Effect of bismuth subcitrate and sucralfate on rat duodenal and human gastric bicarbonate secretion in vivo

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Abstract

Acid and alkali secretion have been examined together with prostaglandin E₂ production in response to two mucosal protective drugs, colloidal bismuth subcitrate and sucralfate. Doses of colloidal bismuth subcitrate in the therapeutic range (120 and 1200 mg) had no effect on alkali secretion or luminal PGE₂ output when perfused into the stomach of human volunteers. Similarly, in the anaesthetised rat, neither gastric acid nor duodenal alkali secretions were influenced by iv (12 mg/kg) or topical (120 mg/ml) administration of colloidal bismuth subcitrate. In contrast, perfusion of the human stomach with 1 g sucralfate stimulated bicarbonate output by 50%, a response which was unaffected by indomethacin (25 mg/h). A rise of 64% in gastric PGE₂ output after sucralfate was, however, prevented by indomethacin pretreatment. Alkali secretion by rat duodenum was also increased by sucralfate but the response depended on the basal secretory rate. Low basal secretors (<3 µmol) showed a 75% stimulation whereas rats with high basal secretory rates (>3 µmol) showed no significant response. All duodenal preparations regardless of basal secretory rate showed a stimulation of bicarbonate output with topical PGE₂. The results suggest that enhancement of gastroduodenal bicarbonate secretion may play a role in the protective action of sucralfate but is unlikely to explain mucosal protection by colloidal bismuth subcitrate.

Sucralfate and colloidal bismuth subcitrate (CBS) have both been shown to protect gastroduodenal mucosa against experimental damage¹⁻³ and to heal peptic ulcers in man.⁴⁻⁷ Neither agent affects acid secretion^{8,9} and their mechanisms of ulcer healing and mucosal protection remain unclear.

Sucralfate, a basic aluminium salt of sucrose octasulphate, was originally proposed to act by adhering to damaged and ulcerated tissue thereby forming a physical barrier against injury by luminal acid, pepsin and bile salts.¹⁰⁻¹² More recent studies indicate that this drug has additional actions on gastroduodenal mucosa which may contribute to its protective effect. For example, sucralfate has been reported to stimulate prostaglandin generation,¹³ bicarbonate secretion,¹⁴ and mucus production¹⁵ in laboratory animals.

Colloidal bismuth subcitrate precipitates in the acidic environment of the stomach which would encourage binding to the mucosal surface

in a similar manner to sucralfate. In addition to the formation of a physical barrier, this adherence could also initiate an irritant reaction which would lead to the reported formation and release of endogenous prostaglandins.^{16,17} Clinical interest in colloidal bismuth subcitrate (De-Nol®, Gist-Brocades) has recently been aroused by reports of lowered duodenal ulcer relapse rates in comparison with H₂ receptor antagonists.¹⁸⁻²⁰ The reasons for this are unclear although the bactericidal action of bismuth against *Campylobacter pylori* is the currently favoured hypothesis.²¹

The present studies were designed to evaluate the actions of sucralfate and colloidal bismuth subcitrate on mucosal bicarbonate secretion in the rat duodenum and human stomach.

Methods

ANIMALS

Experiments were performed using female Sprague-Dawley rats (200-220 g body weight) obtained from ICI Pharmaceuticals animal breeding unit. Rats were starved for 20-24 hours before use in cages with wide mesh bottoms to prevent coprophagy but allowed free access to drinking water.

Measurement of secretion

Duodenal bicarbonate secretion was measured as previously described.²² Briefly, animals were anaesthetised with urethane 1.5 g/kg im. Body temperature was maintained at 37°C by means of a heated table and intrarectal thermistor. A 12 mm segment of the descending part of the duodenum, starting 5 mm distal to the outlet of the bile duct and about 2 cm from the pylorus, was cannulated *in situ*. The bile duct and pylorus were ligated. A femoral vein was cannulated to enable infusion of saline (1 ml/kg/h) to prevent dehydration and for administration of drugs. The duodenal segment was perfused with 4 ml of 0.15 M NaCl at 37°C which was circulated rapidly by a gas lift of 100% oxygen prewashed in Ba(OH)₂. The rate of alkalinisation was determined by continuous titration to pH 7.4 with 25 mM HCl made isotonic with NaCl. Titrant delivery was controlled automatically using standard pH-stat equipment (GK 2321C pH electrode, ABU 80, PHM 62, TTT 80, all Radiometer Copenhagen, Denmark).

