Psychopharmacology (2000) 148:393–399

ORIGINAL INVESTIGATION

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Methoclocinnamox: time course of changes in alfentanil-reinforced responding in rhesus monkeys

Received: 27 April 1999 / Final version: 29 September 1999

Abstract *Rationale*: Methoclocinnamox (MC-CAM) possesses initial partial μ-opioid agonist activity with subsequent long-lasting μ-antagonist effects. This profile of activity is similar to that of buprenorphine, a compound with proposed use in the treatment of opioid abuse, suggesting a possible therapeutic use for MC-CAM as well. *Objective*: The current study assessed the time course of the ability of MC-CAM and buprenorphine to antagonize the reinforcing effects of alfentanil and compared this with that of buprenorphine. *Methods*: Rhesus monkeys self-administered a range of doses of alfentanil (0.03–1 μg/kg per injection) under a fixed-ratio 30, time-out 45 s schedule of i.v. drug delivery. MC-CAM was substituted for alfentanil on occasion, and a dose of 1.0 mg/kg MC-CAM or buprenorphine was given prior to sessions in which alfentanil was available. In the pretreatment studies, a wider range of alfentanil doses was utilized (0.03–30 μg/kg per injection). *Results*: MC-CAM maintained self-administration behavior and was nearly equipotent with buprenorphine as a reinforcer in this paradigm. Both drugs, when given prior to a session in which alfentanil was available, produced a decrease in the reinforcing potency of alfentanil. The antagonist effects of the pretreatments were largest 30 min following administration and decreased over the next several days. The duration of MC-CAM's antagonism of alfentanil was approximately 4 days; the duration of buprenorphine as an antagonist was approximately 2 days. *Conclusion*: These data suggest that MC-CAM has a longer duration of antagonist effects than buprenorphine and it may therefore have an advantage in the treatment of opioid abuse.

Key words Alfentanil · Buprenorphine · Methoclocinnamox · Opioid receptor · Operant responding · Self-administration · Time course

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Introduction

Methoclocinnamox (MC-CAM) has been shown to possess an initial partial μ-opioid agonist effect followed by a long-lasting antagonist effect in rhesus monkeys (Aceto et al. 1989; Woods et al. 1995; Butelman et al. 1996). This profile of activity, which is very much like that of buprenorphine, a compound that is currently in clinical trials for the treatment of opioid abuse, has led to the suggestion that MC-CAM may also hold promise as a therapeutic agent for the treatment of opioid addiction (Kosten et al. 1992; Husbands et al. 1998). One of the important advantages buprenorphine has over the most popular current pharmacotherapy of opioid abuse, methadone, is that it provides a longer duration of protection against the effects of opioid agonists (Amass et al. 1998). The duration of action of a pharmacotherapy is important in client satisfaction with the treatment medication. Thus, the duration of MC-CAM's protective effects against an opioid agonist may enhance its appeal as a treatment medication.

The time course of the analgesic agonist and antagonist properties of MC-CAM has been described in the rhesus monkey using a warm-water tail-withdrawal assay at a mild (50°C) temperature, in which complete analgesia was indicated if the monkey did not withdrawal its tail from the water in less than 20 s. The analgesic effects were related to dose, with 1.0 mg/kg producing complete analgesia 30 min following its s.c. administration (Butelman et al. 1996). A dose of 0.32 mg/kg produced complete analgesia at 120 min following administration, and this full effect remained for the next 3 h with

partial recovery demonstrated 6 h following administration. MC-CAM (0.1 mg/kg and 0.32 mg/kg) produced peak antagonism of morphine's analgesic effects 2 days after MC-CAM administration; these were still evident to a reduced extent 14 days following administration and were gone 19 days following administration.

The agonist and antagonist effects of buprenorphine have been evaluated in a similar preparation (Walker et al. 1993, 1995). Buprenorphine had analgesic effects for up to 48 h following s.c. administration of 3.2 mg/kg. At 72 h, the agonist effect was no longer present and the antagonist effects of buprenorphine became evident. The analgesic effects of full μ agonists were shifted to the right from 10- to 100-fold 72 h after buprenorphine treatment in this assay (Walker et al. 1995). When evaluated 10 days later, no antagonist effects were observed. Although direct comparisons were not made at all time points, and equipotent doses may not have been given, these data suggest that MC-CAM may have shorter lasting μ-agonist effects than buprenorphine, but longer lasting μ-antagonist effects.

