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Restorative Impact of Rabeprazole on Gastric Mucus and Mucin Production Impairment During Naproxen Administration: Its Potential Clinical Significance

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Rabeprazole augments gastric mucus and mucin production in humans. However, its potential restorative impact on gastric mucus and mucin production impairment, resulting from administration of naproxen, remained to be explored. Therefore, we measured the content of mucus and mucin in gastric juice (GJ) before and after administration of naproxen with rabeprazole or placebo. The study was approved by HSC at KUMC and conducted in 21 asymptomatic, *H. pylori*–negative volunteers in a double-blind, placebo-controlled, crossover design. The content of gastric mucus in GJ, after exhaustive dialysis and complete lyophilization, was assessed gravimetrically, whereas the content of mucin was measured after its purification with equilibrium density-gradient ultracentrifugation in CsCl. Gastric mucus secretion during administration of naproxen with placebo declined significantly both in basal (by 44%; $P < 0.001$) and in pentagastrin-stimulated (by 35%; $P < 0.001$) conditions. Coadministration of rabeprazole significantly restored the naproxen-induced impairment in mucus production in basal conditions (by 47%; $P < 0.01$) and by 22% during stimulation with pentagastrin. Gastric mucin secretion during naproxen/placebo administration also declined significantly in both basal (by 39%; $P < 0.01$) and stimulated (by 49%; $P = 0.003$) conditions. Rabeprazole also significantly restored the naproxen-induced decline of gastric mucin output during pentagastrin-stimulated conditions (by 67%; $P = 0.003$) and by 40% in basal conditions ($P = 0.05$). The restorative capacity of rabeprazole on the quantitative impairment of gastric mucus and mucin during administration of naproxen may translate into a clinical benefit of protection of the upper alimentary tract from NSAID-related mucosal injury.

KEY WORDS: gastric mucus; gastric mucin; mucous barrier; naproxen.

Nonsteroidal anti-inflammatory drugs (NSAIDs) represent a category of medications that require continuous reevaluation of their clinical benefits versus risks. Among the risks involved, peptic ulcer, bleeding, and perforation require serious attention, especially in patients with advanced age, comorbidity, comedication with aspirin or warfarin, or a history of active bleeding (1–4).

Equilibrium between aggressive factors and protective mechanisms is the major paradigm determining the integrity of the upper alimentary tract mucosa (5–8).

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Hydrogen ions (H^+), almost always present within the gastric luminal milieu, represent the major aggressive factor and their pharmacological control is posing a formidable challenge across all specialties (9, 10). A high lumen-to-mucosa gradient of H^+ concentration results in back-diffusion of hydrogen ions into the mucosa, a phenomenon that remains strictly concentration dependent (6, 11–13).

This back-diffusing hydrogen ion is counter-balanced by another concentration-driven phenomenon, the deposition of de novo synthesized and secreted gastric mucin (mucus glycoprotein) within the so-called mucus-buffer layer covering the surface epithelium (5–7, 14). The ability of this layer to effectively retard the back-diffusion of hydrogen ion depends on the content of the major components of mucus, such as mucin, highly hydrophobic mucin-associated fatty acids, and lipids as well as non-mucin glycoproteins, prostaglandins, and peptide growth factors (6, 12, 13, 15, 16). This viscoelastic mucus layer retains bicarbonate and nonbicarbonate buffers elaborated by the mucosa and ad hoc released into the mucus layer (7, 8). It has been demonstrated that ulcerogenic properties of NSAIDs are related to their inhibition of prostaglandin synthesis mediated through the Cox1 enzymatic pathway as well as to their direct inhibitory impact on production of mucus and its major mucin component (17, 3, 6, 7).

Rabeprazole represents the newest class of antisecretory agents that are well known for their proton pump (H^+/K^+ ATPase) inhibitor (PPI) activity, most profoundly diminishing gastric acid secretion and, thus, lowering the luminal concentration of hydrogen ions (18). It has recently been demonstrated that rabeprazole is the only PPI among tested (omeprazole, lansoprazole) that augments gastric mucin content in experimental animals (19). Furthermore, this unique pharmacological property of rabeprazole has been recently confirmed in humans (20). After 7 days of its administration, rabeprazole increased highly significantly the content of gastric mucus in the gastric juice by 124% ($P < 0.001$) and gastric mucin content by 167% ($P < 0.0001$) (20). The impact of rabeprazole administration on the rate of impairment of gastric mucus and mucin secretion after administration of naproxen in humans still remained to be explored.

