Effect of loperamide and naloxone on gastric acid secretion in healthy man

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SUMMARY The effect of acute oral administration of three different doses (4, 8, and 16 mg) of loperamide, a peripheral opiate agonist, on basal and submaximal pentagastrin-stimulated gastric acid secretion was evaluated in healthy volunteers. Both basal and stimulated gastric secretion were significantly lowered by 8 and 16 mg of the drug in comparison with a control study, while 4 mg was ineffective. Naloxone, a specific opiate antagonist, decreased slightly but not significantly both basal and pentagastrin-stimulated gastric acid secretion, when infused intravenously at the rate of 30 $\mu\text{g/kg/h}$, but completely abolished the inhibitory effect of loperamide on gastric acidity. These data also suggest that opiates may be involved in the regulation of gastric acid secretion in man by acting at a peripheral site, as loperamide does not cross the blood-brain barrier.

The effects of opiates on gastric secretion have recently been investigated. In man, both morphine and naloxone have been demonstrated to inhibit basal and meal-stimulated gastric acid secretion.¹ Meperidine, another drug with opiate receptor-stimulating properties, has been shown potently to reduce basal gastric acid secretion.² In dogs, both morphine and met-enkephalin have been reported to enhance basal³⁻⁵ as well as histamine-stimulated^{4,5} gastric acid secretion. Conflicting results have been obtained after vagal and pentagastrin stimulation, as Magee⁴ reported that morphine inhibits both vagally and pentagastrin-stimulated gastric secretion, while a dose-dependent augmentation of pentagastrin-induced acid secretion by morphine and met-enkephalin was observed by Konturek *et al.*, an effect which was suppressed by naloxone, an opiate antagonist, as well as by metiamide and atropine.⁵ In cats neither met-enkephalin nor naloxone altered the gastric acid secretion.⁶

Loperamide is a new opiate constipating agent, now widely used in the treatment of diarrhoea.⁷ The drug strongly inhibits gastrointestinal motility, an effect qualitatively similar to that exhibited by morphine and completely blocked by naloxone.⁸

Loperamide, unlike the other opiates,^{9,10} does not cross the blood-brain barrier.¹¹

The aim of the present study was to evaluate the effect of loperamide alone, naloxone alone, and of a combination of the two drugs, on basal and submaximal pentagastrin-stimulated gastric acid secretion in healthy man.

Methods

Thirty-seven healthy subjects who had no history of gastrointestinal diseases volunteered for the study. There were 17 women and 20 men, aged 21-55 years (mean, 42 years). Informed consent was obtained from all subjects and the research was carried out according to the Declaration of Helsinki.

After an overnight fast, a nasogastric tube was passed into the stomach and its position was checked by fluoroscopy. Gastric juice collected by continuous aspiration was pooled in 15 minute fractions. In a group of 21 subjects both basal and submaximal pentagastrin (infused intravenously at the rate of 0.25 $\mu\text{g/kg/h}$)-stimulated gastric acid secretion were evaluated for one hour each, after the first 30 minute portion had been discarded. Either placebo or loperamide at a dose of 4, 8, or 16 mg was administered orally 2-5 hours before the intubation. Each experiment was performed in

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seven different subjects. In the other 16 subjects either basal (N=8) or pentagastrin (0.25 µg/kg/h)-stimulated (N=8) gastric acid secretion was evaluated after the first 30 minute portion, both in the basal and in the pentagastrin study, had been discarded. During the second hour naloxone was infused at the rate of 30 µg/kg/h. On separate days these studies were repeated in the same subjects after oral administration of either placebo or loperamide 8 mg 2.5 hours before the intubation. All these tests were carried out in randomised order at a five day interval.

Gastric acid concentration was measured by titration with 0.1 M NaOH to pH 7.0 using a semi-automatic titrameter. Statistical analysis was performed by the two-tailed Student's *t* test for paired data and by the analysis of covariance for repeated measures within and between subjects, followed by Turkey's *t* test for multiple comparisons as appropriate. The differences in basal acid secretion values, which are not normally distributed, were evaluated by a non-parametric test, the Mann-Whitney U test. *P* values of <0.05 were considered to be significant.

Results

No side-effects were reported by any subject.

Whereas loperamide 4 mg did not significantly modify gastric acid secretion, 8 or 16 mg of the drug significantly decreased basal and submaximal pentagastrin-stimulated gastric acid output and juice volume as compared with the placebo study (Table 1). Gastric acid output and juice volume in basal conditions were decreased by approximately 45% after 8 mg loperamide and by 60% after 16 mg, whereas, after stimulation, gastric acid output as

well as juice volume were reduced by 25% with 8 mg loperamide and by 35% with 16 mg. Analysis of the between drug doses revealed the existence of significant differences only between 4 and 16 mg of loperamide: gastric acid output was further reduced by 16 mg of the drug both in basal conditions and after stimulation (*P*<0.05), and juice volume was even more markedly decreased (*P*<0.01 for basal values, *P*<0.02 after stimulation).

Table 2 Effect of naloxone infusion (30 µg/kg/h) or placebo on basal and pentagastrin (0.25 µg/kg/h)-stimulated gastric acid output and juice volume in eight healthy volunteers

Drug	Acid output (mmol/h)		Volume (ml/h)	
	Basal	Stimulated	Basal	Stimulated
Placebo	3.0 ± 0.5	15.5 ± 2.8	51 ± 8	148 ± 18
Naloxone	2.4 ± 0.7	13.3 ± 2.9	36 ± 9	130 ± 16

No significant differences were observed between naloxone and placebo study.

