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Rapid Substitution Procedure for Intravenous Drug Self-Administration Studies in Rhesus Monkeys[1]

THOMAS G. AIGNER[2] AND ROBERT L. BALSTER

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

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AIGNER, T. G. AND R. L. BALSTER. *Rapid substitution procedure for intravenous drug self-administration studies in rhesus monkeys.* PHARMAC. BIOCHEM. BEHAV. 10(1) 105–112, 1979.—Rhesus monkeys were trained to press a lever one hundred times (FR 100) to obtain either a food pellet or an intravenous drug injection. Two daily experimental sessions, one in the morning and one in the afternoon, were divided into three 15 minute periods each. In Periods 1 and 3 lever pressing behavior was maintained by the delivery of food. Period 2 lever pressing was maintained by the intravenous injection of a drug solution. The drug available each day followed a four day sequence of cocaine (30 μg/kg/injection), saline (1.0 ml/injection), cocaine, and test compound. This four day sequence was repeated to test a series of 16 psychoactive compounds at two doses each. These drugs were compared to saline for their ability to maintain Period 2 responding during the afternoon session. Morphine, oxymorphone, codeine, pentazocine, *d*-amphetamine and methylphenidate all maintained responding at rates significantly greater than for saline. Cyclazocine, naloxone, levallorphan, scopolamine, chlorpromazine, fenfluramine, and (±)-9-nor-9-α-hydroxy-hexahydrocannabinol (α-HHC) did not maintain responding during Period 2. The results with procaine, β-HHC and nalorphine were considered equivocal. The authors suggest the use of a rapid substitution procedure as a method of initial screening of drugs with potential reinforcement efficacy.

Fixed-ratio Drug self-administration Schedule of reinforcement Substitution procedure Monkeys

SINCE the development of procedures for studying self-administration behavior in animals, various classes of drugs with a diversity of pharmacological effects have been shown to function as reinforcers of drug-taking behavior. Although many factors may influence whether or not a drug is abused, the correspondence between drugs which are self-administered by rats and monkeys and drugs which are abused by humans has been repeatedly demonstrated (e.g., [13, 20, 21]). The development of animal procedures which have provided evidence of abuse potential based on a drug's reinforcing properties has been of considerable importance.

Widely used self-administration procedures which yield qualitative data on a drug's reinforcing properties can be divided into two categories, continuous access (e.g., [5,20]) and substitution (cross self-administration) (e.g., [20]). Although each of these procedures has particular advantages, both procedures compare the self-administration rates maintained by the test compound to the rates maintained by the vehicle, usually saline. Both of these procedures as now utilized are relatively time-consuming, often requiring up to eight weeks to test each drug.

Because of the large number of new compounds which should be evaluated for abuse liability, the need exists for procedures which would facilitate the evaluation process by obtaining data more rapidly even if at the loss of complete dose-response information. The purpose of the present experiment is to validate one such procedure.

METHOD

Animals and Apparatus

The animals were 1 female and 4 male rhesus monkeys, *Macaca mulatta*, weighing between 4 and 6 kg. All subjects were naive at the beginning of experimentation. Water was available ad lib. Stable body weights were maintained by feeding approximately 25 g/kg of food (Purina Monkey Chow) minus the amount each animal earned in the daily experimental procedure immediately following the afternoon session. A sugar cube saturated with a liquid vitamin supplement (Vitamino Syrup, Hart-Delta, Baton Rouge, LA) was also given each afternoon.

Each monkey was individually housed in a 90×90×90 cm experimental cubicle with accompanying air filtration unit (Barrier Systems, Lakewood, NJ). The air supply for each chamber was constantly filtered by fiberglass, activated charcoal, and HEPA filters to reduce particulate matter,

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[2]Predoctoral Fellow supported by National Institute on Drug Abuse Fellowship DA-05033. Present address: Department of Psychiatry, The University of Chicago, Chicago, IL 60637.

odors and the chance of infection due to airborne bacteria. Each monkey was fitted with a stainless steel harness [5] connected to a 45 cm steel spring restraining arm (H&M Engineering, Chicago, IL). The restraining arm was fastened by a ball joint to the rear of the experimental cubicle. This arrangement allowed the animal virtually unrestricted movement within the chamber.

