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Buprenorphine and methoclocinnamox: agonist and antagonist effects on respiratory function in rhesus monkeys

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Abstract

Buprenorphine and methoclocinnamox are partial μ-opioid receptor agonists with potential use in the treatment of opioid abuse. The ability of these drugs to suppress respiration as well as their ability to antagonize the respiratory suppressant effects of morphine and heroin were tested in rhesus monkeys. Frequency (f), minute volume (V_e) tidal volume (V_t) in monkeys breathing air or 5% CO_2 in air were recorded using a pressure-displacement plethysmograph. Buprenorphine (0.001–10 mg/kg) produced a dose-dependent decrease in respiratory parameters that plateaued at a dose of 1 mg/kg in both air and 5% CO_2. Methoclocinnamox (0.032–1 mg/kg) also produced dose-dependent respiratory depression that plateaued at a dose of 0.3 mg/kg in air, and was directly related to dose in 5% CO_2. Respiratory suppression produced by buprenorphine 1 and 10 mg/kg lasted for 3 and 7 days, respectively, whereas the suppression produced by the largest dose of methoclocinnamox (1 mg/kg, the solubility limit) lasted less than 24 h. Buprenorphine and methoclocinnamox antagonized morphine- and heroin-induced respiratory depression, and this antagonist effect was observed concomitantly with, as well as following, the μ-opioid receptor agonist effects of buprenorphine and methoclocinnamox. The μ-opioid receptor antagonist effects of buprenorphine (10 mg/kg) and methoclocinnamox (1 mg/kg) lasted for 2 weeks. These results suggest that buprenorphine and methoclocinnamox have a wide margin of safety in clinical use and that these two compounds have a prolonged, insurmountable, μ-opioid receptor antagonist effect after the disappearance of their agonist effects.

Keywords: Respiration; (Rhesus monkey); Buprenorphine; Methoclocinnamox; Opioid receptor agonist; Opioid receptor antagonist

1. Introduction

Buprenorphine is a low-efficacy agonist at the μ-opioid receptor, acting as a μ-opioid receptor agonist in some situations, and as a μ-opioid receptor antagonist in others (Cowan et al., 1977a; Dum and Herz, 1981). Methoclocinnammox has a similar profile of activity. For example, both buprenorphine and methoclocinnamox produce analgesia in the rhesus monkey warm-water tail withdrawal assay when the water temperature is low, but when the water temperature is high, they have no analgesic effects and can antagonize the antinociceptive effects of higher efficacy μ-opioid receptor agonists (Walker et al., 1995; Woods et al., 1995; Butelman et al., 1996). Similarly, both drugs serve as intravenous reinforcers in rhesus monkeys, and both are able to antagonize the reinforcing effects of the higher efficacy μ-opioid receptor agonist alfentanil in the same situation (Winger et al., 1992; Briscoe et al., in press). Buprenorphine is currently undergoing clinical trials for the treatment of opioid abuse. Briscoe et al. (in press) indicated that methoclocinnamox produced a longer duration of antagonism of the reinforcing effects of alfentanil than did buprenorphine, suggesting that it might have some advantage over buprenorphine in this treatment situation.

Issues of toxicity are important in drugs that are being considered for clinical use. The primary toxic side-effect of μ-opioid receptor agonists is respiratory depression, and

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both buprenorphine and methoclocinnamox suppress respiration to a limited extent (Cowan et al., 1977b; Woods et al., 1992, 1995) through a μ-opioid receptor action (Howell et al., 1988; Butelman et al., 1993). Again, the partial μ-opioid receptor agonist properties of buprenorphine were demonstrated by the incomplete suppression of respiration that it produced, and the fact that in the rhesus monkey, it was able to antagonize the greater respiratory depressant effects of higher efficacy μ-opioid receptor agonists (Liguori et al., 1996). The respiratory depressant effects of methoclocinnamox have not been evaluated as thoroughly, and its ability to antagonize the effects of higher efficacy μ-opioid receptor agonists is not known. Also, questions about the duration of methoclocinnamox's μ-opioid receptor agonist and antagonist effects in measures of respiratory depression and how these compare with those of buprenorphine have not been answered.

In this experiment, the extent and time course of the μ-opioid receptor agonist effects of buprenorphine and methoclocinnamox on respiratory function in rhesus monkeys were studied. In addition, the μ-opioid receptor antagonist effects of buprenorphine and methoclocinnamox on heroin- or morphine-induced respiratory suppression were studied and the time course of their μ-opioid receptor antagonist effects were evaluated as well.

2. Materials and methods

2.1. Subjects

Seven adult rhesus monkeys (*Macaca mulatta*) weighing between 4.5 and 11.0 kg were subjects in this study. They were housed individually in cages in a room with controlled temperature and a 6:00 AM–6:00 PM light cycle. Water was available ad libitum, and monkeys were fed approximately 30 Purina Monkey Chow biscuits daily, supplemented twice weekly with fresh fruit. The procedures used in this study were approved by the University of Michigan Committee on the Use and Care of Laboratory Animals.

2.2. Apparatus

The apparatus used has been described previously (Howell et al., 1988; France and Woods, 1990; Butelman et al., 1993). Briefly, a monkey was seated in a restraint chair, a Plexiglas helmet was placed over its head and sealed around its neck by two closely fitting latex shields. The monkey was then placed in ventilated, sound-attenuating chamber. Gas (either air or a mixture of 5% CO_2 in air) flowed into the helmet at a rate of 8 l/min and was pumped out at the same rate. Changes in pressure inside the helmet produced by ventilation were measured with a pressure transducer connected to a polygraph (Grass model 7); the data were recorded on a polygraph trace and in a microprocessor via an analog-to-digital converter. The apparatus was calibrated routinely with known quantities of air.

