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# Reinforcing Effects of a Combination of Ethanol and Methadone Relative to Each Drug Alone

KEITH L. SHELTON, MITCHELL J. MACENSKI AND RICHARD A. MEISCH

*Substance Abuse Research Center, Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center at Houston, 1300 Moursund, Houston, TX 77030-3497*

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SHELTON, K. L., M. J. MACENSKI AND R. A. MEISCH. *Reinforcing effects of a combination of ethanol and methadone relative to each drug alone.* PHARMACOL BIOCHEM BEHAV **61**(4) 367–374, 1998.—Studies report a high incidence of alcohol abuse in methadone maintenance patients. There is, however, little data on the reinforcing effects of combinations of ethanol and methadone. In the present study, oral self-administration of a combination of 1% (w/v) ethanol and 0.2 mg/ml methadone was compared to each drug alone in three rhesus monkeys in which methadone alone was not a reinforcer. In Experiment 1, ethanol and the combination, but not methadone alone, served as reinforcers. In Experiment 2, there was no preference for ethanol or the combination at fixed ratio (FR) 8 or 16. When the FR size was doubled (FR 16 or 32), all three animals preferred the combination to 1% ethanol. Experiment 3 further examined the effect of work requirement on preference for ethanol or the combination by varying FR values [1, 2, 4, 8, 16, or 32]. At lower FRs, ethanol was significantly preferred to the combination. As FR was increased, there was a significant reduction in preference for ethanol over the combination. The results show that an ethanol + methadone combination will be orally self-administered by monkeys and suggest that work requirement differenetially modifies preference for the combination and ethanol alone. © 1998 Elsevier Science Inc.

Ethanol Methadone Self-administration Rhesus monkey Drug combination Polydrug abuse

MULTIPLE drugs are often involved in automobile traffic accidents (10). Drugs such as cocaine and heroin are frequently coabused (6,29), as are a number of other drug combinations. One of the most frequently abused drugs, both alone and in combination with other drugs, is alcohol. Nearly 11% of current alcohol users in the United States also use illicit drugs (30). This is compared with 2% in those who have not used alcohol (30).

The problem of alcoholism in opiate abusers is particularly troublesome, and its consequences can be severe. Studies have suggested that alcohol abuse may be directly or indirectly responsible for as many as 60% of all deaths in methadone maintenance patients (15). Alcoholism is a major contributing factor in the cessation of methadone maintenance treatment for opiate dependence (11). Despite the prevalence of the problem of coabuse of ethanol and opiates, little preclinical research has been undertaken on the self-administration of combinations of ethanol and opiates in general, or methadone in particular (3,38). Such studies would seem necessary to provide a basis for assessing treatment strategies for combined ethanol and opiate abuse.

A large literature has, however, been amassed concerning the behavioral parameters under which ethanol will be self-administered (31). Numerous studies have shown that animals will self-administer ethanol via the oral (2,21), intragastric (1), and intravenous routes (8,16). Ethanol self-administration reliably occurs under a variety of operant schedules and over a broad range of unit doses (22). Substantial literature has also been collected concerning opiate self-administration. Like ethanol, opioids are also self-administered by both the oral (26) and intravenous routes (5,7,28,33,39) under a variety of conditions. The majority of opiate self-administration studies in animals have used relatively short acting opiates such as morphine (13), heroin (9), and etonitazine (26) as reinforcers rather than methadone. Studies in methadone maintenance patients have found that supplemental methadone beyond the normal maintenance dose will serve as a reinforcer (36,37). Methadone has also recently been successfully established as a reinforcer in rhesus monkeys using the oral route (35,27). Following induction procedures, oral methadone self-administration is robust and occurs over a broad range of schedule

Requests for reprints should be addressed to Dr. K. L. Shelton, University of Texas Health Science Center at Houston, Department of Psychiatry and Behavioral Sciences, 1300 Moursund, Houston, TX 77030-3497.

conditions, leading to the possibility that oral drugy delivery may be useful for studying the self-administration of combinations of ethanol and methadone.

