Alimentary tract and pancreas

De-Nol stimulates gastric and duodenal alkaline secretion through prostaglandin dependent mechanism

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SUMMARY This study was designed to determine the effects of colloidal bismuth subcitrate De-Nol on gastric HCO_3^- secretion in 24 healthy subjects and on gastric and duodenal HCO_3^- secretion in dogs with gastric and duodenal fistulae. Alkaline secretion was measured after pretreatment with ranitidine to abolish the H^+ secretion using a constant perfusion aspiration system and back titration of the perfusates to the original pH 6.0. Luminal release of PGE_2 was also measured in the gastric and duodenal perfusates. Addition of De-Nol in gradually increasing concentrations resulted in step wise increments in gastric HCO_3^- secretion in man and in dogs reaching, respectively, about 80% and 55% of the maximal HCO_3^- response to 16, 16dimethyl- PGE_2 (dm PGE_2). The duodenal HCO_3^- response to De-Nol in dogs reached 72% of the dm PGE_2 maximum. These effects were accompanied by a significant increase in luminal release of PGE_2 . Pretreatment with atropine reduced basal and in part De-Nol induced alkaline secretion, whereas pirenzepine did not affect this secretion in man and dogs. Aspirin (in man) and indomethacin (in dogs) reduced the release of PGE_2 by about 80% and suppressed almost completely the gastric and duodenal HCO_3^- response to De-Nol in these species. This study provides evidence that De-Nol stimulates gastroduodenal alkaline secretion through a prostaglandin dependent mechanism.

Bismuth compounds have been used for over two centuries for the treatment of various gastrointestinal disorders because of their local protective and demulcent properties.^{1,2} Colloidal bismuth subcitrate, which is the active ingredient of De-Nol, has been used successfully in peptic ulcer therapy because of its selective binding to the ulcer base, the protection against acid-pepsin attack, the stimulation of mucus secretion and its activity against *Campylobacter pyloridis*.¹⁻³ De-Nol is neither an antisecretory agent

nor an antacid, yet it has an impressive efficacy in the prevention of acute gastric lesions in experimental animals⁴ and in healing of chronic peptic ulcers in man.⁵

Because alkaline secretion has been shown to play an important role in mucosal protection, particularly against luminal acid-pepsin aggression,^{6,9} in various species, including man, we decided to determine the influence of De-Nol on this secretion from the gastroduodenal mucosa. Alkaline secretion depends, in part, upon mucosal prostaglandins (PG)^{10,11} and is under vagal cholinergic control.^{12,13} Thus attempts have been made to evaluate the effects of De-Nol on mucosal production of PG, and further the effects of blockade of cyclooxygenase and muscarinic receptors on De-Nol-induced alkaline secretion in man and in dogs have been examined.

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Methods

SUBJECTS

The study was approved by the Institutional Ethical Committee and informed consent was obtained from each subject tested.

The study was carried out on 24 male volunteers, 20-25 years (mean 21), and weighing 58-74 kg (mean weight 71 kg). All subjects were in good health and without gastrointestinal disorder. Gastroduodenoscopy carried out before the start of the study revealed no abnormalities or peptic ulceration.

Several series of experiments were carried out on the same subjects with five to seven days washout between series. The evening before the examination and on the morning of examination, four tablets of ranitidine (1200 mg) (Glaxo, England) were given to completely suppress gastric acid secretion (luminal pH 7.0 or above) and thus prevent any conversion of HCO_3^- into CO_2 . During the examination, a double lumen gastroduodenal Dreiling tube with endotracheal cuff was inserted and positioned fluoroscopically, the cuff being inflated (with 20 ml water) in the duodenal bulb just beyond the pylorus. This prevented any escape of gastric perfusate into the duodenum and any reflux of the duodenal content into the stomach as described before.¹⁴ A polyethylene catheter attached to the Dreiling tube, with openings in the proximal part of the stomach was used to perfuse the stomach with saline adjusted to pH 6.0, and containing phenol red as a non-absorbable marker (40 $\mu\text{g}/\text{ml}$). Another polyethylene catheter attached to the Dreiling tube was filled with agar-KCl and served as a recording electrode for the measurement of the gastric potential difference (PD) in the oxyntic gland area. The potential difference, expressed in millivolts (mV) referred to the polarity of the gastric lumen compared with the venous blood adjusted to zero. The distal portion of the Dreiling tube with wide lateral openings was located in the distal portion of the stomach for the continuous aspiration of the gastric content. The rate of perfusion was 600 ml/h. This perfusion aspiration procedure was carried out throughout the examination. The volume of gastric aspirate was measured and HCO_3^- contents were determined by back titration of gastric perfusate to the original pH as described before.¹⁵ The samples of the perfusates were saved for phenol red determination by spectrophotometry at 520 nm and for PGE_2 radioimmunoassay using PGE_2 kits (New England Nuclear, Munich, FRG) as described before.^{10,11,16}