2.3. Procedure

Experimental sessions were comprised of several consecutive 30-min cycles, each cycle consisting of a 23-min exposure to air followed by 7-min exposure to 5% CO_2 in air (hereafter referred to as 5% CO_2). A session started with a control cycle in which no drugs were administered. This was followed by four to five cycles in which a drug was administered i.m. during the first 3-min period of each cycle. Respiratory parameters were recorded continuously during each session; data from the last 3 min of exposure to air and the second 3 min of exposure to 5% CO_2 in each cycle were used for data analyses. Data for V_e and f were directly obtained from the polygraph integrator and microprocessor and averaged over consecutive 3-min periods; V_t was calculated as the ratio V_e/f.

2.4. Design

In studies of the effects of increasing doses of buprenorphine (0.001–1.0 mg/kg), methoclocinnamox (0.003–1.0 mg/kg), morphine (0.1–56 mg/kg), and heroin (0.03 or 3.2 mg/kg) on respiration, the drugs were given in a cumulative fashion. The first dose was given 3 min after the initiation of the air component of the second cycle as described above, and increasing cumulative doses were given on the subsequent cycles, 30 min apart. In the case of buprenorphine, the largest (10 mg/kg) dose was given on a separate session as a bolus injection 3 min after the initiation of the second breathing cycle. The acute effect of this dose was observed 30 min following its administration. The data from this bolus administration of buprenorphine 10 mg/kg were used to complete the dose response curve for this drug. In addition, the time course of the effect of this dose was observed for 2 h immediately after the injection, and then on the first respiration cycle on days 1, 3, 7, 10, 14, 17, 21, 24, 28, and 31. Following the observations of the effects of buprenorphine during the first respiration cycle on these days, the effects of cumulative administration of either morphine or heroin were established. Increasing doses of morphine were administered, starting with the second respiration cycle, on days 1, 7, 14, 21, and 28; increasing doses of heroin were administered, starting with the second respiration cycle, on days 3, 10, 17, 24, and 31.

In a similar fashion, buprenorphine 1.0 mg/kg was given as a bolus injection to two groups of three or four monkeys. Four of the monkeys determined the time course of the effects this dose of buprenorphine on the initial respiration cycle on days 1, 2, 3, 4, 7, and 14. The

respiratory effects of cumulative doses of morphine were measured in three of the monkeys during the same session, starting with the second respiration cycle, on days 3 or 4 and 7 following buprenorphine 1.0 mg/kg administration. This dose was given to the second group of three monkeys as a bolus injection, and the effects on the respiratory depressant effects of heroin were observed using a cumulative dosing procedure on days 4 and 7 following buprenorphine administration.

The duration of the effect of the largest two doses of methoclocinnamox (1.0 and 0.1 mg/kg) was evaluated following a bolus injection of each of these doses. The respiratory suppressant effects of methoclocinnamox 1.0 mg/kg were measured every 30 min for 2 h, and subsequently on the first respiratory cycle on days 1, 3, 7, 10, 14, 21, and 24 days following its administration. During the same session that the time course of the μ-opioid receptor agonist effect of methoclocinnamox was being measured, its ability to modify the respiratory depressant effects of heroin and morphine was tested. The effects of cumulative doses of morphine on respiration following administration of methoclocinnamox was evaluated starting with the second respiratory cycle on days 1, 7, 14, and 21 following methoclocinnamox 1.0 mg/kg administration. The effects of cumulative doses of heroin were measured in a similar fashion on days 3, 10, 17, and 24 following this same administration of methoclocinnamox 1.0 mg/kg.

To evaluate the effect of the smaller dose of methoclocinnamox on respiratory depression produced by morphine and heroin, the monkeys were divided into two groups of three monkeys each. One group received cumulative doses of morphine on days 1, 3, 7, and 10 following a bolus injection of methoclocinnamox 0.1 mg/kg. The other group received heroin on these days following a bolus injection of methoclocinnamox 0.1 mg/kg. As in the other tests, cumulative administration of morphine and heroin began with the second respiration cycle of a session. On the first of these cycles for both monkeys receiving heroin and those receiving morphine, residual effects of methoclocinnamox 0.1 mg/kg administration were recorded.

2.5. Drugs

Morphine sulfate (Malinckrodt, St. Louis, MO) and heroin hydrochloride (National Institute on Drug Abuse, Research Technology Branch, Rockville, MD) were dissolved in sterile water. Buprenorphine hydrochloride (National Institute on Drug Abuse, Research Technology Branch, Rockville, MD) and methoclocinnamox mesylate (Dr. John Lewis, Bristol University, Bristol, UK) were dissolved in sterile water with the addition of a few drops of lactic acid. All drugs were injected i.m. in the side of the monkey's thigh.

2.6. Data analysis

Values obtained in each experimental session were expressed as percent of control of the respective parameters collected before buprenorphine or methoclocinnamox administration or as raw numbers. Mean and S.E.M. values were then computed. Data were analyzed by a one-way analysis of variance followed by the Newman–Keuls test for multiple comparison and unpaired Student's *t*-test for comparison between two groups. Analyses of data were done using the computer programs described by Tallarida and Murray (1987).

