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Evaluation of a Suspension System for Intravenous Self-Administration Studies of Water-Insoluble Compounds in the Rhesus Monkey[1]

JOHN M. CARNEY,[2] IBRAHIM M. UWAYDAH[3] AND ROBERT L. BALSTER

Department of Pharmacology, Medical College of Virginia, Virginia Commonwealth University Richmond, VA 23298

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CARNEY, J. M., I. M. UWAYDAH AND R. L. BALSTER. *Evaluation of a suspension system for intravenous self-administration studies of water-insoluble compounds in the rhesus monkey.* PHARMAC. BIOCHEM. BEHAV. 7(4) 357–364, 1977. – A suspension system for water-insoluble drugs was evaluated using the mouse tail-flick test for analgesia and schedule-controlled responding in rhesus monkeys. One group of monkeys was trained to respond for food reinforcement under a chain fixed-interval 9 min fixed-ratio 10 schedule of reinforcement (chain FIFR). Another group of monkeys was trained to respond for intravenous cocaine injections (100 μg/kg/inj) under an FR–10 schedule. Water-insoluble compounds were suspended in emulphor:ethanol:saline. The bioavailability of these drug suspensions was demonstrated to be equivalent to water-soluble compounds by comparing the activity of the water-soluble and water-insoluble salts of (+)-propoxyphene in the mouse tail-flick test. The behavioral effects of these drug suspensions were also determined in the group of monkeys which was trained to respond for food under the chain FI–FR schedule. Dose-related decreases in responding were produced by (+)-propoxyphene HCl (water-soluble), (+)-propoxyphene napsylate (water-insoluble), and a cannabinoid, (±)-9-nor-9β-OH-hexahydrocannabinol (β-HHC) (water insoluble). Doses of (+)-propoxyphene HCl (in saline) and (+)-propoxyphene napsylate (in the emulphor suspension system) were equi-effective in disrupting food-reinforced responding. In addition, these two salts of propoxyphene were equi-effective as reinforcers of self-administration behavior in rhesus monkeys. β–HHC was more potent than (+)-propoxyphene in producing decreases in food-reinforced responding but failed to maintain self-administration behavior in the monkey.

Operant behavior Self-administration (+)–Propoxyphene Suspension vehicle Cannabinols Δ^9–THC Chain schedule Rhesus monkey

NARCOTIC analgesics and a wide variety of other psychoactive compounds have been demonstrated to function as reinforcing stimuli in laboratory animals [29]. With the exception of procaine and some psychotomimetics (e.g., LSD and mescaline), there is good correlation between the ability of a drug to reinforce self-administration behavior in laboratory animals and its likelihood of human abuse. For this reason, it has been proposed that laboratory investigations of the abuse potential of new and potentially useful psychoactive drugs should include an evaluation of their ability to maintain self-administration behavior in laboratory animals [29].

One obstacle in evaluating drugs for self-administration is the degree to which the compound is soluble in water or saline. Self-administration studies generally employ IV delivery of the test drug. Because of this route of administration it is important to consider the possible hematologic and other effects of any vehicle system for the delivery of water-insoluble drugs (hemolysis, serum sickness, etc.). A number of vehicles have been employed to deliver water-insoluble compounds for single dose and chronic intoxication studies [5, 13, 30]. Unfortunately, many of these vehicles are not well suited for use in IV self-administration studies in monkeys. Polyvinylpyrrolidone (PVP) has been used in cannabinoid studies [13, 21, 26]. However, the 40,000 average molecular weight PVP used in these studies has the undesirable effect of not being metabolized by the animal, and studies have shown that

[1] Supported in part by a contract from NAS–NRC Committee on Problems of Drug Dependence and NIDA grant DA–00490. Send reprint requests to Robert L. Balster, Box 726, Medical College of Virginia, Richmond, VA 23298.
[2] NIDA postdoctoral fellow, supported by NIDA grant DA–05017. Present address: Department of Pharmacology, School of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190.
[3] NIDA postdoctoral fellow, supported by NIDA training grant DA–07027.

PVP is deposited in the reticuloendothelial cells of the liver and other organs of the body [27]. PVP is excreted over a period of weeks or months and this long-term retention of the polymer could result in toxic accumulations. The use of albumin as a vehicle for cannabinoids and other water-insoluble compounds is also unsafe in monkeys because of the development of antibodies against the foreign albumin. Rhesus monkey albumin could be used, but the procedure would be complicated and awkward for routine use. Propylene glycol has been used as a solubilizing agent for sedative-hypnotics and minor tranquilizers. However, these glycols are alcohols and may themselves function as reinforcers at the concentrations necessary to keep the drugs in solution since ethanol has been demonstrated to function as a reinforcer of self-administration behavior in monkeys [7,35].

The present study was designed to evaluate the use of a lipoid suspension for the IV delivery of water-insoluble compounds. The vehicle consists of a polyoxyethylated vegetable oil (emulphor, EL–620), ethanol and saline, the properties of which have been described by Craddock *et al.* [8]. The emulphor vehicle system was selected because it yields a very stable suspension and it appeared to have little if any toxic effects when injected intravenously to monkeys [28]. At the dilute concentrations of the vehicle which would be used in self-administration studies the amount of ethanol in the vehicle is too low to function as a reinforcer.

GENERAL METHOD

Animals

The experimental animals were male albino mice (ICR, 20–30 g, Dublin Farms) and male rhesus monkeys *(Macaca mulatta)*. Monkeys were housed in individual primate cages and had free access to water. Mice were housed 6 per cage and had free access to food and water. All animals were housed in temperature controlled rooms which had a 12 hr light/dark cycle.

