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The effect of GR38032F, novel 5-HT_3-receptor antagonist on gastric emptying in the guinea-pig

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The effects of GR38032F a novel, selective and potent 5-hydroxytryptamine (5-HT_3)-receptor antagonist on gastric emptying in the guinea-pig were investigated and compared to those of metoclopramide and haloperidol. Both GR38032F and metoclopramide increased gastric emptying in a dose-dependent manner. In contrast, haloperidol was ineffective. GR38032F was about 200 times more potent than metoclopramide in enhancing gastric emptying over the 2 h period studied.

Introduction The ability of metoclopramide (MCP) to facilitate gastric emptying in both man and animals is well established (Harrington *et al.*, 1983) and has been considered to involve an antagonism at peripheral dopamine receptors (see Berkowitz & McCallum, 1980). However, although metoclopramide is a potent dopamine-receptor antagonist, recent studies have indicated that there is no evidence to link this pharmacological property with a potential to facilitate gastric emptying (see Buchheit *et al.*, 1985). Instead metoclopramide, as well as some other benzamides, has antagonist actions on 5-hydroxytryptamine (5-HT_3) receptors which may be more important to the gastroprokinetic effect (see Buchheit *et al.*, 1985).

In the present series of experiments the effects of a novel, potent and selective 5-HT_3-receptor antagonist GR38032F (1,2,3,9-tetrahydro-9-methyl-3 [(2-methyl-1H-imidazol-l-yl) methyl]-4H-carbazol-4-one, HCl. $2H_2O$ (Brittain *et al.*, 1987) on gastric emptying have been compared to that of metoclopramide and the dopamine antagonist haloperidol.

Methods Conscious Dunkin-Hartley guinea-pigs (500 ± 50 g) were used which were deprived of food overnight (14 h). Gastric emptying was measured by use of a non-invasive X-ray fluoroscopic technique to follow the passage of polystyrene coated barium sulphate spheroids (1 mm in diameter) from the stomach. The radio opaque spheroids were orally loaded in 0.2 ml of a 1% solution of carboxymethyl cellulose with 0.05 ml glycerin and their position determined by X-ray location (50 kV, 40 mA, 0.5–0.8 s) using Kodak plates (NS-2T, 13 × 18 cm). The percentage expulsion of spheroids from the stomach was calculated 1 h and 2 h after drug or vehicle administration.

Metoclopramide monohydrochloride (Beechams) and GR38032F were dissolved in distilled water. Haloperidol (Janssen) was dissolved in 0.01% lactic acid and neutralized with $NaHCO_3$ to pH 6.5. Significant differences from control values were assessed by the Mann-Whitney 'U' test. Doses of drugs given in the text refer to the free bases.

Results GR38032F, 0.001–0.1 mg kg^{-1}, i.p., at considerably lower doses than metoclopramide, 5–10 mg kg^{-1}, i.p., caused dose-related increases in gastric emptying 1 h and 2 h after administration (Table 1). In contrast, haloperidol, 0.5–5 mg kg^{-1}, i.p., failed to induce any alteration in the gastric emptying rate but, unlike GR38032F, haloperidol caused sedation at the highest dose of 5 mg kg^{-1}, i.p.

Table 1 Comparative effects of GR38032F and metoclopramide (MCP) on gastric emptying in the guinea-pig

Drug	*Dose* (mg kg^{-1} i.p.)	*% gastric emptying* $\frac{\text{No. spheroids emptied}}{\text{Total no. spheroids}} \times 100$ 1 h	2 h
Control	—	10 ± 3.7	30 ± 8.5
GR38032F	0.001	21 ± 8.7	57* ± 10.5
	0.01	33* ± 3.6	76* ± 11.2
	0.1	47* ± 7.6	68* ± 5.0
MCP	1	21 ± 6.0	36 ± 9.3
	5	41* ± 12.9	62* ± 13.7
	10	59* ± 10.7	64* ± 10.8

Mean values ± s.e.mean are given. Each mean is calculated from 4 to 6 values. * Significant increase in gastric emptying ($P < 0.05$, as analysed by the Mann-Whitney U test).

Discussion and Conclusions GR38032F is a highly selective, competitive antagonist at 5-HT_3-receptors and, as such, it has no demonstrable action at central or peripheral dopamine receptors (Brittain *et al.*, 1987). In the experiments described here in the guinea-pig, GR38032F was as effective, but considerably more potent than metoclopramide at increasing gastric emptying of barium sulphate spheroids. The effective doses of GR38032F are very similar to those that inhibit the Bezold-Jarisch reflex induced by 5-HT, or the selective 5-HT_3 agonist 2-Me5-HT, in other species (Brittain *et al.*, 1987). Furthermore, since metoclopramide possesses both dopamine and 5-HT_3 antagonist properties, and since haloperidol has no effect on gastric emptying, the results suggest that antagonism of an inhibitory 5-HT pathway is a common mechanism of action for metoclopramide and GR38032F (see also Buchheit *et al.*, 1985). The acetylcholine releasing action of metoclopramide (Harrington *et al.*, 1983) may be fundamental to the effect on gastric emptying and it remains important to determine the effects of other 5-HT_3-receptor antagonists on acetylcholine release and whether 5-HT_3-receptor antagonists increase gastric emptying via a central or peripheral action.

If GR38032F is found to enhance gastric emptying in patients with gastroparesis, then this drug would have clear therapeutic advantages, notably its lack of dopamine-related extrapyramidal side-effects which affect a high proportion of patients receiving metoclopramide (Harrington *et al.*, 1983).

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