D-penicillamine does not increase urinary bismuth excretion in patients treated with tripotassium dicitrato bismuthate

C. U. NWOKOLO & R. E. POUNDER
Academic Department of Medicine, Royal Free Hospital School of Medicine, Pond Street, London NW3 2QG

Twenty-four urinary bismuth excretion was measured in five patients who had been treated with tripotassium dicitrato bismuthate, before and after single 1 g oral dose of D-penicillamine. Before dosing with D-penicillamine, the median 24 h urinary bismuth output was 55 μg 24 h⁻¹ (range 17-156 μg 24 h⁻¹) and following dosing with D-penicillamine the median 24 h urinary bismuth output was 53 μg 24 h⁻¹ (range 12-156 μg 24 h⁻¹). D-penicillamine does not facilitate the urinary excretion of bismuth, hence it is unsuitable for use as an oral chelator in patients with bismuth intoxication.

Keywords bismuth intoxication tripotassium dicitrato bismuthate D-penicillamine

Introduction

Between 1972 and 1979 an epidemic of bismuth toxicity occurred simultaneously in France and Australia (Buge et al., 1978; Burns et al., 1974; Hillemand et al., 1977; Morrow, 1973), but a few bismuth-containing compounds have continued in clinical use. In the United Kingdom these compounds include tripotassium dicitrato bismuthate (De-Nol), bismuth salicylate (Pepto-Bismol), and bismuth subnitrate (Roter tablets). We have observed significant systemic absorption and apparent sequestration of bismuth following dosing with tripotassium dicitrato bismuthate, but not with bismuth salicylate or subnitrate (Gavey et al., 1989; Nwokolo et al., 1989, 1990a,b).

Three recent case reports have described possible neurotoxicity associated with inappropriate ingestion of tripotassium dicitrato bismuthate (Hudson & Mowat, 1989; Playford et al., 1990; Weller, 1988). The aim of this study was to determine whether oral D-penicillamine increases urinary bismuth excretion in patients who had been treated with tripotassium dicitrato bismuthate.

Methods

Five patients were identified from the outpatient Gastroenterology Clinic at the Royal Free Hospital, who had been treated with tripotassium dicitrato bismuthate. The patients had received treatment with four tablets per day of De-Nol for a median of 8 weeks (range 4–20 weeks), and had received their last dose of treatment with tripotassium dicitrato bismuthate a median of 4 weeks prior to entering the study (range 4–8 weeks). All had normal hepato-renal function. Their median age was 61 years (range 45–69 years) and their median weight was 64 kg (range 48–75 kg). All the patients provided written consent prior to entry to the study, which was approved by the Ethics Committee of the Royal Free Hospital.

Each patient made a 24 h collection of urine, which was brought to the hospital on the day of dosing with D-penicillamine. Each patient swallowed D-penicillamine 1 g, washed down with 100 ml of water, under the supervision of an investigator (CUN). The second 24 h urine collection was commenced immediately, and it was returned to the research laboratory the next day.

Urine volumes were measured, and 10 ml aliquots of urine were stored at −20°C for later bismuth analysis. The urinary bismuth concentration was analysed by atomic absorption spectrophotometry, by Rooney Laboratories (Basingstoke, UK), who were blind to the design of the study (Rooney, 1976).

Correspondence: Dr R. E. Pounder, Academic Department of Medicine, Royal Free Hospital School of Medicine, Pond Street, London NW3 2QG
Table 1 Twenty-four hour urinary bismuth excretion in five patients (pre- and post-dosing with D-penicillamine 1 g, who had completed courses of treatment with tripotassium dicitrato bismuthate

<table>
<thead>
<tr>
<th>Patient number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tripotassium dicitrato bismuthate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total course (weeks)</td>
<td>8</td>
<td>20</td>
<td>14</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Last dose (weeks)</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>24 h urine collection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2200</td>
<td>1120</td>
<td>2260</td>
<td>1460</td>
<td>1520</td>
</tr>
<tr>
<td>Post</td>
<td>2500</td>
<td>1420</td>
<td>1510</td>
<td>1100</td>
<td>2960</td>
</tr>
<tr>
<td>Bismuth excretion (µg 24 h⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>55</td>
<td>157</td>
<td>72</td>
<td>18</td>
<td>53</td>
</tr>
<tr>
<td>Post</td>
<td>90</td>
<td>156</td>
<td>50</td>
<td>12</td>
<td>65</td>
</tr>
</tbody>
</table>

Results

The study was well-tolerated, and the patients reported no adverse events.

