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Buprenorphine Self-Administration by Rhesus Monkey

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MELLO, N. K., M. P. BREE AND J. H. MENDELSON. *Buprenorphine self-administration by rhesus monkey.* PHARMAC. BIOCHEM. BEHAV. 15(2) 215–225, 1981.—Intravenous injections of buprenorphine, a partial opiate agonist and antagonist, maintained operant responding under second order schedule control (FR 3 VR 16:S) across a dose range of 0.005 to 0.10 mg/kg/inj. A drug naive monkey and four monkeys with a history of morphine self-administration all self-administered buprenorphine at all doses studied. Four monkeys showed dose-related increases in the total amount of buprenorphine (mg/kg) self-administered each day as the available dose increased from 0.01 to 0.10 mg/kg/inj. Injections per day remained equivalent to the number of injections at the lowest dose studied or increased significantly ($p<0.05$, 0.01), as the dose per injection increased in three monkeys. Even at high buprenorphine doses, there was no evidence of sedation. Monkeys consistently self-administered significantly more buprenorphine than saline in control studies ($p<0.01$). Buprenorphine's agonistic effects appear to persist for 24 to 48 hours. When saline and buprenorphine were available on alternate days, monkeys did not distinguish between them, but when 3 days of saline were alternated with 1 day of buprenorphine (0.03 mg/kg/inj), monkeys took significantly more buprenorphine than saline ($p<0.02$–0.001). Abrupt discontinuation of buprenorphine (0.10 mg/kg/inj) did not result in discernible withdrawal signs. The effects of buprenorphine on food intake were inconsistent, but there were no significant changes in body weight as a function of chronic buprenorphine self-administration or withdrawal. These data indicate that buprenorphine is a positive reinforcer in rhesus monkeys and maintains behavior leading to its administration on second order schedules over a wide dose range. Despite its opiate agonist properties, there was no evidence of physical dependence.

Buprenorphine Mixed agonist-antagonist drugs Drug reinforcement Abuse liability
Drug physical dependence Drug self-administration

BUPRENORPHINE is a partial opiate agonist and antagonist that combines the characteristics of two leading pharmacotherapies for heroin addiction. It is equivalent to naltrexone in duration of opiate antagonism [13, 14, 24] and its opiate agonist effects resemble those of methadone in terms of reported positive subjective effects [13,14]. However, unlike methadone, termination of buprenorphine maintenance does not produce severe and protracted withdrawal signs and symptoms in man [13, 14, 26]. Recent clinical studies have shown that buprenorphine (8 mg/day) significantly suppressed heroin self-administration (21 to 40.5 mg/kg/day) by heroin addicts over 10 days in comparison to placebo buprenorphine [26]. Placebo control subjects took between 93 and 100 percent of all the heroin available [26]. Although buprenorphine appears to be a safe and potentially effective pharmacotherapy for opiate addiction [13, 14, 26], relatively little is known about its basic behavioral pharmacology and potential abuse liability. This study examines the reinforcing properties of buprenorphine in a primate drug self-administration model which has proved useful for the pre-clinical assessment of drug abuse liability [7, 15, 16, 17, 32, 35].

Buprenorphine is an oripavine derivative and its structure has been described by Lewis [22]. Buprenorphine is a congener of etorphine, a potent narcotic agonist, and diprenorphine, a narcotic antagonist. Buprenorphine is an effective narcotic antagonist; 8 mg/day blocked the subjective and miotic effects of high doses of morphine (60–120 mg/day) for up to 29.5 hours [13,14]. Its antagonistic potency is equivalent to that of naloxone [3]. One consequence of the antagonistic properties of buprenorphine is that lethal overdose appears to be almost impossible [1].

The agonistic properties of buprenorphine include morphine-like analgesic, subjective and physiological effects. The analgesic potency of buprenorphine has been shown to be 25 to 40 times that of morphine in clinical [9, 10, 11, 13, 14] and animal [2,3] studies, but its duration of analgesic action is equivalent to that of morphine, about six hours [9, 10, 11]. Pupillary constriction (miosis) occurs later after buprenorphine than morphine, but persists for significantly longer, up to 72 hours [13,14]. Acute and chronic buprenorphine administration has been shown to produce morphine-like subjective effects, including "euphoria" [13,14]. Former heroin addicts identified a single dose of buprenorphine (0.2 to 1.2 mg) as an opiate and reported liking buprenorphine equally well [13,14]. Chronic administration of buprenorphine to former heroin addicts produced generalized feelings of well-being and contentment [26]. The agonistic properties of a maintenance dose of 8 mg of buprenorphine appear equivalent to those of 40 to 60 mg of methadone in clinical studies [13,14]. Since methadone has been subject to consid-

erable illicit abuse [21] study of the possible abuse potential of buprenorphine is relevant to its eventual deployment in outpatient pharmacotherapy.

Prediction of abuse liability in clinical studies has traditionally relied on subjective reports of the similarity of a new compound to a standard drug, usually morphine [12]. However, it is generally agreed that most drugs abused by man are also self-administered by monkey [7, 16, 17, 32] and the primate model has been shown to be a powerful and reliable behavioral predictor of abuse liability [35,38]. One approach to the pre-clinical evaluation of drug self-administration is to substitute a new compound for a standard drug known to maintain responding [32, 35, 38]. In 1977, Woods [37] evaluated buprenorphine, along with 36 other drugs, in a rapid substitution procedure to determine if these drugs maintained operant responding at rates comparable to those maintained by codeine. Substitution of buprenorphine (0.0001 to 0.10 mg/kg/inj) for codeine (0.3 mg/kg/inj) maintained responding on an FR 30 schedule of reinforcement. Response rates for buprenorphine injections were lower than rates for codeine, morphine or heroin in that paradigm [37]. Although there are considerable data which challenge the use of rate of response as a measure of reinforcing efficacy with drugs which directly effect response rates [20, 32, 33], substitution studies indicate that buprenorphine is reinforcing in monkeys [37].

The present study examines the conditions under which buprenorphine is reinforcing, i.e., will maintain operant behavior leading to its intravenous administration in primates, using second-order schedules. Second-order schedules are less sensitive to the direct effects of opiate agonists on rate of response [4, 5, 20]. In addition, the reinforcing properties of buprenorphine were evaluated in a drug naive monkey in which previous drug experience could not effect buprenorphine self-administration. Buprenorphine maintained responding in a drug naive monkey was compared with performance in experienced monkeys with a history of morphine self-administration. The dose range over which buprenorphine was reinforcing was examined and compared with saline in control studies. During saline control studies, monkeys were evaluated for behavioral and physiological signs of opiate withdrawal. The effects of chronic buprenorphine self-administration on concurrent food self-administration were also examined.

