Case study

Polypharmacy precipitating Methemoglobinemia

ABSTRACT

Methemoglobinemia is a potentially fatal condition, can be congenital but mainly acquired after intoxication by certain drugs. To this date there are very few cases associated with use of multiple drugs leading to methemoglobinemia. We report a patient who developed methemoglobinemia secondary to multiple drugs. Our patient had diabetes related micro and macro vascular complication along with non-vascular complication i.e. diabetic gastroparesis along with UTI.She was treated with multiple drugs which included metoclopramide, nitrates, paracetamol which led to methemoglobinemia. All three of these drugs can precipitate methemoglobinemia either individually or in combination with each other. This patient was successfully treated with iv methylene blue

Introduction-

Methemoglobinemia is an altered state of hemoglobin in which the ferrous (fe^{++}) irons of heme are oxidized to ferric (fe^{+++}) state. The ferric hemes of methemoglobin are unable to reversibly bind oxygen. In addition, the oxygen affinity of any remaining globins' ferrous hemes in the hemoglobin tetramer are increased[1].As result, the oxygen dissociation curve is "left shifted". The etiology of methemoglobinemia can be congenital or acquired but vast majority are acquired[2] usually resulting from excessive doses of drugs or other substances. Most common drugs are antimalarial, parcetamol,dapsone,

Nitroglycerin,lidocaine.We present case of 65 years old who was on multiple drugs developed methemoglobinemia which was treated successfully with methylene blue.

Case report

65 years year old female known case of hypertension AHA class 2 and Type 2 diabetes since 15 years with poor glycemic control her last HBAIC was 8.4gms she also had diabetes related micro and macro vascular complications. She had CKD her serum creatinine was 2gm and eGFR was 26ml/min/1.73m^2. She also had coronary artery

disease with angina NYHA class 2 .She also had diabetic gastroparesis. Presently she got admitted to hospital with chief complaints of fever dysuria and recurrent vomiting .On evaluation she was found to have raised TLC 17,600/cu mm, her hemoglobin was 12gms and urine routine showing 45 to 50 pus cells ,her urine culture sensitivity showed growth of E.coli 10^5 CFU .She was started on following treatment injection ceftriaxone 1gm twice day, injection pantoprazole 40mg twice day, injection metoclopramide 10mg three times day and injection paracetamol 1gm three times daily , injection human insulin regular 6units three times daily and tablet linagliptin 5mg once daily, tablet clopidogrel 75mg once daily, tablet atorvastatin 20mg once day, tablet glyceryl trinitrate 2.6mg twice a day, tablet olmesartan 20mg once a day, tablet metoprolol 50mg once a day. On fourth day of admission patient suddenly developed dyspnea with cyanosis of both tongue and peripheries. Her pulse rate was 110 per min, her blood pressure was 146/90mmHg and chest examination was normal (no creptation or ronchi).Her oxygen saturation SpO_2 was 70 to 75% despite high flow oxygen. She was immediately intubated and taken an ambu bag and shifted to intensive care unit. In intensive care unit she was put on ventilator support on assist control mode with 100% fio_2 and tidal volume of 300ml. In spite of appropriate ventilation patients cyanosis and saturation did not improved. On sampling for ABG her arterial blood was chocolate brown in colour. Filter paper test i.e. aeration of sample with oxygen failed to change the colour. Her blood methemoglobin level was found to be 15% while no change in other investigation including normal chest x-ray. This suggested diagnosis of methemoglobinemia precipitated by simultaneous use of drugs like metoclopramide with glyceryl Trinitrate and paracetamol. She was started on methylene blue at dose of 1mg/kg body weight intravenously over 15 minutes following which her spO_2 improved to 80-85% over a period of one hour. A second dose of methylene blue was repeated an hour latter, which resulted in spO^2 of 96% and disappearance of cyanosis. Subsequently her fio_2 was reduced and patient was gradually weaned off from the ventilator and extubated next day. Over next couple of days her fever improved and she was discharged her nitrates were stopped after consulting with cardiologist was advised to avoid metoclopramide in future and use paracetamol very judiciously if needed.