3. Results

3.1. Respiration under control conditions

Untreated monkeys exhibited a consistent pattern of respiration in the head plethysmograph apparatus. A stable baseline rate of respiration was recorded in monkeys

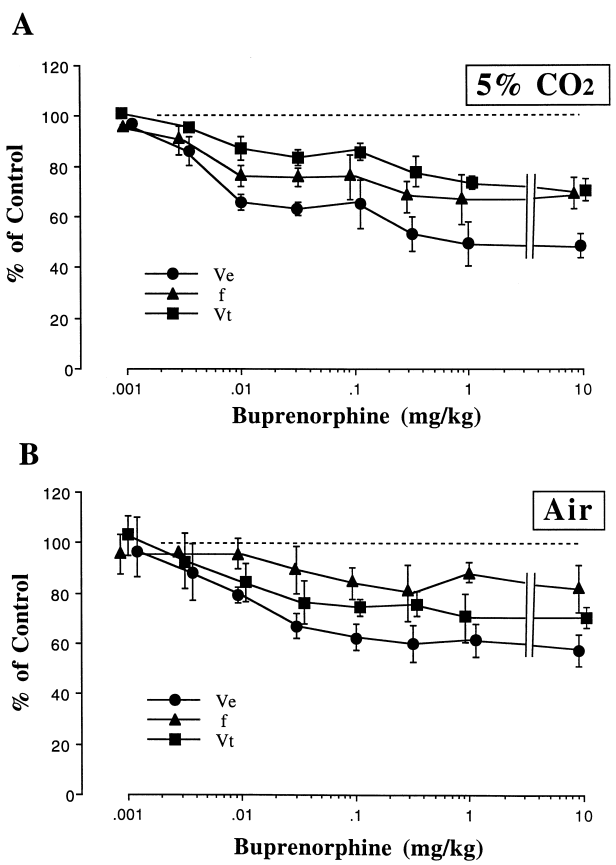

Fig. 1. Dose–response curve of buprenorphine-induced respiratory suppression under 5% CO_2 (A) or air (B) conditions. Buprenorphine (0.001–1 mg/kg) was administered cumulatively and the largest dose of buprenorphine (10 mg/kg) was given separately as a bolus. Data are shown as the percent change from non-drug control. Each value represents the mean ± S.E.M. of three monkeys.

breathing air. When 5% CO_2 was introduced, a prompt increase in all respiratory parameters was observed, with individual monkeys displaying stable patterns of CO_2-induced increases across sessions. The control values for f, V_e, and V_t for monkeys breathing air were 24.3, 2268, and 103.6, respectively. When breathing 5% CO2 in air, these values were 35.9, 7008, and 200.7.

3.2. Agonist properties

3.2.1. Buprenorphine

Cumulative administration of buprenorphine 0.001–1 mg/kg produced dose-dependent suppression of f, V_e and V_t in both air and 5% CO_2 (Fig. 1). A dose of 1 mg/kg buprenorphine produced maximal suppression of f, V_e, and V_t in 5% CO_2, and doses of 0.1 and 3.2 mg/kg buprenorphine produced near maximum suppression of these respiratory parameters in air. V_e was more affected by buprenorphine than was f or V_t under both conditions. Following administration of buprenorphine 1 mg/kg, V_e in 5% CO_2 was suppressed to 49% of control levels and V_e in air was suppressed to 61% of control levels. This dose of buprenorphine suppressed f and V_t in CO_2 to 67% and 73% of control, respectively, and in air, they were suppressed to 88% and 70%, respectively. No additional suppression of respiration was observed following administration of a larger dose of buprenorphine (10 mg/kg).

As shown in Fig. 2, 24 h following administration of buprenorphine 1.0 or 10 mg/kg, respiration continued to be suppressed. The effects of 10 mg/kg were more pronounced than those of 1 mg/kg at that time; V_e continued to be the most affected parameter. Following administration of buprenorphine 1 mg/kg, V_e was not as suppressed at 24 h (64% of control) as it had been 30 min (49% of control) following the injection, whereas, following administration of buprenorphine 10 mg/kg, V_e was as suppressed at 24 h (45% of control) as it was at 30 min (49% of control). Recovery of normal respiration rate and vol-

