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# Opioid agonist and antagonist behavioural effects of buprenorphine

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**1** The agonist and antagonist effects of a range of bupenorphine doses (0.08–20 mg/kg) were studied on the responding of pigeons under a multiple fixed-ratio, fixed-interval schedule of grain presentation. Various doses (0.02–10 mg/kg) of buprenorphine were also tested in pigeons trained to discriminate between injections of 0.05 mg/kg of fentanyl and injections of distilled water.

**2** Buprenorphine, over a broad dose range (0.08–5 mg/kg), increased the rates of responding in the fixed-interval component of the multiple schedule and disrupted patterning of responding within the fixed-interval, without affecting fixed-ratio responding even at a dose of 40 mg/kg. The effects of some of the high doses on fixed-interval responding were still evident one and two days after buprenorphine injection.

**3** Doses of buprenorphine which produced increases in fixed-interval responding were also effective as antagonists of the behavioural depression produced by 40 mg/kg of morphine, and were discriminated as fentanyl-like by pigeons trained to discriminate between injections of fentanyl and injections of water.

**4** These results show that buprenorphine produces marked agonist and antagonist effects over an extremely broad dose range without producing behavioural depressant effects.

## Introduction

Buprenorphine is a member of the oripavine series of narcotic structures and is a close analogue of the potent opioid agonist, etorphine and the antagonist diprenorphine (Cowan, Lewis & MacFarlane, 1977; Cowan, Doxey & Harry, 1977). Buprenorphine exhibits both opioid agonist and antagonist effects in laboratory animals. It produces an analgesic effect at much lower doses than morphine and also antagonizes the analgesic effect of morphine. Like other opioid agonists, buprenorphine produces the Straub tail response and increases locomotor activity in mice, exerts an antitussive effect in guinea-pigs, decreases urinary output and slows gastrointestinal propulsion in rats. Like other opioid antagonists, buprenorphine precipitates signs of opioid abstinence in morphine-dependent mice and monkeys. Thus, buprenorphine has been categorized as a partial agonist-antagonist of the morphine-type (Houde, 1979; Martin, 1979). It is considered to be of the morphine type, in contrast to nalorphine, cyclazocine and pentazocine, which appear to produce their agonist effect at receptors other than the one at which morphine produces its effect (the $\mu$-receptor) (Martin, 1979).

Opioid agonists and antagonists have been extensively studied on schedule-controlled responding in the pigeon (McMillan & Morse, 1967; McMillan, Wolf & Carchman, 1970; Dykstra, McMillan & Harris, 1974; Downs & Woods, 1976; Goldberg, Morse & Goldberg, 1976; 1981). Morphine and morphine-like agonists produce dose-related decreases in the rates of responding which can be completely antagonized by doses of opioid antagonists (naloxone or naltrexone) which have no behavioural effects of their own. For example, 1 mg/kg of naloxone will antagonize the behavioural suppressant effects of morphine, whereas doses of 30 and 56 mg/kg of naloxone alone are required to produce such effects. Both naloxone and naltrexone are considered to be 'pure' opioid antagonists because they exhibit opioid antagonist effects without exhibiting any opioid agonist effects. These drugs contrast with the partial agonist-antagonist drugs, nalorphine, cyclazocine, pentazocine and profadol, which exhibit both opioid

antagonist and agonist effects (Houde, 1979; Martin 1979). Martin (1979) proposed that nalorphine, cyclazocine and pentazocine produce their morphine antagonist effects at a $\mu$-opioid receptor, whereas their agonist effects are produced at the $\kappa$- and $\sigma$-opioid receptors. Profadol, like buprenorphine, is considered to exert both its agonist and antagonist effects at the $\mu$-opioid receptor. Since a recent study showed that profadol was ineffective in antagonizing the effects of morphine on schedule-controlled responding (Leander, 1982a), the present study was undertaken. The purposes of the present study were (1) to determine the effects of buprenorphine on the schedule-controlled responding of the pigeon; (2) to determine if buprenorphine would antagonize the behavioural effects of morphine; and (3) to determine if buprenorphine would produce discriminative effects similar to those produced by fentanyl. If buprenorphine generalizes to fentanyl, as it did in the rat (Colpaert, 1978), it would suggest that buprenorphine was producing its agonist actions at a $\mu$-opioid receptor (Shearman & Herz, 1982). Previous study of the fentanyl cue in pigeons by the author (unpublished) indicated that the cue was $\mu$-like (Herling, Coale, Valentino, Hein & Woods, 1980), that is, other $\mu$-opioids (morphine, (−)-methadone, profadol) were generalized to fentanyl and it was antagonized by low doses of naloxone (0.01 mg/kg).

