Management of Dapsone Poisoning Complicated by Methaemoglobinaemia

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Summary

The currently recommended dosage regimen for methylene blue (intermittent bolus dose) in the treatment of methaemoglobinaemia caused by dapsone is often inadequate. This is due to the long half-life of dapsone which provides a continuing oxidative stress that can cause a recurrence of clinically significant methaemoglobinaemia. Methylene blue infusion is effective, as demonstrated in an illustrative case report, and should be supported by repeated doses of activated charcoal to enhance dapsone elimination. The principles of treatment of methaemoglobinaemia due to dapsone can be applied to methaemoglobinaemia due to any agent producing prolonged oxidative stress.

Clinical experience of the use of dapsone (4,4'-diaminodiphenylsulphone, DDS) spans 40 years, and involves a variety of conditions including leprosy, malarial prophylaxis and a number of dermatological conditions. In therapeutic use and in overdose it can cause methaemoglobinaemia and haemolytic anaemia. In 1 Indian hospital dapsone accounted for 61 paediatric admissions in 1 year, 9.8% of all accidental poisonings (Nair & Philip 1984). The pharmacokinetics of dapsone in overdose and the mechanisms of toxicity have been defined previously but consensus regarding the most appropriate treatment regimen for dapsone-induced methaemoglobinaemia with methylene blue has not been reached (Hall et al. 1986; Jaeger et al. 1987). We report a patient in whom methaemoglobinaemia was maintained at a low level (<10%) only by continuous infusion of methylene blue (tetramethylthionine chloride), and the merits of this form of treatment and its indications for use are presented.

Case Report

A 24-year-old man was admitted to hospital in January 1988, 36 hours after ingesting 8g of dapsone and 1.25g of diphenhydramine. On arrival the patient complained of dizziness and headache which had been present for 24 hours. He was noted to be centrally and peripherally cyanosed without evidence of anticholinergic activity. The patient's blood was noted to be 'chocolate brown'. Arterial blood gases [pCO₂ 38mm Hg (5 kPa); pO₂ 164mm Hg (21.8 kPa); pH 7.46 on 4 L/min intranasal oxygen] and full blood count were normal, with haemoglobin 14.2 g/dl. Haptoglobin, bilirubin and hepatic enzymes were normal apart from a mild elevation of lactate dehydrogenase (LDH) [308 U/L; normal < 250 U/L]. Spectroscopic examination of blood for methaemoglobin and sulphaemoglobin was performed using the methods described by Dacie and Lewis (1984).
Methaemoglobinaemia (40.8%) was confirmed, as was sulphhemoglobinaemia (11.9%).

Treatment began with repeated doses of activated charcoal (30g in 100ml of 20% mannitol, 6-hourly). Following an intravenous dose of 100mg methylene blue infused over 15 minutes there was a reduction in the clinical severity of cyanosis with a corresponding reduction in methaemoglobinaemia to 10% within 2 hours of injection. That night, nursing staff reported that the patient appeared to be hallucinating. The following day the patient was noted to be more cyanosed and complained of headache. He appeared agitated and stated that the nursing staff had been conspiring against him. Blood was taken for methaemoglobin concentration and the patient was given a further dose of methylene blue (100mg). His agitation settled, the pretreatment methaemoglobin concentration was later reported to be 34%, which decreased to 14.4% after treatment. A continuous infusion of methylene blue was then started (50mg methylene blue in 1000ml normal saline), the dose being titrated to keep the level of methaemoglobin below 10%. The required dose varied from 7.5 to 10 mg/h. The infusion was continued for 43 hours, and 4 hours after it ceased there was no significant increase in methaemoglobin (fig. 1).

Three days after the ingestion, the reticulocyte count increased to 3.8%. This was associated with a blood film consistent with a Heinz body haemolytic anaemia, a fall in haptoglobins and a rise in bilirubin (peak level of 50 µmol/L on day 6; normal < 19 µmol/L) with a mild (less than 2-fold) increase in transaminases. To avoid folate deficiency secondary to increased utilisation of folate stores during the period of haemolysis, the patient was administered folate 5mg daily. Evidence of haemolysis was maximal 8 to 9 days post-ingestion and continued for a further 6 days, by which time the haemoglobin had fallen to 10.3 g/dL. The patient was discharged 9 days after ingestion, by which time his transaminase levels had returned to normal. Concentrations of methaemoglobin and sulphhemoglobin had returned to the normal range 16 days post-ingestion (fig. 1). The patient did not attend further follow-up.

**Discussion**

The adverse effects of poisoning with dapsone are predictable and dose related (Manfredi et al. 1979). The major toxic effects are the formation of methaemoglobin and a Heinz body haemolytic anaemia. Toxicity appears to be due to the formation of an hydroxylated metabolite of dapsone, 4-amino-4'-hydroxylaminodiphenylsulphone (DDS-NOH), a powerful oxidising agent (Cucinell et al. 1972; Glader & Conrad 1973; Grossman & Jollow 1988; Hjelm & De Verdier 1965; Kramer et al. 1972; Manfredi et al. 1979; Scott & Rasbridge 1973). Deaths have been reported but the level of methaemoglobinaemia in these patients was not stated nor did the patients receive specific therapy (Davies 1950; Sturt 1967).

In the majority of published reports (table I) the patients presented more than 3 hours after the poisoning. Symptoms of toxicity may be delayed as the development of methaemoglobin and haemolysis is dependent on both the concentration and duration of exposure to DDS-NOH (Grossman & Jollow 1988). Gastric emptying of the drug may also be delayed; Neuvonen et al. (1980) reported tablet return with gastric lavage 5 hours after ingestion. Dapsone has a high volume of distribution of 1.5 L/kg, is extensively protein bound (70 to 90%), and is acetylated in the liver to an active compound, monoacetyl dapsone (MADDS) which is 99% protein bound. Some monoacetyl dapsone is deacetylated to dapsone (Zuidema et al. 1986). Both dapsone and monoacetyl dapsone undergo enterohepatic circulation and bind to activated charcoal. The half-life of both these compounds is about 30 hours with normal therapeutic doses. Neuvonen et al. (1983) reported the mean half-life of dapsone after overdose to be 77 ± 23 hours, which decreased to 12.7 ± 0.7 hours with repeated doses of activated charcoal: this treatment was as effective in eliminating dapsone as haemodialysis. Dapsone is also removed by charcoal haemoperfusion, but this procedure is not without considerable cost and has been associated with complications of hypotension, hypoglycaemia and thrombocytopenia.

Endre et al. (1983) commenced charcoal