

Acute dapsone poisoning in a 3-year-old child: Case report with review of literature

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Abstract

Dapsone (DDS-diamino diphenyl sulphone) is a sulfone antibiotic being used for a variety of clinical conditions. Poisoning in children by DDS is rarely reported. Poisoning in acute cases will be frequently unrecognized due to relative lack of severe signs and symptoms. Methemoglobinemia is the major life-threatening situation associated with poisoning of DDS. Hence, any delay for medical attention can lead to increased rate of mortality. In this case, we describe acute DDS poisoning in a 3-year-old child and the successful management using intravenous methylene blue.

Key words: Dapsone; Methemoglobinemia; Ascorbic acid; Methylene blue; Hemolysis

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Core tip: Dapsone (DDS-diamino diphenyl sulphone), a sulfone antibiotic poisoning in children is rarely reported. Methemoglobinemia is the major life-threatening situation associated with DDS poisoning. Delay in seeking medical attention can lead to increased rate of mortality. Methylene blue 0.1% (2 mg/kg) as slow *iv* is the first line therapy. Furthermore, therapies like exchange transfusions and hyperbaric oxygen therapy are options especially in cases where contraindicated in glucose-6-phosphate dehydrogenase deficiency or if methylene blue therapy is ineffective.

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INTRODUCTION

Dapsone (DDS-diamino diphenyl sulphone), a sulfone antibiotic being used for the prophylactic therapy of various infections in an immunocompromised individual^[1]. DDS poisoning in children are rarely reported. In initial stages of acute poisoning, there will not be any major manifestations and hence there may be delay in seeking medical attention. The life threatening events occur as a result of DDS-induced methemoglobinemia which will eventually affect the oxygen delivery to cells^[2]. Hence, it will be worthwhile to discuss the manifestations and managements of DDS poisoning in order to prevent its adverse effects. In this case study, we present a 3-year-old child with accidental ingestion of DDS.

CASE REPORT

A 3-year-old boy brought to the hospital with complaints of accidental ingestion of DDS. At the onset of admission, the symptoms were lethargy, vomiting and unsteadiness. The child had persisted vomiting and later developed lethargy. He was conscious with blood pressure 106/68 mmHg, respiration rate 68/min, temperature 98.6 °F and pulse rate 150 beats/min. Oxygen saturation (SpO₂) was 91%. He had mild peripheral cyanosis, ataxia and nystagmus. Pupils were equally reacting to light; reflexes were brisk with plantar withdrawal with tone increased in all limbs. Later, the child becomes agitated and stuporous. Arterial blood gas (ABG) analysis showed pO₂ 84 mmHg with hematocrit 29% and SpO₂ 91.6% (Table 1). Evidence for hemolysis characterized by progressive drop in haemoglobin levels and hematocrit values. Packed red cell transfusion was given on 2nd and 3rd day as there was ongoing hemolysis. The initial methemoglobin (MHbA) level was 19.4%. Acute DDS-induced methemoglobinemia and CNS involvement was confirmed. O₂ inhalation and ascorbic acid (CELIN-1000 mg) was administered *via* nasogastric tube along with ranitidine and ondansetron as *iv* Methylene blue 0.1% (2 mg/kg) as slow *iv* was given. SpO₂ was increased to 96%, pO₂ 88 mmHg with hematocrit 29%. Liver function test showed abnormal rise in enzymes till 5th day (Table 1). The renal function test and urinalysis were normal. On 5th day, the MHbA level was found to be 10.2%. On the day 7, another dose of methylene blue was given as he became lethargic with SpO₂ of 82%. The child was improved and discharged on day 14th after admission. During the follow-up, he had no neurological deficits and haemoglobin level was 11.8 g/dL.

DISCUSSION

DDS is an antimicrobial used to treat leprosy, dermatoses, malaria, *etc*^[1]. The most frequent reaction that occur with higher doses of DDS toxicity is hemolytic anemia and methemoglobinemia^[3]. Landers *et al*^[4] reported decrease in hemoglobin (1-2 g/dL) and reticulocyte count (2%-12%) levels in patient with DDS toxicity. Therefore, when the methemoglobinemia causes symptomatic hemodynamic instability, discontinuation of DDS therapy is recommended.