## Methods

### *Animals*

Eight male White Carneaux pigeons were housed in individual cages and maintained at approximately 80% (420–460 g body wt.) of their free feeding weight by pigeon grain (Purina) presented during experimental sessions and by post-session feeding, if necessary. Oyster shell grit was freely available in the home cage, and water was always available in both the home cage and the test cage. The four birds used in the manipulations with the multiple schedule of grain presentation had various histories prior to the beginning of this experiment. Before the present study, which extended over 7 months, all four of these birds had previously been in experiments involving the administration of profadol and morphine (Leander, 1982a) and phenazocine, ethylketazocine, and ketazocine alone and in combination with various doses of naloxone (Leander, 1982b) extending over one year. One of the birds (227) had previously participated in experiments (over 4 years) involving interactions of meperidine with diazepam, pentobarbitone and chlorpromazine (Leander 1979a); fentanyl alone, in interaction with naloxone, and during daily dosing with methadone (Leander, 1978); azabicyclane alone and with naloxone (Leander, 1979b); (−)-methadone alone and with naloxone (Leander & McCleary, 1982), and piribedil alone and with doses of haloperidol and $\alpha$-methyl-tyrosine (Leander, 1982c). The behavioural effects of buprenorphine in this bird were not distinguishable from the effects obtained in the birds without this experience. The four birds trained to discriminate injections of fentanyl had also been tested with various narcotic drugs before the beginning of this experiment. There was no evidence that these histories had any determining effects on the present results.

### *Apparatus*

The experimental chambers were sound-attenuating and ventilated (Ferster & Skinner, 1957). The experimental space was 29 cm high × 27 cm wide and 29 cm long. In the chamber used for the multiple schedule, there was one translucent plastic response key, 2 cm in diameter, which was mounted in the centre of a wall inside the chamber, 22 cm above the wire mesh floor. This response key could be transilluminated by red or blue lights. In the chamber used for the drug discrimination experiment, there were two translucent plastic response keys mounted 7 cm to each side of the midline of a wall about 22 cm above the wire mesh floor. These keys could be transilluminated by green (left key) or red (right key) lights. In either chamber a peck with a minimal force of 0.15 N operated the key, defined a response, and produced an audible 'click' from a feedback relay. Below the response keys was a rectangular opening through which the pigeon could be given access to mixed grain. The experimental space was illuminated by a 7.5 W bulb. During the 4 s grain presentation cycle, all lights in the test chamber were off except one illuminating the grain. Relay programming and recording equipment in an adjacent room controlled events and recorded the data.

### *Procedure*

*Multiple schedule responding* The multiple fixed-ratio 30-response, fixed-interval 5 min schedule (mult FR-30, FI-5) can be described in the following manner (Ferster & Skinner, 1957). When a blue light transilluminated the response key, the 30th response produced the 4 s grain presentation (FR-30). When a red light transilluminated the response key, the first response to occur after 5 min had elapsed produced grain presentation (FI-5). A 40 s limited hold was in effect in both components; i.e., in the FR component, the bird had 40 s to make the 30 responses, and in the FI component, the bird had 40 s after 5 min had elapsed to respond and produce grain presentation. Schedule components alternated after each grain

presentation or when the limited hold elapsed. Sessions were conducted from Monday to Friday for 1 h each day and began in the FR component.

