Pharmacology Biochemistry & Behavior, Vol. 10, pp. 407–414. Printed in the U.S.A.

Interactions of Acetylmethadol or Methadone with Other Drugs in Rhesus Monkeys[1]

DAVID A. DOWNS

Department of Pharmacology, Warner-Lambert/Parke-Davis, Pharmaceutical Research Division
2800 Plymouth Road, Ann Arbor, MI 48105

(Received 18 January 1978)

DOWNS, D. A. *Interactions of acetylmethadol or methadone with other drugs in rhesus monkeys.* PHARMAC. BIOCHEM. BEHAV. 10(3) 407–414, 1979.—Behavioral effects and blood or plasma levels of d-amphetamine, ethanol, cocaine, and diazepam were examined in rhesus monkeys treated chronically with α-*l*-acetylmethadol (LAAM), methadone, or vehicle. Chronic treatment with the opiates failed to alter blood or plasma levels and behavioral effects of d-amphetamine or ethanol. LAAM-maintained monkeys were somewhat less sensitive to rate-decreasing effects of cocaine on schedule-controlled responding, but cocaine plasma levels and half-lives generally did not differ across the chronic treatment conditions. Behavioral depression after diazepam was prolonged substantially in LAAM- and methadone-maintained monkeys, but blood levels of diazepam and metabolites were not increased or prolonged in those animals. Naloxone partially antagonized the residual depression in LAAM- and methadone-maintained monkeys 24 hr after diazepam, but had no effect on the weaker residual depression in vehicle-maintained animals. Thus, diazepam appeared to interfere with the metabolic inactivation of the opiates. One LAAM-maintained monkey showed recurrent episodes of LAAM overdose and eventually died during the course of the study.

d-Amphetamine α-*l*-Acetylmethadol (LAAM) Methadone Operant behavior Diazepam Ethanol Blood levels Cocaine

RECENT studies have demonstrated that chronic treatment with opiate agonists can cause increases in sensitivities to non-opiate drugs [8, 9, 18]. For example, Lal and his associates (see [15]) have shown that aggressive behavior caused by amphetamine or apomorphine is enhanced after chronic treatment with morphine in rodents. Eibergen and Carlson [8] have reported the emergence of dyskinetic effects of methamphetamine in monkeys after chronic treatment with methadone. Enhanced behavioral effects of narcotic antagonists also have been reported in narcotic-dependent or post-dependent monkeys. Downs and Woods [5] found that morphine-dependent monkeys would press a lever to terminate infusions of naloxone at concentrations that were 1000-fold lower than in non-dependent monkeys. Moreover, sensitivity to narcotic antagonists may persist for several months after the termination of chronic narcotic administration [10].

Decreased sensitivity to other drugs also has been reported in narcotic-treated animals. For example, Puri and Lal [18] found that the catalepsy usually produced by haloperidol in rodents was diminished by prior treatment with morphine. Thus, treatment with narcotics can result in quantitative and qualitative changes in the effects of other drugs.

The purpose of the present study was to examine potential interactions of some commonly abused drugs in combination with methadone and α-*l*-acetylmethadol (LAAM), two compounds which currently are being administered on a chronic basis in humans. Blood or plasma levels and behavioral effects of d-amphetamine, ethanol, cocaine, and diazepam were compared across groups of rhesus monkeys chronically treated with LAAM, methadone, or vehicle.

METHOD

Animals were 13 male rhesus monkeys (Macaca mulatta) weighing from 3.9 to 8.3 kg at the start of the study. All monkeys previously had been exposed to acute doses of various drugs. No drugs had been given for about one month prior to the start of the present experiment. The monkeys were maintained at approximately 80% of their free-feeding weights by partial food deprivation. All animals had periodic access to water in their individual home cages. Each monkey received 1/4 fresh orange or apple daily. Standard diet consisted of Purina monkey biscuits which were fed once daily after experimental sessions or before 9:00 a.m. on weekends.

Behavioral experiments were conducted while the monkeys were seated in stainless steel restraint chairs within fiberboard cubicles. Each cubicle contained a wall-mounted intelligence panel with two response levers, a food-pellet

[1]This research was supported in part by NIDA Contract HSM 42-72-167, Project Officer: Dr. Monique C. Braude. The assistance of Larry E. Miller, Donald J. Thomas, Gay H. Humphrey, James N. Wiley, Thomas E. Robinson, and Stephen E. Harrigan is gratefully acknowledged.

receptacle, and an array of colored lamps. The chambers were ventilated by exhaust fans while continuous white noise was delivered through 10 cm speakers to help mask extraneous sounds. Behavioral testing was controlled by solid state programming modules; responses were recorded on digital counters and on cumulative recorders.

Lever pressing was maintained under a chain DRO30 FR30 schedule of food presentation as described by Downs and Woods [4]. Under this schedule, thirty lever presses in the presence of a green light resulted in the delivery of a single 0.3 g banana flavored food pellet (FR30). Upon delivery of each food pellet or after 60 sec of green light illumination, a red light was illuminated. In the presence of the red light, each response delayed the onset of the green light by 30 sec (DRO30). When 30 sec elapsed without a response in the presence of the red light, the green light was reinstated. A white light was illuminated over the food-pellet receptacle for the duration of each session. Each session terminated after the fiftieth presentation of the red light. Sessions, which usually lasted from about 40 to 90 min, were conducted daily except weekends. Gross behavior was observed approximately hourly from 8:00 a.m. until 4:30 p.m. on weekdays and any unusual behavioral effects were noted.