The purpose of the present study was to explore the behavioral interaction of methadone and ethanol using the concurrent oral self-administration paradigm (4,18). Concurrent measures have been effectively used for comparing the relative reinforcing effects of two different doses of the same drug (23) as well as the relative reinforcing effects of drug combinations compared to each of the constituent drugs alone (24). In this study, the reinforcing effects of a combination of a moderate concentration methadone (0.2 mg/ml) and a low concentration ethanol (1%) were compared relative to each drug alone in three rhesus monkeys. Low concentrations of ethanol are readily self-administered in large quantities by rhesus monkeys. We believed that this high intake might increase the probability that significant intake of methadone, when combined with ethanol, would occur. We had successfully used 1% ethanol in a study of the reinforcing effects of a combination of ethanol and pentobarbital (24), and wished to extend and systematically replicate those findings with methadone. A moderate concentration of methadone (0.2 mg/ml), one that in the previous study (35) was on the ascending portion of the dose–effect curve, was used. This concentration of methadone was chosen so that rate increases, due to the addition of ethanol, could be observed as well as to reduce the aversive taste properties of the drug. Finally, we used low to moderate concentrations of both drugs in order to reduce the possibility that liquid intake would be altered by nonspecific rate-reducing drug effects.

Monkeys in which methadone alone did not serve as a reinforcer were selected as subjects to simplify the interpretation of the interaction of ethanol and methadone as well as to determine if the drug combination would serve as a reinforcer in animals in which methadone alone had previously failed to act as a reinforcer. We chose to examine self-administration over a broad range of ratio values to maximize our ability to assess changes in relative reinforcing effects that might not be apparent were a single ratio value to have been used. It has been our observation that differences in relative reinforcing effects between drugs are more apparent at higher ratio values. Studies 1 and 2 were conducted at both a moderate and a relatively high ratio values. To more fully characterize any changes in relative reinforcing effects we also tested the combination of ethanol + methadone vs. ethanol alone at lower ratio values in Experiment 3.

## METHOD

### *Subjects*

Three adult male rhesus monkeys (*Macaca mulatta*) were used as subjects. The three monkeys had, in the prior months, been trained to self-administer methadone using a methadone self-administration acquisition procedure similar to that which has been successfully used to induce methadone intake in previous studies (27,35). All three animals initially self-administered methadone; however, methadone self-administration declined over time to the point at which methadone did not serve as a reinforcer. None of the three animals had access to methadone for at least 2 weeks prior to the beginning of the present study. All three monkeys also had substantial previous experience self-administering ethanol, and were self-administering 1% ethanol alone at the start of the present study. Monkey OP also had a short history of diazepam self-administration 2 years prior. The monkeys were food restricted to approximately 85% of free-feeding weight for the duration of the study to promote self-administration behavior. At the beginning of the study, the animals food restricted weights were 6.96 kg (M-OP), 7.49 kg (M-DW), and 8.32 kg (M-NO). The monkeys were individually housed in two tier stainless steel primate cages (76 × 102 × 81 cm), which were modified to also serve as experimental chambers. The colony room was maintained at 23°C with a 12 L:12 D cycle. Water was available ad lib except 1 h before and 1 h after the test session and 1 h during the daily afternoon feeding period.

### *Apparatus*

One side wall of each animal's home cage was modified to accept a work panel. Each panel had two independent liquid delivery systems. Each system consisted of a brass spout connected via 11-mm Tygon tubing to a suspended, covered liquid reservoir. A solenoid valve controlled the delivery of fluid through the spout. The spouts were separated by 31 cm and protruded 2 cm into the cage, 52 cm above the cage floor. Surrounding the spout were four small 1.1 W stimulus lights (2 green and 2 white). A large 2.8-W green stimulus lamp was located 12 cm above each spout. Liquid was delivered as a result of lip contacts that completed a drinkometer circuit, resulting in the delivery of approximately 0.65 ml of liquid to the subject over a period of not more than 170 ms [for more complete details of the apparatus see (12)]. If mouth contact was broken prior to the completion of the delivery, the solenoid valve closed automatically to avoid liquid spillage.

### *Drugs*

Methadone HCl (National Institute on Drug Abuse, Bethesda, MD) and 95% v/v ethanol (UTHSC stores, Houston, TX) were diluted in deionized water to produce stock solutions of 0.8 mg/ml methadone and 4% (w/v) ethanol. Fresh stock solutions were prepared weekly and stored refrigerated. Self-administered solutions were prepared daily, 2 h prior to the session, by diluting these stock solutions with deionized water to the appropriate concentration. Methadone concentrations are expressed in terms of the salt weight.