Two lever boxes, each with three jeweled stimulus lamps and a single primate response lever (BRS/PRL-001), were mounted 30 cm apart and 25 cm above the floor on the clear acrylic front door of the experimental chamber. A lever press of approximately 50 g constituted a response. A pellet dispenser (BRS/PDC) was mounted on the outside of the door and dispensed 1 g food pellets (Noyes, Formula G) into a trough located midway between the two lever boxes.

All programming was accomplished automatically using solid-state behavioral equipment (BRS 200 series) located in an adjacent room. Data were collected in the form of digital counts and cumulative response records for each animal.

Drug injections were delivered in a volume of 1 ml over an 8 sec interval by a peristaltic pump (Cole-Parmer Masterflex, Chicago, IL) which was located behind the experimental cubicle. No attempt was made to mask the sound of the pump during injections.

Drugs

The drugs chosen for testing in the procedure were as follows: morphine sulfate and codeine phosphate (Mallinckrodt, Inc.); nalorphine hydrochloride (Merck and Co.); oxymorphone hydrochloride and naloxone hydrochloride (Endo Labs); pentazocine lactate and cyclazocine lactate (Winthrop Laboratories); levallorphan tartrate (Roche Laboratories); procaine hydrochloride and scopolamine hydrobromide (Sigma Chemical); fenfluramine hydrochloride (Robins Research Laboratories); chlorpromazine hydrochloride (Smith, Kline and French Laboratories); methylphenidate hydrochloride (CIBA Pharmaceuticals); and *d*-amphetamine sulfate (City Chemical Corp). Both (±)-9-nor-9-α-hydroxy-hexahydrocannabinol (α-HHC) and (±)-9-nor-9-β-hydroxy-hexahydrocannabinol (β-HHC) were synthesized prior to use in the procedure. With the exception of pentazocine, cyclazocine, α-HHC and β-HHC, all doses were calculated as the salt.

Stock solutions were prepared on a monthly basis by dissolving the drug in distilled water. Sterile solutions were prepared by filtering these stock solutions through Millipore filters (Type GA, pore size 0.2 mμ) into multiple use serum bottles. These solutions were stored at approximately 3°C. For solutions to be administered to the animals, small volumes of stock solutions were diluted with sterile saline. These final solutions for administration were used only one day and were prepared as needed immediately prior to the morning session. Both α- and β-HHC were suspended in a 50% (by volume) Emulphor (EL-620, GAF Corp.) in ethanol solution [3,4] so that stock concentrations of approximately 20 mg/ml were obtained. Small portions of these stock solutions were diluted with sterile saline for administration to the animals.

Surgical Procedure

Following an initial harness adaptation and preliminary lever training period of approximately 4 weeks, each monkey was surgically prepared with a chronic indwelling venous catheter (0.79 mm i.d.; 2.36 mm o.d.) made of siliconized rubber (Ronsil, Rodhelm-Reiss, Belle Mead, NJ). The animals were pre-medicated with a 1.0 mg/kg phencyclidine hydrochloride (Sernylan; Bioceutics, St. Joseph, MO) IM to render them immobile and then anesthetized with approximately 20 mg/kg sodium pentobarbital, administered intravenously. Aseptic surgical procedures were strictly adhered to in all cases. The proximal end of the catheter was implanted into one of the major veins so that it terminated near the superior vena cava. The distal end of the catheter was passed subcutaneously to the back where it exited through a stab wound, terminating at a stainless steel needle-tubing juncture attached to the harness. From this point a second section of catheter passed from the juncture through the restraining arm where it terminated at the peristaltic pump. If a catheter became non-functional for any reason, the animal was allowed to recover in a separate holding facility and then re-implanted with another catheter in one of the remaining veins.