Synthesis of (±)–9–nor–9β–OH–Hexahydrocannabinol (β–HHC)

β–HHC was synthesized as described by Wilson and May [33,34]. (+)–Δ^9(11)–Tetrahydrocannabinol was treated with OsO_4 and $NaIO_4$ in THF–H_2O. The ketone formed in this reaction was purified by silica gel column chromatography using ether:pet ether (1:20–3:1). The ketone was reduced with $NaBH_4$ and resulted in an essentially quantitative yield of the (±)–9–nor–9–OH–HHC. The 9β–OH and 9α–OH isomers of the 9-nor-9-OH–HHC were separated by silica gel column chromatography with acetone: pet ether (1:1) which resulted in a yield of the two isomers in a ratio of about 12:1 (β:α). The purity of the α and β isomers was determined by TLC, GLC and IR analysis and compared to the authentic samples obtained from Dr. E. L. May (Department of Pharmacology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298). Details of the synthesis, purification conditions, and spectral data for the HHC's are available upon request.

Drugs

Water-soluble drugs were dissolved in 0.9% saline. Water-insoluble drugs were first dissolved in emulphor:ethanol (1:1) and then rapidly diluted to the final concentration with sterile saline. The weighed sample of the water-insoluble compound was placed in a vial and a volume of the emulphor:ethanol (1:1) just sufficient to solubize the material was added. For example, for Δ^9–THC this results in a stock solution of 100 mg/cc. The vial was then placed in an ultrasonic cleaner (Cole-Parmer, model 8848–4) and sonicated for 15 min. Care was taken to maintain the temperature of the sample at or below room temperature. These stock solutions are stable and can be stored. Δ^9–THC, for example, can be stored for periods of months with less than 1% loss of activity. Prior to testing, saline was rapidly added to an aliquot of the stock and shaken. This diluted solution is a clear liquid which will remain as a stable suspension for several weeks. In the case of Δ^9–THC, concentrations in the range of 20 mg/ml and lower can be easily obtained. Essentially, in our experience the limitation of this vehicle system is the solubility of the test compound in the 1:1 emulphor:ethanol and the compound's potency.

Emulphor (EL–620) was the generous gift of the General Analine and Film Corporation (GAF). (±)–Δ^9(11)–THC and Δ^9–THC were obtained from Dr. R. E. Willette (NIDA, Rockville, MD). (+)–Propoxyphene HCl and (+)-propoxyphene napsylate were gifts of the Eli Lilly Company (Indianapolis, Inc.). Cocaine HCl was purchased commercially.

EXPERIMENT 1: DEMONSTRATION OF THE ANTINOCICEPTIVE ACTIVITY OF THE WATER–SOLUBLE AND WATER–INSOLUBLE SALTS OF (+)–PROPOXYPHENE

Previous work has demonstrated that narcotic analgesics from a wide variety of different chemical classes have antinociceptive effects when tested in rodents [12]. (+)–Propoxyphene HCl has been reported to be about 10-times less potent than morphine in these antinociceptive tests [12]. Because of its limited water solubility, the napsylate salt of (+)-propoxyphene was selected as a positive control to evaluate the applicability of the emulphor suspension system. This experiment represents the first phase in the evaluation of the emulphor suspension system for use in behavioral research. The bioavailability of a water-insoluble narcotic was compared to its water-soluble salt in the mouse tail-flick test for antinociceptive activity.

Method

The animals were male albino mice. They were housed six per cage and kept in the central mouse facility until used. All tail-flick tests were conducted on the same day between 10 a.m. and 12 noon. Subcutaneous injections were administered 30 min before testing in a volume of 1.0 cc/kg. The antinociceptive effects of the two propoxyphene salts were assessed using a modification [11] of the tail-flick method of D'Amour and Smith [9]. Three doses of each salt as well as vehicle were tested. Antinociceptive potencies were calculated as the percentage of the maximum possible effect (% MPE) according to the method of Harris and Pierson [20], with a 10 sec cut-off and a control latency of 2–4 sec. ED_{50} values and confidence limits were determined by the method of Litchfield and Wilcoxon [23]. (+)–Propoxyphene was delivered using the emulphor suspension system as described in the General Methods section. A control group of mice was also tested with the

emulphor suspension system alone at the highest emulphor:ethanol concentration used.

Results and Discussion

As shown in Table 1, both (+)-propoxyphene HCl and (+)-propoxyphene napsylate were active in the mouse tail-flick test. (+)–Propoxyphene base in the form of the napsylate salt appeared to be slightly more potent than the HCl salt, however, this difference in potency was not statistically significant. In addition to the similar potency values for the two salts, the slopes of the two dose-effect curves were not significantly different.

TABLE 1

TAIL-FLICK ACTIVITY OF (+)-PROPOXYPHENE SALTS IN MICE*

Drug	ED_{50}†	Confidence Limits	Slope (r)
(+)-Propoxyphene HCl	7.63	4.5–12.8	1.90 (0.99)
(+)-Propoxyphene Napsylate	4.92	3.26– 7.26	1.65 (0.99)

*Groups of 6 mice/dose with at least 8 doses tested for each salt
†mg/kg of the base

The comparable potency values in the mouse tail-flick test for the two propoxyphene salts demonstrate that the emulphor suspension system is an effective vehicle for testing a water-insoluble narcotic analgesic. The emulphor suspension has been used in testing the behavioral and biochemical effects of a number of water-insoluble cannabinoids [5,15]. Bloom *et al.* [5] reported that β–HHC was equipotent to morphine in the mouse tail-flick test. Because of its water-insolubility, β–HHC was tested using the same emulphor suspension system as used in the present study. In both the Bloom *et al.* study and the present study, the emulphor vehicle was not active in the tail-flick test when given alone.