METHOD

Animals

Five adolescent male rhesus monkeys *(Macaca mulatta)* weighing between 5.5 and 8.2 kg were studied. One monkey (A-319) was experimentally naive at the initiation of the study and had no previous drug self-administration history. Four monkeys (A-187, B-255, B-205 and A-105) had a history of morphine self-administration of 150, 384, 557 and 830 days respectively. Monkeys A-105 and B-255 had also administered an enkephalin analogue for 12 days [25]. One monkey (B-205) was maintained on cocaine (100 mcg/kg/inj) for 74 days immediately prior to buprenorphine substitution.

Monkeys were maintained at ad lib weight throughout the study. They were weighed daily, and given multiple vitamins, fresh fruit and vegetables to supplement a banana pellet diet. Water intake was measured twice daily. Monkeys were maintained in accordance with DHEW guidelines for the care and use of laboratory animals and their health status was periodically monitored by a veterinarian.

After training on a food administration task, monkeys were surgically implanted with chronic indwelling catheters to permit intravenous drug self-administration. All surgical procedures were performed under aseptic conditions. Animals were anesthetized with either pentobarbital (30 mg/kg/IV) or ketamine (25 mg/kg/IM) and a double-lumen, silicon rubber catheter (i.d. 0.8 mm; o.d. 2.4 mm) was placed in the left internal jugular vein. Eventual blockage of the first jugular catheter required implantation of a second catheter into another vein. In this study, one monkey had a jugular catheter and four monkeys had catheters implanted into the right or left internal iliac vein. Following surgery, animals were given 1 ml of longicil IM every other day for a total of 5 injections.

Monkeys worked at an operant task in a specially designed restraining apparatus which allowed completely free movement of the arms and legs [27]. The monkey was able to maintain a comfortable natural posture at all times and jump up and down, but did not have access to the top of his head, the point of the intravenous catheter exit. The restraining apparatus was placed in a well-ventilated experimental chamber equipped with an operant response panel, a water dispenser and an automatic feeder.

Apparatus

Delivery of food (1 g Noyes banana pellets) and drug injections were contingent on the monkeys' operant performance. Schedules of reinforcement were programmed by silent transistor circuitry (BRS-Foringer 200 series). Following completion of the scheduled response requirement, a single banana pellet or one injection of drug solution was automatically dispensed in a train of 10 pulses over 1 second. Each pulse dispensed 10 lambda of fluid and each injection contained a total volume of 100 lambda (0.10 ml). The operation of the injection pump (model 1302 lambda pump, Harvard Apparatus Company) was audible to the monkey.

The conditions of food and drug availability and time-out periods (when responses had no programmed consequence) each were associated with a colored stimulus light (S+) projected on a translucent Plexiglas response key in the center of the operant response panel. When a food pellet or a drug injection was dispensed, there was a 1 second flash of the appropriate colored stimulus light on 3 circles located in a vertical row below the response key. These stimulus light flashes (S+) were also used to signal the completion of each successive component of the second-order schedule response requirements. Detailed descriptions of this apparatus have been published previously [25].

Procedures

Daily sequence of conditions. One hour of food availability was followed by one hour of drug availability and two hours of time-out. The first food availability session began at 7:00 a.m. each day and the first drug availability session began at 8:00 a.m. Four periods of food availability, drug availability, and time-out occurred in 4 hour blocks during each 24 hour period. These recurrent sequences of food, drug and time-out periods were designed to insure maximum food intake before drug intoxication. Experiments continued 24 hours a day, 7 days a week. Daily cleaning and weighing were completed during the morning time-out period between 9:00 and 10:00 a.m. Fruit and vegetable supplements were provided during the late afternoon time-out period at 5:00 p.m.

Reinforcement schedules. Food and drug self-administration were maintained under a second-order schedule of reinforcement, FR 3 (VR 16:S). Naive monkeys were initially

trained on gradually increasing values of the variable ratio schedule for food reinforcement. An average of 16 responses on a variable ratio schedule (VR 16) produced a brief stimulus light (S+) and delivery of a food pellet. However, on the final second-order schedule, a drug injection or a food pellet was delivered only after a fixed ratio of 3 (FR 3) of the VR 16 response requirements had been completed. All monkeys worked on a second-order FR 3 (VR 16:S) schedule for food and drug injections. Drug (or saline) injections were limited to 20 per session and food pellets were limited to 65 per session.

Second-order schedules were used to minimize the possible disruptive or sedative effect of drug infusions on operant responding. In second-order schedules, the interval between successive drug infusions is lengthened, in comparison to simple or multiple schedules. Monkeys worked to produce a discriminative stimulus (S+), previously associated with food or drug delivery, until completion of the specified response requirement yielded reinforcement. Second-order schedules have been shown to be effective in generating stable and sustained responding for drug injections [4, 5, 20].

Buprenorphine administration. Buprenorphine self-administration was studied over a range of doses of 0.005, to 0.10 mg/kg/inj. Each of the 5 buprenorphine doses studied (0.005, 0.01, 0.03, 0.05 and 0.10 mg/kg/inj) was available for 60 consecutive drug sessions over 15 days. Buprenorphine doses were presented in an ascending order. However, the entire range of doses was not completed by all monkeys.

The conditions under which buprenorphine was initially introduced varied as a function of the immediate drug history of the subject. The morphine maintained monkey (A-187) was gradually withdrawn from morphine (0.5 mg/kg/inj) prior to buprenorphine substitution in order to avoid the possibility of buprenorphine precipitated withdrawal. Buprenorphine was immediately substituted for cocaine (100 mcg/kg/inj) without an intervening saline period in monkey B-205. Each monkey began to work for buprenorphine on the same second- order schedule of reinforcement previously required for morphine or cocaine self-administration, FR 3 (VR 16:S). The availability of buprenorphine was indicated by a new discriminative stimulus color (S+) on the response key. The drug naive monkey and the drug free monkeys with a previous morphine self-administration history (A-105 and B-255) were each given access to buprenorphine upon recovery from surgical implantation of an intravenous catheter.

