Br. J. clin. Pharmac. (1990), **29**, 355–358

Single doses of ritodrine delay orocaecal transit in patients with irritable bowel syndrome

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The lactulose hydrogen breath test was used to assess the effect of a single dose of the β_2-adrenoceptor agonist ritodrine on orocaecal transit time in 11 patients (three men) with irritable bowel syndrome. Transit time (median values, range) was significantly longer ($P < 0.01$) after ritodrine than after placebo (120, 50–200 *vs* 75, 40–100 min). Median heart rate was similar before treatments whereas the maximal increase in heart rate was significantly greater ($P < 0.01$) after ritodrine than after placebo.

Keywords β-adrenoceptor agonist breath tests gastrointestinal motility irritable bowel syndrome

Introduction

No data are available on the gastrointestinal effects of ritodrine in man, but it is known that β-adrenoceptor agonists relax gastrointestinal smooth muscles *in vitro* (Ek *et al.*, 1986; Hedges & Turner, 1969; Makhlouf, 1987) and delay human gastric emptying (Rees *et al.*, 1980). We performed a randomized double-blind trial with cross-over design to evaluate whether a single 20 mg dose p.o. of ritodrine delays orocaecal transit in patients with irritable bowel syndrome.

Methods

We studied eleven patients (three men, eight women) with irritable bowel syndrome in view of a suggested clinical application of β-adrenoceptor agonists in these patients (Lyrenas *et al.*, 1985 a). All patients gave informed consent. Their median age was 38 years (range 21–57), median height 165 cm (range 150–173) and median weight 58 kg (range 44–87). They were in good health and organic disease had been excluded by careful physical examination, laboratory tests (ESR, blood count, transaminases, serum albumin, blood urea nitrogen, serum amylase, serum T_3 and T_4, urinalysis, stool examination for occult blood, ova and parasites), rectosigmoidoscopy and abdominal ultrasonography; upper gastrointestinal tract endoscopy and other imaging studies were also performed when indicated. Patients with previous or current cardiovascular diseases or with any electrocardiographic abnormality were excluded. Symptoms were present in all cases, the median duration being 4 years (range 1–20 years). Symptoms reported at the beginning of the study by each patient are shown in Table 1.

Orocaecal transit time was evaluated with lactulose hydrogen breath tests on two separate occasions at least 3 days and no more than 7 days apart. Lactulose hydrogen breath test was performed under standard conditions as previously described (Basilisco *et al.*, 1987). At 09.30 h the fasting subjects ingested 10 g of lactulose suspended in 100 ml of tap water. End-expiratory breath samples were obtained every 10 min after lactulose ingestion using a modified Haldane-Priestley tube (Metz *et al.*, 1976). Each sample was immediately analysed by a gas chromatograph with thermal conductivity detector (mod 3200 DANI, Monza, Italy); two breath samples were also collected before lactulose administration. Hydrogen values were expressed as ppm, corresponding to 0.045

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Table 1 Symptoms reported by 11 patients with irritable bowel syndrome; a cross indicates the presence of the symptom

	Patient number										
Symptoms	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
Abdominal pain	x	x	x	x	x	x	x	x	x	x	x
Diarrhoea				x							
Constipation							x	x			x
Variable bowel habit			x			x					
Bloating			x	x	x		x			x	x
Nausea	x			x					x	x	
Headache	x			x	x				x	x	x
Dyspareunia					x				x		
Urgency at micturition			x							x	
Abdominal pain modified by defaecation	x									x	x

μmol l^{-1}. In our experimental conditions the detection limit for hydrogen was 2 ppm, the mean (s.d.) of 12 determinations of standard samples containing 2 and 50 ppm hydrogen was 2.4 (0.52) and 50.5 ppm (3.17) respectively, and the *r* value of calibration curves obtained from standard samples of hydrogen (2–100 ppm) was 0.94. Orocaecal transit time was defined as the interval between lactulose ingestion and the first definite and sustained rise of breath hydrogen concentration, that is, at least 3 ppm above the baseline level (mean value of two pre–lactulose samples), maintained or further increased for 30 min (Read *et al.*, 1985). On each occasion transit time was independently assessed by two physicians unaware of the treatment.

In similar experimental conditions, the median orocaecal transit of 15 healthy volunteers was 80 min (range 40–170), and the coefficient of the within subjects repeatability, defined according to the British Standard Institution as two s.d.s of the mean difference between the first and the second test in the same subject, was 51 min (Camboni *et al.*, 1988).

On each study day patients were given a different oral treatment 15 min before lactulose: 20 mg (two 10 mg tablets) of ritodrine (*erythro*-2-(4-hydroxy-phenethylamino)-1-(4-hydroxyphenyl)propan-1-ol hydrochloride) or two indistinguishable placebo tablets with a sip of tap water; the treatments were administered double-blindly according to randomized sequences following a cross-over design.

Before placebo or ritodrine administration and every 10 min for the duration of the test, heart rate (radial pulse, beats min^{-1}) was measured. Symptoms during the test were recorded as well as the day of the menstrual cycle. Transit times, heart rates before treatments, and differences between the highest heart rate observed after treatments and heart rate before treatments (maximal increase in heart rate), were compared with Wilcoxon's test. For transit times and heart rate data the sequence effect was examined by comparing the mean differences for the two treatment orders and the carry-over effect by comparing the mean of the patient means for the two treatment orders (ritodrine followed by placebo or *vice versa*) (Pocock, 1983).

