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THE ANIMAL PHARMACOLOGY OF BUPRENORPHINE, AN ORIPAVINE ANALGESIC AGENT

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1 The general pharmacology of buprenorphine, a potent analgesic agent derived from oripavine, is described.

2 After acute administration of buprenorphine, the spontaneous locomotor activity of mice was increased; rats displayed stereotyped licking and biting movements; behavioural depresssion was marked in guinea-pigs but mild in rhesus monkeys. The behaviour of cats was unchanged.

3 In general, buprenorphine reduced heart rate but had no significant effect on arterial blood pressure in conscious rats and dogs.

4 In anaesthetized, open-chest cats buprenorphine (0.10 and 1.0 mg/kg, i.v.) caused no major haemodynamic changes.

5 Buprenorphine (0.01–10 mg/kg, i.a.) and morphine (0.30–30 mg/kg, i.a.) increased arterial P_{CO_2} values and reduced P_{O_2} values in conscious rats. With doses of buprenorphine greater than 0.10 mg/kg (a) the duration of respiratory depression became less, (b) ceiling effects occurred such that the maximum effects produced were less than those obtained with morphine.

6 Buprenorphine was a potent and long-lasting antagonist of citric acid-induced coughing in guinea-pigs.

7 At a dose level 20 times greater than the ED_{50} for antinociception (tail pressure), morphine suppressed urine output to a greater extent than the corresponding dose of buprenorphine in rats.

8 Over the range 0.01–1.0 mg/kg (s.c.), buprenorphine slowed the passage of a charcoal meal along the gastrointestinal tract in rats. After doses in excess of 1 mg/kg, the meal travelled increasingly further such that the distances measured after 10 and 30 mg/kg did not differ significantly from control values. In contrast, the morphine dose-response relationship was linear.

Introduction

Buprenorphine [*N*-cyclopropylmethyl-7*α*-(1-*S*-hydroxy, 1,2,2-trimethylpropyl)-6,14-*endo*ethano-6,7,8,14-tetrahydronororipavine](RX 6029-M) is a new potent antinociceptive agent, chemically related to the narcotic antagonist, diprenorphine (M5050). It has been predicted from studies in rodents and monkeys that buprenorphine will be a long-acting, effective analgesic with a low physical dependence liability in man (Cowan, Lewis & Macfarlane, 1977). In the present paper, a comparison is made of the effects of buprenorphine and reference analgesics on animal behaviour, cardiovascular and respiratory function, experimental cough, urine output and gastrointestinal motility. A preliminary communication on the general pharmacology of buprenorphine was given at the Sixth International Congress of Pharmacology, Helsinki, Finland (July, 1975).

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Methods

Animals

The experiments were carried out on male albino mice (MFI/Ola, 18–24 g), male Sprague-Dawley albino rats in the weight ranges indicated in the text, male albino guinea-pigs (250–350 g), cats (2–3 kg), beagle dogs (8–15 kg) and rhesus monkeys (*Macaca mulatta*, 4–6 kg).

Compounds

The following compounds were dissolved or diluted in 0.9% w/v NaCl solution (saline) and the doses calculated in terms of the free base: buprenorphine hydrochloride (mol. wt. of base is 467.6; Reckitt & Colman), butorphanol tartrate (Bristol), methadone hydrochloride, B.P. (Macfarlan Smith), morphine sulphate, B.P. (Macfarlan Smith), naloxone hydrochloride (Endo) and pentazocine lactate (Sterling-Winthrop). The free base of cyclazocine (Sterling-Winthrop) was dissolved in a

minimal amount of 0.1 N HCl, the pH adjusted to 5 with $NaHCO_3$ solution and made up to volume with saline.

Behavioural effects

Groups of 10 mice were given 3 x 3 min training runs over 1 h on a rota-rod treadmill (Ugo Basile); they were injected subcutaneously with buprenorphine or cyclazocine, then retested 30 or 60 min later. Muscular incoordination was considered present in those mice falling off the rota-rod within 30 seconds.

