ELSEVIER

European Journal of Pharmacology 361 (1996) 253–256

ejp

Gastrointestinal actions of buprenorphine: are different receptors involved?

Sushama A. Bhounsule, Sunita D'Sa, Nazarine Fernandes, Rosa Diniz D'Souza *, Vishwanath G. Dhume

Department of Pharmacology, Goa Medical College, Bambolim Complex, Goa, 403 202, India

Received 13 August 1996; accepted 16 August 1996

Abstract

The effects of buprenorphine on castor-oil-induced diarrhoea, gastrointestinal transit and ethanol-induced gastric lesions in rats were compared to the same effects of morphine. Like morphine, buprenorphine prevented castor-oil-induced diarrhoea. However, it has no effect on gastrointestinal transit per se but prevented the inhibitory action of morphine. While morphine protected against ethanol-induced gastric lesions, buprenorphine aggravated them. It is suggested that different types/subtypes of opioid receptors may be involved in the gastrointestinal actions of buprenorphine.

Keywords: Morphine; Buprenorphine; Castor oil; Diarrhoea; Gastrointestinal transit; Ethanol lesion

1. Introduction

In the rat, μ-opioid receptors have been shown to be involved in the effects of morphine on gastric secretion (Burks et al., 1988) and gastrointestinal transit (Galligan et al., 1984; Koslo et al., 1985; Tavani et al., 1990). Whilst investigating another gastric effect of morphine, viz., its protective effect on ethanol-induced gastric lesions, we found that the potent partial agonist at μ-opioid receptors, buprenorphine, failed to exert a similar action (Bhounsule et al., 1994). Though there are several studies on the gastrointestinal actions of morphine (Porreca and Burks, 1983; Peracchia et al., 1984; Manara et al., 1986; Gyires, 1990), there is a paucity of literature on experimental studies of the gastrointestinal actions of buprenorphine. Buprenorphine has been reported to antagonise the anti-motility action of morphine (Raffa et al., 1982) as well as to slow gastrointestinal transit in rats (Cowan et al., 1977a; Cowan, 1992). However, a constipating effect is not seen clinically (Heel et al., 1979).

In view of the above, this investigation was undertaken to study further the gastrointestinal actions of buprenorphine, in the laboratory setting, on three parameters, viz., castor-oil-induced diarrhoea, gastrointestinal transit of a charcoal meal and ethanol-induced gastric lesions, and compare them with those of the prototype opioid, morphine.

2. Materials and methods

Male Wistar rats (200–250 g) were deprived of food but allowed water ad libitum for 24 h prior to drug administration. The animals were randomly divided into groups and received the following drugs i.p. unless specified otherwise, 30 min before the oral administration of either castor oil, a charcoal meal or ethanol: (a) 0.9% NaCl w/v (saline) in the same volume as other drugs (1 ml/kg); (b) morphine 0.3 and 0.6 mg/kg; (c) buprenorphine 0.006, 0.012 and 0.024 mg/kg; (d) naloxone 1.0 mg/kg (s.c.) 30 min before saline; (e) naxolone 1.0 mg/kg (s.c.) 30 min before morphine 0.6 mg/kg and buprenorphine 0.012 mg/kg; (f) buprenorphine 0.024 mg/kg 30 min before morphine 0.6 mg/kg (in the case of gastrointestinal transit).

2.1. Castor oil-induced diarrhoea

Rats were given by gavage 1 ml of castor oil, weighed and placed in individual observation cages which were

* Corresponding author.

PII S0014-2999(96)00668-1

Table 1
Effect of morphine and buprenorphine on gastrointestinal transit in rats

Drugs	Dose (mg/kg, i.p.)	% Gastrointestinal transit (mean ± S.E.M.)
Saline (control)	1 ml/kg	40.8 ± 3.2
Morphine	0.3	30.2 ± 1.2 [a]
	0.6	16.8 ± 1.5 [a]
Buprenorphine	0.006	46.2 ± 6.8
	0.012	37.5 ± 8.1
	0.024	34.0 ± 6.1
Naloxone	1.0 s.c.	37.8 ± 5.0
Naloxone + morphine	1.0 s.c. + 0.6	42.6 ± 2.8
Buprenorphine + morphine	0.024 + 0.6	44.8 ± 5.4

$n = 30$.
[a] $P < 0.05$ as compared to control.

