Methemoglobinaemia in Cardiac Patients on Nitrate Therapy

Abdel Aziz A. Ghanem, Sohayla M. Attalla, Sherif A. Sakr, Helmy M. Bkr

Corresponding author: Sohayla M. Attalla (sohayla55@yahoo.com)

Correspondence concerning this article should be addressed to Dr. Sohayla M. Attalla; Forensic Medicine & Clinical Toxicology Department, Faculty of Medicine, Mansoura University, Egypt; Email: sohayla55@yahoo.com

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Abdel Aziz A. Ghanem
Forensic Medicine & Clinical Toxicology Department
Faculty of Medicine, Mansoura University, Egypt

Sohayla M. Attalla
Forensic Medicine & Clinical Toxicology Department
Faculty of Medicine, Mansoura University, Egypt
Email: sohayla55@yahoo.com

Sherif A. Sakr
Cardiology Department, Faculty of Medicine
Mansoura University, Egypt

Helmy M. Bkr
Cardiology Department, Faculty of Medicine
Mansoura University, Egypt

Abstract

Background: Methaemoglobinaemia refers to the oxidation of ferrous iron to ferric iron within the haemoglobin molecule, which occurs following oxidative stresses. The subsequent impairment in oxygen transport may lead to progressive hypoxia that is highly dangerous condition especially in borderline patients like the cardiac patient.

Objectives: In the present work, authors explore the extent of methaemoglobinaemia in cardiac patients receiving nitrate therapy.

Methodology: The study included 970 cardiac patients presented in cardiology department, Mansoura Specialised Medical Hospital, Egypt, in the period from February to July 2009. Patients were taking oral, sublingual, dermal preparation or a combination of two preparations.

Results: cases of the study had methemoglobin level 1.1782 ± 0.3476 g/dL with insignificant difference between males and females. Methemoglobin showed positive correlation with carboxyhemogloin and negative correlation with O2 content and O2 saturation. It was significantly higher in cardiac patient with chest infection, anaemia and diabetic patients but didn't differ in hepatic or non hepatic cardiac patients. 3.2% of cardiac patients who receive more than one nitrate preparation (either oral and dermal or oral and sublingual therapy) have methemoglobin level significantly higher than those who receive single preparation. There is significant difference in methemoglobin level in cardiac patients complaining of myocardial infarction "MI", unstable Angina, atrial fibrillation "AF" and hypertensive heart disease "HTN".

Conclusions: It is concluded that commonly used dosages of nitrates are capable of causing elevations of methemoglobin ranged from 0.9 – 5.3 g/dl. Although the elevation in methaemoglobin (MetHb) levels was not of routine clinical significance, there was statistically significant increase in MetHb levels in cardiac patients with another pathologic condition as anaemia, diabetes mellitus or chest infections. Also, it was significantly higher in patients receiving more than one nitrate therapy in combination.

Keywords: Methemoglobinaemia, cardiac toxicity, nitrate therapy

Introduction

Methemoglobinemia is a disorder in which the hemoglobin molecule is functionally altered and cannot transport oxygen. There are both hereditary and acquired forms of the disorder. The hereditary types are rare and usually show up in the first days of life. Most cases of reported methemoglobinemia are drug-induced [1].

In methemoglobinemia, the concentration of metHb in the blood exceeds 1.5 g/dL (8%–12% of the normal Hb level), impairing oxygen transport and causing "anemic hypoxia." The regulatory enzyme NADH-cytochrome b5 reductase keeps Hb in an oxidized state. Hereditary methemoglobinemia, characterized by a deficiency of NADH-dependent cytochrome b5 reductase, has a wide geographic distribution [2].

Drugs that cause acquired methemoglobinemia are prevalent in both the hospital and the outpatient setting. Drugs documented to contribute to methemoglobinemia include benzocaine [3] cetacaine, prilocaine (the 'caines') [4] and the use of both topical lidocaine and topical benzocaine for bronchoscopy [5].