During the determination of dose-effect relationships of buprenorphine alone, injections of vehicle (distilled water) were given on Tuesdays of each week, and various doses of buprenorphine were given on Wednesdays. No injections were given on Mondays, Thursdays or Fridays. In order to determine the morphine-antagonist effects of buprenorphine, various doses of buprenorphine were administered with 40 mg/kg of morphine, a supramaximal dose of morphine for virtually eliminating responding throughout the hour session. The morphine was administered either simultaneously with the buprenorphine or one day after buprenorphine. When two injections were scheduled, one injection was made into the right breast muscle and the second injection was made without delay into the left breast muscle. After injections, the bird was immediately placed in the test chamber and the 60 min test session started 10 min later.

Average rates of responding for each bird during the FR and FI components were computed in responses per second from digital counters and elapsed time meters. Drug effects were then calculated as a percentage of the mean control values obtained in sessions when distilled water (vehicle) was injected (Tuesdays). The dose-effect data were summarized by determining the mean and s.e. mean for the group of birds. The distribution of responses within the FI component of the multiple schedule was obtained by dividing the interval into ten 30 s segments and recording the number of responses in each segment. These data were used to calculate the quarter-life value, a statistic which is independent of response rate and is used to describe quantitatively the positively accelerated pattern of responding that occurs under the FI schedule (Herrnstein & Morse, 1957; Gollub, 1964). The quarter-life value which was calculated is the percentage of the FI required for the bird to emit 25% of the total responses in the FI.

The effects of buprenorphine alone and in interaction with morphine were analyzed for statistical significance by using Dunnett's (1955) test for comparing multiple treatments with a control (Winer, 1962). In Dunnett's test, the level of significance is for the collection of all comparisons of each treatment with control, and is statistically more conservative than a level of significance for each comparison. This test uses a common estimate of experimental error so that the parameter of the Dunnett's $t$ statistic are K = number of treatments (including control) and d.f. = degrees of freedom for MS error. A critical difference for $P<0.05$ was calculated for each control mean, and treatment means exceeding that value were considered statistically significant.

*Fentanyl discrimination* The four birds used in this experiment had been trained previously to discriminate between injections of distilled water and injections of 0.05 mg/kg of fentanyl using procedures somewhat similar to those of Herling *et al.* (1980) and Colpaert, Lal, Niemegeers & Janssen (1975). During training each pigeon was required to make 30 consecutive responses (FR-30) on only one of the two keys in order to produce 4 s access to grain. The appropriate key on which responding would produce grain depended upon whether distilled water or fentanyl had been injected. For two birds the appropriate key after fentanyl injections was the left key, whereas it was the right key for the other two birds (the appropriate key after water injection was opposite the fentanyl key). Responses on the inappropriate key reset the fixed-ratio requirement on the appropriate key. The sessions ended after 40 presentations of grain or after 20 min, whichever occurred first.

Training sessions had been conducted five days a week (Monday to Friday) with either distilled water or 0.5 mg/kg of fentanyl being injected 15 min before each test session. The sequential order of injections was different for each bird and was indentical to that outlined by Colpaert, Niemegeers & Janssen (1977). Training had continued until each pigeon met the criteria of making less than 30 inappropriate responses for 10 consecutive training sessions. Once these animals had met the criteria, they were tested with various narcotic drugs, and those data will be described in another paper.

For testing the discriminative effects of buprenorphine, the fentanyl or distilled water training conditions continued on Mondays and Tuesdays of each week. In the number of inappropriate responses were fewer than 30 responses on those training days, a dose of buprenorphine was injected 15 min before the test session on Wednesday. If the bird was injected with buprenorphine on Wednesday, it was also injected with water on Thursday and Friday, and test conditions were in effect for Wednesdays, Thursdays and Fridays. During test conditions, the first key on which 30 consecutive responses was accumulated was defined as the selected key, and during the remainder of the test session, only responding on that key was reinforced (Colpaert *et al.*, 1975). Data are presented, after various treatment conditions, on the percentage of the four birds which 'selected' the drug key and the response rate as a percentage of the vehicle injection control rate.