EXPERIMENT 2: EFFECTS OF (+)–PROPOXYPHENE SALTS AND β–HHC ON FOOD–REINFORCED RESPONDING IN MONKEYS

A wide variety of drugs affect schedule-controlled responding in animals and humans when the drugs are given as presession injections. Relatively low doses of narcotic analgesics may increase the rate of responding and higher doses produce decreases in responding under a number of different schedules of reinforcement in laboratory animals [25,32]. Dose-related increases and decreases in operant responding also have been reported for cannabinoids [15,24]. The present experiment was the second phase in the evaluation of the usefulness of the emulphor suspension system in behavioral research using rhesus monkeys. The relative behavioral potencies of (+)-propoxyphene HCl, (+)-propoxyphene napsylate, and of the 9β–OH and 9α–OH isomers of HHC were determined using food-reinforced responding under a chain fixed-interval fixed-ratio schedule (chain FI–FR) of food reinforcement.

Method

Four adult male rhesus monkeys which weighed between 5 and 8 kg were deprived to 80% of their ad lib feeding weights and maintained at this weight by postsession supplemental feeding in their home cages. The animals were trained to respond under a chain FI 9 min, FR 10 schedule of food reinforcement as previously described [1,2]. Under this schedule the first lever-press response after 9 min (FI) changed the stimulus light from orange to white and advanced the schedule into the FR 10 component of the chain. During the FR 10 component every tenth response resulted in the delivery of a 1.0 g banana-flavored food pellet (P. J. Noyes). After 1 min had elapsed in the FR component, the white light was turned off, the orange light was turned back on and the schedule was advanced into the next chain FI–FR. The session ended after 8 chain FI–FR's had occurred or after 2 hr had elapsed. IM injections were given 5 min before the start of the session. Sessions occurred daily and drug injections were given every fifth day. Saline or emulphor vehicle injections were periodically tested throughout the study. Baseline data was obtained from the daily non-injection sessions which preceded vehicle or drug injetions. Animals were tested once at each dose in an unsystematic order of drug doses. The order of drug testing in each monkey was β–HHC, α–HHC (+)-propoxyphene HCl and (+)-propoxyphene napsylate. Data are expressed as the percent of the non-injection baseline response rate. Quarter-life values, a measure of the response distributions within the FI, were calculated on the basis of the average responding within successive 1 min segments of the FI 9 min and obtained according to the method of Gollub [18]. The quarter-life statistic represents the average amount of time, expressed as a proportion of the total FI time, required for the emission of one-fourth of the total FI responses.

Results and Discussion

Responding under the chain FIFR schedule of food reinforcement was relatively stable from day to day for each animal. FI 9 min responding in the initial link of the chain was characterized by a positively accelerated pattern of responding (baseline quarter-life = 0.59 ± 0.12 SD). FR 10 responding in the terminal link of the chain occurred at a relatively high and stable rate. The average rates of responding in the FI and FR components were 0.57 (± 0.05 SD) and 1.92 (± 0.15 SD) responses per second, respectively.

The hydrochloride and napsylate salts of (+)-propoxyphene were equipotent in producing dose- related decreases in responding (Fig. 1). Both salts of (+)-propoxyphene appeared to have a similar rate of onset following IM injection. Thus, it appears that the emulphor suspension of (+)-propoxyphene napsylate had an absorption and distribution pattern to the CNS which was comparable to that of the water-soluble hydrochloride salt.

β–HHC also produced decreases in FI and FR responding at the higher test doses (Fig.2). One of the monkeys showed substantial FI rate increases at the low β–HHC doses. The other two monkeys showed only response rate decreases across the β–HHC doses tested. At doses which suppressed responding, β–HHC had a prompt onset following injection. The 9α–OH isomer of HHC was tested at doses up to 10.0 mg/kg and had no behavioral effects. Control injections of emulphor:ethanol:saline were not different from saline and are presented together as the saline vehicle control in Figs. 1 and 2.

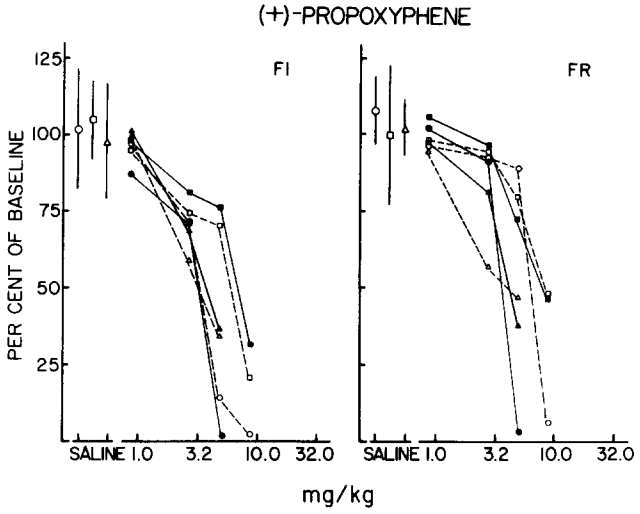

FIG. 1. Effects of (+)-propoxyphene HCl (open symbols) and (+)-propoxyphene napsylate (solid symbols) on food reinforced responding under a chain FI FR schedule of reinforcement. The three different symbols represent the data for three different monkeys. Data points for the two propoxyphene salts represents a single determination at each dose. Saline values are the mean (± SD) of 8 observations in each monkey. Injections (IM) were given 5 min before the start of the session.

