

Effect of loperamide and naloxone on mouth-to-caecum transit time evaluated by lactulose hydrogen breath test

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SUMMARY The effect of loperamide and naloxone on mouth-to-caecum transit time was evaluated by the lactulose hydrogen breath test in four men and four women. Each subject underwent tests during the administration of placebo, loperamide (12-16 mg po), naloxone (40 μ g/kg/h by a three-hour intravenous infusion), and loperamide plus naloxone, carried out at intervals of one or two weeks. The transit time was significantly longer after loperamide, and this effect was antagonised by the concomitant administration of naloxone whereas naloxone administered alone had no effect on mean transit time. No clinically important side effects were reported.

Morphine changes the motility pattern in the gastrointestinal tract,¹ decreases the propulsion of its contents,^{2,3} reduces gastric⁴ and intestinal secretions⁵ and increases water and ions absorption.^{6,7} Loperamide, an opioid agonist, retains most peripheral effects of morphine, many of which are inhibited by the opioid antagonist naloxone,⁸ but is nearly devoid of its central nervous system activity.

In patients with irritable bowel syndrome loperamide slows the small bowel transit of a meal⁹ and increases oro-caecal transit time as measured by lactulose hydrogen breath test.¹⁰ The reproducibility of this simple, non-invasive test has recently been questioned¹¹ and it has been reported to be influenced by sex¹² and menstrual cycle phases;¹³ however, Morley *et al*¹⁴ found it adequate to detect the increase of gastrointestinal transit time caused by gluten peptides which are believed to have an opioid-like activity, and the inhibition of this effect by naloxone.

In rats, the opioid antagonists naloxone and N-methylnaloxone have been shown to reverse the morphine-induced increase in gastrointestinal transit time assessed by measuring the length of

bowel traversed by a charcoal test meal.¹⁵ The present study was designed to assess in healthy human subjects of both sexes the effect of loperamide and naloxone on oro-caecal transit time measured by the hydrogen breath test.

Methods

SUBJECTS

Eight healthy volunteers (four men, age range 25-34 years, mean age 28 years, weight 72, 69, 68, and 64 kg; four women, age range 23-26 years, mean age 25 years, weight 72, 50, 49, and 48 kg) were studied after having given their informed consent. All volunteers belonged to the medical staff of the clinic and were willing to comply with the conditions needed for the test.

The weekly number of bowel movements was five to 10 in six subjects, three to four in one woman and two to three in another woman. None of the subjects took any medication for at least 72 hours or any antibiotics for at least two months before the beginning of the study, or during it. Subjects were asked to have a standard meal consisting of one serving of boiled rice, a steak, and water *ad libitum* at 8 pm the day before the test. Then they did not take anything except for the treatments. Smoking was not allowed between midnight and the end of the test. Studies were performed in a quiet

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environment, subjects being at complete rest.

Orocaecal transit time was assessed by means of the hydrogen breath test.¹⁶ At 9.30 am the fasting subjects ingested 10 g lactulose (Duphalac Philips Duphar, Weesp, Holland, 15 ml) suspended in 100 ml tap water. End expiratory breath samples were obtained just before and every 10 minutes after the ingestion of lactulose using a modified Haldane-Priestley tube.¹⁷ Samples were immediately analysed for molecular hydrogen using a chromatograph with a thermal conductivity detector (mod. 3200 DANI, Monza, Italy) as described by Zuccato *et al.*¹⁸ Values were expressed as ppm corresponding to 0.045 $\mu\text{mol/l}$. The mean of 12 determinations of standard samples containing 50 ppm H_2 were 50.5 ppm \pm 3.17 SD. The *r* values of calibration curves obtained from standard samples of H_2 (2–100 ppm) were 0.994.

Orocaecal transit time was defined as the time elapsing between ingestion of lactulose and the first definite and sustained rise of breath hydrogen concentration – that is, an increase of at least 2 ppm above the baseline, maintained or increased in the three following determinations. Hydrogen breath tests were carried out for at least three hours or until the orocaecal transit time was determined. Orocaecal transit time was assessed by a physician not aware of the treatments.

The subjects were divided into two blocks according to sex; each subject was studied on four separate occasions at intervals of one or two weeks. Each time a different treatment (A, B, C or D) was given, the sequence being as follows: subject 1, CADB; subject 2, ABCD; subject 3, BDAC; subject 4, DCBA; subject 5, BCDA; subject 6, DCBA; subject 7, BDAC; subject 8, CABD. The treatments were known only to the physician in charge of administering them. The treatments were administered as follows: at 10 pm the day before and at 8.30 am on the day of the test the five subjects weighing over 50 kg were given four capsules and the remaining three subjects three capsules with a sip of tap water. On the day of the test from 9–9.30 am each subject was given an intravenous infusion of saline 100 ml, and from 9.30 am–12.30 pm, while the hydrogen breath test was carried out, a further intravenous infusion of saline 500 ml with or without the study drug. If the hydrogen breath test was not stopped at 12.30 a further intravenous infusion of saline (with or without the study drug) was given until the end of the test.

