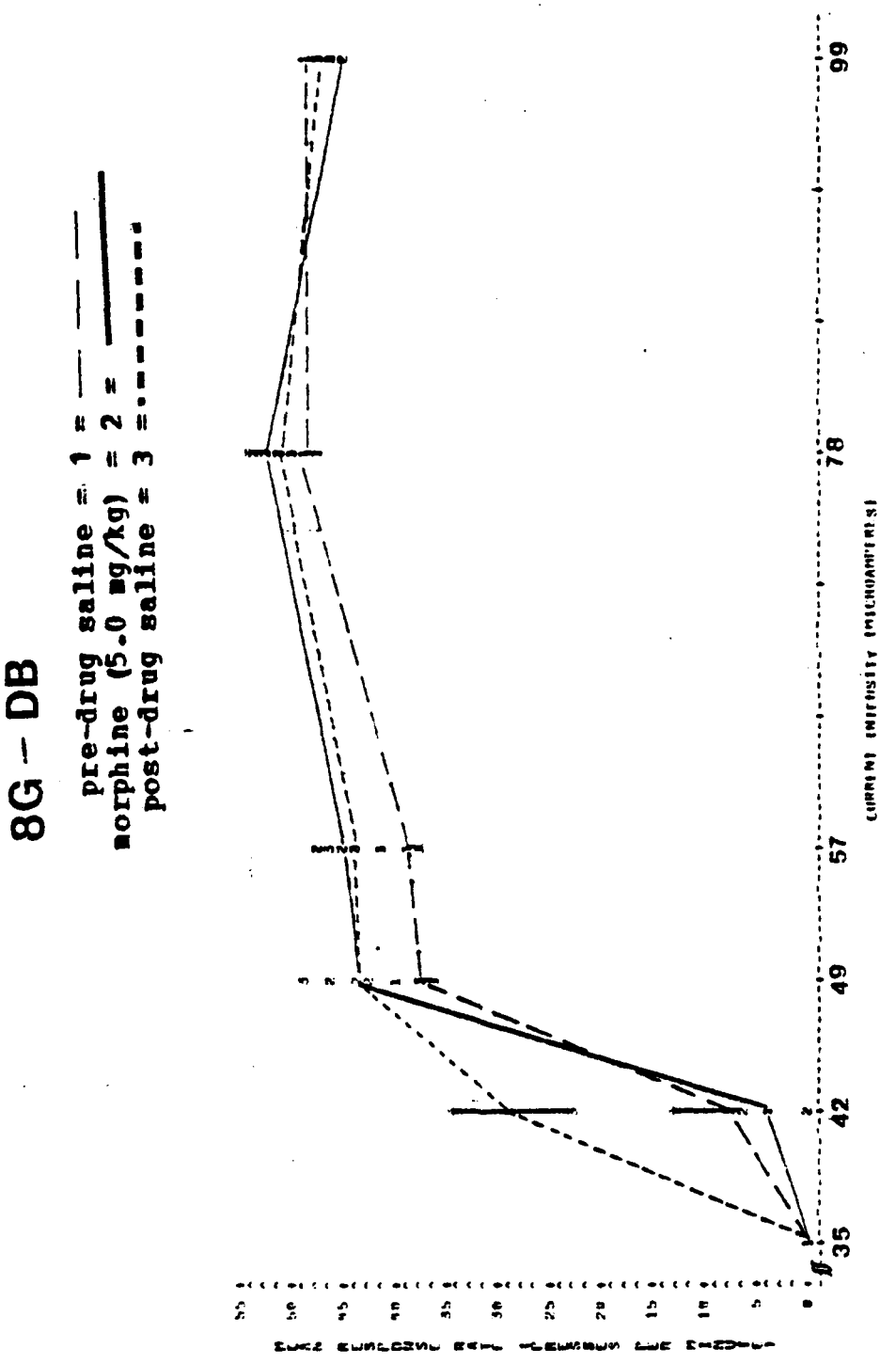


Figure 144

Figure 145


8G – DB
pre-drug saline = 1 = — — —
morphine (5.0 mg/kg) = 2 = ———
post-drug saline = 3 = .-.-.-.-.
99
78
57
49
42
35