In tests undertaken with De-Nol on 12 subjects (group A), gastric perfusion was first carried out with saline for 60 minutes and then De-Nol was added to the perfusate in gradually increasing concentrations

(5-20 mg/ml), each concentration being present for 60 minutes then doubled. At the end of the experiment, 16, 16-dimethyl- PGE_2 (dm PGE_2) was introduced into the stomach in the concentration of 5 $\mu\text{g}/\text{ml}$ which had been shown in other tests to induce maximal HCO_3^- output from the human stomach.¹⁷ In control tests the HCO_3^- output were determined during gastric perfusion with saline without De-Nol for the duration of the experiment.

In a second series of tests done on six subjects (group B), gastric alkaline secretion was measured for a 60 minute period with De-Nol added to the perfusion fluid at a concentration of 20 mg/ml. Ten micrograms per kilograms of atropine or pirenzepine was injected iv the perfusion aspiration procedure being carried out for the next 60 minute period. In control experiments, the response to 20 mg/ml De-Nol alone was carried out for the duration of the test (120 min).

Tests with aspirin (ASA) were carried out on six subjects (group C); gastric HCO_3^- response to De-Nol was measured during a 60 minute period with or without (control tests) pretreatment with 20 mg/kg ASA given po given about 60 minutes before the start of the examination.

STUDIES ON ANIMALS

Six mongrel dogs (16-20 kg) were prepared with gastric fistulae (GF) and duodenal fistulae (DF). The procedure included the ligation of the accessory pancreatic duct and the diversion of bile and pancreatic juice from the duodenum to the upper jejunum by transplantation of the ducts with a piece of surrounding duodenum as described before.¹⁸ One cuff of Dacron mesh was placed around the proximal duodenum just beyond the pylorus and a second was placed around the mid-duodenum just proximal to the cannula of the duodenal fistulae. The cuffs were used to splint the duodenal wall and thus to seal the space between the wall and the inflated balloons of Foley catheter. Two connected Foley catheters were used during the experiment, one with a balloon inflated in the distal portion of the stomach to seal the gastroduodenal junction and another in the mid-duodenum to seal the distal end of the proximal duodenum. The gastric catheter was externalised through the gastric fistulae while the small polyethylene tube attached to it was used to perfuse the stomach. The duodenal catheter was externalised through the duodenal fistulae and used to drain the proximal duodenum between the balloons. A polyvinyl tube attached to the duodenal catheter was used to perfuse the duodenum. The perfused duodenum was about 5 cm long. The perfusion fluid contained a non-absorbable marker, phenol red, at a concentration of 40 $\mu\text{g}/\text{ml}$.

The whole stomach and the upper duodenum (between balloons) were perfused at a rate of 80 ml/h using saline adjusted to pH 6.0. The perfusates were collected separately by gravity drainage and pooled in 15 minute samples. The volume was measured and the amounts of HCO_3^- in the perfusates were determined by back titration to the original pH 6.0 as in the human studies. The samples of the perfusates were also saved and frozen to -20°C to determine the content of PGE_2 using radioimmunoassay.^{10,11}

The potential difference of the gastric and duodenal mucosa was also measured using recording electrodes in the form of 80 cm long polyethylene tubes filled with saturated KCl in 4% agar and placed along the Foley catheter in the proximal part of the stomach and in the upper duodenum. The reference electrode was connected to the peripheral vein as described before.¹⁵

Secretory studies started after about four to five weeks after surgery. Food, but not water, was withheld for about 18 hours before each experiment. Ranitidine (20 mg/kg) was injected iv to suppress gastric acid secretion and then both gastric and duodenal perfusions were started and assayed as in human studies.

Gastric and duodenal perfusions were first carried out for 60 minutes to determine basal HCO_3^- secretion in each experiment. In tests with De-Nol, gradually increased concentrations (10–80 mg/ml) were added to the gastric and duodenal perfusion fluids, each concentration being administered for 60 minutes, and then doubled. During the final 60 minute period of the experiment dmPGE_2 was added to the perfusion fluid at a concentration of $5\mu\text{g/ml}$ which has been shown to induce maximal HCO_3^- secretion from the gastroduodenal mucosa in dogs.¹⁵ In control tests, gastric and duodenal perfusions were done using saline without De-Nol for the duration of the experiment (240 minutes).

