Pharmacology Biochemistry & Behavior, Vol. 15, pp. 425–433, 1981, Printed in the U.S.A.

Locomotor Activity in Morphine-Treated Rats: Effects of and Comparisons Between Cocaine, Procaine, and Lidocaine[1]

BETH E. WIECHMAN,[2] THOMAS E. WOOD AND GEORGE R. SPRATTO

Department of Pharmacology and Toxicology,
School of Pharmacy and Pharmacal Sciences
Purdue University, West Lafayette, IN 47907

Received 24 November 1980

WIECHMAN, B. E., T. E. WOOD AND G. R. SPRATTO. *Locomotor activity in morphine-treated rats: Effects of and comparisons between cocaine, procaine, and lidocaine.* PHARMAC. BIOCHEM. BEHAV. 15(3) 425–433, 1981.—The effects of cocaine, procaine, and lidocaine on open field and spontaneous (actophotometer) locomotor activities were assessed and compared in rats (1) treated acutely with morphine (single injection), (2) made dependent on morphine (SC pellets), (3) implanted with morphine and withdrawn at the time of peak dependence, and (4) implanted SC with lactose-containing pellets (sham). Cocaine-induced (10 or 30 mg/kg) open field and spontaneous locomotor activities were significantly greater in each of the four groups than those of the corresponding groups administered saline. Procaine (50 or 100 mg/kg) significantly reduced open field locomotor activity in all morphine-treated rats and spontaneous locomotor activity in acute rats. Lidocaine (30 mg/kg) significantly depressed spontaneous locomotor activity in acute rats. Upon comparison of the activities induced by the three local anesthetics, open field locomotor activity of sham-implanted rats was greater following cocaine (10 or 30 mg/kg) than following procaine (50 or 100 mg/kg). Only morphine withdrawn rats manifested greater activity following cocaine (10 mg/kg) than following either procaine (50 mg/kg) or lidocaine (10 mg/kg); activities were equivalent in dependent and acute rats. In contrast, cocaine-induced (30 mg/kg) open field locomotor activity of all morphine-treated rats was greater than either procaine- (100 mg/kg) or lidocaine- (30 mg/kg) induced activities. Spontaneous locomotor activity of all groups except acute morphine was greater following both doses of cocaine than following both doses of either procaine or lidocaine. In acute rats, only cocaine (10 mg/kg) induced greater activity than the other local anesthetics. Thus, stimulation of locomotor activity following cocaine treatment is a pharmacological property unique to cocaine and not shared by either procaine or lidocaine. Further, the data indicate that the methods selected for assessing locomotor activity may not give comparable results.

Cocaine Procaine Lidocaine Open field locomotor activity Spontaneous locomotor activity Morphine-treated rats

IT has long been believed that cocaine is unique among local anesthetics in that, in addition to producing local anesthesia, it possesses stimulant and euphoric properties. In rats, cocaine significantly enhances locomotor activity and induces stereotypic behavior [5, 21, 22]. In comparison, few studies have been published concerning the behavioral pharmacology of local anesthetics, other than cocaine in either man or laboratory animals, even though certain of these drugs (e.g. procaine and lidocaine) possess pharmacological properties similar to either cocaine or narcotics. For example, procaine has been shown to produce analgesia [19], has been studied as a geriatric antidepressant [1, 7, 25], has been reported to produce euphoria and drowsiness in humans following intravenous administration [24], and has been shown to maintain responding that leads to intravenous delivery in rhesus monkeys [8, 11, 13, 24]. And, lidocaine has been shown to possess analgesic properties [4, 10, 18], to produce drowsiness following intravenous administration [24], and to produce euphoria indistinguishable from cocaine in experienced human volunteers [23]. In contrast to procaine, lidocaine failed to maintain responding that leads to intravenous delivery in rhesus monkeys [24].

Since procaine and lidocaine possess certain pharmacological properties similar to cocaine, this study was designed to investigate the effects of the three local anesthetics on open field locomotor activity as well as on spontaneous locomotor activity (assessed in actophotometers). It was also of interest to compare the activities induced by the three local anesthetics to determine if the results observed could be related to the chemical structure of the compounds. The

[1]Supported in part by National Research Service Award GM-07095 and DA-01995.

[2]Present address: E. I. DuPont de Nemours & Company, Haskell Laboratory for Toxicology and Industrial Medicine, Elkton Road, Newark, DE 19711.

local anesthetics were administered to rats that had received various types of morphine treatment. By comparing the interactions of the local anesthetics with various types of morphine treatment, further differences with respect to activity between the local anesthetics could be emphasized. In addition, it was of interest to compare the two methods of assessing activity, the open field and actophotometer, in rats.

METHOD

Animals

Male, adult Sprague-Dawley derived rats, approximately six weeks old and weighing 140–160 g, were obtained from Laboratory Supply Company (Indianapolis, IN). Animals were housed eight to twelve per cage and maintained at a constant room temperature of 23°±1°C with a 14 hour artificial lighting cycle (0600-2000 hr). Food (Wayne Lab-Blox®; Allied Mills, Inc., Chicago, IL) and tap water were freely available. Animals were allowed to acclimate to these conditions at least three days prior to experimentation.