Behavioral testing was not conducted on days when blood or plasma levels of drugs were determined. Venous blood samples were obtained via polyethylene catheters temporarily inserted in the saphenous veins of chair-restrained monkeys or by repeated cephalic or saphenous venipunctures. Plasma concentrations of d-amphetamine were determined by gas chromatography with electron capture detection as reported by Anggard *et al.* [1] except that chlorphentermine was used as the internal standard and the extracting solvent was a mixture of 75% hexane and 25% isooctane. Blood ethanol concentrations were determined by gas chromatography as reported by Jain [12] except that a glass column packed with Porapack A was used, acetone served as the internal standard, and a 100° oven temperature was maintained throughout. Plasma concentrations of cocaine were determined by gas chromatography as described by Jatlow and Bailey [13] with minor modifications except that a flame ionization detector was used rather than a selective nitrogen detector. Diazepam and metabolite concentrations in blood were determined by gas chromatography as described by Baselt *et al.* [2] with minor modifications.

For behavioral testing, all drugs given in combination with LAAM, methadone, or vehicle were administered orally by gavage except cocaine which was administered intramuscularly. For blood or plasma level determinations, all drugs were given orally by gavage except cocaine which was administered intravenously. Methadone hydrochloride, LAAM hydrochloride, and d-amphetamine sulfate were dissolved in deionized water for oral administration. Cocaine hydrochloride was dissolved in 0.9% sterile saline for parenteral administration. Doses were calculated in terms of the salts. Ethanol was prepared in deionized water at concentrations less than 25% v/v. Diazepam was suspended in 1% methylcellulose. All monkeys were fasted for at least 18 hr prior to drug administration.

Chronic dosing with LAAM, methadone, and vehicle was initiated about 13 weeks prior to the start of drug interaction studies. During that time, repeated determinations of blood chemistry, hematology, and liver function tests were conducted. The results of those determinations have been reported elsewhere [7].

Animals were assigned to three groups of four monkeys per group. Group 1 received 2 mg/kg of LAAM every 48 hr. Group 2 received 1 mg/kg of methadone every 24 hr. Group 3 received only deionized water every 24 hr. During chronic dosing, methadone, LAAM, and vehicle were administered routinely in sugar cubes which were consumed readily by all monkeys. When drug interactions were being tested, drugs were administered in combination with LAAM, methadone, or vehicle by gavage or by injection as described earlier.

Drugs were administered 30 min prior to the start of behavioral sessions except as noted in the text or before noon on weekends. Naloxone hydrochloride (50 μg/kg) was administered intramuscularly after about 12 weeks of chronic treatment and thereafter approximately every six weeks to assess the severity of precipitated abstinence. On those oc-

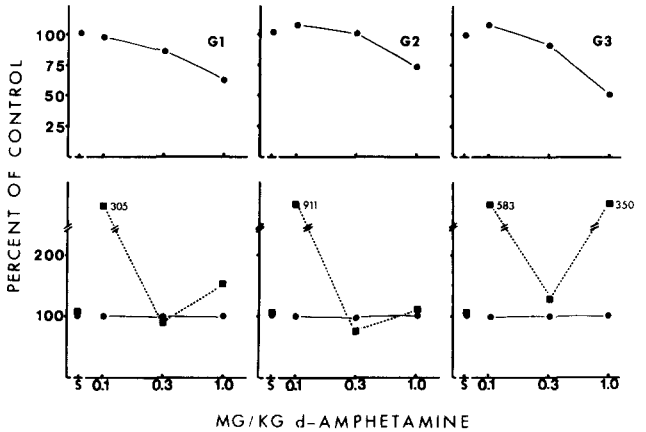

FIG. 1. Effects of orally administered d-amphetamine on responding under a chain DRO30 FR30 schedule of food presentation in rhesus monkeys treated chronically with LAAM (G1), methadone (G2), or vehicle (G3). The upper graphs show the effects on reponse rates in FR30 components. The lower graphs show effects on total DRO time (solid lines) and on response rates (broken lines) in DRO30 components. Each point represents the mean of two observations in each of four monkeys per group. All data for drug effects are expressed as percentages of control values from the preceding session.

TABLE 1

CONTROL RESPONSE RATES UNDER CHAIN DR030 FR30 SCHEDULE OF FOOD PRESENTATION PRIOR TO CHRONIC DRUG ADMINISTRATION*

Chronic Treatment Condition	Fixed Ratio	DRO	
	Resp/Sec	Resp/Sec	Total Sec
G1 (N=4) LAAM	2.92 ± 0.17	0.02 ± 0.003	1541 ± 1.81
G2 (N=4) Methadone	3.66 ± 0.16	0.03 ± 0.003	1550 ± 3.99
G3 (N=4) Vehicle	3.68 ± 0.17	0.03 ± 0.006	1562 ± 9.40

*Each value represents the Mean ± 1 SE for the last 5 sessions prior to chronic dosing with LAAM (G1), methadone (G2), or vehicle (G3).

casions, naloxone was given 15 min prior to the start of behavioral sessions.

All data concerning lever-pressing rates are expressed as drug/control percentages. Control values were obtained from the individual sessions immediately preceding those in which drugs were administered. One-way or repeated-measures analysis of variance was used for statistical comparisons.