Saline control procedure. To determine if buprenorphine maintained responding above saline levels, two control procedures were run. (1) Saline substitution: saline was abruptly substituted for buprenorphine after completion of 15 days (60 sessions) at the highest buprenorphine dose studied (0.10 mg/kg/ inj). Saline was infused through the second lumen of the double-lumen catheter, thereby avoiding the problem of catheter dead-space which can confound substitution procedures run with single lumen catheters (cf. [25]). The availability of saline was associated with a different colored stimulus light (S+) on the response key. This "signaled extinction" procedure [37] insures that the monkeys' saline or subsequent drug self-administration behavior is not confounded by an incorrect discriminative stimulus during saline substitution trials. Saline remained available until monkeys stopped responding for saline infusions and the time-course of extinction of saline maintained responding was observed. Monkeys were observed for signs of opiate withdrawal as described below. The average number of saline injections taken per day during the last 10 days of saline maintained responding were compared with buprenorphine injections at each dose level. (2) Alternation of saline and buprenorphine: To evaluate the conditions under which buprenorphine was readily discriminable from saline, each was alternately available as follows: (a) one day (4 sessions) of buprenorphine was alternated with one day (4 sessions) of saline; (b) one day (4 sessions) of buprenorphine was alternated with two days (8 sessions) of saline; and (c) one day (4 sessions) of buprenorphine was alternated with three days (12 sessions) of saline. The availability of saline and buprenorphine each were associated with a different colored stimulus light (S+) on the response key. At least two buprenorphine doses (0.01, 0.03 or 0.05 mg/kg/inj) were examined in each condition.

Evaluation of opiate abstinence signs. During saline substitution procedures or after unanticipated catheter occlusion, monkeys were observed at least three times each day for signs of opiate withdrawal. A rating scale adapted from one described by Villarreal and Karbowski was used [36], and the presence or absence of each sign was recorded. No quantitative measure of withdrawal signs was attempted. Behavioral changes that could be reliably observed included hyperactivity, peculiar postures, unusual scratching, clutching the abdomen, biting/grimacing and vocalization. Observed involuntary somatic responses included tremors, shivering, twitching and muscular rigidity or weakness. Observable autonomic signs included coughing, retching, vomiting, diarrhea, tachypnea and dyspnea. Monkeys continued to work for food at the operant task during the period of saline substitution so food intake was accurately recorded.

Data analysis. The number and rate of responses and the occurrence of drug or saline injections and food delivery were recorded on Gerbrands SHS-Cumulative Recorders and electro-mechanical counters. Drug injections as a function of buprenorphine dose and comparisons of drug and saline injections were evaluated with t tests.

Drug solutions. Buprenorphine hydrochloride was obtained from the National Institute on Drug Abuse (NIDA) and doses are expressed in terms of salts. Solutions were diluted to the appropriate concentration for individual monkeys. Buprenorphine hydrochloride was dissolved in water adjusted to pH 4 with HCl. The buprenorphine solution (0.30 mg/ml) was passed through a millipore filter to remove pyrogens prior to intravenous administration. Solutions were checked daily to insure that no precipitate had formed. Fresh solutions were prepared every 10 days or more frequently when necessary.

RESULTS

All monkeys self-administered buprenorphine over the range of doses studied (0.005 to 0.10 mg/kg/inj), irrespective of their previous drug history. Four monkeys showed dose related increases in the total amount of buprenorphine (mg/kg) self-administered each day as the available dose of buprenorphine increased from 0.005 to 0.01 mg/kg/inj. Buprenorphine injections per day remained equivalent to injections at the lowest buprenorphine dose studied, or increased significantly ($p<0.05$, 0.01) as the dose per injection increased in three monkeys. Abrupt discontinuation of buprenorphine infusions (0.10 mg/kg/inj) did not result in discernible withdrawal signs. Monkeys consistently self-administered significantly more buprenorphine than saline in control studies and were able to distinguish between buprenorphine and saline. The effects of buprenorphine on food intake were inconsistent, but there were no significant

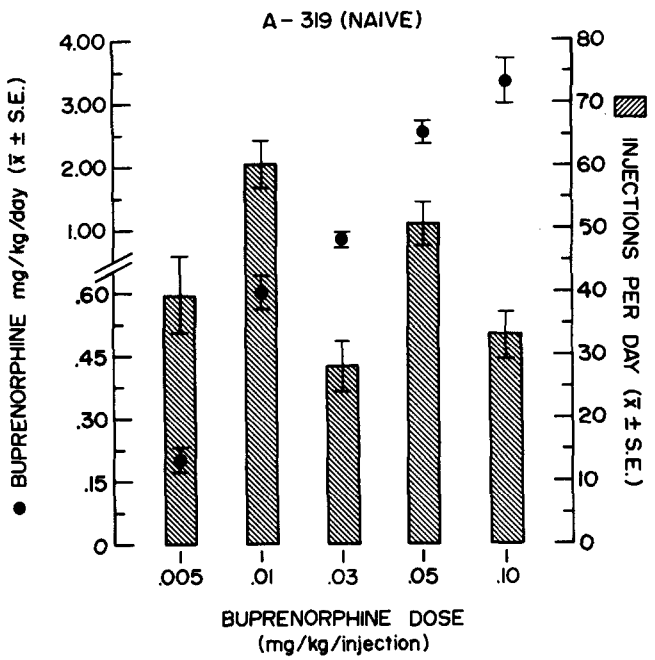

FIG. 1. Buprenorphine self-administration by a drug naive monkey. Average buprenorphine intake (mg/kg) and drug injections per day are shown for each of five buprenorphine doses per injection (0.005 to 0.10 mg/kg). Each data point represents the mean (±SE) of sixty sessions over fifteen consecutive days. All data were obtained on the same schedule of reinforcement, a second-order, FR 3 (VR 16:S). The first 15 days at 0.005 mg/kg/inj represent days 3 through 17 of this monkey's entire drug self-administration history.

changes in body weight as a function of chronic buprenorphine self-administration.

Buprenorphine Self-Administration by a Drug-Naive Monkey

The reinforcing properties of buprenorphine were clearly illustrated in an experimentally naive monkey with no previous drug self-administration history. Monkey A-319 began to self-administer buprenorphine immediately and took 29 injections on the first day of buprenorphine availability at a low dose per injection (0.005 mg/kg). Since buprenorphine is estimated to have between twenty-five and forty times the analgesic potency of morphine, the dose of buprenorphine taken on the first day (0.145 mg/kg) was approximately equivalent to 3.6 or 5.8 mg/kg/day of morphine. During the first two days of buprenorphine availability, within eight sessions, this monkey reached the final second-order schedule response requirement. The initial high rate of buprenorphine self-administration was sustained for sixty consecutive sessions over fifteen days. The monkey self-administered an average of 0.20 mg/kg/day (±0.03) of buprenorphine which is roughly equivalent to between 5 and 8 mg/kg/day of morphine.