Four independent groups of rats were utilized in the assessment of both open field and spontaneous locomotor activities (described below). Animals designated as acute received morphine sulfate, 5 mg/kg, subcutaneously, either 30 minutes prior to the first assessment of open field locomotor activity (at time zero) and subsequent administration of the local anesthetics or saline, or 30 minutes prior to local anesthetic or saline administration and immediate placement into actophotometers. This dosage of acute morphine, administered 30 minutes prior to experimentation, resulted in brain concentrations of morphine at the initiation of the experiment that were comparable to those of dependent rats four days following morphine pellet implantation (Wiechman, unpublished observations). Tolerance to and physical dependence on morphine were induced by subcutaneous implantation of morphine pellets, first described by Maggiolo and Huidobro [16]. Two morphine pellets (total of 202 mg morphine base) were implanted subcutaneously in each rat. Rats were then utilized experimentally four days (96 hours) following morphine pellet implantation; this period of time has been shown to induce peak tolerance to and physical dependence on morphine in our laboratory [14]. In rats designated as withdrawn, the implanted morphine pellets were removed surgically 86 hours following implantation. Withdrawn animals were used experimentally ten hours following removal of the morphine pellets; they exhibited characteristic morphine withdrawal behavior including weight loss, hostility to touch, "wet-dog shakes," and vocalization. The "control" rats or animals designated as sham-implanted received pellets identical to the morphine pellet formulation except lactose replaced morphine. These animals were also utilized experimentally four days (96 hours) following lactose pellet implantation. However, sham pellets were not removed for controls in withdrawal studies.

Drugs

Morphine pellets were made according to the formulation of Gibson and Tingstad [9] by the Industrial Pharmacy Laboratory, Department of Industrial and Physical Pharmacy, Purdue University under the direction of Dr. Garnet E. Peck.

Cocaine hydrochloride (Merck and Co.), procaine hydrochloride (ICN Pharmaceutical Products, Inc.) and lidocaine monohydrate hydrochloride (Astra Pharmaceutical Products, Inc.) were administered intraperitoneally while acute morphine sulfate (MallincKrodt Chemical Works) was administered subcutaneously. All drugs were dissolved in double distilled water and were injected in a volume of 0.1 ml/100 g of body weight. In assessing the effects of the local anesthetics on activity in each of the four groups of rats, saline was employed as the control vehicle and was injected intraperitoneally in a volume of 0.1 ml/100 g of body weight.

The doses of cocaine (10 or 30 mg/kg) and procaine (50 or 100 mg/kg) are approximately equal percentages of the LD_{50}, administered intraperitoneally, for each drug (LD_{50} for cocaine, 70 mg/kg; LD_{50} for procaine, 250 mg/kg) [3]. Equivalent doses of cocaine (10 or 30 mg/kg) and lidocaine (10 or 30 mg/kg) were employed since the intravenous LD_{50} in rats for cocaine, 17.5 mg/kg [17], and lidocaine, 21 mg/kg [12], are approximately the same. Also, VanDyke *et al.* [23] employed equivalent doses of cocaine and lidocaine in their studies.

Determination of Locomotor Activity

The open field test was utilized to evaluate the effects of three local anesthetics on locomotor activity in rats. This method provides a reliable measure of activity and only measures locomotion of the animals. The open field employed in this study consisted of 25 squares (22×22 cm) lined onto a black board (110×110 cm). The outside perimeter of the field was a 46 cm high wall. Initially, the animal was placed in the center square under a box for 30 seconds. The box was removed and the animal was free to move about the field. The total number of squares entered by the rat with all four paws was counted for a period of three minutes. Open field locomotor activity was measured for 3 minutes prior to local anesthetic administration (time zero) and 15, 30, 45, 60, and 90 minutes following local anesthetic administration.

Photoelectric activity cages (round actophotometers, Woodard Research Corporation, Herndon, VA) were employed to assess the effects of the three local anesthetics on spontaneous locomotor activity in rats. The external diameter of the chamber, in which the animal was placed, was 97.8 cm; the height of the chamber wall was 20.3 cm; the width of the chamber was 8.9 cm. The bottom of the chamber was a wire mesh screen, and the inside was painted black. During the measurement of activity, a lid was placed over the chamber. The actophotometer employed six light beams (16.5 cm apart; 1.3 cm from the bottom of the chamber) with infrared filters, which, when broken by the body of the rat triggered a count on a mechanical counter that was inaudible to the subject. One rat was run per cage. Activity was measured as total counts per 15 minutes and was recorded every 15 minutes for a duration of 90 minutes only following local anesthetic administration. Thus, rats were not placed in actophotometers prior to local anesthetic administration. This method of assessing activity not only measures locomotion of the animal, but also stereotypic movements characteristically induced by stimulant drugs such as up and down or side to side head movements, grooming movements, sniffing, and rearing.

Statistical Analyses

Homogeneity of variance was assessed by Burr-Foster Q-Test of Homogeneity. Variances were unequal; thus, all data were transformed and analyzed as log values. In comparing local anesthetic-induced activities with saline-induced activities (open field or spontaneous locomotor activity) in

TABLE 1
EFFECT OF COCAINE, PROCAINE, AND LIDOCAINE ON LOCOMOTOR ACTIVITY

Group	Cocaine		Procaine		Lidocaine	
	10 mg/kg	30 mg/kg	50 mg/kg	100 mg/kg	10 mg/kg	30 mg/kg
Open Field Locomotor Activity						
Sham-Implanted	+	+	0	0	0	0
Dependent	+	+	0	−	0	0
Withdrawn	+	+	−	−	0	+
Acute	0	+	−	−	0	0
Spontaneous Locomotor Activity						
Sham-Implanted	+	+	0	0	0	0
Dependent	+	+	0	0	0	0
Withdrawn	+	+	+	0	0	0
Acute	+	0	−	−	0	−

Open field or spontaneous locomotor activity of local anesthetic-treated and saline-treated rats were compared, n=5 to 6 rats per group.

0=activity following local anesthetic treatment is not significantly different than following saline treatment (2-way ANOVA).

+=activity following local anesthetic treatment is significantly greater than following saline treatment (2-way ANOVA).

−=activity following local anesthetic treatment is significantly less than following saline treatment (2-way ANOVA).

each of the four groups of rats (sham-implanted, dependent, withdrawn, or acute), two-way factorial analysis of variance (ANOVA) was utilized. When comparing the activities (open field or spontaneous locomotor activity) induced by the three local anesthetics in each group of rats, two-way ANOVA for repeated measures was employed. If a significant drug effect was observed, individual time periods were analyzed by Student's *t*-test. If a significant drug times time interaction was noted, the individual drug-time interactions were analyzed by Duncan New Multiple-Range Test. The level of significance chosen was $p \leq 0.05$.