RESULTS

The rates and patterns of lever-pressing under the chain DRO30 FR30 schedule of food presentation prior to chronic drug administration (Table 1) were similar to those reported by Downs and Woods [4] and by Downs and Braude [6] under the same schedule in rhesus monkeys. During the first week of chronic LAAM administration, one monkey (6719) began to show substantial decreases in daily response rates in FR30 components. This same monkey showed the most pronounced gross behavioral effects of LAAM including ataxia, staring, and stupor. These effects usually became evident within two hr after dosing and lasted for four or more hr. In the remaining three LAAM-treated monkeys there were no noteworthy changes in daily response rates and only minimal gross behavioral effects such as staring and mild ataxia. Over the first two weeks of chronic LAAM administration Monkey 6719 showed a gradual recovery of FR30 response rates to pretreatment control levels. Responding under the chain schedule then generally remained stable over the remaining weeks of chronic treatment before beginning the interaction studies. A major exception, however, was that recurrent episodes of gross behavioral depression occurred in the third, seventh, and eighth weeks of chronic LAAM administration in Monkey 6719. During these episodes, Monkey 6719 responded at low rates or not at all in the operant chamber for one or two sessions at a time. The periods of gross depression each lasted for a few days, after which gross behavior and lever pressing returned to normal.

Chronic methadone and vehicle administration produced no observable effects on gross behavior or on lever pressing rates.

Naloxone (50 μg/kg) precipitated signs of at least mild abstinence (piloerection, vocalization, irritability) in all monkeys after about three months of chronic treatment with LAAM and methadone, while no effects of naloxone were apparent in the vehicle-treated monkeys. Although mild abstinence signs were evident when naloxone was administered 15 min prior to operant sessions, there were no effects on the food-maintained responding. Subsequent injections of 50 μg/kg of naloxone at approximately six-week intervals throughout the study produced effects which were similar to those described above.

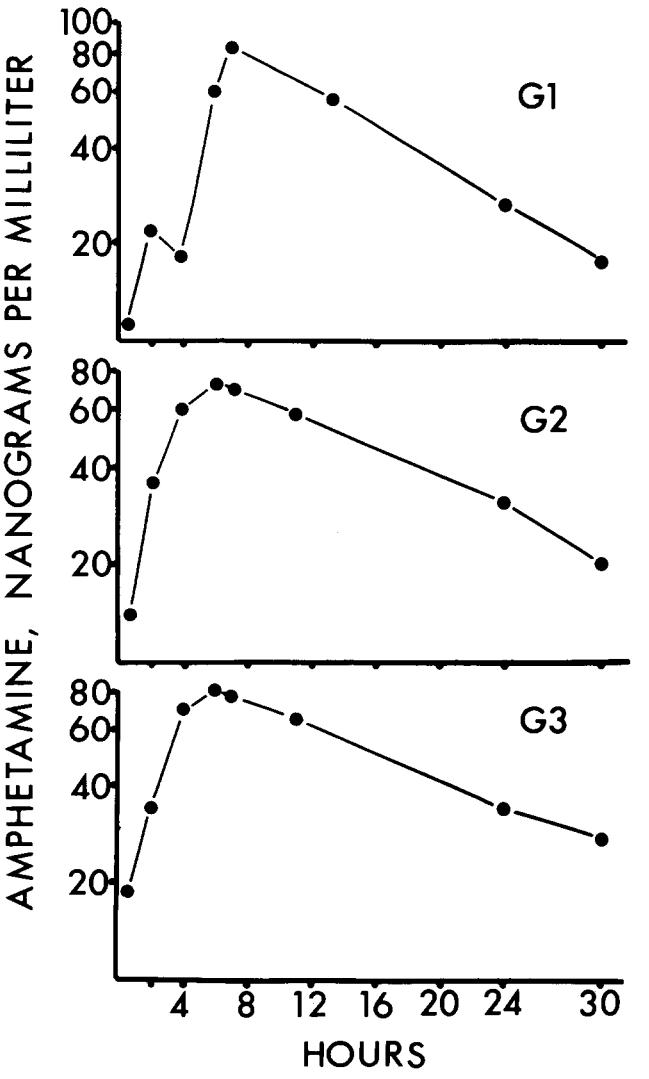

FIG. 2. Plasma concentrations of d-amphetamine over time following oral administration of 1.0 mg/kg of d-amphetamine sulfate in rhesus monkeys treated chronically with LAAM (G1), methadone (G2), or vehicle (G3). Each point represents the mean of a single observation in each of four monkeys per group. d-Amphetamine concentrations were determined by electron capture gas chromatography.

Effects of d-Amphetamine

d-Amphetamine caused dose-related decreases in response rates in FR30 components which were comparable in LAAM-, methadone-, and vehicle-treated monkeys (Fig. 1). However, d-amphetamine failed to increase total DRO time at any dose. There were substantial increases in percentage scores for response rates in DRO30 components at some doses, but these did not appear to be clearly related to dose. Examination of cumulative response records revealed that increases in DRO30 response rates generally were due to extra responses which occurred at the very beginning of DRO components as continuations of the preceding FR30 units. This observation was confirmed by the absence of increases in total DRO time which would have occurred if responding had been distributed throughout individual DRO components. It should be noted also that, because DRO30 control response rates were very low (Table 1), small increases in absolute rates gave rise to large increases when drug effects were expressed as percentages of control values.

Plasma concentrations of d-amphetamine over time following 1.0 mg/kg also were comparable in all three groups regardless of chronic treatment condition (Fig. 2). There was no significant difference ($p>0.05$) between groups in plasma half-life or area under the plasma concentration curve for d-amphetamine (Table 2).

