Effect of ICS 205-930 (a specific 5-HT₃ receptor antagonist) on gastric emptying of a solid meal in normal subjects

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SUMMARY The effects on gastric emptying of a solid meal of the specific 5-HT₃-receptor antagonist ICS 205-930, 10 mg and 20 mg intravenously were assessed with a scintigraphic technique in 12 normals. The 50% emptying time was less, the lag phase was shorter and the post lag emptying rate was faster after 20 mg ICS 205-930 ($p < 0.02$). After 10 mg ICS 205-930 the lag phase was significantly shorter compared with placebo ($p < 0.04$). These results suggest that 5-HT₃ receptors may be involved in the regulation of gastric emptying in man.

ICS 205-930 ([IH]-indol-3-carbonic-acid tropine-ester hydrochloride, Sandoz, Basle, Switzerland), is a recently synthesised compound which is a potent and highly selective antagonist of 5-hydroxytryptamine (5-HT) at excitatory receptors located on peripheral neurones.^{1,2} These low affinity 5-HT-M receptors, which have recently been called 5-HT₃-receptors, are widely distributed through the peripheral nervous system and also occur in the enteric nervous system where they control the release of substance P, which activates the smooth muscle cells of the gut wall.^{2,3}

Data obtained in animal studies indicate that 5-HT₃-receptors may play an important role in the regulation of gastrointestinal motility. *In vitro*, ICS 205-930 and another selective, but less potent 5-HT₃ receptor antagonist, MDL 72222,⁴ increase the electrical field stimulation induced contractions of circular muscle strips from the guinea pig stomach. In fasted guinea pigs gastric emptying of polystyrene coated barium particles is enhanced by ICS 205-930⁵ and another recently synthesised 5-HT₃-receptor antagonist, GR38032F.⁶ In these actions ICS 205-930 appears to be approximately 10–50 times more potent than metoclopramide.⁵ In isolated preparations of guinea pig ileum ICS 205-930 blocks the 5-HT induced spasm of the longitudinal muscle, but does

not affect normal peristalsis,³ in contrast with the functional paralysis which occurs after opiates. ICS 205-930 has a potent antiemetic effect in the model of cisplatin induced emesis in the ferret.⁷ 5-HT induces its peripheral painful effects in man through activation of neuronal 5-HT₃ receptors and these can be selectively and reversibly inhibited by ICS 205-930.²

We have evaluated the effect of ICS 205-930, in intravenous doses of 10 mg and 20 mg, on gastric emptying of a solid meal in normal human volunteers.

Methods

SUBJECTS

Twelve normal volunteers (six men, age range 21–28 years) who were non-smokers, on no medication, within 15% of ideal body weight and without evidence of gastrointestinal disease were studied. Written informed consent was obtained in all cases and the study protocol was approved by the Human Research Review Committee of University Hospital, Utrecht.

All subjects participated in three experiments, each of which was separated by a minimum time interval of seven days. On each of the experimental days 50 ml normal saline, containing either 10 mg ICS 205-930, 20 mg ICS 205-930, or placebo was given at 08.45 hours by intravenous infusion over 15 minutes.

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The test doses were given in single blind fashion, and their order of administration was determined by a randomisation list (Latin square design). As the analysis of each gastric emptying study was done by one of the investigators who did not know which substance was infused, the study was in effect double blind.

Gastric emptying was measured with a previously described scintigraphic technique⁸ starting at 0900 hours and continuing for at least two hours. Each subject had fasted from 2200 hours the previous day. The solid test meal consisted of a pancake containing 8.6 g of protein, 40.2 g of carbohydrate and 8.4 g of fat, labelled with 9 MBq ^{99m}Tc-tin colloid. The subject was seated, leaning backwards at an angle of 60° to avoid overprojection of stomach and intestines, and radioactivity was measured by a ventrally positioned large field of view scintillation camera. Data were acquired in frame mode in a 64 by 64-matrix format with a time resolution of one minute. The data were corrected for subject movement, radionuclide decay and tissue attenuation using previously described methods.⁹ Time activity curves (expressed as percentage retention of the meal v time) were derived for the stomach and the remainder of the abdomen. From each gastric emptying curve the duration of the lag phase before food emptied from the stomach, the linear emptying rate after the lag phase and the time for 50% emptying were derived for subsequent statistical analysis.^{8,9} Each gastric emptying test was analysed and interpreted without knowledge of the study medication.

A standard 12-lead electrocardiogram was done immediately before and after each study and during each intravenous infusion the electrocardiogram was monitored continuously. Other safety evaluations included continuous monitoring of pulse rate, and measurement of blood pressure at least every five minutes and body temperature at least every 15 minutes from the start of the intravenous infusion until the completion of the test. On each study day, a thorough clinical examination, haematological and biochemical blood screen and a standard urinalysis were done before and at the end of the test. Each subject was asked to notify the investigators immediately of the occurrence of any possible adverse events during, or after each study period.

