ORIGINAL RESEARCH PAPER

General Medicine

METHEMOGLOBINEMIA

KEY WORDS:

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Case-1

Samrudhhi shinde 29 year female resident of Mumbai ,came to opd with chief complaints of fever and headache since one day.In past she was diagnosed as ITP(immune thrombocytopenic purpura) and since last one month she was on dapsone treatment.on presentation her room air saturation was 82 %.So we put her on o2 support through face mask, which eventually changed to non-breathable mask to NIV but still her saturation is not improved.Patient is having 80% saturation despite a good respiratory efforts,a clear airway and bilateral breath sounds. haematologist suspecting the possible diagnosis of Methhaemoglobinemia as dapsone is known to cause Methhaemoglobinemia.so we draw the blood and sent it to lab which came out to be positive for Methhaemoglobinemia.

Case-2

Patient Adesh 36 yr male ,a worker in paint factory came to D Y Patil hospital with chief complaints of breathlessness, vomiting and dizziness since 6 hrs.on enquiry patient gave history of spillage of aniline dye on shirt,after 30 minutes of which patient complained above chief complaints.

On presentation his saturation is 74 % on RA.The patient is deeply cyanosed despite a good respiratory effort, a clear airway, and bilateral breath sounds.But patient is conscious and oriented.we put him on o2 support through nonrebreathable mask but still his saturation is not improved. The attending physician is alert to the possible diagnosis of methemoglobinemia because the patient is cyanosed, the cyanosis is unresponsive to ventilation, there is no prior history of respiratory problems, and the patient had been exposed to aniline dye that is known to cause methemoglobinemia.A blood specimen is drawn and test results confirm the diagnosis.

Case-3

Patient Tai 55 yr female,fisherwoman came to D Y Patil hospital with chief complaints of breathlessness and cough since last 15 days,breathlessness was acute in onset and progressive in nature,relived on taking rest,cough is dry.Patient is known case of seizure disorder and was on tab eptoin 100 mg TDS and tab levipil 500 BD.on examination her RA saturation was 70% and she has signs of central cynosis.same as above case we put her on o2 support,but still her saturation is not improving,on auscultation air entry on both side is clear and normal.X-ray is also Normal.so based on history and blood reports we suspected that is Metheglobinemia case.And treated accordingly.

METHODS

Information on methemoglobinemia was obtained through a literature search using MEDLINE ,PUBMED and the following key words: *methemoglobinemia, sulfhemoglobinemia, cyanosis*, and *methylene blue*. Multiple potentially relevant studies were reviewed and considered for inclusion. References from selected articles were also searched.

What is methemoglobinemia ?

Methemoglobinemia is a condition characterised by increased quantities of hemoglobin in which the iron of heme is oxidised to the ferric (Fe3+) form. Methemoglobin is useless as an oxygen carrier and thus causes a varying degree of cyanosis.

Pathophysiology

Methemoglobin is an altered conformation of hemoglobin in which the ferrous (Fe2+) state is oxidised to the ferric (Fe3+) state. The ferric heme in methemoglobin is unable to bind oxygen, resulting in an altered structure. Additionally, there is increased oxygen affinity of the molecule, causing a left shift of the oxygen dissociation curve, interfering with oxygen delivery to tissues. Methemoglobinemia is either congenital or acquired. Congenital methemoglobinemia is due to a deficiency of the enzyme cytochrome *b5* reductase, which reduces methemoglobin to hemoglobin, maintaining a steady-state methemoglobin level of less than 1.0%.However, in individuals with normal cytochrome *b5* reductase levels, exposure to oxidising agents might result in increased production of methemoglobin to the extent that enzymatic reduction cannot compensate for this acute increase.

Signs and symptoms

Patients with an elevated methemoglobin concentration might initially develop relatively mild symptoms such as dyspnea, headache, lethargy, and fatigue. However, at higher methemoglobin levels, profound cyanosis might develop and symptoms might progress to respiratory distress, altered mentation, seizure, dysrhythmias, and death.Patients with comorbidities, such as anaemia or the presence of other abnormal hemoglobin species (eg, sickle cell anaemia), cardiovascular disease, lung disease, or sepsis, might experience moderate to severe symptoms at much lower methemoglobin levels.1 Young infants (< 6 months of age) might be particularly susceptible to methemoglobinemia in the context of gastroenteritis and dehydration owing to low gastric acid production, a large number of nitrite-reducing bacteria, and relative ease of fetal hemoglobin oxidation.