METHODS

Subjects. This study was approved by the Human Investigation Committee at Kansas University Medical Center. All investigated subjects provided informed consent to the experimental procedure.

Twenty-one asymptomatic, *H. pylori*–negative volunteers (11 females and 10 males; mean age, 34; range, 19–58) were enrolled in this study protocol, which was designed as a double-blind, placebo-controlled, crossover study. All volunteers were randomly assigned to 1 week of naproxen (500 mg BID) and rabeprazole (20 mg QD) or placebo (20 mg QD) with a 2-week washout period in between.

Methods. The FlexSure (SmithKline Diagnostics) serologic test was employed for evaluation of *H. pylori* status during the screening procedure.

The samples of gastric juice were collected at baseline (before therapy) and at the end of both administered treatments. On the seventh day of assigned treatment, after an overnight fast, the last tested dose was administered 1.5 hr before the onset of the gastric juice collection procedure. Subjects were intubated with a 14F nasogastric tube, Argyle Salem Sump, with radiopaque sentinel line and eye (Sherwood Medical, St. Louis, MO). The tip of the tube was positioned in the dependent portion of the antrum. After complete aspiration of residual gastric juice, a water recovery test was conducted to assure the optimal position of the tube for aspiration of de novo elaborated secretion. Only recovery of over 95% of the infused solution qualified tube placement for subsequent gastric secretion test.

During 1 hr of basal conditions and 1 hr after administration of pentagastrin (6 μg/kg SC), gastric secretion was collected using intermittent suction (−125 mm Hg) using a Vacutron Suction Regulator (Allied Healthcare Products, St. Louis, MO) and its volume recorded to the nearest 1 ml. Samples of gastric juice, after collection and recording of pH, were neutralized from the starting pH to the final pH 7.0 using a gradually decreasing molarity of NaOH from its starting 1 *M* to 0.01 *M* in such a fashion that the final volume of gastric juice after pH adjustment had never increased above 1% of its starting volume value.

The content of gastric mucus in aspirated secretion was measured after exhaustive dialysis of gastric juice (with Spectra/Por CE DispoDialyzer of 1000-D cutoff) using Spectra/Por EZ-1 Multidialyzer (Spectrum Laboratories, Rancho Dominguez, CA) and subsequent lyophilization using a freeze-drier, and the final results are expressed as milligrams per milliliter.

Measurements of gastric mucin within the freeze-dried mucus were performed after its isolation and purification by equilibrium density-gradient ultracentrifugation in 46% (w/v) cesium chloride in 0.05 *M* phosphate buffer–0.15 *M* NaCl for 48 hr at approximately 280,000*g* using a TI swinging rotor in a preparative ultracentrifuge (Model L5-65; Beckman Instruments, Palo Alto, CA) as outlined before (21).

Data Processing and Statistical Analysis. Data are presented in basal conditions and after stimulation with pentagastrin during administration of placebo or rabeprazole. All results are expressed as mean ± SE for data with a normal distribution after subsequent statistical analysis using parametric tests and as median with 25–75 percentile range for data distributed non normally, with subsequent analysis by Mann–Whitney rank sum test as recommended by professional Σ-Stat software (SPSS Inc.).

RESULTS

The volume of gastric juice during administration of naproxen/placebo combination decreased significantly (by 44%) in basal conditions (38 ml/hr, [range, 29.5–56.2 ml/hr] vs 68 ml/hr [range, 58.0–85.2 ml/hr]; $P < 0.001$) and by 35% in pentagastrin-stimulated conditions (110 ml/hr [range, 98.2–175.5 ml/hr] vs 170 ml/hr [range, 121.2–195.7 ml/hr]; $P = 0.07$) compared to the

