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CASE REPORT

Acquired Methemoglobinaemia

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بِيلَةُ الميتهيموغلوبين المكتسبة

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الملخص: بيلَةُ الميتهيموغلوبين المكتسبة حالة نادرة نسبيا، ولهذا كانت قليلة الورود في الممارسة الطبية الجادة. قد ينجم الاشتباه في الحالة عندما يكون قياس ضغط الأكسجين لا يتناسب مع تشبع الأكسجين التي يتم اكتشافها حين قياسُ التَّأَكْسُج النبضي. نُدرج في هذا التقرير وصفا لحالتين منفصلتين من بيلة الميتهيموغلوبين الناتجة عن استعمال ألكيل نتريت لأغراض الترفيه. راجع المريضان في فترات مختلفة اثنين من المستشفيات التعليمية المختلفة في لندن، المملكة المتحدة. وقد أدى التشابه بين هاتين الحالتين إلى ضرورة رفع مستوى الوعي اتجاه هذه الحالة القاتلة، وارتباطها بالأدوية المتاحة على نطاق واسع للأغراض الترفيهية، لأنه أمر ضروري لضمان التشخيص الصحيح وفي الوقت المناسب.

مفتاح الكلمات: بيلة الميتهيموجلوبين، ميثيلين أزرق، تقرير حالة، المملكة المتحدة.

ABSTRACT: Acquired methemoglobinaemia is a relatively rare condition and, therefore infrequently encountered in acute medical practice. Suspicion of the condition may be triggered when the measured PaO2 is 'out of keeping' with the oxygen saturations that are discovered with pulse oximetry. We describe two separate cases of acquired methemoglobinaemia secondary to the recreational use of alkyl nitrites ('poppers'). The patients presented at separate times to two different teaching hospitals in London, UK. The similarity of these cases has led the authors to conclude that a raised awareness of this potentially fatal condition, and its association with a widely-available recreational drug, is necessary to ensure a correct and timely diagnosis.

Keywords: Methaemoglobinaemia; Methylene blue; Case report; UK.

Methemoglobinaemia is an infrequent haematological disorder that can result from congenital and acquired conditions. The congenital form is rare and not always compatible with life, but acquired methemoglobinaemia is more common and can result from a wide variety of environmental agents, including prescribed and recreational drugs. Oxygen therapy and intravenous methleyne blue is usually the first line treatment for this disorder. A high level of suspicion is necessary for the accurate and timely diagnosis of this condition, as any delay can be catastrophic.

Case One

A 39-year-old male with no significant past medical history presented to the emergency department after collapsing following recreational ingestion of alkyl nitrates ('poppers'). He denied using any other recreational, prescribed, or over-the-counter drugs. Upon presentation, the patient was fully awake and oriented, with a Glasgow Coma Score (GCS) of 15/15, and no significant abnormal findings on initial clinical examination. The electrocardiogram (ECG), chest radiograph, and initial blood investigations were within the normal stated local limits. Pulse oximetry revealed oxygen saturations of 85–88% whilst breathing room air.

Arterial blood gas (ABG) analyses and oxygen saturations as measured on pulse oximetry are shown in Table 1. A diagnosis of acquired methemoglobinaemia was made and, as such, definitive treatment with high flow oxygen (15 litres delivered via a non-rebreathing mask) and intravenous methylene blue (1.5 mg/kg infused over 10 minutes) was initiated. The measured ABG (including methaemoglobin [MetHb] levels) returned to within normal limits within 24 hours of his admission, as shown in Table 1.

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Table 1: Case 1 arterial blood gas (ABG) results and measured oxygen saturation (SaO_2) (on pulse oximetry)

	Normal range	Admission	24 hours after admission
Inspired oxygen (FiO_2)	**Room air (0.21)**	**Room air (0.21)**	**Room air (0.21)**
SaO_2	>96%	85–88%	98%
PaO_2	10–13 kPa	8.5 kPa	12.4
$PaCO_2$	5.4–6.8 kPa	5.7 kPa	5.8 kPa
MetHb %	<1% (non-smokers)	23.5%	0.7%

Legend: FiO_2 = fraction of inspired oxygen; SaO_2 = oxygen saturation; PaO_2 = partial pressure of oxygen in blood; $PaCO_2$ = partial pressure of carbon dioxide in blood; MetHb = methaemoglobin; kPa = kilopascal.

The patient was discharged after an uneventful 48-hour inpatient stay, having received counselling regarding the potential dangers associated with the misuse of poppers.

Case Two

A 40-year-old male with a significant smoking history was found collapsed after ingesting two beers and a bottle of poppers within a period of 30 minutes. The patient voluntarily provided a full glass bottle similar to the one ingested [Figure 1].

On arrival in the emergency department the patient was fully orientated, with a GCS of 15/15.

Figure 1: Bottle of alkyl nitrite provided by Patient 2

On clinical examination he was unkempt with tar-stained fingers. The patient was also noted to be centrally cyanosed with a mild bilateral expiratory wheeze. The rest of the initial clinical examination was largely unremarkable. An ECG revealed a sinus tachycardia with left axis deviation**.** ABG analyses and oxygen saturations as measured on pulse oximetry are shown in Table 2.

