LETTERS TO THE EDITOR

Sucralfate, bismuth subcitrate, and gastric HCO₃ in humans

SIR,—The study by Shorrock *et al*¹ shows a stimulatory effect of sucralfate on gastric bicarbonate secretion in humans. This confirms our previous findings published in 1985² 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,³ 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.²

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 a single dose of the drug is actually much longer or that continuous sucralfate administration for several weeks elicits a lasting response in terms of bicarbonate production.

As for the lack of effect of bismuth subcitrate on gastric alkali secretion in humans, our findings after four weeks of treatment with the drug⁴ are in complete agreement with Shorrock's results during acute administration.

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- 1 Shorrock CJ, Garner A, Hunter AH, Crampton JR, Rees WDW. Effect of bismuth subcitrate and sucralfate on rat duodenal and human gastric bicarbonate secretion *in vivo*. *Gut* 1990; 31: 26–31.
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SIR,—I read with interest two recent papers published in *Gut* on the influence of colloidal bismuth subcitrate (CBS) on gastroduodenal alkaline secretion. In one study¹ carried out *in vitro* using isolated amphibian mucosa, CBS added to luminal solution at 10^{-6} – 10^{-4} 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 dependently 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 us² in humans and that they 'clearly demonstrate' that CBS has no effect on gastroduodenal alkaline secretion in man.

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 gastric alkaline secretion does 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 10 mg/ml. This means that in our study the mucosa was exposed to five times the amounts of CBS per time unit than in the study of Shorrock *et al*.³ In our subjects smaller amounts of CBS (5 mg/ml at the rate of 10 ml/min) which were over twice as much as those in the report of Shorrock *et al*³ 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 secreted bicarbonate by the mucosa and for the adequate exposure of the surface epithelium to the tested drug. Mertz-Nielsen *et al*⁴ 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 mucosa. In their classic paper on alkaline secretion in humans Forsell *et al*⁵ used a rate of gastric perfusion about 30 times higher (1760 ml/h) and this was considered to facilitate not only the collection of alkaline secretion but also to detect rapid alkaline duodenogastroic reflux and to wash out these refluxes.

Another problem with the study of Shorrock *et al*³ was probably inadequate suppression of gastric acid secretion by ranitidine (150 mg orally plus 25 mg/h intravenously) and their failure to provide evidence that such pretreated stomach responded to any standard stimulant 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 secreted HCO₃ 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 a dose of 50 mg/h throughout 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 rates of 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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- 2 Konturek SJ, Bilski J, Kwieciński N, Obtulowicz W, Kopp B, Oleksy J. De-Nol stimulates gastric and duodenal alkaline secretion through prostaglandin dependent mechanism. *Gut* 1987; 28: 1557–63.

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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 alkali secretion in the stomach. Our method of measuring gastric bicarbonate output¹ produced almost identical basal values to methods using very high rates of perfusion² (approx 400 µmol/h). This in itself is evidence that a low perfusion rate used by us in no way invalidates the method by altering 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.³ In addition, we have previously reported validation studies which show a good correlation between infused and recovered bicarbonate in our perfusion system.⁴

We found that the dose of H₂ 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.⁵

At concentrations of colloidal bismuth subcitrate (CBS) of 10 mg/ml we found no stimulation of gastric alkali secretion (we have never studied effects on duodenal secretion in humans), which is clearly at variance with Dr Konturek.⁶ In a steady state perfusion system with a compound displaying negligible absorption, the concentration of CBS adjacent to 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 carbenoxolone.⁷

The conclusions of our study are therefore as stated.

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- 1 Shorrock CJ, Garner A, Hunter AH, Crampton JR, Rees WDW. Effect of bismuth subcitrate and sucralfate on rat duodenal and human gastric bicarbonate secretion *in vivo*. *Gut* 1990; 31: 26–31.
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