RESULTS

Effects of Cocaine, Procaine, and Lidocaine on Locomotor Activity

The results of the comparisons between local anesthetic- and saline-induced open field locomotor activity and spontaneous locomotor activity in each group of rats (sham-implanted, dependent, withdrawn, and acute) are presented in Table 1. With the exception of acute rats administered cocaine (10 mg/kg), the open field locomotor activity observed in all four groups of rats was significantly greater following cocaine (10 or 30 mg/kg) treatment than following saline treatment. Procaine-induced (50 mg/kg) open field locomotor activity in withdrawn and acute rats was significantly less than saline-treated controls while procaine-induced (100 mg/kg) activities of all morphine-treated rats was significantly less than saline-treated controls. Open field locomotor activity following lidocaine treatment (10 or 30 mg/kg) was comparable to that following saline administration in all groups except withdrawn rats administered lidocaine 30 mg/kg when activity was significantly greater than saline-induced activity.

With the exception of acute rats administered cocaine (30 mg/kg), spontaneous locomotor activity in all four groups of rats following cocaine (10 or 30 mg/kg) was greater than that following saline (Table 1). Spontaneous locomotor activity following procaine (50 or 100 mg/kg) administration in sham-implanted and dependent rats was comparable to the respective groups administered saline. On the other hand, withdrawn rats treated with procaine (50 mg/kg) exhibited significantly greater activity than saline-treated withdrawn rats, while activity of withdrawn rats treated with procaine (100 mg/kg), was equivalent to saline-treated rats. Procaine (50 or 100 mg/kg) administration significantly reduced spontaneous locomotor activity of acute rats when compared with saline treatment. The only difference noted in the four groups of rats between lidocaine- (10 or 30 mg/kg) and saline-induced spontaneous locomotor activities was in acute rats where lidocaine (30 mg/kg) significantly depressed activity.

Comparison of the Effects of Cocaine, Procaine, and Lidocaine on Locomotor Activity

The next set of experiments was designed to compare the local anesthetic-induced activities of sham-implanted, dependent, withdrawn, and acute rats using both open field and spontaneous locomotor activities. (Graphs are presented only for the results following the higher doses of the local anesthetics.)

Open field. In sham-implanted rats, the open field locomotor activity induced by the lower doses of cocaine (10 mg/kg; 32 to 47 squares/3 minutes) and lidocaine (10 mg/kg; 26 to 33 squares/3 minutes) were comparable, but significantly greater than that induced by procaine (50 mg/kg; 4 to 8 squares/3 minutes) both 15 and 30 minutes following dosing.