In other tests, atropine (25 $\mu\text{g/kg}$), pirenzepine (25 $\mu\text{g/kg}$) or indomethacin (2.5 mg/kg) was injected iv and then De-Nol was added to the gastric and duodenal perfusion fluids in gradually increasing concentrations as described above. In separate tests, basal HCO_3^- secretion was measured for 60 minutes from the stomach and duodenum during their perfusion with saline (without De-Nol) and then atropine, pirenzepine or indomethacin was injected iv in the same doses as above, the perfusion being continued for the next 60 minute period.

STATISTICAL ANALYSIS

The results from experiments in human volunteers and in dogs are expressed as means + standard error of the means (SEM). Student's *t* (paired) test was used to determine the statistical significance of

differences. *p* Values of less than 0.05 were considered significant.² The increments in HCO_3^- outputs in response to De-Nol alone or combined with atropine, pirenzepine or indomethacin (or ASA) were calculated by subtracting the basal HCO_3^- values from those recorded after De-Nol. The active ingredient of De-Nol, colloidal bismuth subcitrate, was uniformly used in these experiments. It was kindly supplied by Dr D W R Hall (Gist-Brocades NV, Delft, The Netherlands) as De-Nol spray dried powder and dissolved in saline. The original pH of that De-Nol solution was about 5.9 and it was adjusted to final pH 6.0 by adding small amounts of 100 mM NaOH.

Results

STUDIES IN MAN

The basal gastric HCO_3^- secretion in 12 healthy subjects of group A was about $1100 \pm 260 \mu\text{mol/h}$ (mean $\pm$ SEM). The values of HCO_3^- output fluctuated during the observation period within about 30% of the average value. After the addition of De-Nol to the perfusion fluid there was a significant increase in HCO_3^- outputs starting with 10 mg/ml. With higher concentrations of De-Nol in the perfusion fluid (20 mg/ml) the HCO_3^- outputs almost doubled and reached about 80% of the maximal response to dmPGE_2 in these subjects (Fig. 1). In these tests with De-Nol stimulated alkaline secretion, the recovery of the phenol red marker infused into the stomach averaged about 96%.

Fig. 1 Effects of gradually increasing concentrations of De-Nol on gastric alkaline secretion and luminal release of PGE_2 in 12 healthy subjects (group A). For comparison, maximal HCO_3^- response to 16, 16-dimethyl- PGE_2 is presented. Mean $\pm$ SEM of 12 tests on 12 subjects. Asterisks indicate statistically significant ($p < 0.05$) increases above the basal value obtained with saline perfusion of the stomach.

Fig. 2 Increments in gastric HCO_3^- secretion and luminal PGE_2 outputs in tests of gastric perfusion with De-Nol alone and in combination with atropine or pirenzepine (group B subjects) and in combination with aspirin (group C subjects). Mean $\pm$ SEM of six tests on six subjects of group B and C. Asterisks indicate statistically significant decreases ($p < 0.05$) below the value obtained with De-Nol alone.

Basal PGE_2 released into the gastric lumen saline perfusion averaged 118 ± 20 ng/h. Addition of De-Nol at a dose of 10 and 20 mg/ml to the perfusion resulted in a significant increase in luminal release of PGE_2 (Fig. 1).

Basal values of PD averaged -32.8 ± 2.6 mV. De-Nol did not cause any significant change in the potential difference values at any concentration used and these results have been omitted for the sake of clarity.

Atropine (10 $\mu\text{g/kg}$) injected intravenously in six subjects of group B resulted in a significant reduction in basal HCO_3^- output by about 64% and diminished the De-Nol (20 mg/ml) stimulated HCO_3^- outputs by about 36%. In contrast, pirenzepine at the same dose did not affect basal or De-Nol induced HCO_3^- secretion (Fig. 2). Neither atropine nor pirenzepine influenced basal or De-Nol stimulated luminal release of PGE_2 in these tests (Fig. 2).

Pretreatment with ASA reduced basal HCO_3^- outputs by about 70% and that induced by De-Nol by about 80%. Aspirin reduced basal release of PGE_2 by about 85% and almost completely abolished the PGE_2 release by De-Nol (Fig. 2).

