LETTERS TO THE EDITOR

Sucralfate, bismuth subcitrate, and gastric HCO3 in humans

Sr.-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 methods 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.

The final assessment of gastric HCO3 was made 12 hours after the last dose of sucralfate. In Shorrock’s study the increase in alkaline secretion by sucralfate appears to be transient. Our data suggest either that the duration of the stimulatory effect of sucralfate in humans 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 alkaline secretion in humans, our findings after four weeks of treatment with the drug4 are in complete agreement with Shorrock’s results during acute administration.5

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Sr.-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 10–100 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 us4 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 stimulation of bicarbonate 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 5 mg/ml as reported in the report of Shorrock et al.2 In our subjects smaller amounts of CBS (5 mg/ml at the rate of 10 ml/min) which were infused intravenously as those as those in the report of Shorrock et al.2 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 mucosal 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.1 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 gastric duodenalogenic refract to and to wash out these refluxes.

Another problem with the study of Shorrock et al.2 was probably inadequate suppression of gastric acid secretion by ranitidine (150 mg orally plus 25 mg/h intravenously) and their failure to observe how much pretreated stomach responded to any standard stimulant such as PGE. 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 CO2 to HCO3, 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 rate of 50 ml/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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SIR,-In response to Dr Konturek’s comments, we would like to make a number of points to clarify some misconceptions concerning the measurement of alkaline secretion in the stomach. Our method of measuring gastric bicarbonate output1 produced almost identical basal values to methods using very high rates of perfusion (apprrox 400 µmol/h). This in itself is evidence that a low perfusion rate used by us in no way validates the methods used by others for 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.2 In another study, we have previously reported a lack of correlation between concentrations which show a good correlation between infused and recovered bicarbonate in our perfusion system.3

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.4 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.5 In a steady state perfusion system with a compound displaying negligible absorption, the concentration of HCO3 observed in our experiments 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 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 carbonic anhydrase inhibitors. The conclusions of our study are therefore as stated.

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5 Rees WDW, Gibbons LC, Warhurst D, Turner J. Studies of bicarbonate secretion in the normal human stomach in vivo: effect of aspirin, sodium taurocholate and prostaglandin E2, In:
Systemic factors and luminal contents in gut adaptation

Why do patients with ulcerative colitis relapse?

Stir—When dedicated research workers spend much effort employing methodology bound to fail in its objective it is always regrettable. In this instance I refer to reliance on self reported answers by ulcerative colitis sufferers to questionnaires about their emotional feelings and allegedly stressful life events reported in the article by Riley et al (Gut 1990; 31: 179–83).

Given the degree of unanimity of view expressed by critics of the above methods, and of the comparable futility of dependence on only one or two interviews to uncover emotional factors in inflammatory bowel disease, it is surprising that the authors of the article did not discuss these criticisms, or even refer to them.

It is now 40 years since I commented on these emotional aspects in a large series: 'Colitis patients may be ready talkers about their symptoms but they are “dumb” about their emotional feelings.' Suggestions were then offered on how they could be helped to do so. McMahon et al., in criticising the insensitivities of studies by Feldman et al and Mendoloff et al., wrote that 'they view psychotherapy largely in symptomatic terms, and rely heavily on patients’ self-reports,' and added that 'patients with inflammatory bowel disease are notoriously poor reporters of their inner psychic life. (Ref. to Mendoloff’s work)' who wrote that 'it is not surprising that ulcerative colitis patients [referring to Mendoloff’s study] report fewer stressful life events in their lives' and 'the patients’ extensive use of denial suggests that they are often unaware of the stress at a conscious level.' Ford and coworkers, writing of comparable experience of regional enteritis, said that ‘it should not be surprising if patients with a degree of rigidity, repression and guardedness noted in our study were to answer negatively to direct questions about emotional stress' and ‘before these very guarded patients can allow themselves to talk freely a relationship must be established.' Summarising the serious limitations of inventories and questionnaires in the investigation of all psychosomatic disorders, Pelsel and I have said: 'It is inevitable that questionnaires/inventory techniques simply fail to uncover deeply repressed and unconscious feelings in patients whose very disability centres on their poverty of emotional expression.'

In an attempt to be constructive I would respectfully suggest that the answer to Riley et al.’s question is open to any clinician who is prepared to acquire the sensitive interviewing techniques needed to uncover the typically provocative emotional states that these guarded patients, and to recognise that the process is likely to entail interviews over many weeks.

Reply

Stir—Dr Paulley criticises our use of self rated questionnaires in patients with ulcerative colitis as he believes that colitis ‘centres on a poverty of emotional expression.’ Dr Paulley and others’ have for many years championed the psychosomatic model of ulcerative colitis. Their observations are extensive but, as all are uncontrolled, we would respectfully suggest that they are of limited value. Controlled studies have consistently failed to show an excess of psychiatric illness or stressful life events in patients with colitis.

The rating scales we have used have been well validated in both healthy subjects and patients with psychiatric illness. There is no objective evidence to suggest that patients with colitis have difficulty expressing their feelings through such scales.

In our experience most patients with ulcerative colitis will openly discuss psychological factors and, despite our negative findings, many believe that stressful life events precipitate relapse. However, remission, by both patient and doctor, is particularly common at times of disease relapse. Appropriately controlled studies are, therefore, essential if such biases are to be overcome.

In order to investigate events that may precipitate colitis relapse we studied a cohort of patients in established ulcerative colitis. Patients were assessed at 12 weekly intervals and were followed up to either relapse or completion at 48 weeks. The main advantage of such a study is that the patient serves as his or her own control. Using such a design we found that the frequency and severity of life events were equally matched in patients in relapse and remission and that those who relapsed graded life events no more stressful than those who stayed in remission. Anxiety and depression ratings were also similar in the two groups and did not correlate with disease activity.

We did not assess personality characteristics in our patients, although personality differences from controls are often cited to support the role of psychological factors in the patho-