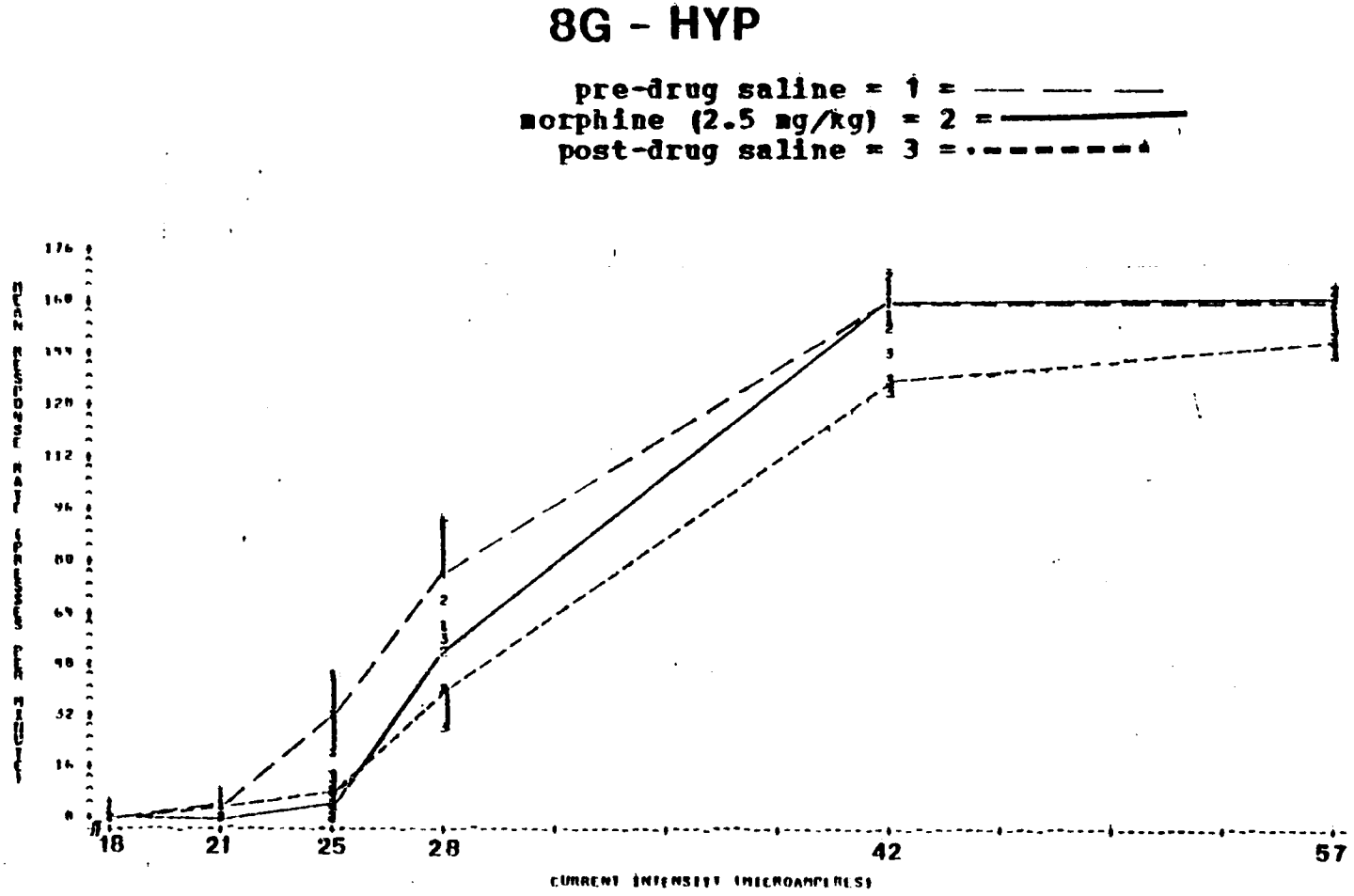

8G - HYP
pre-drug saline = 1 =
morphine (2.5 mg/kg) = 2 =
post-drug saline = 3 =
18
21
25
28
42
57
CURRENT INTENSITY (MICROAMPERES)