STUDIES IN DOGS

In control tests with saline perfusion, basal gastric and duodenal HCO_3^- outputs averaged 120 ± 28 and 185 ± 42 $\mu\text{mol}/30$ min, respectively. Basal HCO_3^- outputs during 240 minutes control period showed fluctuations within about 20-30% of the average value.

De-Nol added to the perfusion fluid resulted in a concentration dependent increase in HCO_3^- outputs, reaching maximum at a concentration of 40 mg/ml. This maximal gastric and duodenal HCO_3^- response to De-Nol amounted to 55% and 72% of the respective maximal gastric and duodenal HCO_3^- responses to dmPGE in these animals (Figs 3 and 4). The recovery rate of the duodenal perfusates in these tests ranged from 80-90%.

In control tests with saline perfusion, the potential difference value in the body of the stomach averaged -52.4 ± 3.8 mV and in the upper duodenum -11.4 ± 1.8 mV. Addition of De-Nol into the gastric or duodenal perfusate did not influence the potential difference value at any concentrations used.

PGE_2 outputs in gastric and duodenal perfusates averaged 46 ± 6 and 71 ± 12 ng/h, respectively. Addition of De-Nol to the perfusion resulted in an

Fig. 3 Effects of gastric perfusion with gradually increasing concentrations of De-Nol on canine HCO_3^- outputs in tests with De-Nol alone or combined with atropine, pirenzepine or indomethacin. For the comparison, the maximal HCO_3^- response to 16, 16-dimethyl PGE_2 is presented. Mean $\pm$ SEM of six tests on six dogs. Asterisks indicate statistically significant ($p < 0.05$) decreases below the value obtained with De-Nol alone.

Fig. 4 Effects of duodenal perfusion with gradually increasing concentrations of De-Nol on canine duodenal HCO_3^- output in tests with De-Nol alone or combined with atropine, pirenzepine or indomethacin. For the comparison, the maximal HCO_3^- response to 16, 16-dimethyl PGE_2 is presented. Mean $\pm$ SEM of six tests on six dogs. Asterisks indicate statistically significant ($p < 0.05$) decreases below the value obtained with De-Nol alone.

increase in PGE_2 contents that were significant at 40 and 80 mg/ml concentrations of De-Nol (Table).

Injection of atropine (25 $\mu\text{g/kg}$) caused significant reduction in basal gastric and duodenal HCO_3^- outputs and decreased the HCO_3^- response to De-Nol by 15-32% depending on the concentrations. Pirenzepine (25 $\mu\text{g/kg}$) did not significantly affect basal or De-Nol induced gastric or duodenal HCO_3^- secretion (Figs 3, 4). Neither atropine nor pirenzepine influenced basal or De-Nol induced luminal release of PGE_2 (Table).

Indomethacin (2.5 mg/kg) did not change significantly basal gastric HCO_3^- outputs but reduced by about 60% basal duodenal HCO_3^- outputs. Indomethacin almost completely abolished gastric and duodenal HCO_3^- responses to De-Nol (Figs 3 and 4). Indomethacin reduced by about 75% basal PGE_2 release and abolished the PGE_2 release induced by De-Nol (Table).

Discussion

This study provides evidence that De-Nol (colloidal bismuth subcitrate) stimulates gastric and duodenal alkaline secretion and that this depends, at least in part, upon the mucosal generation of prostaglandins.

Previous studies showed that alkaline secretion by gastric and duodenal mucosa is an energy dependent process that is under local humoral control involving mucosal prostaglandin^{10,11} and under neural control

Table PGE_2 content (ng/h) of gastric and duodenal perfusates obtained drug saline perfusion (basal) and after addition of De-Nol alone or in combination with atropine, pirenzepine or indomethacin in dogs. Mean $\pm$ SEM of six tests on six dogs.

Group	Dose	PGE_2 Output (ng/h)	
		Stomach	Duodenum
Basal	Saline	46 $\pm$ 6	71 $\pm$ 12
De-Nol	5 mg/ml	50 $\pm$ 7	76 $\pm$ 10
"	10 mg/ml	62 $\pm$ 8	85 $\pm$ 14
"	20 mg/ml	75 $\pm$ 10*	96 $\pm$ 11*
"	40 mg/ml	82 $\pm$ 12*	124 $\pm$ 28*
"	80 mg/ml	98 $\pm$ 16*	130 $\pm$ 18*
De-Nol	20 mg/ml	72 $\pm$ 12*	104 $\pm$ 14*
De-Nol††	Atropine 25 $\mu\text{g/kg}$	82 $\pm$ 17*	97 $\pm$ 12*
De-Nol*††	Pirenzepine 25 $\mu\text{g/kg}$	79 $\pm$ 18*	110 $\pm$ 16*
De-Nol††	Indomethacin 2.5 mg/kg	18 $\pm$ 4†	23 $\pm$ 6†