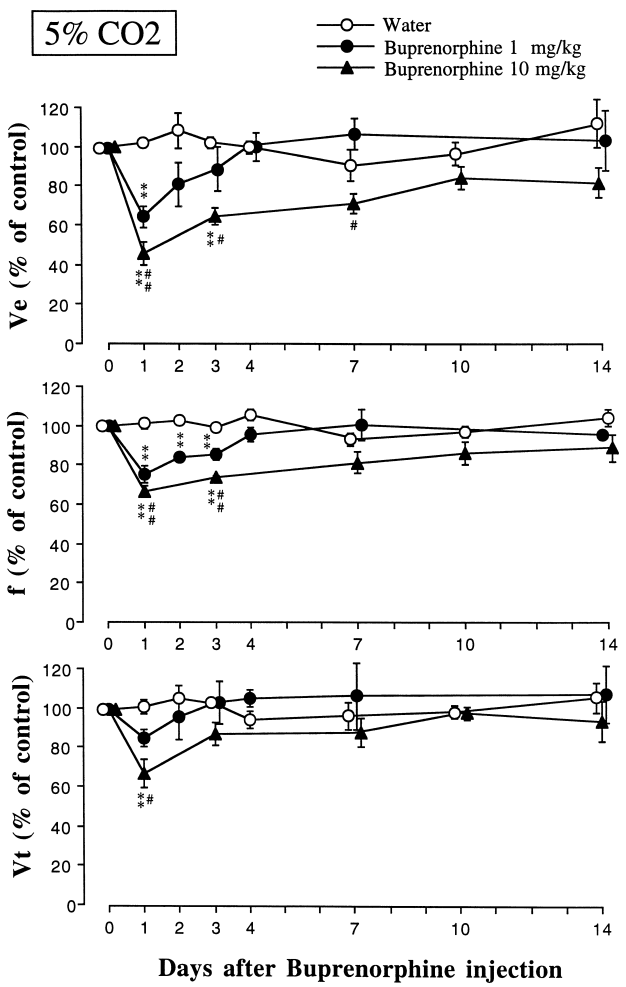

Fig. 2. The time course of the agonist effects of buprenorphine 1 and 10 mg/kg. Data were collected during exposure to 5% CO_2 and are shown as the percent change from values obtained on the first breathing cycle. Each value represents the mean ± S.E.M. of four to five monkeys. $^{**}P < 0.01$, $^{*}P < 0.05$ vs. water control and $\#\#P < 0.01$, $\#P < 0.05$ vs. buprenorphine 1 mg/kg (Newman–Keuls test).

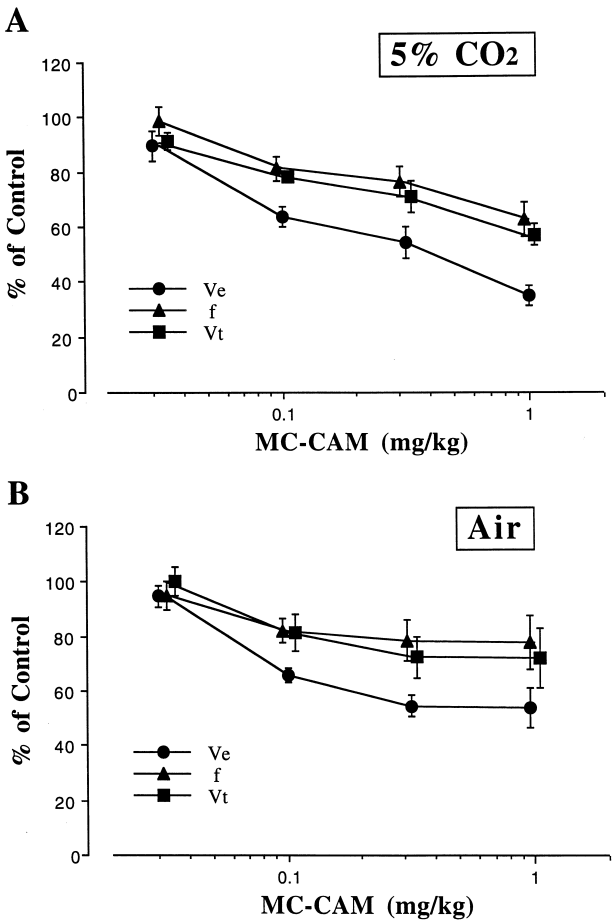

Fig. 3. Dose–response curve of methoclocinnamox-induced respiratory suppression under 5% CO_2 (A) or air (B) conditions. Methoclocinnamox was administered cumulatively. Data are shown as the percent change from the control values for the 5% CO_2 and air conditions. Each value represents the mean ± S.E.M. of six monkeys.

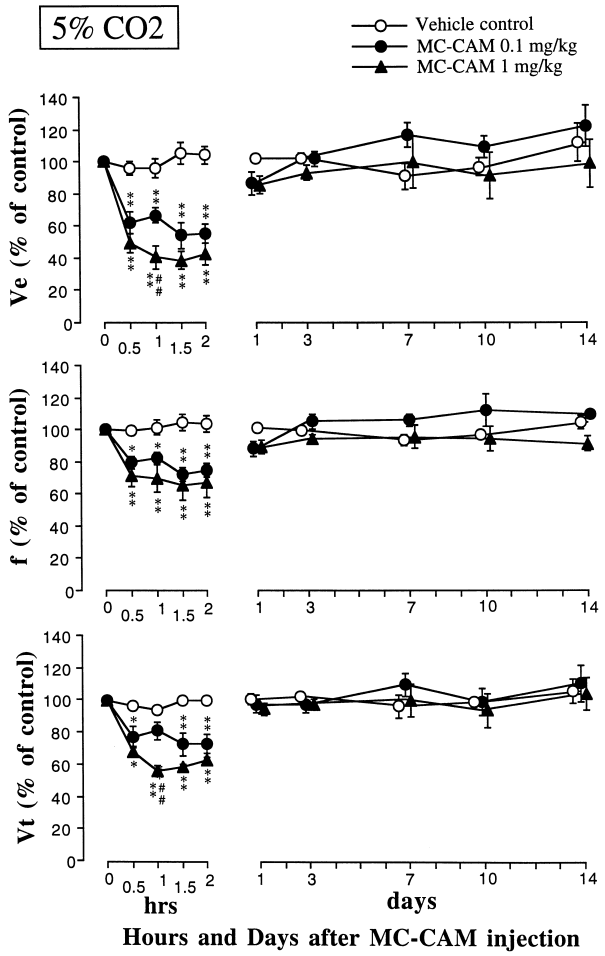

Fig. 4. The time course of the agonist effects of methoclocinnamox. Data were collected during exposure to 5% CO_2 and are shown as the percent change from values obtained on the first breathing cycle. Each value represents the mean ± S.E.M. of four to six monkeys. $^{**}P < 0.01$, $^{*}P < 0.05$ vs. water control and $\#\#P < 0.01$ vs. methoclocinnamox 0.1 mg/kg (Newman–Keuls test).

ume was more rapid following administration of 1 mg/kg buprenorphine as compared with administration of 10 mg/kg buprenorphine. Completely normal breathing parameters were established by day 4 following administration of 1 mg/kg and by day 10 following administration of 10 mg/kg.

