CORRESPONDENCE

Accidental Poisoning Resulting in Severe Methemoglobinemia in a 14-year-old Girl

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To the editor

A 14 year old girl was brought to emergency with vomiting and altered sensorium within 15 min of accidental ingestion of some substance used in printing press. Her father owned a printing press. This substance was kept in an empty bottle of fruit juice that the child accidentally ingested. Her Father said that the substance ingested was a liquid called “Fixer” but its precise nature was unknown. By the time the child arrived at emergency she was drowsy and looked very blue. She was intubated and shifted to PICU. Gastric lavage was not done as the nature of liquid was not clear and a net search done at time of arrival revealed that some substances used in dye industry have corrosive nature in which case It could have been contraindicated.

On arrival at PICU her initial evaluation showed her heart rate was 140/min, blood pressure was 112/74 mm Hg and oxygen saturation was 46 %. Lung compliance and resistance were normal on mechanical ventilation. In view of cyanosis, out of proportion to hemodynamics and lung mechanics the diagnosis of methemoglobinemia was considered with bedside examination of blood drop on filter paper and confirmed by arterial blood gas and laboratory analysis which revealed methemoglobin levels of 67 %. She was treated with methylene blue IV infusion @ 1 mg/kg. There was delay of 1 h in infusing methylene blue due to its unavailability. Although Methylene Blue is inexpensive it is not freely available. Meanwhile it was

confirmed that she is not G6PD (Glucose-6 Phosphate Dehydrogenase) deficient. Same dose was repeated after 30 min because cyanosis had not improved after first dose. Child responded to methylene blue injection and methemoglobin levels came down to 2 %. She remained hemodynamically stable and did not suffer any organ dysfunction. She was extubated within 24 h but her methemoglobin levels resurged to 25 % after 12 h of last methylene blue injection. She required repeat doses of methylene blue every 12 h for first 72 h to keep methemoglobin levels below 20 %.

Her hemoglobin level fell to 6.5 gm % and she was given packed red blood cell transfusion. In view of repeated rise in methemoglobin and ongoing hemolysis, she was given ascorbic acid 100 mg 6 hrly and *n* acetyl cystine 150 mg/kg 4 hrly to increase antioxidant reserve for 48 h. She showed good response to management and her methemoglobin levels did not increase after this intervention. She was discharged from hospital in stable condition.

Profound cyanosis incompatible with the degree of respiratory distress, especially where cyanotic symptoms are unresponsive to oxygen therapy, should raise the suspicion of methemoglobinemia. This diagnosis is supported by the chocolate-brown coloration of blood samples obtained from these patients, and the diagnosis may be confirmed by measuring methemoglobin levels. Normally methemoglobin is kept below 1 % by reductase enzymes; however it becomes clinically significant when levels are above 10 % [1]. Signs and symptoms of methemoglobinemia may correlate with measured methemoglobin level. Arterial blood gas and pulse oximeter measurements offer limited diagnostic help and may be misleading. Symptoms of methemoglobinemia can range in severity from dizziness to coma. Patients may present with cyanosis when the methemoglobin concentration reaches levels of ~10 % of

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the total hemoglobin level and levels above 70 % are known to be fatal [2]. As compared to anemia which is also a condition associated with reduced oxygen carrying capacity, patients with methemoglobinemia tend to present with a more serious condition due to a leftward shift in the oxyhemoglobin dissociation curve [3]. A case of status epilepticus associated with methemoglobinemia has also been reported [4].

The condition may arise as a result of a genetic defect in red blood cell metabolism or hemoglobin structure, or it may be acquired following exposure to various oxidant drugs or toxins. Hereditary methemoglobinemia is a rare, recessively inherited disorder in which there is deficiency of enzyme nicotinamide adenine dinucleotide (NADH) cytochrome b5 reductase. Acquired methemoglobinemia can result from exposure to a wide range of drugs and chemicals, including nitrites and aniline derivatives and other oxidants. Nitrites have been reported to be among the chemical agents that most commonly cause methemoglobinemia. Certain drugs like dapsone, local anesthetics, phenacetin, and antimalarial medications are more commonly associated with methemoglobinemia. A second enzymatic pathway using nicotinamide adenosine dinucleotide phosphate and nicotinamide adenosine dinucleotide phosphate-methemoglobin reductase, is important for the antidotal effect of methylene blue when administered exogenously.

Treatment of methemoglobinemia begins with supportive care. Oxygen supplementation is initiated using a non-re breather face mask. Decontamination with activated charcoal may be necessary if the condition is the result of ingestion of along acting substance like dapsone. In a patient with significant symptoms and signs, reduction of methemoglobin levels by administration of methylene blue should be considered. Methylene blue is administered intravenously, 1 mg/kg over 3–5 min. Dose of methylene blue may be repeated in 30 min if cyanosis does not improve [5]. Methylene blue acts as a cofactor that accelerates the efficiency of NADPH methemoglobin reductase. Methylene blue in its active form which is

leukomethylene blue, acts as an electron donor to the ferric iron, reducing it back to ferrous state. The primary contraindication is G-6PD deficiency because in absence of G6PD, NADPH is not available and methylene blue cannot activate the alternate pathway to reduce methemoglobin. Secondly in absence of G6PD oxidative stress caused by methylene blue can induce hemolysis. In July 2011, the Food and Drug Administration (FDA) issued a safety notice regarding use of methylene blue [6] which can have adverse events including hypertension, confusion, anemia and serotonin syndrome. In cases of rebound rise in methemoglobin levels, which is known to occur with aniline dye poisoning, *N* acetyl cystine and ascorbic acid have been used with good results [2]. Aim of this letter is to highlight that for any patient who presents with severe cyanosis which is unresponsive to oxygen therapy, methemoglobinemia must be considered as a differential diagnosis. Treating physician should also be familiar with the dosing and administration of methylene blue as well the appropriate ways to manage or avoid potentially serious adverse events associated with its use.

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