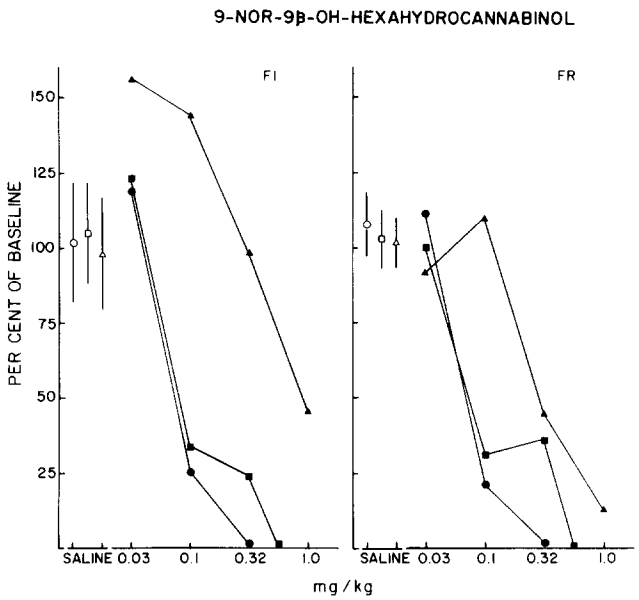

FIG. 2. Effects of (±)-9-nor-9β-OH-hexahydrocannabinol (β–HHC) on food-reinforced responding under a chain FI FR schedule of reinforcement. Different symbols represent the data for three different monkeys. The corresponding symbols for saline represent the effects of saline plus the highest concentration of emulphor: ethanol (1:1) used to suspend β–HHC in the present study. Each saline point is the mean (± SD) of 4 observations in each monkey. Injections (IM) were given 5 min before the start of the session.

Compared to the effects of morphine on the chain FIFR responding (Balster and Harris, unpublished data) (+)-propoxyphene is about 1/3 as potent in producing disruption of schedule-controlling responding. This relative potency value for (+)-propoxyphene is similar to that observed for codeine pretreatments, compared to morphine, under a multiple FR schedule of food and intravenous codeine reinforcement in the rhesus monkey [6]. The comparable behavioral potencies in the monkey for (+)-propoxyphene and codeine relative to morphine agree well with the relative potency estimates obtained in rodent antinociceptive tests [12].

Compared to morphine, β–HHC was about 3 times more potent. The α–HHC was inactive at doses up to 10.0 mg/kg. Bloom *et al.* [5] and Wilson *et al.* [34] have reported that the β-isomer of HHC is a potent antinociceptive agent, while the α-isomer is considerably less potent or inactive in the tail-flick test for antinociceptive activity. Δ⁹–THC is also considerably less active in this procedure [5].

The data obtained for the IM injection of the water-insoluble compounds in monkeys responding under a chain FI FR schedule of food reinforcement demonstrate that the emulphor suspension system was an effective vehicle for evaluating the behavioral effects of water-insoluble analgesics. (+)–Propoxyphene napsylate is poorly water soluble, less than 1.5 mg/cc [19], and the α- and β-isomers of HHC are of comparable water insolubility to Δ⁹–THC, 0.77 mg/liter [16]. It would have been impossible to test these compounds without the use of a suspension system. In addition, under these test conditions the emulphor vehicle was without behavioral effects and did not appear to affect the relative potency of (+)-propoxyphene when the water-soluble and water-insoluble salts were compared. Thus, it appears that the emulphor vehicle would be an ideal vehicle for studying the self-administration of these and other water-insoluble compounds.

EXPERIMENT 3: SELF–ADMINISTRATION OF WATER–SOLUBLE AND WATER–INSOLUBLE DRUGS IN RHESUS MONKEYS

This experiment was conducted to determine the effectiveness of the emulphor suspension system in studying the reinforcing properties of water-insoluble drugs. In order to validate the use of emulphor, the water-soluble and water-insoluble salts of (+)-propoxyphene were used as positive controls since the water-soluble hydrochloride salt has been reported to maintain self-administration behavior in the monkey [22,31]. Δ⁹–THC was included to serve as the negative control since previous studies have shown that it does not function as a reinforcer of self-administration behavior in the monkey [21]. β–HHC was also tested for self-administration because it is a potent antinociceptive agent in the rodent and has potent behavioral effects in the monkey.

Method

The subjects were 5 adult male rhesus monkeys which weighed between 5 and 8 kg. The animals had free access to water and food throughout the study. They were housed in individual self-administration cubicles which have been previously described [14]. Under phencyclidine-pentobarbital anesthesia the animals were surgically prepared with chronic indwelling IV catheters [10]. After surgery the animals were restrained by a metal harness attached to the rear wall of the cubicle by a flexible metal arm. The

infusion catheter passed through the metal arm and was connected to the implanted catheter at the back of the monkey. IV drug injections (1.0 cc in 10 sec) were delivered by a peristaltic pump (Cole-Parmer). Solid-state programming and control equipment, digital counters and cumulative recorders (Ralph Gerbrand, Inc.) were located in the adjoining room.