Figure 146

7G - DB

pre-drug saline = 1 = — — —
morphine (7.5 mg/kg) = 2 = ———
post-drug saline = 3 = - - - - -

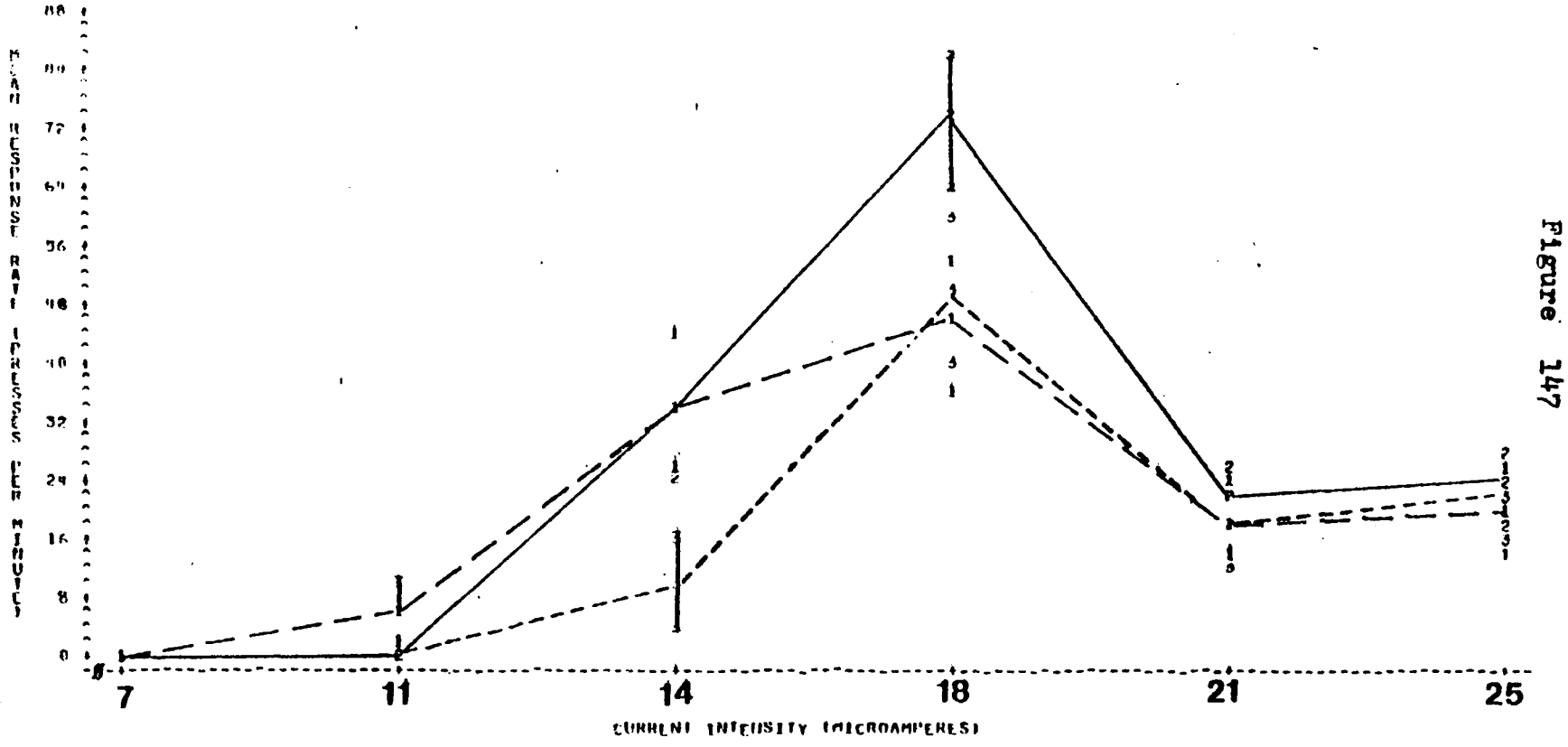