Figure 1 shows buprenorphine intake (mg/kg/day) as a function of the dose per injection. This monkey self-administered progressively more buprenorphine at each increase in the dose per injection. Buprenorphine intake across a range of 0.01 to 0.10 mg/kg/inj was significantly greater ($p<0.001$) than buprenorphine intake at a dose of 0.005 mg/kg/inj. A ten-fold increase in the dose of buprenorphine, from 0.005 to 0.05 mg/kg/inj resulted in more than twelve-fold increase in buprenorphine self-administration.

The number of buprenorphine injections per day were also significantly higher ($p<0.01$) at doses of 0.01 mg/kg/inj than at the lowest dose per injection. However, injections per day at doses of 0.03 and 0.10 mg/kg/inj were lower than the lowest dose of buprenorphine. This may reflect the sequence of buprenorphine dose presentation. After 60 sessions at doses of 0.005, 0.01 and 0.05 mg/kg/inj, the monkey's catheter became occluded. The catheter was reimplanted after 51 drug-free days, and buprenorphine at doses of 0.03 and 0.10 mg/kg/inj each were available for 60 sessions. The monkey promptly resumed buprenorphine self-administration after recatheterization and took 22 injections on the first day of buprenorphine availability (0.03 mg/kg/inj).

Even at high doses of buprenorphine, there was no evidence of sedation. In marked contrast to monkeys self-administering comparable doses of morphine [25,27], this monkey was alert and did not show signs of motor retardation. Figure 2 shows cumulative records of responding for buprenorphine on an FR 3 (VR 16:S) schedule of reinforcement. A steady high rate of responding, between 2 and 2.5 responses per second, was maintained across a ten-fold increase in the buprenorphine dose per injection. The cumulative record at a dose of 0.05 mg/kg/inj shows that self-administration of 1 mg/kg of buprenorphine within an hour did not suppress response rates. This dose of buprenorphine is roughly comparable to 25 to 40 mg of morphine.

Buprenorphine Self-Administration by Drug-Experienced Monkeys

Three of four monkeys with a previous history of morphine self-administration also showed progressive increases in buprenorphine intake as the dose per injection was increased. Figure 3 shows the average buprenorphine self-administered (mg/kg/day) by each monkey over a dose range of 0.005 to 0.10 mg/kg/inj. In comparison to a low buprenorphine dose of 0.01 mg/kg/inj, three monkeys each took significantly more buprenorphine at doses of 0.03, 0.05 and 0.10 mg/kg/inj ($p<0.001$). At the highest dose per injection Monkey A-105 took an average of 2.95 (±0.24) mg/kg/day buprenorphine, which is approximately equivalent to 74 to 118 mg/kg/day of morphine. One monkey (B-205) did not show progressive increases in buprenorphine intake across the range of doses per injection studied. This monkey averaged about 0.158 mg/kg/day which is approximately equivalent to 3.9 to 6.3 mg/kg/day of morphine.

Although all four monkeys had a long history of morphine self-administration, there were differences in their immediate pre-buprenorphine history which may have affected buprenorphine self-administration. Monkey B-205 was maintained on cocaine for seventy-four days prior to buprenorphine substitution. Monkeys B-255 and A-105 were drug-free for 497 and 492 days respectively and reimplanted with a venous catheter immediately before introduction of buprenorphine. Monkey A-187 was maintained on morphine until 2 days before buprenorphine substitution.

The number of buprenorphine injections per day taken by each monkey across the dose range studied is summarized in Table 1. Monkeys A-105 and B-255 took equivalent or significantly more buprenorphine injections as the dose per injection increased than at the lowest dose studied. Monkey

