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

SIR,—The report by Playford et al.1 provides important information. There is only one other report of bismuth intoxication with the use of the subcitrate formulation in humans.2 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).3,4 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 concentrations5,6 tend to intoxicated patients7,8 give values of 18–20 days. If renal elimination alone determines elimination half life, then a longer half life should have resulted with prolongation proportionally to renal clearance.

There is evidence in both animals and humans for excretion of bismuth into gut via bile on acute dosing.9,10 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 coworkers1 is 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 samples1 are shown in the Figure.

Until another class of agents is discovered with equal efficacy,11 there will be a need to continue the use of bismuth in type B gastritis and ulcer disease.12 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 assays13 allows plasma monitoring to be used to optimize safe usage, according to accepted plasma level guidelines.14

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

R.J. LAMBERT
Monash University Department of Medicine

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 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

Table

<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>Lee 1981</td>
<td>24</td>
<td>4–6</td>
<td>Liquid</td>
<td>3–35</td>
</tr>
<tr>
<td>Hamilton et al. 1983</td>
<td>20</td>
<td>6</td>
<td>Chew tablet (4x1)</td>
<td>5–51</td>
</tr>
<tr>
<td>Dekker et al. 1986</td>
<td>76</td>
<td>4</td>
<td>Chew tablet (4x1)</td>
<td>3–34*</td>
</tr>
<tr>
<td>Froomes et al. 1989</td>
<td>12</td>
<td>6–8</td>
<td>Swallow coated (4x1)</td>
<td>2–21*</td>
</tr>
<tr>
<td>Gavey et al. 1989</td>
<td>9</td>
<td>6</td>
<td>Chew tablet (4x1)</td>
<td>8–58</td>
</tr>
<tr>
<td>Nwokolo et al. 1989</td>
<td>6</td>
<td>4–18</td>
<td>Swallow coated (2x2)</td>
<td>4–38</td>
</tr>
</tbody>
</table>

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


Plasma concentration after chronic treatment with colloidal bismuth subcitrate

<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>Lee 1981</td>
<td>24</td>
<td>4–6</td>
<td>Liquid</td>
<td>3–35</td>
</tr>
<tr>
<td>Hamilton et al. 1983</td>
<td>20</td>
<td>6</td>
<td>Chew tablet (4x1)</td>
<td>5–51</td>
</tr>
<tr>
<td>Dekker et al. 1986</td>
<td>76</td>
<td>4</td>
<td>Chew tablet (4x1)</td>
<td>3–34*</td>
</tr>
<tr>
<td>Froomes et al. 1989</td>
<td>12</td>
<td>6–8</td>
<td>Swallow coated (4x1)</td>
<td>2–21*</td>
</tr>
<tr>
<td>Gavey et al. 1989</td>
<td>9</td>
<td>6</td>
<td>Chew tablet (4x1)</td>
<td>8–58</td>
</tr>
<tr>
<td>Nwokolo et al. 1989</td>
<td>6</td>
<td>4–18</td>
<td>Swallow coated (2x2)</td>
<td>4–38</td>
</tr>
</tbody>
</table>

* Represents peak blood concentration rather than steady-state concentration.
Anomalous short plasma elimination half life in a patient intoxicated with bismuth subcitrate.

A J McLean, S Islam and J R Lambert

Gut 1990 31: 1086
doi: 10.1136/gut.31.9.1086

Updated information and services can be found at:
http://gut.bmj.com/content/31/9/1086.1.citation

Email alerting service

These include:
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/