TABLE 1. INVESTIGATED PARAMETERS OF GASTRIC JUICE BEFORE AND DURING ADMINISTRATION OF NAPROXEN WITH PLACEBO

	Baseline		*Naproxen with placebo*	
	Basal conditions	*Stimulated conditions*	*Basal conditions*	*Stimulated conditions*
Volume (ml/hr)				
Median	68.0	170	38.0	110
Range, 25–75%	58.0–85.2	121–196	29.5–56.2	98.2–175
SE				
P vs baseline			<0.001 (MWT)	0.07 (MWT)
pH				
Median	1.61	1.14	1.58	1.09
Range, 25–75%	1.47–2.15	1.11–1.18	1.29–2.29	1.02–1.13
SE				
P vs baseline				0.08 (MWT)
Mucus concentration (mg/ml)				
Average or *median*	4.53	2.46	4.57	*1.76*
SD or range, 25–75%	±1.73	2.06–2.88	±1.66	1.57–2.13
SE	±0.38		±0.36	
P vs baseline				0.002 (MWT)
Mucus output (mg/hr)				
Average	333	405	188	265
SD	±124	±142	±76.8	±129
SE	±27.1	±31.0	±16.8	±28.1
P vs baseline			<0.001 (StT)	0.002 (StT)
Mucin concentration (mg/ml)				
Average or median	1.01	0.54	1.13	0.42
Range, 25–75%	0.77–1.88	0.40–0.77	0.63–2.02	0.22–0.47
SE			±0.17	
P vs baseline				<0.05 (MWT)
Mucin output (mg/hr)				
Average or median	86.9	88.1	53.1	45.0
Range, 25–75%	53.5–135	49.3–131	27.1–81.9	31.0–61.7
SE				
P vs baseline			<0.01 (MWT)	0.003 (MWT)
Nonmucin glycoprotein (mg/ml)				
Average or Median	0.49	0.29	0.54	0.20
SD or range, 25–75%	0.42–0.81	±0.15	0.32–0.95	±0.11
SE		±0.03		±0.02
P vs baseline				<0.05 (StT)
Nonmucin glycoprotein output (mg/hr)				
Average or median	39.6	39.8	22.0	18.6
Range, 25–75%	26.9–60.0	27.2–60.0	11.4–31.7	14.0–34.9
SE				
P vs baseline			0.001 (MWT)	0.002 (MWT)

Note. StT, Student's *t* test; MWT, Mann–Whitney rank sum test.

corresponding values recorded at baseline (Table 1). The pH of gastric juice during administration of naproxen/placebo combination and its baseline and values remained similar.

The concentration of gastric mucus in gastric juice during administration of naproxen/placebo combination did not change in basal conditions but declined (by 28%) significantly during stimulation with pentagastrin (1.76 mg/ml [range, 1.57–2.13 mg/ml] vs 2.46 mg/ml [range, 2.06–2.88 mg/ml]; $P = 0.002$) from the baseline values (Table 1). Gastric mucus output, however, during administration of naproxen/placebo combination declined significantly both in basal (by 44%; 188 ± 16.8 vs 333 ± 27.1 mg/ml; $P < 0.001$) and in pentagastrin-stimulated (by 35%; 265 ± 28.1 vs 405 ± 31.0 mg/ml; $P = 0.002$) conditions from its corresponding baseline values.

The ultracentrifugation of the mucus samples at 280,000*g* for 48 hr resulted in an overall density gradient of CsCl from 1.61 g/ml in the first 1-ml fraction at the bottom of the centrifugation tube to 1.20 g/ml in the last 12th 1-ml fraction collected from the top of the tube. The pure gastric mucin was recovered from fractions accumulating between 1.55 g/ml (second 1-ml fraction from the bottom) and 1.37 g/ml (fifth 1-ml fraction from the bottom)

density of cesium chloride after equilibrium density-gradient centrifugation in 46% (w/v) starting CsCl solution. These fractions were dominated by a high content of carbohydrates and low content of proteins, a typical chemical feature of mucin. In addition, fractions between the 6th and the 11th, representing nonmucin glycoprotein, with a ratio of carbohydrates to protein <1, were collected separately (density gradient between 1.33 and 1.24 g/ml). Fractions of purified mucin and nonmucin glycoprotein were exhaustively dialyzed and lyophilized, and the final content of mucin was calculated per milliliter of the starting volume of gastric juice processed through all steps of mucus and mucin purification.

Administration of naproxen/placebo combination resulted in a significant decline (by 22%) of gastric mucin concentration from its baseline value (0.42 mg/ml [range, 0.22–0.47 mg/ml] vs 0.54 mg/ml [range, 0.40–0.77]; $P < 0.05$) in pentagastrin-stimulated conditions, whereas concentrations in basal conditions remained similar (Table 1).

The output of gastric mucin during administration of naproxen/placebo combination declined significantly both in basal (by 39%; 53.1 mg/hr [range, 27.1–81.9 mg/hr] vs 86.9 mg/hr [range, 53.5–135 mg/hr]; $P < 0.01$) and in pentagastrin-stimulated (by 49%; 45.0 mg/hr [range, 31.0–61.7 mg/hr] vs 88.1 mg/hr [range, 49.3–131 mg/hr]; $P = 0.003$) conditions.

Of 21 investigated subjects, 20 responded with a decline in gastric mucin output in basal or stimulated conditions and 13 subjects exhibited diminished mucin secretion in both basal and stimulated conditions simultaneously. A decline in gastric mucin output by at least 50% was detected in 10 subjects in basal and in 11 patients in stimulated conditions, and 6 patients exhibited a decline in gastric mucin output by at least 50% in basal and stimulated conditions simultaneously.