Groups of 5 mice or 3 rats (100–120 g) received saline (s.c.) at 10 h 00 min and spontaneous locomotor activity in the home (makrolon) cage was recorded at 15 min intervals for the following 6 h with an Animex monitor (Farad Electronics, sensitivity and tuning set at 40 μA). The same animals were injected with test drug 24 h later and the cumulative activity counts were again recorded.

The cataleptic effects of buprenorphine and morphine were estimated 0.5, 1.5 and 2.5 h after subcutaneous administration to groups of 10 guinea-pigs. The number of animals leaving both hind legs over a horizontal metal rod (4 cm above bench level) for longer than 45 s was recorded.

The behaviour of 5 cats (grouped in a large animal room) was monitored for 6 h after subcutaneous injection of saline. One week later each cat received buprenorphine subcutaneously and the animals were observed over the following 6 h and at regular intervals throughout the following day.

Rhesus monkeys (in two groups of 3 and 2) whose behavioural patterns had previously been recorded were injected subcutaneously with buprenorphine and observed through a one-way mirror for the following 6 hours.

Cardiovascular effects

The descending aorta of rats (200–250 g) was cannulated as described by Weeks & Jones (1960). Three days later each animal was placed in a restraint cage and the cannula was connected to a pressure transducer which, in turn, was linked to a polygraph (Physiograph, E & M Instrument Co.) via a preamplifier. Two control measurements of blood pressure and heart rate were recorded, heart rate being measured directly from the trace by counting beats over a 10 s period. Groups of at least 4 rats were injected intraperitoneally with either saline or test compound and the effects were then monitored for 3 hours.

Cats were anaesthetized with a halothane/oxygen mixture. The femoral vein was cannulated and drugs were injected by this route. Anaesthesia was maintained with chloralose (75 mg/kg, i.v.). Artificial respiration with an Ideal respiration pump (20 strokes/min, 10 ml/kg room air) was started immediately the thorax was opened. Mean aortic blood flow in the brachiocephalic artery and the descending aorta was monitored with 2 electromagnetic flow probes linked via a twin-channel blood flowmeter (Biotronex) to 2 separate potentiometric recorders. The left subclavian artery was used to record blood pressure. A strain guage was sutured to the wall of the right ventricle. All recordings were displayed on a polygraph (Hewlett Packard 7700). The following parameters were measured or derived: myocardial force of contraction, heart rate, mean arterial blood pressure, cardiac output (cardiac index), stroke volume (stroke index) and peripheral resistance (mean arterial pressure, mmHg/cardiac index, l min^{-1} m^{-2}). The surface area (m^2) of the cat was calculated from the formula, K = area (cm^2)/weight $(g)^{2/3}$, using Thomas' constant for the cat (K = 10) (Altman & Dittmer, 1964).

Heart rate and blood pressure were monitored in beagle dogs trained to stand in a Pavlovian sling. An electrosphygmograph (E & M Instrument Co.) was used to record (indirectly) systolic and diastolic blood pressure. The electrosphygmograph combines a pressure transducer and a preamplifier to produce single-channel recordings of occluding cuff pressure and superimposed Korotkoff sounds. A wrap-round cuff with attached microphone (E & M 93-40074) was used to monitor blood pressure from the right foreleg. Drugs were injected via the cephalic vein. Respiratory rate was counted visually.

Respiratory effects

Control rates of respiration of mice were measured with a pressure transducer coupled to an instant ratemeter. Groups of 10 animals were then injected subcutaneously with either saline or test compound and the rates were again measured 30 min later.

The descending aorta of rats (200–300 g) was cannulated as described by Weeks & Jones (1960). Two days later the animals were placed in individual restraint cages. Two arterial blood samples were taken from each rat and immediately analysed for PCO_2 and PO_2 with a Blood Gas Analyser (Model 48C, Electronic Instruments Ltd.). Test compounds or saline were then given (1 ml/kg, i.a.) and further measurements of PCO_2 and PO_2 were taken 15,30 and 45 min later.