### *Procedures*

*General procedure.* Drug self-administration sessions were conducted 7 days per week for 3 h daily, beginning at 1100 and ending at 1400 h. Each day consisted of an intersession and session period. The intersession period began at 1500 h and ended at 1000 h the following day, with a 1-h time out at 1600 h for the afternoon feeding. During the intersession interval, water was available under a fixed-ratio 1 schedule from one of the two spouts, as determined by a double alternation schedule (L-L-R-R) over days. The active spout was signaled by the constant illumination of the large green stimulus light above that spout. Lip contacts on the active spout resulted in delivery of 0.65 ml of tap water and the illumination of the two white stimulus lights surrounding the spout. During the 1-h time-out period prior to the drug self-administration session, intersession responses and water deliveries were recorded. The remaining water was then measured and the reservoirs were filled with drug solutions.

The onset of each 3-h drug self-administration session was signaled by the illumination of the large 2.8-W green stimulus lights above both spouts. The lights blinked at 10 Hz for the duration of the session. Each lip contact during the session resulted in the illumination of the two green 1.1-W lamps sur-

rounding that spout for the duration of the contact. The completion of a fixed-ratio requirement on either spout resulted in a single liquid delivery from that spout. Response requirements on each spout were independent. Liquid position was alternated daily between spouts to control for possible side bias, and there were no distinctive exteroceptive stimuli correlated with the positions of each solution. During the time-out period following the completion of the drug self-administration session, drug solution responses and deliveries were recorded, volumes of remaining solutions were measured, and intersession water was placed in the appropriate reservoir. Each experimental condition was tested until six sessions of stable behavior were exhibited.

*Experiment 1: Reinforcing effects of ethanol, methadone, and an ethanol + methadone combination vs. the water vehicle.* The first experiment examined the reinforcing effects of 1% ethanol, 0.2 mg/ml methadone, and a combination of the two drugs compared to water. Monkeys OP and NO were tested at FR8 and DW was tested at FR16. FR8 or FR16 was chosen individually for each subject and was the ratio value that maintained the highest level of ethanol responding without evidence of ratio strain. The study employed a balanced design in which the ethanol + methadone combination solution, methadone, and ethanol were tested, in that order. A retest of methadone and the combination was then conducted.

*Experiment 2: Reinforcing effects of an ethanol + methadone combination vs. water, ethanol, and methadone.* The second experiment examined the reinforcing effects of the 1% ethanol + 0.2 mg/ml methadone combination relative to the constituents. The 1% ethanol + 0.2 mg/ml methadone combination was tested against water, 0.2 mg/ml methadone, 1% ethanol, 0.2 mg/ml methadone (retest), and water (retest). A low and a high ratio value were tested for each subject. The low value was that FR that maintained peak response rates for 1% ethanol in each individual animal. The high ratio value was twice the low value. Monkeys NO and DW were tested at FR16 (low) and FR32 (high), monkey OP was tested at FR8 (low) and FR16 (high).

*Experiment 3: Comparison of the reinforcing effects of an ethanol + methadone combination vs. ethanol alone across fixed-ratio values.* The third experiment compared the relative reinforcing effects of a 1% ethanol + 0.2 mg/ml methadone mixture vs. 1% ethanol over a range of fixed-ratio values. All three subjects were tested over an ascending series of ratios. The series of ratios were as follows: FR1, 2, 4, 8, 16, and 32. The data were then combined and presented as mean values for the group.

### *Data Analysis*

Responses, deliveries of liquid, and volume consumed were recorded for each animal daily. The mean responses, deliveries, and drug intake in mg/kg (±SEM) for each animal were calculated for the final six sessions of stable behavior in each condition. Stable behavior was operationally defined as six sessions in which there were no increasing or decreasing trends in responding as verified by visual inspection of the data. At least two different investigators were required to agree that the behavior had stabilized prior to beginning the next condition. Under most conditions the time to reach stability typically ranged between 6 and 12 sessions. The session time courses were collected graphically using paper cumulative recorders (Gerbrands, Arlington, MA). Statistical analysis of Experiment 3 was performed using the MANOVA module of "Statistica" (StatSoft, Tulsa, OK). All post hoc analysis used Tukey HSD tests performed with the same statistical package. Preference for a particular drug solution was judged to be present when deliveries of that drug solution exceed deliveries of the other concurrently available drug solution and the SEMs of the two solutions did not overlap.