The possibilities for DDS ingestion and poisoning in children are high. The blood MHbA level determines the clinical severity of the symptoms and signs. Most of the patients are found to be asymptomatic until approximately 30% of hemoglobin is presented as MHbA^[1]. However, levels especially greater than 15% may be associated with cyanosis. In this child, the initial MHbA was 19.4%. Headache, lethargy, tachycardia and dizziness may be presented at levels between 20%-45%, whereas dyspnea, acidosis, seizures, cardiac dysrhythmias, heart failure and coma may occur at level above 45%. Furthermore, high mortality rate is associated with levels above 70%^[5]. The patient in this case study had metabolic acidosis as evidenced from the lowered blood pH and bicarbonate level one day after the admission.

Acquired methemoglobinemia can be caused by nitrites and nitrates, nitric oxide, sulphones (*e.g.*, dapsone), local anesthetics (*e.g.*, benzocaine), aniline dyes, chlorates, pyridium, phenacetin, sulphonamides, *etc*^[6]. Use of topical DDS as treatment for acne vulgaris has also been associated with MHbA levels as high as 20%^[7]. In oxygenated and deoxygenated hemoglobin, iron remains in the ferrous (Fe²⁺) form which is essential for the oxygen transportation. Oxidation of Fe²⁺ to ferric form yields MHbA, which does not bind to oxygen. Followed by the MHbA formation, the oxygen affinity of any remaining Fe²⁺-hemes in the hemoglobin tetramer is increased and the oxygen dissociation curve is "left-shifted". Therefore, the circulating MHbA as well as the remaining oxyhemoglobin which has increased oxygen affinity can cause impaired oxygen delivery to the tissues. The net effect is that patients with acutely increased concentrations of MHbA have a functional anemia (*i.e.*, the amount of functional hemoglobin is less than the measured level of total hemoglobin). The existence of underlying diseases of lung, heart or blood may exacerbate the toxicity of MHbA. About 3% of the Fe²⁺ of deoxy Hb is slowly oxidized to MHbA per day. The intra-erythrocytic MHbA reducing enzyme systems such as NADH-dependant cytochrome b5 reductase, mainly and NADPH-MHbA reductase and NADPH-glutathione reductase, to a lesser extent help to keep its level below 1%. Level of MHbA above 2% is abnormal.

Management of DDS includes oral administration of activated charcoal and intravenous treatment with methylene blue. In this patient, we could not administer activated charcoal due to persistent vomiting. The

Table 1 Laboratory investigations

Investigations	1 d after admission	5 d after admission
Hemoglobin (g/dL)	10.5	9.7
Platelet count/ μ L	250000	210000
Total WBC count/ μ L	10760	14094
Differential leucocyte count (%): Neutrophils; Lymphocytes; Eosinophils; Monocytes; Basophils	65; 26; 3.3; 2.5; 2	48; 43; 5; 2; 2
Serum Na ⁺ (mmol/L); K ⁺ (mmol/L)	137; 4.3	138; 4.1
Bicarbonate (mmol/L)	17	23
Serum glutamic-pyruvic transaminase (U/L)	150	162
Blood gas analysis pH; pCO ₂ (mmHg); pO ₂ (mmHg); hematocrit (%) and SpO ₂ (%)	7.37; 16; 84; 29; 91.6	7.41; 22; 88; 29; 96.6
Methaemoglobin (%)	19.4	10.2

plasma elimination half-life of DDS was found to be dose dependent which varies from 10 to 80 h. The renal excretion of unchanged DDS is limited to approximately 20% of the administered dose. DDS is metabolised in the liver for its elimination resulted a moderate elevation of SGPT (150-162 U/L) during the initial few days but normalised on 14th day (45 U/L). After the initial dosage of methylene blue, an additional dose may be repeated if there is an insufficient response. In this case, an additional dose of methylene blue was given since the MHbA level was high on 5th day. This may be due to the enterohepatic circulation of DDS which resulted in a rebound methemoglobinemia as high as 60% up to 18 h of methylene blue injection.

