Case Reports
Toxicology International, *Sept-Dec 2015 / Vol-22 / Issue-3, 147-150*
ISSN (Print) : 0971-6580
ISSN (Online) : 0976-5131
DOI: 10.22506/ti/2015/v22/i3/137639

A Case of Severe Methemoglobinemia with Shock and High Saturation Gap following Suicidal Ingestion of Sodium Nitrite-Saved by Oral Methylene Blue

Pahadiya Hans Raj, Choudhary Akanksha, Lakhotia Manoj, Gandhi Ronak, and Mohamed Sadik

[1]Department of Medicine, Dr. SNMC, Jodhpur - 342003, Rajasthan, India; drhans05sms@gmail.com
[2]Department of Anesthesia, Dr. SNMC, Jodhpur - 342003, Rajasthan, India

Abstract

Here we report a case of sodium nitrite ingestion for suicidal attempt, presented in unconsciousness, shock and deeply cyanosed condition. He was pulseless and had no recordable BP with methemoglobin level of 77% and saturation gap of 20. He was put on ventilator in ICU and treated with ionotropes, oral methylene blue and parental ascorbic acid. He completely recovered after two days with normal methemoglobin level. Survival in a case of methemoglobinemia with extremely high level of methemoglobin, non recordable BP and deep cyanosis is rarely reported. We report this case for awareness about the severity of signs and symptoms depend on the methemoglobin concentration in blood, false results of pulse oximetry and high saturation gap in methemoglobinemia, and about the management of the lethal effect of poisoning.

Keywords: Methemoglobinemia, Oral Methylene Blue, Saturation Gap, Shock, Sodium Nitrite

Received: 28-04-2015 **Revised:** 26-10-2015 **Accepted:** 28-10-2015

1. Introduction

Sodium nitrite is used in industry during manufacture of synthetic dyes. It is also used as a colour enhancer in meats, a preservative, an antimicrobial agent, and therapeutic agent. Poisoning by sodium nitrite is mostly accidental and rarely suicidal. Acute exposure to excessive dosages leads to methemoglobinemia which is responsible for the signs and symptoms of poisoning. Sodium nitrite is a strong oxidiser which oxidizes the Fe^{2+} of the hemoglobin to Fe^{3+} and converts hemoglobin to Methemoglobin (MetHb), which loses its ability to bind and transport oxygen and leads to hypoxia (Hall *et al.*, 1986). We herein report a case of acute methemoglobinemia with shock due suicidal ingestion of unknown quantity of sodium nitrite. Our patient had very high MetHb level in blood, high saturation gap, non recordable BP, deep cyanosis and was pulseless. He was successfully managed in the ICU on ventilator support with inotropes, oral methylene blue and parental ascorbic acid.

2. Case History

An 18-year-old, dye worker, unmarried male brought in emergency department in unconscious state 2 hours after ingestion of an unknown quantity of an unknown substance for suicidal attempt. Unconsciousness was preceded by 8-10 episodes of watery vomiting. His family involved in dye industry and they usually kept this substance at their home for printing of cloths. This was identified as sodium nitrite by attending physician (Figure 1). On examination he was unconscious, and not responding to command, collapsed and deeply cyanosed. He was pulseless, blood pressure was not recordable, respiratory rate was 12 breaths/min and periphery of

* *Author for correspondence*

body was cool and clumsy. His pupils were bilaterally semi dilated and sluggishly reactive to light. Pulse oximetry showed oxygen saturation of 80%. Urgently blood samples for routine investigations and Arterial Blood Gas analysis (ABG) drawn, the blood was chocolate brown in colour. Intravenous GNS and vasopressor support with nor-adrenaline was started. We passed oxygen through the blood sample, but the colour did not change. He was shifted to ICU and put on ventilator. He was ventilated on SIMV mode with PEEP 12 and fiO_2 100%. The initial ABG showed a pH of 7.26, PO_2- 553 mm Hg, SpO_2- 100%, PCO_2- 27.4 mm Hg, HCO3- 12.1 mEq/L and MetHb levels- 77.0%, Despite full ventilatory support his cyanosis and BP was still not improving. Laboratory profile showed haemoglobin of 12.5 g/dL, leukocyte of 8750/mm^3 with normal differential count. Platelet counts were 235000/mm^3. Liver functions, renal function and electrolytes were within normal limit. ECG showed sinus tachycardia. His chest X-ray, echocardiogram and urinalysis were normal. Methemoglobinemia and central cyanosis was considered because of sodium nitrite dye poisoning. He was given oral methylene blue (50 mg) with naso-gastric tube in a dose of 1 mg/kg body weight as an antidote. Later on after 2 hour MetHb level decreased to 45%, cyanosis, blood pressure and sensorium improved (Table 1). Two more dosage of methylene blue was repeated at interval of 4 hours. He was also treated with parental 500 mg ascorbic acid 12 hourly for two days. Vasopressor support was tapered off. After 24 hour his MetHb level, BP, oxygen saturation and saturation gap returned to normal level and weaned off from ventilator. On the 4th day he was discharged in stable hemodynamic condition. We tabulated the results of few cases of sodium nitrite poisoning from Pubmed to compare with our case (Table 2).