Buprenorphine serves as a reinforcer in non-human primates as well as acting as an antagonist of the reinforcing effects of other μ opioids. Cowan et al. (1977) and Lukas et al. (1983) reported that buprenorphine maintained more behavior than did saline, but less behavior than did the reference compounds of codeine and cocaine, respectively. When buprenorphine was made available on a daily basis, it maintained behavior well above that maintained by saline (Mello et al. 1981). There was no dose–rate interaction, however, which might not be surprising with chronic administration when the long-lasting agonist effects and longer-acting antagonist effects could be influencing the reinforcing effects of the compound. The ability of buprenorphine to antagonize the reinforcing effects of alfentanil in a surmountable fashion was shown by Winger and Woods (1996), and Winger et al. (1992) found that buprenorphine was much more potent in suppressing opioid self-administration than in suppressing cocaine self-administration, indicating the opioid antagonist nature of buprenorphine. A similar profile of MC-CAM activity has been shown in preliminary studies (Woods et al. 1995).

The current study evaluated the acute reinforcing effects of i.v. MC-CAM in monkeys with a history of alfentanil-reinforced responding. Additionally, MC-CAM and buprenorphine were given as pretreatments prior to sessions in which alfentanil was available, and the time-course of their ability to antagonize alfentanil-maintained responding was assessed and compared.

Material and methods

Subjects

Four individually housed adult rhesus monkeys (*Macaca mulatta*), two male and two female, were the subjects of this experiment. All monkeys had a varied history of i.v. self-administration of opiates and other drugs. The duration of the experiments lasted between 1 year and 2 years, depending on the animal. The male monkeys (L998 and 171F) were 6.6 kg and 8.0 kg at the start of the study and finished the study at 9.4 kg and 13.0 kg, respectively. The female monkeys (RC237 and B3) were 5.1 kg and 6.6 kg at the start of the study and finished the study at 5.5 kg and 6.7 kg, respectively. Monkeys received approximately 180 g of Purina monkey chow twice daily, at least 60 min prior to the start of the experimental sessions. This diet was supplemented with a piece of fresh fruit each afternoon, approximately 2 h after the morning session, along with occasional treats such as peanuts or raisins. Water was provided ad libitum. The animals were maintained on a 12-h/12-h light/dark cycle. All experiments were conducted in accord with the guidelines from the National Institutes of Health and the University of Michigan's animal care and use committee.

As previously described (Winger et al. 1989), monkeys were surgically implanted with a silicone catheter (Mox-Med, Portage, Wis.) into one of eight major veins (external or internal jugular, femoral or brachial vein) using aseptic technique. The monkeys were anaesthetized using a combination of 10 mg/kg ketamine i.m. and 2 mg/kg xylazine i.m. The proximal end of the catheter was inserted close to the heart and the distal end was passed subcutaneously from the incision site toward the back, exiting at the mid-scapular region. The catheter was held firmly in place with nylon anchor sutures in surrounding muscle tissue. The monkeys were maintained on antibiotics for a period of 3–5 days following catheter placement. To protect the catheters, monkeys wore steel tubular harnesses (Deneau et al. 1969) and/or a teflon web jacket (Alice King Chatam Medical Arts, Los Angeles, Calif.). The jacket or harness was connected by a hollow, flexible tether to the back of the cage. The catheter passed through this tether and was attached through a metal junction to a length of silicone tubing that was connected to a roller infusion pump (Watson and Marlow Co., model MHRK 55, Falmouth, UK).

Apparatus

Monkeys were housed in stainless-steel cages (83.3×76.2×91.4 cm). Each cage was equipped with a lever panel with two response levers. Above these levers were three stimulus lights: a red light on the right indicating drug availability; a green light in the center indicating that drug was being infused; the left light was not used in these experiments. The red and green lights were illuminated using Christmas-tree light bulbs or an array of light-emitting diodes (LEDs). The lever box was attached to a computer via an interface (Med-Associates, St. Albans, Vt.) which controlled all contingencies and recorded all data.