Antitussive effects

Groups of 15 guinea-pigs received oral injections of either distilled water or test compound; 30 min later each animal was individually confined in a test chamber and exposed to an atmosphere of citric acid. This was delivered as an aerosol containing approximately 4 mg citric acid/l of air, at a flow rate of

7.5 litres/minute. After an equilibration time of 3 min, the incidence of coughing was monitored over the following 5 min using pressure transducers connected to a polygraph (Van Gogh). One week later the animals were retested on a cross-over basis. The reduction in the number of coughs at each dose level was assessed by comparison with the controls. The dose required to inhibit the number of coughs by 50% was estimated. Approximate durations of action were obtained by noting the time taken for the antitussive effect, caused by an ED_{50} dose, to return to control values in groups of 15 guinea-pigs.

Effect on urine output

Rats (120–140 g) were deprived of food for 18 h but allowed water until 1 h before the test. Groups of 8 animals were then water-loaded (3 ml/100 g, orally), injected subcutaneously with saline or test compound and placed in metabolism cages. Urine volumes were recorded every 30 min for 6 hours. Each group received the same treatment on a further 4 occasions. A minimum of 72 h elapsed between successive treatments.

Effect on gastrointestinal propulsion

Groups of 10 rats (120–140 g) were deprived of food for 18 h but allowed water until 1 h before the test. Saline or test drug was administered subcutaneously or orally and a charcoal meal (5 ml/kg; Green, 1959) was given by stomach tube 20 min (s.c.) or 50 min (orally) later. A further 10 min later each rat was killed by cervical dislocation. The distance travelled by the meal along the small intestine from the pyloric sphincter was measured and calculated as a percentage of the total length.

Acute toxicity

Acute median lethal doses were estimated 7 days after intravenous, intraperitoneal, subcutaneous and oral administration of buprenorphine to groups of 10 male and female mice (18–22 g) and rats (60–80 grams).

Statistical evaluation

Quantal data were subjected to logit analyses using Bliss 17, a computer programme written by Professor D.J. Finney (see Finney, 1971). Figures in parentheses in the Results section refer to the 95% confidence limits of the ED_{50} or LD_{50}.

Results

The ED_{50} value for buprenorphine in the mouse rota-rod test was >100 mg/kg; an optimal value of 3.2 mg/kg (1.6–4.9) was obtained with cyclazocine at 30 minutes.

Buprenorphine (0.10, 0.30 and 1.0 mg/kg) increased the spontaneous locomotor activity of groups of 5 mice in relation to control sessions with the same animals. High doses of naloxone, when injected 5 min before a standard dose of buprenorphine (0.10 mg/kg), antagonized the potentiating effects of the latter compound in a dose-related manner (Table 1). Although buprenorphine (0.10–3.0 mg/kg) increased the spontaneous locomotor activity of groups of 3 rats over 6 h sessions, the animals initially remained immobile and adopted a characteristic hunchbacked ('hedgehog') posture; preening and huddling (Giurgea & Van Kemeulen, 1973) were absent. The rats reacted normally to auditory and tactile stimuli. Repetitive licking and biting of the limbs and the cage, and occasionally fighting, occurred mainly 4–5 h after injection of buprenorphine.

Both buprenorphine and morphine produced catalepsy in guinea-pigs. The logit lines did not differ significantly from parallelism; at the time of peak effect (30 min) the ED_{50} values were 0.007 mg/kg (0.003–0.015) and 2.2 mg/kg (1.2–3.8), respectively.

Table 1 The effect of naloxone on increases in locomotor activity caused by buprenorphine in mice

Treatment		*Mean activity counts*
−5 min (i.p.)	*0 min (s.c.)*	
Saline	Saline	3346
Naloxone (10 mg/kg)	Saline	3281
Naloxone (30 mg/kg)	Saline	3671
Naloxone (100 mg/kg)	Saline	2660
Saline	Buprenorphine (0.10 mg/kg)	12560
Naloxone (10 mg/kg)	Buprenorphine (0.10 mg/kg)	8712
Naloxone (30 mg/kg)	Buprenorphine (0.10 mg/kg)	5775
Naloxone (100 mg/kg)	Buprenorphine (0.10 mg/kg)	3612

Total counts were obtained from 2 different groups of 5 mice run between 10 h 00 min and 16 h 00 min.