For measurement of acid secretion, the stomach was perfused at 7 ml/min with saline through the oesophagus and fluid collected by an outlet tube in the pylorus. Secretion was

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stimulated with the H₂ agonist dimaprit (SK&F, Welwyn, UK) given as a 10 mg/kg bolus and 30 mg/kg/h sc infusion. Acid output was determined every 10 min for a total of two hours by titration of samples with 20 mM NaOH to pH 6.4.

Experimental design

After completion of surgery, the preparation was allowed to stabilise for about one hour. Alkalisation ($\mu\text{mol}/\text{cm}/\text{h}$) was determined at 15 minute intervals and mean rates of secretion (SEM) compared before and after drug treatment by paired *t* test.

Basal alkali secretion was measured for 60 minutes then either sucralfate or bismuth subcitrate added to the luminal solution in 100 μl volumes to give a final concentration of 1 mg/ml for sucralfate and 11.7 or 117 mg/ml (10 and 100 μmol) for bismuth subcitrate. The effects of iv administration of colloidal bismuth subcitrate (11.7 and 117 mg/kg) were also determined in a separate series of experiments. In the case of sucralfate, drug addition induced transient fluctuations in the pH of the luminal perfusate. A 20 minute re-equilibration period was therefore allowed after drug addition before recommending measurement of alkali secretion for a further 60 min. The viability and sensitivity of individual preparations was assessed at the end of each experiment by recording maximal secretory response 45 min after adding 10 $\mu\text{g}/\text{ml}$ prostaglandin E₂ (PGE₂) to the luminal solution.

Drugs

Sucralfate was obtained as an amorphous powder (Ayerst Laboratories, Andover, UK) and formulated as a saline suspension. Addition of 100 μl to the luminal solution was equivalent to adding 1 mg/ml of the aluminium salt of sucrose octasulphate.

Bismuth subcitrate was also obtained as an amorphous powder (Gist-Brocades, Delft, The Netherlands) and prepared as a concentrated solution in saline at room temperature so that addition of 100 μl produced a final concentration of 117 mg/ml.

PGE₂ (Sigma Chemicals, St Louis, MO) was dissolved in ethanol, stored at -20°C and added to the luminal solution in a volume of 30 μl to produce a final concentration of 10 $\mu\text{g}/\text{ml}$.

HUMAN STUDIES

Subjects

Studies were performed in 20 male and six female healthy volunteers aged between 18 and 27 years who were taking no medication. Four groups of subjects received either 1 or 10 mg/ml bismuth subcitrate (both $n=6$), 8 mg/ml sucralfate ($n=8$), or sucralfate plus 0.21 mg/ml indomethacin ($n=6$).

Measurement of secretion

Gastric bicarbonate secretion by the intact human stomach was measured by an intubation

method described previously.²³ After an overnight fast the volunteers swallowed a multilumen polyethylene tube which was positioned by fluoroscopy with its tip in the second or third part of the duodenum. Ranitidine (150 mg orally one hour beforehand and 25 mg/h iv during the study) was given to maintain intragastric pH between 6 and 7. Saliva was continuously removed by suction which reduced salivary contamination to below 3% of measured gastric bicarbonate. After aspiration of resting gastric contents, the stomach and duodenum were perfused at 2 ml/min with saline containing 12.5 $\mu\text{Ci/l}$ of ³H-polyethylene glycol and ¹⁴C-polyethylene glycol respectively. Aspirates were collected by continuous suction at 10 minute intervals from the antrum and duodenum for measurement of marker concentration. Aliquots (1 ml) were frozen for later assay of PGE₂ concentration. In the middle of each sampling period a separate 1 ml aliquot was aspirated into a cooled syringe for immediate determination of pH and pCO₂.

Analytical methods

Concentrations of ³H-PEG and ¹⁴C-PEG in the samples were measured by liquid scintillation counting (LKB Wallac 2000 Beta Counter) with external quench correction. The pH and pCO₂ of the samples were measured using a Corning 170 Blood Gas Analyser. Prostaglandin E₂ concentrations were measured by radioimmunoassay after extraction into 2 ml diethyl ether, evaporation then resuspension into 1 ml radioimmunoassay buffer. Recovery experiments revealed a good correlation between amounts of PGE₂ added and measured (102 (15)% of that added, mean (SD), $n=8$) suggesting low cross-reactivity with potential interfering substances.