The highest dose, 1.0 mg/kg, caused mild agitation and/or

TABLE 2

DRUG ELIMINATION HALF-LIFE ($t_{1/2}$), AREA UNDER BLOOD OR PLASMA DRUG CONCENTRATION CURVE (AUC), AND ETHANOL DISAPPEARANCE RATE IN RHESUS MONKEYS TREATED CHRONICALLY WITH LAAM (G1), METHADONE (G2), OR VEHICLE (G3)*

d-Amphetamine	$t_{1/2}$ (hr)	AUC (ng hr/ml)
G1	11.02	1210.5
G2	13.53	1313.3
G3	16.13	1494.5
Ethanol	Disappearance (mg/100 ml/hr)	
G1	13.8	
G2	15.1	
G3	14.7	
Cocaine	$t_{1/2}$ (min)	AUC (ng hr/ml)
G1	37.9	24225
G2	37.1	15675
G3	37.9	17650
Diazepam	AUC (ng hr/ml)	
G1	655.5†	
G2	2669.3	
G3	3068.7	
Desmethyldiazepam	AUC (μg hr/ml)	
G1	646.6	
G2	612.0	
G3	652.0	

*Values were calculated on the basis of group mean data.
†$p<0.05$.

repetitive lip smacking in some monkeys, but there were no noteworthy differences in the gross behavioral effects of d-amphetamine across the three groups.

Monkey 6719 died during the six-week period of testing with d-amphetamine. All indications suggested a recurrence of LAAM-induced depression as on previous occasions in the third, seventh, and eighth weeks of chronic dosing in this monkey. Necropsy revealed no gross pathology; histopathological examination failed to reveal pathology which could be attributed to chronic LAAM or acute amphetamine administration. Because of the death of Monkey 6719, ethanol and cocaine were tested in only three LAAM-maintained monkeys while a fourth monkey was being prepared (12 weeks of chronic LAAM administration) as a replacement in Group 1.

Effects of Ethanol

Like d-amphetamine, ethanol generally caused dose-related decreases in FR30 components which were comparable in LAAM-, methadone-, and vehicle-treated monkeys (Fig. 3). Unlike d-amphetamine, however, ethanol substantially prolonged total DRO time at doses of 3.0 or 4.0 g/kg in all groups in addition to increasing response rates in DRO components. Inspection of cumulative response records revealed that increases in DRO30 response rates often were due to erratic responding throughout DRO components. Dextrose solution, isocaloric to 4.0 g/kg of ethanol, had negligible effects on responding.

Blood-ethanol concentrations (Fig. 4) and disappearance rates (Table 2) following 3.0 g/kg also were comparable in all three groups of monkeys.

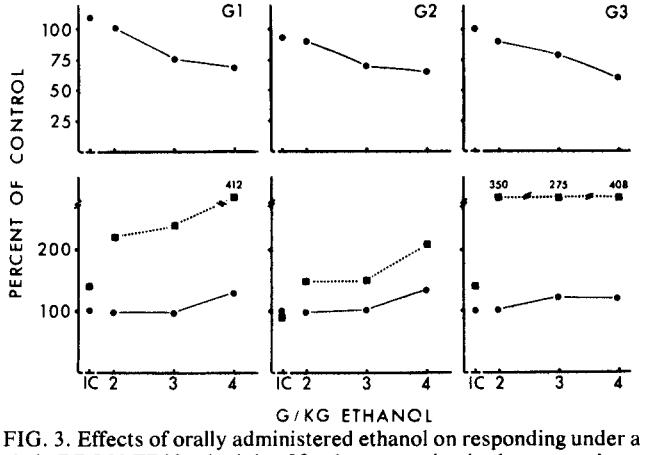

FIG. 3. Effects of orally administered ethanol on responding under a chain DRO30 FR30 schedule of food presentation in rhesus monkeys treated chronically with LAAM (G1), methadone (G2), or vehicle (G3). Other details as in Fig. 1 except that only three monkeys were used in Group 1.

Although 4.0 g/kg of ethanol caused only modest decreases in FR30 response rates, all of the monkeys were markedly ataxic when released from their restraint chairs immediately after operant sessions. Most of the animals became stuporous shortly after being placed in their home cages. These gross behavioral effects lasted for several hours and were about the same regardless of chronic treatment condition.

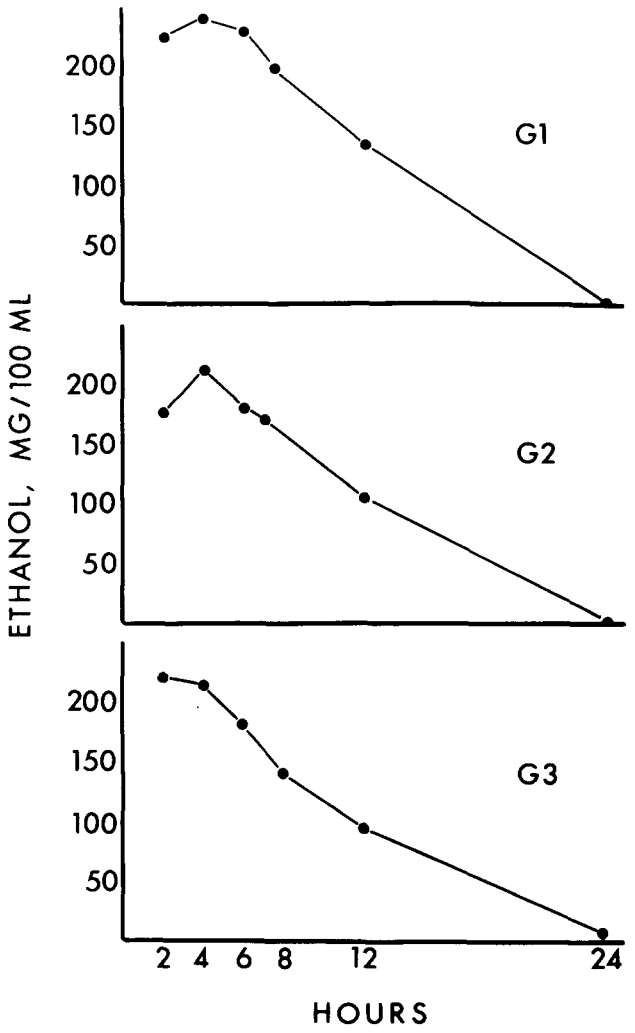

FIG. 4. Blood ethanol concentrations over time following oral administration of 3.0 g/kg in rhesus monkeys treated chronically with LAAM (G1), methadone (G2), or vehicle (G3). Ethanol concentrations were determined by gas chromatography. Other details as in Fig. 2 except that only three monkeys were used in Group 1.