Administration of naproxen/placebo combination resulted in a significant decline (by 31%) of gastric nonmucin glycoprotein concentration from its baseline value (0.20 ± 0.02 vs 0.29 ± 0.03 mg/ml; $P < 0.05$) in pentagastrin-stimulated conditions and remained unchanged in basal conditions (Table 1).

The output of gastric nonmucin glycoprotein during administration of naproxen/placebo combination significantly declined from its corresponding baseline values both in basal (by 44%; 22.0 mg/hr [range, 11.4–31.7 mg/hr] vs 39.6 mg/hr [range, 26.9–60.0 mg/hr]; $P = 0.001$) and in pentagastrin-stimulated (by 44%; 18.6 mg/hr [range, 14.0–34.9 mg/hr] vs 39.8 mg/hr [range, 27.2–60.0 mg/hr]; $P = 0.002$) conditions (Table 1).

Administration of the naproxen/rabeprazole combination improved the profoundly detrimental changes within gastric secretion protective components induced by naproxen/placebo (Table 2).

The volume of gastric juice during administration of naproxen/rabeprazole combination increased by 37% (52.0 ml/hr [range, 45.7–61.2 ml/hr] vs 38.0 ml/hr [range, 29.5–56.2 ml/hr] during naproxen/placebo; $P = 0.06$) in basal conditions but declined significantly (by 34%) in pentagastrin-stimulated conditions (72.0 ml/hr [range, 60.0–91.7 ml/hr] vs 110 ml/hr [range, 98.2–125 ml/hr] during naproxen/placebo; $P < 0.001$).

The pH of gastric juice during the administration of the naproxen/rabeprazole combination increased by 4.4-fold (7.02 [range, 4.69–7.61] vs 1.58 [range, 1.29–2.29] during naproxen/placebo; $P < 0.001$) in basal conditions and 2.3-fold in pentagastrin-stimulated conditions (2.46 [range, 1.55–6.79] vs 1.09 [range, 1.02–1.13] during naproxen/placebo; $P < 0.001$).

The concentration of gastric mucus in gastric juice during administration of naproxen/rabeprazole combination increased significantly (by 123%) in pentagastrin-stimulated conditions (4.33 ± 0.34 mg/ml) from the corresponding values revealed during naproxen/placebo administration (1.94 0.17 mg/ml; $P < 0.001$) (Table 2) and increased by 14% during basal conditions.

The output of gastric mucus in gastric juice during administration of naproxen/rabeprazole combination increased by 22% in pentagastrin-stimulated conditions (322 ± 31.1 mg/hr) from the corresponding values revealed during naproxen/placebo administration (265 ± 28.1 mg/hr) (Table 2) and increased significantly (by 47%) during basal conditions (277 ± 26.5 mg/hr) from the corresponding values revealed during naproxen/placebo administration (188 ± 16.8 mg/hr; $P < 0.01$) (Table 2).

The concentration of gastric mucin in gastric juice during administration of naproxen/rabeprazole combination increased significantly (by 160%) in pentagastrin-stimulated conditions (1.09 mg/ml; range, 0.81–1.44 mg/ml) from the corresponding values revealed during naproxen/placebo administration (0.42 mg/ml; range, 0.22–0.47 mg/ml; $P < 0.001$) (Table 2) and remained unchanged during basal conditions.

The output of gastric mucin in gastric juice during administration of naproxen/rabeprazole combination increased significantly (by 67%) in pentagastrin-stimulated conditions (75.3 mg/hr; range, 55.0–113 mg/hr) from the corresponding values revealed during naproxen/placebo administration (45.0 mg/hr; range, 31.0–61.7 mg/hr; $P = 0.003$) and increased by 40% in basal conditions (75.8 ± 8.97 mg/hr) from the naproxen/placebo values (54.1 ± 5.99 mg/hr; $P = 0.05$) (Table 2 and Figure 1).

