LESSON OF THE MONTH

Acute arsenic poisoning: absence of polyneuropathy after treatment with 2,3-dimercaptopropanesulphonate (DMPS)

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Abstract

Two men aged 19 and 21 years ingested 1 g and 4 g respectively from 3 kg of a white crystalline powder that they thought was a substance of abuse. It was later identified as almost pure arsenic trioxide. Both had nausea and vomiting and one developed acute renal failure. Each was treated with 2,3-dimercaptopropanesulphonate (DMPS), and made a full recovery with no evidence of prolonged renal or neurological impairment. The DMPS-arsenic complex is probably associated with lower penetration into the CNS and as a consequence treatment with DMPS may result in lower acute and chronic neurotoxicity than treatment with the currently standard recommended chelating agent dimercaprol (British Anti-Lewisite; BAL).

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Arsenic is used in the manufacture of pesticides and rodenticides with agricultural products accounting for about 80% of its use.¹ Other applications include glass manufacture, and use in pigments, paints, and alloy manufacture. Many arsenic salts are colourless and odourless, and it has a reputation as a homicidal poison. A review by Hutton *et al*² of 17 cases of arsenic poisoning indicated accidental exposure in seven subjects, suicidal intent in a further seven, and homicide in only two, with malingering in a single subject. Other sources of exposure to arsenic are ethnic remedies³ and water supplies.⁴ Acute arsenic exposure seems to be fatal in most cases,⁵⁻⁹ the toxic dose being in the range 120 to 200 mg.¹⁰ There are, however, some cases in whom early diagnosis was made and aggressive treatment instituted with resulting survival. For example, Fesmire *et al*¹¹ reported a 30 year old man who ingested 2.15 g of metallic arsenic contained in 6 ounces of "Blue Ball" rat killer. Resuscitation was started within two hours of exposure followed within six hours by haemodialysis and 250 mg dimercaprol (BAL) given intramuscularly every four hours. After a protracted clinical course the patient was discharged with severe

neurological deficits that resulted in him being wheelchair bound. In a similar report by Fincher and Koerker¹² of a 20 year old man who had ingested 1 g of sodium arsenite, treatment was started with 5mg/kg BAL every six hours for six doses followed by D-penicillamine (24 mg/kg orally every six hours for 10 days). This patient showed limited long term recovery over the next two years with persistent peripheral neuropathy and encephalopathy. In two cases described by Bollinger *et al*¹³ diagnosis was delayed for eight days after which both patients were treated four hourly with 3 mg/kg BAL. Both developed an arsenical induced polyneuropathy that was not diminished by treatment with BAL.

Jenkins¹⁴ reviewed 57 cases of exposure to inorganic arsenic in North Carolina between 1952 and 1964. A total of 37 patients developed peripheral neuropathy, usually within seven to 14 days of exposure. Although Jenkins stresses the difficulty in assessing the retrospective risk of neuropathy after acute arsenic exposure, he concludes, based on his 57 patients and on other case reports of suicidal ingestion, that adults rarely if ever escape neurological complications when arsenic ingestion results in a "severe gastrointestinal illness".

2,3-Dimercaptopropanesulphonate (DMPS), a water soluble derivative of dimercaprol developed in the Soviet Union in 1956 by Petrunkin¹⁵ has gradually been introduced into clinical practice in the United States and western Europe over the past 10-15 years.¹⁶ Experience is still limited and our report apparently represents the first documented clinical usage of DMPS in acute arsenic poisoning to be published in the English language.

Case report

Two brothers aged 21 and 19 years with a history of substance misuse discovered a 3 kg container of white crystalline powder on parkland. It had the appearance to them of cocaine. They attempted to ascertain the powder's psychoactive properties by carefully weighing 4 g and 1 g on an accurate scales. The older brother ingested the 4 g and the younger brother the 1 g, after which they

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Whole blood arsenic concentrations and urinary arsenic/creatinine ratio for patients 1 and 2.

went out for a curry meal. After about three hours they returned home and both experienced severe upper abdominal pain, profuse watery diarrhoea, and vomiting, which they attributed to food poisoning. Both remained unwell and six hours after ingestion of the powder they presented to their local accident and emergency department where both were admitted. The 21 year old (patient 1) had a plasma creatinine of 167 $\mu\text{mol/l}$ on admission and when reviewed the next morning was found to be hypotensive at 90/50 mm Hg with a creatinine concentration of 280 $\mu\text{mol/l}$ and a urine output of less than 30 ml/h. A renal opinion was sought and the patient was transferred to the regional renal unit on inotropic support where he was noted, 26 hours after ingestion, to be alert and orientated with a pulse rate of 80 beats/min, blood pressure of 80/50 mm Hg, and central venous filling of 10 cm H_2O . The remainder of the physical examination including a full neurological assessment was normal. A further blood chemistry analysis 24 hours after ingestion gave a creatinine concentration of 450 $\mu\text{mol/l}$ and creatinine kinase activity of 1200 U/l. Other investigations including haemoglobin, full blood count, clotting studies, urinalysis, ECG, and chest radiograph were normal except for a dipstick test of urine which showed blood (+) and protein (+). On review of the clinical findings of acute renal failure, hypotension, and severe diarrhoea, a likely diagnosis of heavy metal poisoning was assumed, most probably either arsenic or mercury. An emergency analysis of the powder gave an arsenic concentration of 730 mg/g, a mercury concentration of 0 mg/g, and an antimony concentration of 3.5 mg/g (arsenic purity about 96.2%; analysis performed by atomic absorption spectroscopy). Blood samples taken 26 hours after ingestion gave an arsenic concentration of 400 $\mu\text{g/l}$ (toxic >50 $\mu\text{g/l}$) and a mercury concentration of 1 $\mu\text{g/l}$ (toxic >50 $\mu\text{g/l}$). Treatment with intravenous DMPS was urgently instituted 32 hours after ingestion in a dosage regimen of 5 mg/kg every four hours. Just before treatment he developed increasing shortness of breath

