THE EFFECTS OF DOMPERIDONE ON GASTRIC EMPTYING OF LIQUID IN MAN

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- 1 The effects of domperidone (20 mg) i.v. and saline i.v. on gastric emptying of 500 ml of fluid have been compared in a blind study in six normal male volunteers.
- 2 Gastric emptying was measured by real-time ultrasound.
- 3 Domperidone significantly reduced the volume in the stomach 5 min after the drink (domperidone 306 ± 17 ml, saline 404 ± 31 ml, $P < 0.02$).
- 4 Domperidone had no significant effect on the half-life of gastric emptying measured between 5 and 60 min ($T_{1/2}$ domperidone 21.2 ± 1.17 min, $T_{1/2}$ saline 21.3 ± 1.58 min).
- 5 A similar pattern of gastric emptying to that produced by domperidone could be produced by giving a drink of a smaller volume.

Introduction

The control of gastric emptying is complex and involves central and peripheral mechanisms (Hunt & Knox, 1968). Drugs are known to alter gastric emptying, and the actions of pharmacological agents on the stomach have been investigated in a variety of ways including: the serial test meal (Hunt & Spurrell, 1951); radio-isotope labelled meals (Griffin *et al.*, 1966); barium meal examination (Kreel, 1973); measurement of the rate of drug absorption (Heading *et al.*, 1973).

We have already described a new non-invasive technique based on real-time ultrasound to monitor the gastric emptying of liquid meals (Bateman & Whittingham, 1982). We report here the effects of intravenously administered domperidone on gastric emptying in normal volunteers as measured by this technique.

Methods

Subjects

Six male volunteer subjects (22–28 years) attended the laboratory at 09.00 or 10.00 h after fasting from midnight, and having drunk no alcohol on the previous day. They received, in blind randomised order, 7 days apart, either domperidone 20 mg intravenously or an injection of an equal volume of saline. Ten minutes

later the subjects drank 500 ml of 20% orange cordial at 37°C. Gastric volumes were measured directly by ultrasound at regular intervals after the drink (5, 10, 15, 20, 30, 40, 50 and 60 min) with the subjects sitting upright in a firm chair.

The procedure was repeated on a subsequent day with a 400 ml drink. The volunteers were asked about subjective sensations resulting from the drug or placebo injections while still blind to the protocol.

Ultrasonic measurement of gastric emptying

This method has been described previously (Bateman & Whittingham 1982) and only brief details are given here. The equipment consists of a commercial real-time ultrasonic scanner (Toshiba SAL 20A), a mechanical gantry to support the probe of the scanner, an inexpensive microcomputer (Apple 11+) and a video-cassette recorder. The ultrasonic scanner produces cross-sectional images of a plane of tissue defined by the position of the probe, giving particularly clear definition of the walls of a liquid filled stomach. In this application the probe is swept along the axis of the stomach (Figure 1A) to produce a series of cross-sectional views (Figure 1B) spaced at 1 cm intervals.

Scanning sweeps are made along the full length of the stomach with the subject holding his breath in inspiration. This avoids artefacts due to respiration and helps to keep the gastric contents clear of over-

Figure 1 Diagram to illustrate the calculation of stomach volume by representing the stomach as a series of parallel cross-sectional slices (B) at regular intervals along its long axis (A).

lying ribs and lung. Each sweep takes 5–10 s to complete and thus gastric contractions, which occur about three times per minute, do not interfere with the volume measurement.

The probe position and time are both monitored by the microcomputer and recorded on video-tape along with the ultrasonic images. The microcomputer is also used to measure the cross-sectional areas of the stomach sections as well as the total volume, during subsequent playback of the videotape.

Results

The emptying of liquid from the stomach in individual subjects was found to be mono-exponential over the time period which volumes were recorded (5–60 min). Under the conditions of these experiments a log linear relationship resulted in better correlation than the use of the square root of the volume related to time, and this is in contrast to findings when using the serial test meal (Hopkins, 1966). The serial test meal does however, take gastric secretion into account and the ultrasound method ignores this. It has thus been possible to define and measure the half-life of emptying of liquid from the stomach. The results are shown in the graphs (Figures 2, 3 and 4) and have been expressed as mean values $\pm$ s.e. mean. Since the individual subjects have a mono-exponential decline

the regression for all the data points taken together has been plotted.

Figure 2 Gastric emptying of 500 ml meal following placebo (●—●) and domperidone 20 mg intravenously (○---○). The lines drawn are the least squares regression analyses for the total data points for six subjects in each group. * $P < 0.05$, ** $P < 0.02$.

Figure 3 Gastric emptying of liquid following 500 ml and placebo pretreatment (●—●) and 400 ml meal with no drug therapy (▲—▲) $n = 6$.

Figure 4 Gastric emptying of 500 ml of liquid following domperidone 20 mg intravenously pretreatment (O---O) and 400 ml liquid with no drug treatment (▲---▲) $n = 6$.