The concentration of nonmucin glycoprotein in gastric juice during administration of naproxen/rabeprazole

TABLE 2. INVESTIGATED PARAMETERS OF GASTRIC JUICE DURING ADMINISTRATION OF NAPROXEN WITH PLACEBO OR RABEPRAZOLE

	Naproxen with placebo		*Naproxen with rabeprazole*	
	Basal conditions	*Stimulated conditions*	*Basal conditions*	*Stimulated conditions*
Volume (ml/hr)				
Median	38.0	110	52.0	72.0
Range, 25–75%	29.5–56.2	98.2–175	45.7–61.2	60.0–91.7
SE				
P vs placebo			0.06 (MWT)	<0.001 (MWT)
pH				
Median	1.58	1.09	7.02	2.46
Range, 25–75%	1.29–2.29	1.02–1.13	4.69–7.61	1.55–6.79
SE				
P vs placebo			<0.001 (MWT)	<0.001 (MWT)
Mucus concentration (mg/ml)				
Average	4.57	1.94	5.20	4.33
SD	±1.66	±0.76	±2.08	±1.57
SE	±0.36	±0.17	±0.45	±0.34
P vs placebo				<0.001 (StT)
Mucus output (mg/hr)				
Median	188	265	277	322
SD	±76.8	±129	±122	±144
SE	±16.8	±28.1	±26.5	±31.3
P vs placebo			<0.01 (StT)	
Mucin concentration (mg/ml)				
Average or *median*	1.38	0.42	1.42	1.09
SD or range, 25–75%	±0.76	0.22–0.47	±0.65	0.81–1.44
SE	±0.17		±0.14	
P vs placebo				<0.001 (MWT)
Mucin output (mg/hr)				
Average or *median*	54.1	45.0	75.8	75.3
SD or range, 25–75%	±27.4	31.0–61.7	±41.1	55.0–113
SE	±5.99		±8.97	
P vs placebo			0.05 (StT)	0.003 (MWT)
Nonmucin glycoprotein (mg/ml)				
Median	0.54	0.17	0.58	0.41
Range, 25–75%	0.32–0.95	0.13–0.29	0.50–0.76	0.28–0.63
SE				
P vs placebo				<0.001 (MWT)
Nonmucin glycoprotein output (mg/hr)				
Median	22.0	18.6	28.5	30.7
Range, 25–75%	11.4–31.7	14.0–34.9	18.1–46.6	26.7–50.8
SE				
P vs placebo			0.05 (MWT)	<0.05 (MWT)

Note. StT, Student's *t* test; MWT, Mann–Whitney rank sum test.

combination increased significantly (by 141%) in pentagastrin-stimulated conditions (0.41 mg/ml; range, 0.28–0.63 mg/ml) from the corresponding values revealed during naproxen/placebo administration (0.17 mg/ml; range, 0.13–0.29 mg/ml; $P < 0.001$; Table 2) and remained unchanged during basal conditions.

The output of nonmucin glycoprotein in gastric juice during administration of naproxen/rabeprazole combination increased significantly (by 65%) in pentagastrin-stimulated conditions (30.7 mg/hr; range, 26.7–50.8 mg/hr) from the corresponding naproxen/placebo values (18.6 mg/hr; range, 14.0–34.9 mg/hr; $P < 0.05$) (Table 2) and increased by 30% in basal conditions (28.5 mg/hr; range, 18.1–46.6 mg/hr) from the corresponding naproxen/placebo values (22.0 mg/hr; range, 11.4–31.7 mg/hr; $P = 0.05$) (Table 2).

The response of individual subjects in terms of their mucin output in stimulated conditions during naproxen/placebo or naproxen/rabeprazole administration is illustrated in Figure 1.

Administration of naproxen/placebo resulted in a decline in gastric mucin output by more than 50% vs the corresponding baseline values in nine subjects. Five subjects responded with a decline in mucin output of more than 25% but less than 50% and three subjects with a decline of more than 1% but less than 25%.

Administration of naproxen/rabeprazole resulted in an increase in gastric mucin output by more than 50% vs