Experimental Procedure

Intravenous drug self-administration behavior was studied using a three component multiple schedule consisting of food-drug-food periods of reinforcement. The sequence was: 15 min of responding on the right lever maintained by the delivery of food reinforcement (Period 1), followed by 15 min of responding on the left lever maintained by the delivery of drug reinforcement (Period 2), followed again by 15 min of right lever responding maintained by the delivery of food reinforcement (Period 3). Illumination of the stimulus lights over the appropriate lever signalled the schedule component in effect. Two daily experimental sessions were run, one in the morning (approximately 9:00 a.m.) and one in the afternoon (approximately 1:00 p.m.). The drug available each day followed a four day sequence of cocaine, saline, cocaine, and a test compound. This sequence was repeated to evaluate a series of test compounds at two doses each. Both doses of each compound were evaluated before beginning the sequence for another compound.

Preliminary training for each animal consisted of reinforcing with food each lever press which occurred in the presence of the illuminated stimulus lights over either the right or the left lever. The number of lever presses was gradually increased until 100 (fixed-ratio [FR] 100) responses were necessary to obtain a single food pellet. Twice each day, food reinforced sessions were run which consisted of 15 min of right lever responding, 15 min of left lever responding, and then 15 min of right lever responding again. Surgery was performed when food reinforced responding on both levers was stable.

In all cases, the left lever was designated the drug reinforced lever and the right lever was designated the food reinforced lever. When the stimulus lights above the appropriate lever were illuminated, responses were reinforced under a FR 100 schedule. Responses occurring at other times had no consequence. After recovery from surgery, drug reinforced training was carried out. For this phase, responding on the left lever was maintained by a 30 μg/kg injection of cocaine hydrochloride.

After responding for cocaine had stabilized, saline (1.0 ml/injection) was substituted in both daily sessions until left lever responding had extinguished (2–4 days). After this period, cocaine and saline were alternated on a daily basis for approximately 10–20 days. The same solution was always

available in the morning and afternoon sessions. This phase of training was to enable the animals to quickly discriminate between cocaine and saline. The high FR requirement was designed to discourage inappropriate or persistent lever pressing on saline days as well as to produce an increase in behavior with a reduction in the possibility of drug toxicity on drug days.

Since the drug available to the animal changed on a daily basis, special care was taken to insure that the catheters were flushed of all drug each day following the afternoon session. A volume of saline (3–5 ml) calculated to exceed the volume of the catheter was infused via the peristaltic pump. Immediately prior to the start of the morning session, a volume of the new drug (1–2 ml) calculated to equal the volume of the catheter was infused. This was carried out to infuse the remaining saline so that when the animal completed the first FR 100 on the drug reinforced lever, an immediate injection of the appropriate drug resulted. The injection of drug was not given prior to the afternoon session since this would have injected an amount of the available drug into the animal.

Each compound was compared to saline for its ability to maintain responding during Period 2 of the afternoon session. Period 2 of the morning session was designated as a sampling session, while the number of injections in Period 2 of the afternoon session was used for purposes of data analysis. For each animal, the mean number of saline injections for the afternoon sessions during the testing of each drug group was calculated. From these data, a 95% confidence interval (two-tailed test) was determined. If the number of injections of the test compound by each animal was greater than the upper confidence limit for that animal, the compound was designated to be self-administered at rates significantly above saline. Group data were expressed for each test dose as the number of animals self-administering the compound by that criterion.

After the initial phases of training, a series of psychoactive compounds was evaluated using the four day sequence of drug presentation. When possible, drugs were chosen which had been previously tested in the more lengthy substitution procedures in order to validate the present method. The doses tested for each compound were determined in the following manner. Based on previously reported values from various testing procedures, the initial unit dose was set at 10 μg/kg/injection. This dose was believed to be within the dose-effect curve for all compounds to be tested. Period 3 of the morning session served as an indicator of the animal's ability to press the lever. If the amount of test drug self-administered during the morning session at the 10 μg/kg unit dose decreased Period 3 food reinforced responding by more than 50% of Period 1 rates, the unit dose for testing in the second four day sequence was reduced by a factor of 10. If the 10 μg/kg unit dose had no significant effect on Period 3 responding, the unit dose for testing in the second sequence was increased by a factor of 10. An additional criterion for determining the second test dose was included for drugs which might possess a slow onset or extended duration of action. Period 1 of the afternoon session was also examined for decreases in rate as compared to the morning sessions. An attempt was made to maintain a similar treatment for all of the animals for purposes of validating the procedure. Decisions concerning test doses were often based on the results of one or two animals. Thus, all animals received the same two doses of each test drug in the same order.