*Drugs*

The drugs used and the forms in which doses were calculated were: buprenorphine hydrochloride (obtained from the National Institute on Drug Abuse),

**Table 1** Control data for individual birds

**A** *Control data (mean ± s.d.) for buprenorphine under the multiple FR-FI schedule.*

| *Bird number* | *1383* | *227* | *3137* | *1593* |
|---|---|---|---|---|
| Resp./s FR | 2.79 ± 0.16 | 2.38 ± 0.24 | 1.63 ± 0.28 | 2.15 ± 0.48 |
| Resp./s FI | 0.54 ± 0.09 | 0.76 ± 0.13 | 0.73 ± 0.13 | 0.78 ± 0.18 |
| Quarter life | 59 ± 4% | 63 ± 5% | 64 ± 4% | 59 ± 5% |
| Number of control sessions | 21 | 22 | 22 | 22 |

**B** *Control data (mean s.d.) for the fentanyl-water discrimination*

| *Birds* | *Water Res p./s* | *Fentanyl Res p./s* | *Number of sessions* |
|---|---|---|---|
| 4642 | 2.24 ± 0.18 | 1.92 ± 0.50 | 6 |
| 4547 | 1.99 ± 0.31 | 1.94 ± 0.27 | 7 |
| 4614 | 1.47 ± 0.17 | 1.37 ± 0.40 | 5 |
| 3735 | 2.03 ± 0.26 | 2.78 ± 0.22 | 8 |