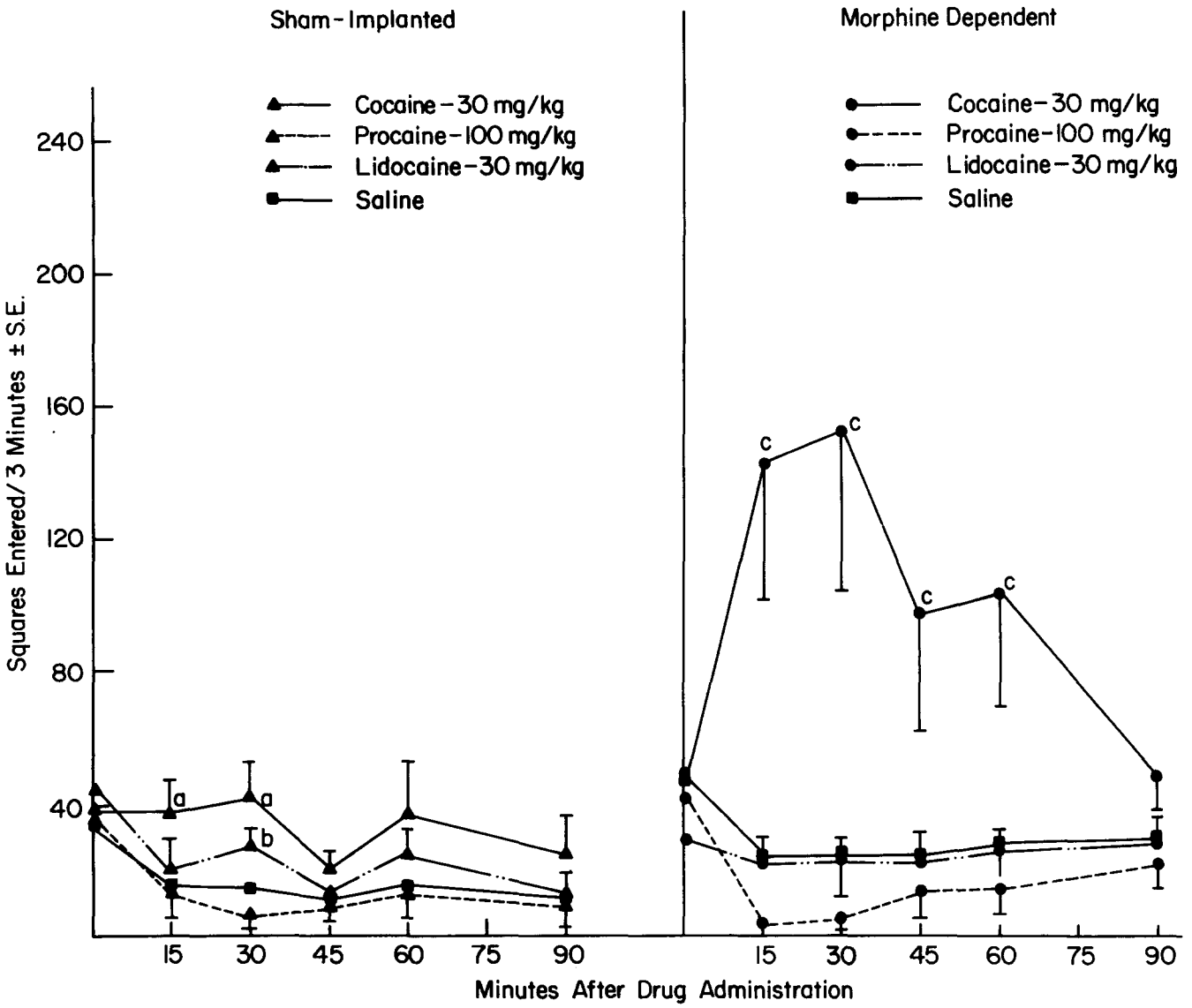

FIG. 1. Comparison of the effect of cocaine (30 mg/kg), procaine (100 mg/kg), and lidocaine (30 mg/kg) on open field locomotor activity in sham-implanted and morphine dependent rats. a=Significant drug effect; cocaine is different from procaine at that time period (2-way ANOVA for repeated measures, Student's *t*-test). b=Significant drug effect; lidocaine is different from procaine at that time period (2-way ANOVA for repeated measures, Student's *t*-test). c=Significant drug times time interaction; cocaine is different from either procaine or lidocaine at that time period (2-way ANOVA for repeated measures, Duncan's New Multiple-Range Test).

For up to 45 minutes following treatment, open field locomotor activity of withdrawn rats treated with cocaine (10 mg/kg; 41 to 47 squares/3 minutes) was significantly greater than that induced by either procaine (50 mg/kg; 3 to 6 squares/3 minutes) or lidocaine (10 mg/kg; 9 to 16 squares/3 minutes).

Although the activity observed following cocaine treatment in dependent and acute rats was greater than activity following either procaine or lidocaine treatment, no significant differences in open field locomotor activities were observed between the three local anesthetics.

Figure 1 compares the open field locomotor activities following treatment with the higher doses of the local anesthetics in sham-implanted and dependent rats. Sham-implanted rats administered cocaine (30 mg/kg) manifested significantly greater activity than rats treated with procaine (100 mg/kg) 15 and 30 minutes following treatment; at 30 minutes, lidocaine-induced activity was also greater than that induced by procaine. Cocaine- and lidocaine-induced activities were comparable in sham-implanted rats. Cocaine-treated (30 mg/kg) dependent rats exhibited significantly greater open field locomotor activity than either procaine- or lidocaine-treated dependent rats for up to 60 minutes following local anesthetic administration (Fig. 1).

Similarily, Fig. 2 illustrates that the open field locomotor activities in both withdrawn and acute rats were significantly greater following cocaine (30 mg/kg) administration than following either procaine (100 mg/kg) or lidocaine (30 mg/kg) treatment. In addition, withdrawn rats administered lido-