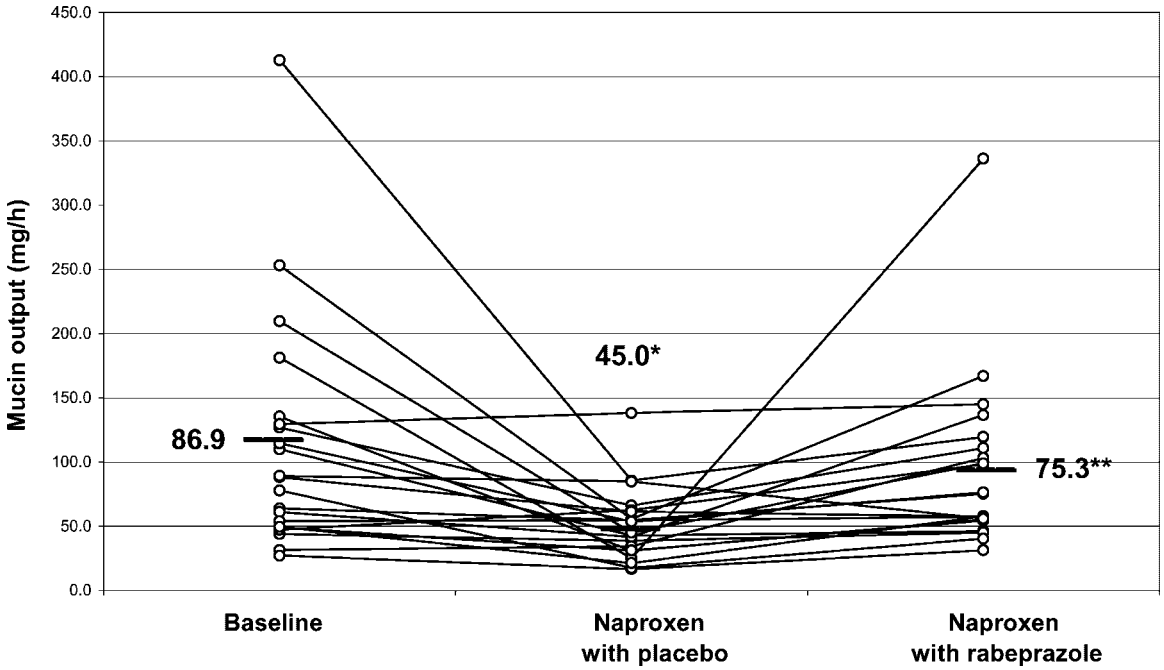

Fig 1. Purified mucin output of individual subjects in pentagastrin-stimulated gastric juice collected at baseline and during naproxen/placebo or naproxen/rabeprazole administration. $^{*}P = 0.003$, naproxen/placebo vs baseline. $^{**}P = 0.003$, naproxen/rabeprazole vs naproxen/placebo.

the corresponding naproxen/placebo values in 12 subjects. Three subjects responded with an increase in mucin output of more than 25% but less than 50%, and four subjects with an increase of more than 1% but less than 25%.

DISCUSSION

Although selective COX2 inhibitors are increasingly prescribed for the treatment of chronic inflammation and pain within the musculoskeletal system, conventional NSAIDs are still widely used both during inpatient and outpatient pharmacotherapy and in the OTC setting. Among NSAIDs, naproxen is one of the most popular medications.

Conventional NSAIDs, however, impose on the potential user the risk of severe complications that are inherited with its detrimental impact on the COX1 enzymatic pathway, pivotal for maintenance of integrity of the alimentary tract mucosa (22–24). Furthermore, numerous experimental studies have demonstrated that this risk is also mediated by inhibition of production of gastric mucus and its major component, mucin (17, 3, 6, 7). The impact of conventional NSAIDs, including naproxen, on gastric mucus and mucin production in *H. pylori*–negative asymptomatic volunteers has never been explored.

PPIs are well known for their ability to both heal and prevent the development of NSAID-induced complications within the upper alimentary tract mucosa and this beneficial impact is mediated predominantly by inhibition of gastric acid secretion and prevention of gastric pepsinogen activation, driven by the low pH of gastric juice (25). It has recently been demonstrated that rabeprazole is the only PPI among those tested (omeprazole, lansoprazole) that augments gastric mucin production in experimental animals (19). Furthermore, it has also recently been demonstrated that rabeprazole also augments gastric mucus and mucin production in humans (20). The potential restorative impact of rabeprazole administration on naproxen-induced gastric mucus and mucin production impairment in humans remains to be explored.

We demonstrate for the first time in humans that administration of naproxen resulted in a profound and significant decline in gastric mucus production in basal (by 44%) and pentagastrin-stimulated (by 35%) conditions, mimicking the natural food-stimulated conditions scenario.

Administration of naproxen also significantly diminished gastric mucin secretion in basal (by 41%) and pentagastrin-stimulated (by 55%) conditions. Of note, 20 subjects (of 21 tested) responded with a decline in gastric mucin output in basal or stimulated conditions and 13 subjects exhibited diminished mucin secretion in both basal and stimulated conditions simultaneously. Furthermore, six subjects exhibited a decline in gastric mucin output by at least 50% in both basal and stimulated conditions.

One may hypothesize, therefore, that these six subjects (28% of the investigated group) are potential candidates for development of alimentary tract complications such as ulcer, bleeding, and perforation. However, this hypothesis would require testing of the gastric mucin output impairment during administration of NSAIDs in a prospective and long-term clinical study in *H. pylori*–negative individuals. If confirmed, this could help to predict which patients will require copharmacotherapy with agents capable of diminishing or eliminating the risk of NSAID-related complications.