The drugs chosen for testing were divided into two groups. Group 1 consisted of the 10 opioid-like drugs. Group 2 consisted of the 6 drugs chosen from various other pharmacological classes of compounds. The order of drug presentation within each group was carried out in a random manner.

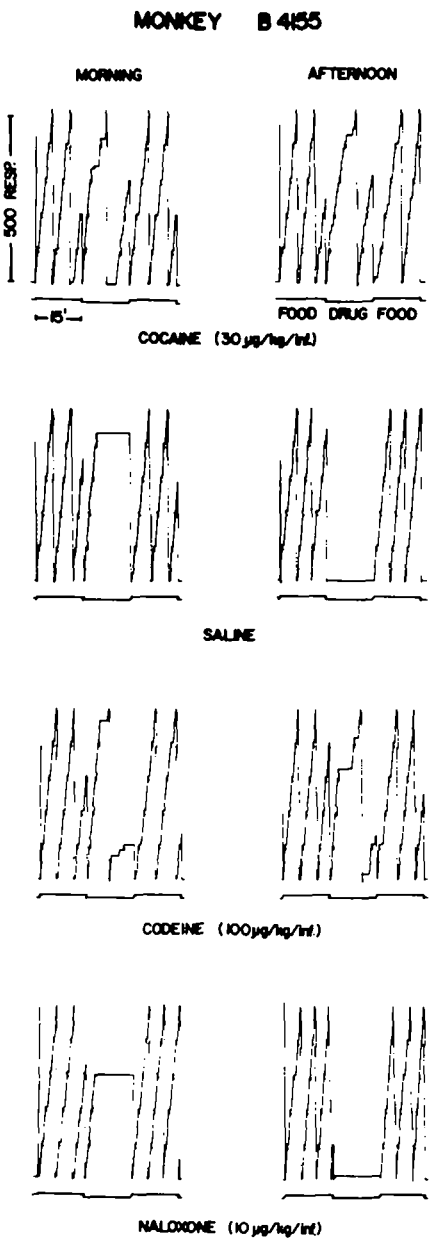

FIG. 1. Representative cumulative records for Monkey 4155 demonstrating results from the rapid substitution procedure for four compounds in morning and afternoon sessions.

RESULTS

To illustrate the nature of the data obtained in the rapid substitution procedure, cumulative records for monkey 4155 demonstrating representative results for four compounds are shown in Fig. 1. In both the morning and afternoon sessions, drug reinforced responding is indicated by the downward deflection of the lower pen tracing for each record. Typical

TABLE 1

MEAN NUMBER OF REINFORCEMENTS OBTAINED IN EACH OF THREE PERIODS OF MORNING AND AFTERNOON COCAINE AND SALINE SESSIONS DURING TESTING OF GROUP 1 COMPOUNDS

	Morning			Afternoon		
	1	2	3	1	2	3
Monkey 4152						
Cocaine						
Mean	28.2	10.4	27.3	25.0	10.4	25.0
SEM	0.5	0.6	0.6	1.0	0.5	1.1
Saline						
Mean	27.0	5.0	26.3	25.8	1.0	24.8
SEM	0.9	0.5	0.6	1.0	0.4	0.7
Monkey 4070						
Cocaine						
Mean	23.7	6.2	20.8	24.0	7.8	25.4
SEM	0.9	0.4	1.4	1.1	0.8	1.1
Saline						
Mean	22.8	7.0	23.5	23.2	1.0	24.5
SEM	1.8	0.6	1.9	1.6	0.6	2.0
Monkey 4155						
Cocaine						
Mean	13.5	5.8	11.6	12.6	6.3	10.5
SEM	0.5	0.3	0.4	0.4	0.3	0.6
Saline						
Mean	12.8	5.0	13.4	13.2	1.7	13.9
SEM	0.5	0.4	0.5	0.5	0.3	0.6
Monkey 4159						
Cocaine						
Mean	22.5	4.6	22.7	24.4	5.4	21.9
SEM	1.4	1.9	1.2	1.3	0.4	1.1
Saline						
Mean	23.8	3.6	23.0	24.6	0.9	21.9
SEM	1.7	0.6	1.5	2.0	0.4	1.5

