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Effects of Misoprostol on Gastric Acid and Mucus Secretion in Man

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Misoprostol, a synthetic prostaglandin E_1 analog, at doses of 200, 400, or 800 μg, and placebo were administered orally in random fashion to eight healthy male volunteers. The effects on basal and pentagastrin (0.6 μg/kg/hr) -stimulated acid and mucus (N-acetyl-neuraminic acid measurement) secretion were then determined. Misoprostol in 200-, 400-, and 800-μg doses reduced basal acid secretion by 91%, 93%, and 93%, respectively. Mean 2-hr acid secretion was reduced by 27%, 33% ($P < 0.01$), and 51% ($P < 0.01$), respectively. Reductions in secretory volumes paralleled acid changes. Mucus secretion increased by 37%, 82%, and 95% during the basal period following misoprostol doses of 200, 400, and 800 μg, respectively. Increase in mucus of 27%, 31%, and 38% was observed during maximal acid inhibition (1–30 min) by misoprostol in 200-, 400-, and 800-μg doses. The concentration of gastric juice mucus was significantly increased. Subjects experienced no significant side effects during the study, and there were no significant changes in hematological or chemical blood studies. Misoprostol, a potent inhibitor of gastric acid secretion, also stimulates mucus secretion. This mucogenic effect may be important in the mucosal protective action of misoprostol and its antiulcer efficacy in man.

Misoprostol, [(±)-methyl-(11,13*E*)-11,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oate], a synthetic prostaglandin E_1 analog, is a potent antisecretory agent in animals (1, 2). Several reports have also indicated that it has mucosal protective effects in animals and, more recently, in man (3–5). Misoprostol has been shown to be effective therapy for ulcer disease in man (6).

Prostaglandins may accelerate ulcer healing due to their acid antisecretory actions. However, the mucosal protective effects, or cytoprotection, of these compounds can be separated from their effects on acid secretion in animal studies and, therefore, may also play a role in ulcer healing (7). Although the mechanism of prostaglandin-induced mucosal protection is not precisely known, prostaglandins affect a number of parameters, including the gastric mucosal barrier, gastric mucosal blood flow, bicarbonate and mucus secretion, and cell proliferation and migration (8–16). Prostaglandins have previously been shown to stimulate gastric mucus secretion in animals and man and to increase mucus synthesis in the rat gastric mucosa (10–12). It is possible that this mucogenic effect may play a role in the mucosal protective actions of prostaglandins.

In the present study, we have compared the effects of single 200-, 400-, and 800-μg doses of misoprostol with placebo on basal gastric acid and mucus secretion and on gastric acid and mucus secretion following pentagastrin stimulation.

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MATERIALS AND METHODS

Eight healthy men, aged 22–33 years, were given placebo and each of three doses of misoprostol (200, 400,

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TABLE 1. EFFECTS OF MISOPROSTOL ON BASAL AND PENTAGASTRIN-STIMULATED GASTRIC MUCUS SECRETION*

	Secretion (μg)			
		Misoprostol (μg)		
Time (min)	*Placebo*	*200*	*400*	*800*
−15 to 0 (Basal)	1464 ± 300	2004 ± 546	2670 ± 845	2860 ± 795
1–30	2686 ± 542	3382 ± 444	3522 ± 782	3709 ± 405
31–60	2487 ± 438	2020 ± 313	2530 ± 522	2187 ± 319
61–90	2317 ± 268	2506 ± 523	2913 ± 754	2471 ± 429
91–120	2584 ± 369	2223 ± 263	2425 ± 439	2608 ± 482

*Results are mean ± 1 SEM (N = 8). Measured as total N-acetylneuraminic acid (NANA).