This finding confirms experimental data in animals and points to the potential mechanism of naproxen-induced mucosal injury and complications in addition to its negative impact on generation of housekeeping prostaglandins through the enzymatic activity of the COX1 pathway.

Furthermore, we also demonstrate for the first time in humans that coadministration of rabeprazole with naproxen has a restorative impact on the gastric mucus and mucin production impairment revealed during administration of naproxen with placebo.

The output of gastric mucus in gastric juice during administration of naproxen/rabeprazole combination increased by 22% in pentagastrin-stimulated conditions and increased significantly (by 47%) during basal conditions from the corresponding values revealed during naproxen/placebo administration.

The output of gastric mucin in gastric juice during administration of naproxen/rabeprazole combination increased significantly (by 85%) in pentagastrin-stimulated conditions and increased by 40% in basal conditions from the naproxen/placebo.

Of note, the majority of subjects who responded with a profound decline in gastric mucin output during naproxen/placebo administration also exhibited an impressive degree of mucin output restitution during cotherapy with naproxen and rebaprazole (Figure 1).

It is not difficult to envision that this restorative impact of rabeprazole on gastric mucus and mucin production impairment induced by administration of naproxen could have a beneficial impact on the protective quality of the gastric mucous barrier, which serves as the first line of mucosal defense against luminal mechanical and chemical injury. This may also indicate that the beneficial effect of rabeprazole on the naproxen-induced impairment of the gastric mucous barrier, in addition to its profound inhibitory impact on gastric acid and pepsin secretion, may provide it with additional strength in both prevention and repair of gastric mucosal injury induced by administration of naproxen. One would anticipate, therefore, that rabeprazole may even cause faster healing of naproxen-induced gastric ulcers than other PPIs and also may provide a higher degree of prevention of gastric mucosal injury by NSAIDs. These hypothetical assumptions, however, would require confirmation in further clinical studies that may provide a new therapeutic strategy in the prevention of NSAID-induced mucosal injury and complications within the alimentary tract mucosa.

Gastric mucin, after its release from mucous cells, mediated by cholinergic, histaminergic, gastrinergic, peptidergic, and prostanoid-mediated pathways, is deposited on the surface of the mucosa, augmenting the thickness of the mucus-buffer layer, instrumental for maintaining a pH gradient through its ability to retard hydrogen ion diffusion and its content of buffers (6–8). Hydrogen ion diffusion by this mucus layer is greatly retarded due to its content of hydrophobic components such as covalently bound fatty acids and non–covalently bound phospholipids (6, 26, 27). Since the thickness of the mucus-buffer layer in humans is rather constant in physiological conditions, in the range of 160 to 180 μm and never exceeding 450 μm, augmented secretion of gastric mucin at a constant luminal pH will inevitably result in a parallel release and augmentation of the mucin content in the gastric juice (5, 7, 8).

On the other hand, when the pH of gastric juice falls below 4.0 to the vicinity of 1.8–2.0, the strong proteolytic activity of luminal pepsins leads to degradation of mucin in the luminal aspect of the mucus gel layer and release of degraded mucin into gastric lumen, diminishing the thickness of the mucus gel layer (5, 7). However, when the mucus gel layer becomes thinner, the back-diffusing hydrogen ions will lead to a gradual decline in its pH gradient and its value at the luminal perimeter of the surface epithelium. Thus, luminal acid, by lowering the pH, is a strong stimulus for a further increase in the rate of mucin release from the mucous cells, for restoration of the thickness of the mucus-buffer layer, and for restitution of its protective pH gradient (7, 28). Therefore, measurement of gastric mucus and pure mucin in gastric secretion provides valuable insight into the role of mucus and mucin in the pathophysiology of upper alimentary tract disorders (3, 4, 6, 7, 21, 29).

An increase in pH within the gastric lumen after administration of rabeprazole results in diminished stimulation of mucin secretion by a relatively low rate of hydrogen ion back-diffusion and, subsequently, should lower the content of gastric mucus and mucin in gastric juice. The demonstrated increase in mucus and mucin secretion in gastric juice during administration of rabeprazole indicates that this phenomenon is driven by augmented mucin synthesis within the mucous cells and subsequent release into the gastric lumen. This may represent a novelty in clinical pharmacology, as diminished gastric acid production and augmented gastric mucus and mucin