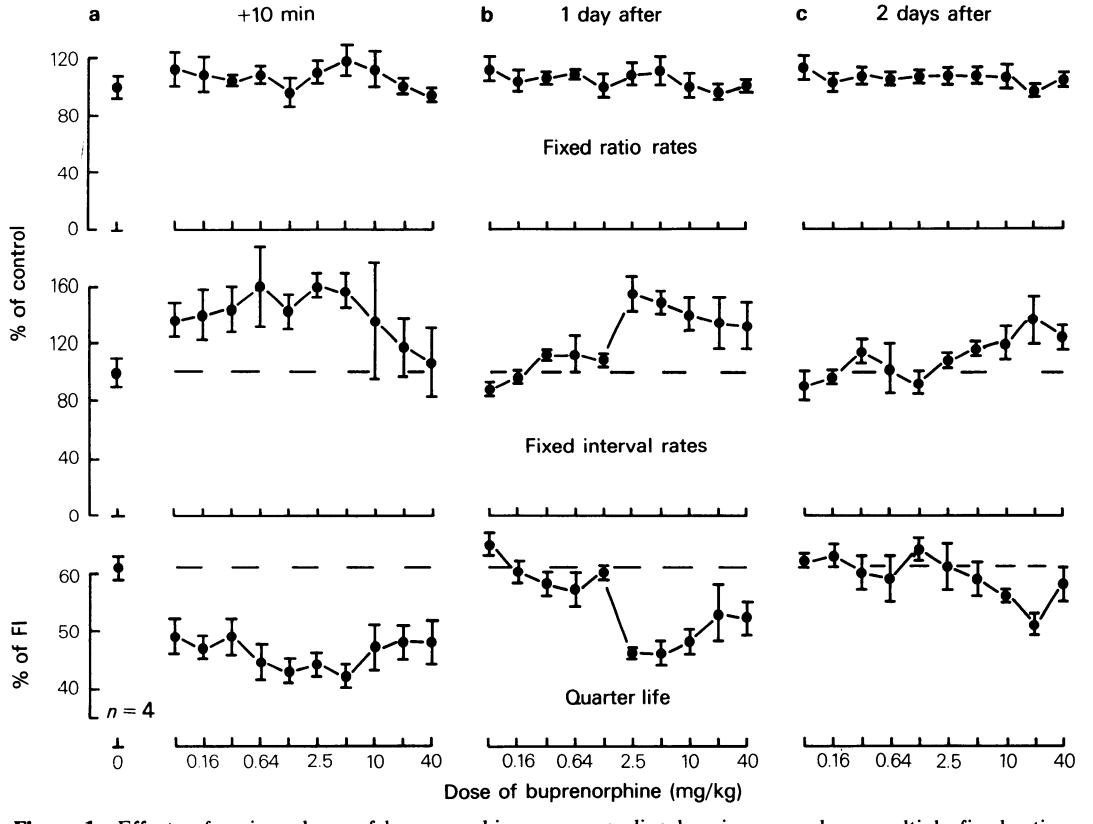


**Figure 1** Effects of various doses of buprenorphine on responding by pigeons under a multiple fixed-ratio, fixed-interval schedule of grain presentation. Column (a) shows the effects on an hour session beginning 10 min after injection of buprenorphine. Column (b) and (c) show the effects on hour sessions beginning one and two days, respectively, after injection of buprenorphine. The top and middle rows show the effects on mean rates of responding under the fixed-ratio and fixed-interval components, respectively, of the multiple schedule plotted as a percentage of the control values in Table 1. The lower row shows the effects of buprenorphine on the patterning of responding within the fixed-interval as quantified by the quarter-life value (see Methods section). The dose range tested was from 0.08 mg/kg to 40 mg/kg. Each point indicates the mean and vertical lines indicate s.e. for 4 birds.

morphine sulphate, and fentanyl citrate (gift from McNeil Laboratories, Fort Washington, PA, U.S.A.). All drugs were dissolved in distilled water (with heating if necessary) and distilled water was used for vehicle injections. All injections were given in a volume of 1 ml/kg of body weight, except doses of buprenorphine above 5 mg/kg. These large doses were administered in a 5 mg/ml solution and the volume injected was increased. Doses above 40 mg/kg were not studied because of the limited solubility, the large injection volume required for high doses, and the very limited amount of drug which was available for these studies.

## Results

### *Effects of buprenorphine alone on multiple FR-FI responding*

Table 1A shows the control data for the individual birds under the multiple FR-FI schedule. The control performances were similar to those previously described for pigeons responding under similar test conditions (Ferster & Skinner, 1957; McMillan & Morse, 1967 Goldberg *et al.*, 1981). At the beginning of each FR component, there was a brief pause which was followed by a high rate of responding for 30 responses and subsequent grain presentation. At the beginning of each FI component, there was no responding, which was followed by a positively accelerated pattern of responding until the end of the FI and grain presentation occurred. This positively accelerated pattern is quantified by the quarter-life value.

Figure 1 shows the effects of various doses of buprenorphine alone on the day injected (+10 min) and one and two days after injection. In the sessions which began 10 min after injection of buprenorphine, there was no effect on the rates of responding in the FR component, but there was a tendency to increase responding in the FI component over the dose range of 0.08–5 mg/kg, with the increases after 0.64 and 2.5 mg/kg being significant ($P<0.05$, Dunnett's $t$, d.f. = 30, treatments = 11). On the day of injection, all doses of buprenorphine from 0.08 to 40 mg/kg significantly decreased ($P<0.05$, Dunnett's $t$, d.f. = 30, treatments = 11) the FI quarter-life values, indicating that there was increased responding early in the FI and a lessening of the positively accelerated pattern of responding in the FI. FI response rates were still elevated significantly and quarter-life values were still decreased significantly ($P<0.05$, Dunnett's $t$, d.f. = 30, treatments = 11) one day after injections of 2.5, 5 and 10 mg/kg buprenorphine. The small increases in FI rates and decreases in the quarter-life values observed two days after injection of the highest doses of buprenorphine were not statistically different from control values.