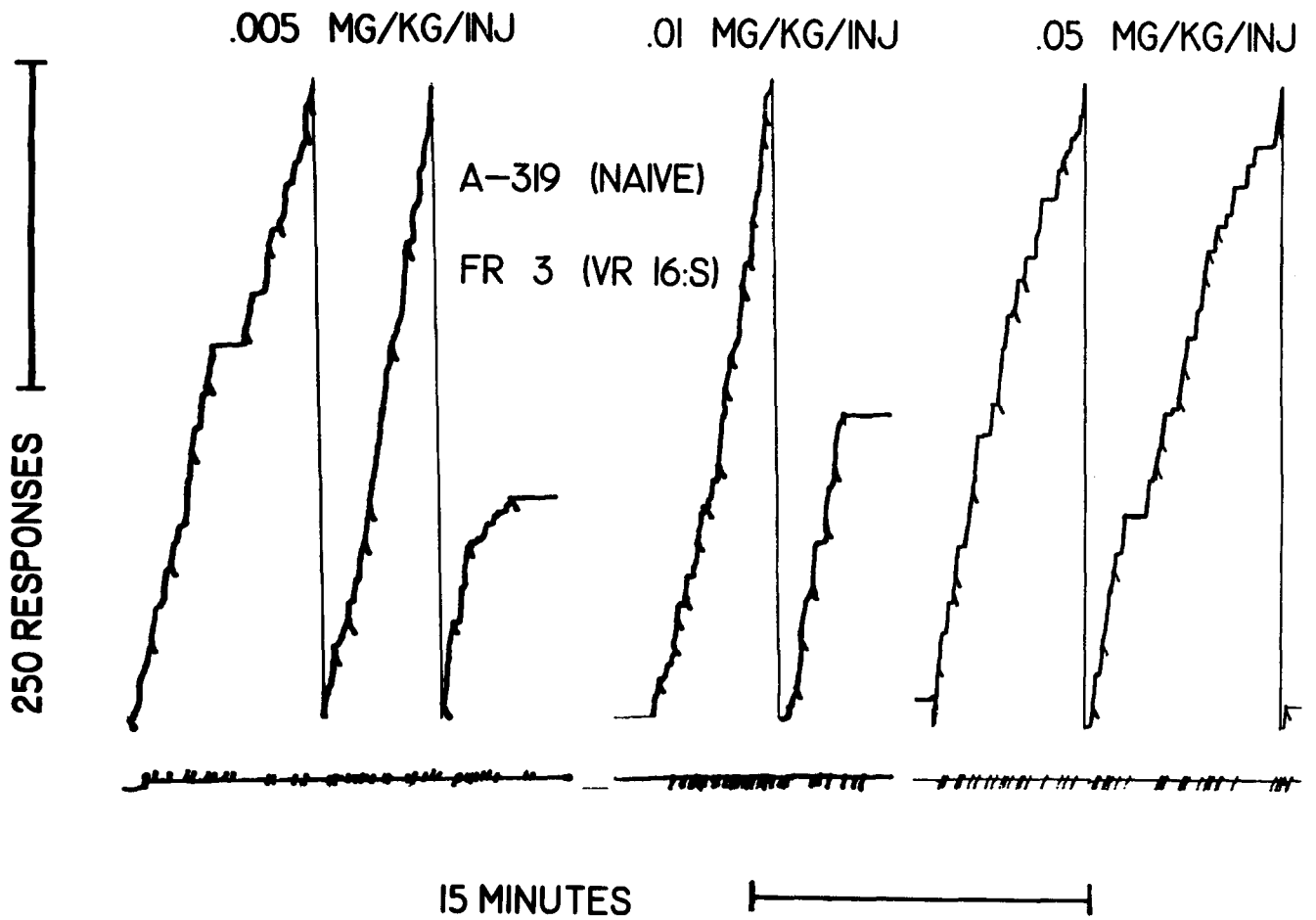

FIG. 2. Cumulative records of responding for buprenorphine at three doses per injection by a drug-naive monkey. Responding was maintained under a second-order FR 3 (VR 16:S) schedule of reinforcement and drug injections were limited to 20 per session. Cumulative records are shown for day 11 at a buprenorphine dose of 0.005 mg/kg/inj; for day one at a dose of 0.01 mg/kg/inj; and for day one at a dose of 0.05 mg/kg/inj. Each downward deflection of the response pen indicates a buprenorphine injection. Each downward deflection of the baseline pen indicates a secondary reinforcing light stimulus (S+).

B-205 took progressively fewer buprenorphine injections ($p<0.05$, 0.001) as the dose per injection increased. Monkey A-187 was more erratic but took significantly fewer injections at 0.01 than at 0.005 mg/kg/inj ($p<0.01$).

Comparisons of the number of morphine and buprenorphine injections taken over a comparable time period are limited by differences in relative dose. The baseline doses of morphine (0.25 and 0.5 mg/kg/inj) were 25 to 100 times higher than the lowest dose of buprenorphine studied. Even if the analgesic potency of 0.005 and 0.01 mg/kg/inj of buprenorphine is estimated to be approximately equivalent to between 0.2 and 0.4 mg/kg/inj of morphine, baseline doses of morphine were still higher. However, at some doses, three monkeys (A-187, B-205, B-255) took significantly more buprenorphine injections than morphine and one monkey (A-105) took significantly fewer buprenorphine injections (Table 1).

Substitution of Saline for Buprenorphine

After Monkeys B-255 and A-319 had completed sixty sessions of buprenorphine self-administration at the highest dose, 0.10 mg/kg/inj, saline was abruptly substituted for buprenorphine on the same second order schedule requirement. Immediately prior to saline substitution, Monkey A-319 had taken an average of 3.33 (±0.38) mg/kg/day and Monkey B-255 had taken an average of 0.94 (±0.09) mg/kg/day of buprenorphine. Monkey B-255 had self-administered buprenorphine (0.005 to 0.10 mg/kg/inj) for one hundred and five consecutive days (420 sessions). Monkey A-319 had self-administered buprenorphine for thirty consecutive days (120 sessions), at doses of 0.03 and 0.10 mg/kg/inj.

Neither monkey showed any evidence of opiate withdrawal signs when saline was substituted for buprenorphine. Monkeys B-255 and A-319 were observed for 21 and 35 consecutive days respectively. Previously, Monkey A-319's catheter became occluded after forty-five days of buprenorphine self-administration. During the fifteen days immediately prior to catheter occlusion, he had taken 2.55 mg/kg/day (±0.17) of buprenorphine, a dose equivalent to 63 to 102 mg/kg/day of morphine. Subsequently, he was observed for 51 days and there were no signs of opiate withdrawal.

The temporal pattern of extinction of saline maintained

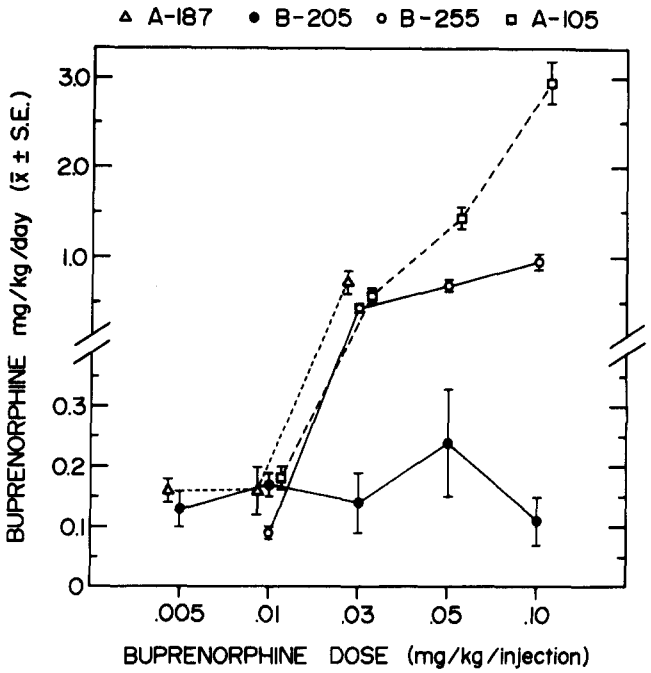

FIG. 3. Buprenorphine self-administration by drug-experienced monkeys as a function of dose per injection. Each data point represents the average dose of buprenorphine (mg/kg/day) (±SE) in sixty sessions over fifteen consecutive days. Buprenorphine was available on a second order FR 3 (VR 16:S) schedule of reinforcement.

responding for each monkey is shown in Fig. 4. The range of buprenorphine injections across all doses per injection studied are shown at the right for comparison. Monkey B-255 continued to self-administer saline at a relatively high rate for the first ten days, then saline injections gradually declined. The number of saline injections taken during the last ten days of saline substitution were significantly fewer than during the first ten days ($p<0.001$). Buprenorphine, at all doses per injection, maintained self-administration behavior significantly ($p<0.01$–0.001) above the last ten days of saline.

Monkey A-319 persisted in an erratic pattern of saline self-administration for twenty-five days before extinction of saline maintained responding was complete. The number of saline injections taken during the last ten days (days 26–35) was significantly fewer ($p<0.01$) than the immediately preceding ten days and fewer ($p<0.001$) than the first ten days of saline substitution. The number of buprenorphine injections self-administered at all dose levels (0.005–0.10 mg/kg/inj) were significantly greater ($p<0.001$) than the number of saline injections during the last ten days of saline self-administration.

