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RESEARCH ARTICLE

SARIDON INDUCED METHAEMOGLOBINEMIA: A RARE CAUSE OF CYANOSIS IN A YOUNG ADULT MALE

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ABSTRACT

Saridon (Propyphenazone 150mg, Paracetamol 250 mg & Caffeine 50mg) is a very commonly prescribed analgesic and also a easily available over the counter pain killer. Methemoglobinemia is a known but rarely reported complication of saridon, probably because the drug has been banned in many countries. We describe our experience of 25yr old male patient with cyanosis. The key points instrumental in suspecting methemoglobinemia in our case were history of drug overdose, lethargy, cyanosis and the presence of saturation gap (low SpO2 on pulse oximeter & normal/high arterial partial pressure of oxygen (PaO2) in Arterial Blood Gas analysis). Prompt administration of methylene blue and improvement of cyanosis helped us in confirming drug induced methemoglobinemia much before the lab results of methemoglobin levels arrived, thus establishing our diagnosis.

INTRODUCTION

A 25yr old male patient presented to us with complaints of headache, lethargy, weakness, decreased appetite, difficulty in breathing and bluish discoloration of face and extremities of 3 days duration. Patient had taken 4-5 tablets of Saridon 3 days ago for severe headache after which the symptoms were noticed. No history of fever, cough or expectoration, chest pain or altered sensorium. No past history of similar complaints. Patient was an addict of spasmoproxyvon since 8yrs but as per father he had left taking spasmoproxyvon since last 6-8months. Patient also had drug seeking behavior, he used to consume any drug found at home. Even after repeated questioning, attendants assured no ingestion of any other drug by the patient. On examination he was conscious but used to get drowsy, he followed verbal commands but didn't speak much and appeared confused. Spontaneous movements in all 4 limbs present. Central & peripheral cyanosis present. Pulse rate- 127/minute, regular, hyperdynamic and bilateraly equal, all peripheral pulses felt normally. Blood pressure - 160/80 mmHg (right arm). Respiratory rate - 32/min, thoraco-abdominal, accessory muscles were being used. SpO_2 74% without O2 and 77% on oxygen face mask 8l/min. BMI - 18kg/m2. Systemic examination- did not reveal any abnormal finding. In emergency department, ryle's tube inserted for gastric lavage done and gastric aspirate sent for analysis. Patient shifted to ICU for hemodynamic monitoring and respiratory support. Treatment initiated with inj ceftriaxone 1gm iv 12hrly, inj pantocid 40mg iv once daily, inj ondansetron 4mg iv sos, iv fluids & oxygen through face mask given @8l/min but Spo2 remained low(75-77%). Day-1 ICU: ABG performed simultaneously revealed pH-7.49, SpO2-100%, HCO3-24, pC02-31mmHg, pO2-213mmHg. Chest skiagram (CXR) was within normal limits. 2D-Echo revealed normal left ventricular systolic/diastolic function with ejection fraction of 55%, normal sized chambers, mild concentric LVH, normal valves, no vegetations. Thus with lung and cardiac pathology ruled out, suspicion of methaemoglobinaemia grew for which we sent methaemoglobin level along with G_6PD (Glucose-6- Phosphate Dehydrogenase) levels. His blood investigations were normal except for raised WBC count of 14,700/mm^3 (polymorphs-86%). Two hours in ICU: Patient had an episode of generalisied tonic clonic seizures. Neurologist made an impression of toxic/septic encephalopathy. iv inj lorazepam 4mg was given and inj levetiracetam 1000mg loading dose with 500mg iv bd.

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MRI brain done revealed cytotoxic brain odema. Patient's drowsiness increased. Patient remained cyanosed & SpO_2 remained low (75-80%). G_6PD levels reported normal and suspicion of methaemoglobinemia grew. Inj Methylene Blue (MB-1%), 50mg over 10min in 100ml normal saline (NS) was administered. SpO2 only marginally improved to 80-82%. Repeat dose of 75mg over 10min in 100ml NS administered after 30min. Patient alertness improved, cyanosis started disappearing and SpO2 100% noted on oxygen facemask @ 8l/min, tapered and stopped over next 2-4hrs. Ryles tube feeding initiated.