3.2.2. Methoclocinnamox

Respiratory rate, V_e and V_t were suppressed by cumulative administration of methoclocinnamox 0.032–1 mg/kg in a dose dependent manner (Fig. 3). When the monkeys were breathing air, the effects of methoclocinnamox on all three measures of respiration were no greater following administration of methoclocinnamox 1.0 mg/kg than following administration of 0.32 mg/kg methoclocinnamox. When the monkeys were breathing 5% CO_2, the larger dose produced a greater suppression than the smaller dose. As was shown with buprenorphine, V_e was the most sensitive measure of the effects of the opioids.

Respiration became slightly more depressed over the 2 h that followed administration of methoclocinnamox 1.0 mg/kg and remained suppressed over the 2 h that followed administration of methoclocinnamox 0.1 mg/kg (Fig. 4). The effects of methoclocinnamox 0.1 mg/kg paralleled those of the larger dose, but at a slightly reduced level. There was significant suppression of all measures of respiration 1 and 2 h following administration of methoclocinnamox 0.1 and 1.0 mg/kg with the exception that V_t was not significantly suppressed 1 h following administration of methoclocinnamox 0.1 mg/kg. By day 1 or 3, complete recovery had occurred in all parameters.

3.3. Antagonist properties

3.3.1. Buprenorphine

When given alone, morphine suppressed V_e in a dose-dependent manner across a range of doses from 0.1 to 17.8 mg/kg. At the largest dose (17.8 mg/kg), V_e was reduced to approximately 2.2 l per min from a control value of

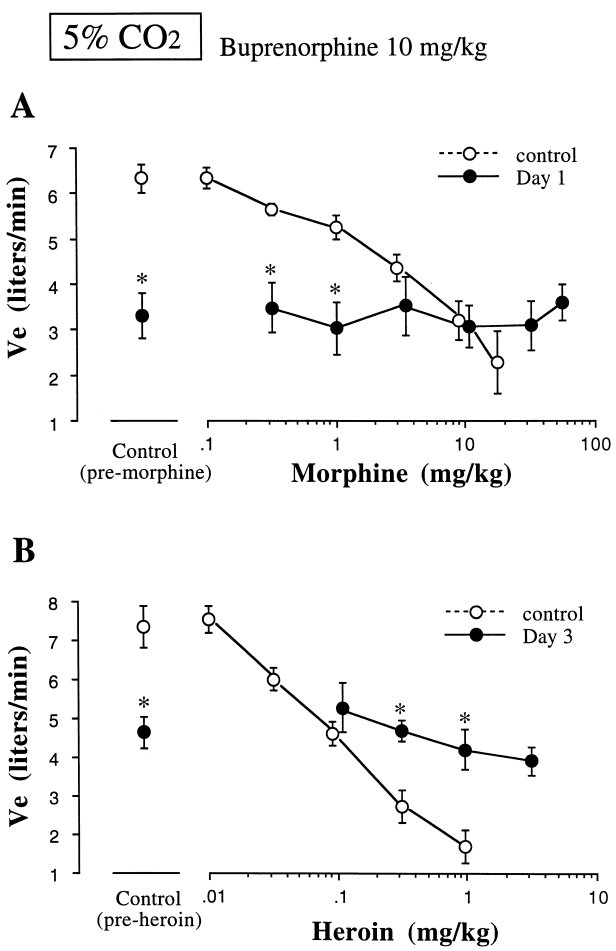

Fig. 5. Dose–response curves of morphine (A) and heroin (B) on day 1 (morphine) and day 3 (heroin) after administration of buprenorphine 10 mg/kg. Data were collected during exposure to 5% CO_2 and are shown as raw values of V_e. Each value represents the mean ± S.E.M. of five monkeys. $^{*}P < 0.05$ vs. control (Student's *t*-test).