Anesthetic – endotracheal intubation, transoesophageal echocardiography, bronchoscopy, topical for hemorrhoids and dental/teething preparations, dapsone Prophylaxis for pneumocystic carinii in patients with human immunodeficiency virus (HIV). Also dermatologic applications, EMLA creams eutectic mixture of local anesthetics, flutamide in prostate cancer, nitrates food additives, well water, by product of fertilizer run-off and incorporation into foods preservative, nitric oxide pulmonary vasodilatation, nitroglycerin cardiac vasodilatation, sodium nitroprusside intravenous antihypertensive, vasodilator, sodium nitrate preservative salt used in meat & fish, sulfonamides broad spectrum antibiotics [6].

Nitrate ion readily oxidises haemoglobin to MetHb. Severe poisoning can result from the ingestion of nitrates by infants. In infants the high PH of the gastrointestinal contents is associated with the presence of certain bacteria, especially Escherichia coli at more proximal enteric foci than in adults. Consequently, nitrites are formed by bacterial reduction of unabsorbed nitrates, and the former are the immediate toxic agents [7].

Excessive levels of methemoglobin reduce the oxygen content of blood by reducing

the oxygen-carrying capacity of hemoglobin. First, the oxidized ferric ion has a reduced affinity for binding oxygen. Second, methemoglobin results in a leftward shift of the oxygen dissociation curve causing normal hemoglobin to bind oxygen more tightly and preventing the oxygen from unloading freely at the peripheral tissues [8].

The key clinical endpoint in methemoglobinemia is the severe tissue hypoxemia and metabolic acidosis (lactic acidosis) resulting from diminished oxygen delivery to peripheral tissues [9]. Methemoglobinemia is usually asymptomatic, even when methemoglobin (metHb) levels are as high as 40% of the total hemoglobin (Hb) value [2].

Significant MetHb levels are underestimated by conventional pulse-oximeter readings. Definitive identification of methemoglobinemia relies on co-oximetry. Co-oximetry uses four wavelengths of light to measure the absorptive characteristics of oxy- and deoxyhemoglobin, methemoglobin, and carboxyhemoglobin species. It requires a sample of venous or arterial blood and is the most accurate method for determining the oxygen saturation of blood and the percentage of MetHb [8].

Methemoglobin (MetHb) is a form of hemoglobin that does not bind oxygen. When its concentration is elevated in red blood cells, pulse oximetry readings report lower measured oxygen saturation than those calculated from arterial blood gas readings [10 & 11].

The present study aimed to explore the extent of methaemoglobinaemia in cardiac patients receiving nitrate therapy.

Patients and Methods

The study included 970 cardiac patients aged from 24 to 87 years old presented in cardiology department, Mansoura Specialised Medical Hospital in the period from February to July 2009. All patients were on therapeutic doses of nitrate therapy in one or two of the following types:

1- Oral: Nitromak capsules (nitroglycerin 2.5 or 5 mg / cap given twice daily).

2- Sublingual (SL): Nitroglcerin SL (used, as needed for chest pain 0.4 mg every 5 min three times per day).

3- Dermal: Nitroderm patch 5 & 10mg (nitroglycerin patch 0.2 - 0.8 mg / h patch on for 12 h and off for 12 h).

All data about patients' medical history and recent investigation were retrieved from patients' hospital file. Patients' consent for participation in the study was assured before sampling.

Venous blood samples were collected in heparinized syringes and examined

immediately. Methemoglobin, oxyhemoglobin, and carboxyhemoglobin saturations were measured to the nearest 0.1% using a hemoximeter (model OSM3; Radiometer). The coefficient of variation for methemoglobin saturation measurement was 0.5% of measured values with MetHb% in the range studied and 13% of measured values with MetHb% at baseline levels [12].

Statistical analysis

Data were compared by using student's t-test (to compare two groups); independent samples t-test (to compare two groups), paired sample test (to compare before and after test groups) and Anova test for multiple groups' comparison. Pearson Correlation was used to test association between variables. Significance was considered when P value is less than 0.05. These data were run on an IBM compatible personal computer by using MedCalc® program version 10.0.1 [(13)].

Results

Methemoglobin was 1.1782 ± 0.3476 g/dL with positive Correlation with Carboxyhemogloin (r = 0.155 and P=0.000) and negative correlation with O2 content (r = -0.095 and P = 0.003) and O2 saturation (r = -0.035 and P = 0.274) (table 1).