Alternation of Saline and Buprenorphine

When saline was substituted for buprenorphine (0.01, 0.03, 0.05 mg/kg/inj) on alternate days, monkeys had difficulty distinguishing saline from buprenorphine even though each was associated with a different discriminative stimulus. There were no significant differences between the number of saline and buprenorphine injections during a single day alternation sequence (Table 2). Since buprenorphine appears to have a long duration of action [8, 13, 14, 29, 30], these data suggested that buprenorphine agonist effects persisted during the twenty-four hours of saline substitution.

When one day of buprenorphine availability was alternated with two days of saline availability only one monkey took significantly more buprenorphine injections than saline ($p<0.01$). When three days of saline availability were alternated with one day of buprenorphine availability, three monkeys took significantly more buprenorphine injections than saline at a moderate dose of 0.03 mg/kg/inj. At a low dose of buprenorphine (0.01 mg/kg/inj) two monkeys took more buprenorphine than saline but the differences were not statistically significant (Table 2).

TABLE 1

DRUG INJECTIONS PER DAY OVER 15 DAYS (60 SESSIONS) (MEAN ± S.E.)

Monkey	Previous Morphine Baseline (0.5 mg/kg/inj)¶	Buprenorphine Dose per Injection (mg/kg) 0.005	0.01	0.03	0.05	0.10
A-187	14.8 (±1.34)	32.93††† (±4.08)	15.73** (±3.56)	24.20† (±4.26)	—	—
B-205§	12.40 (±0.89)	26.47††† (±2.92)	16.93* (±2.40)	2.13***††† (±0.84)	4.80***†† (±1.77)	1.13***††† (±0.38)
A-105¶	34.0 (±2.25)	—	19.27††† (±2.08)	19.27††† (±2.42)	28.87** (±2.56)	29.47** (±2.44)
B-255	11.0 (±0.87)	—	8.73 (±1.48)	15.20***†† (±1.10)	12.33* (±1.13)	9.20 (±0.84)

Significant change from lowest buprenorphine dose: *=$p<0.05$, **=$p<0.01$, ***=$p<0.001$.
Significant difference from morphine baseline: †=$p<0.05$, ††=$p<0.01$, †††=$p<0.001$.
§Cocaine (100 mcg/kg/mg) baseline=43.47 (±2.16) injections per day over 15 days.
¶Morphine was available at 0.25 mg/kg/inj during baseline for A-105.

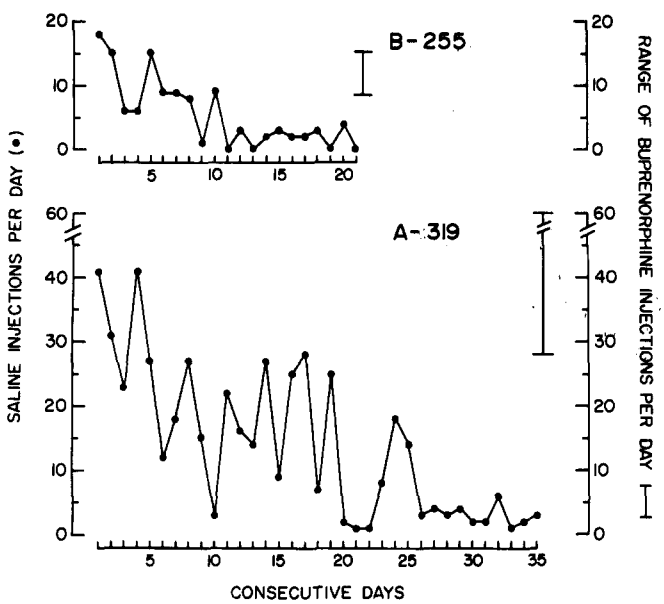

FIG. 4. Saline self-administration after high dose buprenorphine intake (0.10 mg/kg/inj). Each data point is the number of saline injections per day taken on an FR 3 (VR 16:S) schedule of reinforcement. The range of the average number of buprenorphine injections across the dose range studied (0.005–0.10 mg/kg/inj) is shown at the right.

Effects of Buprenorphine on Food Maintained Responding

Table 3 summarizes the effects of buprenorphine on food maintained responding in individual monkeys. When buprenorphine was first introduced, four monkeys increased food intake in comparison to the previous food baseline. The drug-free monkey (A-319) increased food intake significantly ($p<0.001$) in comparison to his immediately preceding food baseline. Two other monkeys also showed significant increases in food intake in comparison to their last food baseline during morphine self-administration ($p<0.001$). Food intake was somewhat variable at higher buprenorphine doses. Pellets earned tended to decline at the highest buprenorphine doses in the four monkeys that self-administered substantial amounts of the drug (A-319, A-187, B-205, and A-105). The decreases in pellets earned in comparison to the lowest dose of buprenorphine studied were significant in several instances.

Effects of Saline Substitution on Food Maintained Responding

The abrupt substitution of saline for a high dose of buprenorphine did not result in measurable weight loss. The average number of food pellets earned during the entire period of saline substitution did not differ significantly from pellets earned at the highest dose of buprenorphine (0.10 mg/kg/inj). During the first fifteen days of saline substitution, Monkey A-319 earned slightly more pellets (mean = 170.67 ± 11.80) than during the last fifteen days on buprenorphine (0.10 mg/kg/inj). Food pellets earned on saline availability days and buprenorphine days during alternation of saline and buprenorphine were not significantly different in either the two day or the three day alternation condition.

DISCUSSION

Reinforcing Properties of Buprenorphine

Buprenorphine appears to be a positive reinforcer in a monkey self-administration model according to several generally accepted criteria. The capacity of buprenorphine to maintain responding leading to its self-administration far exceeds the usual criterion of reinforcement accepted for studies of abuse potential using substitution procedures, i.e., "If more than 50% of the monkeys self-administered more of the test drug than saline at least at one dose, the test drug was considered a positive reinforcer" [16]. In this study, all monkeys exposed to buprenorphine have self-administered it over the dose range studied. We conclude that buprenorphine is an effective positive reinforcer in monkey for the following reasons:

TABLE 2

ALTERNATION OF SALINE AND BUPRENORPHINE INJECTIONS PER DAY (MEAN ± S.E.)