Daily self-administration studies were conducted in the animals' home cages for 2 hr at the same time each day. Monkeys were trained to respond under an FR 10 schedule of IV cocaine reinforcement as previously described [3, 4, 14]. Under this schedule, every tenth response resulted in the delivery of an intravenous injection of cocaine (100 μg/kg/inj). The availability of cocaine injections under the FR 10 schedule was indicated by the illumination of two orange lights immediately above the response lever. During cocaine injections the orange lights were extinguished and a white light was illuminated over the lever. At the end of the 2 hr session all of the lights over the lever were extinguished. A substitution procedure [3, 4, 14] was used to test for positive reinforcing properties of the two salts of (+)-propoxyphene, Δ^9–THC and β–HHC. Doses of test compounds or vehicle were substituted for cocaine for six consecutive daily sessions. Which of the 5 animals were tested with each compound can be determined from the subject identification numbers included in Figs. 3–5. For (+)-propoxyphene, equimolar doses of each salt were tested in sequence before the next pair of doses. For the cannabinoids, β–HHC was tested before Δ^9–THC. Blocks of 6 cocaine self-administration sessions alternated with 6 sessions in which test compounds were substituted for cocaine. The last 3 of the 6 days of drug self-administration were compared to the last 3 days of saline or emulphor vehicle substitution. A drug was identified as a positive reinforcer if response rates on the last 3 days of drug self-administration were above and did not overlap with rates on the last 3 days of vehicle self-administration.

Results and Discussion

Cocaine-reinforced responding under the FR 10 schedule of reinforcement was fairly stable from day to day. The range of cocaine injections per 2 hr session was between 25 and 55 for the group of 5 monkeys. Monkeys self-administered the greatest amount of cocaine in the first 30 min portion of the 2 hr sesssions and then progressively reduced their intake of cocaine in the remaining 90 min of the session. This within-session pattern of responding was similar to that previously reported for cocaine-reinforced responding at a unit dose of 100 μg/kg/inj [14].

Substitution of (+)-propoxyphene HCl or (+)-propoxyphene napsylate for cocaine reliably maintained self-administration responding in all three of the monkeys tested (Fig. 3). Both the high and low doses of either propoxyphene salt maintained responding above vehicle control values. The low dose of both propoxyphene salts resulted in substantially greater self-administration rates then observed with cocaine at the 100 μg/kg/inj dose. The high dose of both propoxyphene salts also maintained self-administration responding above saline rates and at about the same level as the baseline cocaine self-administration rate. The two salts appeared to be equipotent as reinforcers when the doses were calculated as μg/kg/inj of base. At the high (+)-propoxyphene napsylate dose (750 μg/kg/inj) the injection solution concentration ranged

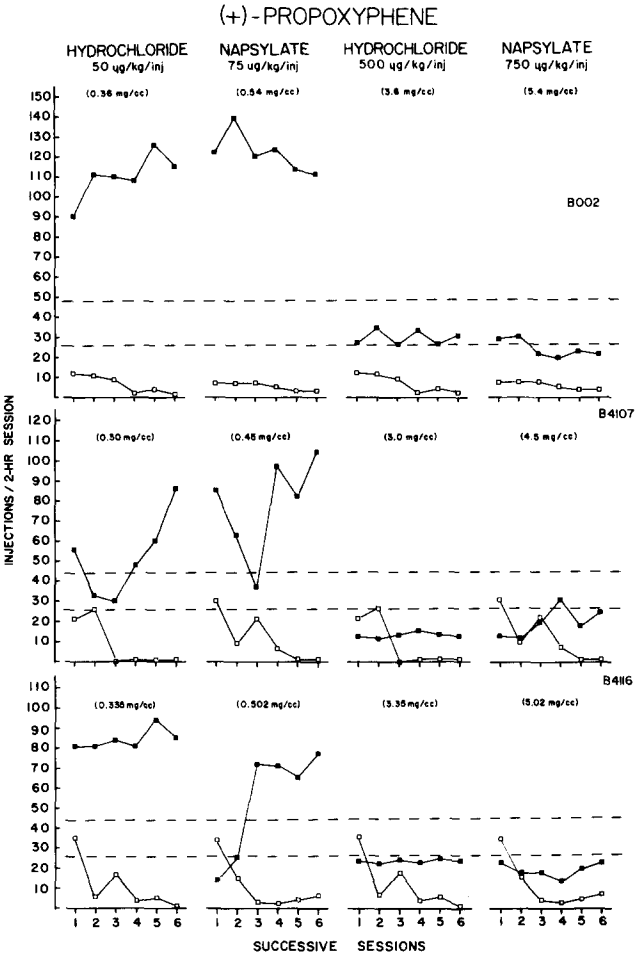

FIG. 3. Mean number of injections per session for 6 successive daily sessions at two dose levels of (+)-propoxyphene HCl and (+)-propoxyphene napsylate are represented by solid symbols. The horizontal dashed lines represent the range of baseline cocaine (100 μg/kg/inj) injection rates obtained from 30 cocaine injection sessions for each monkey. Injection rates after substitution of the injection vehicle alone are indicated by the open symbols. The vehicle for (+)-propoxyphene HCl was 0.9% saline and the vehicle for (+)-propoxyphene napsylate was the emulphor suspension system. The (+)-propoxyphene doses refer to the salt. The high and low doses of (+)-propoxyphene represent equimolar doses of (+)-propoxyphene base at the two dose levels. The concentrations of the injected solutions are indicated in parenthesis for each monkey.

between 4.5 and 5.4 mg/cc. This exceeds the water-solubility of the compound (1.5 mg/cc; ref. [19]). Thus, without the use of the emulphor suspension system it would not have been possible to test this high dose of (+)-propoxyphene.