Methemoglobin showed insignificant difference between males (1.1874 ± 0.3100 g/dL) and females (1.1715 ± 0.3731 g/dL) with P = 0.4799. Methemoglobin showed significant increase in cardiac patients with chest infection more than those without chest infection (1.1938 ± 0.3579 and 1.0430 ± 0.1929 g/dL respectively with P < 0.0001). Also, it was higher in anaemic cardiac patients more than non-anaemic patients (1.2247 ± 0.3955 and 1.1591 ± 0.3242 g/dL respectively with P = 0.0074). It was also significantly higher in diabetic patients more than the non-diabetic patients (1.2736 ± 0.4839 and 1.1293 ± 0.2362 g/dL respectively with P < 0.0001) but there was no significant difference between hepatic and non-hepatic cardiac patients (1.1892 ± 0.3723 and 1.1754 ± 0.3409 g/dL respectively with P = 0.6151) (table 2).

Table 3 shows that 3.2% of cardiac patients who receive combined therapy (more than one nitrate preparation either oral and dermal or oral and sublingual therapy) have methemoglobin level (1.4126 ± 0.6170 g/dL) significantly higher (F-ratio=5.694, P = 0.001) than cardiac patients who receive oral therapy (1.168 ± 0.3158 g/dL) (t= 4.224, P<0.0001), sublingual (1.1660 ± 0.3499 g/dL) (t=3.196, P=0.0017) or dermal (1.203 ± 0.4690 g/dL) (t=1.921, P=0.0579) preparation only. There is no significant difference between those who receive oral, sublingual or dermal therapy alone.

There is significant difference (F-ratio = 3.958, P = 0.008) in methemoglobin level in cardiac patients complaining of myocardial infarction "MI" (1.1286 ± 0.1853 g/dL), unstable Angina (1.2367 ± 0.3979 g/dL), atrial fibrillation "AF" (1.1513 ± 0.4440 g/dL) and hypertensive heart disease "HTN" (1.1592 ± 0.2685 g/dL) (table 4).

Table 1: Statistical correlation between methaemogobin and carboxyhaemogloin, O2 content and O2 saturation in the studied cases

	Met haemoglobin	Carboxy haemoglobin	O2 content	O2 saturation
Min	0.9	0	0.3	9.9
Max.	5.3	14.9	29.2	100.5
MetHb (Mean ± SD)	1.1782 ± 0.3476	1.4076 ± 0.8848	16.2144 ± 3.6234	91.69 ± 10.7968
Correlation test		r=0.155 P=0.000*	r=-0.095 P=0.003*	r=-0.035 P=0.274

*Correlation is significant at r > 0.75 ($p < 0.05$ show the significance of r value)**.**

Table 2: statistical comparison of some factors affecting methemoglobin level in the studied cases

	No. of cases (%)	Methemoglobin level (mean±SD) in g/dL		Test of significance
		Range	**Mean ± SD**	
Sex: **Male** **Female**	413 (42.6%) 557 (57.4%)	0.900 - 3.800 0.900 - 5.300	1.1874 ± 0.3100 1.1715 ± 0.3731	t= -0.707 P = 0.4799
Chest infection: **+** **-**	870 (89.7%) 100 (10.3%)	0.900 - 5.300 0.900 - 1.700	1.1938 ± 0.3579 1.0430 ± 0.1929	t= 4.143 P < 0.0001*
Anemia: **+** **-**	283 (29.18%) 687 (70.82%)	0.900 - 4.200 0.900 - 5.300	1.2247 ± 0.3955 1.1591 ± 0.3242	t= 2.682 P = 0.0074*
Diabetes Mellitus: **+** **-**	329 (33.9%) 641 (66.1%)	0.900 - 5.300 0.900 - 3.900	1.2736 ± 0.4839 1.1293 ± 0.2362	t= -6.237 P < 0.0001*
Hepatic disease: **+** **-**	203 (20.93%) 767 (79.08)	0.900 - 3.900 0.900 - 5.300	1.1892 ± 0.3723 1.1754 ± 0.3409	t= -0.503 P = 0.6151