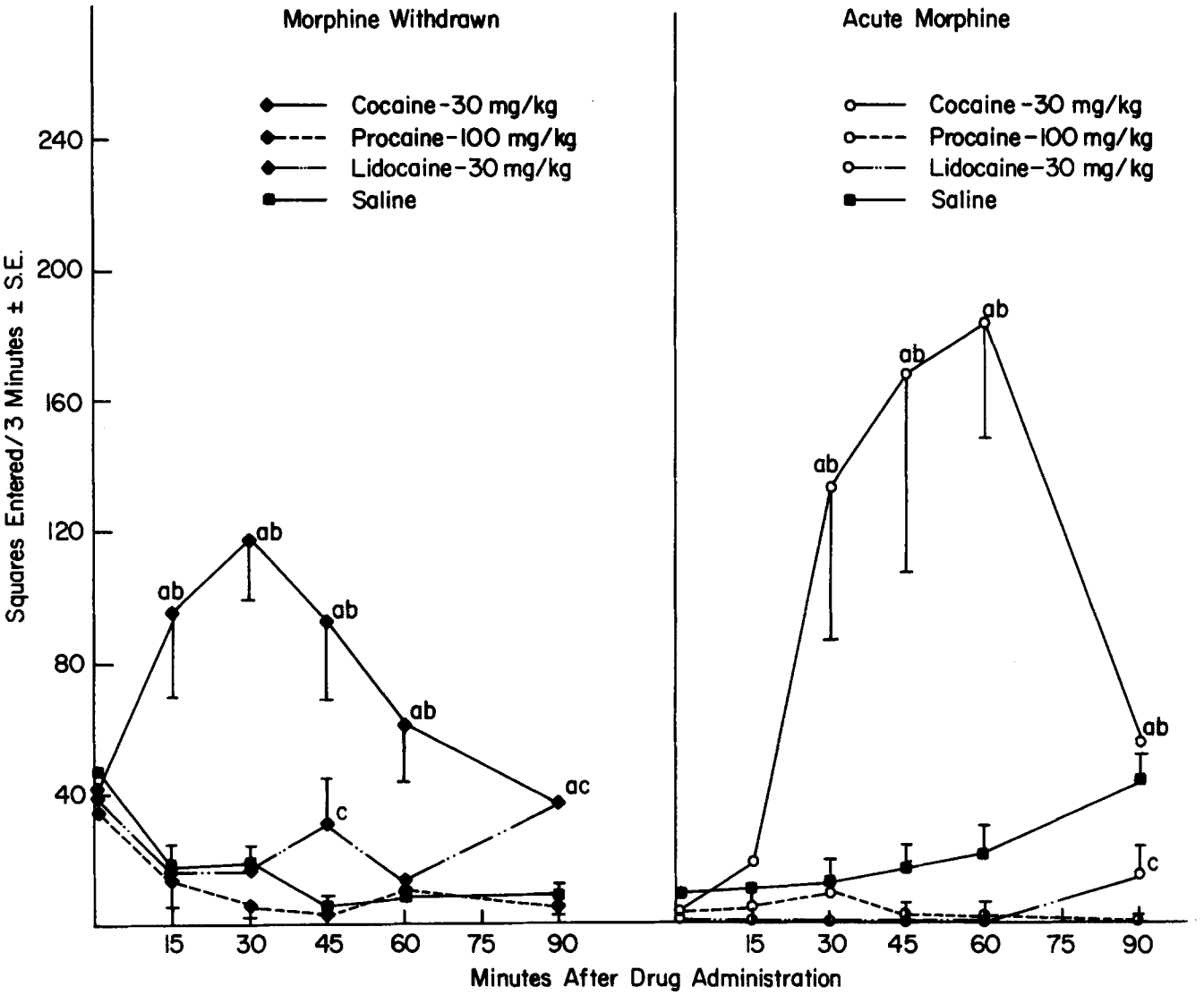

FIG. 2. Comparison of the effect of cocaine (30 mg/kg), procaine (100 mg/kg), and lidocaine (30 mg/kg), on open field locomotor activity in morphine withdrawn and acute morphine rats. a=Significant drug times time interaction; cocaine is significantly different from procaine at that time period (2-way ANOVA for repeated measures, Duncan's New Multiple-Range Test). b=Significant drug times time interaction; cocaine is different from lidocaine at that time period (2-way ANOVA for repeated measures, Duncan's New Multiple-Range Test). c=Significant drug times time interaction; lidocaine is different from procaine at that time period (2-way ANOVA for repeated measures, Duncan's New Multiple-Range Test).

caine exhibited significantly greater activity than those treated with procaine 45 and 90 minutes following dosing. It is interesting to note that the increase of the open field locomotor activity induced by cocaine (30 mg/kg) in all morphine-treated rats (dependent, withdrawn, and acute) was approximately three to eight times greater than the activity observed in sham-implanted rats following the same dose of cocaine (30 mg/kg).

Spontaneous locomotor activity. In contrast to that observed in the open field, cocaine-induced (10 mg/kg; 1420 to 1930 counts/15 minutes) spontaneous locomotor activity (as measured in actophotometers) in sham-implanted rats was significantly greater than either procaine- (50 mg/kg; 450 to 720 counts/15 minutes) or lidocaine-induced (10 mg/kg; 290 to 670 counts/15 minutes) activity for up to 30 minutes following dosing. For up to 45 minutes after treatment, cocaine-induced (10 mg/kg) spontaneous locomotor activities in both dependent (920 to 2140 counts/15 minutes) and acute (210 to 970 counts/15 minutes) rats were significantly greater than their respective group administered either procaine (50 mg/kg; dependent, 135 to 640 counts/15 minutes; acute, 15 to 95 counts/15 minutes) or lidocaine (10 mg/kg; dependent, 190 to 570 counts/15 minutes; acute, 20 to 170 counts/15 minutes). In withdrawn rats, cocaine-induced (10 mg/kg; 1960 to 1990 counts/15 minutes) spontaneous locomotor activity was greater than activity induced by either

