Preliminary Communications

Gastrointestinal Effects of Metoclopramide in Man. In Vitro Experiments with Human Smooth Muscle Preparations

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Summary: Metoclopramide (N-(diethylaminoethyl)-2-methoxy-4-amino-5-chlorobenzamide) has been investigated with human gastrointestinal smooth-muscle preparations in vitro. Small-intestinal and colonic circular muscle was contracted by metoclopramide. This effect was antagonized by atropine. Gastric and colonic longitudinal muscle was sensitized by metoclopramide to acetylcholine. Atropine acted here as a partial antagonist of metoclopramide.

The interference of acetylcholine and metoclopramide is of a hitherto undescribed pharmacological type. The effects of metoclopramide in vivo—where its action is predominantly on the stomach and pylorus—are not fully explained by these in vitro experiments in which the effect was found to be most pronounced on the colon.

INTRODUCTION

The unique gastrointestinal effects of metoclopramide are well documented (Justin-Besançon, 1964; Grivaux, Cornet, and Watzet, 1964; Chevrot, Roux, and Menard, 1965; Sickinger, Fiedler, Bokermann, and Emmrich, 1965). Its mode of action is as yet poorly understood. Metoclopramide (N-(diethylaminoethyl)-2-methoxy-4-amino-5-chlorobenzamide), a derivative of procainamide, was synthesized in 1961 (Justin-Besançon, Laville, and Thominet, 1964).

In animal experiments and clinical trials the following effects have been found:

(1) *Antiemetic Effect* (Justin-Besançon and Laville, 1964a; Justin-Besançon, 1964).—This is due to an influence on the trigger zone in the medulla oblongata. Metoclopramide is 35 times more effective than chlorpromazine against apomorphine in dogs. Metoclopramide has no sedative effect and no influence on labyrinthic stimuli.

(2) *Effect on Motility of Stomach, Pylorus, and Small Intestine* (Justin-Besançon, Grivaux, and Watzet, 1964; Chevrot *et al.*, 1965; Jacoby and Brodie, 1967).—Metoclopramide causes intensified peristalsis of the stomach and dilatation of the pylorus, duodenum, and small intestine which lead to rapid emptying of the stomach and a short transit time through the small intestine. How metoclopramide induces these changes in motility has not been elucidated. Evidence of a direct or indirect effect on gastrointestinal smooth muscle is lacking (Justin-Besançon and Laville, 1964b). From in vivo experiments on the rat, dog, and monkey Jacoby and Brodie (1967) assume that metoclopramide involves activation of the intramural cholinergic neurones responsible for modifying gastric motility but not acid secretion either by direct stimulation or by removal of inhibitory circuits or pathways. To clarify further the mode of action of metoclopramide, experiments on human gastrointestinal smooth-muscle preparation were undertaken, as it has been shown that human smooth muscle may behave pharmacologically differently from animal preparations (Misiewicz, Waller, and Eisner, 1966).

METHODS AND MATERIAL

The method of Bennett and Whitney (1966) was followed. Surgical specimens that were macroscopically free from disease were placed in Krebs-Ringer solution. Strips of the muscular layer (about 3 by 20 mm.) were cut and immediately suspended

in an organ bath at 37° C. and aerated with 95% O₂ and 5% CO₂. The movements against a load of 1 g. were recorded by a lever writing on a smoked drum. After an incubation period of at least one hour the drugs were added. Drug concentrations refer to the salt in micrograms per millilitre of fluid in the bath.

The following drugs were used: acetylcholine hydrochloride, isoprenaline sulphate, 5-hydroxytryptamine-creatinine sulphate, neostigmine methylsulphate, atropine sulphate, procaine hydrochloride, and metoclopramide hydrochloride. When no effect was seen with metoclopramide alone, acetylcholine or isoprenaline or 5-hydroxytryptamine was added. The Table gives the number of specimens examined.

Number of Surgical Specimens Examined

Stomach	{ Body 10	Small intestine	{ Longitudinal .. 8
	{ Antrum 16		{ Circular .. 7
Pylorus 5		Colon	{ Circular .. 18
Duodenum 10			{ Taenia .. 16

RESULTS

Stomach.—No effect was seen with metoclopramide up to a concentration of 100 µg./ml. But in the presence of metoclopramide the contraction to acetylcholine was increased (Fig. 1). Metoclopramide sensitized smooth muscle to acetylcholine. This effect was shown with 1 and 10 µg. of metoclopramide. It was found on 7 out of 10 strips from the body of the stomach and in 14 out of 16 from the antrum. Metoclopramide partially antagonized atropine; a small and delayed contraction occurred with acetylcholine in the presence of atropine and metoclopramide.

