Action of oral metoclopramide on the gastrooesophageal junction in man

J. B. DILAWARI¹ AND J. J. MISIEWICZ

From the Medical Research Council Gastroenterology Unit, Central Middlesex Hospital, London

SUMMARY The effect of oral metoclopramide, 10 mg, was studied with intraluminal manometry in 20 patients suffering from symptoms of gastrooesophageal reflux. The drug increased cardiac sphincter pressure and the amplitude of oesophageal peristaltic waves, but gastric motility was stimulated in only half of the patients. The clinical value of these pharmacological effects should be confirmed in therapeutic trials.

Metoclopramide (Maxolon, Primperan) is frequently prescribed for heartburn or regurgitation, the symptoms of gastrooesophageal reflux. Although metoclopramide increases cardiac sphincter pressure in normal people when given intravenously (Heitmann and Möller, 1970), it is not known whether it has a similar effect when given to patients by mouth. We have therefore measured the effect of oral metoclopramide on the pressures in the oesophagus, cardiac sphincter, and the stomach in patients with symptoms of reflux.

Patients and Methods

Twenty-five patients, all with symptoms of reflux, were studied: brief clinical details are in table I. The

	No.	Men/Women	Radiology		
			Reflux	Duodenal Ulcer	Negative
Placebo	5	5/0	4	—	1
Metoclopramide	20	11/9	6	5	9

Table I Clinical details of patients

patient's informed consent to the test was obtained in each case. Five patients were studied with a placebo, in order to assess the stability of the oesophageal pressures during the two-hour test. The remaining 20 patients received metoclopramide 10 mg by mouth.

Intraluminal pressures were measured with an assembly of four polyvinyl tubes (internal diameter 1.2 mm) with side-opening tips 5 cm apart; the tubes were perfused with water at the rate of 7 μ l sec⁻¹. Pressures were recorded on a multichannel pen writer. Swallowing was monitored with a pneumograph placed over the larynx. The patients were intubated following an overnight fast. With the patient supine, the tube assembly was positioned so that the two proximal tips were in the oesophagus, the third in the cardiac sphincter, and the fourth in the stomach. The cardiac sphincter was identified as a zone of high pressure which relaxed on swallowing. Pressures were continuously recorded for a basal 30 minutes. The patient then swallowed a tablet of metoclopramide 10 mg (20 patients) or a placebo (lactose 100 mg, five patients) with 100 ml of water. The pressures were then recorded for a further 90 minutes.

The pressure tracings were analysed in consecutive 10-min periods. The average cardiac sphincter pressure was calculated in each period as the difference between end expiratory fundal and sphincteric pressures. In each 10-min period the mean amplitude of oesophageal peristaltic contractions and the duration and amplitude of gastric pressure waves were also measured.

The action of metoclopramide on the cardiac sphincter was analysed in three different ways, with each patient acting as his own control. First, the mean sphincteric pressures in the group of patients given the placebo or metoclopramide were compared before and after the drug for each 10-min period, and the differences examined with Student's *t* test. Secondly, the highest sphincter pressure attained

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after the drug was compared in each patient with his mean basal pressure. Lastly, the onset, duration, and persistence of the drug's action was assessed in each patient in terms of a 'response', which was arbitrarily defined as a rise in cardiac sphincter pressures of 100% or more above the mean basal level in any 10-min period. The value of 100% was adopted, because although pressures during the basal period were generally stable, they did vary by 50% from the mean in three of the patients.

Results

In the five patients given the placebo pressure levels in the oesophagus, the cardiac sphincter, and the stomach showed no consistent changes during the two-hour test (fig 1).

By contrast, the mean pressure in the cardiac sphincter increased in the group of 20 patients given 10 mg of metoclopramide. The increase in mean pressure became apparent approximately 20 min after the drug and persisted to the end of the study (fig 1). Although the increase in sphincteric pressure was highly significant in comparison with mean basal levels ($p < 0.02$ to < 0.001), the observed rise in pressure averaged only 6-7 mm Hg. The relaxation of the cardiac sphincter after swallowing was not affected by the drug.