Procedure

The experimental sessions lasted 130 min. These sessions occurred twice daily, one at 1000 hours and the second at 1600 hours. Each session was divided into four components of either 25 min or 20 injections, whichever came first. Each 25-min component was followed by a 10-min black-out period during which the lights were not illuminated and responses had no programmed consequence. Responses on the lever were reinforced with an i.v. injection of alfentanil on a fixed-ratio schedule of 30, followed by a 45-s time out. Each component was associated with a different dose of alfentanil; drug concentrations remained constant within an experimental session and the dose per injection was controlled by the duration of the infusion by the roller pump. When, in a given session, the doses per injection were increased, this was accomplished by increasing the concentration of alfentanil for that session. Infusion durations were 0.5, 1.7, 5.0, and 16.7 s in the four components of the session. Four different infusion duration orders were used: ascending, descending, or one of two mixed orders.

Under baseline conditions, either alfentanil in doses of 0.03, 0.1, 0.3, or 1 μg/kg per injection or saline was delivered contingently on responding in the presence of the red light. Saline was substituted for alfentanil approximately every third session. When

rates of alfentanil-maintained responding were positively related to the dose per injection of alfentanil and greater than one response per second at the largest dose, and when rates of saline-maintained responding were less than 0.5 responses per second at all four infusion durations, MC-CAM or buprenorphine was substituted for alfentanil, or administered as a pretreatment. The pretreatment dose of MC-CAM and buprenorphine was 1 mg/kg; these drugs appeared to be nearly equipotent both as reinforcers, as shown here and by Winger et al. (1992), and as analgesics (Walker et al. 1995; Butelman et al. 1996). On sessions in which either MC-CAM or buprenorphine was given prior to sessions of alfentanil availability, the ascending infusion duration order for alfentanil was used, and the concentration of alfentanil was usually increased so that larger doses were available. Monkeys were tested multiple times to evaluate the effects of MC-CAM and buprenorphine. The last four observations were used in the data presentation.

Alfentanil was made available 30 min following the s.c. administration of 1.0 mg/kg MC-CAM or buprenorphine. Typically, alfentanil was again available 4 h later (if the pretreatment was given prior to a morning session) or 18 h later (if the pretreatment was given prior to an afternoon session), and every 4 h or 18 h thereafter. Thus, except for an occasional substitution of saline, the time course of the ability of MC-CAM or buprenorphine to modify the reinforcing potency of alfentanil could be monitored until the reinforcing potency of alfentanil returned to baseline. The concentration of alfentanil that was made available following a pretreatment was decreased by a half log unit when the dose of alfentanil that maintained the highest rates of responding shifted from the largest available dose to the next largest available dose.

Data analysis

Data were assessed by visual inspection of each individual animal's data. Additionally, $ED_{50,control}$ was calculated for the animals in the antagonism experiments similar to that previously reported by Zernig et al. (1997).

Drugs

Alfentanil HCl was provided by Janssen Pharmaceuticals (Beerse, Belgium) and buprenorphine HCl was supplied by Reckitt and Colman (Kingston-upon-Hull, UK). Methoclocinnamox mesylate was supplied by Dr. John Lewis (Bristol University, Bristol, UK) and was dissolved in sterile water with the addition of a few drops of lactic acid. All drug doses are expressed as the weight of the aforementioned salts.

Results

Rates of responding maintained by alfentanil and MC-CAM for three monkeys (B3, 171F, L998) are shown in Fig. 1. Monkey L998 was used only in this study for the assessment of the reinforcing effectiveness of MC-CAM. The maximum total intake of drug allowed by this schedule was 88 µg/kg MC-CAM and 28.6 µg/kg alfentanil. The rate of opioid-maintained responding increased as the dose per injection of both compounds increased, with the mean observed peak of alfentanil-maintained response rate of 1.98 responses per second at a dose of 1 µg/kg per injection and the mean observed peak of MC-CAM-maintained response rate of 2.05 responses per second at a dose of 3 µg/kg per injection.

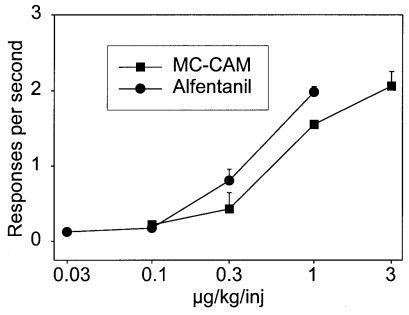

Fig. 1 Mean rates of responding (±SEM) maintained by i.v. infusions of either methoclocinnamox (MC-CAM) or alfentanil. The *closed circles* represent alfentanil-maintained responding and the *closed squares* represent MC-CAM-maintained responding. Each *point* represents the mean of three monkeys each of which were observed four times in each treatment condition