Experimental design

After an equilibration period of one hour, basal bicarbonate secretion was measured for 60 minutes. The gastric perfusate was then changed to ³H-PEG containing either sucralfate in suspension (8 mg/ml) or a bismuth subcitrate solution (1 or 10 mg/ml) and perfusion continued for a further hour. Total amounts perfused were equivalent to 1 g sucralfate and either 120 or 1200 mg bismuth subcitrate. In the third hour there was a return to the original perfusate.

To study the effects of cyclooxygenase inhibition on the response to sucralfate, the gastric perfusate was changed to ³H-PEG containing indomethacin (0.21 mg/ml) halfway through the first basal period. After 30 min the gastric perfusate was again changed to ³H-PEG containing indomethacin (0.21 mg/ml) plus sucralfate (8 mg/ml) for a further hour before returning to the original perfusate (³H-PEG alone) in the third hour.

Drugs

Bismuth subcitrate was obtained as an amorphous powder and made up as a solution in ³H-PEG to give a final concentration of either 1 mg/ml or 10 mg/ml. Although colloidal bismuth

Figure 1: Effect of topical and iv colloidal bismuth subcitrate on rat duodenal alkali secretion. The alkali response to topical PGE₂ (10 μg/ml) is also shown (○=topical colloidal bismuth subcitrate, mean (SE), n=5, *p<0.01; ●=iv colloidal bismuth subcitrate, n=6, *p<0.01).

subcitrate possesses little buffering capacity, the suspension was titrated to pH 7.4 before administration.

Sucralfate was obtained in suspension and diluted to produce a concentration of 8 mg/ml. This formulation was also titrated to pH 7.4 before use.

Indomethacin (Sigma Chemicals, Poole, UK) was prepared as an aqueous solution of concentration 0.21 mg/ml at pH 7.4.

Calculation of results

Gastric and duodenal volumes were calculated from marker dilution and perfusion rate. Duodenogastric reflux was calculated from the amount of ¹⁴C-PEG appearing in the gastric aspirate. Free bicarbonate concentration was calculated using the Henderson-Hasselbach equation and was added to that bicarbonate in the form of CO₂ (pCO₂ × solubility constant of 0.031) in order to determine total bicarbonate concentration. Output was calculated as the product of volume and concentration corrected for refluxed bicarbonate. Similarly, prostaglandin E₂ output was the product of concentration and volume. All results are expressed as means (SEM) and differences assessed by paired *t* test.

Results

ANIMAL STUDIES

Bismuth subcitrate

Topical application of 10 and 100 μmol colloidal bismuth subcitrate had no effect on alkali secretion by rat distal duodenum (Fig 1). The preparation responded to topical PGE₂ (10 μg/ml) which induced a peak stimulation of 110% from 6.60 (1.65) to 15.4 (2.63) μmol/cm/h (p<0.01, n=5).

Similarly, intravenous administration of 10 μmol/kg had no effect on alkalinisation while topical PGE₂ (10 μg/ml) increased secretory rate by 120% from 4.30 (0.60) to 9.0 (1.56) μmol/cm/h (p<0.01, n=6) (Fig 1). This dose of colloidal bismuth subcitrate was without effect on dimaprit stimulated gastric acid secretion in the rat over a two hour period (acid secretion=174 (14) μmol in controls and 182 (19) μmol in treated animals, p>0.1, n=10). When the higher dose of colloidal bismuth subcitrate (100 μmol/kg (117 g/kg)) was administered systemically, all the animals died.

Sucralfate

Sucralfate induced two distinct responses depending upon basal secretory rate. Topical application of sucralfate 1 mg/kg to rats with high rates of basal alkali secretion (>3 μmol/cm/h, n=4) had no effect on alkali secretion. Thus secretory rate during drug exposure (5.45 (1.30) μmol/cm/h) was similar to that during the basal period (5.55 (1.36)) although PGE₂ (10 μg/ml) stimulated secretion by 90% from 4.90 (1.17) to 9.30 (1.31) μmol/cm/h, p<0.05 (Fig 2).

