

## LETTERS TO THE EDITOR

### Anomalous short plasma elimination half life in a patient intoxicated with bismuth subcitrate

SIR,—The report by Playford *et al*<sup>1</sup> provides important information. There is only one other report of bismuth intoxication with the use of the subcitrate formulation in humans.<sup>2</sup> This report was marred by the absence of assay data.

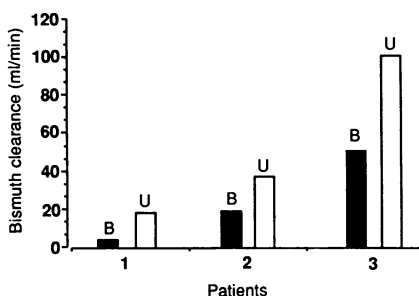
The levels reported by Playford *et al* are well outside the values reported from other studies involving bismuth subcitrate (Table).<sup>3-8</sup> These increased levels are consistent with a doubling of dose and renal impairment, if it is assumed that bismuth clearance reduces proportionally to creatinine clearance. Specifically, if upper steady-state limits of 58 µg/l are assumed in patients with normal renal clearance (≈120 ml/min) (see Table),<sup>6</sup> and a creatinine clearance of 15 ml/min in the patient is assumed (case report value), then upper limits of 480 µg/l could be predicted. If daily doses were doubled, then values of 960 µg/l would be predicted, in close accord with the case report values of 880 µg/l.<sup>1</sup>

There is, however, an anomaly related to estimated half life of elimination in plasma in this patient. We derive a value of 13–15 days from the published figure using terminal phase data. Previous reports of elimination half life values in both urine and plasma in the normal range of plasma bismuth concentrations<sup>9</sup> and in intoxicated patients<sup>10</sup> give values of 18–20 days. If renal elimination alone determines elimination half life, then a longer half life should have resulted with prolongation proportional to renal clearance change.

There is evidence in both animals and humans for excretion of bismuth into gut via bile on acute dosing.<sup>11,12</sup> Such a mechanism of parallel, extrarenal elimination would need to be invoked to allow preservation of a short half life as reported. The apparent anomaly of a high level and a short half life can be resolved if altered absorption is proposed together with parallel hepatic and renal clearance. The altered absorption in this patient reported by Playford and coworkers<sup>1</sup> may be explained by upper gastrointestinal surgery with rapid gastric emptying.

Because of direct relevance to this discussion we present preliminary data from three

patients given 430 mg daily of bismuth subcitrate (Denol) for four days after cholecystectomy and placement of a T-tube in the common bile duct. Blood, urinary, and biliary collections were made over six hours after the morning dose on the fifth day. Relative clearances in urine and bile after assay of samples<sup>13</sup> are shown in the Figure.



Biliary (B) and urinary (U) clearances (ml/min) of bismuth in each of three patients (1, 2, and 3). These patients had a biliary T-tube in the common bile duct after cholecystectomy and were given 107.7 mg bismuth in the form of chew colloidal bismuth subcitrate tablets (Denol) four times a day for four days.

Until another class of agents is discovered with equal efficacy<sup>14-17</sup> there will be a need to continue the use of bismuth in type B gastritis and ulcer disease.<sup>18</sup> There is a need to understand the processes of bismuth handling before restriction policies can be made. Caution must be exercised in patients with renal impairment and possibly hepatic impairment. The ready availability of simple assays<sup>13</sup> allows plasma monitoring to be used to optimise safe usage, according to accepted plasma level guidelines.<sup>19</sup>

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### Macrophage activity in inflammatory bowel disease

SIR,—We reply to the letter from Dr Andrew Williams (*Gut* 1990; 31: 481) in which he disagrees with the conclusion in our paper<sup>1</sup> that the majority of macrophages isolated from normal colon and ileum are downregulated. This statement is based on the results presented in the paper and evidence from other studies as quoted in the discussion.

Our study shows that a significantly greater proportion of macrophages isolated from mucosa with active ulcerative colitis and Crohn's disease (and not just Crohn's disease) were able to undergo respiratory burst compared to those isolated from normal mucosa. In the latter, a large proportion did not show evidence of a release of oxygen radicals in response to three different triggers. Despite stimulation with interferon-gamma (perhaps the most potent activator of macrophages), a large proportion of macrophages from normal

### Plasma concentration after chronic treatment with colloidal bismuth subcitrate

Reference	No of subjects	Duration of treatment (weeks)	Formulation	Range of steady-state concentration (µg/l)
Lee (1981)	24	4–6	Liquid	3–35
Hamilton <i>et al</i> (1983)	20	6	Chew tablet (4×1)	5–51
Dekker <i>et al</i> (1986)	76	4	Chew tablet (4×1)	3–34*
	67	4	Swallow (coated) (4×1)	2–21*
Froomes <i>et al</i> (1989)	12	6–8	Chew tablet (4×1)	8–58
Gavey <i>et al</i> (1989)	9	6	Swallow (coated) (2×2)	4–38
Nwokolo <i>et al</i> (1989)	6	4–18	Swallow (coated) (2×2)	2–12

\* Represents peak blood concentration rather than steady-state concentration.

mucosa were not able to undergo respiratory burst. We suggest therefore that these cells which are unresponsive to interferon-gamma are 'desensitised' or downregulated. It is possible that the small proportion of macrophages from normal mucosa that are able to release oxygen radicals may enhance their production of these reactive metabolites after stimulation with interferon-gamma. However, this still leaves a large proportion that did not show evidence of being able to undergo respiratory burst after stimulation.