Effects of Cocaine

Intramuscular injections of cocaine caused slight increases in FR30 responding at 0.1 mg/kg in all three groups of animals and at 0.3 mg/kg in the LAAM-treated monkeys (Fig. 5). Dose-related decreases in FR30 responding were obtained at the two higher doses in the methadone- and vehicle-maintained groups, while only the highest cocaine dose (1.0 mg/kg) caused a decrease in responding in FR30 components in the LAAM-maintained animals. Thus, the cocaine dose-effect curve appeared to be shifted to the right in the LAAM-treated monkeys although the difference was not statistically significant ($p>0.05$). Like d-amphetamine, cocaine failed to increase total DRO time at any dose despite occasionally large increases in DRO response rates (Fig. 5). However, such DRO rate increases were not clearly related to cocaine dose. Inspection of cumulative response records revealed that DRO rate increases with cocaine, like d-amphetamine, were due to brief bursts of extra responses after the ends of preceding FR30 components.

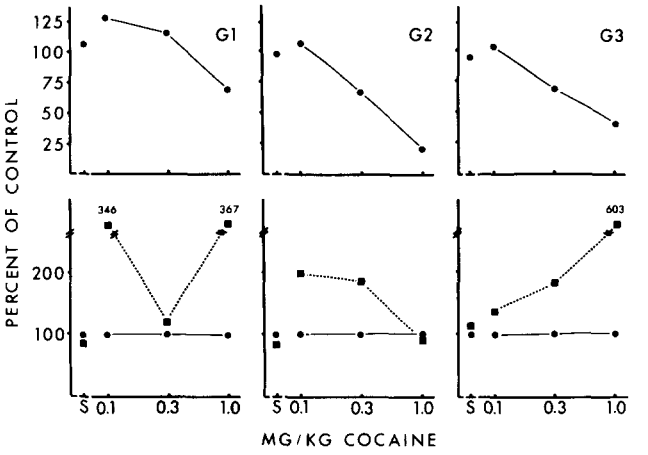

FIG. 5. Effects of intramuscularly administered cocaine on responding under a chain DRO30 FR30 schedule of food presentation in rhesus monkeys treated chronically with LAAM (G1), methadone (G2), or vehicle (G3). Other details as in Fig. 1 except that only three monkeys were used in Group 1.

Plasma concentrations of cocaine over time following intravenous injection of 1.0 mg/kg were similar in all three groups through 120 minutes (Fig. 6). Plasma half-lives, calculated on the basis of data from 10 through 120 min, were similar ($p>0.05$) across all groups (Table 2). In contrast, detectable plasma levels of cocaine were still present at 180 min in the LAAM- and methadone-treated groups, but not in the vehicle-maintained animals. Nevertheless, there was no significant difference ($p>0.05$) across groups in area under the plasma concentration curve (Table 2).

Gross behavioral effects of cocaine were about the same in all groups regardless of chronic treatment condition. At the highest dose, 1.0 mg/kg (IM), pronounced agitation was apparent for about an hour after dosing; most monkeys struggled in their restraint chairs and appeared to be more apprehensive and irritable than usual.

Effects of Diazepam

Diazepam caused dose-related decreases in FR30 response rates which were comparable across all groups at the usual pretreatment interval of 30 min (Fig. 7). Increases in DRO30 response rates were obtained at the higher doses (10 or 30 mg/kg) in all groups and at the lowest dose (3 mg/kg) in the vehicle-treated monkeys. As with ethanol, increases in total DRO time were obtained with diazepam at 30 mg/kg in all three groups. Although effects of all doses of diazepam on operant responding were about equivalent across groups with the 30 min pretreatment interval, the effects of 30 mg/kg were greater after four-hr pretreatment intervals in the LAAM- and methadone-maintained groups than in the vehicle-maintained group (Fig. 8).

Diazepam caused pronounced gross behavioral depression in all monkeys beginning about two hr after 30 mg/kg and lasting for at least 24 hr. However, the severity and duration of this effect clearly was greatest in the LAAM-treated animals, which remained ataxic for several days after 30 mg/kg of diazepam. The persistence of gross behavioral depression corresponded with suppression of food-maintained lever pressing following the highest dose of diazepam. For example, in successive sessions after admin-

