LETTERS TO THE EDITOR

Sucralfate, bismuth subcitrate, and gastric HCO3 in humans

Sir,—The study by Shorrock et al shows a stimulatory effect of sucralfate on gastric bicarbonate secretion in humans. This confirms our previous findings published in 1985 in a paper unfortunately not quoted in Shorrock’s reference list. Yet the two studies somehow complement each other. Shorrock’s experiment was performed in acute conditions and in healthy volunteers, while our study was carried out in duodenal ulcer patients treated with sucralfate for six weeks. Basal gastric bicarbonate secretion, assessed by means of Feldman’s method,1 proved to be normal in all subjects before treatment and was significantly increased (p<0.01) at the end of the therapeutic course in both healed and unhealed patients.

The final assessment of gastric HCO3 was made 12 hours after the last dose of sucralfate. In Shorrock’s study the increase in alkali secretion by sucralfate appears to be transient. Our data suggest either that the duration of the stimulatory effect of sucralfate is actually much longer or that continuous sucralfate administration for several weeks elicits a lasting response in terms of bicarbonate production.

As the lack of effect of bismuth subcitrate on gastric alkali secretion in humans, our findings after four weeks of treatment with the drug are in complete agreement with Shorrock’s results during acute administration.

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Sir,—I read with interest two recent papers published in Gut on the influence of colloidal bismuth subcitrate (CBS) on gastric duodenal alkaline secretion. In one study1 carried out in vitro using isolated amphibian mucus cells, CBS added to luminal solution at 10-10 M, produced a remarkable and dose dependent increase in HCO3 secretion, probably involving transcellular electroneutral exchange rather than passive diffusion of HCO3 across the damaged epithelium. These results agree well with our in vivo studies using perfused canine stomach and upper duodenum where CBS at concentrations of 20 mg/ml or higher (but not 10 mg/ml) was found to stimulate dose dependent gastric and duodenal alkaline secretion without affecting transmucosal electrical potential difference.2 Since both aspirin and atropine partially reduced the alkaline response to CBS it was suggested that prostaglandins and muscarinic receptors may be involved in the mechanism of alkaline secretion.

In a more recent paper the same group of investigators3 using an ex vivo perfused segment of distal duodenum of rat and in vivo perfused human stomach found that CBS instilled at the concentration of 10 mg/ml was ineffective in the stimulation of alkaline secretion. It has been concluded that these results are at variance with those reported by us in humans and that they ‘clearly demonstrate’ that CBS has no effect on gastroduodenal alkaline secretion.

We believe that neither of these conclusions is correct. The fact that CBS infused at the rate of 2 ml/min and at the concentration of 10 mg/ml did not affect basal bicarbonate secretion did not necessarily disagree with our results. In our study in humans the stimulation of gastric alkaline secretion was achieved when CBS was instilled at the rate of 10 ml/min and at the concentration of 5 mg/ml which were over ten times as those in the report of Shorrock et al.4 In our subjects smaller amounts of CBS (5 mg/ml at the rate of 10 ml/min) which were over ten times as those in the report of Shorrock et al.4 were also ineffective in the stimulation of gastroduodenal alkaline secretion. The high rate of the perfusion of the stomach seems to be of great importance for complete recovery of the osmotic bicarbonate by the mucus and for the adequate exposure of the surface epithelium to the tested drug.

Mertz-Nielsen et al.5 recently reported that the perfusion of the human stomach with CBS at 10 mg/ml but at a rate of 5 ml/min resulted in a significant and sustained increase in the formation of prostaglandin E (PGE) by the gastric mucus. In their classic paper on alkaline secretion in humans Forsell et al. used a rate of gastric perfusion about 30 times higher (1760 m1/h) and this was considered to facilitate not only the collection of alkaline secretion but also to detect rapid gastric duodenogastroduodenal reflux and to wash out these reflexes.

Another problem with the study of Shorrock et al. was probably inadequate suppression of gastric acid secretion by ranitidine (150 mg orally plus 25 mg/h intravenously) and their failure to observe gastric ulcers which were present in each stomach responded to any standard stilimant such as PGE2, According to our experience such a dose may be too low to bring the gastric pH to neutrality and this could cause a marked conversion of bicarbonate to CO2, resulting in low rates of recorded bicarbonate secretion. This is why we used doses of ranitidine eight times larger (1200 mg) the night before the examination and usually we infused ranitidine intravenously at the beginning of the experiment to achieve a starting pH of about 7-0 before the application of CBS. The failure to suppress acid secretion adequately was probably the cause of relatively low basal alkaline secretion in the study by Shorrock et al compared to ours. Thus, the data presented in their paper do not seem to provide a ‘clear demonstration’ that CBS does not affect gastric alkaline secretion in humans.

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Reply

Sir,—In response to Dr Konturek’s comments, we would like to make a number of points to clarify any misconceptions concerning measurement of alkaline secretion in the stomach. Our method of measuring gastric bicarbonate output produced almost identical basal values to methods using very high rates of perfusion (approx 400 μmol/h). This in itself is evidence that a low perfusion rate used by us in no way validates the methods by changing CO2 losses. Indeed, the relative impermeability of gastric mucosa to CO2, on which the method depends, was first described in a system where fluid was just instilled into the stomach.1 In addition, we have previously described pilot studies which show a good correlation between infused and recovered bicarbonate in our perfusion system.2

We found that the dose of H, receptor antagonist used in our studies was adequate at keeping luminal pH between 6-4 and 7-1 when most of the gastric bicarbonate is in the free form and not as CO2. The effect of PGE2 was not investigated in this study, having previously been shown not to stimulate bicarbonate secretion in the present system.3

At concentrations of colloidal bismuth subcitrate (CBS) of 10 mg/ml we found no stimulation of gastric alkaline secretion (we have never studied effects on duodenal secretion in humans), which is clearly at variance with Dr Konturek’s view.4 In a steady state perfusion system with a compound displaying negligible absorption, the concentration of bicarbonate in the mucosa should remain more or less constant and is independent of perfusion rates. In our experiments we have tried to use concentrations of CBS which are likely to occur in the stomach after conventional oral doses of De-Nol. Higher concentrations are not only irrelevant but may in fact damage the mucosa, resulting in passive diffusion of bicarbonate as observed by us in vitro with carbamoxine.5 These conclusions of our study are therefore as stated.

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5 Rees WDW, Gibbons LC, Warhurst G, Turgern B. Studies of bicarbonate secretion in the normal human stomach in vivo: effect of aspirin, sodium taurocholate and prostaglandin E1. In: