

METOCLOPRAMIDE AND EXPERIMENTALLY-INDUCED GASTRIC ULCERATION IN GUINEA-PIGS

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Summary : Anti-gastric activity of metoclopramide was studied in guinea pigs using three different models of gastric ulceration. The effect of metoclopramide on gastric acidity was also studied. It was observed that metoclopramide affords protection against all types of experimentally induced gastric ulceration, without affecting the gastric acid secretion. The protective effect, therefore, is probably due to its ability to promote gastric drainage and to prevent the pyloric reflux, thus preventing corrosive effects of bile and acid on the stomach mucosa.

Key words : metoclopramide
dopamine antagonist

experimental gastric ulcer
antigastric ulcer activity

INTRODUCTION

Metoclopramide is a dopamine antagonist having diverse pharmacological actions. Its actions on gastro-intestinal tract include regulatory effect on gastric motility (3), promotion of gastric emptying (1), coordination of antral and duodenal contractions (9) and prevention of oesophageal and gastric reflux (2). It also has antiemetic action which is thought to be mainly mediated centrally via chemoreceptor trigger zone (9) but probably there is also a peripheral mechanism (1).

Although metoclopramide stimulates the smooth muscle of the stomach, particularly the antrum (9), the exact mechanism of this effect is not known. The effect is probably peripheral in origin, since vagotomy does not affect it and like the central action may involve dopamine antagonism (1).

The present study was undertaken to investigate the effect of metoclopramide on experimentally induced gastric ulcers in guinea pigs and on the gastric acidity and peptic activity, since these aspects of pharmacological profile of metoclopramide are not studied well so far.

MATERIAL AND METHODS

Acute gastric ulceration was produced in guineapigs of either sex weighing between 300 to 600 g. Animals were fasted for 24 hr prior to the experiments but water was provided *ad libitum* during this time. Neither food nor water was allowed during the experiments. Animals were housed individually in cages at room temperature under natural light cycles.

Experimental induction of gastric ulcers :

(i) *Histamine-induced acute gastric ulceration* : Histamine (5 mg/kg, ip) was given in 20 animals; they were sacrificed 6 hr later (6). Half the animals had received metoclopramide (ip) 1 hr before histamine, the other half (vehicle controls) were given normal saline (ip).

(ii) *Aspirin-induced acute gastric ulceration* : Aspirin was suspended in 1% gum acacia and was given orally (200 mg/kg) to 20 animals 1 hr after treatment with metoclopramide (ip, n=10) or normal saline (ip, n=10). The animals were sacrificed 6 hr later (7).

(iii) *Ulcers induced by pyloric ligation (Shay ulcer)* : Animals were lightly anaesthetized with ether and pyloric ligation was done. The animals were treated 1 hr before with metoclopramide (ip, n=10) or normal saline (ip, n=10). Animals were sacrificed 6 hr after pyloric ligation.

Gastric acidity was estimated by titrimetric method (5). For this purpose 20 animals were fasted for 24 hr. Half animals were given metoclopramide (ip, n=10) and half were given normal saline (ip, n=10). Animals were sacrificed 1 hr after treatment and gastric contents were collected.

Abdomen was opened by a midline incision; stomach was removed and opened along the greater curvature. It was washed with Ringer solution and was inspected for breach of continuity of mucous membrane which was taken as a criterion for the presence of an ulcer. Total number of ulcers were counted and the ulcer index was determined for each animal by totalling the length (mm) of all ulcers (8).

Drugs used were histamine acid phosphate, aspirin and metoclopramide monohydrochloride. Results were statistically analysed by applying students 't' test.

RESULTS

Effect of metoclopramide on number of gastric ulcers and ulcer index : In all the models studied, the number of ulcers per stomach and the ulcer index were reduced

significantly ($P > 0.001$) by metoclopramide (Table I). The anti-gastric ulcer activity of metoclopramide was seen only with 10 mg/kg dose. Lower doses (2.5 mg/kg and 5.0 mg/kg) were ineffective and higher doses (20 mg/kg) did not show any significant antiulcer activity.

TABLE I : Effect of metoclopramide (10 mg/kg, ip) on experimentally-induced acute gastric ulceration in guinea-pigs.

Ulceration		Control group (n=10)	Treated group (n=10)
Histamine-induced	Mean No. of ulcers \pm S.E.M.	17.9 \pm 1.56	7.8 \pm 1.08*
	U.I. \pm S.E.M.	268.8 \pm 58.48	51.3 \pm 13.38*
Aspirin-induced	Mean No. of ulcers \pm S.E.M.	11.2 \pm 3.17	3.2 \pm 0.63*
	U.I. \pm S.E.M.	67.2 \pm 41.46	7.6 \pm 2.69*
Pyloric ligation induced	Mean No. of ulcers \pm S.E.M.	8.6 \pm 1.31	3.9 \pm 0.48*
	U.I. \pm S.E.M.	27.3 \pm 3.98	10.7 \pm 1.82*

*Value differs significantly from control ($P < 0.001$)

U.I. = Ulcer index, showing total length of ulcer (mm).

Effect of metoclopramide on gastric acidity and peptic activity:

In control group (n=10), the mean gastric acid volume (ml, \pm SEM) was 6.4 \pm 0.76, and the mean total acidity (mEq/l, \pm SEM), 5.4 \pm 0.69. These were not significantly altered by metoclopramide. Likewise, the drug had no major influence on peptic activity (1.31 \pm 0.19, U/1) found in control group.

DISCUSSION

Metoclopramide clearly reduced the number of ulcers and ulcer index in 3 types of experimentally induced gastric ulcers in guinea pigs. It was observed that metoclopramide showed a "therapeutic window-like" effect, drug activity being significant only of dose level of 10 mg/kg. Explanation of this phenomenon is not readily available. Our results also show that metoclopramide had no direct effect on gastric acidity and peptic activity.

Acid secreted into the gastric lumen, diffuses back into the mucosa very slowly. If the mucosa is normal, it serves as a barrier to back diffusion. Breaking of this barrier is one of the known factors which can lead to gastric ulceration (7). Bile acid, which can diffuse into the stomach by duodenogastric reflux, is one of the chemical agents capable of breaking this barriers. Metoclopramide, by synchronizing the duodenogastric activity may reduce this reflux of bile acid into the stomach. Though the exact role of gastric emptying in the pathogenesis of gastric ulceration is not known, reduced gastric emptying is also observed in some patients with gastric ulcer without pyloric stenosis (7). Metoclopramide has ability to increase the gastric motility, thus reducing the time of contact of acid to the gastric mucosa. It is, hence, proposed that metoclopramide protects the gastric mucosa from bile as well as acid, which may explain protection it gives against ulcerogenesis. The possibility of stimulation of mucous secretion is not ruled out in present work.

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