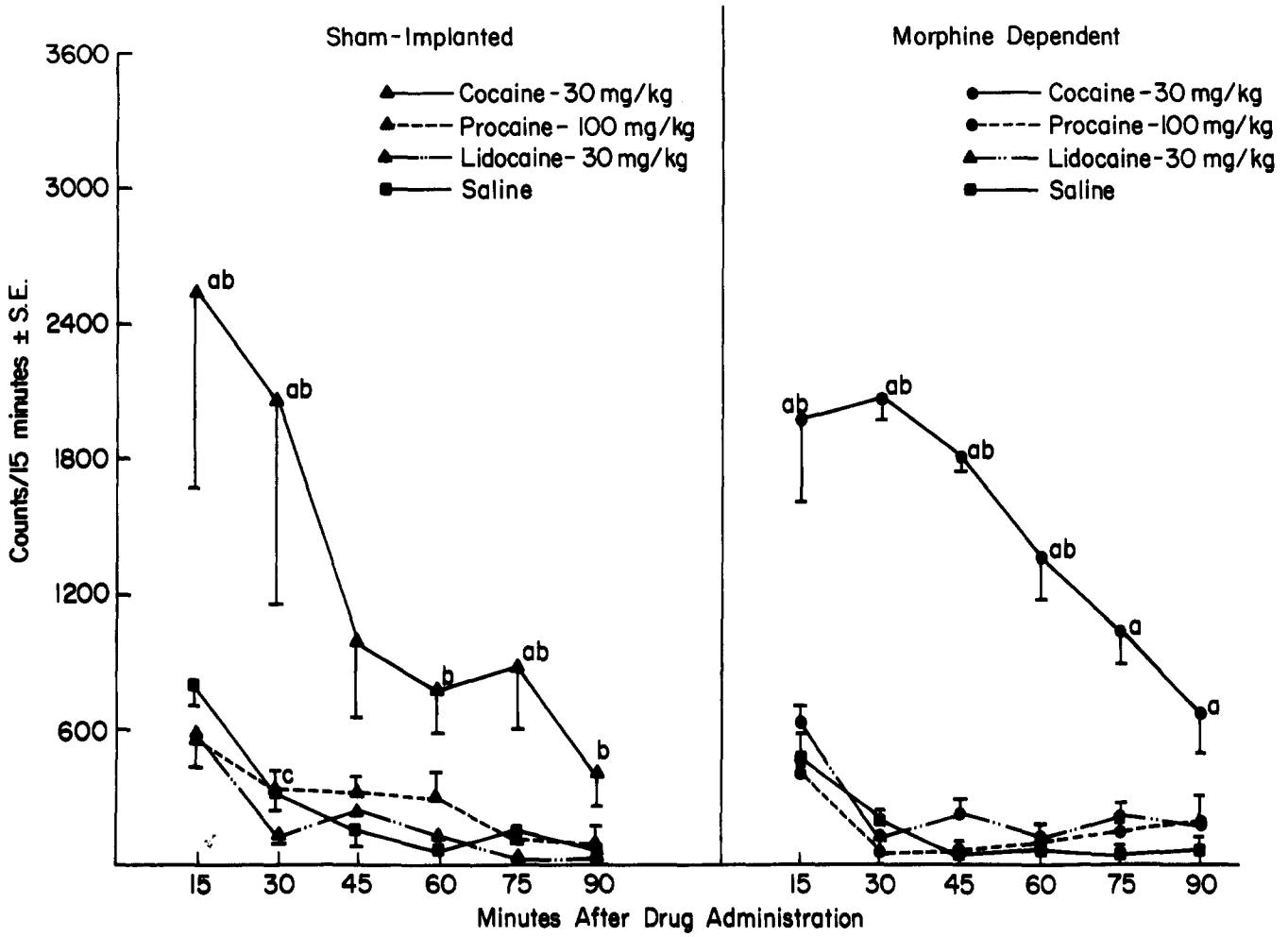

FIG. 3. Comparison of the effect of cocaine (30 mg/kg), procaine (100 mg/kg), and lidocaine (30 mg/kg) on spontaneous locomotor activity in sham-implanted and morphine dependent rats. a=Significant drug effect; cocaine is different from procaine at that time period (2-way ANOVA for repeated measures, Student's *t*-test). b=Significant drug effect; cocaine is different from lidocaine at that time period (2-way ANOVA for repeated measures, Student's *t*-test). c=Significant drug effect; procaine is different from lidocaine at that time period (2-way ANOVA for repeated measures, Student's *t*-test).

procaine (50 mg/kg; 220 to 860 counts/15 minutes) or lidocaine (10 mg/kg; 170 to 590 counts/15 minutes) 30 minutes following local anesthetic treatment.

Spontaneous locomotor activities in each of the four groups of rats following the administration of the higher doses of the local anesthetics are compared in Figs. 3 and 4. When compared with the activity induced by either procaine (100 mg/kg) or lidocaine (30 mg/kg), the activity induced by cocaine (30 mg/kg) was significantly greater for at least 30 minutes following treatment in both sham-implanted and dependent rats (Fig. 3). Similar results were observed for withdrawn rats, in which cocaine-induced (30 mg/kg) activity was significantly greater than either procaine- (100 mg/kg) or lidocaine-induced (30 mg/kg) activity for the duration of the experiment (Fig. 4). Fifteen and thirty minutes following dosing, procaine-induced (100 mg/kg) spontaneous locomotor activity was significantly greater than lidocaine-induced (30 mg/kg) activity in acute rats (Fig. 4). Only at the 90 minute time period was the activity induced by cocaine (30 mg/kg) greater than that induced by either procaine or lidocaine in these rats (Fig. 4). In contrast with that observed in the open field, the magnitude of the activities (counts/15 minutes) exhibited following cocaine (30 mg/kg) treatment was equivalent in sham-implanted, dependent and withdrawn rats; however, the magnitude of cocaine-induced activity in acute rats was as much as four to twenty times less than in sham-implanted rats.

DISCUSSION

The effects of cocaine, procaine, and lidocaine on both open field and spontaneous locomotor activities in sham-implanted as well as morphine-treated rats were examined. The results presented confirm the findings of others [5,22] that cocaine administration does enhance spontaneous locomotor activity in "control" or sham-implanted rats. It should be pointed out that in acute rats only cocaine, 30 mg/kg, significantly increased open field locomotor activity;