with falling oxygen saturations. Intubation and ventilation were followed by an asystolic cardiac arrest from which he was successfully resuscitated. Overnight he was haemodynamically stable with satisfactory oxygenation and by 44 hours after ingestion inotropic support was withdrawn with the blood pressure being maintained at 110/70 mm Hg. Urine output by this time was 300 ml/h with a plasma creatinine concentration of 300 $\mu\text{mol/l}$. Two and a half days after ingestion he was extubated and at seven days EMG and peripheral nerve conduction studies were normal except for a previous L5 root problem. No clinical or electrophysiological signs of arsenic induced neuropathy were seen. By this time the plasma creatinine was 84 $\mu\text{g/l}$ and as the patient's diarrhoea had resolved he was transferred to oral DMPS (400 mg every four hours). This was continued for the next seven days and the patient was discharged on day 13 after ingestion. Follow up four weeks later showed normal renal function with no evidence of any neurological dysfunction. The younger patient (patient 2) who had ingested 1 g of the powder had a predictably less problematic clinical course. He was admitted with persistent vomiting and associated colicky abdominal pain and profuse mucous diarrhoea. Blood pressure on admission and subsequently was 130/70 mm Hg. Neurological examination was normal. The plasma creatinine concentration of 167 $\mu\text{mol/l}$ on admission fell to 66 $\mu\text{mol/l}$ within 24 hours and his blood arsenic concentration 36 hours after ingestion was 98 $\mu\text{g/l}$. Treatment with intravenous DMPS was initiated 48 hours after ingestion at 5 mg/kg every four hours intravenously for 24 hours with transfer to oral 400 mg DMPS every four hours for a further five days. There was no evidence of any neurological dysfunction on follow up either clinically or on electrophysiological examination.

Discussion

Both these patients had ingested a potentially lethal dose of arsenic, yet having started on DMPS within about 32 hours of ingestion (patient 1) and 48 hours (patient 2) neither patient died and there was no clinically apparent morbidity after the acute illness. These cases raise one of the unanswered questions in metal chelation treatment¹⁷—namely, whether the conventionally recommended treatment with BAL is able to avert peripheral neuropathy after arsenic intoxication. BAL is known to be lipophilic and is normally given by intramuscular injection with vegetable oil as a base. On the other hand, DMPS is water soluble. Lipid soluble agents achieve greater penetration of the central and peripheral nervous tissue provided that there is no associated carrier mediated transport¹⁸ so that treatment with a lipid soluble agent might paradoxically worsen potential neurological insult. Experimental work by Schäfer *et al* on white male mice exposed to arsenic trioxide at 8.4 mg/kg and treated with BAL in oil or BAL in saline had significantly

increased penetration of the percentage of the total arsenic dose/organ compared with controls and even greater penetration compared with DMPS treatment which was less than the control levels, indicating a preferential redistribution of arsenic by BAL into the neuraxis. This interpretation is consistent with the reported neurological morbidity in cases surviving arsenic intoxication and treated with intramuscular BAL; features that are in complete contrast with the present cases. A similar exacerbation of the neurological deficit has been observed in thallium toxicity treated with dithiocarb.²⁰ Experimental data obtained by one of us (IMH) shows that partitioning²¹ of some metal ions into the lipid phase is enhanced by the use of chelating agents, most dramatically in the case of antimony and dithiocarb. The oil phase partition of the BAL-arsenic complex was also found to be significant, supporting the data of Schäfer *et al*⁹ of an enhanced CNS penetration whereas the arsenic—DMPS complex was totally confined to the water phase. Schäfer *et al* also found the penetration of inorganic arsenic trioxide into mouse brain to be low over an eight hour experimental period and not significantly dissimilar from the CNS distribution obtained after treatment with DMPS. Such experimental evidence together with the accumulated clinical experience of the poor neurological outcome in arsenic cases treated with BAL should put a question mark over its value in this clinical context. The water soluble chelators have a further advantage in that they will maintain the metal-chelator complex in the compartment from which it can be eliminated by the kidneys. Further experience with DMPS in the treatment of heavy metal intoxication is undoubtedly required, but the results obtained for our patients should encourage further use and assessment of DMPS in acute arsenic poisoning.

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