Effects of domperidone

Domperidone significantly reduced the volume of liquid in the stomach at 5, 10, 15 and 20 min (paired t -test $P < 0.02$, $P < 0.05$, $P < 0.02$, $P < 0.02$ respectively) (Figure 2). The mean volumes in the stomach at 5 min for example were 404 ± 31 ml after placebo and 306 ± 17 ml after domperidone.

The half-life of emptying over the period during which the volume measurements were obtained was not significantly affected by domperidone (placebo 21.3 ± 1.58 min, domperidone 21.2 ± 1.17 min (Table 1).

Two of the subjects complained of drowsiness and a feeling of depression on the day of the domperidone

injection but did not have that feeling after placebo. No other subjective complaints were recorded.

400 ml meal

Since the principal effect of domperidone was to reduce the volume in the stomach the subjects all received a meal of smaller volume (400 ml) on a subsequent day. The stomach volumes recorded after the meal of 400 ml were as expected significantly lower than those obtained with 500 ml and placebo pre-treatment (Table 1). However the half-life was not significantly changed with one smaller volume meal (400 ml, 21.2 ± 1.17 min; 500 ml, 21.3 ± 1.58 min) (Figure 3).

Comparison with the emptying curve obtained after treatment with domperidone (Figure 4) suggests that the actions of the drug are similar to results obtained with a reduction in the meal volume, but by an amount slightly less than 100 ml.

Discussion

When liquid is drunk and enters the stomach the musculature of the organ relaxes to accommodate it. The process of adaptive relaxation has not been extensively studied in man. Domperidone has been reported to affect human gastric adaptive relaxation after proximal gastric vagotomy (Sinnott & Leathard, 1981). Sinnott & Leathard's (1981) experiments, however, were based on the response of the stomach to introduction of air. Our technique allows the assessment of adaptive relaxation by direct volume measurement during the early part of a liquid meal. The amount of liquid remaining in the stomach at 5 min is a reflection of gastric relaxation and hence the stomach's response to the drink. Whether changes in the initial volume of the stomach are solely dependent on adaptive relaxation or whether pyloric muscle tone is involved too is unclear.

Our results have shown that domperidone significantly decreases the volume of liquid in the stomach 5 min after a drink. There was no significant effect on

Table 1 Half-life of gastric emptying (min) of liquid

Subject	Meal		
	500 ml + placebo	500 ml + domperidone	400 ml + no drug
1	15	23.6	24.0
2	23.5	19.8	16.3
3	23.5	19.5	18.4
4	18.1	18.3	25.2
5	24.9	25.8	17.3
6	22.7	20.3	26.0
Mean	21.3	21.2	21.2
$\pm$ s.e. mean	1.58	1.17	1.77

the half-life of emptying measured from this point. We thus infer that domperidone affects the adaptive response to a liquid meal. The studies with a meal volume of 400 ml suggest that the effects of domperidone may be equivalent to the results obtained with a meal of smaller volume.

Domperidone is a dopamine receptor antagonist and has been shown in experiments on animals to inhibit gastric relaxation caused by dopamine (Van Neuten & Janssen, 1980). One particular problem in interpreting the effects of drugs on the stomach in man is that many different techniques have been applied which are not directly comparable. Thus Proctor and co-workers (1981) have reported that domperidone when given intravenously half way through the emptying of a meal reduces the volume of liquid subsequently measured in the stomach. Balyens and co-workers (1979) examined the effects of domperidone on the emptying of barium from the stomach by looking at radiographs taken at 30, 60 and 90 min after the meal was given. They found that pretreatment with intravenous, or 20 mg oral doses of, domperidone increased the emptying of barium under these conditions (Balyens *et al.*, 1979). The effects of domperidone we have observed could well produce results similar to those these authors describe. In contrast, Broekart (1979) reported that domperidone increased their rate of emptying of liquid from the stomach when measured by the dye dilution double-sampling technique. In these experi-

ments 750 ml of liquid is introduced into the stomach directly by nasogastric tube over a period of three minutes, thus avoiding swallowing, which may be important in the process of gastric adaptive relaxation (Jahnberg, 1977). Since the meal we give is drunk within 30–40 s the results are obviously not comparable to experiments where liquid is introduced directly into the stomach at a much slower rate.

We have reported that metoclopramide, another dopamine receptor blocking agent, increases gastric emptying of fluid in man but has, in contrast to domperidone, no significant effect on the volume in the stomach 5 min following the drink (Bateman & Whittingham, 1982). Under the conditions of our experiments metoclopramide and domperidone appear to have different effects on gastric motor function. One possible explanation for these findings is that domperidone has much less central nervous system activity than metoclopramide because it penetrates the CNS less well (Van Neuten & Schuurkes, 1981). The findings in this study however are compatible with the hypothesis that dopamine receptors are involved in the control of gastric motor function, and more particularly in the control of the adaptive relaxation of the stomach.

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