Table 3
Effect of morphine and buprenorphine on ethanol-induced gastric lesions

Drugs	Dose (mg/kg, i.p.)	Area of haemorrhagic lesions (mm^2) (mean ± S.E.M.)
Saline (control)	1 ml/kg	79.8 ± 5.0
Morphine	0.3	20.5 ± 3.8 [a]
	0.6	11.6 ± 0.8 [a]
Buprenorphine	0.006	83.5 ± 6.8
	0.012	98.2 ± 4.6 [a]
	0.024	116.4 ± 5.2 [a]
Naloxone	1.0 s.c.	80.2 ± 6.4
Naloxone + morphine	1.0 s.c. + 0.6	81.5 ± 5.8
Naloxone + buprenorphine	1.0 s.c. + 0.012	78.5 ± 3.6

$n = 10$.
[a] $P < 0.05$ as compared to control.

lined at the bottom with pre-weighed sheets of white absorbent paper. 2 h after the administration of castor oil, the presence or absence of diarrhoea (loose stools) was noted and the following parameters were evaluated: (a) incidence of diarrhoea (number of rats with diarrhoea/total number of rats tested) expressed as a percentage; (b) weight of stools (mg).

2.2. Gastrointestinal transit

Rats were fed by gavage 2 ml of a test meal consisting of 12.5% charcoal + gum acacia in water. 5 min later, the animals were killed by decapitation, the small intestine was removed and its length was measured from the pyloric sphincter to the ileocaecal junction. The distance travelled by the test meal was recorded as a percentage of the total length of the intestine (percentage gastrointestinal transit).

2.3. Induction of gastric lesions

Rats were given 1 ml of 75% ethanol orally and killed after 1 h. The stomach was opened along the greater curvature and rinsed with normal saline. The length and width of each red haemorrhagic band was measured with a mm rule, the area was calculated and summed for each stomach. One of us performed the experiments, and two others inspected each coded stomach independently.

2.4. Statistical analysis

All data are expressed as mean ± S.E. and were analysed by either analysis of variance (pair-wise differences among treatments being analysed with the Neuman-Keuls test), or by Z test for proportion. Significance was accepted at the 0.05 level.

3. Results

The effects of morphine and buprenorphine on gastrointestinal transit and castor oil-induced diarrhoea can be seen in Tables 1 and 2, respectively. While morphine inhibited both, buprenorphine inhibited only castor oil-induced diarrhoea. Though buprenorphine did not affect gastrointestinal transit per se, it prevented the inhibitory effect of morphine. Naloxone prevented both intestinal actions of morphine as well as the effect of buprenorphine on castor oil diarrhoea.

Table 3 shows the effect of morphine and buprenor-

Table 2
Effect of morphine and buprenorphine on castor oil-induced diarrhoea in rats

Drugs	Dose (mg/kg, i.p.)	% Incidence of diarrhoea (mean ± S.E.M.)	Weight of stools (mg) (mean ± S.E.M.)
Saline (control)	1 ml/kg	100	1825 ± 200
Morphine	0.3	13.3 ± 0.06 [a]	105 ± 85 [a]
	0.6	0 [a]	0 [a]
Buprenorphine	0.006	20.0 ± 0.07 [a]	290 ± 140 [a]
	0.012	0 [a]	0 [a]
	0.024	0 [a]	0 [a]
Naloxone	1.0 s.c.	100	1700 ± 290
Naloxone + morphine	1.0 s.c. + 0.6	93.3 ± 0.05	1640 ± 320
Naloxone + buprenorphine	1.0 s.c. + 0.012	96.6 ± 0.03	1750 ± 300

$n = 30$.
[a] $P < 0.05$ as compared to control.

phine on ethanol-induced gastric lesions. While morphine exerted a protective effect, buprenorphine aggravated the lesions at the two higher doses. Naloxone prevented the protective effect of morphine as well as the aggravating effect of buprenorphine.

4. Discussion

The results confirmed that morphine inhibits castor oil-induced diarrhoea, slows gastrointestinal transit and protects against ethanol-induced gastric lesions. All these actions can be prevented by pretreatment with naloxone, showing that they are mediated by opioid receptors.

