

Effective role of ascorbic acid as an alternative treatment of methemoglobinemia: A case report

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ABSTRACT

Introduction: Methemoglobinemia is a rare clinical disorder characterized by increase in the blood level of methemoglobin (MetHb) which leads to tissue hypoxia. Methemoglobinemia may be congenital, but acquired type is more common and occurs after exposure to oxidizing agents. Treatment of choice is methylene blue (MB). The side effects of MB restrict its usage in special conditions. Ascorbic acid is a good alternative drug with limited experience in methemoglobinemia. **Case Report:** Eight years old male patient presented with cyanosis after dapsone exposure and diagnosis of methemoglobinemia was confirmed. The patient was managed successfully with ascorbic acid. **Conclusion:** Ascorbic acid could be used as an alternative treatment for methemoglobinemia when methylene blue is not available or contraindicated.

Keywords: Ascorbic acid, Dapsone, Methemoglobinemia

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INTRODUCTION

Methemoglobinemia is a medical emergency requiring immediate treatment. Methemoglobinemia is a condition in which iron atom in hemoglobin is transformed from a ferrous (Fe^{2+}) state to a ferric (Fe^{3+}) state due to effect of oxidizing agent exposure. Thus, beside the inability of methemoglobin (MetHb) to carry O_2 , MetHb shifts the oxygen - hemoglobin dissociation curve to the left, hindering the release of O_2 to the tissues [1]. There are many drugs and toxins such as nitrate, dapsone, prilocaine, antimalarial drugs and sulphonamides responsible for acquired methemoglobinemia [2]. Methylene blue (MB) is considered the commonest and the usual treatment of methemoglobinemia which may lead to serious complications and also it is contraindicated in some patients like those with glucose-6-phosphate dehydrogenase (G6PD) deficiency [3]. In this case report, we presented a child with methemoglobinemia induced by dapsone and the patient was treated and improved with ascorbic acid to highlight its effectiveness as an alternative treatment.

CASE REPORT

An eight years old male child presented with unexplained cyanosis suspecting methemoglobinemia.

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The mother gave history that her child was kept on dapsone since three days (50 mg PO qDay) and last dose was four hours before presentation. The drug was prescribed by child’s doctor for treatment of skin condition. Twenty four hours after starting dapsone treatment the mother noticed bluish discoloration peripherally which intensified and involved lips on the 3rd day of treatment and there was an attack of vomiting. The child was diabetic and kept on insulin but didn’t have any cardiac disease or asthmatic episodes. There was no history suggestive of foreign body inhalation or glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Examination of the child revealed central and peripheral cyanosis. The patient was conscious, alert (Galscow Coma Scale (GCS) 15/15), pulse rate was of 112/minute (min), regular rhythm, systolic blood pressure of 100 mmHg, respiratory rate of 24/min, and body temperature of 37° c axillary. Oxygen saturation with pulse oximetry was 78% on room air. The rest of the physical examination was normal.

Blood collected for laboratory investigations was chocolate brown in color. Laboratory results revealed hemoglobin (11.7 g/dl) and total leukocyte count ($6.5 \times 10^3/\text{mm}^3$), Platelets count (305000/ cmm). Serum bilirubin was 1.9 mg%, blood urea, creatinine and serum electrolytes were within normal limits. Arterial blood gas analysis was (pH - 7.36, PCO_2 - 33.5mmHg, PO_2 - 65.1mmHg, HCO_3 - 23.8mEq/l and SpO_2 - 92.3%). The methemoglobin level was 24.8%. There was saturation gap between SpO_2 in ABG and pulse oximetry. The investigations are presented in (Table 1).

In view of history of dapsone exposure, cyanosis, chocolate color of blood and the saturation gap, a clinical diagnosis of dapsone induced methemoglobinemia was made and was confirmed by MetHb level.

Table 1: Laboratory results follow up

Laboratory investigation	On admission	On discharge
pH	7.36	7.33
PCO_2 (mmHg)	33.5	48
PO_2 (mmHg)	65.1	70
O sat. %	92.3	90
Met Hb%	24.8	1.9
Na (mEq/l)	133	135
K (mEq/l)	4.2	5.3
Hb g/dl	11	10.8
PLT/ mm^3	305	275
TLC/ mm^3	6.5	8

Abbreviations: pH: negative log of hydrogen ion, PCO_2 : Partial pressure of carbon dioxide, PO_2 : patial pressure of oxygen, sat: saturation, MetHb: methemoglobin, Hb: hemoglobin, PLT: platelet count. TLC: total leukocyte count.

After confirming diagnosis, dapsone was stopped and the child was kept on oxygen inhalation by nasal prong, while on oxygen, the saturation only raised to 83%. Multiple dose activated charcoal 1g/kg was given orally to the child, methylene blue was not available, thus slow intravenous administration of 1gm ascorbic acid was started . Injection ascorbic acid was continued as 1gm/4hs (for 8 doses), no side effects occurred. The child showed signs of improvement, saturation gap and cyanosis disappeared, MetHb level was repeated after six hours of ascorbic acid therapy, day two and day three of admission which was 12.6%, 5.7% and 1.9% respectively, indicating successful therapy with ascorbic acid. The child was discharged with full recovery on the third day of admission.