In the animals with low basal alkali secretion (<3 μmol/cm/h, n=4) topical sucralfate produced a rise in alkali secretion of 175% from 1.20 (0.33) to 3.3 (0.97) μmol/cm/h, p<0.05. These preparations appeared more sensitive to PGE₂ which increased secretory rate by 460% over the initial basal value (from 1.20 (0.33) to 7.0 (1.85) μmol/cm/h, p<0.05).

Figure 2: Effect of topical sucralfate and PGE₂ on rat duodenal alkali secretion in high (●) and low (○) basal secretors (mean (SE), n=4 for both groups).

Figure 3: Effect of sucralfate (1 g) on human gastric bicarbonate and luminal PGE_2 outputs (mean (SE), $n=8$, $*p<0.01$).

HUMAN STUDIES

Bismuth subcitrate

Neither concentration of bismuth subcitrate influenced alkali secretion or luminal PGE_2 output by the human stomach (Table).

Sucralfate

During perfusion of the stomach with 1 g sucralfate over one hour there was a significant increase in alkali secretion from 494 (74) to 741 (88) $\mu\text{mol}/\text{h}$ ($n=8$, $p<0.01$) which returned towards basal values when the drug containing suspension was replaced by PEG during the third hour (Fig 3). There was no change in bicarbonate originating from duodenogastric reflux during the three study periods. There was no significant change in PGE_2 output when the basal period (1099 (103) pmol/h) and sucralfate perfusion period (1136 (121) pmol/h) were compared ($p>0.1$). However a significant rise ($p<0.05$) in PGE_2 output was recorded during the final hour (1799 (205)). The stimulation in bicarbonate output induced by sucralfate was due to an increase in gastric fluid secretion with the volume rising from 66 (15) to 135 (33) ml/h during drug perfusion (Fig 4). There was no significant increase in bicarbonate concentration during exposure to sucralfate (3.09 (0.22) and 3.40 (0.27) mmol/l , $p>0.1$). The increase in

TABLE Gastric bicarbonate ($\mu\text{mol}/\text{h}$) and luminal PGE_2 (pmol/h) outputs during perfusion of the human stomach with either 1 or 10 mg/ml colloidal bismuth subcitrate (mean (SE), $n=6$ for each concentration). Colloidal bismuth subcitrate was perfused during the second hour only

Concentration	Output	1st hour	2nd hour	3rd hour
1 mg/ml	HCO_3^-	593 (118)	611 (163)	631 (124)
	PGE_2	1005 (130)	1210 (165)	1106 (163)
10 mg/ml	HCO_3^-	453 (114)	412 (86)	489 (108)
	PGE_2	898 (126)	998 (110)	1060 (134)

PGE_2 output, however, was not a result of the increase in fluid secretion since the PGE_2 and volume response were clearly dissociated.

Indomethacin and sucralfate

Perfusion of the stomach with indomethacin alone (12.5 mg over 30 minutes) produced a fall in basal alkali secretion, although this reduction did not achieve statistical significance (696 (160) $\mu\text{mol}/\text{h}$ basally and 384 (93) during indomethacin perfusion, $n=6$, $p=0.058$). A higher dose of indomethacin (25 mg) caused a similar, insignificant reduction in alkali output and had no influence on the stimulation of alkali secretion induced by 1 g sucralfate which increased from 384 (93) $\mu\text{mol}/\text{h}$ to 782 (132) $\mu\text{mol}/\text{h}$ ($p<0.05$) and then returned to basal values during the final hour (Fig 5).

Luminal PGE_2 output was lower during the period of indomethacin perfusion alone but this reduction failed to reach statistical significance ($p=0.068$). No further change in PGE_2 output occurred during or after perfusion of the stomach with indomethacin plus sucralfate (Fig 5), in contrast with the rise in luminal PGE_2 output observed during this final hour with sucralfate alone (Fig 3).

Discussion

Our results show quite different effects for two commonly used mucosal protective and ulcer healing agents. In the case of colloidal bismuth subcitrate we have been unable to show any effects on human gastric and rat duodenal bi-

Figure 4: Effect of sucralfate on human gastric secretory volume and bicarbonate concentration (mean (SE), $n=8$, $*p<0.05$).