Buprenorphine (0.50, 1.0, 2.0, 5.0 and 10 mg/kg) did not alter the behaviour of 5 cats and morphine-like mania did not occur. Mydriasis was observed at all dose levels and occasional bursts of running were noted with the highest dose.

After injection into 5 drug-naïve rhesus monkeys, buprenorphine (0.03, 0.10, 0.30, 1.0 and 3.0 mg/kg) caused only a slight behavioural depression (eyes closing momentarily and dazed facial expressions) which lasted about 40 min and which was not dose-related. The animals reacted normally to environmental stimuli at all times.

In normotensive, conscious rats the two lower doses of buprenorphine (0.10 and 1.0 mg/kg, i.p.) reduced the heart rate, whereas the top dose (10 mg/kg) had the opposite effect. At a dose level of 10 mg/kg, morphine caused a marked bradycardia 0.5 and 1.0 h after injection (Table 2). A general trend of higher blood pressure readings occurred in the same rats after administration of saline or the analgesics. Thus,

Table 2 The effect of test compounds on the heart rate and blood pressure of conscious rats

Compound	*Dose (mg/kg, i.p.)*	n	*Mean heart rate (s.e. mean) (beats/min)*				
			Pre-drug	0.5 h	1 h	2 h	3 h
Saline	10 ml/kg	8	403 ± 8	404 ± 27	411 ± 17	404 ± 13	443 ± 13
Morphine	1.0	4	406 ± 10	375 ± 24	403 ± 15	400 ± 11	423 ± 25
	10	4	411 ± 11	298 ± 10***	368 ± 10***	423 ± 15	428 ± 25
Buprenorphine	0.10	9	434 ± 9	411 ± 20	404 ± 16	416 ± 31	423 ± 33
	1.0	9	432 ± 12	374 ± 13*	418 ± 13	419 ± 15	433 ± 16
	10	9	408 ± 8	408 ± 7	429 ± 12	441 ± 12**	423 ± 13
			Mean arterial blood pressure (s.e. mean) (mmHg)				
Saline	10 ml/kg	8	122 ± 3	127 ± 4	134 ± 4**	129 ± 4**	135 ± 5*
Morphine	1.0	4	122 ± 3	125 ± 4	130 ± 7	119 ± 4	124 ± 5
	10	4	123 ± 3	131 ± 4	144 ± 3*	133 ± 3*	125 ± 3
Buprenorphine	0.10	9	130 ± 4	138 ± 6*	139 ± 5**	137 ± 5*	135 ± 6
	1.0	9	129 ± 4	137 ± 6**	136 ± 5*	142 ± 8*	136 ± 6*
	10	9	125 ± 2	134 ± 4*	134 ± 4*	129 ± 4	128 ± 6

*$P < 0.05$; **$P < 0.01$, ***$P < 0.001$ (Student's t test for paired data).

Table 3 The effect of test compounds on the heart rate and blood pressure of conscious dogs

Compound	*Dose (mg/kg, i.v.)*	n	*Mean heart rate (s.d.) (beats/min)*			
			Pre-drug	+5 min	+15 min	+30 min
Saline	0.10 ml/kg	3	123 ± 6	117 ± 2	107 ± 6*	116 ± 7
Buprenorphine	0.01	3	121 ± 5	112 ± 24	113 ± 29	114 ± 24
	1.0	3	115 ± 9	80 ± 10*	80 ± 8*	80 ± 0*
Morphine	0.10	3	113 ± 6	117 ± 6	113 ± 6	107 ± 15
	10	3	123 ± 6	91 ± 36	92 ± 39	92 ± 39
			Mean arterial blood pressure (s.d.) (mmHg)			
Saline	0.10 ml/kg	3	103 ± 3	105 ± 8	117 ± 6*	116 ± 5
Buprenorphine	0.01	3	129 ± 20	113 ± 21	124 ± 24	127 ± 31
	1.0	3	109 ± 20	121 ± 7	112 ± 10	111 ± 7
Morphine	0.10	3	110 ± 13	106 ± 7	93 ± 3	100 ± 10
	10	2	100	99	90	96

* $P < 0.05$ (Student's t test for paired data).