TABLE 2

MEAN NUMBER OF REINFORCEMENTS OBTAINED IN EACH OF THREE PERIODS OF MORNING AND AFTERNOON COCAINE AND SALINE SESSIONS DURING TESTNG OF GROUP 2 COMPOUNDS

	Morning			Afternoon		
	1	2	3	1	2	3
Monkey 4152						
Cocaine						
Mean	27.3	9.5	20.7	22.0	11.1	18.8
SEM	1.4	0.6	1.9	1.5	0.4	2.2
Saline						
Mean	22.9	4.1	21.8	20.7	1.4	24.6
SEM	1.8	0.7	2.0	2.8	0.4	1.4
Monkey 4070						
Cocaine						
Mean	15.0	5.9	11.5	14.2	8.5	15.8
SEM	1.3	0.5	1.4	1.3	0.6	1.3
Saline						
Mean	14.5	3.8	15.2	15.8	0.7	17.2
SEM	1.4	0.7	1.6	1.6	0.3	1.9
Monkey 4168						
Cocaine						
Mean	8.8	4.8	9.6	9.7	5.3	10.3
SEM	0.6	1.2	0.7	0.8	0.7	0.7
Saline						
Mean	8.7	2.5	9.1	11.4	0.2	11.2
SEM	0.6	0.9	0.9	1.1	0.1	0.9
Monkey 4155						
Cocaine						
Mean	16.4	7.2	16.2	15.8	7.3	14.7
SEM	0.8	0.3	0.6	0.5	0.4	0.5
Saline						
Mean	16.4	5.3	17.4	16.5	0.5	16.9
Saline	0.9	0.7	0.8	0.8	0.2	0.7

response patterns for drugs with positive reinforcing properties are demonstrated by cocaine or codeine. Both of these drugs maintained high rates of responding in both the morning and afternoon sessions. Typical response patterns for drugs considered not to be reinforcing are demonstrated by saline and naloxone. Although these two compounds were self-administered in the morning session, neither maintained Period 2 responding in the afternoon session.

Tables 1 and 2 present individual animal data on the number of reinforcements obtained in each of three periods of the morning and afternoon cocaine or saline sessions during testing of Group 1 and 2 compounds, respectively. Although there were marked differences in the number of reinforcers obtained among animals, the number for individual animals was quite stable, both across sessions as well as across periods within sessions. In addition, food maintained responding (Periods 1 and 3) in either the morning or afternoon sessions did not differ significantly when cocaine (30 μg/kg/injection) or saline was available in Period 2. For all of the animals, the mean number of cocaine injections in the morning session was less than or equal to the number of cocaine injections in the afternoon session. The opposite results were seen for saline, where the mean number of injections in the morning were from 3–7 times greater than the mean number of injections in the afternoon. These results may be interpreted as demonstrating that saline reinforced responding extinguished as a consequence of the morning session.