Though the antimotility and antisecretory actions of morphine are well known, the issue of which receptors are involved is still not settled. Studies in rats have generally implicated the μ-opioid receptor in the inhibitory action of morphine on gastrointestinal transit (Manara et al., 1986; Tavani et al., 1990).

Buprenorphine, a partial agonist at μ-opioid receptors (Martin et al., 1976; Dum and Herz, 1981; Martin, 1984), has been shown to be 30–40 times more potent than morphine as an analgesic on i.p. or s.c. administration and as such should have exerted a marked inhibitory effect on gastro-intestinal transit. However, buprenorphine failed to affect transit. The doses of buprenorphine used in our study correspond approximately with the therapeutic dose in humans and the reported ED_{50} for the analgesic effect in rats, 0.016 mg/kg i.p. (Cowan et al., 1977b). Our observations differ from those of Cowan et al. (1977a), who reported that buprenorphine slows gastrointestinal transit in rats, but are consistent with the reported lack of constipating effect seen clinically (Heel et al., 1979). Our results are also in agreement with those of Raffa et al. (1982) in that buprenorphine prevents the slowing of gastrointestinal transit caused by morphine, suggesting an antagonistic action at the receptor involved. On the other hand, the effect of buprenorphine on castor oil-induced diarrhoea was the same as that of morphine: it decreased, and at higher doses, completely prevented the diarrhoea.

Separation of antitransit and antidiarrhoeal effects has previously been shown with the selective δ-opioid receptor agonist [D-Pen^2, D-Pen^5] enkephalin (DPDPE) on i.c.v. administration. Though it exerts an antidiarrhoeal action, it has no effect on gastrointestinal transit (Burks et al., 1988). This leads us to think that different receptors may be involved in the 'constipating' action of opioids as measured by inhibition of gastrointestinal transit and the 'antisecretory' action as reflected by protection against castor oil-induced diarrhoea. Our results suggest that buprenorphine acts as an agonist at the receptor/site involved in the inhibition of castor oil-induced diarrhoea and as an antagonist at the receptor/site responsible for slowing gastrointestinal transit. However, we cannot rule out the possibility that a partial agonist such as buprenorphine may be able to exert only an antidiarrhoeal effect while an antitransit action may require a more efficacious full agonist.

Buprenorphine has also been reported to exert an antagonistic action at κ-opioid receptors (Richards and Sadee, 1985). However, various studies have shown that selective κ-opioid receptor agonists do not affect gastrointestinal transit in rats (Tavani et al., 1984; La Regina et al., 1988).

The effect of buprenorphine on ethanol-induced gastric lesions was also different from that of morphine. While morphine had a protective effect, buprenorphine aggravated the lesions. The protective effect of morphine as well as the aggravating effect of buprenorphine were prevented by naloxone, suggesting that both actions are mediated by opioid receptors. Such divergent effects of opioids have been reported for gastric secretion. For example, gastric secretion is decreased by morphine and increased by a selective κ-opioid receptor agonist (Fox and Burks, 1988).

In conclusion, the results of our study showed that: (1) Buprenorphine has different effects on castor oil-induced diarrhoea and on gastrointestinal transit. However, it prevents the antitransit action of morphine. (2) Buprenorphine aggravates ethanol-induced gastric lesions, an effect opposite to that of morphine. (3) These gastrointestinal effects of buprenorphine are difficult to explain in terms of its known partial agonistic action at μ-opioid receptors and antagonistic action at κ-opioid receptors. Further work is needed to clarify the mechanisms of these diverse gastrointestinal effects.

Acknowledgements

We thank Mr. M.S. Kulkarni, Lecturer in Demography, Goa Medical College, for his help with statistical evaluation of the results.

References

Bhounsule, S.A., R.S. Diniz D'Souza and V.G. Dhume, 1994, Gastric cytoprotective effect of morphine is probably not mediated by mu receptors, Arch. Int. Pharmacodyn. 328, 99.

Burks, T.F., D.A. Fox, L.D. Hirning, J.E. Shook and F. Porreca, 1988, Regulation of gastrointestinal function by multiple opioid receptors, Life Sci. 43, 2177.