Table 1. Serial Arterial Blood Gas (ABG) analysis

Time/ Parameters	At admission (0 hours)	4 hours	8 hours	12 hours	24 hours
Ph	7.26	7.35	7.36	7.4	7.43
PaO2 (mmHg)	553	315	253	76	91
PaCO2(mmHg)	27.4	35	33.6	32	33.6
Methemoglobin%	77.0	45.9	20.8	7.5	0.7
HC03- mmol/L	12.1	19	18.6	22	21.9
SaO2%	100	99.9	99.8	97.1	97.3
SpO2% (Pulse Oximetry)	80	85	85	90	97
Saturation Gap	20	14.9	14.8	7.1	0.3

Table 2. List of reported cases of methemoglobinemia due to sodium nitrite poisoning and outcome

Reports	MetHb (%)	Treatment	Out-come	General condition BP mmHg
Gowans et al.(1990)	34% (Postmartum)	i.v. MB	E	Cyn, resp dis, SBP-90
Nishiguchi et al.(2015)	83.4% (Autopsy)		E	
Saigal et al. (2014)	64.2%	i.v. MB	S	Cyan, uncon,SBP-60
Sohn et al. (2014)	06 cases;32.4-71.5	i.v. MB	All S	Cyn, resp dis, seizure
Harvey et al.(2010)	82.6	i.v. MB	E	Uncon, Cardiac arrest
(CDC)	05 cases; 21.1, 62, 49.5, 72.7, 87.0	i.v. MB	All S	Dizzines, headache, cyn, resp dis, uncons, shock
Kaplan et al. (1990)	10 cases; One had 79	i.v. MB iv AA	9-S 1-E	Cyno, tachyc, resp dis,uncon, shock
Saito T et al. (1996)	76 (Postmartum)	i.v. MB	E	
El-Husseini, et al.(2010)	10.8	i.v. MB	E	
Matteucci et al. (2008)	Case 1: 32.70 Case 2: 63.00	i.v. MB& Hyperbaric-O2	S	Cyn,tachyc, resp dis, uncon
Maric et al. (2008)	05 Cases 21-57	MetHb 21-Sup i.v MB	All S	Cyn, resp dis
Jain MD et al. (2013)	55.2	i.v. MB oral AA	S	Cyn, tachyc, syncope
Walley and , Flanagan (1987)	03 Cases: 23, 7.7, 66	i.v. MB	S	Cyno, tachyc, resp dis.
Ellis M et al. (1992)	2 Cases: 75	i.v. MB	E	Cyno, tachyc, uncon
Finan et al. (1998)	03 cases; 77, 38	i.v. MB	S	Cyno, tachyc, uncon.
Chongtham et al. (1997)	56.5	Oral MB, iv AA	S	V, uncon;120/70
Pahadiya et al. (2016)	66.7	oral MB oral AA	S	cyno, uncon, tachyc 110/78
Our case	77	Oral MB, iv AA	S	Cyno, uncons Not recordable

Abbervation: MB- Methylene blue, AA- Ascorbic acid, i.v.- intravenous, Sup- Supportive, E- Expired, S-Survived, V- Vomiting, Cyn-Cynosis, Uncos- Unconscious, Resp Dist- Respiratory distress, Tachyc- Tachycardia.