For the time course of the antagonist effects of 1 mg/kg MC-CAM, $ED_{50,control}$ was calculated for alfentanil-maintained responding for each monkey using a procedure similar to that previously described by Zernig et al (1997). The group means (±SEM) are detailed in Table 1 for each time point. The time course of the antagonist effects of 1 mg/kg MC-CAM is shown in Fig. 2 for each of three monkeys. The largest effect of MC-CAM was observed at the first observation time, 30 min following administration of MC-CAM. At this time, MC-CAM produced more than a 1.5 log-unit decrease in the potency alfentanil as a reinforcer in each of the three monkeys. Thus, whereas a dose of 1.0 µg/kg per injection alfentanil had maintained maximum rates of responding prior to administration of MC-CAM, 30 min following administration of MC-CAM, a dose of 30 µg/kg per injection alfentanil was unable to maintain high rates of behavior in two monkeys and was unable to maintain any behavior in one monkey (#RC237). At 24 h following administration of MC-CAM, there was some recovery in the reinforcing potency of alfentanil. A dose of 30 µg/kg per injection alfentanil maintained higher rates of responding at this time than it had at the 30-min pretreatment time in each of the three monkeys, although these rates were still substantially less than the maximum rates maintained by alfentanil prior to administration of MC-CAM. At 48 h following MC-CAM adminis-

Table 1 Estimates of ED_{50} values for alfentanil self-administration following pretreatment. ED_{50} expressed as mean (±SEM) in three monkeys following pretreatment with either 1 mg/kg methoclocinnamox (MC-CAM) or 1 mg/kg buprenorphine. Data are expressed as µg/kg

	Control	24 h	48 h	72 h	96 h	120 h
MC-CAM	0.26±0.01	11.51±2.11	2.10±0.53	0.88±0.29	0.67±0.15	0.34±0.03
Buprenorphine	0.26±0.01	1.79±0.33	1.58±0.49	0.32±0.03		

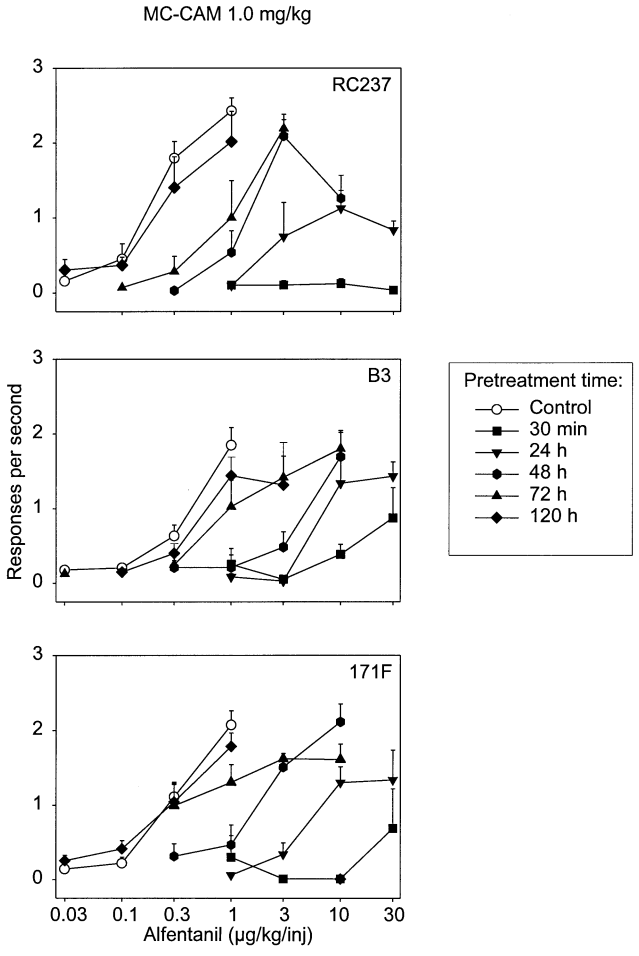

Fig. 2 Mean rates of responding (±SEM) maintained by i.v. infusions of alfentanil in three monkeys following pretreatment with 1.0 mg/kg s.c. methoclocinnamox (MC-CAM) at 30 min and 24, 48, 72, and 120 h. Each *point* represents the mean of four observations in each treatment condition