## RESULTS

### *Experiment 1: Reinforcing Effects of Ethanol, Methadone, and an Ethanol + Methadone Combination vs. the Water Vehicle*

The combination of ethanol + methadone served as a reinforcer in all three subjects (Fig. 1). Deliveries of the combination varied from 323 deliveries for monkey OP to 466 deliveries for monkey NO. The combination was preferred to water in the initial as well as the retest condition. Water deliveries were near zero for two of the three animals tested and no more than 35% of the mean combination deliveries for the third animal (M-NO). Ethanol also served as a reinforcer for all three subjects when compared to concurrently available water. In all three subjects, the number of 1% ethanol deliveries exceeded combination deliveries at the initial fixed-ratio values tested.

In contrast to the combination solution and ethanol alone, the 0.2 mg/ml methadone concentration was not a reliable reinforcer for any of the subjects. Although the mean number of methadone deliveries exceeded water (vehicle) deliveries, there was substantial overlap in the range of methadone and water deliveries for all three animals over the six-session period. Furthermore, in monkey DW upon retest, methadone deliveries were less than water deliveries, indicating that methadone may have even been aversive.

Table 1 shows ethanol and methadone intake in mg/kg for all three monkeys in this phase of the study. In the first combination vs. water condition, ethanol intake varied between 242 mg/kg (M-OP) and 339 mg/kg (M-DW), and methadone intake varied from a high of 6.8 mg/kg (M-DW), to a low of 4.8 mg/kg (M-OP). In the methadone vs. water conditions, total methadone ingested over the 3-h period was between 0.6 mg/kg and 2.2 mg/kg for the initial determination and from 0.6 mg/kg to 2.0 mg/kg upon retest. For all three subjects, total ethanol intake was greater in the ethanol vs. water, condition ranging from 441 mg/kg to 527 mg/kg, than in the combination condition.

### *Experiment 2: Reinforcing Effects of an Ethanol + Methadone Combination vs. Water, Ethanol, and Methadone*

This series of manipulations compared the reinforcing effects of the 1% ethanol + 0.2 mg/ml methadone combination to those of 1% ethanol, 0.2 mg/ml methadone, and water. As was the case with the previous series of manipulations, the ethanol + methadone combination continued to serve as a reinforcer for all of the animals at both fixed-ratio values (Fig. 2). Combination deliveries were much greater than concurrently available water deliveries in both the first and second determination in all three animals (Fig. 2). When the FR value was doubled, the mean number of combination deliveries decreased (Fig. 2, right panels). However, combination deliveries still exceeded water deliveries by a large margin for all monkeys.

In the previous series of manipulations, the data indicated that 0.2 mg/ml methadone was not an efficacious reinforcer in any of the monkeys. When the 1% ethanol + 0.2 mg/ml methadone combination was tested concurrently against 0.2 mg/ml methadone alone, the combination was preferred to metha-