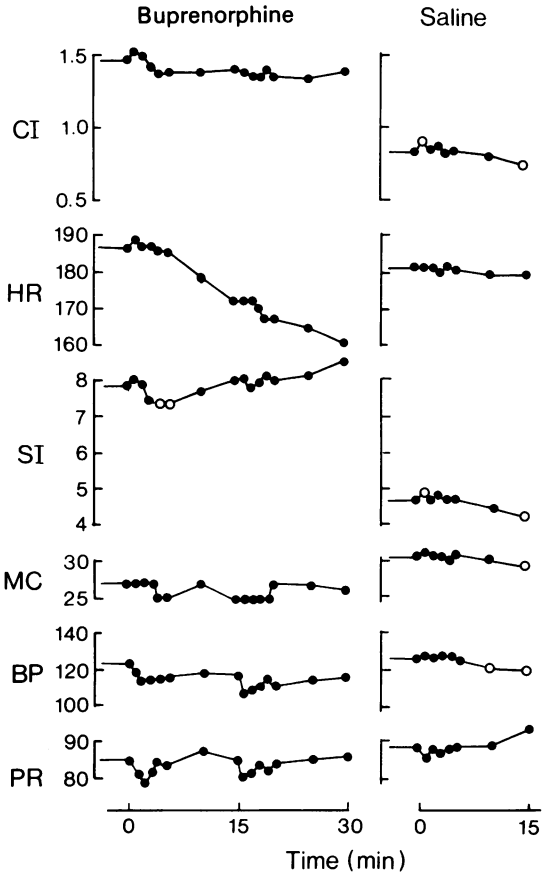

Figure 1 The haemodynamic effects of buprenorphine and saline in open-chest cats anaesthetized with chloralose (75 mg/kg, i.v.). Buprenorphine was injected at 0 min (0.10 mg/kg) and again at 15 min (1.0 mg/kg) into the femoral veins of 3 cats. Saline (1.0 mg/kg, i.v.) was injected at 0 min into 5 different cats. Mean values represented by open circles are significantly different from initial values ($P < 0.05$, Student's t test for paired data). CI, cardiac index (l min^{-1} m^{-2}); HR, heart rate (beats/min); SI, stroke index (ml $beat^{-1}$ m^{-2}); MC, myocardial force of contraction (g); BP, mean arterial blood pressure (mmHg); PR, peripheral resistance (arbitrary units).

the statistically significant values for buprenorphine should be interpreted with caution since saline induced a similar rise in blood pressure over the 3 h session.

In anaesthetized, open-chest cats buprenorphine (0.10 and 1.0 mg/kg, i.v.) caused no major haemodynamic effects (Figure 1). The observed bradycardia did not reach a statistically significant level probably because a group size of only 3 cats was used.

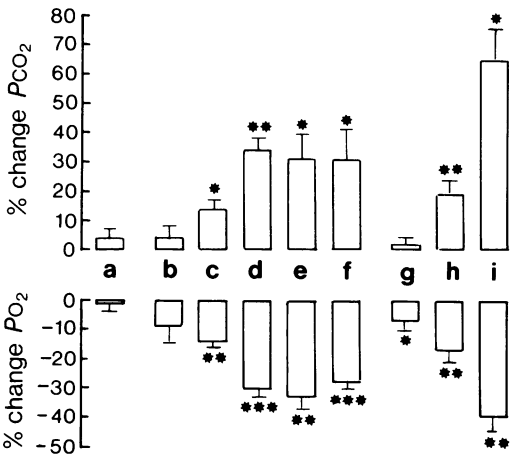

Figure 2 The mean percentage change in arterial P_{CO_2} and P_{O_2} values 15 min after (a) intra-arterial injection of saline (1 ml/kg), (b–f) buprenorphine (0.01, 0.03, 0.10, 1.0 and 10 mg/kg) or (g–i) morphine (0.30, 3.0 and 30 mg/kg) to groups of 5 conscious rats. Vertical lines show s.e. means. $*P < 0.05$, $**P < 0.01$ and $***P < 0.001$ (Student's t test for paired data).