Gastric emptying data were analysed using the Wilcoxon's rank-sum test for paired data and changes in cardiovascular, haematological, and biochemical parameters were assessed using analysis of variance.

Results

All subjects tolerated the study well and no significant effects on cardiovascular, haematological or

Table 1 Gastric emptying of a solid meal in 12 subjects (mean (SE)) given intravenous placebo, ICS 205-930 (10 mg) and ICS 205-930 (20 mg)

	Placebo	ICS 205-930 10 mg	ICS 205-930 20 mg
Lag phase (min)	17.5 (2.8)	12.2 (2.1)*	11.3 (2.0)*
Linear emptying rate (%/h)	52.9 (3.2)	64.0 (4.9)	63.9 (3.5)*
50% emptying time (min)	76.9 (5.7)	61.9 (4.8)	59.8 (3.8)*

*Significantly different from placebo (p<0.05).

biochemical parameters were observed. Two subjects reported mild symptoms of constipation and abdominal fullness for approximately 24 hours after the 20 mg dose of ICS 205-930 and one of these two subjects had similar symptoms for approximately 24 hours after the 10 mg dose of ICS 205-930. Otherwise no adverse events were reported.

In all subjects gastric emptying of the solid meal was characterised by an initial lag phase, followed by an emptying phase which closely approximated a linear pattern. The duration of the lag phase was less (p<0.01), the linear emptying rate was faster (p<0.02) and the 50% emptying time was less (p<0.01) after 20 mg of ICS 205-930 compared with placebo (Table). After the 10 mg ICS 205-930 the lag phase was less (p<0.04) and there were non-significant trends (p<0.055) for a more rapid linear emptying phase and a shorter 50% emptying time, compared with placebo (Table). There was no significant difference between the 10 mg and 20 mg ICS 205-930 for any of the three parameters.

Discussion

Previous studies have confirmed that ICS 205-930 is a potent and selective antagonist of neuronal 5-HT₃ receptors.^{1,2} Because the affinity of the drug for other common neurotransmitter receptors is negligible, no adverse cardiovascular or central nervous system effects have been reported. ICS 205-930 was well tolerated and effective in 11 patients treated with the drug to prevent cisplatin induced vomiting.¹⁰ ICS 205-930 has been reported to be effective in the treatment of secretory diarrhoea associated with the carcinoid syndrome, but one of the three patients in this study developed pyrexia and a skin rash which resolved on discontinuation of the drug.¹¹ Our study also indicates that intravenous doses of ICS 205-930 are generally well tolerated. The symptoms of constipation and abdominal fullness observed by two subjects were mild, but may have been related to the use of the drug.

The results of our study suggest that 5-HT₃-receptors may be involved in the regulation of gastric

emptying in normal man – that is, an effect of ICS 205-930 is only expected where the underlying mechanisms include the activation of 5-HT₃-receptors,² but further studies are required to confirm this hypothesis. The most likely explanation for the effect of ICS 205-930 to facilitate gastric emptying is direct antagonism of 5-HT₃-receptors in the stomach, but an action on central nervous system control mechanisms is also possible. The effects of ICS 205-930 on gastric emptying were relatively small (mean reduction in 50% emptying time of approximately 20%), but prokinetic drugs, such as cisapride and metoclopramide, have minimal or no effect on gastric emptying in the normal stomach.¹² The more rapid gastric emptying of digestible solid food after ICS 205-930 probably results from an increase in antral motility and/or antroduodenal coordination,¹³ but this requires objective evaluation.

The physiological and pathophysiological role of 5-HT₃ receptors in the gastrointestinal tract needs further clarification before the implications of therapy – for example, for gastroparesis, with 5-HT₃ antagonists such as ICS 205-930 are apparent.² 5-HT in the gastrointestinal tract is mainly stored in the enterochromaffin cells and lower quantities are found in neurones within the myenteric and submucosal plexus.¹⁴ Very little is known about the conditions which regulate the release of 5-HT from the neuronal stores. Several stimuli, such as acidification of the duodenal mucosa¹⁵ increased intraluminal pressure in the intestine¹⁶ and neuronal stimulation¹⁷ have been shown to stimulate 5-HT release from the enterochromaffin cells.

Results of animal studies suggest that 5-HT₃-receptor activation may be involved in some disorders of gastrointestinal motility¹⁴⁻⁵ and if this occurs in man 5-HT₃-receptor antagonists may be therapeutically useful. ICS 205-930 may also offer some therapeutic advantage over treatments such as anticholinergics, cholinomimetic agents, and opiates, because in contrast with these drugs it appears to have little effect on basal motility.³ While metoclopramide is also a 5-HT₃ receptor antagonist,¹⁸ central nervous system side effects occur frequently as a result of its dopamine receptor blocking activity.

Our results indicate that studies evaluating the effect of ICS 205-930 in various forms of gastroparesis are now appropriate.

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