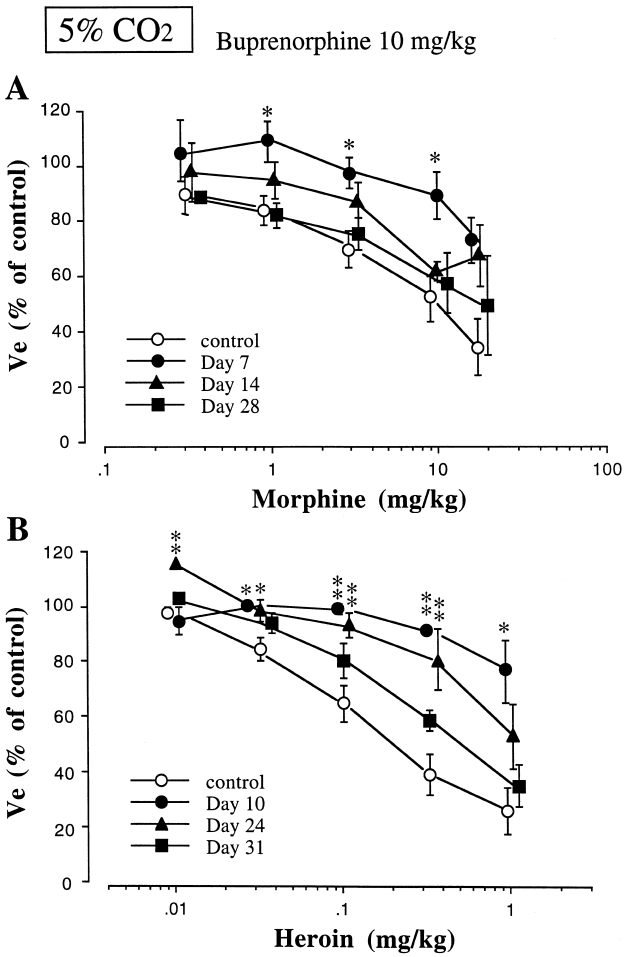

Fig. 6. Time course of the antagonist effects of buprenorphine 10 mg/kg against morphine (A)- and heroin (B)-induced decreases in minute volume (V_e). Data were collected during exposure to 5% CO_2 and are shown as the percent change from V_e on the first breathing cycle. Dose–response curves for morphine and heroin were obtained in the same monkeys on different days following buprenorphine administration. Each value represents the mean ± S.E.M. of five monkeys. $^{**}P < 0.01$, $^{*}P < 0.05$ vs. control (Newman–Keuls test).

approximately 6.3 l per min (Fig. 5A). When given 24 h following administration of buprenorphine 10 mg/kg, doses of morphine from 0.1 to 10 mg/kg did not further modify rates of respiration that were suppressed by this dose of buprenorphine at this time. Administration of 32 and 56 mg/kg morphine, which would likely have completely suppressed respiration if given alone, also did not modify V_e after buprenorphine administration. Thus, the ability of buprenorphine to block the effects of morphine on respiration was demonstrated at the larger doses of morphine (Fig. 5A). This was true of all three respiratory parameters when the animals were breathing either air or 5%CO_2 (data not shown for f and V_t).

Administration of increasing doses of heroin alone also produced respiratory suppression, with V_e values following administration of 1 mg/kg heroin reaching approximately 1.8 l per min (Fig. 5B). Heroin was approximately 10 times more potent than morphine in suppressing respiration. On the third day following administration of buprenorphine 10 mg/kg, respiration was significantly suppressed, and heroin, like morphine, did not modify this suppression. Blockade of the respiratory depressant effects of heroin at doses of 0.32, 1.0, and 3.2 mg/kg was observed at this time (Fig. 5B).

Seven days following administration of buprenorphine 10 mg/kg, no respiratory depressant effect remained. At this time, the ability of morphine to produce a dose-dependent suppression of respiration was restored, but significantly larger doses of morphine were required to effect this suppression than had been the case prior to administration of buprenorphine (Fig. 6A). Thus, buprenorphine continued to have μ-opioid receptor antagonist effects once its μ-opioid receptor agonist effects were no longer apparent. Sensitivity of respiration to morphine was nearly completely restored at 28 days following administration of buprenorphine 10 mg/kg.

The pattern of effect of heroin on minute volume was similar to that of morphine when it was measured 10 days

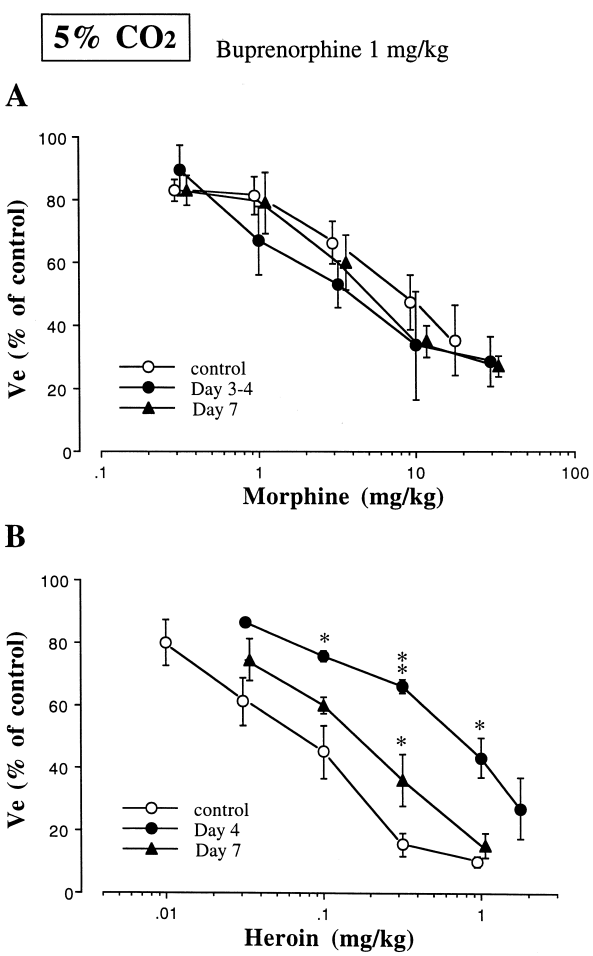

Fig. 7. Time course of the antagonist effects of buprenorphine 1 mg/kg against morphine (A)- and heroin (B)-induced decreases in minute volume. Other details are as in Fig. 6.

following administration of buprenorphine 10 mg/kg. There was, however, an absence of a heroin dose–response function at this time, suggesting a slightly greater protection by buprenorphine against the respiratory depressant effects of heroin. This is supported by the finding that the effects of heroin had not returned completely to the pre-buprenorphine levels even 31 days following buprenorphine administration (Fig. 6B).