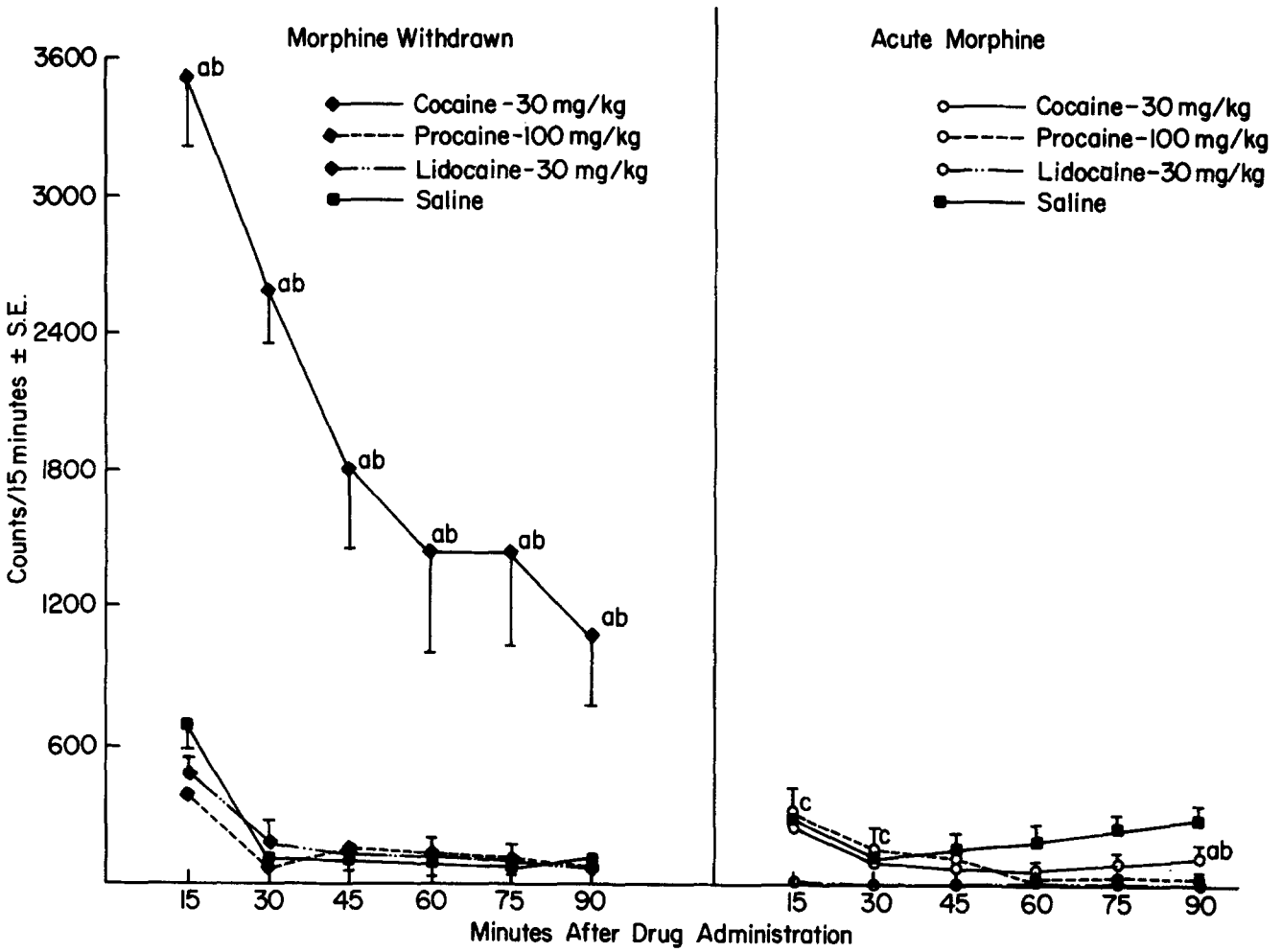

FIG. 4. Comparison of the effect of cocaine (30 mg/kg), procaine (100 mg/kg), and lidocaine (30 mg/kg) on spontaneous locomotor activity in morphine withdrawn and acute morphine rats. a=Significant drug effect; cocaine is different from procaine at that time period (2-way ANOVA for repeated measures, Student's *t*-test). b=Significant drug effect; cocaine is different from lidocaine at that time period (2-way ANOVA for repeated measures, Student's *t*-test). c=Significant drug effect; procaine is different from lidocaine at that time period (2-way ANOVA for repeated measures, Student's *t*-test).

however only cocaine, 10 mg/kg, significantly increased spontaneous locomotor activity in acute rats. Other investigators have reported that pretreatment with acute morphine abolished cocaine-induced motor hyperactivity and stereotypy in rats with approximately equivalent doses of the two drugs [6], which is consistent with the results noted in the open field. Perhaps the differences in the two methods utilized to assess activity may explain in part the different results noted in cocaine-treated acute rats.

Neither procaine nor lidocaine significantly altered either open field or spontaneous locomotor activity in sham-implanted rats. These are interesting observations since both local anesthetics have been reported to produce drowsiness in man [24]. However, it should be pointed out that the doses of lidocaine utilized may have been insufficient to manifest any effects on locomotor activity. Although procaine administration significantly depressed open field locomotor activity in all morphine-treated rats, only procaine-treated acute rats manifested significantly decreased spontaneous locomotor activity. Again, differences in the two methods of assessing activity may explain these observations.

The effects of the three local anesthetics on locomotor activity were compared in sham-implanted as well as morphine-treated rats. The results indicated that by examining the interactions of the local anesthetics with the various morphine treatments, the pharmacological differences between the local anesthetics could be emphasized further. For example, in sham-implanted rats, the open field locomotor activities induced by the low doses of cocaine and lidocaine were comparable but greater than the activity induced by the low dose of procaine. On the other hand, in withdrawn rats, the open field locomotor activity induced by the low dose of cocaine was significantly greater than that induced by either the low dose of procaine or lidocaine. Further, upon examination of activities following the high doses of the local anesthetics, all morphine-treated rats (dependent, withdrawn, and acute), manifested significantly greater open field locomotor activity following treatment with cocaine

than following treatment with either procaine or lidocaine. In contrast, cocaine- and lidocaine-induced activities were comparable in sham-implanted rats.

Upon measuring activity in actophotometers, the pharmacological differences between the three local anesthetics was emphasized again. Sham-implanted, as well as morphine-treated rats (except acute rats treated with the high doses of the local anesthetics), manifested significantly greater spontaneous locomotor activity following cocaine administration than following treatment with either procaine or lidocaine. In contrast, it is interesting to note that, at least in the environment of the actophotometers, the interaction of the high doses of the three local anesthetics with acute morphine treatment appeared to be of a "depressant" nature, particularly with lidocaine. Thus, of the local anesthetics examined, cocaine is unique in its ability to stimulate either open field or spontaneous locomotor activity in rats. In addition, this pharmacological property is not shared by either procaine or lidocaine.

The results of this study indicate that the two methods of assessing locomotor activity do not give comparable results for a given treatment (e.g. administration of cocaine in acute rats; administration of procaine in dependent and withdrawn rats). Similar differences between methods of assessing activity have also been reported for amphetamine [2,15]. The following lists some inherent differences between the two methods which may account in part for the inconsistencies noted in the data: (a) the area in which open field locomotor activity is measured is considerably larger than the area of the actophotometer; (b) the surroundings of the two methods are different; in the open field, the animal can see the observer and the surroundings about it, while in the actophotometer the animal is secluded; (c) the lighting in the open field is similar to that of the surroundings while in the actophotometer the lighting is restricted due to the cover that is placed over the activity cage; (d) the open field method only measures locomotion of the animal while actophotometers may also measure drug-induced stereotypic movements, such as rearing, up and down or side to side head movements, grooming, and sniffing, in the animal. In conclusion, caution must be exercised in interpreting results when utilizing various methods to measure activity.

One of the most interesting findings of the study is that the stimulating effects of cocaine (30 mg/kg) on open field locomotor activity were enhanced by the various morphine treatments. In contrast, when activity was measured in actophotometers, morphine treatment did not enhance cocaine-induced activity. In fact, acute morphine treatment apparently reversed the stimulating effects of the high dose of cocaine (30 mg/kg). Presently, the mechanism explaining the altered response to cocaine in morphine-treated rats is not known. Examination of either altered *in vivo* biotransformation of cocaine by morphine treatments or altered brain uptake or brain levels of cocaine as a result of the various morphine treatments indicated that these mechanisms do not account for the altered response to cocaine in these animals (Wiechman, unpublished observations). However, the altered response may be the result of an increase in sensitivity to a given dose of cocaine in the morphine-treated animals.

