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Case report

Methemoglobinemia caused by dapsone overdose: Which treatment is best?

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ABSTRACT

Increase of methemoglobin level is named as methemoglobinemia characterized by functional anemia and tissue hypoxia. Methemoglobinemia can be congenital, but acquired form are more often caused by various drugs and toxins. Methylene blue is the most effective antidote for acquired methemoglobinemia. When methylene blue is not available, alternative treatments such as ascorbic acid and hyperbaric oxygen can be useful. In this paper we presented a case of methomoglobinemia due to dapsone overdose.
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1. Introduction

Methemoglobin (MetHb) (oxidized hemoglobin or ferric hemoglobin) occurs when iron atom in hemoglobin transforms from a ferrous (Fe+2) state into a ferric (Fe+3) state as a result of oxidation. Methemoglobin forms less than 1% of hemoglobin in normal individuals. Cyanosis occurs when 10–25% of total haemoglobin turns into methemoglobin.[1]

Methemoglobinemia can be congenital, but the acquired form is more often caused by various drugs and toxins. Forty different factors, particularly dapsone, nitrates, prilocaine, antimalarial drugs, and sulphonamides, were deemed responsible for acquired methemoglobinemia[2] (Table 1).

Diagnosis of acquired methemoglobinemia depends on clinical suspicion, drug history of the patient, and methemoglobin level measured with co-oximetry.[3]

We report and discuss a patient who developed methemoglobinemia due to overdose of dapsone and was treated with ascorbic acid, hyperbaric oxygen, and methylene blue.

2. Case report

A 34-year-old male patient was admitted to the emergency department with complaints of vomiting, diarrhea, imbalance, and amnesia. Blood pressure was 144/116 mmHg, pulse was 125 beat/minute, respiratory rate was 40/minute, and oxygen saturation was 84%. Physical examination was normal except for his cyanotic appearance. Patient was administered non-rebreather mask at 10 L/min speed. ECG and chest x-ray were normal. The patient's medical history was significant for lichen planus. His regular medications included Dapsone 100 mg tablets twice a day. Patient took 1000 mg Dapsone tablet at one time 6 h before he was admitted to emergency department because he had not taken his medication for three days.

In the blood gas analysis administered while the patient was receiving oxygen, pH was 7.48, pCO_2 was 32.7 mmHg, pO_2 was 141.9 mmHg, HCO_3 was 23.8 mmol/L, base excess was 0.9 mmol/L, carboxihemoglobin rate was 4.9%, lactate was 1.04 mmol/L, methemoglobin rate was 28.2%, and oxyhemoglobin rate was 65.8%. Routine laboratory results were normal apart from mild coagulopathy and leucocytosis. Laboratory values from the fifth and seventh days of the first admission of the patient are demonstrated in Table 2.

Activated charcoal 1 g/kg per was orally administered to the patient. Methylene blue was absent in our city, so we intravenously infused 2000 mg ascorbic acid (30 mg/kg) in an hour. Side effects were not apparent after treatment. Methemoglobin rate was minimally decreased (MetHb rate 21.9% after 8 h presentation), even though not at the required level. Patient was administered hyperbaric oxygen for two hours at 2.5 atm. No side effects occurred, and no reduction in the level of methemoglobin (MetHb rate 24% after 16 h presentation) was observed. 1.5 mg/kg

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Table 1
Laboratory findings of the patient in the case.

	Admission	5 day	7 day
WBC (K/uL)	13.7	8.89	11.9
Hemoglobin (gr/dL)	12.6	9.97	9.8
Hematocrit (%)	38.3	32.1	29.2
Platelet (K/uL)	199	151	262
Sodium (mmol/L)	145	134	138
Potassium (mmol/L)	4.2	4.6	4.9
Total bilirubin (mg/dL)	0.4	2.5	1.9
Direct bilirubin (mg/dL)	0.1	0.4	0.3
Aspartate transaminase (U/L)	24	33	48
Alanine aminotransferase (U/L)	26	28	29
INR	1.3	1.5	1.1
Time of prothrombin (s)	14.9	17.3	12.6

INR: internatioanal normalization ratio, WBC: white blood cell.

methylene blue (100 mg) acquired from neighboring city was administered to the patient at the eighteenth hour of his admission. It was detected that the methemoglobin rate dropped to 2.4% (after 18 h presentation) in 1 h after treatment. Chronologic observation of patient's methemoglobin levels and its relation with treatments administered is shown in Fig. 1. The patient was determined to be healthy and was discharged after one-week follow-up in intensive care unit.