The highest sphincter pressure observed in each patient during 90 min following the drug is shown in figure 2. In all the patients except two, cardiac

CARDIAC SPHINCTER

Fig 1 Cardiac sphincter pressures before (○) and after (●) oral metoclopramide ($n = 20$, upper curve), or placebo ($n = 5$, lower curve). Symbols show mean $\pm$ SEM.

CARDIAC SPHINCTER

Fig 2 Cardiac sphincter pressures before and after oral metoclopramide in individual patients. Left column: mean basal pressure; right column: maximal pressure attained during 90 min after the drug in any 10-min period.

sphincter pressure increased at some time after metoclopramide. However, the highest pressures were recorded in the patients who had high basal pressures to start with. The time of onset and persistence of the drug's action are shown in terms of the 'response' in figure 3. Analysed in this way, four patients showed no 'response' to metoclopramide during the period of study. In the remainder, the 'response' was observed at 10 to 90 min after the drug. The duration and persistence of the 'response' were also variable (fig 3).

Mean amplitude of oesophageal peristaltic contractions increased by 4-10 mm Hg in most 10-min periods after metoclopramide (table II). Gastric motility was stimulated in half the patients, the remainder being unaffected. No unwanted effects of the drug were observed.

Discussion

This study shows that 10 mg of oral metoclopramide augments the amplitude of oesophageal peristaltic contractions, raises the cardiac sphincter pressure, and stimulates gastric motility in patients suffering

Site of Tube above Cardiac Sphincter (cm)	Pressure in mm Hg (Means $\pm$ SEM)									
	Average Basal (30 min)	Minutes after Metoclopramide								
		10	20	30	40	50	60	70	80	90
10	34 $\pm$ 2	37 $\pm$ 2	39 $\pm$ 3	38 $\pm$ 2	39 $\pm$ 3	41 $\pm$ 2	39 $\pm$ 3	42 $\pm$ 3	43 $\pm$ 3	41 $\pm$ 2
5	38 $\pm$ 3	41 $\pm$ 3	43 $\pm$ 3	44 $\pm$ 3	44 $\pm$ 2	47 $\pm$ 2	47 $\pm$ 2	48 $\pm$ 3	48 $\pm$ 3	48 $\pm$ 2

Table II Amplitudes of oesophageal peristaltic waves

CARDIAC SPHINCTER

Fig 3 Duration and onset of the 'response' of cardiac sphincter in individual patients. Thick bars indicate sphincteric pressures $\geq 100\%$ above mean basal level.

from symptoms of gastroesophageal reflux. The effect on the sphincter was observed in the majority of fasting patients 20 min after the drug was given. These changes are in line with effects of the drug which follow parenteral administration (Heitmann and Möller, 1970), and are potentially valuable in the management of heartburn and regurgitation.

Our data, however, do not provide direct evidence that the gastroesophageal junction was made competent by metoclopramide, nor do they indicate

how the effect of the drug may be modified by meals. Moreover, the response to metoclopramide was variable and although the cardiac sphincter was stimulated in most patients, the increase was greatest in those with initially high pressures. Similar findings have been reported during intravenous administration (Heitmann and Möller, 1970) and may set a limit to the efficacy of the drug. Experiments *in vitro* suggest that metoclopramide sensitized human alimentary muscle to acetylcholine (Eisner, 1968), although an additional mode of action on intramural nerves may also be present, at least in laboratory animals (Jacoby and Brodie, 1968; Bianchi, Beani, and Crema, 1967). The effects of metoclopramide are partially prevented by atropine (Eisner, 1968; Jacoby and Brodie, 1968), so that anticholinergic drugs should not be prescribed with it. Now that oral metoclopramide has been shown to exert a pharmacological action on the cardiac sphincter, its therapeutic value should be assessed in clinical trials.

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