Acquired methemoglobinaemia with possible previously unidentified chronic obstructive pulmonary disease was diagnosed; therefore, the patient was started on monitored high flow oxygen therapy with serial clinical assessments and ABGs, as well as intravenous methylene blue. The patient was discharged after education about the potential effects of abusing poppers, smoking cessation advice, and inhaled bronchodilator therapy for his probable chronic obstructive pulmonary disease. He was also given follow-up appointments with the chest clinic for further evaluation of his chest condition, but he did not attend.

Discussion

Methemoglobinaemia is a disorder in which the haemoglobin (Hb) molecule is altered to prevent efficient carriage of oxygen, essentially shifting the oxygen dissociation curve to the left, leading to a functional anaemia. A variety of aetiologies including genetic, dietary, idiopathic, and toxicological have been implicated.[1] Acquired methemoglobinaemia is much more common than the hereditary form, occurring when an exogenous substance oxidises Hb to methaemoglobin (MetHb) at rates of 100 to 1000 times greater than it can be reduced back to its original form [Figure 2].[2] Congenital methemoglobinaemia can occur from a cytochrome b5 reductase deficiency or from a structural Hb defect, collectively called HbM. There

Table 2: Case 2 arterial blood gas (ABG) results and measured oxygen saturation (SaO_2) (on pulse oximetry)

	Normal range	Admission	24 hours after admission
Inspired oxygen (FiO_2)	**Room air (0.21)**	**Non-rebreathe reservoir mask at 15L/min O_2 (~ 0.90)?**	**Room air (0.21)**
SaO_2	>96%	90%	96%
PaO_2	10–13 kPa	8.3 kPa	8.3 kPa
$PaCO_2$	5.4–6.8kPa	6.2 kPa	6.1 kPa
MetHb %	<1% (non-smokers)	46.0%	0.5%

Legend: FiO_2 = fraction of inspired oxygen; SaO_2 = oxygen saturation; PaO_2 = partial pressure of oxygen in blood; $PaCO_2$ = partial pressure of carbon dioxide in blood; MetHb = methaemoglobin; kPa = kilopascal.

are two types of congenital methaemogloninaemia. In type 1, the enzyme deficiency is confined to the red blood cells, whereas in type 2 a range of cells, including brain cells, is affected. Type 2 usually results in mental retardation, neurological abnormalities, or death in childhood. Lifelong use of agents having the same effect as the deficient reducing enzyme, such as ascorbic acid (vitamin C) and/or riboflavin (vitamin B_2) can be used to try to alleviate some of the clinical features of the condition, especially in type 1. HbM results from a single amino acid substitution in either alpha or beta polypeptide chains at the region where the iron-containing heme portion is attached. This results in a failure to convert MetHb to Hb.[3]

Normally, there is a continuous conversion of Hb to MetHb, and vice versa. The reduction of MetHb to Hb happens through two different pathways. The nicotinamide dinucleotide (NADH)-dependent cytochrome b5-methaemoglobin reductase pathways account for 99% of MetHb reduction to Hb. The other mechanism depends on utilising nicotinamide-adenine dinucleotide phosphate hydrogenase (NADPH) generated by glucose-6-phosphate dehydrogenase (G6PD) in the hexose monophosphate pathway. This mechanism is physiologically inactive and needs extrinsic agents, like methylene blue, to activate it. Whereas the former mechanism is the main physiologically active reducing mechanism, the later pathways are highly important when the physiologically active mechanism is overwhelmed and the therapeutic correction of MetHb is attempted via methylene blue.[3]

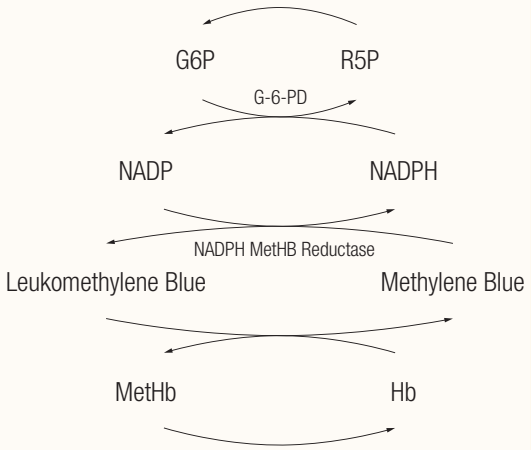

Figure 2: The role of methylene blue in the treatment of methaemoglobinemia

Legend: G6P = glucose 6 phosphate; G-6-PD = glucose-6-phosphate dehydrogenase; R5P = ribose-5-phosphate; NADP = nicotine adenine dinucleotide phosphate; NADPH = nicotine adenine dinucleotide phosphate hydrogenase; MetHb = methaemaglobin; Hb = haemoglobin