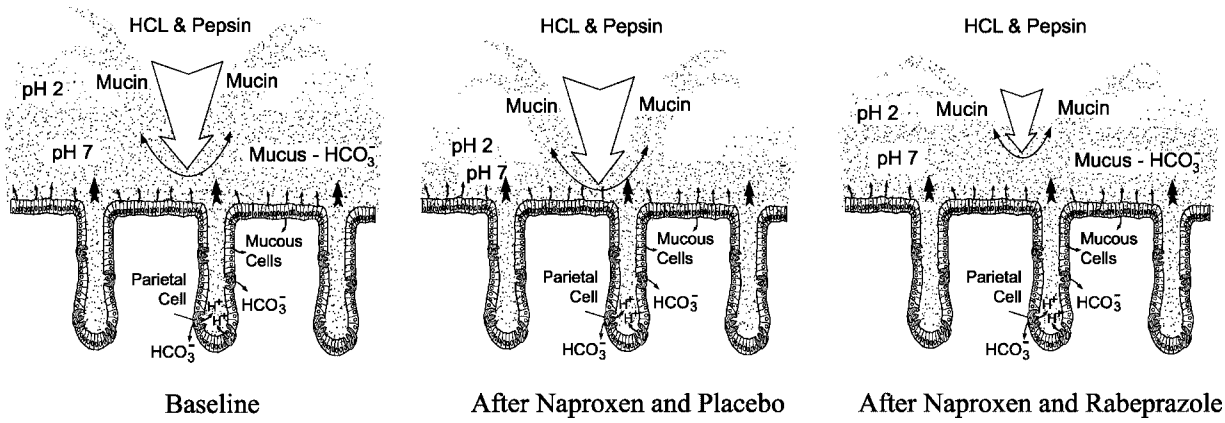

Fig 2. Schematic outline of the gastric mucous barrier before and during naproxen–placebo or naproxen–rabeprazole administration.

secretion would create near-perfect conditions for restoration of the equilibrium between aggressive factors and protective mechanisms within the gastric mucosal barrier (Figure 2).

Stimulation of gastric mucin and mucus production during administration of rabeprazole could potentially be mediated by an increase in the serum level of gastrin, as the rabeprazole-induced increase in gastric luminal pH eliminates a natural feedback of inhibition of gastrin release by luminal acid. This mechanism is less likely since short-term administration of rabeprazole may only slightly increase serum gastrin, with its value remaining within the range of physiological oscillations. Of note, the stimulatory effect of rabeprazole on mucus and mucin production was also clearly revealed during exogenous pentagastrin administration. Therefore, the possible explanation of this phenomenon relates to the fact that rabeprazole has in its chemical structure a hydrophobic $–CH_2–CH_2–CH_2$ $–OCH_3$ side chain, the longest among all PPIs. This side chain may have a stimulatory impact on gastric mucin production through hydrophobic interaction with hydrophobic structures of the cell membrane of mucous cells. Hydrophobicity of mucin, the mucus gel layer, and the mucous cell membrane is a well-established phenomenon in the pathophysiology of upper alimentary tract secretion and mucosal protection in health and disease (30–35).

We assume that the phenomenon of augmented mucin production by rabeprazole could remain its unique feature since animal studies testing rabeprazole, omeprazole, and lansoprazole demonstrated that only rabeprazole enhanced mucin production (19). Since pantoprazole, the only PPI not tested in animals, is structurally closer to omeprazole than rabeprazole, one may hypothesize that its having a stimulatory impact on gastric mucus production, similar to that of rabeprazole, in animals is less likely. However, our hypothesis requires confirmation by a similar crossover human study involving all PPIs.

Our ultimate goal in therapy of acid-related disorders is to reach equilibrium among the luminal concentration of hydrogen ions, the corresponding proteolytic activity of pepsins determined by activity of hydrogen ions, and the protective mechanisms represented by integral components of the mucus-buffer layer.

This restorative impact of rabeprazole administration on the rate of gastric mucus and mucin secretion compromised by administration of naproxen seems to represent a new phenomenon in the pharmacodynamics of PPIs in humans. This may translate into substantial clinical benefits, as a higher content of gastric mucus and mucin in gastric juice may profoundly benefit the gastric mucosal barrier.

These data may further the understanding of the pathophysiology and therapy of NSAID-related mucosal injury and complications and provide a rationale for further exploration of this phenomenon looking at the potentially augmented rate of prevention of the alimentary tract injury and complications during coadministration of rabeprazole (7, 18, 8, 22–24).

In conclusion, the restorative effect of rabeprazole on the quantitative impairment of gastric mucus and mucin during administration of naproxen may translate into a clinical benefit of protection of the upper alimentary tract from NSAID-related mucosal injury.

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