Figure 2 shows the morphine antagonist effects of buprenorphine. These data are the mean effects in three birds; the data for bird 3137 were not included because 40 mg/kg of morphine produced such a severe depression of responding in the bird. In the three birds used (227, 1383 and 1593), 40 mg/kg of morphine produced almost complete suppression of responding with mean FR rates of 8% of control and FI rates of 14% of control. When all buprenorphine treatments are compared to morphine alone, 1.25 mg/kg of buprenorphine significantly antagon-

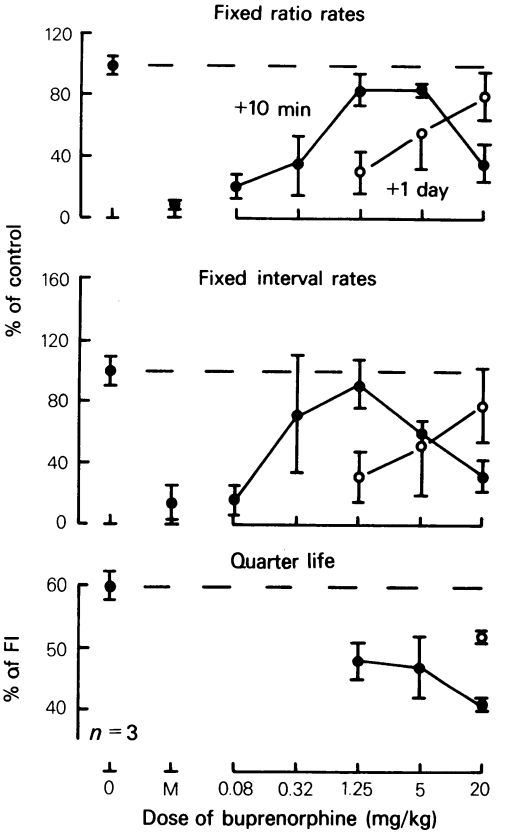


**Figure 2** Effects of various doses of buprenorphine as an antagonist of the behavioural depressant effects of 40 mg/kg of morphine on responding under the multiple fixed-ratio, fixed-interval schedule of grain presentation. The filled circle above M shows the effects of 40 mg/kg of morphine alone. The filled circles to the right show the effects of that dose of morphine administered concurrently with the indicated doses of buprenorphine. The open circles show the effects of 40 mg/kg of morphine administered one day after the indicated doses of buprenorphine. Other details are with Figure 1, except each point and vertical line indicates the mean and s.e. for 3 birds. The quarter-life value was not plotted if responding by all 3 birds did not exceed 0.1 response/s in the FI.

**Table 2** Effects (mean ± s.d.) of buprenorphine on the fentanyl-water discrimination

| | *Resp. rate % of control)* | *% animals selecting fentanyl key* |
|---|---|---|
| Water | 100 ± 6 | 0 |
| 0.05 mg/kg fentanyl | 103 ± 9 | 100 |
| 0.02 mg/kg buprenorphine | 103 ± 5 | 0 |
| 0.08 mg/kg buprenorphine | 108 ± 15 | 100 |
| 0.32 mg/kg buprenorphine | 113 ± 16 | 100 |
| 1.25 mg/kg buprenorphine | 98 ± 23 | 100 |
| (+1 day) | (88 ± 9) | (0) |
| 10 buprenorphine | 107 ± 20 | 100 |
| (+1 day) | (105 ± 22) | (100) |
| (+2 days) | (95 ± 17) | (75) |

ized the behavioural suppressing effects of 40 mg/kg of morphine in both schedule components. Higher doses were less effective in antagonizing the effect of morphine. When the doses of buprenorphine were administered one day before the 40 mg/kg dose of morphine, the 1.25 mg/kg dose of buprenorphine was not effective in antagonizing morphine, whereas 20 mg/kg of buprenorphine was effective in significantly antagonizing the suppression of responding in the FR component produced by 40 mg/kg of morphine. Note that during sessions when the morphine-induced response rate decreases were antagonized by buprenorphine, the quarter-life values were different from control values. Since 40 mg/kg of morphine so markedly suppressed FI responding, no quarter-life value could be calculated. In bird 3137, which was so markedly depressed by 40 mg/kg of morphine, the dose of 20 mg/kg of morphine decreased response rates to less than 10% of control in both schedule components. This effect was antagonized by administration of low (0.04 or 0.08 mg/kg) doses of buprenorphine. It was also antagonized by 5 mg/kg, but not 1.25 mg/kg, of buprenorphine administered the day before the morphine.