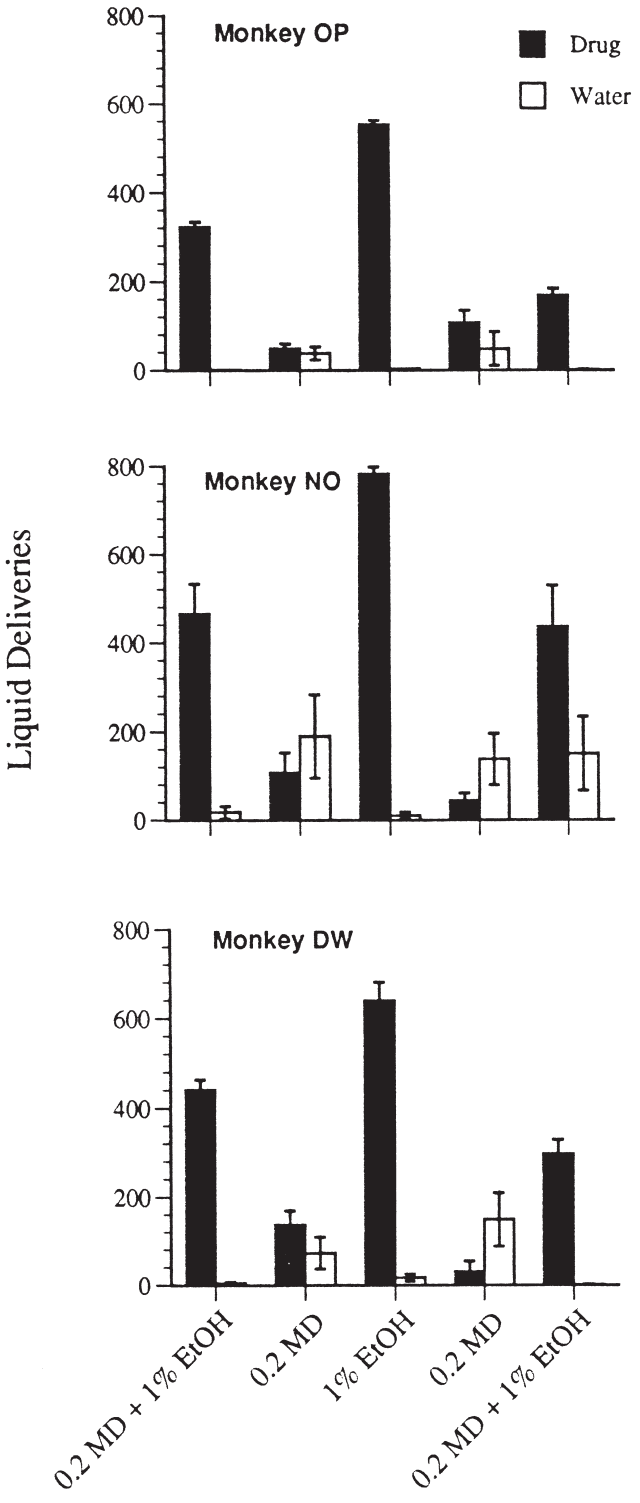


FIG. 1. Mean deliveries of the ethanol + methadone combination, methadone, and ethanol (filled bars) compared to concurrently available water vehicle (open bars). The pairs include retest points for methadone and the combination. Each bar represents the mean (± SEM) of six consecutive sessions of stable behavior.

TABLE 1

MEAN, DAILY INTAKE (MG/KG) OF ETHANOL AND METHADONE FOR EACH OF THE THREE MONKEYS DURING EXPERIMENT 1

| | Ethanol (mg/kg) | | | Methadone (mg/kg) | | |
|---|---|---|---|---|---|---|
| | M-OP | M-NO | M-DW | M-OP | M-NO | M-DW |
| Combintation 0.2 mg/ml Methadone | 242.8 | 288.5 | 339.6 | 4.8 | 5.8 | 6.6 |
| 1% Ethanol 0.2 mg/ml Methadone | — | — | — | 0.6 | 0.1 | 2.2 |
| (retest) | 441.1 | 480.8 | 527.0 | — | — | — |
| Combination (retest) | — | — | — | 2.0 | 0.6 | 0.5 |
| | 156.6 | 298.1 | 244.3 | 3.1 | 6.0 | 4.9 |

done by all three monkeys. As a group, well over 95% of all deliveries obtained were of the combination solution rather than methadone. The preference for the combination relative to methadone alone was consistent at both the lower and higher ratio values (Fig. 2).

The combination was also tested concurrently against 1% ethanol alone. At the lower ratio value, there was no preference for either the combination or ethanol. When the ratio value was doubled, overall combination and ethanol deliveries were reduced. However, all three animals preferred the combination solution to 1% ethanol at this higher ratio value, indicating that the combination was more reinforcing than ethanol alone.

