LETTERS TO THE EDITOR

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

Sir,—The report by Playford et al provides important information. There is only one other report of bismuth intoxication with the use of the subcitrate formulation in humans. 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). 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 levels of 58 μg/l are assumed in patients with normal renal clearance (~120 ml/min) (see Table), 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.

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 found in intoxicated patients 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 than found.

There is evidence in both animals and humans for excretion of bismuth into gut via bile on acute dosing. 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 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 are shown in the Figure.

<table>
<thead>
<tr>
<th>Patients</th>
<th>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 mg bismuth in the form of bismuth subcitrate tablets (Denol) four times a day for four days.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Biliary (B)</td>
<td>120</td>
</tr>
<tr>
<td>Urinary (U)</td>
<td>90</td>
</tr>
</tbody>
</table>

Until another class of agents is discovered with equal efficacy, there will be a need to continue the use of bismuth in type B gastritis and ulcer disease. 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 allows plasma monitoring to be used to optimise safe usage, according to accepted plasma level guidelines.

A J McLEAN
S ISLAM
Clinical Pharmacology Department,
Alfred Hospital,
Prakan, Victoria, 3181
Australia

J R LAMBERT
Monash University Department of Medicine


Macroscopic 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 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 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

---

**Reference**

<table>
<thead>
<tr>
<th>Reference</th>
<th>No of subjects</th>
<th>Duration of treatment (days)</th>
<th>Formulation</th>
<th>Range of steady-state concentration (μg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton et al (1983)</td>
<td>20</td>
<td>6</td>
<td>Chew tablet</td>
<td>5–51</td>
</tr>
<tr>
<td>Dekker et al (1986)</td>
<td>76</td>
<td>4</td>
<td>Chew tablet</td>
<td>3–34*</td>
</tr>
<tr>
<td>Froomes et al (1989)</td>
<td>12</td>
<td>6–8</td>
<td>Swallow (coated)</td>
<td>2–21*</td>
</tr>
<tr>
<td>Gavey et al (1989)</td>
<td>6</td>
<td>6</td>
<td>Swallow (coated)</td>
<td>8–58</td>
</tr>
</tbody>
</table>

---

* 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 the chemotactic molecules released 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.

Some 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. 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-10 (IL-10) than cells from normal mucosa. Lipopolysaccharide enhanced IL-10 production by cells from inflamed mucosa but not from normal mucosa. Our studies suggest enhanced antigen presenting capacity by macrophages from mucosa with active inflammatory bowel disease.

We suggest, therefore, that a large proportion of the 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-10 production – are due in large part to the enhanced 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.

We do not think that prostaglandin E, is likely to be important in priming macrophages, as studies have shown that at very low concentrations it can inhibit class II expression. Enhanced antigen presentation is a feature of activated macrophages.

Intragastrectic acidity and serum gastrin after sufotidine

Sir,-The recent paper by Smith and Pounder (Gut 1990; 31: 291–3) shows that the new competitive H2 receptor antagonist sufotidine, taken in doses of 600 mg bi, induces virtually 24 hour gastric acidity. Thus its antiserotonic effect closely resembles that of the proton pump inhibitor omeprazole.

The study, however, is not without relevant methodological and interpretative problems. The hour step sampling rate is inappropriate to represent what is happening to gastric acidity in time-dependent manner. The usual index values calculated from low frequency acquired pH profiles are almost invariably unreliable.

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 shorter than the duration of the shortest fluctuation of the function to be integrated. Since the circadian pH profile shows many rapid pH fluctuations (the one hour step does not allow the use of this numerical integration method)

The experimental data not included in their paper for 1000 and 2000 hours in duodenal ulcer patients, although 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 H2 receptor antagonist, such as sufotidine. Moreover, since the integral of equally spaced series of data reflects the arithmetic mean, this replacement is simply useless.

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 2.7, k being the number of couples.

With a sample size of k>7, as that studied by Smith and Pounder, the minimum p value one can obtain is 2.7/1/128=0.008. Therefore, the authors could not have found a probability level lower than 0.001. Moreover, since in one of these tests the measured integral did not increase, it is incorrect to report a p value of less than 0.001.

G S MELA  
E CAPUTO  
G VILLA  
Istituto Scientifico di Medicina Interna, Cattedra di Clinica Medica R

V SARAVINO  
P ZENTILIN  
Cattedra di Gastroenterologia, Genova, Italy


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 H2 receptor antagonist sufotidine, taken in doses of 600 mg bi, induces virtually 24 hour gastric acidity. Thus its antiserotonic effect closely resembles that of the proton pump inhibitor omeprazole.

The study, however, is not without relevant methodological and interpretative problems. The hour step sampling rate is inappropriate to represent what is happening to gastric acidity in time-dependent manner. The usual index values calculated from low frequency acquired pH profiles are almost invariably unreliable.

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 shorter than the duration of the shortest fluctuation of the function to be integrated. Since the circadian pH profile shows many rapid pH fluctuations the one hour step does not allow the use of this numerical integration method.

The experimental data not included in their paper for 1000 and 2000 hours in duodenal ulcer patients, although 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 H2 receptor antagonist, such as sufotidine. Moreover, since the integral of equally spaced series of data reflects the arithmetic mean, this replacement is simply useless.

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 2.7, k being the number of couples.

With a sample size of k>7, as that studied by Smith and Pounder, the minimum p value one can obtain is 2.7/1/128=0.008. Therefore, the authors could not have found a probability level lower than 0.001. Moreover, since in one of these tests the measured integral did not increase, it is incorrect to report a p value of less than 0.001.

SIR,-The recent paper by Smith and Pounder (Gut 1990; 31: 291–3) shows that the new competitive H2 receptor antagonist sufotidine, taken in doses of 600 mg bi, induces virtually 24 hour gastric acidity. Thus its antiserotonic effect closely resembles that of the proton pump inhibitor omeprazole.

The study, however, is not without relevant methodological and interpretative problems. The hour step sampling rate is inappropriate to represent what is happening to gastric acidity in time-dependent manner. The usual index values calculated from low frequency acquired pH profiles are almost invariably unreliable.

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 shorter than the duration of the shortest fluctuation of the function to be integrated. Since the circadian pH profile shows many rapid pH fluctuations the one hour step does not allow the use of this numerical integration method.

The experimental data not included in their paper for 1000 and 2000 hours in duodenal ulcer patients, although 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 H2 receptor antagonist, such as sufotidine. Moreover, since the integral of equally spaced series of data reflects the arithmetic mean, this replacement is simply useless.

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 2.7, k being the number of couples.

With a sample size of k>7, as that studied by Smith and Pounder, the minimum p value one can obtain is 2.7/1/128=0.008. Therefore, the authors could not have found a probability level lower than 0.001. Moreover, since in one of these tests the measured integral did not increase, it is incorrect to report a p value of less than 0.001.

The study, however, is not without relevant methodological and interpretative problems. The hour step sampling rate is inappropriate to represent what is happening to gastric acidity in time-dependent manner. The usual index values calculated from low frequency acquired pH profiles are almost invariably unreliable.