*Effects of buprenorphine on the fentanyl-water discrimination*

Table 2 shows the results from testing various doses of buprenorphine in pigeons trained to discriminate between 0.05 mg/kg of fentanyl and distilled water. After water, all birds responded on the water-appropriate response key, whereas after 0.05 mg/kg of fentanyl all responding was on the fentanyl-appropriate response key. All responding occurred on the water-appropriate key after the lowest dose of buprenorphine (0.02 mg/kg). With higher doses of buprenorphine, all responding occurred on the fentanyl-appropriate key when tested 15 min after buprenorphine injection. Water-appropriate responding was present the day after all doses of buprenorphine except 10 mg/kg. After this dose all responding occurred on the fentanyl-appropriate key following a water injection the day after buprenorphine. Even two days after 10 mg/kg buprenorphine, the fentanyl-appropriate response key was selected 75% of the time.

## Discussion

The present results show that buprenorphine increases the rates and decreases the positively-accelerated pattern of responding under the FI schedule over a large dose range (>500 fold increase in dose) without affecting the rates of responding under the FR schedule. These effects on responding under the FI were still apparent one and two days after the higher doses of buprenorphine. Morphine and methadone have been reported to increase FI rates slightly and decrease quarter-life values under test conditions similar to the present conditions (McMillan *et al.*, 1970; Downs & Woods, 1976; Goldberg *et al.*, 1976), but usually they have this effect over a very small dose range and with only small increases in average rates. By comparison, the present results are robust. Other opioid partial agonists or mixed agonists/antagonists (morphine, pentazocine, cyclazocine, profadol) do not increase FI rates as markedly or decrease quarter-life over such a broad dose range nor do they exhibit such a lack of graded effect over that dose range (McMillan & Morse, 1967, Downs & Woods, 1976; Goldberg *et al.* 1976; Leander, 1982a).

In the birds trained to discriminate between injections of 0.05 mg/kg of fentanyl and injections of distilled water, doses from 0.08 to 10 mg/kg of buprenorphine were discriminated similarly to fentanyl. Previous studies by the author (unpublished) of other opioid agonists, and interactions with naloxone, indicate that the fentanyl cue was a typical opioid agonist discriminative effect, similar to opioid agonist discriminative effects described previously (Colpaert *et al.*, 1975; Schaefer & Holtzman, 1977; Jarbe, 1978;

Herling *et al.*, 1980; Herling & Woods, 1981). The major difference between the discriminative effects of opioids in pigeons and those in other species is that prototype κ-agonists, ketazocine and ethylketazocine, have been generalized to μ-agonists, morphine (Herling *et al.*, 1980; Herling & Woods, 1981) and fentanyl (unpublished experiments by the author). In the present study, buprenorphine produced opioid agonist-like discriminative effects over the dose range of 0.08 to 10 mg/kg. Colpaert (1978) found that buprenorphine was completely generalized to the fentanyl cue in rats also at 0.08 mg/kg. Like the effects on FI responding under the multiple schedule, the discriminative effects were also present one and two days after the highest dose of buprenorphine.

The mixed agonists/antagonists, cyclazocine and nalorphine, have frequently been shown to produce inverted U-shaped dose-response curves in discrimination experiments with morphine or fentanyl as the training drug (Colpaert *et al.*, 1976; Shannon & Holtzman, 1976; Herling *et al.*, 1980); It has been hypothesized that this effect is characteristic of mixed agonists/antagonists (Colpaert, 1978). In contrast, buprenorphine (in the present study and Colpaert, 1978) and profadol (Shannon & Holtzman, 1976) do not exhibit such inverted U-shaped dose-response curves. This is probably due to the fact that buprenorphine and profadol are partial agonists; that is, they produce their antagonist actions at the same receptors as they produce their agonist actions (Martin, 1979). Nalorphine and cyclazocine are truly mixed agonists/antagonists since at higher doses they have significant κ- and σ-type opioid agonist activities (Martin, 1979). The inverted U-shaped dose-effect curve in drug discrimination experiments with nalorphine and cyclazocine are probably due to these actions becoming predominant and thus masking the μ-opioid discriminative effects.