Discussion

Methemoglobin is a condition characterized by increased quantities of hemoglobin in which the iron of haem is oxidized to the ferric (fe^{3+}) form. The normal range of methemoglobin is 0% to1% of total hemoglobin level[3] , with any increase above this value being called methemoglobinemia. The net effect is that patients with acutely increased concentration of methemoglobinemia have functional anemia and may develop compensatory polycythemia[4]. It can be congenital or acquired, congenital causes include cytochrome b5 reductase deficiency, Hemoglobin M disease, and cytochrome b5 deficiency. Most of cases are acquired these may be due to medications over doses or poisoning but may also occur with medications given at standard dose. In

this case patient was on three drugs i.e. metoclopramide, paracetamol, glyceryl trinitrite all of them can cause methemoglobinemia. Now whether culprit was any of these single drug or combination of these drug is difficult to comment.

Methemoglobin causes a variable degree of cyanosis. It should be suspected in any patient with significant central cyanosis in whom there is no evidence of cardiorespiratory disease. The degree of cyanosis produced by 5gm/dl of deoxygenated hemoglobin can be produced by 1.5g/dl of methemoglobin. Methemoglobin concentration of 10% are tolerated quite well. Much depends on the rapidity at which it is formed. Many patients with lifelong methemoglobinemia are asymptomatic, while induvial who accumulate a similar level of methemoglobinemia acutely may be acutely dyspneic .At higher methemoglobin levels, respiratory depression, altered sensorium, coma, shock, seizures, and death may occur[5,6].

Several methods are available for detecting the presence of methemoglobinemia and assessing the severity of disease. The preferred method is analysis for methemoglobin directly, rather than assessment of oxygen saturation or blood gas analysis. This is done by analyzing a freshly obtained blood sample (venous or arterial) for its absorption spectrum; methemoglobin has peak absorbance at 631 nm. A fresh blood specimen should always be obtained as methemoglobin levels increase with storage.

The standard method of assaying methemoglobin uses a microprocessor-controlled, fixed wavelength co-oximeter. This instrument interprets all readings in the 630 nm range as methemoglobin; thus, false positives may occur in the presence of other pigments, including sulfhemoglobin, methylene blue (MB), and certain drugs [7,8]. Optimally, methemoglobin detected by the co-oximeter is confirmed by the specific Evelyn-Malloy method [9].

Routine pulse oximetry is generally inaccurate for monitoring oxygen saturation in the presence of methemoglobinemia and should not be used to make the diagnosis of this disorder. The reason is that methemoglobin absorbs light at the pulse oximeter's two wavelengths, and this leads to error in estimating the percentages of reduced and oxyhemoglobins. A high concentration of methemoglobin causes the oxygen saturation to display as approximately 85 percent, regardless of the true hemoglobin oxygen saturation [10] . Blood gas analysis measures arterial oxygen partial pressure and estimates oxygen saturation by comparison with a standard curve. Since arterial oxygen partial pressure is normal in patients with methemoglobinemia, blood gas analysis will give falsely high levels of oxygen saturation in the presence of methemoglobin.

Treatment of acquired methemoglobinemia includes discontinuation of offending agents.

Patients with symptomatic and severe degrees of methemoglobinemia should be managed in the intensive care unit for stabilization of their airway, breathing, and circulation. This may require the use of oxygen supplementation, inotropic agents, and

mechanical ventilation [11,12] . Blood transfusion, especially in anemic subjects, or exchange transfusion may be helpful in patients who are in shock; hyperbaric oxygen has been used with anecdotal success in severe cases [13,14]. If the patient is symptomatic or if the methemoglobin level is >20 percent, which is often the case in deliberate or accidental overdoses or toxin ingestion, specific therapy is urgently indicated. The two treatments most often employed are methylene blue (MB) and ascorbic acid (vitamin C). While there have been no randomized trials comparing these two agents, the general experience has been that the action of a single dose of MB in this setting rapidly reduces toxic levels of methemoglobin to non-toxic levels (eg, <10 percent) within 10 to 60 minutes, whereas treatment with ascorbic acid requires multiple doses and may take 24 or more hours to reach similarly low levels and is therefore a poor alternative in emergency situations [12]. MB, given intravenously in a dose of 1 to 2 mg/kg over five minutes, provides an artificial electron transporter for the ultimate reduction of methemoglobin via the NADPH-dependent pathway . MB should not be administered to patients with known G6PD deficiency, since the reduction of methemoglobin by MB is dependent upon NADPH generated by G6PD. As a result, MB may not only be ineffective, but it is also potentially dangerous since MB has an oxidant potential that may induce hemolysis in G6PD-deficient subjects, precipitating acute hemolysis, thus further decreasing oxygen delivery .

Conclusion- Avoid use of multiple drugs which can precipitate methemoglobinemia. Combination of these drugs even in recommended therapeutic dose lead to methemoglobinemia.

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