Monkey	Days	Buprenorphine Dose (mg/kg/inj)	Saline	Buprenorphine	
			1 Day Saline vs 1 Day Buprenorphine		
B-205	42	0.01	4.24 (±1.01)	4.72 (±0.69)	NS
B-205	44	0.03	8.00 (±2.88)	5.00 (±1.21)	NS
A-105	10	0.05	22.80 (±3.94)	29.60 (±5.47)	NS
			2 Days Saline vs 1 Day Buprenorphine		
B-255	30	0.03	39.5 (±0.92)	6.00 (±2.01)	NS
A-105	45	0.03	9.23 (±1.79)	23.13 (±5.23)	$p<0.01$
			3 Days Saline vs 1 Day Buprenorphine		
A-319	20	0.01	9.13 (±2.43)	14.20 (±6.33)	NS
A-105	36	0.01	2.59 (±0.88)	5.00 (±2.20)	NS
B-255	36	0.03	7.11 (±1.24)	22.44 (±3.06)	$p<0.001$
A-319	40	0.03	13.53 (±1.85)	26.10 (±3.62)	$p<0.01$
A-105	24	0.03	1.11 (±0.38)	3.67 (±1.36)	$p<0.02$

TABLE 3

BUPRENORPHINE EFFECTS ON FOOD SELF-ADMINISTRATION FOOD PELLETS PER DAY OVER 60 SESSIONS (MEAN ± S.E.)

Monkey	Baseline (60 Sessions)	Buprenorphine Dose per Injection (mg/kg) 0.005	0.01	0.03	0.05	0.10
Drug Naive						
A-319	109.33 (±13.68)	186.27* (± 8.55)	170.8 (±11.12)	180.33 (± 9.91)	117.93† (±14.42)	167.67 (± 9.25)
Morphine History						
A-187	91.47 (± 5.08)	110.33 (±13.01)	115 (±11.01)	49.53† (± 7.04)	—	—
B-205	79.27 (±13.44)	72.27 (± 4.38)	95.87 (± 8.07)	148.47† (±4.75)	134.80† (± 3.94)	133.40† (± 6.44)
A-105	106.27 (± 8.47)	—	171.53* (± 6.45)	126.53‡ (± 6.68)	155.53* (± 8.70)	156.20* (± 7.15)
B-255	103.67 (±19.78)	—	200.13* (± 7.06)	161.67‡ (± 6.72)	146.67‡ (± 5.06)	140.27‡ (± 5.43)

*Different from baseline ($p<0.001$).
†Different from lowest dose (0.005 mg/kg/inj) buprenorphine ($p<0.001$).
‡Different from lowest dose (0.01 mg/kg/inj) buprenorphine ($p<0.001$).

(1) Buprenorphine initiated and maintained self-administration in a naive monkey with no previous drug self-administration history (Figs. 1, 2). Consequently, the effects of buprenorphine, rather than generalization from a previous drug self-administration experience presumably accounted for the behavior observed. Moreover, the naive monkey reached the final schedule requirement for buprenorphine self-administration very rapidly, within 8 sessions over 2 days. In contrast, the acquisition of codeine self-administration by a naive monkey on an FR 30 reinforcement schedule required almost 3 weeks [37]. We also observed that acquisition of morphine self-administration by naive monkeys on a VR 32 schedule of reinforcement required three to four weeks [27]. Rapid acquisition of buprenorphine self-administration on a second-order schedule is consistent with the interpretation that it is highly reinforcing.

(2) Buprenorphine initiated and maintained responding in two morphine experienced monkeys (A-105, B-255) that had been abstinent from all drugs for over 16 months. These monkeys also reached the final second-order schedule response requirement for buprenorphine very rapidly, within 3 and 9 days respectively. Although it might be argued that the rapid resumption of drug self-administration with buprenorphine could be attributed in part to these monkeys' previous drug experience, if buprenorphine were not reinforcing, this behavior should gradually decline. In fact, monkeys continued to self-administer buprenorphine for 75 days over the dose range studied (Fig. 3, Table 1).

(3) Substitution of buprenorphine for either cocaine or morphine in drug experienced monkeys also maintained responding on the same second-order schedule response requirement (Fig. 3). It is not possible to compare the reinforcing efficacy of cocaine, morphine and buprenorphine quantitatively because of the problems in equating doses. Significantly more cocaine injections than either buprenorphine or morphine injections were taken by monkey B-205 (Table 1). Baseline morphine doses per injection were considerably higher than the low doses of buprenorphine, even when the relative analgesic potency of buprenorphine is taken into account. The extent to which the analgesic effects of opiates contribute to their reinforcing properties is unknown. Despite these qualifications, the number of buprenorphine injections were equivalent or significantly higher than morphine injections in three of the four drug experienced monkeys (Table 1). This finding is consistent with clinical reports of equivalent subjective liking scores for morphine and buprenorphine [13,14].

(4) Finally, buprenorphine maintained responding significantly above saline control levels (Fig. 4). The time course of extinction of saline maintained responding on a second-order schedule was between 10 and 26 days. Each monkey maintained low levels of saline injections for 10 days that were significantly less than the number of buprenorphine injections at all doses studied.

(5) Progressive increases in the total dose of buprenorphine self-administered as a function of increases in the dose per injection (Fig. 3) is consistent with the interpretation that buprenorphine is a positive reinforcer. However, some increase in average daily doses would have occurred if buprenorphine injections remained equivalent to those at the lowest dose or declined. Those instances where injections per day increased as a function of increases in dose per injection (Fig. 1, Table 1) do provide additional evidence of buprenorphine's reinforcing properties.

These data are consistent with clinical evaluations of the morphine-like agonistic properties of buprenorphine. These data confirm and extend observations from other laboratories that buprenorphine is a reinforcer in substitution procedures ([37] and Yanagita, personal communication, 1980). Woods [37] reported that buprenorphine (0.001–0.10 mg/kg/inj) maintained operant responding on an FR 30 reinforcement schedule at rates between 0.50 to 1.50 responses

per second. Response rates observed were lower than those for the standard drug, codeine (0.3 mg/kg/inj) which maintained rates of about 2.5 responses per second. Maximum rates of response for buprenorphine were also lower than for morphine, heroin and methadone in the rapid substitution procedure. In Wood's [37] studies rate of response was the primary behavioral measure and absolute doses of drug self-administered were not described. Differences in schedules of reinforcement, monkey drug history, and overall procedures limit more detailed comparisons between these studies.