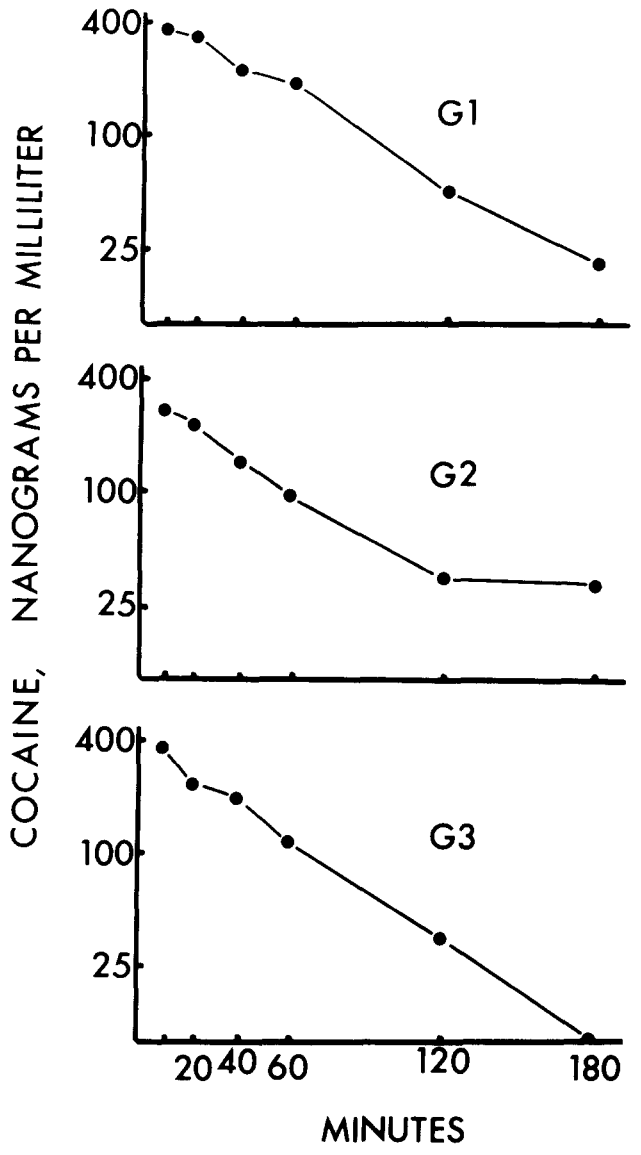

FIG. 6. Plasma concentrations of cocaine over time following intravenous administration of 1.0 mg/kg of cocaine hydrochloride in rhesus monkeys treated chronically with LAAM (G1), methadone (G2), or vehicle (G3). Cocaine concentrations were determined by flame ionization gas chromatography. Other details as in Fig. 2 except that only three monkeys were used in Group 1.

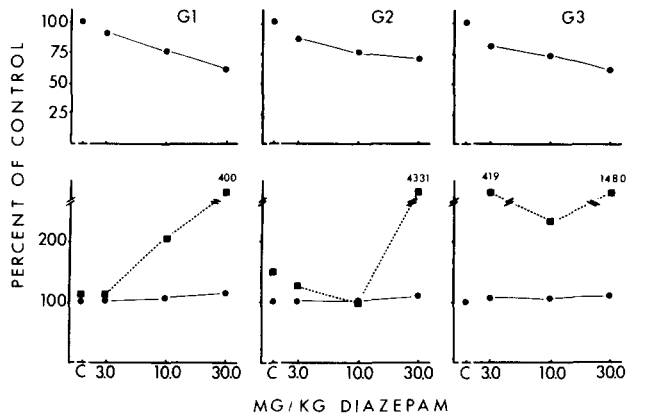

FIG. 7. Effects of orally administered diazepam on responding under a chain DRO30 FR30 schedule of food presentation in rhesus monkeys treated chronically with LAAM (G1), methadone (G2), or vehicle (G3). Other details as in Fig. 1.

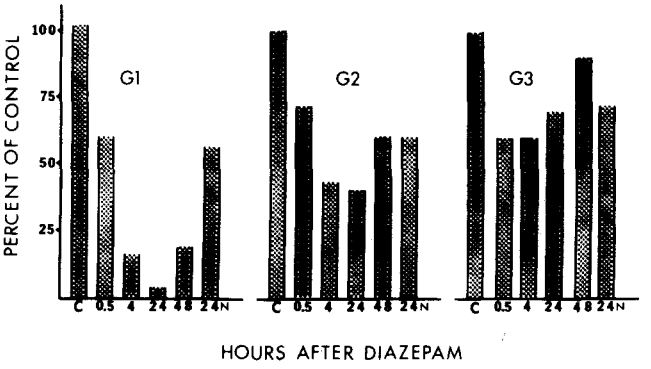

FIG. 8. Recovery of responding in FR30 components of a chain DRO30 FR30 schedule of food presentation following oral administration of 30.0 mg/kg of diazepam. The hours which are indicated represent the interval between diazepam administration and the start of operant sessions. The last bar in each group represents the effects of naloxone (50.0 μg/kg IM) administered 15 min prior to a session which was preceded by approximately 24 hr with an oral dose of 30.0 mg/kg of diazepam. Each bar represents the mean of a single observation in each of four monkeys per group except at 0.5 hr, which was based on two observations in each of four monkeys per group. Chronic treatment conditions were as described in Fig. 1.

istration of 30 mg/kg of diazepam, recovery of FR30 responding to control levels occurred within 48 hr in the vehicle-maintained animals, while respectively longer disruption of lever pressing was obtained in the methadone- and LAAM-treated monkeys (Fig. 8). However, when naloxone (50 μg/kg) was injected intramuscularly 24 hr after the high dose of diazepam (i.e. 15 min prior to a session which was started 24 hr after 30 mg/kg of diazepam), there were no differences in FR30 response rates across groups. Thus, naloxone antagonized the excess behavioral depression in the LAAM- and methadone-maintained monkeys, but did not alter the effect of diazepam in the vehicle-maintained animals (Fig. 8).