Neither Δ^9–THC nor β–HHC functioned as reinforcers when substituted for cocaine (Figs. 4 and 5). In general, the data for the two cannabinoids closely paralleled the vehicle substitution (extinction) data across the 6 substitution days. One exception was monkey B002 at the 3.0 and 30.0 μg/kg/inj doses of β–HHC. At the 3.0 μg/kg/inj dose, responding appeared to alternate across the days between relatively high and relatively low self-administration rates compared to vehicle rates, with a general trend downward

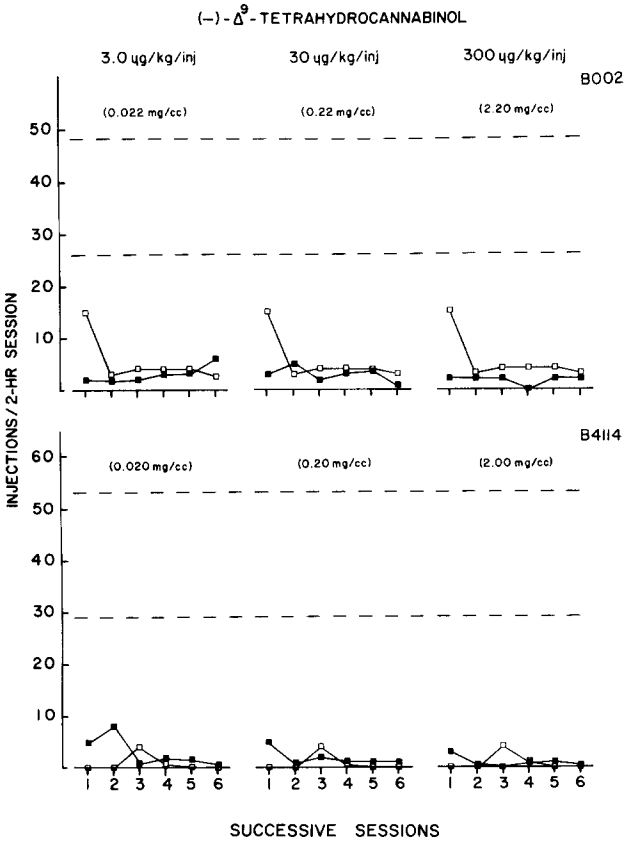

FIG. 4. Number of Δ^9-tetrahydrocannabinol (Δ^9–THC) injections (solid symbols) per session at three dose levels across the 6 successive days of substitution. Open symbols represent the number of emulphor vehicle injections. Horizontal dashed lines represent the control range of cocaine injections (100 µg/kg/inj) for each monkey. The concentration of Δ^9–THC at each of the dose levels are indicated in parenthesis for each monkey.

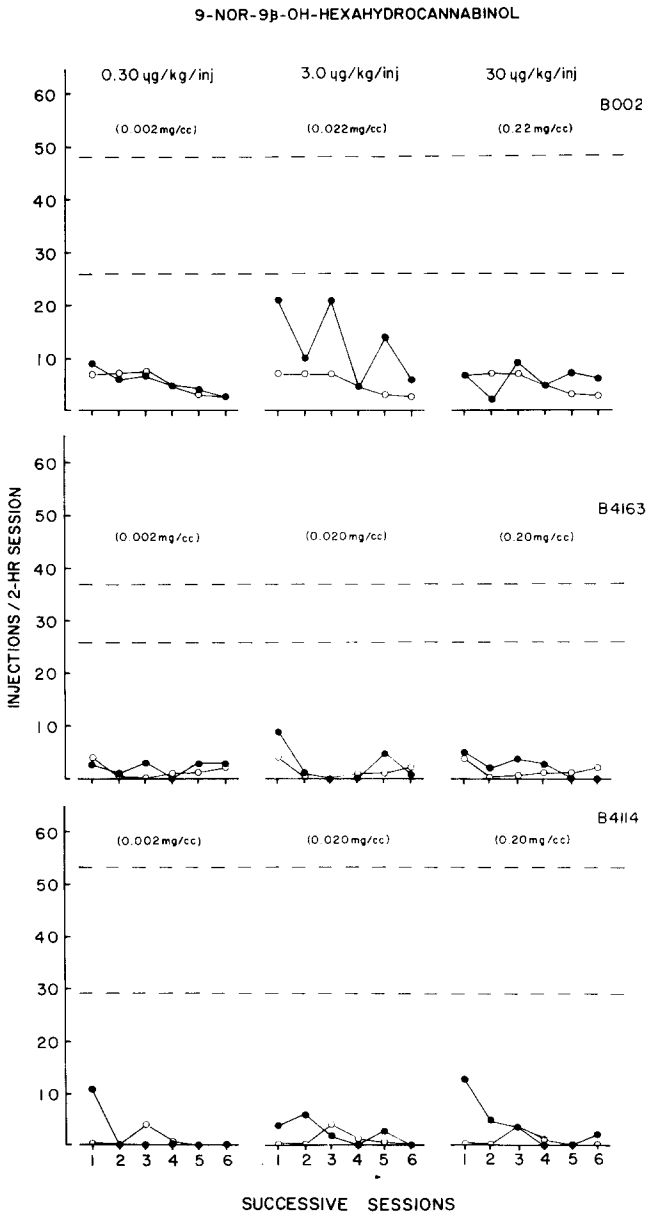

FIG. 5. Number of (±)-9-nor-9β-OH-hexahydrocannabinol (β–HHC) injections (solid symbols) per session at three dose levels across the 6 successive days of substitution. Open symbols represent the number of emulphor vehicle injections. Horizontal dashed lines represent the control range of cocaine injections (100 µg/kg/inj) for each monkey. The concentrations of β–HHC at each of the dose levels are indicated in parenthesis for each of the monkeys.

to the vehicle injections rates at the end of the 6 days. At the 30.0 µg/kg/inj dose responding appeared to be more stable across days, with the last 2 days slightly above vehicle control values. However, even for monkey B002, self-administration behavior did not satisfy the criterion of no overlap of the drug injection rate with the vehicle control values. Both of these cannabinoids are essentially water-insoluble and could not have been tested if a vehicle was not employed. The emulphor suspension vehicle did not result in self-administration rates that were different from saline substitution values. Thus, under the present experimental conditions neither Δ^9–THC nor β–HHC functioned as a positive reinforcer of self-administration responding in monkeys. In addition, the use of the emulphor suspension system did not interfere with the determination of the reinforcing properties of drugs which function as positive reinforcers.