*Significant at $p < 0.05$

Table 3: Statistical comparison of methaemogobin level (g/dL) in the studied cases classified according to type of therapy

	Oral	**Sub Lingual**	**Dermal**	**Combined**
No. (%)	738 (76.1%)	141 (14.5%)	60 (6.2%)	31 (3.2 %)
MetHb (Mean ± SD)	1.168 ±0.3158	1.1660 ± 0.3499	1.203 ± 0.4690	1.4126 ± 0.6170
t test		t= -0.0745 P =0.9407	t= 0.795 P = 0.4268	t= 4.224 P < 0.0001*
t test			t= 0.623 P = 0.5338	t= 3.196 P = 0.0017*
t test				t= 1.921 P = 0.0579*
Anova test	F-ratio 5.694 (P = 0.001*)			

*Significant at p < 0.05

Table 4: Statistical comparison of methaemogobin level (g/dL) in the studied cases classified according to cardiac diagnosis

	Myocardial Infarction (MI)	**Unstable Angina**	**Atrial fibrillation (MI)**	**Hypertensive heart disease (HTN)**
No. (%)	63 (6.49%)	283 (29.18%)	193 (19.9%)	431 (44.43%)
MetHb (Mean ± SD)	1.1286± 0.1853	1.2367 ± 0.3979	1.1513± 0.4440	1.1592 ± 0.2685
t test		t= 2.106 P = 0.0360*	t= 0.395 P = 0.6933	t= 0.874 P = 0.3825
t test			t= -2.194 P = 0.0287*	t= -3.111 P = 0.0019*
t test				t= -0.273 P = 0.7849
Anova test	F-ratio 3.958 (P = 0.008)			

*Significant at p < 0.05

Discussion

The oxygen-carrying properties of haemoglobin depend on oxygen binding to ferrous ion at each of the four heme groups. Once ion is in the ferric (Fe^{3+}) state, as in methemoglobin, it is unable to combine reversibly with oxygen and transport it in the body. Clinically, methemoglobin concentrations >10–20% result in obvious cyanosis, with headaches, weakness, and breathlessness becoming apparent at levels of 35% or greater. Approximately 2–3% of all hemoglobin in the body is converted to methemoglobin each day as a result of endogenous oxidative stresses. Given the 120-day lifespan of the erythrocyte and endogenous rates of methemoglobin production, nearly all hemoglobin would be in an oxidized form where it is not for the activity of

methemoglobin-reducing enzymes within the erythrocyte. By reducing iron back to its ferrous state, these enzymes restore functional hemoglobin. Thus the competing processes of methemoglobin production and reduction are in equilibrium such that methemoglobin levels are typically <1% of total pigment [12].

The present study included 970 cardiac patients receiving therapeutic doses of nitrate therapy. Their blood was tested for MetHb level and results revealed MetHb range from 0.9 to 5.3 g/dl, concluded that therapeutic doses of nitrate therapy is unexpectedly capable of inducing methaemoglobinaemia in cardiac patients. Previous study has concluded that nitrate ions liberated during metabolism of isosorbide dinitrate could oxidize hemoglobin into methemoglobin. However, about 1 mg/kg of isosorbide dinitrate should be required before any of these patients manifests clinically significant (≥10%) methemoglobinemia in patients with normal reductase function. Not withstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible [14].

On the other hand, the effectiveness and safety of inhalation of nebulized nitroglycerin (Neb-NTG) was tested in children with ventricular septal defect and pulmonary hypertension (VSD-PH) and MetHb level was below 1.5% [15].