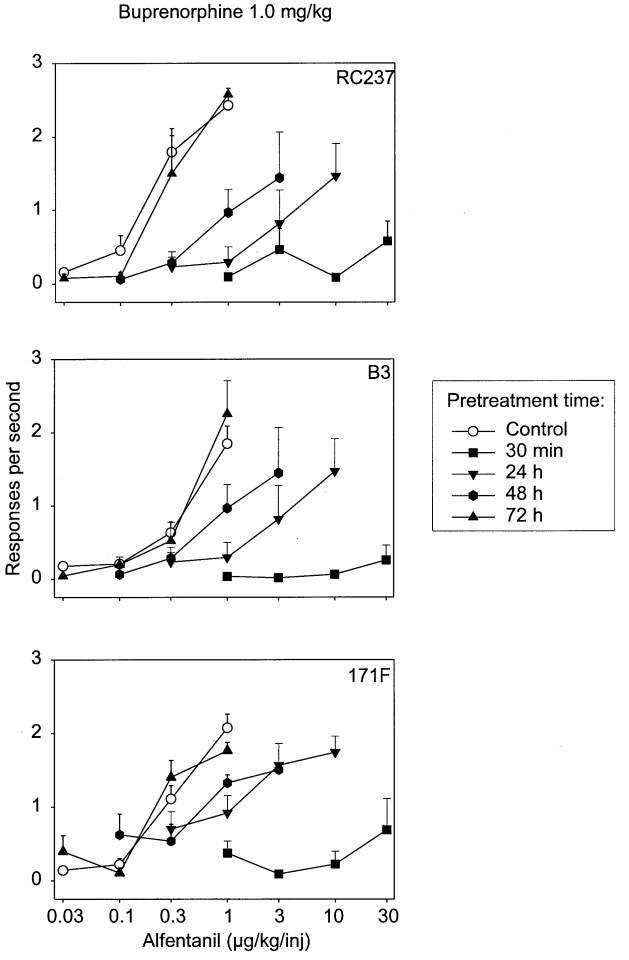

Fig. 3 Mean rates of responding (±SEM) maintained by i.v. infusions of alfentanil in three monkeys following pretreatment with 1.0 mg/kg s.c. buprenorphine at 30 min and 24, 48, and 72 h. Each *point* represents the mean of four observations in each treatment condition

tration, rates of responding had returned to nearly the same level as they were prior to MC-CAM administration, although the reinforcing potency of alfentanil remained decreased relative to the baseline condition. At 120 h following administration of MC-CAM, there was nearly complete recovery of the reinforcing potency of alfentanil in the three monkeys.

For the time course of the antagonist effects of 1.0 mg/kg buprenorphine, $ED_{50,control}$ was calculated for alfentanil-maintained responding for each monkey using a procedure similar to that previously described by Zernig et al. (1997). The group means (±SEM) are detailed in Table 1 for each time point. The time course of the blockade of the effects of alfentanil by buprenorphine is shown in Fig. 3 for each of three monkeys. The maximum suppression of alfentanil-maintained responding by buprenorphine was observed 30 min following its administration and involved a decrease in the effectiveness of alfentanil as a reinforcer in each of the three monkeys. Rates of responding maintained by alfentanil were suppressed completely in one monkey and to levels below 0.5 responses per second in the other two. Twenty-four hours following administration of buprenorphine, the effectiveness of alfentanil as a reinforcer had returned in two of the three monkeys, although alfentanil's reinforcing potency remained decreased by a half log unit or greater than the baseline condition. A substantial decrease in alfentanil's reinforcing potency was observed for up to 48 h in all three monkeys studied, and a return to baseline rates and patterns of alfentanil-maintained responding was observed 72 h after buprenorphine pretreatment in all three monkeys.

Discussion

MC-CAM is a low-efficacy µ-opioid agonist with long-lasting opioid antagonist effects, a profile of activity that resembles closely that of buprenorphine. These properties are likely responsible for the success of buprenorphine in clinical trials for the treatment of heroin abuse (Bickel and Amass 1995) and raise the question of

whether a similar indication is appropriate for MC-CAM. We evaluated the abilities of MC-CAM and buprenorphine to modify the potency of intravenous alfentanil as a reinforcer. In particular, we were interested in comparing these drugs with respect to the magnitude and the duration of decreases they produced in alfentanil's reinforcing potency.