Day 2 & 3: Fever (101^0F) was noted. Repeat WBC count $21,300/mm^3$ (polymorphs-95%). CXR revealed new infiltrates in right middle & lower zones. Inj piperacillin–tazobactam 4.5gm iv 6hourly started. Patient developed hematuria, icterus (total/ direct/indirect - 9 /2 /7mg%; SGOT/SGPT/LDH - 855/254/752), fall in hemoglobin from 9g% to 5.6g% noted along with normal platelets/APTT/PT with stool for occult blood negative. We suspected methylene blue induced intravascular hemolysis. Managed with 2unit PRBC transfusion and generous intravenous fluids to maintain fluid balance & adequate urine output.

Day 4: Patient's urine cleared, hemoglobin - 7.3g% & icterus (total/ direct/indirect - 4/1 /3mg%; SGOT/SGPT/LDH - 348/133/210) improved and started on liquid diet. 2unit PRBC repeated.

Day 5: Patient's hemoglobin - 9.6g% and no icterus. Patient started on soft oral diet and shifted to HDU (high dependency unit).

Day 6: Results of methaemoglobin level arrived - 42.4%, which confirmed our provisional diagnosis of methaemoglobinaemia. Cause : Saridon induced as this was the only history available to us. A strong possibility that he ingested other toxic substance also present, but no such revalation made. Further hospital stay uneventful and patient discharged 2days later.

DISCUSSION

Methemoglobinemia as a cause of cyanosis should be promptly recognized and treated in all patients where cardiac and lung causes of cyanosis are ruled out. Methaemoglobinaemia can be congenital in which cyanosis is present from birth. It remains asymptomatic and requires no definite treatment (Mansouri 1993). Acquired methemoglobinemia is most common and there is always history of exposure to toxin/drug/chemical. Methaemoglobinaemia can be caused by nitrates/nitrites found in vegetables, industrial and chemical agents, household products (inorganic/organic nitrites & aniline dyes) (Donovan 1990). Therapeutic drugs such as topical and local anesthetic (Chung *et al.*, 2010) (lidocaine, benzocaine, prilocaine), dapsone, acetaminophen, phenacetin, atovaquone, phenazopyridin, primaquine, chloroquine, sulfonamides, metaclorpromide have also been implicated (Ashurst *et al.*, 2010). Benzene derivatives, dinitrophenol, chlorates, nitroethane (nailpolish remover), naphthalene and recreational drugs like phenylamine, cocaine available in market have also been reported to cause methemoglobinemia (Ash-Bernal *et al.*, 2004). Methemoglobin causes shift of oxygen dissociation curve to left and decreases the delivery of oxygen to tissue, causing tissue hypoxia (Sharma *et al.*, 2002). Signs and symptoms co relate with the level of methaemoglobin level in the blood.

</= 1% - Normal.
3-15% - Skin discoloration.
20% - Cyanosis.
25-50% - Headache, lightheadedness, weakness, lethargy, chest pain, confusion.
50-60% - Depressed sensorium, lactic /metabolic acidosis.
60-70% - Delirium, seizure, arrhythmias, hemodynamic unstability.
>70% - Death (Curry 1982; Mansouri 1993; Donovan 1990; Chung *et al.*, 2010; Ashurst *et al.*, 2010; Ash-Bernal *et al.*, 2004; Sharma *et al.*, 2002; Dunn 1998).