3. Discussion

Methemoglobinemia is an unusual and potentially fatal condition. The common causes of methemoglobinemia are the ingestion or inhalation of oxidizing agents such as sodium nitrates or nitrites, aniline dye, nitrobenzene, benzocaine, naphthalene and Dapsone (Wright *et al.,* 1999). When MetHb concentration in blood exceeds the normal level (0-1 %), is called methemoglobinemia. Sodium nitrite poisoning can occur via ingestion or inhalation route. The World Health Organization has indicated a toxic dose of 0.4-200 mg/kg body weight and a lethal dose of 33-250 mg/kg body weight for nitrites taken orally (Mary Denshaw-Burke , 2014). The fatal period for nitrites is within few hours to few days. Sodium nitrite is a strong oxidiser, it oxidise ferrous iron (Fe^{2+}) of haemoglobin to ferric iron (Fe^{3+}) and form MetHb. This molecule impairs the ability of hemoglobin to transport oxygen, produces functional anemia, and leads to tissue hypoxia (Hall *et al.,* 1986). These patients have characteristically "Chocolate brown" colour of arterial blood because of cyanosis. Cyanosis in Methemoglobinemia does not improve with oxygen supplementation. In these patients oxygen saturation is not measured accurately by conventional pulse oximetry. The pulse oximeter only measures the relative absorbance of 2 wavelengths of light (660 nm and 940 nm) to differentiate oxyhemoglobin from deoxyhemoglobin. MetHb increases absorption of light at both wavelengths (more at 940 nm) and therefore offers optical interference to pulse oximetry by falsely absorbing light, hence measure incorrect. ABG usually shows falsely elevated value of oxygen saturation in these patients. The difference between the oxygen saturation measured on pulse oximetry and the oxygen saturation calculated on the basis of ABG results is called as "saturation gape" is a possible clue for methemoglobinemia. Co-oximetry or multi-wavelength pulse oximeters should be performed if available (Mary Denshaw-Burke; Pahadiya *et al. (2016).*

The symptoms and signs of sodium nitrite poisoning are usually related to anoxia resulting from MetHb in the blood. The patients with MetHb level approximately 15-20 % develop cyanosis and chocolate brown blood, but are usually asymptomatic. The common presenting symptoms of poisoning are generalized blue-grey cyanosis, headache, fatigue, dizziness, exercise intolerance, syncope, tachycardia, and CNS depression. Coma, seizures, dyspnoea, cardiac failure, shock, cardiac arrhythmias, and metabolic acidosis and even death are common over concentration of MetHb more than 50. When the MetHb levels exceed 70% the condition can be fatal and associated with high incidence of mortality. Sodium nitrite poisoning leads to hypotension because of potent vasodilatory property of the nitrates through nitric oxide generation (Hall, 1986; Mary Denshaw-Burke).

The treatment of nitrite poisoning requires supportive measures including oxygen therapy, respiratory support, gastric lavage and correction of failure, shock and acid-base imbalance. The methylene blue is the antidote of choice in sodium nitrite poisoning. Methylene blue cause reduction of Fe^{3+} ion in haemoglobin to Fe^{2+} ion in the presence of cytochrome-b5-MetHb reductase or NADPH MethHb reductase enzyme so that hemoglobin can accept oxygen and transport resulting in decreased MethHb. Patients with congenital NADPH MetHb reductase deficiency and human red cells deficient in glucose-6-phosphate dehydrogenase are more susceptible to nitrates and nitrites. These patients do not respond to Methylene blue as glucose-6-phosphate dehydrogenase enzyme is essential for the generation of NADPH (Hall, 1986; Mary Denshaw-Burke). Also, there is increased risk for hemolysis when methylene blue given to such patients. Patient with severe renal dysfunction also have contraindication to give methylene blue. Dextrose should also be given because it is a source of NADPH through HMP shunt which is necessary for methylene blue to be effective. Methylene blue is indicated in acquired methemoglobinemia when patient is symptomatic and MetHb levels are greater than 20% (Mary Denshaw-Burke). The initial dosage is 1 to 2 mg/kg or 0.1 to 0.2 ml/kg of a 1% solution, administered intravenously over 5-10 minutes. Dose can be repeated if patient is still symptomatic after 1-2 hour. The total dose of methylene blue should not exceed 7 mg/kg because methylene blue itself is an oxidant, it can cause induce methemoglobinemia and hemolysis at higher doses (Hall, 1986; Mary Denshaw-Burke). In the unavailability of IV preparation of methylene blue, oral can be given and successfully managed (Chongtham *et al.,*1997). Ascorbic acid also reduces the oxidised haemoglobin but effect is very slower. N-acteyl cysteine has also been used in few studies but not approved for methemoglobinemia treatment (Mary Denshaw-Burke). Hyperbaric oxygen and exchange transfusion are reserved only for those patients who do not respond to methylene blue or have contraindication (Mary Denshaw-Burke).

Our patient presented in altered sensorium with shock, was pulse less and in deeply cyanosed condition.

He had chocolate brown colour of blood with extremely high level of MetHb and saturation gap of 20. Shock was because of vasodilator property of nitrites. He was treated successfully with 3 doses of oral methylene blue and parental ascorbic acid in ICU setting on ventilator till normalisation of MetHb level and stable hemodynamic. Hence in a suspected case of methemoglobinemia, antidote methylene blue should be given in IV or oral preparation as availability to overcome the toxic effect of MetHb and save the life of patient. Ascorbic acid can also be added.

