

## CASE REPORTS

## Bismuth induced encephalopathy caused by tri potassium dicitrato bismuthate in a patient with chronic renal failure

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### Abstract

A 68 year old man with a creatinine clearance rate of only 15 ml/min took twice the recommended dose of tripotassium dicitrato bismuthate (TDB) as DeNol™ liquid; 10 ml qds; a total of 864 mg bismuth daily for two months. Whole blood bismuth concentrations rose to 880 µg/l and he developed global cerebral dysfunction with hallucinations, ataxia, and an abnormal EEG. Renal clearance of bismuth rose from 0.24 to 2.4 ml/min when the heavy metal chelator 2-3 dimercapto-1 propane sulphonic acid (DMPS) was given by mouth. Bismuth was measured by a novel method involving inductively coupled plasma source mass spectrometry. Fifty days after stopping TDB, whole blood bismuth concentrations fell to 46 µg/l and the patient's EEG returned to normal. His mental function also recovered completely. The case serves as a timely reminder that TDB should not be administered to patients with renal disorders, as stated in the data sheet.

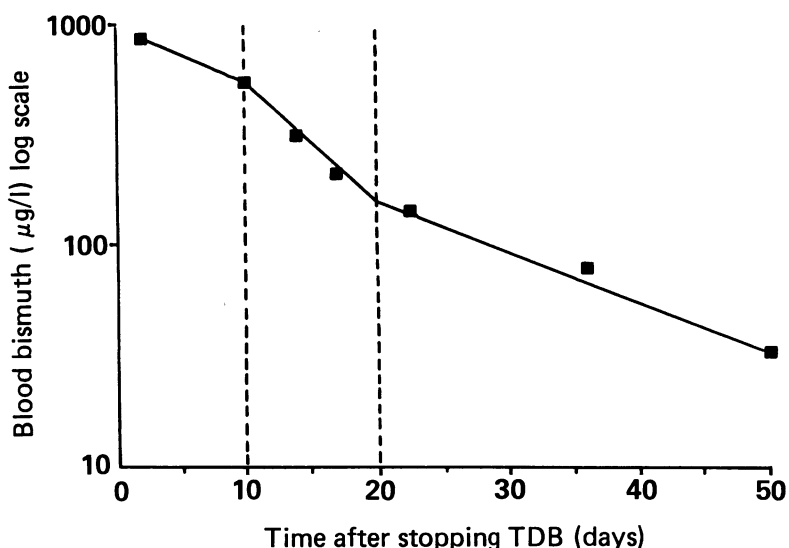
### Case report

A 68 year old man presented with progressive confusion and difficulty walking over two weeks. He had a history of splenectomy for hereditary

spherocytosis, maturity onset diabetes, hypertension, ischaemic heart disease and chronic renal impairment with a creatinine clearance rate of 15 ml/min for the past two years. For 10 years he had suffered repeated upper gastrointestinal bleeding. This had continued despite subtotal gastrectomy the year before. Before admission, gastritis was diagnosed and sucralfate; 1 g qds and TDB as DeNol™ liquid; 5 ml qds prescribed. The patient actually took sucralfate 1 g qds, but 10 ml DeNol™ qds. He therefore ingested 864 mg bismuth per day which is twice the recommended dose. He had continued this dose for an uninterrupted period of two months. At the same time he was taking frusemide, enalapril, glibenclamide, ferrous sulphate, and vitamin B<sub>12</sub>.

On examination he was alert, but there was evidence of global cerebral dysfunction, including disinhibited behaviour, urinary incontinence, bilateral grasp reflexes, visual hallucinations, and ataxia. There were no focal neurological signs, however, and no other abnormal physical findings.