and 800 μg) at weekly intervals, in a randomized, double-blind crossover study. Following an overnight fast, the subjects swallowed either placebo or drug, supplied as four identical white tablets, with 150 ml of water. Forty-five minutes later, a nasogastric tube (18F) was placed in the dependent portion of the stomach, and stomach contents were evacuated. A basal specimen of gastric juice was then collected for 15 min, after which gastric secretion was stimulated by the intravenous infusion of pentagastrin in normal saline at a dose of 0.6 μg/kg/hr. For the next 2 hr (divided into eight 15-min collection periods), gastric contents were collected by continuous aspiration and stored on ice. Throughout the procedure, subjects were questioned and observed closely for possible side effects. Immediately before and after the experimental time periods, subjects underwent complete physical examinations and a series of laboratory tests, including urinalysis, CBC, and a standard blood chemistry panel (glucose, BUN, Na^+, Cl^-, K^+, CO_2, Ca^{++}, creatinine, uric acid, SGOT, SGPT, alkaline phosphatase, bilirubin, LDH, GGT, cholesterol, and triglycerides). A history was also taken.

Following the test period, each 15-min specimen was analyzed as follows. The volume of the sample was measured, and a 1-ml aliquot was titrated to pH 7.0 with 0.1 N NaOH in an automatic titrator (TTT 81 Digital Titrator, Radiometer, Copenhagen), in order to determine gastric acid content. The remainder of the gastric juice was homogenized by hand and an aliquot assayed for mucus content by determining the amount of glycoprotein-bound N-acetylneuraminic acid (NANA), using the thiobarbituric acid method of Warren (17) as modified by Roboz et al (18). NANA is the major sialic acid identified in human mucus glycoprotein. These determinations may not precisely reflect changes in the glycoprotein molecule (19).

Statistical Analysis. The data from the 15-min, pentagastrin-stimulated collections were pooled into half-hour collection periods for statistical analysis of NANA, gastric acid, and volumes. A paired t test was employed with $P < 0.05$ denoting statistical significance.

RESULTS

During the basal period, misoprostol in doses of 200, 400, and 800 μg increased mucus (NANA) secretion by 37%, 82%, and 95%, respectively (Table 1). A stimulatory effect on mucus output could also be seen with pentagastrin-stimulated secretion. During the first 30 min of pentagastrin stimulation following misoprostol doses of 200, 400, and 800 μg, mucus secretion was increased by 26%, 31%, and 38%, respectively (Table 1). Mucus concentration was significantly increased by misoprostol during

TABLE 2. EFFECTS OF MISOPROSTOL ON BASAL AND PENTAGASTRIN-STIMULATED GASTRIC MUCUS CONCENTRATION (NANA)*

	Concentration (μg/ml)			
		Misoprostol (μg)		
Time (min)	*Placebo*	*200*	*400*	*800*
Basal	37.5 ± 3.8	55.7 ± 6.7†	72.6 ± 10.8†	87.6 ± 21.1
1–30	26.8 ± 5.6	62.6 ± 26.2	48.4 ± 4.9	49.6 ± 2.6†
31–60	20.5 ± 3.2	25.8 ± 4.2	30.7 ± 4.3	29.7 ± 3.7
61–90	21.6 ± 2.5	23.3 ± 3.0	27.3 ± 3.3	32.4 ± 3.8‡
91–120	24.0 ± 2.9	24.9 ± 1.7	24.6 ± 2.9	30.1 ± 3.3‡

*Results are mean ± 1 SEM.
†$P < 0.05$.
‡$P < 0.01$.