A high dose of buprenorphine (1 mg/kg, i.v.) significantly decreased the heart rate of conscious dogs but had no marked effect on arterial blood pressure (Table 3). At this dose level all 3 dogs began to pant and showed head-nodding movements. Immediately after a high dose of morphine (10 mg/kg, i.v.), the dogs displayed 'sham rage' for about 15 s (Domer & Josselson, 1964) and then collapsed. It was difficult to monitor the blood pressure with an electrosphygmograph in these animals since the pulse was so weak; indeed, in one dog a blood-pressure trace could not be obtained.

The respiratory rate of mice was decreased in a dose-related manner by morphine (1,5 and 10 mg/kg, s.c.); the top dose caused a 56% reduction ($P < 0.001$, Student's t test for paired data). The maximum effect with buprenorphine (0.001–10 mg/kg, s.c.) occurred after 0.10 mg/kg when a 22% reduction was recorded ($P = 0.02$).

Buprenorphine (0.01–10 mg/kg, i.a.) and morphine (0.30–30 mg/kg, i.a.) increased arterial P_{CO_2} values and reduced P_{O_2} values at 15 min in conscious rats (Figure 2). With buprenorphine, depression of respiration reached a plateau over the dose-range 0.10–10 mg/kg. Interestingly, the duration of respiratory depression became less as the dose of buprenorphine was increased; thus, after 10 mg/kg, the P_{CO_2} and P_{O_2} values had returned to control levels at 45 minutes. In contrast, the response to morphine increased linearly with dose and showed no signs of recovery at 45 minutes.

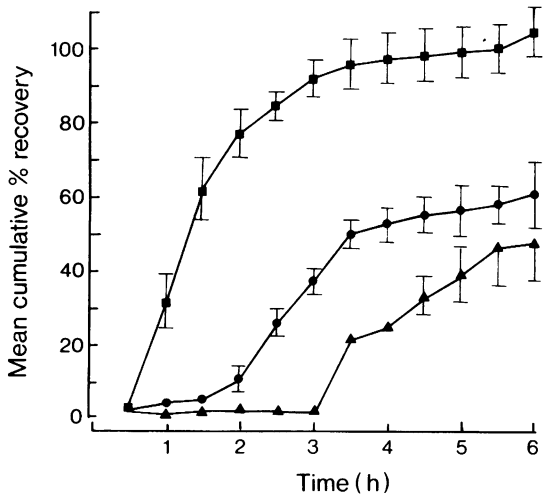

Figure 3 Effect of saline (■), buprenorphine (0.48 mg/kg, s.c. ●) or morphine (35 mg/kg, s.c. ▲) on the urine output of groups of 5 rats over 6 hours. Each group received the same treatment on 5 occasions. The mean cumulative percentage recovery of the oral water-load (3 ml/100 g) is shown on the ordinate scale. Vertical lines show s.e. means.

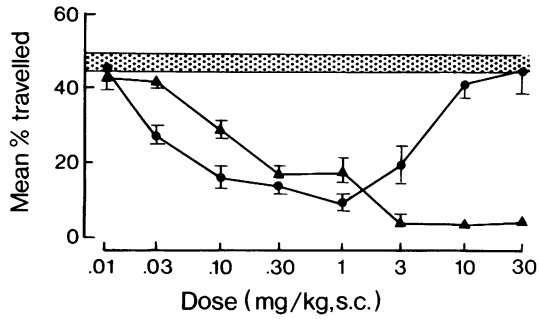

Figure 4 The effect of buprenorphine (●) and morphine (▲) on intestinal motility in rats ($n=10$). Each point gives the mean distance travelled by a charcoal meal expressed as a percentage of the total length of the small intestine. Vertical lines show s.e. means. The stippled band represents the mean percentage distance (with s.e. mean) travelled by the meal in 30 control rats.