The agonist effects of MC-CAM were evident in the ability of the compound to maintain self-administration behavior. The highest rates of responding maintained by MC-CAM were similar to those maintained by alfentanil, a high efficacy μ-opioid agonist. Although this might call into question the position that MC-CAM has low efficacy, it has been demonstrated that measures of the reinforcing potency of many opioids using the i.v. route of administration and relatively low fixed-ratio requirements are extremely sensitive. For example, partial μ agonists such as nalbuphine maintained high rates of responding under these conditions, although differences in reinforcing effectiveness between a low (nalbuphine) and high (alfentanil) efficacy μ agonist were shown when ratio requirements were increased (Winger et al. 1996). The partial μ-agonist profile of MC-CAM is supported by the fact that in the rhesus monkey tail-withdrawal assay, MC-CAM was an analgesic when 50°C water but not when 55°C water was the thermal stimulus (Butelman et al. 1996). At the higher temperatures, MC-CAM antagonized the analgesic effects of μ agonists with higher efficacy (Butelman et al. 1996). Importantly, the agonist effects of MC-CAM were sufficient to block morphine withdrawal in morphine-dependent monkeys; withdrawal signs appeared slowly over a 3-day period when a single dose of MC-CAM was administered as morphine administration was discontinued (Aceto 1989 as reported in Woods et al. 1995).

The dose per injection of MC-CAM that maintained the maximum rates of responding was not clearly established; rates were highest at the largest dose tested and could have increased with further increases in dose per injection. Nevertheless, at the largest dose per injection used (3.0 μg/kg per injection), relatively high rates of responding were observed (2.05 responses per second). These rates might have been maintained if the dose had been increased another one half log unit, but it is unlikely that they would have increased significantly. Using a very similar procedure, buprenorphine also maintained self-administration behavior in rhesus monkeys, and the peak rates of responding were also maintained at 3.0 μg/kg per injection (Winger et al. 1992). These data suggest that MC-CAM and buprenorphine have similar potencies as reinforcers under these circumstances and were used to help justify administration of the same dose (1.0 mg/kg) of these drugs prior to sessions in which alfentanil was available. Additionally, Woods et al. (1995) demonstrated that 1.0 mg/kg MC-CAM did not significantly alter cocaine-maintained responding using procedures identical to those in the current study, whereas 3.2 mg/kg suppressed cocaine-maintained responding. Similar results with buprenorphine have also been demonstrated by Winger et al. (1992), who showed that 1.0 mg/kg buprenorphine did not significantly alter cocaine-maintained responding using the same procedures as the current study, whereas 3.2 mg/kg did. These data suggest that the dose chosen for the current antagonism studies (1.0 mg/kg) was one that would avoid non-selective suppression of behavior.

In analgesia assays, MC-CAM was perhaps one half log unit more potent than buprenorphine (Walker et al. 1995; Butelman et al. 1996). This suggests that 1.0 mg/kg MC-CAM may have been a slightly more effective dose than 1.0 mg/kg buprenorphine and this may have contributed to MC-CAM's longer duration of antagonist action. However, in the analgesia assay, a smaller dose of MC-CAM had a longer duration of antagonist action than buprenorphine. In addition, although comparisons would be particularly interesting, there is as yet no indication that the potencies of MC-CAM and buprenorphine as agonists reflect the magnitude or duration of their antagonist actions, and there are few data that can be used to compare antagonist potencies.

The first time point at which the effects of the pretreatment agents were observed was 30 min following their s.c. administration. At this time, rates of alfentanil-maintained responding were markedly suppressed in three of the four observations. Although it is possible that these initial effects were due to opioid agonist and general suppressant properties, we do not think this was the case for the effects of MC-CAM and buprenorphine observed here. It is clear from previous data using buprenorphine in circumstances similar to those used here that even its initial effects on alfentanil-maintained responding are due primarily to buprenorphine's action as an opioid antagonist. In a study (Winger et al. 1992) comparing the effects of buprenorphine and other opioids on responding maintained by either cocaine or alfentanil, buprenorphine was much more potent in suppressing alfentanil-maintained responding than in suppressing cocaine-maintained responding. Other opioid agonists were equipotent in suppressing behavior maintained by both drugs. This suggests that buprenorphine may have been acting through a mechanism other than its opioid agonist property (i.e., its opioid antagonist property) to suppress alfentanil-maintained responding. In a later study (Winger et al. 1996), a range of doses of buprenorphine produced surmountable antagonism of the reinforcing effects of alfentanil 30 min following buprenorphine administration. This supports the supposition that, in the current set of data, it is the opioid antagonist effects of buprenorphine that are responsible for the marked decrease in the ability of alfentanil to maintain responding in the initial observation period, 30 min following buprenorphine administration. We have no similar data with MC-CAM to allow us to posit that it is also acting as an alfentanil antagonist 30 min following buprenorphine administration. However, its effects are so similar to those of buprenorphine in all other situations in which it has been evaluated, that it is likely that it too is modifying alfentanil's reinforcing effects through an antagonist mechanism throughout its time course. In addition, in the current data with