Treatment A consisted of placebo infusion and placebo capsules, treatment B of placebo infusion and loperamide capsules, treatment C of naloxone infusion and placebo capsules, and treatment D of naloxone infusion and loperamide capsules.

Loperamide (Lopemid Gentili, Pisa, Italy) was given as capsules of 2 mg each and naloxone hydrochloride (Narcain Crinos, Villa Guardia, Italy) was given at doses of 40 $\mu\text{g/kg/h}$.

Symptoms and bowel movements during the 48 hours after the start of the test were recorded as well as the day of the menstrual cycle. The female subjects were not on oral contraceptives; four of the 16 tests on these subjects were undertaken during the luteal phase of the menstrual cycle.

Statistical analysis was performed with split-plot design (between-within subjects ANOVA) followed by Tukey's test for multiple comparisons¹⁹ and Fisher's exact test for frequency data.

Results

The orocaecal transit time in each subject according to treatments and the results of the analysis of variance are reported in the Table.

The difference in transit time between sexes was not statistically significant. In men and women loperamide prolonged transit time in comparison with the other treatments (Tukey's test: $p < 0.05$) while transit times during naloxone and loperamide plus naloxone administration were not statistically different from placebo or from each other. Only in subject 7, who had two to three bowel movements per week, transit time was not affected by loperamide and was reduced by naloxone.

During the 48 hours after the start of the test there

Table Orocaecal transit time in minutes according to treatments in 4 males and 4 females

	Treatments			
	A Placebo	B Loperamide	C Naloxone	D Loperamide + naloxone
Men				
1	90	180	90	90
2	60	110	60	80
3	60	200	70	50
4	50	140	50	40
mean	65.0	157.5	67.5	65.0
SD	17.3	40.3	17.1	23.8
Women				
5	50	90	30*	50
6	80*	170	80	60
7	140*	140*	100	150
8	120	220	130	120
mean	97.5	155.0	85.0	95.0
SD	40.3	54.5	42.0	47.9

* Female subjects in luteal phase of menstrual cycle.

Analysis of variance: between sexes NS.

between treatments $p < 0.000004$.

sexes \times treatments NS.

was a higher frequency of subjects with no bowel movements after administration of loperamide with (five subjects) or without (six subjects) naloxone compared with placebo (two subjects) or naloxone (one subject). Borborygmi, pain and abdominal distension were present in nearly the same frequency in all treatments. Headache was more frequent in subjects treated with naloxone alone (four subjects) or with loperamide (three subjects) compared with placebo (no subjects) or loperamide (two subjects) with a statistically significant difference ($p=0.03$) between treatments A and C. Borborygmi, pain, abdominal distension and headache always disappeared within eight hours after the start of the test and were mild and easily tolerated.

Discussion

Gastrointestinal transit time in rats, assessed by charcoal test meal, is prolonged by morphine and this effect is antagonised by naloxone or by its peripherally selective N-methyl analogue.^{2 15} These data are consistent with our findings in man, showing the increase in transit time induced by the peripheral opioid agonist loperamide was antagonised by naloxone.

In seven of our eight subjects the administration of naloxone did not seem to affect the oro-caecal transit time, as previously suggested by similar results in rats.²⁰ Rees *et al* reported a modification by naloxone of the antroduodenal motility pattern in man,²¹ but Feldman *et al* showed that the gastric emptying of a liquid meal is not influenced by this drug.⁴ Moreover, gastric emptying of liquids does not seem to affect human oro-caecal transit time assessed by lactulose hydrogen breath test.²²

In our study the inhibition of the effect of loperamide by naloxone was obtained by administering the antagonist by the intravenous route to avoid the first passage through the liver; other authors¹⁴ reported that naloxone administered po had an effect on mouth-to-caecum transit time delayed by hydrolysed gluten, suggesting a possible purely local effect on the gut.

Lawson *et al* reported that the oro-caecal transit time in women was significantly longer than in men.¹² This result was not confirmed by our study probably because of the large inter-individual variability and the small number of subjects studied.

A possible bias which might increase the intra-individual variability of the test in women is the luteal phase of the menstrual cycle which is reported to prolong transit time.¹³ We carried out four of the 16 tests in women in the luteal phase of the menstrual cycle in order to limit the time between

the four tests in each subject, and the variations were not so great as to prevent obtaining a statistically significant result in the group of women.

Our results were obtained using the lactulose hydrogen breath test, a simple and well tolerated investigation technique: the side effects reported were mild, quickly self-limiting and easily tolerated by the volunteers.

Recently La Brooy *et al* denied the reproducibility of the lactulose hydrogen breath test in and between individuals.¹¹ We did not study the reproducibility of the test and no data are available to compare with La Brooy *et al*'s results. In our experimental conditions, however, and using each subject as his-her own control, in accordance with Corbett *et al*'s previous findings,¹⁰ the reproducibility in individuals of this technique was adequate to detect the effect of loperamide on mouth-to-caecum transit time.

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