Buprenorphine was more potent and longer acting than either butorphanol or methadone as an oral antitussive agent in guinea-pigs (Table 4).

The doses of buprenorphine (0.48 mg/kg) and morphine (35 mg/kg) chosen for the urine output study were each 20 times higher than the antinociceptive (tail pressure) ED_{50} values obtained with the same batch of rats. Both analgesics suppressed urine output. The time taken to recover 40% of the water load was 1.25 h after injection of saline and 3.25 and 5.25 h in the case of buprenorphine and morphine, respectively (Figure 3).

After subcutaneous injection, buprenorphine (1 mg/kg) and morphine (3 mg/kg) were essentially equi-efficacious in slowing the passage of a charcoal meal along the small intestine of rats. Doses of buprenorphine within the range 0.01–1.0 mg/kg progressively reduced the distance travelled by the meal. On the other hand, after doses in excess of 1 mg/kg, the meal travelled increasingly further such that the distances measured after 10 and 30 mg/kg did not differ significantly from control values. This phenomenon did not occur with morphine (Figure 4). After oral administration, the dose-response curve of buprenorphine (0.001–100 mg/kg) was also curvilinear (U-shaped); the maximum constipative effect was again associated with a dose level of 1 mg/kg but this was significantly less than that obtained with high doses of morphine (30 and 100 mg/kg).

The median acute lethal doses of buprenorphine after intravenous, intraperitoneal and oral administration are presented in Table 5. Most deaths occurred within 24 h of injection and were a consequence of respiratory depression. Although LD_{50} values were computed after intraperitoneal administration to both mice and rats, values after subcutaneous injection could not be obtained even after doses of 300 mg/kg to mice and 600 mg/kg to rats.

The value of the LD_{50} for morphine (i.p.) in male rats in this laboratory in the past was found to be 306 mg/kg (237–395) and therefore the therapeutic

Table 4 The antitussive effects of test compounds in guinea-pigs

Compound	*ED_{50} (mg/kg, orally)*	*Potency ratio*	*Length of action (h)**
Buprenorphine	0.067 (0.019–0.22)	31 (11–87)	>8 <12
Butorphanol	0.12 (0.039–0.26)	19 (8–47)	>0.5 <1
Methadone	3.6 (1.3–6.6)	1.0	>2 <4

Groups of 15 guinea-pigs were individually exposed for 5 min to a citric acid aerosol, 30 min after administration of drugs or water.

* The time taken for the antitussive effect, caused by the ED_{50} dose, to return to control values ($P<0.05$, Student's t test for paired data).

Table 5 Acute toxicities of buprenorphine in mice and rats

		Mouse	*Rat*
Sex	*Route*	LD_{50} *(mg/kg)*	LD_{50} (mg/kg)
M	i.v.	24 (21–27)	38 (28–51)
F	i.v.	29 (26–31)	31 (26–37)
M	i.p.	97 (84–112)	197 (145–277)
F	i.p.	90 (65–125)	207 (168–255)
M	oral	261 (234–291)	>600
F	oral	260 (233–304)	>600

index (LD_{50}/ED_{50} in the rat tail pressure test) is 464. The corresponding index for buprenorphine is 12,313, representing a greatly increased margin of safety.