*Experiment 3: Comparison of the Reinforcing Effects of an Ethanol + Methadone Combination vs. Ethanol Alone Across Fixed-Ratio Values*

To further examine the preference between the 1% ethanol + 0.2 mg/ml methadone combination and 1% ethanol, the two solutions were tested concurrently over a series of ascending fixed-ratio values. In contrast to Experiments 1 and 2, Experiment 3 examined the group effects of FR on ethanol and the combination self-administration. A two-way MANOVA (liquid × FR) showed a main effect of both liquid, $F(1, 2) = 33.06$, $p < 0.05$, and FR size, $F(5, 10) = 5.44$, $p < 0.05$. There was also a significant liquid × FR interaction, $F(5, 10) = 11.07$, $p < 0.001$. Post hoc analysis indicated that the effect of FR size was totally a function of decreasing 1% ethanol intake at successively higher ratio values. FR size had no significant effect on self-administration of the 1% ethanol + 0.2 mg/ml methadone combination. Deliveries of 1% ethanol were significantly ($p < 0.05$) greater than combination deliveries only at FR1 and FR2. Cumulative records indicated that the majority of responding occurred early in the session. All three animals actively tracked the position (right or left side) of 1% ethanol at lower ratio values. At intermediate ratio values the animals generally responded on a single side, regardless of solution. At higher ratio values, the animals tended to track the combination solution, although this trend was not statistically significant.

## DISCUSSION

The results show that 1% ethanol will serve as an orally delivered reinforcer in rhesus monkeys. Responding for 1% eth-