There was no evidence of gastrointestinal bleeding, infection, or myocardial infarction, and no change in his diabetic control or renal or hepatic function to account for the change in his cerebral function. A cranial computed tomography scan showed no focal lesion, but an EEG showed loss of alpha rhythm and diffuse slow waves consistent with a metabolic encephalopathy. Serum calcium, aluminium, magnesium, B<sub>12</sub>, and folate concentrations were all normal. The plasma urea concentration was 15.8 mmol/l (normal range 2.5-7.5 mmol/l), and the plasma creatinine concentration was 179 µmol/l (normally 50-110 µmol/l) in keeping with his chronic renal impairment. A clinical diagnosis of bismuth-induced encephalopathy was made and treatment with TDB was discontinued. The whole blood bismuth concentration was subsequently found to be 880 µg/l. Urinary concentration at the same time was 230 µg/l. The patient was then given 100 mg tds of the heavy metal chelator 2-3 dimercapto-1-propane sulphonic acid (DMPS) by mouth for 10 days. Renal clearance of bismuth increased from 0.24 ml/min before introduction of DMPS to 2.4 ml/min during treatment with the chelator. Over the next 50 days whole blood bismuth concentrations fell (Figure) and there was a marked improvement in his cerebral function. The



Whole blood bismuth concentrations during the patient's admission. Tri-potassium dicitrato bismuthate (TDB) was discontinued on day 0. The dashed lines indicate the beginning and end of treatment with the chelator 2-3 dimercapto-1-propane sulphonic acid (DMPS).

patient's EEG was normal six weeks after admission. He was discharged home seven weeks after admission and remains well four months later. All the signs of cerebral dysfunction described above disappeared.

#### BISMUTH ESTIMATION

Bismuth concentrations were measured by the method of inductively coupled plasma source spectrometry (ICP-MS). This is a new, extremely sensitive analytical technique in which sample solutions are nebulised into a high temperature (10 000 K) argon plasma to produce analyte ions which are extracted into a quadrupole mass spectrometer for separation and measurement. Almost all elements of clinical and biochemical significance can be measured at picomolar and nanomolar concentrations using only 100–200  $\mu$ l volumes of blood, serum, or urine.<sup>1</sup> The accuracy and precision of the data are within  $\pm 3\%$  of the reported values.

#### Discussion

Bismuth induced encephalopathy was first described in 1973, in an Australian who took bismuth subgallate as an ileostomy deodorant.<sup>2</sup> Nearly a thousand cases occurred in France over the next five years in patients taking various bismuth salts.<sup>3</sup> This led to the withdrawal of bismuth salts from several countries. Victims had usually taken high doses for long periods; typically 1.5–20 g bismuth per day for three months–20 years. Clinical features included confusion, ataxia, and often myoclonus. Median concentrations of bismuth were 800  $\mu$ g/l in serum and 16  $\mu$ g/l in cerebrospinal fluid. When bismuth was withdrawn, most patients recovered as blood bismuth concentrations fell.

Prescription of TDB has increased recently because it produces longer remissions of duodenal ulcer disease than a course of H<sub>2</sub> blockers.<sup>4</sup> This may be because TDB suppresses the growth of *Helicobacter pylori*,<sup>5</sup> or because bismuth remains in the body for at least 12 weeks after a course of TDB.<sup>6</sup>

Tripotassium dicitrato bismuthate was licenced in the UK in 1971 for the treatment of peptic ulceration. The recommended dose contains 0.432 g bismuth per day. Treatment is

taken for 28 days followed by a further 28 days if necessary. Maintenance is not indicated but a course may be repeated after an interval of one month. It has been generally recommended that treatment should be stopped if plasma bismuth concentrations are above 100  $\mu$ g/l. Nwokolo *et al* have pointed out, however, that peak plasma concentrations are frequently greater than 100  $\mu$ g/l in normal individuals on TDB, and suggest that trough levels should be measured.<sup>7</sup> Our patient took twice the usual dose for two months and showed failure to concentrate bismuth in the urine in the face of high blood levels. He ingested a total of about 48 g of bismuth.

Weller recently described a patient who took the recommended dose of TDB, but for a prolonged period of two years, and developed depression and paraesthesia. Symptoms resolved on stopping treatment.<sup>8</sup> Bismuth levels, however, were not measured.

2-3 Dimercapto-1-propane sulphonic acid (DMPS) has been used effectively to chelate various heavy metals, and is a safe, orally active drug.<sup>9</sup> Its use has not previously been described in bismuth intoxication. The tenfold increase in urinary clearance of bismuth without side effects leads us to recommend its use in bismuth toxicity.

The use of TDB is increasing at present and this case is a timely reminder that TDB is contraindicated in renal failure.

We would like to thank Miss Famida Nadiadi for typing the manuscript.

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