The action of metoclopramide on human gastroduodenal motility

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SUMMARY The action of metoclopramide on gastroduodenal motility was studied in 23 subjects: eight symptomless volunteers and 15 patients with varying upper abdominal conditions. The response depended on the basal contraction pattern before the drug was given, irrespective of the clinical diagnosis. The size of the antral contractions was consistently increased and the duodenal contractions became more closely linked to those of the antrum. This demonstrates a mechanism for the increased rate of gastric emptying that is observed clinically after metoclopramide.

The action of metoclopramide (Maxolon) in increasing the strength of gastric contractions has been well established in animals (Jacoby and Brodie, 1967; Johnson, 1970). In man it has been found to speed gastric emptying when this is studied radiologically (James and Hume, 1968; Kreel, 1970) or by a dye dilution method (Connell and George, 1969). The effect on the duodenum is more variable but in animals metoclopramide tends to produce a closer linkage between the timing of antral and duodenal contractions (Johnson, 1971), while in radiological studies in man it produces good filling of the duodenal cap with barium. It has been found to act on the stomach after vagotomy (Jacoby and Brodie, 1967; Banke, 1968), and also to produce contractions of muscle strips *in vitro* provided acetylcholine is also present (Eisner, 1968).

It is claimed that metoclopramide 'regularizes' gastric contractions, and this study was designed to test its effects on gastroduodenal motility in patients and symptomless volunteers.

Definition of Terms

The term 'contraction' refers to an increase in intraluminal pressure and 'rate' to the number of contractions in a given period of time. 'Rhythm' means the distribution or spacing of contractions over a period of time. 'Activity' merely refers to the presence of contractions without any implication about their strength, rate, or rhythm. The term 'motility index' has not been used to avoid ambiguity.

Subjects and Methods

RECORDING TECHNIQUE

A triple lumen polyvinyl tube was used, each lumen

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having an internal diameter of 1.5 mm and two side holes near the tip. One lumen recorded from the duodenum, one from the antrum, and the third was used for gastric aspiration. The distance between the openings of the duodenal and antral recording tubes was 12 cm. The tube tips had radioopaque markers and were screened into position, the antral marker being placed at the left border of the vertebral column, and the duodenal marker in the cap or the upper second part of the duodenum. The positions were checked at intervals during the study and at the end. Figure 1 shows a diagram of the tubes in position. The recording tubes were filled with saline and connected via Statham P23 D6 pressure transducers to an SE ultraviolet 300 6 recorder with a paper speed of 50 mm/minute.

The patients did not eat or drink for four hours before the studies but did not starve overnight. The stomach was aspirated as completely as possible before recording commenced and subsequently at 10-minute intervals. All recordings were done with the patient in the supine position and at least 15 minutes' basal recording was allowed before metoclopramide (10 mg iv) was given.

SELECTION OF SUBJECTS

There were 23 subjects consisting of eight symptomless volunteers, four male and four female, with an average age of 22 years, and 15 patients, seven male and eight female, with an average age of 45 years. The patients were all under investigation for dyspeptic symptoms: eight had normal barium meals, two had persistent dyspepsia after biliary operations but the stomach was normal at operation, two had persistent dyspepsia after vagotomy and pyloroplasty, and three after pyloroplasty alone. The

Fig. 1 Diagram of recording tubes in position

symptomless volunteers did not have radiological investigations.

mediately before and the five-minute period after injection of metoclopramide that showed the maximum effect. Special attention was paid to the rate and rhythm and the relationship between antral and duodenal activity which comprised the contraction patterns before and after injection of the drug.

Results

Metoclopramide increased the strength of gastric antral contractions in all subjects where they were present during the basal period, except one. The effect started three to five minutes after beginning the injection and the size of contractions increased up to 15 to 20 minutes and then gradually decreased. The total effect lasted about 30 to 40 minutes, although it is difficult to judge the exact point at which contractions returned to their basal height. Figure 2 gives an example of a recording from a symptomless volunteer. The responses to metoclopramide depended, in both volunteers and patients, on what contractions were occurring in antrum and duodenum at the time the injection was given, and on this basis can be divided into the four types set out below.

Type	Basal Contraction Pattern	Response to Metoclopramide
A	Small antral and duodenal contractions	Both increased in size, a large single or double duodenal contraction tending to follow each antral contraction.
B	Moderate-sized antral and duodenal contractions, already in phase	Slight increase in size of antral contractions only
C	Small antral contractions but strong rapid duodenal contractions (9-11/min)	Antral contractions increased in size and duodenal slowed to antral rate and rhythm.
D	No significant antral or duodenal contractions	No significant effect

ANALYSIS OF RECORDINGS

Both antral and duodenal recordings were analysed as the number and average strength of contractions (in mm Hg) during the five-minute period im-

mediately before and the five-minute period after injection of metoclopramide that showed the maximum effect. Special attention was paid to the rate and rhythm and the relationship between antral and duodenal activity which comprised the contraction patterns before and after injection of the drug.

Fig. 2 Recording showing marked increase in the strength of antral contractions after metoclopramide. (Vertical lines denote one-minute intervals.)

Fig. 3a.

Fig. 3b.