Table 1 Effect of acute oral administration of different doses of loperamide or placebo on basal and pentagastrin (0.25 µg/kg/h)-stimulated gastric acid output and juice volume in healthy volunteers (mean ± SE)

Subjects (no.)	Drug	Acid output (mmol/h)		Volume (ml/h)	
		Basal	Stimulated	Basal	Stimulated
7	Placebo	3.0 ± 0.4	16.0 ± 3.0	55 ± 8	153 ± 18
	Loperamide (4 mg)	2.9 ± 0.3	15.8 ± 3.0	56 ± 10	146 ± 13
7	Placebo	3.3 ± 0.5	16.6 ± 2.4	58 ± 7	157 ± 20
	Loperamide (8 mg)	1.9 ± 0.5*	12.4 ± 1.9*	32 ± 7*	118 ± 14*
7	Placebo	3.2 ± 0.5	16.9 ± 2.8	56 ± 9	150 ± 16
	Loperamide (16 mg)	1.4 ± 0.3†	10.3 ± 3.0*	24 ± 4†	82 ± 10†

**P* < 0.05.

†*P* < 0.01.

Fig. 1 Mean ± SE values of basal gastric acid output and juice volume before and during naloxone infusion after placebo (—) or loperamide 8 mg (---) orally administered 2.5 hours before intubation in eight healthy subjects.

Naloxone infusion decreased slightly but not significantly both basal (acid output, $P=0.25$; juice volume, $P=0.18$ according to Mann-Whitney U test) and pentagastrin-stimulated (acid output, $P=0.48$; juice volume, $P=0.35$ according to Student's t test) gastric acid secretion in comparison with placebo (Table 2). The inhibitory effect of loperamide pretreatment was abolished by naloxone, the values of gastric acid secretion returning to the placebo rates (Figs. 1 and 2).

Fig. 2 Mean $\pm$ SE values of pentagastrin-stimulated gastric acid output and juice volume before and during naloxone infusion after placebo (—) or loperamide 8 mg (---) orally administered 2.5 hours before intubation in eight healthy subjects.

Discussion

The present study shows that acute loperamide administration is associated with decreased basal and submaximal pentagastrin-stimulated gastric acid secretion at drug doses of 8 and 16 mg, but not at the lowest dose of 4 mg, which is, however, able strongly to inhibit peristaltic gut activity,¹² possibly *via* stimulation of specific opiate receptors.⁸

Loperamide, even at large doses, does not exert central opiate activity.¹³ Stahl *et al.*¹⁴ provided evidence that, although the drug shows high affinity binding to opiate receptors in brain homogenate, it does not produce narcotic-like action after *in vivo* systemic administration, because of its poor penetration through the blood-brain barrier.¹¹

The present results are in agreement with human studies showing reduced gastric acid output by intramuscular administration of meperidine,² another opiate agonist, and by intravenous infusion of morphine.¹ The mechanism of action of these drugs has been attributed to an anticholinergic effect, either *via* reduction of the release rate of acetylcholine from nerve endings^{1,2}—an action common to other exogenous opiates¹⁶—or through blockade of muscarinic receptors.² While a specific role of opiate receptors *per se* has not been considered in the meperidine study,² the hypothesis that direct stimulation of opiate receptors may instead be responsible has been ruled out on the basis of the author's finding that even naloxone alone was able to inhibit gastric acid secretion.¹ However, the effect of morphine plus naloxone has not been investigated in that study.

Loperamide is a synthetic opiate agonist which, similarly to other opiates, has been shown to inhibit acetylcholine release in guinea-pig ileum and does not seem to possess other pharmacological properties except a weak antihistaminic effect at high drug concentration.¹⁷ The present finding of complete reversal of loperamide inhibition of gastric acid secretion by concomitant naloxone infusion strongly suggests that opiate receptor stimulation is indeed the mechanism by which loperamide acts on the stomach. Although naloxone alone failed to lower significantly gastric acidity in our study, a trend downward was observed both in basal and pentagastrin-stimulated acid secretion. The partial disagreement with the data by Feldman *et al.*¹ depends on the failure of two of eight subjects to show an antisecretory response to naloxone. Although the similarity of the effects induced by an opiate agonist and the antagonist naloxone on gastric secretion seems quite paradoxical, similar effects on lower oesophageal sphincter pressure in the opossum and on gastric emptying rate in man have been obtained with morphine or naloxone administration,^{18,19} moreover, the morphine effect on the oesophagus has been antagonised by naloxone.¹⁸ As higher doses of naloxone than those used in the present investigation are needed to inhibit opiate δ receptors, while μ receptors are responsive to small doses,²⁰ the possibility that higher drug doses may stimulate gastric acid secretion remains to be evaluated.

The present results, as well as those reported with meperidine and morphine in man,^{1,2} do not agree with studies showing increased gastric acid secretion by morphine and met-enkephalin in dogs³⁻⁵ and lack of effect in cats.⁶ This discrepancy may probably be related either to the different animal species, or to the different doses of drug and routes of administration.

The finding that a peripherally acting opiate agonist like loperamide is able to inhibit gastric acid secretion supports the hypothesis of Solomon²¹ that the effects of exogenous and endogenous opiates on the stomach are not centrally mediated.

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