Pathogenesis and diagnosis

Acquired methemoglobinemia is most often caused by exposure to exogenous oxidising substances. While many substances have been implicated, topical anaesthetics, dapsone, and antimalarial medications are the most common.1 Methemoglobinemia has also been identified in patients exposed to various environmental agents (ie, nitrogen-containing compounds) and in certain medical conditions such as sepsis.1,2

Noninvasive methods of estimating methemoglobin levels

have been developed. When methemoglobin levels rise above 20%, the blood develops a chocolate-brown colour.3,4 A low-cost quantitative test—a blood colour chart—was developed by Shihana et al and can be used at the bedside.4 By using this colour chart, clinicians can estimate the methemoglobin level based on the colour of the blood. Pulse oximeters that can estimate methemoglobin levels have also been developed, now commonly known as co-oximeters. Earlier models of co-oximeters were inaccurate in patients with oxygen saturation levels less than 95%; however, newer models used for humans were shown to be efficacious in the presence of oxygen saturation levels as low as 74%.5 When compared with arterial blood gas analysis—considered to be the criterion standard test—co-oximeters have been shown to accurately detect methemoglobin levels of 15% or less.6,7 Given their accuracy at low levels, co-oximeters are useful screening tools, but more studies are needed to validate them at methemoglobin levels greater than 15%.

Drugs

Acetanilid	Dapsone	Nitrites	Sulfasalazine
Alloxan	Dimethyl sulfoxide	Nitrofuron	Sulfonamide
Aniline	Dinitrophenol	Nitroglycerin	Trinitrotoluene
Arsine	Exhaust fumes	Sodium nitroprusside	
Benzene derivative	Ferricyanide	Paraquate	
Benzocaine	Flutamide	Phenol	
Bivalent copper	Hydroxylamine	Phenytoin	
Bismuth subnitrate	Lodocaine hydrochloride	Prilocaine hydrochloride	
Bupivacaine hydrochloride	Metoclopromide hydrochloride	Primaquine phosphate	
Chlorates	Methylene blue	Rifampin	
Chloroquine	Nitrates	Silver nitrate	
Chromates	Napthalene	Sodium valproate	
Clofazimine	Nitric oxide	Smoke inhalation	

Treatment

The course of hereditary methemoglobinemia type I is benign, but these patients should not be administered oxidant drugs. Treatment may be required for cosmetic reasons or for an inadvertent use of oxidant drugs. Ascorbic acid, 300 to 600 mg orally daily divided into 3 or 4 doses, is helpful.8

For methemoglobinemia due to drug exposure, traditional first-line therapy consists of an infusion of methylene blue (1-2 mg/kg infused over 5 min,patient will improve within one hour,should not exceed 7 mg/kg), whose action depends on the availability of reduced nicotinamide adenine nucleotide phosphate (NADPH) within the red blood cells. After an acute exposure to an oxidising agent, treatment should be considered when the methemoglobin is 30% in an asymptomatic patient and 20% in a symptomatic patient.9Patients with anaemia or cardiorespiratory problems should be treated at lower levels of methemoglobin. Methemoglobinemia due to hemoglobin M does not respond to ascorbic acid or methylene blue.

Dextrose should be given10 because the major source of NADH in the red blood cells is the catabolism of sugar through glycolysis. Dextrose is also necessary to form NADPH through the hexose monophosphate shunt, which is necessary for methylene blue to be effective.

Methylene blue is an oxidant; its metabolic product Leuko methylene blue is the reducing agent. Therefore, large doses of methylene blue may result in higher levels of methylene blue rather than the Leuko methylene blue, which will result in hemolysis and, paradoxically, methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.11 Patients with G6PD deficiency also may not produce sufficient NADPH to reduce methylene blue to Leuko methylene blue; thus, methylene blue therapy may be ineffective in these patients.11

Some drugs, such as dapsone, benzocaine, and aniline, produce a rebound methemoglobinemia, in which methemoglobin levels increase 4 to 12 hours after successful methylene blue therapy.12

N-Acetylcysteine, cimetidine, and ketoconazole are experimental therapies in the treatment of methemoglobinemia that have shown some promising results.13-14-15 Exchange transfusion is reserved for patients in whom methylene blue therapy is ineffective.

The patients were treated with intravenous methylene blue and dextrose infusion, with a good response. There cyanosis and blood oxygenation improve, as does his consciousness level. There urine output is monitored, and a close eye is kept on there biochemistry. Blood tests are repeated after 24 hours for evidence of hemolysis and rebound methemoglobinemia. There G6PD status is ascertained and found to be normal. Both does not show any evidence of hemolysis or renal impairment and makes a complete recovery.

Summary points

- Severe methemoglobinemia is a medical emergency, requiring prompt recognition and appropriate treatment
- A good history and high level of suspicion are required to make the diagnosis
- Exposure to medication is the most common cause of methemoglobinemia
- For methemoglobinemia due to drug exposure, traditional first-line therapy consists of the infusion of methylene blue

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