DISCUSSION

Methemoglobinemia is a life-threatening condition; there is infrequent data on this condition in Africa [1]. MetHb is the oxidized form of hemoglobin that is unable to bind oxygen and also shift oxygen dissociation curve to the left, thus tissue oxygenation decreased resulting in cyanosis [3].

Toxic methemoglobinemia results from various drugs and toxins with oxidizing effects. The most common agents include: Nitroglycerine, dapsone, sulfonamides, phenacetin, and local anesthetics [2].

Methemoglobinemia in the present case was developed after therapeutic dose of dapsone. Dapsone is commonly used in treatment of leprosy but its use has expanded into the treatment of many skin diseases [4]. Methemoglobinemia associated with dapsone commonly as an adverse effect of the drug like patients use dapsone for pseudomonas jiroveci pneumonia prophylaxis in stem cell transplantation [5, 6].

Methemoglobinemia diagnosis is difficult and should be suspected in patient with unexplained cyanosis and low saturation on pulse oxymetry not responding to oxygen in addition to the saturation gap between arterial blood gas analysis and pulse oximetry which help in the diagnosis when MetHb level is not available [1, 6]. These were the clinical features of the present case, and the diagnosis was confirmed by MetHb level assessment.

The clinical picture of methemoglobinemia depends on the methemoglobin level in the blood. Cyanosis starts with MetHb around 15%, the chocolate brown blood appear with level 15-30%. Dyspnea develops between 30-50%. Severe manifestations as metabolic acidosis, arrhythmias, coma and convulsions occur at 50-70%. Methemoglobin levels of 70% or more may be fatal, however mortality with lower level of MetHb(10.8%) have also been reported [1].

Dapsone induces a continuing oxidative stress due to the long half-life, thus serial measurements of methemoglobin levels should be done [4]. Initial management of acquired methemoglobinemia includes

Table 2: Case reports of methemoglobinemia treated with ascorbic acid

Author	Age	Causative agent	Initial MetHb (%)	Indication of ascorbic acid	Dose of Ascorbic acid	Duration of therapy (hours)	Other specific treatment
Deo P. et al. [8]	15 years	Napthalene ball	25.3	G6PD deficiency	0.5 gm q 12 hs (16 doses)	192	No
Reeves D. et al. [9]	46 years	Rasburicase	14.5	G6PD deficiency	5 gm q 6 hs (6 doses)	36	No
Sahu K. et al. [10]	45 years	Dapsone	18.3	Unavailable MB	1 gm q 12 hs (14 doses)	168	No
Tokar I. et al. [2]	34 years	Dapsone	28.2	Unavailable MB	2 g (1 dose)	1	Hyperbaric oxygen, MB
Topal H. et al. [7]	70 days	local prilocaine	24.5	Unavailable MB	300 mg (24 hs infusion)	24	No
Current case	8 years	Dapsone	24.8	Unavailable MB	1gm q 4hs (8 doses)	32	No

Abbreviations: MB: Methylene blue, hs: hours, G6PD: glucose-6-phosphate dehydrogenase

identification and discontinuation of the offending agent and increasing tissue oxygenation by administration of reducing agent as MB and ascorbic acid [1].

Methylene blue is the usual treatment for methemoglobinemia, however methylene blue is potentially hazardous. Methylene blue can conversely cause methemoglobinemia in high doses by its oxidant effect and induce hemolysis in cases of G6PD deficiency in addition to turning the skin blue, which is the commonest side effect [2, 7]. Therefore, alternative treatments are required. Ascorbic acid is a strong reducing agent that takes part in many oxidation–reduction reactions, so ascorbic acid directly reduce methemoglobin and is proven to treat cyanosis [3]. In many case reports, ascorbic acid was used successfully in treatment of methemoglobinemia with different doses and durations as discussed in Table 2 [8–10]. In the present case, a decline of 12.2% in methemoglobin levels after six hours of administration of 2 g ascorbic acid was noticed.

On contrary, other study reported that acquired methemoglobinemia does not respond to ascorbic acid, because its capacity to reduce MetHb is much inferior to that of endogenous enzymatic systems [11]. However, failure of ascorbic acid in treatment of methemoglobinemia could be attributed to using lower doses or shorter durations of therapy [2].

The use of activated charcoal improve clearance rates of methemoglobin at lower concentrations of methylene blue, also multiple dose activated charcoal enhance elimination of dapson by interrupting its enterohepatic circulation. The child was given multiple doses of activated charcoal in the present study [2, 5].

CONCLUSION

Although, there is an experience with the use of methylene blue as specific antidote in treatment of methemoglobinemia, ascorbic acid should be used as

an alternative treatment when methylene blue is not available or contraindicated. Successful management of the present case highlight the importance of ascorbic acid as effective, cheap, and easily available alternative with no side effects. Dapsone has a long half-life and undergo enterohepatic circulation so may cause recurrence of methemoglobinemia, thus multiple dose activated charcoal should be given. Dapsone may induce life-threatening methemoglobinemia so restriction of its expanded use is recommended.

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Author Contributions

Eman Abdelfath Mohammed – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

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Alaa Essam Mohmoud – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor of Submission

The corresponding author is the guarantor of submission.

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Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest

Authors declare no conflict of interest.

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