Our other studies have also shown that the macrophages from normal colonic mucosa are also not able to express interleukin-2 receptors despite stimulation by interferon-gamma. In contrast, significant proportions of macrophages from mucosa with active inflammatory bowel disease expressed these receptors.<sup>2</sup> That these latter cells are activated was shown by their capacity to release oxygen radicals. Macrophages isolated from mucosa with active inflammatory bowel disease also produce more interleukin-1 $\beta$  (IL-1 $\beta$ ) than cells from normal mucosa. Lipopolysaccharide enhanced IL-1 $\beta$  production by cells from inflamed mucosa but not from normal mucosa.<sup>3</sup> Our studies also suggest enhanced antigen presenting capacity by macrophages from mucosa with active inflammatory bowel disease.<sup>4</sup>

We suggest, therefore, that a large proportion of macrophages in normal ileal and colonic mucosa are downregulated in their capacity to perform a number of functions. This downregulation may be required under normal physiological conditions to protect against injury. As we have reported, we suggest that the enhanced functions by macrophages from mucosa with active inflammatory bowel disease – for example, respiratory burst capacity and IL-1 $\beta$  production – are due in large part to the elicited population of cells (most likely circulating monocytes migrating into the mucosa) which are primed or in an enhanced state of activation. In the mucosa these cells may be phenotypically different.<sup>5</sup>

We do not think that prostaglandin E<sub>2</sub> is likely to be important in priming macrophages, as studies have shown that at very low concentrations it can inhibit class II expression.<sup>6,7</sup> Enhanced class II expression is a feature of activated macrophages.<sup>8</sup>

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#### Intragastric acidity and serum gastrin after sufotidine

SIR, — The recent paper by Smith and Pounder (*Gut* 1990; 31: 291–3) shows that the new competitive H<sub>2</sub> receptor antagonist sufotidine, taken in doses of 600 mg bd, induces virtually 24 hour gastric anacidity. Thus its antisecretory effect closely resembles that of the proton pump inhibitor omeprazole.<sup>1</sup>

The study, however, is not without relevant methodological problems.

(1) The gastric circadian acidity pattern is characterised by high frequency real pH fluctuations both in basal conditions and during drug induced events. These changes can be properly described using a scanning rate equal to or lower than one point per minute.<sup>2</sup>

The hourly sampling rate is inappropriate to represent what is happening to gastric acidity in time-dependent measurements<sup>3,4</sup> and the usual acidity indexes calculated from these low frequency acquired pH profiles are almost invariably unreliable.<sup>4</sup>

(2) The trapezoidal rule is a fairly robust way of calculating integrals of functions that are not very smooth, provided that the increment is several times lower than the duration of the shortest fluctuation of the function to be integrated.<sup>5</sup> Since the circadian pH profile shows many rapid real pH fluctuations<sup>2</sup> the one hour step does not allow the use of this numerical integration method.

(3) The experimental data not included in their paper for 1000 and 2000 hours in duodenal ulcer patients, albeit in clinical remission, cannot be replaced with datapoints obtained in normal subjects. More important, acidity measurements pertaining to healthy subjects are unlikely to correspond to those achieved with a very powerful H<sub>2</sub> receptor antagonist, such as sufotidine. Moreover, since the integral of equally spaced series of data reflects the arithmetic mean, this replacement is simply useless.

(4) The authors state that the significance of the difference between the integrated 24 hour values were assessed using Wilcoxon's matched pair signed rank test. Even in an ideal case in which all the after treatment values are lower or higher than the before treatment values, by definition a test of this type cannot provide a probability level lower than 2<sup>-k</sup>, k being the number of couples.<sup>6</sup>

With a sample size of k=7, as that studied by Smith and Pounder, the minimum p value one can obtain is 2<sup>-7</sup>=1/128=0.008. Therefore, the authors could not have found a probability level lower than 0.001. Moreover, since in one of the seven cases the gastrin integral did not increase, it is incorrect to report a p value of less than 0.001.<sup>7</sup>

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#### Reply

SIR, — We reject three out of four of Mela *et al*'s criticisms.

(1) Twenty four hour intragastric acidity can be measured by either aspiration or the use of an intragastric probe. We have used the former method for the last 16 years,<sup>1</sup> and it has certain advantages. It is extremely reproducible,<sup>2</sup> and has produced reliable estimates of the effect of a range of antisecretory drug regimens.<sup>3</sup> The use of a pH probe results in such an avalanche of data that Savarino and Mela have concluded that 'hourly pH values of continuous intraluminal monitoring and those of simultaneous gastric aspiration appeared to be better correlated if the elimination of noise disturbing the in vivo pH-metry curves is obtained.'<sup>4</sup>

(2) The use of the trapezoidal rule is another type of 'smoothing' – certainly the integration of observed values of either acidity or gastrin provides an easily understood measure of individual 24 hour responses.

(3) The samples for 1000 and 2000 hours were not aspirated, because they occurred immediately after a main meal and oral dosing with either sufotidine or placebo. We did not want to remove any active drug from the stomach. We know that intragastric acidity in either patients or healthy subjects is overwhelmed at these times by food buffer (see the similar value for 14 00 hours in the same experiments). The substituted values tend to underestimate the antisecretory effect of sufotidine.

(4) The results of dosing with sufotidine 600 mg bd are so clear that statistical analysis is almost superfluous, although we agree that the p values in Figures 2 and 4 are incorrect, and should be <0.01 and <0.05, respectively.

A wide range of techniques can be used for the mathematical and statistical analysis of 24 hour data. We believe that the advantages of our technique are that it is simple to perform and the mathematical presentation produces a clear result – some statisticians tend to overinterpret 24 hour data.

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