As described earlier, the μ-opioid receptor agonists effects of a cumulative dose of buprenorphine 1 mg/kg had dissipated by 3 to 4 days following its administration. At this time, this dose of buprenorphine did not modify the respiratory depressant effects of morphine (Fig. 7A). It did, however, produce a significant decrease in the potency of heroin as a respiratory depressant, yielding a parallel shift to the right in the heroin dose–response curve (Fig. 7B). Seven days following administration of buprenorphine 1 mg/kg, the potency of heroin as a respiratory depressant had made a substantial recovery (Fig. 7B).

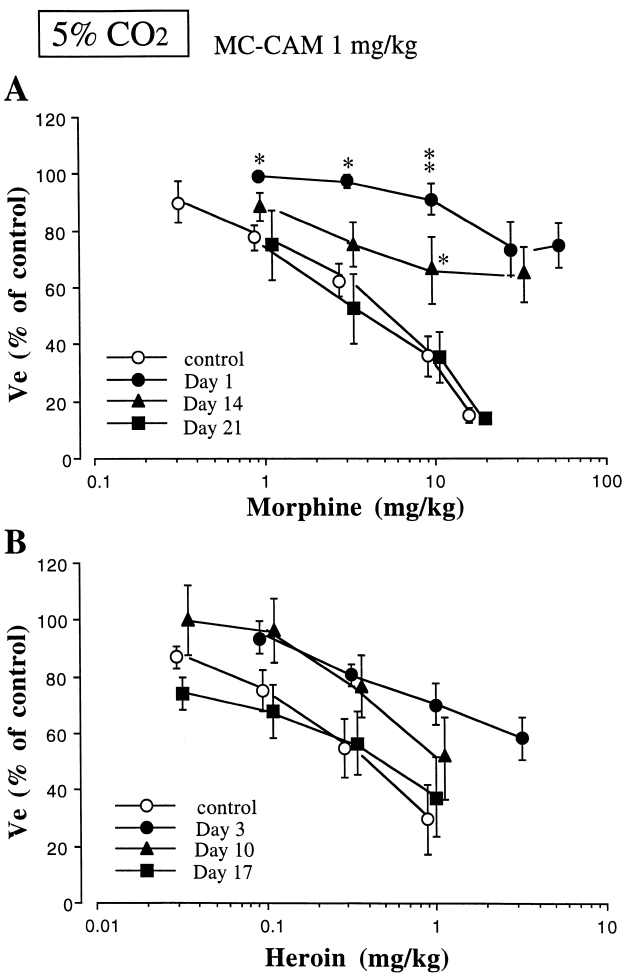

Fig. 8. Time course of the antagonist effects of methoclocinnamox 1 mg/kg on morphine (A)- and heroin (B)-induced decreases in minute volume. Other details are as in Fig. 6.

3.3.2. Methoclocinnamox

At 24 h following administration of methoclocinnamox, as described earlier, there was no residual μ-opioid receptor agonist effect observed. At this time, the potency of morphine as a respiratory depressant was markedly decreased (Fig. 8A). A dose of morphine (32 mg/kg) that would have suppressed respiration completely if given alone, produced only a 20% decrease in V_e when it was given 24 h following administration of methoclocinnamox 1 mg/kg. The potency of morphine had recovered somewhat at 14 days following methoclocinnamox administration, and the sensitivity of the system was normal at 21 days following methoclocinnamox administration.

Although the variability of the response to heroin was such as to preclude observations of significant methoclocinnamox-induced decreases in potency, the general picture was the same as that with morphine. Three days following methoclocinnamox administration, the potency of heroin as a respiratory depressant was decreased non-significantly, with a movement towards normalcy at 10 days following methoclocinnamox administration and complete recovery measured at 17 days post-methoclocinnamox (Fig. 8B).

The smaller dose of methoclocinnamox 0.1 mg/kg did not modify the effects of morphine on respiration at 1, 3, or 7 days following administration of methoclocinnamox. A slight, but non-significant decrease in the potency of heroin was observed 1 day following this dose of methoclocinnamox, and sensitivity to heroin was recovered on the seventh day after methoclocinnamox 0.1 mg/kg administration (data not shown).

4. Discussion

Up to the limit of solubility that either buprenorphine or methoclocinnamox could be given to rhesus monkeys, they appear to be limited respiratory depressants. The μ-opioid receptor agonist effects of buprenorphine appeared to plateau at a dose of 0.32 mg/kg, and no further decreases in respiration were observed with doses up to and including 10 mg/kg. Methoclocinnamox also appeared to have a limit on its ability to produce respiratory depression in monkeys breathing air. The largest dose of methoclocinnamox that could be tested (1.0 mg/kg) did not produce a greater suppression of breathing in air than did 0.32 mg/kg. There was, however, a tendency for methoclocinnamox 1.0 mg/kg to produce a greater suppression of breathing than did 0.32 mg/kg when the monkeys were breathing 5% CO_2. This may indicate a greater respiratory depressant potential for methoclocinnamox than buprenorphine in a therapeutic setting. In comparison with heroin and morphine, which clearly have the potential to produce complete respiratory arrest, both buprenorphine and methoclocinnamox were quite limited in their ability to suppress respiration. Liguori et al. (1996) also found that buprenor-

phine in doses up to and including 10 mg/kg had less ability to suppress respiration than did a number of μ-opioid receptor agonists with greater efficacy. Thus, neither buprenorphine or methoclocinnamox would be expected to produce serious respiratory depression under clinical circumstances, unless they were administered along with non-opioid respiratory depressants such as a benzodiazepine, alcohol, or a barbiturate.