Most local anesthetics can be classified structurally into two groups, ester-linked and amide-linked [20]. The results of this study indicated that cocaine (10 or 30 mg/kg), an ester-linked local anesthetic, induced greater open field locomotor activity and greater spontaneous locomotor activity than either procaine (50 or 100 mg/kg) another ester-linked local anesthetic, or lidocaine (10 or 30 mg/kg) an amide-linked local anesthetic, in sham-implanted and morphine-treated rats. Although procaine and lidocaine do possess certain pharmacological properties similar to cocaine, stimulation of locomotor activity in rats is not one such property. In addition, no correlation can be made between alteration of activity and chemical structure of local anesthetics.

The findings of the pharmacological differences between the three local anesthetics noted in this study may have clinical significance. Cocaine, procaine, and lidocaine have the potential to either be used clinically and/or abused with morphine. The results of this study suggest that an interaction between cocaine and morphine could lead to greater stimulation than would be expected with cocaine alone. In addition, the interaction of either procaine or lidocaine with morphine could result in a "depressed" response, particularly an interaction with acutely administered morphine.

REFERENCES

1. Aslan, A. A. A new method for the prophylaxis and treatment of aging with Noracain: Eutropic and rejuvenating effects. *Therapiewoche* **7:** 14–22, 1956.
2. Babbini, M., M. Gaiardi and M. Bartoletti. Motility effects of methamphetamine in rats treated chronically with morphine. *Neuropharmacology* **17:** 979–983, 1978.
3. Barnes, C. D. and L. G. Eltherington. *Drug Dosages in Laboratory Animals*, Revised ed. Berkeley: University of California Press, 1973, p. 212.
4. Bartlett, E. E. and O. Hutaserani. Xylocaine for the relief of post-operative pain. *Anesth. Analg.* **40:** 296–304, 1961.
5. Bhattacharyya, A. K. and S. N. Pradhan. Interactions between motor activity and stereotypy in cocaine-treated rats. *Psychopharmacology* **63:** 311–312, 1979.
6. Blumberg, H. and C. Ikeda. Naltrexone, morphine, and cocaine interactions in mice and rats. *J. Pharmac. exp. Ther.* **206:** 303–310, 1980.
7. Cohen, S. and K. S. Ditman. Gerovital H_3 in the treatment of the depressed aging patient. *Psychosomatics* **15:** 15–19, 1974.
8. Ford, R. D. and R. L. Balster. Reinforcing properties of intravenous procaine in rhesus monkeys. *Pharmac. Biochem. Behav.* **6:** 289–296, 1977.
9. Gibson, R. D. and J. E. Tingstad. Formulation of a morphine implantation pellet suitable for tolerance-physical dependence studies in mice. *J. Pharm. Sci.* **59:** 426–427, 1970.
10. Gilbert, C. R., I. R. Hanson, A. B. Brown and R. A. Hingson. Intravenous use of xylocaine. *Curr. Res. Anesth. Analg.* **30:** 301–313, 1951.
11. Hammerbeck, D. M. and C. L. Mitchell. The reinforcing properties of procaine and d-amphetamine compared in rhesus monkeys. *J. Pharmac. exp. Ther.* **204:** 558–569, 1978.
12. Hunter, A. R. The toxicity of xylocaine. *Br. J. Anaesth.* **23:** 153, 1951.
13. Johanson, C. The reinforcing properties of procaine, chloroprocaine, and proparacaine in rhesus monkeys. *Psychopharmacology* **67:** 189–194, 1980.
14. Lesher, G. A. and G. R. Spratto. Brain and plasma concentrations of morphine during the development of physical dependence and tolerance. *J. Pharm. Pharmac.* **28:** 843–844, 1976.
15. Lesher, G. A. and G. R. Spratto. Potentiation of hexobarbital and amphetamine effects in male and female rats physically dependent on morphine. *Psychopharmacology* **57:** 175–183, 1978.

16. Maggiolo, C. and F. Huidobro. Administration of pellets of morphine to mice: abstinence syndrome. *Acta physiol. latinoam.* **11:** 70–78, 1961.
17. *Merck Index.* 9th ed. Rahway, NJ: Merck & Co., Inc., 1976, p. 315.
18. Moore, P. A. and R. G. Burney. Analgesic properties of lidocaine in mice. *Anesth. Analg.* **58:** 85–87, 1979.
19. Mushin, W. W. and L. Rendell-Baker. Intravenous procaine. *Lancet* **1:** 619–620, 1949.
20. Ritchie, J. M. and P. J. Cohen. Cocaine; procaine and other synthetic local anesthetics. In: *The Pharmacological Basis of Therapeutics,* edited by L. S. Goodman and A. Gilman. New York: MacMillan, 1975, pp. 379–403.
21. Taylor, D. and B. T. Ho. The role of serotonin in cocaine-induced hypermotility in rats. *Res. Communs Psychol. Psychiat. Behav.* **4:** 447–456, 1979.
22. Wilson, M. C. and J. M. Holbrook. Actometric effects of intravenous cocaine in rats. *Archs int. Pharmacodyn. Thér.* **238:** 244–256, 1979.
23. VanDyke, C., P. Jatlow, J. Ungerer, P. Barash and R. Byck. Cocaine and lidocaine have similar psychological effects after intranasal application. *Life Sci.* **24:** 271–274, 1979.
24. Woolverton, W. L. and R. L. Balster. Reinforcing properties of some local anesthetics in rhesus monkeys. *Pharmac. Biochem. Behav.* **11:** 669–672, 1979.
25. Zung, W. K., D. Gianturo, E. Pfeiffer, W. Hsioh-Shan, A. Whanger, T. P. Bridge and S. G. Potkin. Pharmacology of depression in the aged: Evaluation of Gerovital H3 as an antidepressant drug. *Psychosomatics* **15:** 127–131, 1974.