4. Conclusion

In conclusion that in a case of unexplained central cyanosis and hypoxia, with chocolate brown arterial blood which is not reversible with oxygen supplementation and saturation gap more than 5, methemoglobinemia should be considered as a differential diagnosis in which there is no obvious cardio-respiratory cause. In these cases pulse oximetry can give faulty results. The symptoms and signs of poisoning depend on level of MetHb in blood. At low concentration cyanosis, gastrointestinal upset and tachycardia is common while at high concentration patient may develop shock, unconsciousness cardio-respiratory arrest. Methemoglobinemia is a medical emergency; hence early recognition and cause for methemoglobinemia should be looked urgently and treatment of MetHb with methylene blue and ascorbic acid should be undertaken. In unavailability of IV methylene blue, oral preparation can be given and life can be saved successfully even in fatal poisoning with extremely high level of MetHb.

5. References

1. Hall AH, Kulig KW, Rumack BH. Drug- and chemical-induced methaemoglobinaemia. Clinical features and management. Med Toxicol. 1986; 1:253–60.
2. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: Etiology, pharmacology, and clinical management. Ann Emerg Med. 1999; 34:646–56.
3. Mary Denshaw-Burke. Methemoglobinemia. Available from: emedicine.medscape.com/article/204178
4. Feiner JR, Bickler PE, Mannheimer PD. Accuracy of methemoglobin detection by pulse CO-oximetry during hypoxia. Anesth Analg. 2010; 111(1):143–8.
5. Chongtham DS, Phurailatpam J, Singh MM, Singh TR. Methaemoglobinaemia in nitrobenzene poisoning. J Postgrad Med. 1997; 43:73–4.
6. Gowans WJ. Fatal methaemoglobinaemia in a dental nurse. A case of sodium nitrite poisoning. Br J Gen Pract. 1990; 40:470–1.
7. Nishiguchi M, Nushida H, Okudaira N, Nishio H. An autopsy case of fatal methemoglobinemia due to ingestion of sodium Nitrite. J Forensic Res. 2015; 6:1.
8. Saigal R, Goyal LK, Agrawal A, Wadhwani D, Mittal P, Yadav RN, Meena PD. Methaemoglobinaemia as a result of nitrite poisoning. J Assoc Physicians Ind. 2014; 62:737–8.
9. Sohn CH, Seo DW, Ryoo SM, Lee JH, Kim WY, Lim KS, Oh BJ. Life-threatening methemoglobinemia after unintentional ingestion of antifreeze admixtures containing sodium nitrite in the construction sites. Clin Toxicol (Phila). 2014; 52(1):44–7.
10. Harvey M, Cave G, Chanwai G. Fatal methaemoglobinaemia induced by self-poisoning with sodium nitrite. Emerg Med Australas. 2010; 22:463–5.
11. Centers for Disease Control and Prevention (CDC). Methemoglobinemia following unintentional ingestion of sodium nitrite- New York; 2002. MMWR Morb Mortal Wkly Rep 2002; 51:639–42.
12. Kaplan A, Smith C, Promnitz DA, Joffe BI, Seftel HC. Methemoglobinaemia due to accidental sodium nitrite poisoning. Report of 10 cases. S Afr Med J. 1990; 77(6):300–1.
13. Saito T, Takeichi S, Yukawa N, Osawa M. Fatal methemoglobinemia caused by liniment solutions containing sodium nitrite. J Forensic Sci. 1996; 41(1):169–71.
14. El-Husseini A, Azarov N. Is threshold for treatment of methemoglobinemia the same for all? A case report and literature review. Am J Emerg Med. 2010; 28:748.e10.
15. Matteucci O, Diletti G, Prencipe V, Giannatale ED, Marconi MM, Migliorati G. Two cases of methemoglobinaemia caused by suspected sodium nitrite poisoning. Vet Ital. 2008; 44(2):447–53.
16. Maric P, Ali SS, Heron LG, Rosenfeld D, Greenwood M. Methaemoglobinaemia following ingestion of a commonly available food additive. Med J Aust. 2008; 188:156–8.
17. Jain MD, Nikonova A. Methemoglobinemia from curing salt. CMAJ. 2013; 185(16):771.
18. Walley T, Flanagan M. Nitrite-induced methaemoglobinaemia. Postgrad Med J. 1987; 63:643–4.
19. Ellis M, Hiss Y, Shenkman L. Fetal methemoglobinemia caused by inadvertent contamination of a laxative solution with sodium nitrite. Isr J Med Sci. 1992; 28(5):289–91.
20. Finan A, Keenan P, Donovan FO, Mayne P, Murphy J. Methaemoglobinaemia associated with sodium nitrite in three siblings. BMJ. 1998; 317:1138–9.
21. Pahadiya HR, Lakhotia M, Gandhi R, Prajapati GR.The Mysterious Story of brown blood and high Saturation Gap. Indian J Hematol Blood Transfus. 2016;32:517-8.