Gastroduodenal motility — a comparison between domperidone and metoclopramide

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Summary

Domperidone (Motilium) speeds the emptying rate of the smallest particle size of a digestible solid (radioactive cubed liver) but has no effect on the emptying rate of 400 ml of 5% dextrose in the normal canine stomach. Conversely, metoclopramide (Maxolon) speeds the emptying of the liquid, but slows the emptying rate of the digestible solid.

The effect of domperidone on canine gastric electrical activity is to increase the frequency and strength of action potentials in the stomach after fasting and to slow the rate of discharge of the pacesetter potential, an effect similar to that seen after feeding.

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Much information has been gained over the past years concerning the effects and mode of action of metoclopramide (Maxolon) on gastroduodenal motility. This drug, probably a dopamine receptor blocker, has been shown to reverse the slowing of gastric emptying produced by dopamine and to speed the gastric emptying of liquids, barium and solid meals.[1,2] The action of metoclopramide appears to begin within 5 minutes and to last for at least 13 minutes. Terminal antral contractions and intragastric pressure increase and there is better co-ordination between antral and duodenal contractions. These effects have also been demonstrated in patients after vagotomy. Howard and Sharp[3] were able to produce more rapid emptying of the stomach of women in labour with metoclopramide than with placebo. Others have found no effect in subjects with normal rates of gastric emptying but were able to speed the emptying rate in patients with delayed gastric emptying.[4] Metoclopramide has found a valuable place in the treatment of patients with impaired motility of the upper gastro-intestinal tract and has also been of use in upper gastro-intestinal radiology and the placement of naso-intestinal tubes.[5]

Similarly, domperidone (Motilium) antagonizes apomorphine-retarded gastric emptying[6] and has the same effect on dopamine-retarded gastric emptying.[7] These authors showed that it speeds the initial gastric emptying of a solid meal but has no effect on a semi-solid meal. Domperidone produces dilation of the pylorus.[8]

The aim of this study was to compare the effect of domperidone and metoclopramide on the gastric emptying of a liquid (5% dextrose) and a digestible solid (radioactive cubed liver) in dogs. In addition we studied the effect of domperidone on the electrical activity of the antrum and duodenum in dogs.

Material and methods

Gastric emptying studies

Ten mongrel dogs each weighing approximately 15 kg were subjected to laparotomy under general anaesthesia, after which a Thomas cannula was implanted into the duodenum approximately 10 cm distal to the pylorus. The cannulas were brought through the anterior abdominal wall in the right flank and were kept tightly closed with brass plugs when not being used for gastric emptying studies. The animals were able to eat a normal diet while the cannulas were in place and gained weight. When the dogs had recovered from the operations, gastric emptying studies using either 5% dextrose or radioactive cubed liver were carried out.

Prior to a gastric emptying test each dog was starved of food but not water for 24 hours. The animals were then placed in loose-fitting canvas slings, where the cannula was unstopped and washed out with water. A Foley catheter was then directed via the cannula into the distal duodenum, where the bulb of the catheter was inflated with 8 - 12 ml water containing mercurochrome as a marker to indicate whether the balloon had burst. The inflated balloon allowed for the total diversion of duodenal

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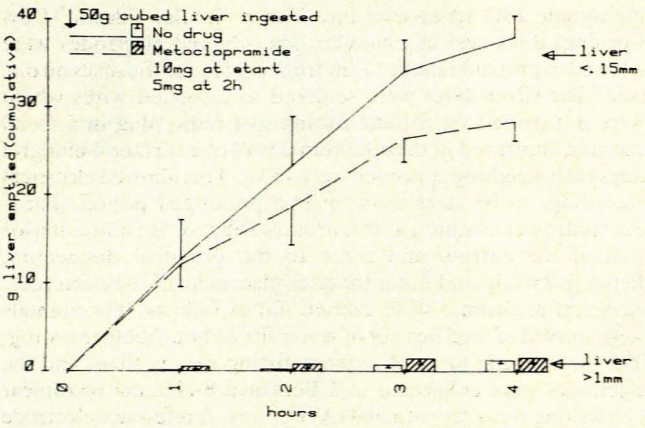

Fig. 2. Cumulative emptying of liver particles < 0,15 mm in size (line graphs) is slower with metoclopramide than without. Metoclopramide does not change the rate of emptying of liver particles > 1 mm in size (histograms).

cumulative emptying of liver of particle size < 0,15 mm in line graphs in Figs 1 and 2.

Domperidone produced a small but significant increase in the amount of liver of particle size < 0,15 mm emptied ($P < 0,02$). Metoclopramide, however, significantly slowed the rate of emptying of liver of particle size < 0,15 mm ($P < 0,025$).