Pylorus and Duodenum.—Metoclopramide (0.1–10 µg.) sensitized 4 out of 5 pyloric strips and 6 out of 10 duodenal strips to acetylcholine.

Small Intestine.—Metoclopramide alone contracted 11 out of 15 (eight longitudinal and seven circular) muscle strips (Fig. 2). The minimal effective concentration of metoclopramide was 0.1 to 1 µg. with the different strips as compared with 0.001 to 0.1 µg. of acetylcholine. Metoclopramide altered the spontaneous rhythmic activity in the majority of the small-intestinal preparations. But this effect was variable and unpredictable. Moreover, during longer periods of observation similar changes occurred spontaneously.

Colon, Circular Muscle.—Ten out of 18 strips were contracted by metoclopramide (0.1–10 µg.). Atropine partially antagonized metoclopramide (Fig. 3). A small and delayed contraction was seen with metoclopramide in the presence of a concentration of atropine, which blocked acetylcholine completely.

Colon, Longitudinal Muscle.—Metoclopramide alone had no effect. It sensitized the strips to acetylcholine (Fig. 4). Fourteen out of 16 strips were sensitized with 0.1–10 µg. of metoclopramide. Procaine decreased the contraction of the strips to acetylcholine.

General Observation.—Metoclopramide had no effect on the relaxation or contraction of isoprenaline or 5-hydroxytryptamine.

DISCUSSION

From the data presented it is evident that metoclopramide acts on human gastrointestinal smooth muscle in vitro. The mode of action is different at the different sites of the gut. This is not surprising, since similar properties are known about other

substances (Misiewicz *et al.*, 1966). Metoclopramide has no visible effect on gastric and colonic longitudinal muscle. Its action is apparent only with acetylcholine and consists in sensitizing the smooth muscle to acetylcholine. In the presence of metoclopramide acetylcholine leads to about a tenfold greater contraction. Atropine is partially antagonized by metoclopramide.

Small-intestinal and colonic circular muscle is contracted by metoclopramide alone. The contraction is inhibited by atro-

lished traces suggest a mode of action similar to that found in our experiments.

In experimental animals (Jacoby and Brodie, 1967) and during radiological examinations in man (Grivaux *et al.*, 1964; Justin-Besançon *et al.*, 1964; Chevrot *et al.*, 1965) metoclopramide acts predominantly on stomach, pylorus, and small intestine. In vitro the colonic smooth muscle is most sensitive. The in-vitro studies, therefore, are unable to explain fully the mode of action of metoclopramide on the gastrointestinal tract.

FIG. 1.—Response of a muscle strip from stomach to acetylcholine (Ac) and metoclopramide (M). In the presence of metoclopramide the contraction to acetylcholine is increased. Arrow indicates wash-out. Time: 1 mm.=10 sec. FIG. 2.—Response of an ileal muscle strip to metoclopramide (M) and acetylcholine (Ac). Note change in rhythmic activity. Arrow indicates wash-out. Time: 1 mm.=10 sec. FIG. 3.—Response of a colonic circular muscle strip to acetylcholine (Ac) and metoclopramide (M) in the presence of atropine (Atr). Contraction to metoclopramide is small and delayed. Arrow indicates wash-out. Time marker: 6 sec. FIG. 4.—Response of a muscle strip from taenia coli to acetylcholine (Ac) in the presence of procaine (P) and metoclopramide (M). Sensitivity of strip to acetylcholine is decreased by procaine and increased by metoclopramide. Arrow indicates wash-out. Time: 1 mm.=10 sec.

pine. Metoclopramide alters the spontaneous rhythmic activity. As changes in rhythmic activity may be seen during longer periods of observation and the changes after metoclopramide are variable and unpredictable, it is impossible to draw any conclusions.

Metoclopramide is a derivative of procaine. On the gastrointestinal smooth muscle their action is opposite: procaine decreases and metoclopramide increases the effect of acetylcholine.

Our data suggest that metoclopramide has a common receptor with acetylcholine. To explain the unique interference of metoclopramide and acetylcholine two different but mutually interfering receptors for the contraction of smooth muscle must be postulated, but the existence of two such receptors is not proved (Ariëns, 1964).

Whether metoclopramide has an effect on smooth muscle outside the gastrointestinal tract cannot be answered from our experiments. In all experiments and clinical trials published to date no action other than in the gastrointestinal tract and the central nervous system has been found. Justin-Besançon and Laville (1964b) failed to demonstrate an action of metoclopramide on isolated smooth-muscle preparations. With ortho-chloroprocainamide, a compound similar to metoclopramide, a cholinergic action was found by Besançon (1957), and his pub-

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