Type	No. of Contractions in Five Minutes	Average Strength in mm Hg
A	Antrum	
	Before metoclopramide	7
	After metoclopramide	7
		Very small
B	Duodenum	
	Before metoclopramide	15
	After metoclopramide	6
		2
C	Antrum	
	Before metoclopramide	5
	After metoclopramide	4
		2
D	Duodenum	
	Before metoclopramide	9
	After metoclopramide	10
		12
E	Antrum	
	Before metoclopramide	45
	After metoclopramide	10
		22
F	Duodenum	
	Before metoclopramide	9
	After metoclopramide	10
		15

Table I Examples of each kind of response

3/min rate. The rate of the duodenal contractions, however, was altered and, if rapid, was reduced to near that of the antrum, each large contraction occurring after an antral contraction. Table II shows the distribution of subjects by clinical diagnosis and type of response. It will be seen that the response did not depend on the clinical diagnosis, and that a

Diagnosis	Response			
	Type A	Type B	Type C	Type D
Symptomless volunteers	2	1	1	3
Radiograph negative	2	2	2	2
After biliary operations	1	1	—	—
After vagotomy and pyloroplasty	1	—	1	—
After pyloroplasty alone	1	—	—	1

Table II Distribution by clinical diagnosis and type of response

Fig. 3c Recording of type C response (duodenal pressures only).

Fig. 3d Recording of type D response (vertical lines denote one-minute intervals).

Fig. 3c

Fig. 3d.

type C response was seen even after a vagotomy and pyloroplasty. Twenty-one of the 23 subjects showed one of these four types of response. Of the remaining two, one with a pyloroplasty showed a sudden increase in both rate and size of duodenal contractions with a rise in basal pressure associated with some sweating. The other was a volunteer who was very nervous and showed an inhibition of the slight basal activity (see below).

THE EFFECT OF INTRADUODENAL ARACHIS OIL
The type D response needs special clarification, as in four of the subjects in this group intraduodenal arachis oil (7 ml) was given to inhibit gastric and duodenal contractions. Metoclopramide given during this period of complete inhibition had no significant effect. The other two subjects had no arachis oil but there was no basal activity in either antrum or duodenum and no response to metoclopramide. In

subsequent studies a delayed response to metoclopramide given during a period of fat inhibition has been found.

THE PLACEBO EFFECT OF THE INJECTION

It might be argued that the observed effect is caused by the injection itself. Figure 4 shows the marked inhibition of antral and duodenal activity produced by an injection of N saline (2 ml) in a patient who subsequently responded in the normal way to an injection of metoclopramide. Several patients showed a temporary inhibition of activity for the duration of the injection (1 min) and a similar explanation is likely in the one subject who showed inhibition of gastroduodenal contractions after metoclopramide. There is, therefore, no evidence that the injection itself produced the increase in the strength of antral contractions that was consistently

Fig. 4 Recording showing inhibition of both antral and duodenal contraction by injection of *N* saline (2 ml) (vertical lines denote one-minute intervals).

observed, but that this occurred despite some degree of psychological inhibition.

Discussion

This study was designed to assess the effect of metoclopramide on varying basal motility patterns and gives no information on the difference in the motility patterns in different diseases.

The findings reported here compare closely with those reported in anaesthetized dogs (Johnson, 1971). Although some increased linkage between the gastric and duodenal rhythm was seen in animals it was more marked in human subjects (Fig. 3), and still occurred after vagotomy and pyloroplasty (Table II).

Code (1970) has recently reviewed the mechanism of linkage between the antral and duodenal contractions. There are three possible mechanisms: (1) neurogenic transmission of impulses across the pylorus; (2) myogenic transmission; and (3) the mechanical distension of the duodenal cap by gastric contents. The last is unlikely in the present situation as the stomach was kept as empty as possible. Probably there is neurogenic or myogenic transmission of the antral electrical slow wave across the pylorus, making 'spiking' more likely in the duodenum. Bortoff and Davis (1969) found that the antral rate could be superimposed on that of the duodenum, particularly following augmentation by vagal stimulation. The augmentation of antral contractions by metoclopramide may produce a similar effect.

The observation that the drug had little effect when there were no spontaneous contractions is probably explained by the fact that local acetylcholine release is required before metoclopramide has any effect (Eisner, 1968), and that this does not occur during these 'resting' periods, despite the continued presence of the electrical slow wave (pacemaker potential of Code, 1970).

CORRELATION OF MOTILITY RECORDS WITH CLINICAL EFFECTS OF METOCLOPRAMIDE

The most consistent clinical effect of metoclopramide is the speeding of gastric emptying, but this is less marked if the emptying time was previously normal (Connell and George, 1969). During the peak period of gastric emptying there are strong antral contractions and the duodenal contractions occur during terminal antral contraction (Thomas and Crider, 1935; Carlson, Code, and Nelson, 1966). This is not only the most favourable situation for gastric emptying but also prevents reflux of duodenal juice into the stomach. If this pattern is already present (type B, Fig. 3b) metoclopramide would be expected to have relatively little effect on emptying, but if there is marked duodenal activity with weak antral contractions (type C; Fig. 3c) emptying will be slow (Weisbrodt, Wiley, Overholt, and Bass, 1969) and a change in this pattern will greatly affect gastric emptying.

Conclusions

Metoclopramide increases the strength of gastric antral contractions. It increases the linkage between antral and duodenal contractions and can, therefore, be said to 'regularize' gastro-duodenal motility. It is probably through these two mechanisms that the gastric emptying rate is increased. It has little effect when there are no spontaneous contractions.

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