Gastric emptying of 5% dextrose

The dextrose solution appeared in the duodenum within a few minutes of administration and a mean of 89% of the 400 ml administered emptied progressively over the next 150 minutes. Domperidone did not significantly alter the rate or profile of emptying of the dextrose solution (Fig. 3), whereas metoclopramide increased the emptying rate of the dextrose solution, with a maximum effect at 15 minutes ($P < 0,10$) (Fig. 4).

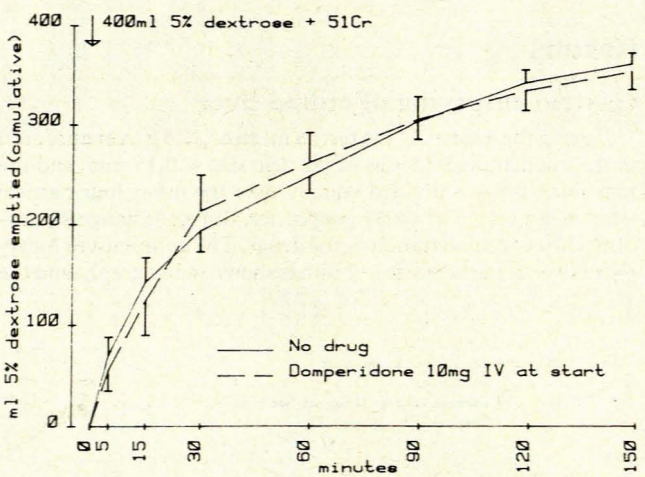

Fig. 3. Cumulative emptying of 400 ml 5% dextrose over 150 minutes. No change is noted after domperidone 10 mg intravenously at the start of the test.

Electrical studies

Satisfactory recordings of the IDMEC were usually obtained. In the dogs which had fasted the incidence of action potentials increased significantly both in the antrum and in the duodenum after the administration of domperidone (from 14% to 41% in the antrum and from 10% to 63% in the duodenum) ($P < 0,05$). The strength of action potentials also usually increased after domperidone (Figs 5 and 6); this effect began within 5 minutes after administration and lasted for at least 35 minutes. In addition, there was a significant fall in the frequency of the pacesetter potential both in the antrum and in the duodenum in the fasted animals, but not after feeding, which had already caused a fall in the frequency (Table I). Of interest is the fact that the effect in the fasted animals is similar to the effect seen after feeding them 200 g lean minced beef.[9] We were not able to demonstrate a clear co-ordination of duodenal and antral action potentials. After proximal gastric vagotomy, results were essentially the same.

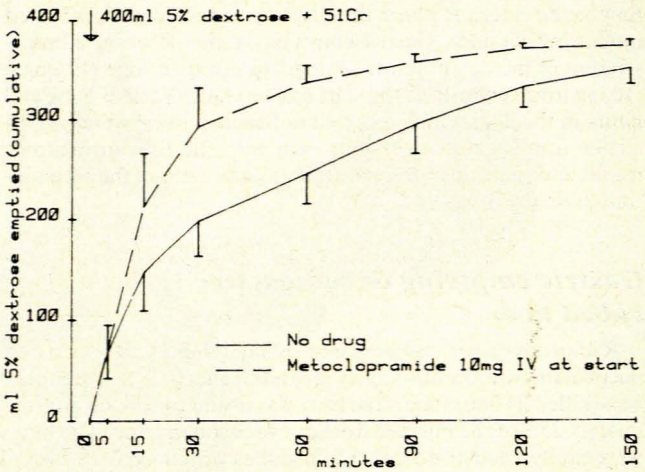

Fig. 4. Cumulative emptying of 400 ml 5% dextrose over 150 minutes. Faster emptying occurs with metoclopramide 10 mg intravenously at the start of the test.

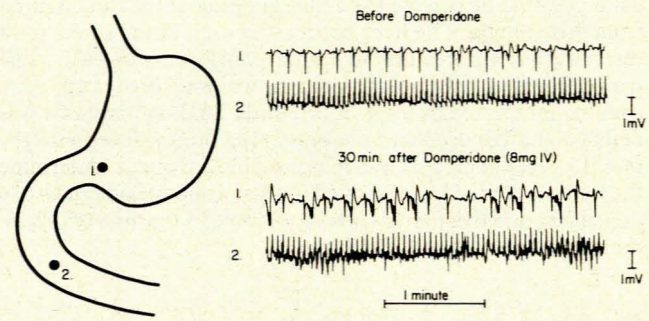

Fig. 5. Canine gastroduodenal electrical activity in fasted dogs before and 30 minutes after domperidone 8 mg intravenously. Domperidone produces frequent, strong action potentials. There is no clear antroduodenal co-ordination of action potentials.