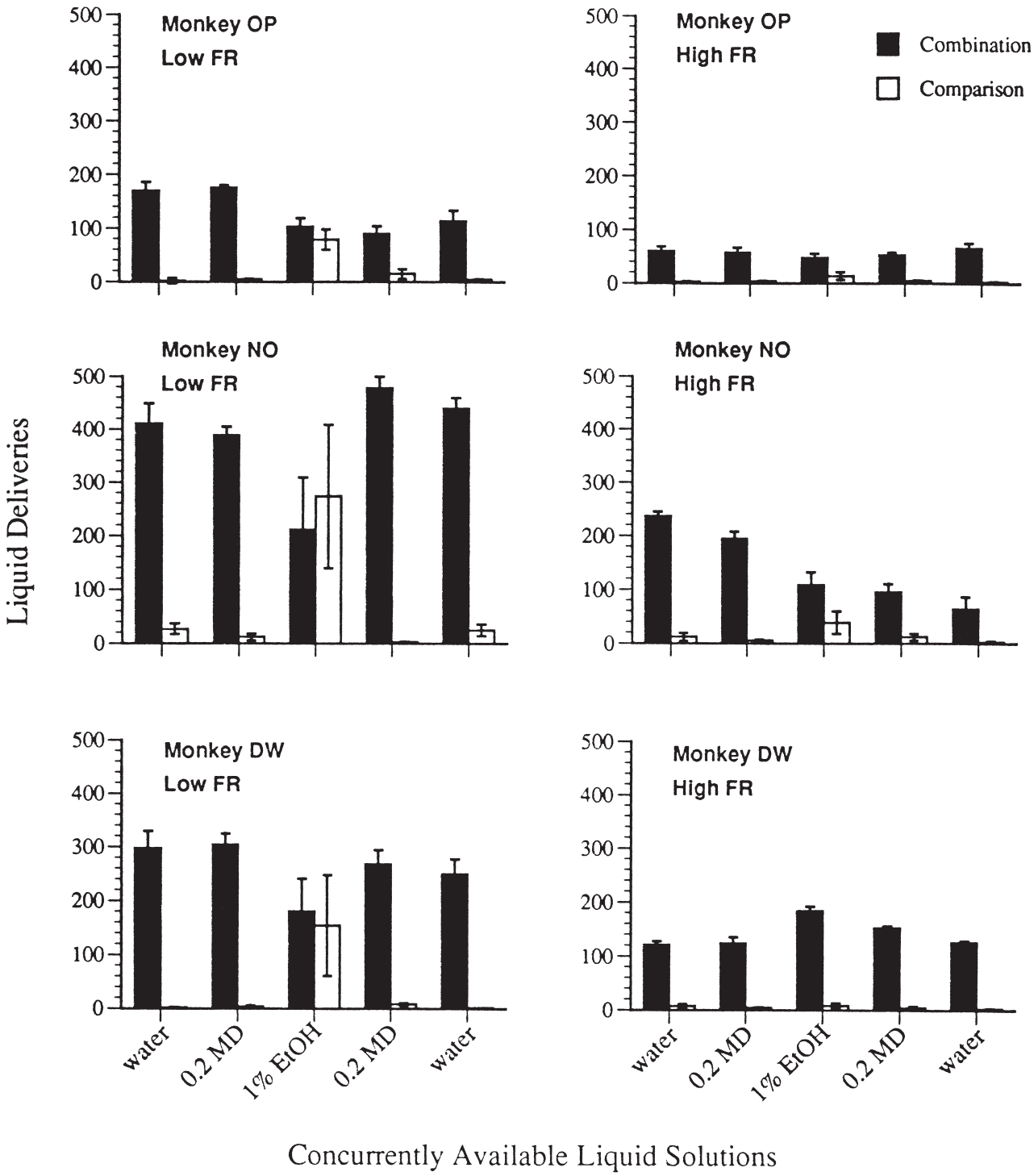


FIG. 2. Deliveries of the ethanol + methadone combination (filled bars) compared to ethanol, methadone, and water vehicle alone (open bars). The left panels show the data from the lower of two FR values tested (FR8 or FR16). The right panels show the values from the higher ratio values tested (FR16 or FR32). The pairs include restests of the combination compared to methadone and water. Each bar represents the mean (± SEM) of six consecutive sessions of stable behavior.

anol was well maintained at both the high and low fixed-ratios. Previous studies have consistently shown that monkeys will readily self-administer low concentrations of ethanol with little or no training, probably because of the preferred sweet taste of ethanol (21). In the present study, self-administration of 1% ethanol alone was unlikely to have produced high blood ethanol levels given the relatively small total amount self-administered (441 to 527 mg/kg). It is difficult to deter-

mine if these total doses of ethanol produced pharmacological effects alone, although rodent studies have shown that doses of ethanol as low as 330 mg/kg produce centrally mediated discriminative stimulus effects (41), and rodents typically require larger drug doses than primates to produce similar behavioral effects. Regardless of the mechanism, 1% ethanol clearly served as an effective reinforcer in these subjects.

In contrast to ethanol, 0.2 mg/ml methadone alone did not consistently function as a reinforcer for any of the monkeys. However, when combined with 1% ethanol, the mixture of 1% ethanol and 0.2 mg/ml methadone supported responding across a wide range of fixed-ratio values. The mean daily intake of methadone by each monkey, when combined with ethanol in Experiment 1, was between 4.8 and 6.8 mg/kg, well above the less than 1 mg/kg daily dose in methadone maintenance patients (32,37). Pharmacologically meaningful methadone blood levels were likely achieved in these animals, even given the fact that monkeys require significantly higher doses of most psychoactive drugs than humans in order to produce similar effects. There were no outwardly observable behavioral effects of self-administered methadone in any of the monkeys.

The data clearly show that an ethanol + methadone combination will be self-administered. One interpretation of this effect is that the monkeys ingested large volumes of the combination solution solely due to positive taste of ethanol alone or in combination with methadone. Low concentration of ethanol have a appetitive taste, and are readily self-administered by monkeys without requiring the use of any induction procedure; it is, therefore, possible that taste, rather than pharmacological effects, were responsible for the self-administration behavior observed in the present study. This hypothesis was addressed by comparing concurrent self-administration of the 0.2 mg/ml methadone + 1% ethanol combination to 1% ethanol alone across a broad range of fixed-ratio values. At the lower ratio values, deliveries of the drug combination were initially much less than those of 1% ethanol (Fig. 3). These results are consistent with a conclusion that the combination was self-administered because of 1% ethanol's taste. In fact, the decreased ethanol intake when combined with methadone in Experiment 1 argues that 1% ethanol's positive taste may have been diminished by the presence of methadone.

The balance of the results, however, do not favor a solely taste-based effect. As the fixed-ratio requirement was increased, a relatively greater proportion of total deliveries were of the combination than of 1% ethanol. This point is clearly shown in Experiment 3, in which FR size had no significant effect on combination deliveries, whereas 1% ethanol deliveries were significantly decreased by increases in FR value. These results strongly suggest that the combination's reinforcing effects were more resistant to alteration by FR size than ethanol's reinforcing effects, leading to the possibility that the combination became relatively more reinforcing than ethanol alone as response cost increased. Changes in preference for higher drug concentrations as a function of ratio value have also been shown with methadone alone, indicating that alteration in preference as a function of FR size is not unique to ethanol + methadone combinations (27).