Cowan, A., 1992, Buprenorphine and gastrointestinal transit in rats: effect of naloxone on the biphasic dose-response curve, Clin. Exp. Pharmacol. Physiol. 19, 47.

Cowan, A., J.C. Doxy and E.J.R. Harry, 1977a, The animal Pharmacology of buprenorphine, an oripavine analgesic agent, Br. J. Pharmacol. 60, 547.

Cowan, A., J.W. Lewis and I.R. Macfarlane, 1977b, Agonist and antagonist properties of buprenorphine, a new antinociceptive agent, Br. J. Pharmacol. 60, 537.

Dum, J.E. and A. Herz, 1981, In vivo receptor binding of the opiate partial agonist, buprenorphine correlated with its agonistic and antagonistic actions, Br. J. Pharmacol. 74, 627.

Fox, D.A. and T.F. Burks, 1988, Role of central and peripheral mu, delta

and kappa opioid receptors in the mediation of gastric acid secretory effects in the rat, J. Pharmacol. Exp. Ther. 244, 456.

Galligan, J.J., H.I. Mosberg, R. Hurst, V.J. Hruby and T.F. Burks, 1984, Cerebral delta opioid receptors mediate analgesia but not the intestinal motility effects of intracerebroventricularly administered opioids, J. Pharmacol. Exp. Ther. 229, 641.

Gyires, K., 1990, Morphine inhibits ethanol-induced gastric damage in rats, Arch. Int. Pharmacodyn. 306, 170.

Heel, R.C., R.N. Borgden, T.M. Speight and G.S. Avery, 1979, Buprenorphine: a review of its pharmacological properties and therapeutic efficacy, Drugs 17, 81.

Koslo, R.J., J.L. Vaught, A. Cowan, D.E. Gmerek and F. Porreca, 1985, Intrathecal morphine slows gastrointestinal transit in rats, Eur. J. Pharmacol. 119, 243.

La Regina, A., P. Petrillo, M. Sbacchi and A. Tavani, 1988, Interaction of U-69, 593 with m-, d- and k-opioid binding sites and its analgesic and intestinal effects in rats, Life Sci. 42, 293.

Manara, L., G. Bianchi, P. Ferreti and A. Tavani, 1986, Inhibition of gastrointestinal transit by morphine in rats results primarily from direct drug action on gut opioid sites and 237in rats results primarily from direct drug action on gut opioid sites, J. Pharmacol. Exp. Ther. 237, 945.

Martin, W.R., 1984, Pharmacology of opioids, Pharmacol. Rev. 35, 283.

Martin, W.R., C.G. Eades, J.A. Thompson, R.E. Hupper and P.E. Gilbert, 1976, The effects of morphine and nalorphine like drugs in the nondependent and morphine-dependent chronic spinal dog, J. Pharmacol. Exp. Ther. 197, 517.

Peracchia, F., G. Bianchi, R. Fiocchi, P. Petrillo, A. Tavani and L. Manara, 1984, Central and peripheral inhibition of gastrointestinal transit in rats: narcotics differ substantially by acting at either or both levels, J. Pharm. Pharmacol. 36, 699.

Porreca, F. and T.F. Burks, 1983, The spinal cord as a site of opioid effects on gastrointestinal transit in the mouse, J. Pharmacol. Exp. Ther., 227, 22.

Raffa, R.B., F. Porreca, A. Cowan and R.J. Tallarida, 1982, Morphine receptor dissociation constant and the stimulus-effect relation for inhibition of gastrointestinal transit in the rat, Eur. J. Pharmacol. 79, 11.

Richards, M.L. and W. Sadee, 1985, Buprenorphine is an antagonist at the kappa opioid receptor et al.an antagonist at the kappa opioid receptor, Pharmaceutical Res. 4, 178.

Tavani, A., M.C. Gambino and P. Petrillo, 1984, The opioid K-selective compound U-50, 488H does not inhibit intestinal propulsion in rats, J. Pharm. Pharmacol. 36, 343.

Tavani, A., P. Petrillo, A. La Regina and M. Sbacchi, 1990, Role of peripheral mu, delta, and kappa receptors in opioid-induced inhibiiton of gastrointestinal transit in rats, J. Pharmacol. Exp. Ther. 254, 91.