Blood concentrations of diazepam reached a lower peak and declined more rapidly in the LAAM-treated animals compared to the methadone- and vehicle-treated groups (Fig. 9). Area under the diazepam blood concentration curve (Table 2) was significantly less ($p<0.05$) for the LAAM-treated monkeys than for the other two groups. Elimination half-lives were not calculated for diazepam or desmethyldiazepam because of difficulty in discerning log-linear components of the plasma concentration curves. In contrast, levels of the active metabolite desmethyldiazepam were comparable and there was no significant difference ($p>0.05$) in area under the curve (Table 2) across the three groups. Attempts were made to evaluate levels of oxazepam in blood, but the remaining sample volumes were too small in most cases to allow complete comparisons across groups. Nevertheless, at the few sample times where data from at least three monkeys per group could be compared,

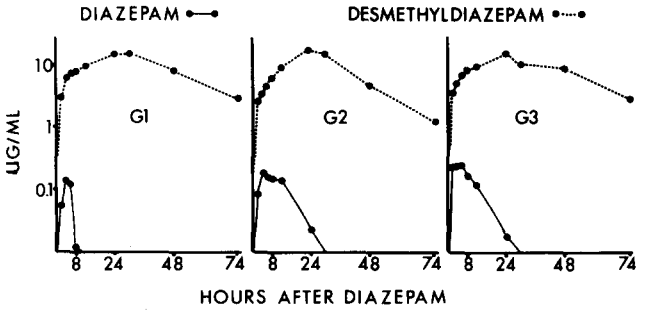

FIG. 9. Blood concentrations of diazepam (solid lines) and desmethyldiazepam (broken lines) over time following oral diazepam administration (30.0 mg/kg) in rhesus monkeys treated chronically with LAAM (G1), methadone (G2), or vehicle (G3). Drug concentrations were determined by flame ionization gas chromatography. Other details as in Fig. 2.

oxazepam concentrations did not differ significantly ($p>0.05$) across treatment conditions.

DISCUSSION

Behavioral effects and plasma concentrations of d-amphetamine in the present study were similar to those reported by Downs and Braude [6]. In general, d-amphetamine caused dose-related decreases in response rates in FR30 components. Although amphetamine also can increase some low rates of schedule-controlled responding, such increases have not been consistent under the chain DRO30 FR30 schedule of food presentation (present study; [6]). In the present study, DRO rate increases after d-amphetamine were due to "spillover" of responses from preceding FR30 components into DRO30 components. Because of the very low control rates in DRO components, these extra responses sometimes caused large increases when expressed as percentages of control rates, but did not appreciably prolong total DRO time.

d-Amphetamine's behavioral effects were not altered as a consequence of chronic treatment with LAAM and methadone. Lucot *et al.* [16] observed a similar lack of change in behavioral effects of d-amphetamine during chronic treatment with morphine in rats. The lack of change in sensitivity to d-amphetamine during chronic treatment with narcotics contrasts markedly with the enhanced effects of amphetamines which have been reported in animals after withdrawal from chronic treatment with narcotics [8, 14, 15].

Behavioral effects of ethanol also were similar to those reported by Downs and Braude [6]. In general, ethanol caused dose-related decreases in FR30 response rates, while DRO30 response rates and total DRO times were increased. These effects were comparable in monkeys treated chronically with LAAM, methadone, and vehicle. Although ethanol disappearance rates were somewhat lower in the present experiment than in that of Downs and Braude [6], there were no significant differences between groups due to chronic treatment with LAAM, methadone, or vehicle.

Effects of cocaine in the present study were comparable to those reported by Woods and Tessel [21] under similar behavioral conditions in rhesus monkeys. Cocaine, like d-amphetamine, did not increase total DRO time at any dose despite occasionally large increases in percent of control values for DRO response rates. Monkeys treated chronically with LAAM apparently were less sensitive to the FR30 response rate decreasing effects of cocaine compared to methadone- and vehicle-treated monkeys. Nevertheless, the FR30 response rate differences between vehicle-treated and narcotic-treated groups were not significant and plasma levels of cocaine were similar in all groups regardless of chronic treatment condition.

A clearer interaction was present with diazepam in the LAAM-maintained animals. That is, behavioral depression after a high dose of diazepam was prolonged substantially in the LAAM-treated monkeys. Similar, but less pronounced effects were obtained with diazepam in the methadone-maintained monkeys.

Two lines of evidence suggest that diazepam prolongs the effects of LAAM and methadone rather than vice-versa. First, blood concentrations of diazepam and desmethyldiazepam were not increased or prolonged in the LAAM- or methadone-maintained monkeys. In fact, diazepam concentrations reached lower peaks and declined more rapidly in the LAAM-treated group than in the two other groups. Second, naloxone antagonized the excess depression 24 hr after diazepam in the narcotic-treated groups but had no effect on the residual depression in the vehicle-maintained group. These results are consistent with previous findings that diazepam can prolong the effects of methadone in rats by interfering with methadone metabolism [20].

Such interactions may be of significance for humans in LAAM or methadone maintenance treatment programs, since the long durations of action of diazepam, LAAM, and methadone could present serious hazards due to CNS depression, narcotic overdose, or interactions with still other drugs.

Doses of LAAM and methadone in the present study were chosen in the hope of allowing long-term maintenance without cumulative toxic effects. Nevertheless, one LAAM-treated monkey showed recurrent episodes of LAAM overdose and eventually died during the course of the experiment. Similar results have been reported by Misra *et al.* [17] under comparable treatment conditions in rhesus monkeys. Methadone also can cause sudden episodes of depression during chronic oral administration of high doses in monkeys, where large increases in plasma levels of methadone were found to be associated with the sudden behavioral manifestations of methadone toxicity [19]. Moreover, Henderson *et al.* [11] found in humans that two out of eleven patients receiving chronic LAAM experienced overdosing symptoms; plasma levels of LAAM metabolites in those two patients were significantly higher than in the other patients. Since LAAM plasma levels were not monitored in the present study or that of Misra *et al.* [17], it is not known if there were similar spontaneous increases in LAAM or LAAM metabolite plasma levels in the monkeys which showed LAAM toxicity.