Table 3 presents a summary of the number of drug injections of Group 1 compounds self-administered in the afternoon session compared to saline for four monkeys. The mean number of saline injections in the afternoon session during testing of the Group 1 series and the 95% confidence interval for these saline injections in each monkey are shown at the lower portion of Table 3. The number of animals tested with injection rates above the upper 95% confidence limits of saline are shown in the extreme right column. Morphine, oxymorphone, codeine, and pentazocine were self-administered by all of the monkeys at both unit doses with the exception of one monkey at the low dose of pentazocine. Cyclazocine, naloxone, levallorphan, and α-HHC were not self-administered by the animals at either dose tested. The

TABLE 3

SUMMARY OF THE NUMBER OF GROUP 1 INJECTIONS SELF-ADMINISTERED IN THE AFTERNOON SESSION COMPARED TO SALINE FOR FOUR MONKEYS IN THE RAPID SUBSTITUTION PROCEDURE

		Monkey				
Drug	Dose†	4152	4070	4155	4159	Number with Rates Above Saline
Morphine	10	7*	5*	6*	4*	4
	100	2*	3*	3*	3*	4
Nalorphine	10	8*	10	2	0	2
	100	6*	0	1	0	1
Oxymorphone	10	3*	8*	4*	3*	4
	1	3*	9*	5*	5*	4
Codeine	10	14*	7*	4*	7*	4
	100	7*	6*	6*	4*	4
Pentazocine	10	1	9*	6*	4*	3
	100	6*	8*	7*	3*	4
Cyclazocine	10	1	0	0	1	0
	1	0	0	0	0	0
Naloxone	10	0	0	0	0	0
	100	0	0	0	0	0
Levallorphan	10	0	0	2	0	0
	100	0	0	0	1	0
β-HCC	10	7*	4*	2	3*	3
	100	0	0	1	3*	1
α-HHC	10	0	0	0	1	0
	100	0	0	2	0	0
Emulphor		0	0	—	0	0
Mean No. Saline Injections		0.96	1.0	1.67	0.90	
95% Confidence Limits		0.2–1.7	0.0–2.2	1.0–2.4	0.0–1.9	

*Greater than upper confidence limit.
†All doses in μg/kg/injection.

results with β-HHC and nalorphine were considered equivocal. At the 10 μg/kg unit dose, two animals self-administered nalorphine at rates above saline. At the 100 μg/kg unit dose of nalorphine only one monkey self-administered this drug at rates significantly greater than for saline. Similar results were seen for β-HHC.

Table 4 summarizes the results of the number of drug injections of Group 2 compounds self-administered in the afternoon sessions compared to control for four monkeys. The total number of animals with injection rates greater than the upper 95% confidence limit for saline injections during testing of Group 2 compounds is again shown in the extreme right column. Methylphenidate and *d*-amphetamine were self-administered at both unit doses at rates above saline in all four animals. Scopolamine and chlorpromazine were not self-administered by any of the animals in the afternoon session at either dose. One monkey (4168) self-administered one injection of fenfluramine at the 10 μg/kg unit dose, which happened to be very close to the confidence limits for saline for this subject. However, none of the animals self-administered the 100 μg/kg dose in the afternoon session. The results with procaine were equivocal, with two animals self-administering this compound at rates above saline for each unit dose tested.

Tables 5 and 6 show the number of reinforcers earned during Period 3 of the morning session on test days. The decision to increase or decrease the test dose for the second four-day sequence was based on these results. Four compounds (oxymorphone, cyclazocine, scopolamine and *d*-amphetamine) were evaluated at a lower dose. Rates of responding maintained by food in Period 3 were reduced by more than 50% in 3 out of 4 animals following self-administration of these 4 compounds at a test dose of 10 μg/kg/injection.

DISCUSSION

Two manipulations were incorporated into the present

TABLE 4

SUMMARY OF THE NUMBER OF GROUP 2 DRUG INJECTIONS SELF-ADMINISTERED IN THE AFTERNOON SESSION COMPARED TO SALINE FOR FOUR MONKEYS IN THE RAPID SUBSTITUTION PROCEDURE

Drug	Dose†	Monkeys 4152	4070	4168	4155	Number with Rates Above Saline
Scopolamine	10	0	0	0	0	0
	1	0	1	0	0	0
d-Amphetamine	10	14*	8*	9*	10*	4
	1	15*	12*	11*	9*	4
Chlorpromazine	10	0	0	0	0	0
	100	0	0	0	0	0
Methylphenidate	10	12*	10*	4*	10*	4
	100	3*	9*	5*	2*	4
Fenfluramine	10	0	0	1*	0	1
	100	0	0	0	0	0
Procaine	10	9*	1	0	5*	2
	100	2	3*	0	6*	2
Mean No. Saline Injections		1.36	0.75	0.20	0.50	
95% Confidence Limits		0.4–2.3	0.0–1.5	0.0–0.5	0.1–0.9	