*Statistically significantly higher than the basal values (saline);

†Statistically significantly lower than the value obtained with De-Nol (20 mg/ml); ‡De-Nol was perfused at 20 mg/ml.

involving a vagal cholinergic component.^{12,13} The stimulation of the gastric or duodenal HCO_3^- secretion by the presence of acid in the gut lumen is well documented in various species.⁷ The involvement of the mucosal generation of prostaglandin has been documented by direct determination of its increased release from the mucosa exposed to acid¹¹ and by the demonstration that the blockade of cyclooxygenase by indomethacin abolishes both the release of prostaglandin and HCO_3^- secretion induced by mucosal acidification.^{9,11}

Furthermore, most of the exogenous prostaglandin of the E and F series, particularly their methylated analogues, induce copious alkaline secretion after their topical application to the gastroduodenal mucosa.¹⁵ This study has utilised the methylated PGE analogue to elicit the maximal secretory capacity for HCO_3^- both in human gastric mucosa and canine gastroduodenal mucosa.

The major finding of this report is the demonstration that the topical application of De-Nol in gradually increasing concentrations results in a concentration dependent increase in alkaline secretion both from the gastric and duodenal mucosa. In human stomach, the highest HCO_3^- output in response to De-Nol reached about 80% of the dmPGE induced maximal HCO_3^- secretion and in canine stomach it attained about 55% of the dmPGE maximum. In the canine duodenum the respective HCO_3^- response to De-Nol reached 72% of the prostaglandin-maximum. Because the concentrations of De-Nol used in our study were within the range which may occur in the stomach or duodenum after ingestion of the therapeutic dose of this agent (single

tablet of De-Nol is 300 mg colloidal bismuth), it may be concluded that the stimulation of alkaline secretion belongs to the spectrum of pharmacological actions of De-Nol. This HCO_3^- stimulatory effect may contribute to the therapeutic effects of the drug.

The mechanism of the alkaline stimulatory action of De-Nol is not immediately obvious. It is known for example that any mucosal damage results in copious alkaline secretion because of increased mucosal permeability and passive HCO_3^- diffusion from the extracellular fluid into the gastric lumen.^{7,19} There is no evidence that De-Nol causes such damage to the gastroduodenal mucosa as the transmucosal potential difference which is an indicator of the mucosal integrity, was not affected by the drug. The fact that the increase in gastroduodenal alkaline secretion was paralleled by the rise in luminal release of PGE_2 suggests that local prostaglandin may be involved in the De-Nol stimulated alkaline secretion. The crucial role of prostaglandin in the mechanism of De-Nol stimulated alkaline secretion is supported by our finding that aspirin or indomethacin, which are potent inhibitors of cyclooxygenase,²⁰ abolished both the alkaline secretion and the release of prostaglandin in response to De-Nol.

Colloidal bismuth subcitrate has been previously reported to stimulate mucus secretion and to form a local protective barrier, especially over the ulcerated area.^{1,24} Stimulation by De-Nol of alkaline secretion into the mucus gel adherent to the epithelial surface may enhance mucosal protection, particularly against the damaging effect of luminal acid and pepsin.

Gastroduodenal alkaline secretion may also be stimulated by vagal-cholinergic excitation. Vagal stimulation by sham feeding was reported to increase this stimulation,^{7,12} whereas anticholinergics were found to cause the inhibition of this secretion.^{7,12} Safsten and Flemstrom²¹ reported recently that pirenzepine, which is classified as an M1-selective muscarinic antagonist, increased rather than inhibited the duodenal alkaline secretion possibly by acting through the M1 receptors in the brain. Thus we compared the influence of atropine and pirenzepine on basal and De-Nol stimulated alkaline secretion in man and dogs. We confirmed that atropine strongly suppressed basal alkaline secretion but had only little influence on the increase of alkaline secretion in response to De-Nol. Pirenzepine did not affect basal or De-Nol induced alkaline secretion from the stomach or duodenum. Neither of the antimuscarinic agents affected mucosal formation of PGE_2 . We found that atropine strongly reduced basal gastroduodenal alkaline secretion in human subjects and in dogs, whereas pirenzepine did not interfere with that secretion, which indicates that muscarinic receptors are involved in the mechanism of alkaline secretion.

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