Treatment with methylene blue can be complicated by the presence of underlying glucose-6-phosphate dehydrogenase deficiency. Therefore, alternative therapies like exchange transfusions and hyperbaric oxygen therapy are the remaining options in patients with glucose-6-phosphate dehydrogenase deficiency or if methylene blue therapy is ineffective^[8]. But the efficacy of these therapies not yet been elucidated. Ascorbic acid rarely reduces the cyanosis associated with chronic methemoglobinemia but has no role in treatment of acute acquired methemoglobinemia. Furthermore, Cimetidine, used as a selective inhibitor of N-hydroxylation, may be effective in increasing patient tolerance to dapsone, chronically lowering the MHbA level by more than 25%. Since it works slowly, cimetidine is not helpful for the management of acute symptomatic methemoglobinemia arising from the use of DDS.

Methylene blue is a phenothiazine-related heterocyclic aromatic molecule most commonly used as a reducing agent in the treatment of methemoglobinemia and for the treatment of cyanide and carbon monoxide poisoning^[3,9]. It has dose-dependent effect on cardiac index and pulmonary artery occlusion pressure as well as oxygen delivery and lactate concentrations. The dosing of methylene blue is not entirely clear, but 1-2 mg/kg is used for the treatment of methemoglobinemia. However, methylene blue above 7 mg/kg is associated with adverse effects such as paradoxical induction of MHbA, hemolytic anemia and detrimental effects on pulmonary function^[10,11]. Therefore, methylene blue

should not be recommended in patients with pulmonary hypertension, underlying glucose-6-phosphate dehydrogenase deficiency and acute lung injury^[11]. Clinicians should also be aware of potential adverse effects and drug interactions with serotonergic agents when considering therapy with methylene blue^[12].

According to Wright *et al.*^[13], the diagnosis may be complicated by the effect of MHbA on arterial blood gas and pulse oximeter oxygen saturation results. In the presence of the increased MHbA fraction, pulse oximeter values will trend toward 85% underestimating the actual oxygen saturation. Guay^[14] demonstrated the discrepancy between the pulse oximeter saturation ($\leq 90\%$) and the arterial oxygen partial pressure (≤ 70 mmHg) in subjects with MHbA. Therefore, the routine pulse oximetry is generally inaccurate for monitoring oxygen saturation in the presence of methemoglobinemia. Acute hemolytic anemia in DDS can be explained with the DDS-induced continued oxidative stress or may also be due to the doses of methylene blue^[15]. Charcoal hemoperfusion has also been reported for the rapid clearing of dapsone^[16].

This case report concluded that patient with dapsone poisoning should be evaluated for serial measurements of methemoglobin levels following treatment with methylene blue in order to evaluate for the subsequent worsening and the need for additional treatment.

COMMENTS

Case characteristics

A 3-year-old boy presented with persisted vomiting and lethargy.

Clinical diagnosis

The patient had mild peripheral cyanosis, ataxia and nystagmus.

Differential diagnosis

Other causes for the drug induced acquired methemoglobinemia.

Laboratory diagnosis

Methemoglobinemia greater than 2% and lowered haematocrit value.

Treatment

Methylene blue 0.1% (2 mg/kg) as *iv*.

Related reports

Accidental acute dapsone poisoning in children are rarely reported. Management includes charcoal hemoperfusion, exchange transfusions and hyperbaric oxygen therapy.

Term explanation

Dapsone, a sulfone antibiotic being used for the prophylactic therapy of various infections in an immunocompromised individual, induces methemoglobinemia at higher doses. The level of methemoglobin in the blood determines the clinical severity of the symptoms and signs.

Experiences and lessons

Patient with dapsone-induced methemoglobinemia required serial measurements of methemoglobin levels following treatment with methylene blue in order to evaluate the subsequent worsening and the need for additional treatment. Routine pulse oximetry is generally inaccurate for monitoring oxygen saturation in the presence of methemoglobinemia.

Peer-review

This is a useful review of dapsone poisoning and its treatment.

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