The correlation coefficient was used to measure the degree of linear relation between transit times after placebo and the differences in transit times after ritodrine and placebo.

Results

Baseline hydrogen values ranged from non detectable to 5 ppm (median non detectable); no sustained rise of more than 3 ppm was seen before the increase we considered to indicate lactulose arrival at the caecum, and this was always followed in 20 min by an increase of at least 10 ppm (median 18, range 10–60). The two physicians interpreting transit time agreed in all cases. Five of the six women of reproductive age were tested in the same phase (follicular or luteal) of the menstrual cycle.

Transit time was significantly longer after ritodrine than after placebo ($P < 0.01$); median values (range) were 120 (50–200) and 75 (40–140) min respectively (Figure 1). Heart rate (median, range) was similar before ritodrine and placebo (74, 60–88 *vs* 73, 60–90 beats min^{-1}), whereas the maximal increase in heart rate was significantly greater ($P < 0.01$) after ritodrine

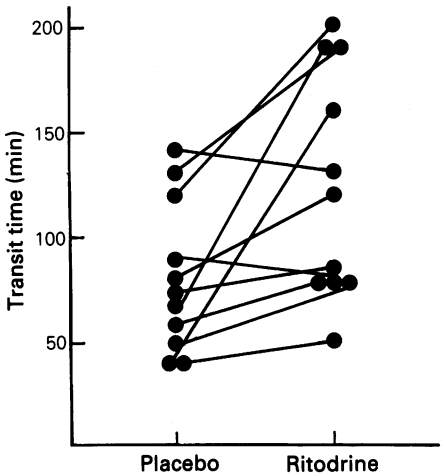

Figure 1 Orocaecal transit time after placebo and ritodrine in 11 patients with irritable bowel syndrome.

than after placebo (+18, +4 to +34 *vs* 0, −4 to +8 beats min^{-1}). No sequence or carry-over effects were found for either transit times or heart rate data. No correlation was found (r = 0.17; P = NS) between transit times after placebo and the differences in transit times after ritodrine and placebo.

The tests were well tolerated and only minor side effects were reported after ritodrine in six patients: tremors in two, palpitations in three, flush in two, restlessness in two, nausea in one.

Discussion

Ritodrine significantly delayed orocaecal transit of lactulose in patients with irritable bowel syndrome. This result is consistent with the inhibitory effect of β-adrenoceptor agonists on gastric and small bowel smooth muscle *in vitro* (Ek *et al.*, 1986; Hedges & Turner, 1969; Makhlouf, 1987) and with the delay of gastric emptying observed after salbutamol in man (Rees *et al.*, 1980).

McIntyre *et al.* (1987), with a method similar to ours, showed that the β_2-adrenoceptor agonist salbutamol did not prolong orocaecal transit in healthy volunteers. The discrepancy between the effects of salbutamol and ritodrine could be due to a different selective action of the two drugs on the gastrointestinal tract even though salbutamol and ritodrine have similar potency in the inhibition of spontaneous colonic motility in anaesthetized rats (Giudice *et al.*, 1989). Moreover, patients with irritable bowel syndrome could be more sensitive than healthy volunteers to the effect of β-adrenoceptor agonists on orocaecal transit due to abnormal orocaecal transit time (Cann *et al.*, 1983), dysmotility of the small intestine (Kellow *et al.*, 1988) or altered autonomic response to stress (Fielding & Regan, 1984) observed in some patients with this syndrome. However, similar doses of terbutaline inhibit rectosigmoid motility both in healthy volunteers and in patients with irritable bowel syndrome (Lyrenas *et al.*, 1985b).

The number of our cases was too limited to allow an evaluation of the effect of ritodrine according to patients' symptoms or bowel habit. However, we found no correlation between the transit time after placebo and the effect on transit time induced by the drug, and it is known that in patients with irritable bowel syndrome and diarrhoea orocaecal transit is shorter than in those with constipation (Cann *et al.*, 1984).

The delay of orocaecal transit induced by ritodrine in our study could be due to an inhibitory effect on gastric and/or small intestinal transit of the liquid meal, and could explain at least in part the nausea and vomiting commonly observed during intravenous administration of this drug (Caritis *et al.*, 1984).

Ritodrine significantly increased heart rate in our patients. In a study on anaesthetized rats this β_2-adrenoceptor agonist had greater gut *vs* cardiovascular specificity than isoprenaline (Giudice *et al.*, 1989). However, the effect of ritodrine on heart rate was evident in our patients and was described by three of them as palpitations. This suggests that smaller doses of ritodrine or more gut-selective compounds would be needed before the relaxing properties of β-adrenoceptor agonists on gastrointestinal smooth muscle could find clinical applications in irritable bowel syndrome for patients with gastrointestinal 'hypermotility' possibly related to the syndrome (Lyrenas *et al.*, 1985a).

The authors thank Ms Alix Green for help in the preparation of the manuscript.

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(Received 31 July 1989, accepted 7 November 1989)