The maintenance doses of LAAM and methadone in the present study were pharmacologically active in that mild abstinence could be elicited when naloxone was administered. However, the doses of LAAM and methadone should not be considered to have been equieffective, since there was no independent comparison of their activities or potencies under these conditions. In addition, methadone appears to be absorbed poorly or metabolized rapidly after oral administration in monkeys compared to effects in humans [3,19]. This may or may not be the case with LAAM.

Thus, differences between the magnitudes of effects of LAAM and methadone in combination with other drugs simply may have been due to different effective dose levels of the opiates in the present study.

REFERENCES

1. Anggard, E., L.-M. Gunne and F. Niklasson. Gas chromatographic determination of amphetamine in blood, tissue, and urine. *Scand. J. clin. Lab. Invest.* **26:** 137–143, 1970.
2. Baselt, R. C., C. B. Stewart and S. J. Franch. Toxicologic determinations of benzodiazepines in biological fluids and tissues by flame ionization gas chromatography. *J. Anal. Toxic.* **1:** 10–13, 1977.
3. Crowley, T. J., M. Hydinger, A. J. Stynes and A. Feiger. Monkey motor stimulation and altered social behavior during chronic methadone administration. *Psychopharmacologia* **43:** 135–144, 1975.
4. Downs, D. A. and J. H. Woods. Food- and drug-reinforced responding: Effects of DITA and d-amphetamine. *Psychopharmacologia* **43:** 13–17, 1975.
5. Downs, D. A. and J. H. Woods. Naloxone as a negative reinforcer in rhesus monkeys: Effects of dose, schedule, and narcotic regimen. *Pharmac. Rev.* **27:** 397–406, 1976.
6. Downs, D. A. and M. C. Braude. Time-action and behavioral effects of amphetamine, ethanol, and acetylmethadol. *Pharmac. Biochem. Behav.* **6:** 671–676, 1977.
7. Downs, D. A., D. J. Thomas and M. C. Braude. Chronic effects of acetylmethadol and methadone in rhesus monkeys. *Life Sci.* **21:** 719–726, 1977.
8. Eibergen, R. D. and K. R. Carlson. Dyskinesias elicited by methamphetamine: Susceptability of former methadone-consuming monkeys. *Science* **190:** 588–590, 1975.
9. Gianutsos, G., M. D. Hynes, S. K. Puri, R. B. Drawbaugh and H. Lal. Effect of apomorphine and nigrostriatal lesions on aggression and striatal dopamine turnover during morphine withdrawal: Evidence for dopaminergic supersensitivity in protracted abstinence. *Psychopharmacologia* **34:** 36–44, 1974.
10. Goldberg, S. R. and C. R. Schuster. Nalorphine: Increased sensitivity of monkeys formerly dependent on morphine. *Science* **166:** 1548–1549, 1969.
11. Henderson, G. L., J. A. Weinberg, W. A. Hargreaves, D. H. M. Lau, J. Tyler and B. Baker. Accumulation of *l*-α-acetylmethadol (LAAM) and active metabolites in plasma following chronic administration. *J. Anal. Toxic.* **1:** 1–5, 1977.
12. Jain, N. C. Direct blood-injection method for gas chromatographic determination of alcohols and other volatile compounds. *Clin. Chem.* **17:** 82–85, 1971.
13. Jatlow, P. I. and D. N. Bailey. Gas chromatographic measurement of cocaine in plasma using a nitrogen detector. *Clin. Chem.* **21:** 946, 1975.
14. Lal, H., J. O'Brien and S. K. Puri. Morphine withdrawal aggression: Sensitization by amphetamines. *Psychopharmacologia* **22:** 217–223, 1971.
15. Lal, H. Narcotic dependence, narcotic action and dopamine receptors. *Life Sci.* **17:** 483–495, 1975.
16. Lucot, J. B., D. E. McMillan and D. J. Leander. Behavioral interactions between *d*-amphetamine and chronic morphine consumption in the rat. *The Pharmacologist* **18:** 143, 1976.
17. Misra, A. L., J. Vardy, R. Bloch, S. J. Mule and G. E. Deneau. Pharmacokinetics and metabolism of (-)-α-[2-^{3}H] acetylmethadol (LAAM) in the monkey: Evidence for a new metabolite. *J. Pharm. Pharmac.* **28:** 316–318, 1976.
18. Puri, S. K. and H. Lal. Tolerance to the behavioral and neurochemical effects of haloperidol and morphine in rats chronically treated with morphine or haloperidol. *Naunyn-Schmiedeberg's Arch. exp Path. Pharmac.* **282:** 155–170, 1974.
19. Snyder, E. W., R. E. Dustman, R. C. Straight, A. W. Wayne and E. C. Beck. Sudden toxicity of methadone in monkeys: Behavioral and electrophysiological evidence. *Pharmac. Biochem. Behav.* **6:** 87–92, 1977.
20. Spaulding, T. C., L. Minium, A. N. Kotake and A. E. Takemori. The effect of diazepam on the metabolism of methadone by the liver of methadone-dependent rats. *Drug Metab. Disp.* **2:** 458–463, 1974.
21. Woods, J. H. and R. E. Tessel. Fenfluramine: Amphetamine congener that fails to maintain drug-taking behavior in the rhesus monkey. *Science* **185:** 1067–1069, 1974.