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Ascorbic acid as an effective alternative for treatment of dapsone poisoning in a child: A case report

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ABSTRACT

Dapsone (DDS – Diamino diphenyl sulfone), a sulfonamide derivative acts by inhibiting PABA incorporation into folic acid. It is commonly used in treating skin diseases. Accidental poisoning in children is uncommon. It results in methaemoglobinemia by causing oxidative stress. Principle of treatment relies on treating methemoglobinemia by using reducing agents like methylene blue or ascorbic acid. Due to the long half-life, dapsone provides a continuing oxidative stress that can cause a recurrence of clinically significant methaemoglobinaemia and hence takes long to treat. Ascorbic acid is effective in treating methemoglobinemia associated with dapsone poisoning as demonstrated in this case report of a four and half year old child's accidental ingestion of dapsone tablets and presenting with cyanosis. The child was managed successfully with ascorbic acid and supportive treatment.

Keywords: Dapsone, Methemoglobinemia, Ascorbic acid.

Dapsone (DDS – Diamino diphenyl sulfone), a sulfonamide derivative acts by inhibiting Para Amino Benzoic Acid (PABA) incorporation into folic acid. Although, it is traditionally an antileprosy drug, the use of dapsone has expanded into the treatment of dermatologic conditions, including pyoderma gangrenosum and dermatitis herpetiformis. Dapsone has several off-label uses such as treatment of *Pneumocystis jiroveci* pneumonia, bullous systemic lupus erythematosus, and severe aphthous ulcers [1].

Accidental dapsone poisoning during childhood is uncommon [2,3]. There is paucity of literature regarding the incidence of dapsone-induced methemoglobinemia in children. However, in hematopoietic stem cell transplant recipients receiving dapsone for *Pseudomonas jiroveci* pneumonia prophylaxis, the incidence is approximately 3% [4].

CASE REPORT

A four and half year-old male child presented to Pediatric department emergency with irritability, restlessness and difficulty in breathing which started immediately after waking up in morning. There was history of accidental ingestion of 4 dapsone tablets (100 mg each) around 12 hours back. The drug was being taken by his mother for the treatment of lichen planus. There was no history of fever, cough, or chest pain, or any history suggestive of foreign body inhalation. There was no history of asthmatic episodes in past or in family.

Examination of the child at the time of presentation revealed central cyanosis, pulse rate of 108/min, regular rhythm and normal volume, respiratory rate was 36/min with nasal flaring, normal body temperature and blood pressure was 100/60 mm-Hg. SPo2 was 82% on room air

which increased to only 85% with oxygen (4 L/min). The respiratory system was normal on examination and rest other systems were also normal.

Arterial and venous blood drawn for investigations was chocolate brown in colour. His routine laboratory investigations including hemoglobin (10.5 g/dl) and total leukocyte count (7400/mm3), blood urea and creatinine and serum electrolytes were within normal limits. Arterial blood gas analysis was within normal limits (pH - 7.49, PCO2 - 26.4, PO2 - 103, HCO3 - 19.9 and O2 saturation - 98.5%). However, the methemoglobin level was significantly elevated (19%).

The child was started on supportive treatment. Gastric lavage was done and child was kept under oxygen by nasal prongs. As, injection methylene blue was unavailable and patient's G6PD status was not known [5], treatment was initiated by intravenous injection of ascorbic acid 500 mg at admission. Injection ascorbic acid was continued on next day at same dose and then the child was started on oral ascorbic acid, once he showed signs of improvement. Patient remained cyanosed till 4th day of admission after which his saturation returned to normal. His methemoglobin level was decreased to 2% on day 7 of admission. The patient was discharged successfully and was doing well on one and two months follow-up.

DISCUSSION

Accidental dapsone poisoning is a pediatric emergency in young preschool children [6]. Dapsone, a sulfone, is a structural analog of paraaminobenzoic acid (PABA) and a competitive inhibitor of dihydropteroate synthase in the folate pathway. After oral administration, absorption is complete; the elimination t½ is 20-30 hours. It undergoes N – acetylation by N-Acetyltransferase 2 (NAT2). Dapsone hydroxylamine enters red cells leading to methemoglobin formation. Sulfones tend to be retained for up to 3 weeks in skin and muscle and especially in liver and kidney. Intestinal reabsorbtion of sulfones excreted in bile lead to long term effects.

The most frequent reaction to occur with dapsone toxicity is hemolytic anemia and methemoglobinemia. Hemoglobin levels can decrease by 1–2 g/dL with an increase of 2–12% in the reticulocyte count [7]. The clinical symptoms of methemoglobinemia vary and depend on the methemoglobin concentration in the blood. Cyanosis occurs at around 15% methemoglobin concentration, and tissue hypoxia can occur as levels raise further–methemoglobin levels of 70% or higher can be fatal [8]. Methemoglobin is incapable of binding oxygen and also increases the affinity of the unaltered hemoglobin for oxygen, shifting the oxygen dissociation curve to the left; thus, further impairing oxygen delivery resulting in difficulty in breathing and low saturation. The CNS manifestations like irritability, hypotonia, truncal ataxia, choreiform movements, dysarthritic speech and cerebellar signs also occur in children with dapsone poisoning. Cerebral anoxia due to methemoglobinemia has been attributed as the main cause for CNS manifestations [9].

In acute dapsone toxicity, initial attempts should be directed towards gut decontamination (gastric lavage, activated charcoal orally) and improvement of oxygen delivery. To improve oxygen delivery, main emphasis is on administration of reducing agents such as methylene blue and ascorbic acid. Methylene blue is reduced to leukomethylene blue by flavin reductase, accepting electrons from Nicotinamide Adenine Dinucleotide Phosphate (NADPH). Leukomethylene blue acts as an electron donor to reduce methemoglobin to hemoglobin, converting back to methylene blue in a cyclical redox reaction. Conversely, because methylene blue is an oxidizing agent, it can itself cause methemoglobinemia by oxidizing hemoglobin at high concentrations. It is the mainstay of treatment in severe methemoglobinemia.

Ascorbic acid is a strong reducing agent that takes part in many oxidation–reduction reactions. Ascorbic acid might be fructuous where methylene blue is not available or is contradicted due to deficiency or absence of glucose-6-phosphate dehydrogenase enzymes [10,11]. Ascorbic acid 200-500 mg can be given intravenously, as was successfully used in the present case. Exchange transfusion had been tried in case not responding to methyleneblue [12].

Patients with dapsone-induced methemoglobinemia require serial measurements of methemoglobin levels following treatment 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 as a saturation gap exists [13]. It is suggested that cases previously perfectly normal and presenting with unexplained central cyanosis with history of ingestion of

dapsone be considered as having methemoglobinemia. Dapsone, a commonly used drug in the treatment of leprosy should be kept out of reach of children to prevent significant morbidity and mortality.

CONCLUSION

Dapsone poisoning results in methemoglobinemia which can be life threatening if not attended promptly. Ascorbic acid can be used effectively for the treatment of methemoglobinemia. It is suggested that dapsone should be kept out of reach of children and in cases of accidental ingestion, prompt management has to be done.

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