Two of the most common clinical measures of blood oxygen levels are the pulse oximetry-derived oxygen saturation (So_2) and the arterial blood gas-derived oxygen content (Po_2) and So_2. However, neither of these tests is adequate for detecting or measuring metHb. Pulse oximetry measures the relative absorbance of 2 wavelengths of light (660 nm and 940 nm) that correspond to the absorption of oxy-hemoglobin (O_2Hb) and deoxy-hemoglobin (HHb), respectively. Although metHb absorbance at 660 nm is similar to that of HHb, metHb absorbance at 940 nm is markedly greater than that of either HHb or O_2Hb. This increases the numerator and the denominator of the 660nm to 940nm absorbance ratio and causes the derived So_2 measurement to be in error. The arterial blood gas-derived Po_2 reflects plasma-dissolved oxygen content, which does not correspond to the oxygen-carrying capacity of Hb. The reported Po_2 may remain within the normal reference range in patients who have methemoglobinemia. The So_2, when measured by means of arterial blood-gas analysis, is calculated from the blood PH, the Po_2, and the standard Hb oxygen dissociation curve. Unfortunately, this approach to calculating the So_2 assumes a normal oxygen dissociation curve, and metHb can falsely elevate the calculated So_2. One possible clue to the diagnosis of methemoglobinemia is the presence of a "saturation gap". This occurs when there is a difference between the So_2 that has been measured by means of pulse oximetry (the lower value) and the So_2 that has been calculated by means of arterial blood-gas analysis. Typically, this saturation gap is greater than 5% in cases of metHb[10].

Results of the present study showed that the patients' MetHb level are not significantly correlated with oxygen saturation (r = -0.035 and P = 0.274). This may explain the undetectability of cases of methaemoglobinaemia in routine hospital work, which depend on the use of pulse oxymetry. Because pulse oximetry often gives near normal readings, definitive diagnosis requires co-oximetry.

The under-representation of the true number of methemoglobinaemia cases was referred to the incidental discovery of cases and reported that co-oximetry testing is done only on orders from the physician. They also reported that their institutions' cost of traditional invasive testing for methemoglobin was $25 for each evaluation. This testing is cost-prohibitive to do on all patients along with arterial blood gases. If all blood aliquots sent for arterial blood gas analysis had been tested with co-oximetry, the incurred cost would have created approximately $9 million in incremental hospital expenses for their 28-month study [6].

Co-oximetry is the appropriate test for detecting and measuring the metHb level. The co-oximeter measures light absorbance at 4 different wavelengths that correspond to the absorption characteristics of HHb, O2Hb, carboxyhemoglobin, and metHb. Accordingly, co-oximetry can distinguish among these 4 configurations of Hb while providing a more accurate measurement of SO_2[16]. When cyanosis and a saturation gap are detected, co-oximetry should be ordered to confirm the presence of methemoglobinemia; thus, avoiding more-invasive testing and a delayed diagnosis [17]. It is imperative that the practitioners understand that the oxyhemoglobin saturation reported by the pulse oximeter should be considered inaccurate [18].

The present study detected that MetHb level differs significantly according to the cardiac diagnosis; MI, angina, AF or HTN. Authors attributed this to the type of therapy the patient receive as the met haemoglobin was highest in cases of angina who usually receive combination therapy either oral and SL or oral and dermal. It also may be due to exacerbated hypoxic state in the cardiac patient.

Results of the present study revealed also that there is significant increase in MetHb level in cardiac patients with infection more than those without chest infection (P < 0.0001). These results coincide with other studies that reported elevated methemoglobin in patients with sepsis [19 & 20].

It is detected also that methemoglobin level is higher in diabetic cardiac patients than non-diabetic patients (P<0.0001) and also higher in anaemic patients than non-anemic cardiac patients (P = 0.0074).

It is important to note that patients with anemia, cardiovascular disease, lung disease, and sepsis may experience symptoms of methaemoglobinaemia at far lower levels. For pediatric patients, gastroenteritis, dehydration, and sepsis increase the risk of developing methemoglobinemia [6].

In conclusion, methemoglobinemia is a rare complication encountered by various clinicians. Severe cases may lead to morbidity and mortality especially in cardiac patients because of attendant tissue hypoxemia. Diagnosis requires a high index of suspicion, because pulse oximetry often gives near normal readings. Definitive diagnosis requires co-oximetry. Rapid recognition and treatment can decrease morbidity, and serial MetHb levels should be used to judge adequate treatment to prevent rebound methemoglobinemia. Anaemia, infection and DM must be corrected in cardiac patients. A heightened awareness of methemoglobinemia is essential to optimize outcome.

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