Chocolate coloured cyanosis along with dark brown coloured blood which doesn't change colour on exposure to oxygen. Methemoglobinemia should be suspected when O2 Sat (ABG) > O2 Sat (pulse-oximetry). Pulse-oximetry - Methemoglobin absorbs light equally at both wavelengths (940nm/660nm) and has R value of 1 corresponding to SpO2 of 85%. Regardless of patient status (hypoxia/hyperoxia), pulse-oximeter will show 85% or lower (Vijaylakshmi 2002). Multiple wavelength spectrophotometry (Co-oximetry) is based upon analysis of methemoglobin absorption spectra which has peak absorbance at 631nm. Co-oximetry is diagnostic test of choice for methemoglobinemia. Accuracy is within 1% for various forms of hemoglobin (Barker *et al.*, 1989). Evelyn-Malloy method is the confirmatory method for detection of methemoglobin (Curry 1982). The quick bedside diagnosis of methaemoglobinemia can be made by arterial blood gas analysis (co-oximetry) or by continuous non invasive co-oximetry (massimo rainbow pulse co oximetry technology). In our patient, the delayed diagnosis of methemoglobinemia (on day-6 ICU) was because of unavailability of co-oximetry at our institute. In our patient, cause of methemoglobinaemia is thought to be ingestion of 5 tablets of Saridon (Propyphenazone, Paracetamol, Caffeine). There are case reports of methemoglobinemia with acetaminophen when it is either used in high doses or when combined with other methemoglobin inducers (Kobayashi *et al.*, 2000; Nash Oehme 1984) but in saridon, paracetemol is present in very small amount - 250mg which solely is unlikely to cause methemoglobinemia. Leaflet package information about MIGRADON-Tablets (Propyphenazone-250mg, Paracetamol-150mg, Caffeine-46mg) suggests side-effects are very rare (occur in less than 1 out of 10,000 patients) and include allergic reactions of bone marrow (pancytopenia, leucocytopenia, thrombocytopenia, agranulocytosis), certain blood diseases (methemoglobinemia), asthma, hay fever, swelling of the nasal mucous membrane (http://www.trenka.at/index.php?option=com_content&task=view&id=21&Itemid=35&lang=en). Thus, methemoglobinemia is a known but rarely reported complication of saridon. This is because saridon usage has been banned in many countries. This probably is the first ever reported case in rohilkhand region of Uttar Pradesh of methaemoglobinemia due to saridon toxicity. Treatment begins with administration of high flow oxygen and removal of the offending agent. Gastric lavage with activated charcoal is indicated in cases of drug overdose presenting <6hrs. It is

advisable to treat methemoglobin > 20%. Intravenous Methylene Blue (MB-1%) 1-2 mg/kg over 3-5 minutes is treatment of choice & can be repeated at 1 mg/kg after 1 hour if no improvement in symptoms appear. Methylene blue is an oxidant at doses >7 mg/kg & can cause methemoglobinemia. Once methylene blue has been used, co-oximetry cannot be repeated as methylene blue is read as methemoglobin by the machine (Curry 1982; Ying-Fu *et al*., 2012) Methylene blue acts on the NADPH enzyme to exert its effects. Methylene blue donates electrons to the NADPH pathway and thus increases its ability to reduce methemoglobin back to hemoglobin. NADPH is produced using G6PD and therefore in patients with a G6PD deficiency, methylene blue is ineffective & contraindicated. Methylene blue can cause hemolysis and methemoglobinemia in such patients (Curry 1982; Harvey and Keitt 1983). We would like to quote an old saying on the use of methylene blue in methemoglobinemia: "A blue thing (methylene blue) given to a blue (cyanosed) patient turns him red (normal)… but if G6PD deficiency is not taken into account then, a blue thing (methylene blue) given to a blue (cyanosed) patient turns him red (normal) then white (hemolysis-pallor-anemic) then yellow (icterus)".

Conclusion

Methemoglobinaemia should be considered in all cyanotic patients who remain unresponsive to oxygen therapy. Clinical manifestations of methemoglobinemia are mainly because of tissue hypoxia & range from lethargy, weakness, headache to seizures, arrhythmias and death. Saridon as a cause of methemoglobinemia has probably been reported for the first time in rohilkhand region in Indian literature. The importance of knowing G6PD levels before administration of methylene blue and possibility of hemolysis should always be borne in mind. This is of great clinical significance to all practicing physicians as use of saridon is very common in India. A thorough drug history, careful evaluation of patient's condition, a high index of suspicion & alertness of the clinician along with timely discussion with patient's attendants regarding the risks and benefits of methylene blue administration and appreciation of limited experience and literature with this kind of clinical situation will go a long way in improving the patient outcome and safeguarding the clinicians from any possible mishap.

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