DISCUSSION

The present study demonstrates that the emulphor suspension system is an effective vehicle for studying the self-administration and other behavioral effects of water-insoluble compounds. Under the substitution paradigm both the HCl and napsylate salts of (+)-propoxyphene maintained self-administration behavior above vehicle control. Moreover, the two salts appeared to be equi-active in terms of the amount of behavior maintained at the doses tested. The data for (+)-propoxyphene HCl are similar to that reported in a study of Hoffmeister and Schlichting [22]. In their study the maximum number of (+)-propoxyphene injections incurred at 50 µg/kg/inj; higher doses resulted in correspondingly less self-administration behavior. A similar relation between doses and response rate

was observed in the present study for both propoxyphene salts and has been demonstrated for a wide variety of self-administered drugs at doses above those which maintain maximum rates [3, 4, 7, 14, 17, 22, 35]. The decline in responding observed at the high propoxyphene dose may have been due to the response-rate decreasing effects of (+)-propoxyphene, since pre-session injections of propoxyphene did produce dose-related decreases in food-reinforced responding. As shown in Fig. 1, decreases in food-reinforced responding occurred at or above doses of 1.0 mg/kg (HCl) or 1.5 mg/kg (napsylate). Such a propoxyphene dose would be achieved after the second injection at the high propoxyphene dose in the self-administration experiment. Whether the decrease in the number of propoxyphene injections/session at the high dose was the result of a generalized disruption of operant behavior or if it was the result of a reinforcer-specific satiation-like effect [6] of propoxyphene self-administration cannot be determined from the presently available data.

Neither Δ^9–THC nor β–HHC functioned as reinforcers when substituted for cocaine at the doses tested. Similar negative data for Δ^9–THC self-administration was reported by Harris *et al.* [21]. In their study, Δ^9–THC failed to maintain self-administration responding when it was substituted for cocaine, when naive monkeys were allowed 12 hr access to THC injections, or after monkeys had been exposed for 30 days to programmed THC infusions. Pickens *et al.* [26] reported THC self-administration in rhesus monkeys that had been trained to respond under a phencyclidine self-administration baseline. However, responding for THC was not consistently maintained across sessions and, as suggested by Harris *et al.* [21], the apparent THC self-administration may have been due to some stimulus property of THC which was common to that of phencyclidine and functioned as a secondary reinforcer, which would extinguish at a slower rate than saline substitution. The failure of β–HHC to maintain self-administration responding is of interest since it is a potent antinociceptive compound in the rodent [5]. β–HHC is about 3 times more potent than morphine in disrupting operant behavior. Thus, the failure of β-HHC to function as a reinforcer was not due to a relatively weak behavioral potency. It appears that cannabinoids like β–HHC may represent a class of centrally active analgesics which have potent antinociceptive effects and potent effects in disrupting schedule-controlled responding, but which do not function as positive reinforcers in IV self-administration studies in monkeys.

ACKNOWLEDGEMENTS

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REFERENCES

1. Balster, R. L. and L. D. Chait. The behavioral pharmacology of phencyclidine. *Clin. Toxic.* **9**: 513–528, 1976.
2. Balster, R. L., L. D. Chait and G. W. King III. The effects of acute and chronic phencyclidine on schedule-controlled behavior in the rhesus monkey. *Fedn Proc.* **35**: 564 (abstract), 1976.
3. Balster, R. L., C. E. Johanson, R. T. Harris and C. R. Schuster. Phencyclidine self-administration in the rhesus monkey. *Pharmac. Biochem. Behav.* **1**: 167–172, 1973.
4. Balster, R. L. and C. R. Schuster. A comparison of *d*-amphetamine, ℓ-amphetamine and methamphetamine self-administration in rhesus monkeys. *Pharmac. Biochem. Behav.* **1**: 276–281, 1973.
5. Bloom, A. S., W. L. Dewey, L. S. Harris and K. K. Brosius. 9–nor–9β–Hydroxyhexahydrocannabinol, a cannabinoid with potent and antinociceptive activity: Comparisons with morphine. *J. Pharmac. exp. Ther.* **200**: 263–270, 1977.
6. Carney, J. M. Selective modulation of codeine-reinforced responding in rhesus monkeys. Doctoral Thesis submitted to faculty of the University of Michigan, Ann Arbor, 1976.
7. Carney, J. M., M. E. Llewellyn and J. H. Woods. Variable interval responding maintained by intravenous codeine and ethanol injection in the rhesus monkey. *Pharmac. Biochem. Behav.* **5**: 577–582, 1976.
8. Cradock, J. C., J. P. Davignon, C. L. Litterst and A. M. Guarino. An intravenous formulation of Δ^9-tetrahydrocannabinol using a nonionic surfactant. *J. Pharm. Pharmac.* **25**: 345, 1973.
9. D'Amour, F. E. and D. L. Smith. A method for determining loss of pain sensations. *J. Pharmac. exp. Ther.* **72**: 74–79, 1941.
10. Deneau, G., T. Yanagita and M. H. Seevers. Self-administration of psychoactive substances by the rhesus monkey. A measure of psychological dependence. *Psychopharmacologia* **16**: 30–48, 1969.
11. Dewey, W. L., L. S. Harris, J. F. Howes and J. A. Nuite. The effects of various neurohumoral modulators on the activity of morphine and the narcotic antagonists in the tail-flick and phenylquinone tetst. *J. Pharmac. exp. Ther.* **175**: 435–442, 1970.
12. Eddy, N. B., H. Friebel, K.–J. Hahn and H. Halbach. *Codeine and Its Alternatives for Pain and Cough Relief.* WHO Publication, 1970.
13. Fenimore, D. C. and P. R. Lory. Injectible dispersion of delta-9-tetrahydrocannabinol in saline using polyvinylpyrrolidone. *J. Pharm. Pharmac.* **23**: 310, 1971.
14. Ford, R. D. and R. L. Balster. Reinforcing properties of intravenous procaine in rhesus monkeys. *Pharmac. Biochem. Behav.* **6**: 289–296, 1977.
15. Ford, R. D., R. L. Balster, W. L. Dewey and J. S. Beckner. Δ^9–THC and 11–OH–Δ^9–THC: Behavioral effects and relationship to plasma and brain levels. *Life Sci.* **20**: 1993–2004, 1977.
16. Garret, E. R. and C. A. Hunt. Physiochemical properties, solubility and protein binding of Δ^9-tetrahydrocannabinol. *J. Pharmac. Sci.* **63**: 1056–1964, 1974.
17. Goldberg, S. R., Hoffmeister, U. U. Schlichting and W. Wuttke. A comparison of pentobarbital and cocaine self-administration in rhesus monkeys. *J. Pharmac. exp. Ther.* **197**: 277–283, 1971.
18. Gollub, L. R. The relation among measures of performance on fixed-interval schedules. *J. exp. Anal. Behav.* **7**: 337–343, 1964.
19. Gruber, C. M., V. C. Stephens and P. M. Terrill. Propoxyphene napsylate: Chemistry and experimental design. *Toxic. appl. Pharmac.* **19**: 423–426, 1971.
20. Harris, L. S. and A. K. Pierson. Some narcotic antagonists in the benzomorphan series. *J. Pharmac. exp. Ther.* **143**: 141–148, 1964.