*Greater than upper confidence limit.
†All doses in μg/kg/injection.

procedure in order to train the animals to quickly discriminate between reinforcing and non-reinforcing compounds. The incorporation of a high FR requirement as well as the use of two sessions each day were designed for this purpose. This cocaine and saline data during the testing of Group 1 compounds tend to suggest the success of these two manipulations.

The results of testing the Group 1 series are, for the most part, consistent with the known reinforcing property of these compounds. The narcotic agonists morphine, codeine, and oxymorphone have previously been reported to reinforce self-administration behavior in rhesus monkeys (e.g., [1, 6, 22]). In the present procedure, these drugs were self-administered by all four monkeys at both of the doses tested. The results with the mixed agonist-antagonist pentazocine suggest that this drug is a reinforcer in the rapid substitution procedure. This result also agrees with previous reports [10,12].

Naloxone, cyclazocine, and levallorphan were not self-administered at rates above saline in the afternoon session at either test dose by any of the monkeys. Naloxone is considered to be a relatively pure antagonist; that is, it possesses little or no agonist activity [13, 14, 17]. Hoffmeister and Wuttke [11], using an escape-avoidance procedure designed to test the aversive properties of drugs, reported that naloxone injections were neither escaped from nor avoided at rates significantly different from saline. Jasinski *et al.* [14] administered naloxone to post-dependent human volunteers. Subjects' responses to the Addiction Research Center Inventory (ARCI) of subjective drug effects revealed no significantly different effects between naloxone and placebo, suggesting that at the doses tested, no positive or negative effects were discriminable. Cyclazocine is a mixed agonist-antagonist, but it has been reported to produce unpleasant effects in humans [18] and to maintain avoidance behavior in rhesus monkeys [11]. In the present procedure, none of the four animals tested self-administered cyclazocine at either dose at rates greater than for saline. Disturbing mental effects following administration of levallorphan to naive human subjects have been reported [16]. This compound was also not self-administered in the present procedure at rates greater than for saline in the afternoon session.

For two compounds, nalorphine and β-HHC, the results were considered equivocal. At the 10 μg/kg unit dose of nalorphine, two of the monkeys self-administered the compound, and the 100 μg/kg unit dose was self-administered by one animal. These results were somewhat difficult to interpret in view of previous reports on the lack of reinforcing properties of this compound in rhesus monkeys [10, 12, 24]. However, acute subcutaneous administration of low doses of nalorphine to post-dependent human volunteers has been reported to be opiate-like with a small degree of "liking" expressed [18]. Haertzen [8,9], using the ARCI reported that low and intermediate doses of nalorphine resulted in a number of responses more similar to morphine than did high doses of nalorphine. The results of testing nalorphine in the rapid substitution procedure are not totally inconsistent with the reports in humans. However, the fact that nalorphine is self-administered by some monkeys and liked by some humans still does not correspond with the low incidence of human abuse. The results with β-HHC were also equivocal, with three animals self-administering the 10 μg/kg dose and

TABLE 5

SUMMARY OF THE NUMBER OF FOOD REINFORCERS OBTAINED IN PERIOD 3 OF THE MORNING SESSION DURING TESTING OF GROUP 1 COMPOUNDS

		Monkey			
Drug	Dose†	4152	4070	4155	4159
Morphine	10	27	28	15	29
	100	8*	2*	9	6*
Nalorphine	10	27	30	17	18
	100	24	20	15	24
Oxymorphone	10	0*	26	7*	16*
	1	22	27	4*	22
Codeine	10	28	19	13	16
	100	23	25	11	16
Pentazocine	10	29	29	10	18
	100	0*	24	10	3*
Cyclazocine	10	12*	19	5*	10*
	1	27	24	13	21
Naloxone	10	26	27	15	32
	100	21	26	16	30
Levallorphan	10	26	19	10	24
	100	24	12	9	19
β-HHC	10	21	20	12	15
	100	0*	25	13	0*
α-HHC	10	22	23	13	12
	100	27	25	14	19

*A greater than 50% reduction in responding from Period 1 rates in the same session.