Discussion

Buprenorphine resembled morphine by increasing spontaneous locomotor activity in mice and by causing catalepsy in guinea-pigs. In contrast to the curvilinear dose-effect realtionship observed for catalepsy with buprenorphine in rats (Cowan, Lewis & Macfarlane, 1977), catalepsy was still maintained in guinea-pigs after high doses (0.10–10 mg/kg) of this compound. According to Fog (1970) and Costall & Naylor (1974), morphine does not induce stereotyped behavioural patterns in rats after a single subcutaneous injection but does so in rats tolerant to morphine. Buprenorphine, therefore, differs from morphine but resembles the long-acting analgesic (–)-α-acetylmethadol (Henderson & Westkaemper, 1975), since it caused a stereotyped behavioural syndrome in rats (licking and biting of the cage, mutilation of the limbs) which was optimal about 4 h after *acute* administration. Effects such as catalepsy and stereotypy, as well as results from other behavioural studies (Cowan, Dettmar & Walter, 1975a,b), are indicative of buprenorphine interacting with central dopaminergic systems. This suggestion is supported by the finding that buprenorphine (3 and 10 mg/kg, s.c.) significantly increases the content of homovanillic acid (but not that of 5-hydroxyindoleacetic acid or 3-methoxy-4-hydroxyphenylglycol) in the forebrains of rats (Cowan, Dettmar & Walter, 1976).

Buprenorphine differs from morphine in causing no mania in cats and no deep ('narcotic') depression in monkeys. Unlike cyclazocine (Villarreal, 1972), buprenorphine does not cause muscular incoordination and ataxia in mice and monkeys. Moreover, the bizarre behavioural signs elicited by cyclazocine in rats, and thought to be indicative of psychotomimetic potential (Schneider, 1968), are not observed after administration of buprenorphine.

A reduction in heart rate was generally observed after the administration of buprenorphine to conscious rats and dogs and to anaesthetized, artificially respired cats. Relative to control values, the analgesic had no significant effect on arterial blood pressure in these species. In the study with dogs, a high intravenous dose of buprenorphine caused unusual head-nodding movements while 'sham rage', salivation, urination, defaecation and narcosis characterized the morphine-syndrome. Vomiting was not associated with either drug. Buprenorphine did not produce effects in open-chest cats that would contraindicate its use in the clinic. Thus, after doses of 0.10 and 1.0 mg/kg intravenously there was no evidence of depressed myocardial contractility while the cardiac index, stroke index and peripheral resistance were essentially unchanged.

Buprenorphine and morphine both caused respiratory depression in conscious rats. However, there were potentially important differences in the character of the respiratory depression. First, the PCO_2 and PO_2 dose-response curves of buprenorphine were shallower than those of morphine. Second, ceiling effects occurred with increasingly larger doses of buprenorphine such that the maximum effects produced were less than those obtained with morphine. Finally, it is of interest that respiratory depression caused by the highest dose of buprenorphine tested (10 mg/kg, i.a.) was of shorter duration than that induced by morphine (0.30–30 mg/kg, i.a.).

Buprenorphine caused a dose-related decrease in the frequency of (chemically-induced) coughing in unanaesthetized guinea-pigs. The oral potency of buprenorphine as an antitussive agent and its duration of action compare favourably with that of methadone and the recently introduced narcotic antagonist analgesic, butorphanol. The latter compound is, in fact, one of the most potent cough suppressants of its type (Cavanagh, Gylys & Bierwagen, 1976).

Buprenorphine resembled morphine in suppressing urine output in rats loaded with water. Additional experiments are necessary to establish whether or not buprenorphine has a direct renal effect and/or stimulates the release of antidiuretic hormone.

Morphine delays gastric emptying time and/or decreases propulsive contractions of the small intestine of rats in a linearly-related manner (Figure 4). The effect of buprenorphine on the transit of a test meal does not show a simple relationship to dose. The plot of log dose against response is U-shaped rather than linear and is reminiscent of the curvilinear relationship obtained with buprenorphine in certain rodent antinociceptive tests, the rat catalepsy test (Cowan, Lewis & Macfarlane, 1971; 1977) and on respiratory rate in mice (see Results section). In view of the qualitatively different dose-response lines obtained for buprenorphine and morphine in the

present experiments, it is not possible to compare potencies of the two analgesics in causing constipation. However, the results have shown that morphine is more efficacious than buprenorphine as a constipative agent after oral administration while maximal effects are of the same order after subcutaneous administration. At the receptor level, it would be of interest to know if the shape and position of the buprenorphine dose-response curve alters when rats are pretreated with either naloxone or methysergide (Burks & Long, 1967) or receive multiple injections of buprenorphine. Experiments designed to clarify these points are now in progress.

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