TABLE I. MEAN PACESETTER POTENTIAL FREQUENCY (IMPULSES/MIN) (± SE)

	Before PGV		After PGV	
	Fasting	Fed	Fasting	Fed
Control				
Antrum	4,9 ± 0,2	4,4 ± 0,1	4,8 ± 0,1	4,3 ± 0,3
Duodenum	18,8 ± 0,2	18,2 ± 0,4	18,5 ± 0,3	18,2 ± 0,2
Domperidone				
Antrum	4,5 ± 0,2*	4,2 ± 0,2	4,5 ± 0,1*	4,4 ± 0,1
Duodenum	18,0 ± 0,2*	17,9 ± 0,3	18,1 ± 0,3*	18,2 ± 0,2

*Significantly different from the result before domperidone ($P < 0,05$) (paired t test).
PGV = proximal gastric vagotomy.

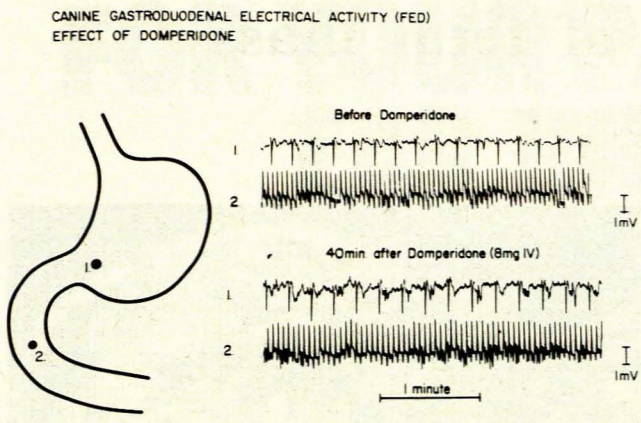

Fig. 6. Canine gastroduodenal electrical activity in fed dogs before and 40 minutes after domperidone 8 mg intravenously. Most pacesetter potentials have an associated action potential before administration of the drug. These are stronger after administration of the drug.

Discussion

Domperidone, a dopamine receptor blocker, produces changes in the electrical potentials in the fasted canine stomach similar to those seen after feeding. In addition this drug speeds the rate of emptying of liver of particle size $< 0{,}15$ mm in the normal canine stomach but does not alter the rate of emptying of a dextrose solution. In contrast, metoclopramide speeds the emptying of the liquid solution but slows the emptying of cubed liver. This result suggests that these two drugs, similar in many respects, have minor but important differences. It is not clear from this study whether this difference is a result of a specific site or mode of action. Metoclopramide may cause more antral spasm than domperidone, resulting in less efficient trituration and breakdown of the digestible solid. The tone of the proximal stomach is said to control the emptying of liquids and the grinding action of the antrum controls the emptying of solids. The two drugs may exhibit their action on different parts of the stomach, or they may act via different receptor sites.

This study indicates the importance of taking into account the composition of a meal in interpreting results from gastric emptying studies. It is of the utmost importance to specify and employ meals of different consistency, osmolality and composition before general conclusions can be reached. From this study it could be inferred that domperidone should be used in disorders of emptying of solids, and metoclopramide in disorders of emptying of liquids. This leads to the next question — which, if either, of the drugs should be used in preventing duodenogastric reflux? Metoclopramide but not domperidone speeds the emptying of a liquid, but clinical studies with both drugs indicate that they are both of value in controlling these symptoms. The electrical studies show no clear co-ordination between antral and duodenal action potentials after the administration of domperidone in the fasted stomach. If anything, the recordings show that at times the duodenum contracts while the antrum is relaxed, an action which would promote duodenogastric reflux. However, Schuurkes *et al.*[10] have shown that such co-ordination occurs after the administration of domperidone in isolated guinea pig stomachs.

These dopamine antagonists act at much lower concentrations than those required for the modification of neuronal control, suggesting that they act via gastro-intestinal dopamine receptors such as have indeed been found in the upper gastro-intestinal tract.[11] Of interest is the fact that the effect of metoclopramide on contractions of guinea-pig stomachs is critically dependent on intrinsic stores of acetylcholine.[12] Both metoclopramide and domperidone have been shown to increase the tone of the lower oesophageal sphincter, but neither drug significantly alters gastric secretions. The small changes produced by these drugs on the emptying patterns of the normal stomach do not necessarily mean that these results can be extrapolated to events in the abnormal stomachs in which these drugs will usually be employed. Hancock *et al.*[4] have shown that metoclopramide is effective only in patients with delayed emptying. The results of these experiments should therefore be assessed in the light of clinical trials on patients with motility abnormalities of the upper gastro-intestinal tract.

Our results indicate that domperidone does modify the electrical pattern in a way in which motility should be facilitated, and has much the same effect on the antrum and duodenum after proximal gastric vagotomy.

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