Case Report

Clofazimine-induced methemoglobinemia: A rare incidence

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Abstract

Clofazimine is commonly used for the treatment of leprosy and chronic use of it can lead to methemoglobinemia, which is a rare but major concern. Iron of hemoglobin remains in the form of ferric (Fe3+) in methemoglobinemia as compared with ferrous form (Fe2+) in normal situation. This transformation prevents oxygen carriage and results in higher level of MetHb in blood which could be dangerous to life. In normal patients the level of MetHb is <1%. We report a case where acute ingestion of many tablets of clofazimine resulted in methemoglobinemia. Cyanosis was not apparent in this case leading to delayed diagnosis, and despite >30% MetHb levels, the clinical presentation was not very suggestive. Because of the nonavailability of intravenous methylene blue and parenteral ascorbic acid, tablet ascorbic acid was used for the management. Gradual decrease of MetHb levels was observed, with amelioration of symptoms and improvement in patient's condition. Review of the literature failed to reveal publication of acute methemoglobinemia with such presentation in the past. Awareness about possibility of methemoglobinemia and its possible contributors will help primary care physician and emergency physician suspect this condition early in patients presenting with history of unknown drug overdose and work in proper direction.

Keywords: Ascorbic acid, clofazimine, methemoglobinemia, methylene blue, overdosage

Introduction

Clofazimine is commonly used for treatment of leprosy and its chronic use can cause skin pigmentation and rarely methemoglobinemia. Higher level of MetHb in blood (ferric form) may result in anemic hypoxia.[1] Methemoglobinemia depending upon the blood level can cause mild-to-severe life-threatening symptoms.[2] Despite very high concentration of MetHb, lack of cyanosis and associated serious symptoms were a rare presentation in this case of accidental overdosing caused by consumption of multiple tablets of clofazimine (no such case reported in the literature). Methemoglobinemia was not suspected initially because of rare presentation. Oral ascorbic acid and other supportive management helped in reduction of MetHb level and clinical improvement.

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Case History

A 55-year-old hypertensive and diabetic female was brought to emergency department with alleged history of vomiting following accidental intake of several tablets while at home. She had been prescribed tab. clofazimine for Hansen's disease and tab. prednisolone for backache long ago, but had not taken the medicines in the last 2 months.

While examination, she was conscious (E4M6V4) with slightly unclear speech, and the investigations revealed temperature was 99°F, pulse rate 96/min, and blood pressure 140/80 mmHg with no pallor, icterus, or cyanosis. Respiratory rate was 26/min with mild accessories and 87% SpO2 with oxygen 5 L/min. She was initially treated in ward with gastric lavage, oxygen, intravenous (iv) fluids, antacids, and antiemetics. Investigations including ECG, chest X-ray, 2D echo were within normal limits. High blood sugar of 444 mg/dL (ketones absent) was managed with insulin.

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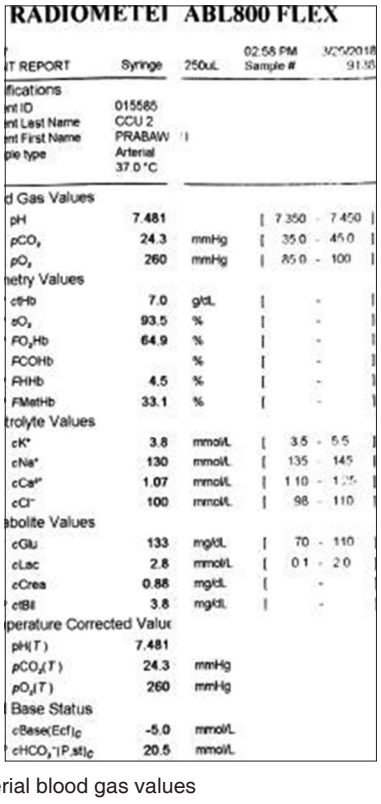
Her SpO2 further deteriorated to 78% with oxygen 10 L/min and she was shifted to critical care unit subsequently. Arterial blood gas analysis showed pH 7.43, pCO2 23.4 mmHg, pO2 191 mmHg, SaO2 94%, lactate 2.7 mmol/L, serum creatinine 0.92 mg/dL, and base excess − 7.9. Marked difference between SpO2 and SaO2 values was appreciated and MetHb level was found to be high (26.7 mg%). Blood gas was repeated after 2 h to verify MetHb level, which showed a rising trend (33.1 mg%) as shown in Figure 1. The provisional diagnosis was clofazimine-induced methemoglobinemia.

Blood test for G6PD deficiency was negative and treatment with intravenous methylene blue and ascorbic acid was planned, but both medications were not available in local pharmacies. Procurement from outside the town was time-consuming. As last resort, oral ascorbic acid 500 mg 6 hourly (2000 mg/day) and tab. N-acetylcysteine 600 mg 8 hourly were used along with other supportive treatment. MetHb level started showing a declining trend after 24 h. Her clinical condition improved over next few days. Serial arterial blood gas (ABG) tests showed a downward trend of MetHb [Table 1], indicating that the therapy was effective. She was shifted to ward on Day 4 and then discharged on Day 9 in stable condition after counseling. ABG report showed normal MetHb levels.