Figure 5: Effect of indomethacin and sucralfate on human gastric bicarbonate output (corrected for duodenogastric reflux) and luminal PGE_2 output (mean (SE), $n=6$, * $p<0.01$ compared with immediately before adding sucralfate).

carbonate secretion or luminal PGE_2 output in therapeutically relevant doses. These findings are at variance with a previous study in which stimulation of bicarbonate secretion was observed in man and dogs with similar concentrations of bismuth subcitrate.²⁴ Stimulation of bicarbonate secretion by colloidal bismuth subcitrate has also been reported in studies on isolated amphibian gastric and duodenal mucosae by a mechanism independent of the local generation and release of prostaglandins.²⁵ While our present study provides a clear demonstration that colloidal bismuth subcitrate has no effect on gastroduodenal bicarbonate secretion, the overall data from *in vivo* studies is conflicting.

In contrast with findings with colloidal bismuth subcitrate, therapeutic doses of sucralfate stimulated both human gastric and rat duodenal alkalinisation. In the human stomach there was a delayed rise in luminal PGE_2 output. The temporal dissociation between stimulation of gastric luminal alkalinisation and increased lumina PGE_2 output suggests that the two phenomena may not be linked, particularly as only the bicarbonate increase was coupled to volume flow. This is reinforced by the finding that pretreatment with the cyclooxygenase inhibitor indomethacin failed to prevent stimulation of bicarbonate secretion by sucralfate although

stimulation of luminal PGE_2 output was blocked. These observations support earlier *in vitro* experiments which showed that sucralfate induced alkali secretion was not inhibited by indomethacin pretreatment of amphibian gastric mucosa.¹⁴ A similar finding has been reported in respect of stimulation of mucus production by sucralfate.¹⁵

It is possible that sucralfate acts on the (prostaglandin-independent) $\text{Cl}^-/\text{HCO}_3^-$ exchange component of duodenal alkali secretion. This contention is reinforced by the fact that sucralfate stimulates alkali secretion in the stomach where anion exchange is thought to be the major mechanism of HCO_3^- transport.²⁶ If, in the group of rats with high basal alkali secretion, $\text{Cl}^-/\text{HCO}_3^-$ exchange is operating maximally then an agent stimulating such exchange would be expected to show little or no effect on bicarbonate output whereas an agent stimulating electrogenic secretion such as PGE_2 would remain effective. Such an explanation is consistent with our results which show that high basal secretion in the duodenum is associated with a response to PGE_2 but not sucralfate while low basal secreting preparations responded to both sucralfate and PGE_2 .

These observations raise the intriguing possibility that sucralfate may act in three separate ways. First, by adhering to ulcerated mucosa it may produce a physical barrier to luminal acid and pepsin. Second, stimulation of endogenous prostanoid metabolism may enhance endogenous protective mechanisms that influence both ulcer healing and mucosal protection. Finally, sucralfate may directly stimulate the production of mucus gel and transport of bicarbonate by surface epithelial cells, possibly by a local irritant reaction.²⁷ The latter effects would seem unlikely to play a role in ulcer healing but may be important in preventing damage to the intact epithelium.

It is possible that different components of sucralfate are responsible for these various actions. For example, sucrose may contribute to the ability of the complex to adhere to the mucosa and thus form a physical barrier, while aluminium can directly stimulate bicarbonate secretion.¹⁴ Further, the protective action of sucralfate on oesophageal mucosa has been proposed to result from the presence of sulphate.²⁸ It thus seems likely that the protective action of sucralfate is multifactorial with different components activating various mechanisms of gastroduodenal mucosal defence.

Both sucralfate and colloidal bismuth subcitrate (De-Nol®) are primarily ulcer healing agents. Stimulation of bicarbonate secretion by sucralfate would be expected to enhance pre-epithelial acid disposal in the stomach and duodenum. In theory, such a property could prevent ulcer recurrence after initial healing, alleviate NSAID induced gastric damage, and reduce stress ulceration in severely ill patients. It is difficult to envisage, however, what role this would have in accelerating chronic peptic ulcer healing. Indeed, the absence of a viable epithelium in the region of an ulcer implies that the diseased mucosa would be unable to respond to stimulants of bicarbonate secretion. Thus we

suspect increased rates of alkalinisation may be of little relevance to the chronic ulcer healing actions of sucralfate or colloidal bismuth subcitrate in man.

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