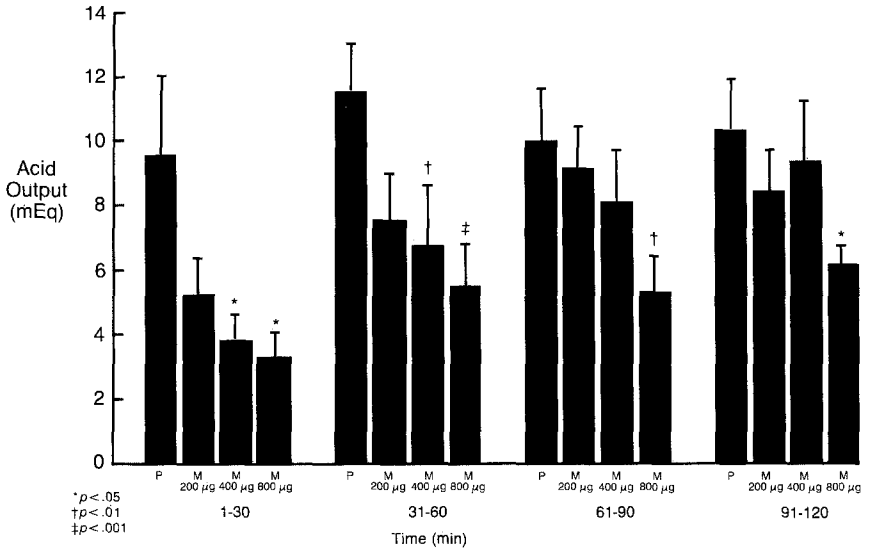

Fig 1. Effect of misoprostol in doses of 200, 400, and 800 μg on pentagastrin-stimulated gastric acid output during four consecutive 30-min intervals. Mean ± 1 SEM.

the basal period. The misoprostol 800-μg dose also significantly increased mucus concentration during pentagastrin stimulation (Table 2).

Basal acid secretion decreased from 1.67 ± 0.90 meq to 0.15 ± 0.08, 0.11 ± 0.11, and 0.12 ± 0.10 meq following misoprostol doses of 200, 400, and 800 μg, respectively. The 800-μg dose of misoprostol significantly inhibited pentagastrin-stimulated acid secretion during the entire 2-hr period, while the 400-μg dose significantly reduced acid secretion for 1 hr (Figure 1). Maximal inhibition occurred during the first 30-min period and was 45%, 60%, and 65% for misoprostol doses of 200, 400, and 800 μg, respectively. Mean 2-hr gastric secretion was significantly reduced by misoprostol at all three doses (Table 3).

Subjects experienced no significant side effects during the study, and there were no significant changes in hematological or chemical blood studies or urinalyses.

DISCUSSION

The antisecretory effects of misoprostol on basal and stimulated gastric acid secretion in man were confirmed in the present study. In addition, misoprostol increased both the total output and concentration of mucus in gastric juice. In general, a dose–response was observed, with misoprostol 800 μg causing a doubling of mucus output during the basal period. However, these changes were not statistically significant ($P < 0.10$). Similarly, the increases in total mucus output observed during pentagastrin stimulation were not significant. However, significant increases in NANA concentrations were observed during the basal and stimulation periods.

Prostaglandin-induced mucosal protection, termed cytoprotection, is multifactorial. While the gastric mucosal barrier does not appear to be of major importance in explaining cytoprotection, vascular

TABLE 3. EFFECTS OF MISOPROSTOL ON PENTAGASTRIN-STIMULATED GASTRIC SECRETION*

		Misoprostol (μg)		
	Placebo	*200*	*400*	*800*
Acid (meq)	41.56 ± 6.58	30.47 ± 3.72	28.10 ± 5.75†	20.36 ± 3.22†
Volume (ml)	453 ± 32	357 ± 25‡	355 ± 40‡	313 ± 33†

*Results are mean ± 1 SEM.
†$P < 0.01$.
‡$P < 0.05$.

permeability and change in mucosal blood flow together with maintenance of the mucus gel layer appear to be viable mechanisms. Prostaglandin stimulation of glycoprotein and bicarbonate secretion into the mucus gel layer has been well documented (20, 21). It is likely that no currently proposed single prostaglandin-induced event can fully define cytoprotection, but that multiple simultaneous events with differing degrees of importance (depending upon the insulting agent) combine to effect the prostaglandin action. Mucogenesis has previously been suggested as the major mechanism by which carbenoxolone exerts its antiulcer effect. Recent studies indicate that carbenoxolone may increase mucosal prostaglandin levels by reducing the metabolism of prostaglandins (22).

The mucogenic effects of misoprostol may be important to the efficacy of this compound in treating and preventing mucosal injury.

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