The increased preference for the drug combination relative to ethanol at higher ratios supports the interpretation that the combination solution was not being self-administered simply due to the taste of ethanol in the solution. If the taste of ethanol in the combination solution was totally responsible for combination self-administration, there should have been no change in preference for the combination solution relative to ethanol alone at any of the ratio values tested. This contention is supported by the fact that the addition of methadone to the ethanol solution decreased ethanol self-administration when the combination was initially tested, arguing that methadone has aversive taste properties.

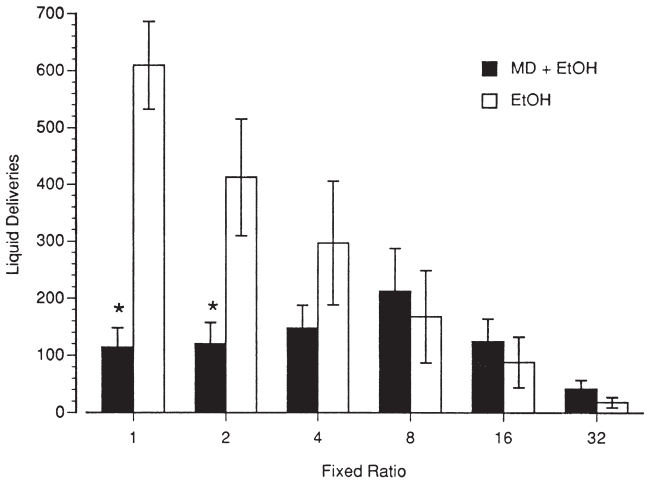


FIG. 3. Mean deliveries of the ethanol + methadone combination (filled bars) compared to ethanol alone (open bars) across ascending fixed-ratio values. Each bar represents the mean (± SEM) of six consecutive sessions of stable behavior for three monkeys. *Indicate significant ($p < 0.05$) differences between combination and ethanol deliveries.

The mechanism responsible for the change in preference as a function of increasing ratio values is uncertain. One possible interpretation is that both taste and pharmacological effects were controlling self-administration behavior at low FR values. At low FR's total drug intake was not greatly restricted; therefore, intoxication may have been achieved by the positive tasting ethanol solution alone. However, at high FRs, drug intake was substantially limited. In these cases, ethanol alone may not have produced positive pharmacological effects. This could have resulted in a shift in responding to the combination solution, despite its aversive taste properties, in order to maintain an intoxicating drug effect. Another hypothesis is that the taste of methadone served as a conditioned reinforcer and discriminative stimulus that may have been more pronounced at higher ratio values, resulting in the increases in preference for the combination at the higher ratio values.

Overall, the interaction between work requirement and relative reinforcing effects of the combination and ethanol was stable and reproducible across all three monkeys. Preliminary findings indicate that similar effects may occur with combinations of cocaine and ethanol (M. J. Macenski, unpublished observation) and do occur with pentobarbital and ethanol (19). This interaction between drugs and schedules could have implications in the area of assessment of the relative abuse liability of individual drugs as well as drug combinations (17). If such drug/schedule interactions are consistent over other drug classes, it may complicate the ability to determine the reinforcing effects of one drug by comparing it to another, especially if such testing is only done under a limited range of schedule requirements (14,40). For example, if the present study had been conducted only using a FR value of 4, the finding that the combination became relatively more rein-

forcing as work requirement increased would not have been detected.

In summary, the results of this study show that a low concentration of ethanol in combination with methadone will be self-administered by rhesus monkeys that do not self-administer methadone alone. These findings are consistent with previous studies showing that ethanol increases the oral intake of a number of behaviorally active drugs that do not initially serve as reinforcers. Drugs from diverse classes including: barbiturates (19,20), benzodiazepines (34), and psychomotor stimulants (25) are included in this group. Based on the these findings, it may be the case that oral self-administration of other drugs of abuse, regardless of pharmacological class, may also be enhanced by the addition of ethanol. The present study also shows that a combination of ethanol and methadone may become more reinforcing, relative to ethanol alone as FR size increases. These results point to the possibility that the reinforcing effects of ethanol may be more pronounced in methadone maintenance patients than other persons. Those patients, especially ones with histories of ethanol abuse, may need to be particularly closely monitored to insure that ethanol and methadone are not coabused.

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