Reinforcing Efficacy of Other Mixed Agonist-Antagonist Drugs

Profadol and propriam, like buprenorphine, are partial agonists of the morphine type [9] and have also been shown to be reinforcers in a monkey self-administration model [7,16]. Among the drugs usually classified as mixed agonist-antagonists [9], nalbuphine, butorphanol and pentazocine have been shown to maintain responding in a monkey self-administration model using substitution procedures, although evaluations of pentazocine have yielded inconsistent data across laboratories [7]. One exception is the mixed agonist-antagonist nalorphine which has not been shown to be an effective reinforcer in substitution procedures [7,16]. However, in general it appears that the combination of agonist and antagonist properties in the same drug is consistent with that drug maintaining behavior leading to its self-administration.

Behavioral Pharmacology of Buprenorphine

It is interesting to consider the possible behavioral effects of drugs which have both antagonistic and agonistic properties. It is possible that accumulation of the antagonist could block the agonistic effects which presumably contribute to a drug's reinforcing potency. For example, since buprenorphine has been shown to effectively antagonize high doses of morphine for almost 30 hours [13,14], it might seem reasonable to postulate that repeated administration of an agonist-antagonist combination might eventually antagonize the agonistic component. Recent studies of the effects of buprenorphine on EEG and gross behavior in rat indicate that duration of drug-induced "stupor" increased up to a dose of 1 mg/kg and decreased at higher doses of 10 and 30 mg/kg [19]. These data were interpreted as evidence that high doses of buprenorphine antagonize the agonistic effects evident at lower doses [19]. The lack of sedation observed in the present study (Fig. 2) reflects the lower dose range studied, as well as possible species differences. Acute administration of 0.03, 0.10, 0.30, 1.0 and 3.0 mg/kg buprenorphine to drug naive rhesus monkeys resulted in a slight behavioral depression which was not dose related [2]. Rance [29] has reviewed evidence from animal studies that buprenorphine dose-response curves plateau at less than maximal effect, i.e. a ceiling effect. This characteristic is consistent with the classification of buprenorphine as a partial agonist of the morphine type [23].

Data reported here suggest that the agonistic component of buprenorphine remains salient even under conditions of repeated administration over a dose range of 0.005 to 0.10 mg/kg/inj. In man, the maximal euphoric effects of buprenorphine were seen in a dose range of 0.8 to 1.2 mg [13,14] which is equivalent to 0.0114 to 0.0171 mg/kg for a 70 kg man. This dose (0.01 mg/kg/inj) is at the lower end of the dose range shown to be reinforcing in rhesus monkey (Figs. 1,3).

When saline and buprenorphine were available on alternate days, persistence of buprenorphine's agonist effects appeared to compromise the monkeys' ability to discriminate saline from buprenorphine (Table 2). This inference is consistent with clinical data that miosis persists for 72 hours following a single dose of buprenorphine and subjective and behavioral effects persisted for two to three days [13,14]. When a 72 hour saline period was interposed between successive doses of buprenorphine, monkeys consistently took more buprenorphine than saline. At moderate buprenorphine doses (0.03 mg/kg/inj) each monkey took significantly more drug than saline (Table 2).

Buprenorphine is a highly lipophilic compound [29] and has been shown to dissociate slowly from receptor binding sites in both in vitro [8] and in vivo studies [30]. The dissociation rate is unaffected by sodium ion concentration which suggests that buprenorphine acts primarily as an antagonist in a binding assay [8]. Rance and Dickens [30] report that administration of the narcotic antagonist, diprenorphine, concurrently with or 15 minutes before or after buprenorphine administration significantly reduced the level of stereospecific binding of buprenorphine. Rance [29] concludes that the partial agonist profile and buprenorphine's slow receptor kinetics are compatible with its prolonged analgesic efficacy.

Absence of Abstinence Signs

The absence of discernible withdrawal signs or changes in food self-administration or weight suggest that prolonged buprenorphine self-administration at very high doses does not lead to the development of physical dependence in rhesus monkey. These data are consistent with previous observations of buprenorphine maintained monkeys exposed to antagonist challenge [2,34]. Buprenorphine also does not produce significant physical dependence in man [13, 14, 26]. Only a mild abstinence syndrome was observed three days after abrupt discontinuation of buprenorphine in former heroin addicts, and more marked symptoms appeared on the 13th and 14th day after buprenorphine withdrawal. There are some, as yet unexplained species differences in the capacity of buprenorphine to induce physical dependence (cf. [23]). Buprenorphine abstinence signs have not been reported in monkeys, mice or rats, however some mild abstinence signs have been seen in man and dog [2, 3, 23, 29].

Conclusions and Implications for Abuse Potential

Buprenorphine is a positive reinforcer in rhesus monkey and maintains behavior leading to its administration on second-order schedules of reinforcement. It appears comparable to morphine in reinforcing efficacy. These findings are concordant with clinical studies of heroin addicts reactions to buprenorphine, i.e., addicts like buprenorphine and identify it as an opiate [13,14]. Parallel findings between clinical studies and animal drug self-administration studies have two major implications:

(1) First, these data attest to the validity of the animal drug self-administration model. It has been generally agreed that the monkey self-administration model can be a sensitive predictor of human drug abuse potential, insofar as most drugs abused by man are self-administered by monkeys [7, 15, 16, 17, 32, 35]. Griffiths and Balster [6] have compared clinical and animal studies of opiate effects and report a high

concordance between subjective reports and animal drug self-administration data.

(2) A second implication of these findings is that the concordance of addicts reports of "liking" buprenorphine and its reinforcing properties in monkey suggest that buprenorphine, like morphine and methadone, may have some abuse potential in man. The agonistic properties of a maintenance dose of buprenorphine (8 mg/day) appear to be approximately equivalent to those of 40–60 mg of methadone [13,14]. Since methadone has been used illicitly, presumably for its mood elevating effects, it is entirely possible that buprenorphine would also be subject to some abuse. Although the available information does not permit estimation of the relative abuse potential of buprenorphine and methadone, it appears that abuse of buprenorphine would have less serious medical consequences than the illicit deployment of methadone [21]. Buprenorphine does not induce significant physical dependence and its antagonistic properties virtually preclude over-dose deaths [1].

The abuse potential of any drug must be balanced against its safety and efficacy relative to other available compounds. Buprenorphine maintenance effectively reduces heroin self-administration by heroin addicts [26] and it appears to offer some advantages as an analgesic [9]. Moreover, it is entirely possible that drugs which do not have an agonistic component, and consequently some abuse potential, may not be widely effective in the treatment of heroin addiction. For example, although the narcotic antagonist naltrexone effectively blocks opiate effects [24,28] it has been quite difficult to retain heroin addicts in naltrexone treatment programs [18,31]. In our opinion, the safety and potential therapeutic benefits of buprenorphine probably outweigh the possible risks associated with its abuse potential.

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