MC-CAM, there is a tendency in two of the three animals for larger doses of alfentanil to maintain more behavior than smaller doses, a pattern that is also suggestive of antagonist interaction. Twenty-four hours after administration of buprenorphine or MC-CAM, the reinforcing effectiveness of alfentanil remained decreased, but rates of responding had begun to recover. These measures indicated that, at this time, MC-CAM produced a greater decrease in the reinforcing potency of alfentanil (1 to 2 log-unit decrease) than did buprenorphine (0.75–1 log-unit decrease).

Recovery of the reinforcing effects of alfentanil was more rapid following administration of buprenorphine (approximately 2 days) than MC-CAM (approximately 4 days). The antagonist effects of MC-CAM have been postulated to result from its metabolism to the irreversible μ antagonist C-CAM (Woods et al. 1995; Zernig et al. 1995, 1997; Butelman et al. 1996; Husbands et al. 1998). In similar studies of the antagonist action of C-CAM, Zernig et al. (1997) noted that as many as 7 days were required for alfentanil to recover its original reinforcing potency following administration of 1 mg/kg C-CAM. These data are not directly comparable with those described here because the original dose of C-CAM was followed every 24 h by a supplemental dose (0.1 mg/kg). But they do support the possibility of a long duration of antagonist action of MC-CAM if this action is through C-CAM. However, a metabolite-based mechanism of MC-CAM's antagonist effects has not been established definitively and can be questioned by the findings of Butelman et al. (1996) in that quadazocine prevented the antagonist as well as the agonist effects of MC-CAM. It is possible that the mechanism of MC-CAM's antagonist effects are similar to those of buprenorphine, which are thought to be a result of unusually slow kinetics at the μ receptor (Hambrook and Rance 1976; Lewis 1985). MC-CAM, like buprenorphine, is difficult to displace from the μ receptor (Woods et al. 1995), which supports receptor kinetics as a mechanism for its antagonist effects.

These data indicate that MC-CAM produced both a greater and a longer-lasting antagonism of the reinforcing effects of μ-opioid drugs than did buprenorphine and support the position that MC-CAM may have significant advantages in the treatment of opioid abuse. A relatively longer duration of action can permit longer periods of time between treatment administration; clients may prefer infrequent dosing and the resulting fewer trips to the clinic, as has been shown with buprenorphine (Amass et al. 1998). The fact that MC-CAM is self-administered by the monkeys suggests that heroin-abusing clients would be willing to take the medication. The partial-agonist profile, as demonstrated in previous studies (Woods et al. 1995; Butelman et al. 1996) indicates that MC-CAM would have little respiratory depressant effects and, therefore, a low risk of overdose from MC-CAM itself, as well as good protection from overdose from abused opioids.

MC-CAM had a shorter duration of analgesic agonist effects than did buprenorphine (Walker et al. 1995; Butelman et al. 1996), and it remains to be determined how important agonist versus antagonist properties are in the treatment of opioid abusers. The agonist effects of treatment medications may be critical in protecting heroin-abusing clients from the motivation to take additional heroin. It is not entirely clear that buprenorphine reduces heroin intake by reducing this motivation through an agonist mechanism or whether it reduces heroin intake by blocking the effects of heroin through an antagonist mechanism. If it is the former, then a long duration of agonist action may be more protective than a long duration of antagonist action. Evaluation of these compounds in both preclinical and clinical situations may reveal more about the critical aspects of drugs that have been found useful in reducing the problem of illicit opioid use. MC-CAM might be of particular utility in individuals who are interested in treatment for opioid abuse but who are not strongly dependent on abused opioids, and who are highly motivated. It might thus represent a compromise between treatment with a pure antagonist such as naltrexone and a pure agonist such as methadone.

Acknowledgements This work was supported by USPHS grants P50 DA00254-28 and 5T32 DA07268. The technical assistance of Debbie Huntzinger and Amy Foster are gratefully acknowledged.

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