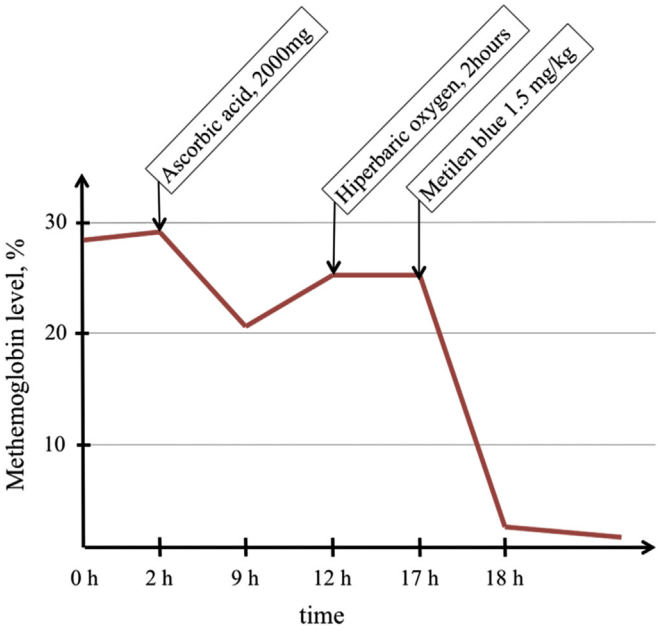

Fig. 1. Chronologic observation of patient's methemoglobin levels and its relation with treatments.

3. Discussion

Methemoglobinemia caused by dapsone is commonly the result of acute poisoning secondary to either accidental ingestion or suicidal purpose. In multicenter study, dapsone has been shown to be a major cause of drug-induced methemoglobinemia.[4]

It was emphasized in literature that multiple dose activated charcoal increased the elimination of dapsone. Repetitive charcoal is recommended to interrupt the enterohepatic circulation of dapsone.[5] In our case activated charcoal was administered once.

Ascorbic acid is a strong reducing agent that takes part in many oxidation–reduction reactions. Ascorbic acid might be fructuous where methylene blue is contradicted due to glucose-6-phosphate dehydrogenase deficiency or is absent. In recent in vitro study and case reports, ascorbic acid is shown to be beneficial in methemoglobinemia treatment. In these studies, ascorbic acid was given in different doses and durations (300 mg/kg IV bolus, 300 mg IV in 24 h, and 10 g IV in 6 h).[6–9] There is no concurrence in the dose and duration of ascorbic acid treatment in methemoglobinemia. In our case, a decrease of 6.3% was observed in the level of methemoglobin with usage of 2 g ascorbic acid. Suboptimal reduction of MetHb rate can be explained with lower dosage and the shorter treatment duration of ascorbic acid.

In cases of life-threatening methemoglobinemia, hyperbaric oxygen therapy is among alternative therapies.[10,11] However, in our case no decline in the level of MetHb with hyperbaric oxygen therapy was observed. This situation can be explained by delayed treatment of hyperbaric oxygen therapy. However, there is no clinical research indicating that hyperbaric oxygen treatment alone is useful.

In serious cases early intervention and tight follow-ups are vital in the treatment of methemoglobinemia, while in mild cases it is enough to cut the responsible agent. The most effective antidote is methylene blue.[2] Methemoglobin rate is not a singly decisive factor for indication of treatment.[12] Methylene blue must be given to patients with symptomatic hypoxia and methemoglobin rate greater than 20%.[13] A 1% solution (10 mg/mL) of methylene blue must be infused intravenously in 1–2 mg/kg doses every 3–5 min to the patient. If no improvement is seen in 30 min, infusion might be repeated in 1 mg/kg dose. Methylene blue should reduce the methemoglobin rate meaningfully in less than 1 h. Drugs such as dapsone and aniline might cause rebound methemoglobinemia in 4 or 12 h after methylene blue treatment is administered.[14] The most common side effect of methylene is for the skin to turn blue. Methylene blue itself may cause methemoglobinemia in doses over 7 mg/kg due to its oxidant effect.[15]

In our case, the agent responsible for toxicity was taken in a high dose and underwent enterohepatic circulation; therefore, the cure could be provided with repetitive methylene blue administrations.

Table 2
Causes of drug induced methemoglobinemia.

Nitrite/nitrates
Amyl nitrate, sodium nitrate, nitro-glycerine, nitroprusside, nitric oxide, nitrous oxide[12]
Antineoplastics
Cyclophosphamide, ifosfamide, flutamide[8]
Local anaesthetics
Benzocaine, lidocain, prilocain[8]
Sulphonamides
Sulfasalazine, sulphanilamide, sulphatiazide, sulfapyridine[2]
Antimalarial drugs
Chloroquine, primaquine[1,12]
Antibiotics
Dapsone, sulfamethoxazole[12]
Several agents
Metoclopramide, sodium valproate, phenytoin[11]

4. Conclusion

Although methylene blue is a conclusive treatment for methemoglobinemia, ascorbic acid should be considered when methylene blue is not available. Methemoglobinemia cases due to drugs that undergo enterohepatic circulation such as dapsone are substantial for recurrence risk, and multiple dose activated charcoal should be applied as supplemental therapy.

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