†All Doses in μg/kg/injection.

TABLE 6

SUMMARY OF THE NUMBER OF FOOD REINFORCERS OBTAINED IN PERIOD 3 OF THE MORNING SESSION DURING TESTING OF GROUP 2 COMPOUNDS

		Monkey			
Drug	Dose†	4152	4070	4155	4168
Scopolamine	10	3*	0*	1*	10
	1	27	16	13	8
d-Amphetamine	10	0*	9*	4*	14
	1	25	5*	20	14
Chlorpromazine	10	28	1*	13	11
	100	23	14	6*	16
Methylphenidate	10	10	0*	14	7
	100	0*	0*	15	9
Fenfluramine	10	4*	23	13	12
	100	13*	7*	12	6*
Procaine	10	26	3	25	12
	100	23	1*	15	8

*A greater than 50% reduction in responding from Period 1 rates in the same session.

†All doses in μg/kg/injection.

one animal self-administering the 100 μg/kg dose. Carney *et al.* [3] have recently reported no evidence for reinforcing properties for β-HHC. Although none of the animals self-administered the α-isomer, there remained the possibility that the Emulphor-Ethanol vehicle could have accounted for the self-administration of β-HHC. However, in vehicle tests alone, none of the three monkeys tested self-administered a single injection of Emulphor-Ethanol, suggesting that the vehicle suspension system was not reinforcing.

The results with the Group 2 series also generally agree with earlier reports using other procedures. For example, the results with *d*-amphetamine and methylphenidate, two central nervous system stimulants, are consistent with numerous reports which have shown both compounds to be effective reinforcers of self-administration behavior (e.g., [15,19]). Fenfluramine, a phenethylamine of similar structure and anorexigenic activity of amphetamine, has been reported to be devoid of central nervous system stimulant effects [2,25] and has been reported not to be self-administered in animals [23]. The results with the present study agree with these results, with none of the four animals self-administering the 100 μg/kg dose, and only one animal self-administering the 10 μg/kg dose at rates above saline. When the results with fenfluramine are compared with those for *d*-amphetamine, the specificity of the rapid substitution procedure is evident.

As mentioned, the results with procaine are equivocal. Ford and Balster [7] have reported procaine to be a reinforcer of self-administration behavior in rhesus monkeys. However, much higher unit doses (0.10–10.0 mg/kg/injection) were used in the Ford and Balster study. The equivocal data reported here could reflect a selection of doses which represent threshold levels in terms of reinforcing properties. As shown in Tables 5 and 6, rates of responding maintained by food reinforcement are decreased following the self-administration of some of the compounds at the doses tested. The inclusion of food reinforced periods is intended to show that behaviorally active doses of the drugs were tested. With results such as for procaine in the present procedure, this could mean that inappropriate doses of the drug may have been selected.

Drugs which were known reinforcers such as morphine or *d*-amphetamine were self-administered at greater rates than saline, usually by all of the animals tested. For the drugs which were not self-administered or were perhaps aversive such as scopolamine, chlorpromazine, or cyclazocine, again there was little variation in results among animals. With results such as these, the identification of drugs with reinforcing properties is readily determined However, with results such as were obtained with nalorphine, procaine, or β-HHC, this identification is not as easy. How the resolution of the fate of equivocal compounds is approached will, of course, depend on the general interest in the specific compound.

Drug screening is a process concerned with the testing of chemical compounds for a desired activity, as in the present procedure where activity as a reinforcer of self-administration behavior is examined. The purpose of screening, or other preliminary procedures, is to provide information on the compound which will be used in deciding the type and extent of further testing. It is this factor of the rapid substitution procedure, the ability to quickly and effectively

screen compounds with reinforcement efficacy, which increases the overall efficiency of the evaluation process.

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