Table 1 shows the urinary volume and 24 h urinary bismuth excretion before and after dosing with oral D-penicillamine. The median 24 h urinary excretion before dosing with D-penicillamine was 55 µg 24 h⁻¹ (range 17–156 µg 24 h⁻¹), and 24 h immediately after dosing with oral D-penicillamine the median urinary excretion was 53 µg 24 h⁻¹ (range 12–156 µg 24 h⁻¹). The difference is non-significant.

Discussion

Bismuth is a trace metal, and earlier experiments performed at the Royal Free Hospital reported that before treatment with tripotassium dicitrato bismuthate the median urinary bismuth excretion of nine dyspeptics was 2.9 µg 24 h⁻¹ (Gavey et al., 1989); median bismuth excretion had risen to 1012.2 µg 24 h⁻¹ at the end of 6 weeks treatment with De-Nol two tablets twice daily. After cessation of dosing the urinary bismuth excretion declined rapidly, but 3 months after cessation of treatment the median urinary bismuth output was still significantly elevated at 9.5 µg 24 h⁻¹.

In the present study, the patients were investigated 4–8 weeks after cessation of treatment with tripotassium dicitrato bismuthate, and all the subjects showed evidence of loading with bismuth, with a urinary bismuth excretion ranging from 17–156 µg 24 h⁻¹. A single large dose of D-penicillamine did not influence urinary bismuth excretion, suggesting that this compound will not act as a clinically-useful chelator of bismuth.

It has been reported that D-penicillamine decreases the mortality in mice receiving a lethal dose of bismuth (Basinger et al., 1983). There is a report of the use of D-penicillamine in a patient with AIDS, who developed acute neurological symptoms following the treatment of his diarrhoea with extremely large doses of bismuth salicylate (Mendelowitz et al., 1990); the patient died too soon for D-penicillamine’s value to be assessed. It has been suggested that dimercaprol increased the renal clearance of bismuth 60-fold in a single patient (Nogue et al., 1985), and clinical improvement has been described in two patients who received treatment with dimercaprol for bismuth toxicity (Molina et al., 1989). However, another report described no change in urinary bismuth excretion following treatment with a single bismuth-intoxicated patient with dimercaprol (Goule et al., 1975). The heavy metal chelator 2-3 dimercapto-1-propane sulfonic acid was given by mouth for 10 days to a patient in chronic renal failure, with bismuth-induced encephalopathy caused by inappropriate treatment with tripotassium dicitrato bismuthate (Playford et al., 1990; Vasken-Aposhian, 1983); renal clearance of bismuth increased from 0.24 ml min⁻¹ before introduction of the chelator to 2.4 ml min⁻¹ during treatment with a chelator.

Bismuth has been a traditional treatment for peptic ulceration (Brinton, 1855), but its popularity has increased due the recent discovery and recognition of Helicobacter pylori (Dooley & Cohen, 1988; Graham, 1989; Marshall et al., 1988). The eradication of Helicobacter pylori may be associated with prolonged duodenal ulcer remission, and eradication of the organism...
is usually achieved using the combination of a bismuth-containing compound with one or more antibiotics (Rauws, 1989; Rauws et al., 1988). Accidental or deliberate overdosage with bismuth can be associated with significant toxicity (Rauws, 1989; Winship, 1983) and there is a need for an effective oral chelator. The results of this present study indicate that D-penicillamine does not appear to facilitate the excretion of bismuth in man.

This manuscript was prepared by Miss Doris Elliott.

References


(Received 19 March 1990, accepted 11 June 1990)