RADIOMETER ABL800 FLEX

T REPORT	Syringe	250uL	02:58 PM Sample #	M/D/2018 91:55
fications				
nt ID	015585			
nt Last Name	CCU 2			
nt First Name	PRABAW			
pie type	Arterial			
	37.0 °C			
d Gas Values				
pH	7.481		[7.350 - 7.450]	
pCO_2	24.3	mmHg	[35.0 - 45.0]	
pO_2	260	mmHg	[85.0 - 100]	
metry Values				
ctHb	7.0	g/dL	[-]	
sO_2	93.5	%	[-]	
FO_2Hb	64.9	%	[-]	
FCOHb		%	[-]	
FHHb	4.5	%	[-]	
FMetHb	33.1	%	[-]	
trolyte Values				
cK+	3.8	mmol/L	[3.5 - 5.5]	
cNa+	130	mmol/L	[135 - 145]	
cCa++	1.07	mmol/L	[1.10 - 1.25]	
cCl-	100	mmol/L	[98 - 110]	
abolite Values				
cGlu	133	mg/dL	[70 - 110]	
cLac	2.8	mmol/L	[0.1 - 2.0]	
cCrea	0.88	mg/dL	[-]	
ctBil	3.8	mg/dL	[-]	
perature Corrected Value				
pH(T)	7.481			
$pCO_2(T)$	24.3	mmHg		
$pO_2(T)$	260	mmHg		
Base Status				
cBase(Ecf)c	-5.0	mmol/L		
$cHCO_3^-$(P,st)c	20.5	mmol/L		

Figure 1: Arterial blood gas values

Table 1: Trend of MetHb level

Days	Day 1	Day 1	Day 2	Day 4	Day 8
MetHb %	33.5	31.5	26.5	18	7.2
SpO2	78	82%	85%	87%	92%
SaO2	94%	96%	98%	98%	98%

Discussion

Methemoglobinemia is a rare disorder characterized by increased MetHb in blood, and the normal levels being under 1%. The oxidized ferric form prevents oxygen-carrying capacity of hemoglobin.[3] Deficiency of MetHb reductase and presence of abnormal Hb are inherited while it is acquired subsequent to chronic use of drugs and chemicals exposure.[4]

Methemoglobinemia is suspected based on clinical findings, that is, generalized cyanosis, not co-relating with respiratory status and normal PaO2.[5] Pulse oximeter usually reads 85% saturation irrespective of actual oxygenation status and co-oximetry is therefore advocated. SaO2–SpO2 gap of more than 5% should also be viewed seriously.[6] Clofazimine, an anti-myobacterial agent is used for treatment of leprosy.[7] Clofazimine-induced methemoglobinemia as a result of overdose has not been reported in the literature and this is a key finding in our patient. Absence of cyanosis or failure to detect was intriguing but this can be missed in dark-colored individual and under artificial light. Both conditions were true in this case. The SaO2–SpO2 difference helped in suspecting the abnormality and very high MetHb level clinched the diagnosis here. The oximeter showed quite low reading (<80%) in contrast to the 85% saturation expected, as highlighted in the literature.[8-10] Excessive reliance on cyanosis therefore is not advocated.

Another interesting feature in our case was lack of serious signs and symptoms despite high level of MetHb (>30%). There was no breathlessness, headache, dizziness, or syncopal attacks in our patient. This suggests that patient can tolerate methemoglobinemia levels as high as 33.5% without any deterioration contrary to earlier reports that serious symptoms occur above 30%. Our patient tolerated it as evident by acceptable base excess and lactate levels. Low PaCO2 was possibly because of anxiety-induced hyperventilation, and noninvasive ventilator support was provided for assistance.

Advocated treatment of methemoglobinemia includes oxygen therapy, hyperbaric oxygen, methylene blue, ascorbic acid, exchange transfusion, and supportive therapy.[11] Methylene blue (1%) solution has been the drug of choice, at dose of 1–2 mg/kg and repeated after 30 min, particularly when MetHb level is above 30% or patient is symptomatic at lower levels.[12] Availability of iv methylene blue, however, is an issue because of its infrequent consumption. It is also known to cause serious complications in patients having G-6-PD deficiency, and extreme caution is necessary while using the medication. Care is also exercised in impaired renal dysfunction.[12] Ascorbic acid is another option when methylene blue is nonavailable or contraindicated.[13] Ascorbic acid has been found to be beneficial but advocated regime varies from 300 mg to 2 gm iv over 24 h to 10 gm iv in 6 h.[14] Positive result has been observed in 1–4 days.[14,15] N-acetylcysteine, ketoconazole, and cimetidine are also promising.[16-18]

Owing to nonavailability of methylene blue and iv ascorbic acid, we resorted to oral ascorbic acid, although this route has not been prescribed in the literature. Tab. vitamin C 500 mg 6 hourly amounting to 2000 mg/day was started. Positive impact was observed within 24 h and it finally brought down MetHb to 7.2% on Day 8.

Summary

Acute excessive ingestion of clofazimine leading to methemoglobinemia should be borne in mind when dealing with patients of unknown drug poisoning. Cyanosis might not be a standard finding in all such cases and its absence or lack of detection could be misleading. Higher SaO2–SpO2 gap should be viewed with suspicion and MetHb assessment should be done.

On the basis of this case, we feel that treatment modality should be based on severity of presentation and not on elevated MetHb level alone. Reported cases in the past have been treated aggressively either because of precarious condition or very high MetHb levels. Disparity between severity of presentation and MetHb is possible, therefore, should not be ignored even if presentation is not matching to the concentration of MetHb. When such presentations of unknown drug overdose are seen by the primary care physician or at the emergency, a low SpO2 should trigger an alarm.

Awareness about the possibility of methemoglobinemia, its possible contributors and intriguing history will help the primary care physician to channelize further treatment in proper direction. Vitamin C can be used as an option to manage MetHb if situation so demands, although dramatic response might not be observed.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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