The μ-opioid receptor agonist effects of buprenorphine persisted in a dose dependent manner. In the case of the largest dose (10 mg/kg), effects were detected for a week following administration. This too supports an earlier finding of Liguori et al. (1996). The duration of methoclocinnamox's μ-opioid receptor agonist effects did not appear to be dose dependent. Both 0.1 and 1.0 mg/kg of methoclocinnamox had effects that persisted for 2 h and were nearly gone at 24 h.

Data on reinforcing (Winger et al., 1992; Briscoe et al., in press) and analgesic (Walker et al., 1995; Butelman et al., 1996) potencies of methoclocinnamox and buprenorphine suggest that comparisons of μ-opioid receptor agonist effects of these drugs on respiration are appropriately done at the same dose. At a dose of 1 mg/kg, buprenorphine appeared to have a slightly longer duration of μ-opioid receptor agonist action than did methoclocinnamox. The effects of 1 mg/kg buprenorphine on rate of breathing was significantly decreased 48 h following its administration, and the effects on V_e were also decreased at this time, although not significantly. The ability of 1 mg/kg methoclocinnamox to suppress respiration had nearly completely disappeared at 24 h following its administration. The duration of the analgesic effects of methoclocinnamox 0.32 mg/kg in the rhesus monkey was 5 h, with complete recovery demonstrated at 24 h (Butelman et al., 1996). Buprenorphine 3.2 mg/kg produced full analgesia for 48 h following its administration, and the tail-withdrawal response had returned to normal at 72 h (Walker et al., 1995). These results are only suggestive of a longer duration of buprenorphine's analgesic response because potentially larger μ-opioid receptor agonist doses of buprenorphine than methoclocinnamox were used.

In the only study in which direct comparisons were made of the duration of μ-opioid receptor antagonist effects of equipotent μ-opioid receptor agonist doses of buprenorphine and methoclocinnamox, the ability of methoclocinnamox 1 mg/kg to antagonize the reinforcing effect of alfentanil lasted somewhat longer than a similar ability of 1 mg/kg buprenorphine (Briscoe et al., in press). In studies of duration of the antagonism of the analgesic effects of buprenorphine and methoclocinnamox, the potency and effectiveness of morphine as an analgesic recovered slowly over 21 days following a dose of 1 mg/kg methoclocinnamox (Butelman et al., 1996). There was recovery of the analgesic effects of alfentanil 10 days following administration of buprenorphine 3.2 mg/kg, but a faster recovery of the effects of a μ-opioid receptor agonist with greater efficacy (alfentanil in the study by Walker et al., 1995) is expected compared with a μ-opioid receptor agonist with less efficacy (morphine in the study of Butelman et al., 1996). In the present study, the antagonist effects of buprenorphine 1 mg/kg and methoclocinnamox 1 mg/kg are somewhat confusing. Buprenorphine at this dose produced a significant antagonism of the respiratory effects of heroin that were still present to a reduced extent 7 days following administration of buprenorphine. Under identical conditions, buprenorphine 1 mg/kg had little effect on the respiratory depressant effects of morphine. These puzzling results are not supported by the data with methoclocinnamox 1 mg/kg, which produced larger and more significant antagonism of the respiratory depressant effects of morphine than of heroin. Perhaps, the most that can be said of these data is that when buprenorphine 1 mg/kg produced an antagonism of a μ-opioid receptor agonist (heroin), that antagonism lasted for as long as 7 days. When methoclocinnamox 1 mg/kg produced an antagonism of the respiratory effect of a μ-opioid receptor agonist (morphine), that antagonism lasted as long as 14 days. With the clear restrictions presented by the data, they suggest that following administration of an equipotent μ-opioid receptor agonist dose, methoclocinnamox has a longer duration of μ-opioid receptor antagonist action than does buprenorphine.

The effects of a large dose of buprenorphine (10 mg/kg), which had no greater μ-opioid receptor agonist effect on respiration than did 1 mg/kg 30 min following its administration, produced only a slightly longer duration of antagonism of the respiratory depressant effects of both morphine and heroin. Marked decreases in the potency of morphine and heroin were observed at 7 and 10 days, respectively, following administration of buprenorphine 10 mg/kg. This antagonism resolved over the course of 28 to 31 days.

Buprenorphine 10 mg/kg also produced marked blockade of the effects of large doses of morphine and heroin while buprenorphine itself still had μ-opioid receptor agonist effects on respiratory measures (1 and 3 days following buprenorphine administration). This is a typical profile of activity of a μ-opioid receptor partial agonist which has the capacity to reduce the effect of a μ-opioid receptor agonist with greater intrinsic activity to the level produced by the partial μ-opioid receptor agonist (Kenakin, 1993). In the case of a competitive μ-opioid receptor partial agonist, the effects of the μ-opioid receptor agonist should be decreased but not blocked completely as the dose of the μ-opioid receptor agonist is increased. The inability of morphine and heroin to produce any effects on respiration above those produced by buprenorphine and methoclocinnamox most likely reflect the receptor kinetics of these agents, whereby they are very slowly dissociated from the μ-opioid receptor. Thus, morphine and heroin, having very little access to the receptor, remain ineffective even at

large doses. This indicates that acute administration of either buprenorphine and methoclocinnamox would protect against the lethal effects of μ-opioid receptor agonists such as heroin if the treatment agents were given in the recent past. What is not known is how these μ-opioid receptor partial agonists would affect respiration or how they would modify the respiratory depressant effects of heroin and morphine if the μ-opioid receptor partial agonists were given on a chronic basis, as they would be given for the treatment of opioid abuse.

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