Buprenophine was an effective antagonist of the behavioural suppression produced by 40 mg/kg of morphine in the present study. The 40 mg/kg dose of morphine was a supramaximal dose for producing suppression, since others have found similar levels of behavioural suppression in pigeons using doses of morphine from 10 to 30 mg/kg (McMillan *et al.*, 1970; Goldberg *et al.*, 1976; Downs & Woods, 1976; Leander & McMillan, 1977). The behavioural suppression produced by 10 mg/kg of morphine in the pigeon responding under the multiple FR-FI schedule can be antagonized completely by selected doses of naloxone (1 mg/kg: Downs & Woods, 1976; 1 and 10 mg/kg: Goldberg *et al.*, 1976; 0.3–30 mg/kg: McMillan *et al.*, 1970) and cyclazocine (0.1 and 1 mg/kg: McMillan *et al.*, 1970). In contrast, suppression produced by 30–32 mg/kg of morphine can only be partially antagonized by naloxone or cyclazocine, irrespective of the dose of antagonist used (Downs & Woods, 1976; Leander & McMillan, 1977). Thus, the antagonism of 40 mg/kg of morphine produced by 1.25 mg/kg of buprenorphine in the present study was remarkable.

Although buprenorphine antagonized the morphine-induced response rate decreases, the quarter-life values were well below control levels. This reflects the agonist effects of buprenorphine on FI patterning since the quarter-life values obtained in the presence of 40 mg/kg of morphine are similar to those obtained with the same doses of buprenorphine alone (Figure 1). In contrast, relatively 'pure' opioid antagonists such as naloxone and naltrexone antagonize the effects of opioid agonists on response patterning as well as on average response rates (McMillan *et al.*, 1970). That was not the case with buprenorphine in the present study. With buprenorphine, the agonist effects on the quarter-life are apparent during the antagonism of morphine. Thus, these morphine antagonist effects complement the results in rodents where buprenorphine antagonizes the analgesic effects of morphine (Cowen *et al.*, 1977), and extends these findings to include schedule-controlled patterns of responding. On both the schedule-controlled responding and the analgesic measures, the antagonist effects of buprenorphine occur over the same dose range as the agonist effects.

The present results indicate that after intramuscular injection of buprenorphine, effects of high doses were demonstrable one and two days later. Thus, both its agonist and antagonist effects were very long-lasting. These effects complement the results of Mello, Bree & Mendelson (1981) who showed that the effects of buprenorphine on monkeys persisted for 24 to 48 h. This also is consistant with long-lasting effects in man (Jasinski, Pevnick & Griffith, 1978).

The discrimination study indicated that the pigeon discriminated buprenorphine as being similar to fentanyl, a classical opioid agonist. Mello *et al.*, (1981) showed that buprenorphine could serve as a positive reinforcer, which strengthens the interpretation that its subjective effects are similar to other opioid agonists. Heroin addicts have also found that buprenorphine produces subjective effects similar to other morphine-like opioid agonists (Jasinski *et al.*, 1978; Mello & Mendelson, 1980). This agonist activity of buprenorphine makes it preferred by addicts as an antagonist to block the effects of heroin, as compared to naltrexone, an antagonist without concomitant agonist activity (Mello & Mendelson, 1980).

Thus, the present studies show that buprenorphine exhibits both opioid agonist activity (of the morphine type) and opioid antagonist activity over the same range of doses. Likewise, both the agonist and antagonist activities are of long duration after large doses. No behavioural or respiratory signs of central

nervous system depression were observed with buprenorphine even with intramuscular doses of 40 mg/kg.

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