Poppers are potent oxidisers of oxyhaemoglobin (converting Fe^{2+} to Fe^{3+}) resulting in the formation of MetHb, and are volatile liquids that are sometimes abused by both sexes for euphorigenic rushes and altered states of consciousness. The name 'poppers' may have been derived from the sound caused by breaking open the glass vials which were originally used to store the volatile contents.[4] Methemoglobinaemia has been reported to develop after the ingestion of as little as 10 ml of alkyl nitrite.[5] Factors that may predispose to pharmacologically-induced methemoglobinaemia include the use of large quantities of the offending agent, any discontinuation of the body's normal mucosal barriers, and the concomitant use of other drugs known to cause methaemoglobinaemia, such as acetaminophen (paracetamol), primaquine, or cocaine.[6] In addition, dapsone has been implicated in almost 50% of cases of acquired methaemoglobinaemia, which is clinically important as, due to its relatively long half-life, cimetidine may be required to try to block its

Table 3: Common clinical features associated with approximate MetHb concentration

MetHb concentration %	Possible clinical features may include
<10	Often asymptomatic
10–20	Cyanosis, skin discolouration
20–30	Anxiety, light-headedness, headaches, tachycardia
30–50	Fatigue, confusion, dizziness, tachypnoea
50–70	Coma, seizures, acidosis, arrhythmias
>70	Death

metabolism via hepatic microsomal cytochrome P450 (CYP450).[7] Topical local anaesthetic agents (e.g. lidoncaine or benozocaine) for procedures such as bronchoscopy, laryngoscopy, or upper gastroduodenoscopy can also result in acquired methaemoglobinaemia.[2] Another risk factor for developing pharmacologically-induced methemoglobinaemia is the presence of concomitant illnesses, including cardiac and respiratory diseases.[8]

This condition should be suspected if cyanosis develops after suspected exposure to potent oxidizing agents, or if chocolate brown arterial blood does not turn red on exposure to air.[1] Some of the more common non-specific clinical features are listed in Table 3.[6] However, clinical presentation may vary greatly and definitive treatment with methylene blue might not always be needed depending on the clinical condition.

Pulse oximetry is a useful tool to diagnose suspected methaemoglobinaemia. It basically works by emitting lights at two different wavelengths (660 nm in the red spectrum wavelength and 940 nm in the infrared spectrum wavelength). These wavelengths are absorbed differently by deoxyhaemoglobin and oxyhaemoglobin (i.e. deoxyhaemoglobin absorbs more light at 660 nm wavelengths and oxyhaemoglobin absorbs more light at 940 nm wavelengths). By calculating the differences, the microprocessor in the pulse oximeter can measure the SaO_2 (sometimes referred as SpO_2 when measured by a pulse oximeter). Whereas MetHb absorbs more light than either oxyhaemoglobin and deoxyhaemoglobin at 940 nm wavelength, its absorption is similar to that of deoxyhaemoglobin at 660 nm wavelengths resulting in falsely low SaO_2 due to an incorrectly high deoxyhaemoglobin perception by the pulse oximeter. However, newer pulse oximeters are able to omit light at 8 different wavelengths making it possible to measure MetHb and carboxyhaemoglobin as well.[9]

The diagnosis of methemoglobinaemia can be confirmed with an ABG sample that demonstrates a discrepancy between arterial oxyhaemoglobin saturation (SaO_2) and measured arterial oxygen partial pressure (PaO_2).[6] A high saturation gap should also lead to the suspicion of methaemoglobinaemia. The gap is defined as the difference between oxygen saturation measured by the pulse oximeter and that calculated by ABG. This gap is usually >5 in cases of methaemoglobinaemia.[10]

Methylene blue can be an effective treatment for acquired methemoglobinaemia [Figure 2] and should be administered at a dose of 1–2 mg/kg intravenously over 3–10 minutes. An obvious clinical improvement should be evident within one hour, but if cyanosis persists, a second dose may be considered.[8] Higher doses of methylene blue (>7 mg/kg) may cause haemolysis and persistent cyanosis, as the agent can paradoxically oxidise haemoglobin to MetHb, as opposed to acting as a reducing agent at lower doses.[5] Relapsing methemoglobinaemia has also been described in the literature with a delayed, biphasic rise in the level of MetHb. This may be due to a secondary paradoxical cyclical formation of MetHb by the offending agent (e.g. dapsone or methylene blue). CYP450 inhibitors (e.g. cimetidine) and exchange transfusion might be needed to treat these patients.[8] Also, individuals with G6PD deficiency may not produce sufficient NADPH to reduce methylene blue to leukomethylene blue, potentially rendering the therapy ineffective.[6] Furthermore, methylene blue might induce haemolysis in G6PD-deficient patients. Alternative treatments with cimetidine, ascorbic acid, and possibly exchange transfusions ,should be considered in patients with a G6PD, deficiency. N-acetylcysteine is also under study as a possible treatment for this category of patients.[8]

Conclusion

We report a fatal medical condition which may result from the abuse of a widely-available recreational drug. Physicians in acute medical specialities should have a raised clinical suspicion

for this condition when there is a possible history of drug misuse and a significant discrepancy between the clinical picture and measured SaO_2 and PaO_2 levels. This raised level of awareness can ensure acquired methaemoglobinaemia's accurate diagnosis and timely treatment. Both of our patients were discharged safely after timely diagnosis and management of a potentially life-threatening condition.

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