21. Harris, R. T., W. Waters and D. McLendon. Evaluation of reinforcing capability of delta-9-tetrahydrocannabinol in rhesus monkeys. *Psychopharmacologia* **37:** 23–29, 1974.
22. Hoffmeister, F. and U. U. Schlichting. Reinforcing properties of some opiates and opioids in rhesus monkeys with histories of cocaine and codeine self-administration. *Psychopharmacologia* **23:** 55–74, 1972.
23. Litchfield, J. T., Jr. and F. Wilcoxon. A simplified method of evaluating dose effect experiments. *J. Pharmac. exp. Ther.* **96:** 99–113, 1949.
24. McMillan, D. E. Behavioral pharmacology of the tetrahydrocannabinols. In: *Advances in Behavioral Pharmacology,* Vol. I, edited by T. Thompson and C. B. Dews. New York: Academic Press, 1977, pp. 1–34.
25. McMillan, D. E. and W. H. Morse. Some effects of morphine and morphine antagonists on schedule-controlled behavior. *J. Pharmac. exp. Ther.* **157:** 175–184, 1957.
26. Pickens, R., T. Thompson and D. Muchow. Cannabis and phencyclidine self-administration by animals. In: *Bayer Symposium IV: Psychic-Dependence,* edited by L. Goldberg and F. Hoffmeister. New York: Springer-Verlag, 1973, pp. 78–86.
27. Ravin, H. A., A. M. Seligman and J. Fine. Polyvinylpyrrolidone as a plasma expander. Studies on its excretion distribution and metabolism. *New Engl. J. Med.* **247:** 921–929, 1952.
28. Schaeppi, U. and R. S. Phelan. Emulphor (EL–620) vehicle: Blood pressure effects of IV infusion in dogs and rhesus monkeys. U.S. Department of Commerce National Technical Information Service, PB–220 052, 1972.
29. Schuster, C. R. and C. E. Johanson. The use of animal models for the study of drug abuse. In: *Research Advances in Alcohol and Drug Problems,* edited by R. S. Gibbons, Y. Israel, H. Kalant, R. E. Popham, W. Schmidt and R. G. Smart. New York: John Wiley and Sons, 1974, pp. 1–31.
30. Sofia, R. D., R. K. Kubena and H. Barry III. Comparison of four vehicles for intraperitoneal administration of Δ^1-tetrahydrocannabinol. *J. Pharm. Pharmac.* **23:** 889–891, 1971.
31. Talley, W. H. and I. Rosenblum. Self-administration of dextropropoxyphene by rhesus monkeys to the point of toxicity. *Psychopharmacologia* **27:** 179–182, 1972.
32. Thompson, T., J. Trombley, D. Luke and D. Lott. Effects of morphine on behavior maintained by four simple food-reinforcement schedules. *Psychopharmacologia* **17:** 182–192, 1970.
33. Wilson, R. S. and E. L. May. Analgesics properties of the tetrahydrocannabinols, their metabolites and analogs. *J. Med. Chem.* **18:** 700–703, 1975.
34. Wilson, R. S., E. L. May, B. R. Martin and W. L. Dewey. The 9-nor-9-hydroxy-hexahydrocannabinols. Synthesis, some behavioral and analgesic properties and comparison with tetrahydrocannabinols. *J. Med. Chem.* **19:** 1165–1167, 1976.
35. Winger, G. D. and J. H. Woods. The reinforcing property of ethanol in the rhesus monkey: I. Initiation, maintenance and termination of intravenous ethanol-reinforced responding. *Ann N.Y. Acad. Sci. U.S.A.* **215:** 162–175, 1973.