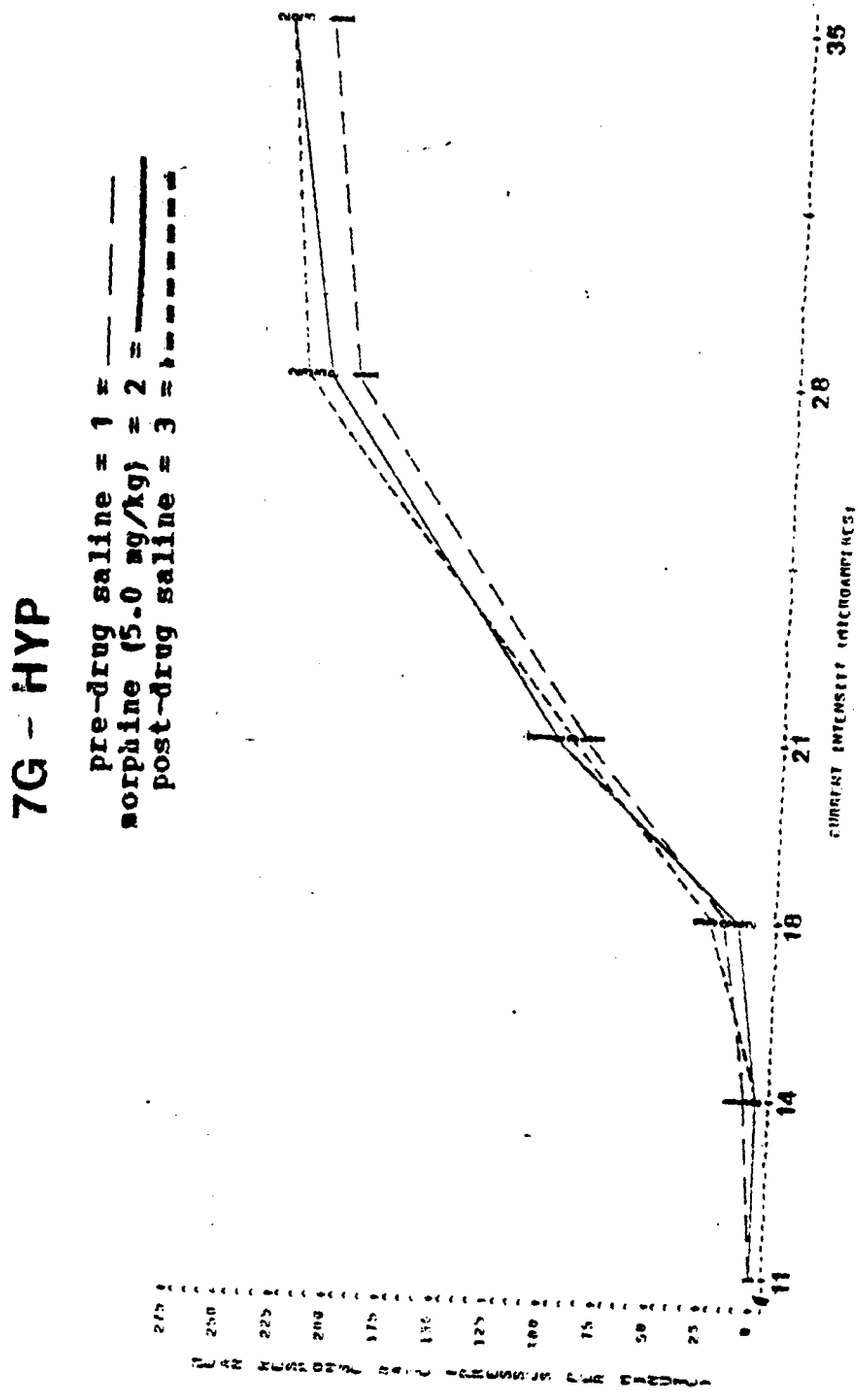


Figure 147

Figure 148


7G - HYP
pre-drug saline = 1 =
morphine (5.0 mg/kg) = 2 =
post-drug saline = 3 =
11
14
18
21
28
35