Relation between chest wall and cannula.

treatment of tension pneumothorax by paramedic staff.

1 Committee on Trauma. *Advanced trauma life support course manual*. American College of Surgeons, 1993.

Methaemoglobinaemia presenting with status epilepticus

Raman Malhotra, Geoff Hughes

Abstract

A case is reported of methaemoglobinaemia presenting with recurrent fits in the absence of cyanosis. A low oxygen saturation measured on pulse oximetry that fails to improve with oxygen treatment, the presence of "chocolate brown" blood that does not change on exposure to air, and a high P_{aO_2} arterial blood gas with oxygen therapy should support such a diagnosis. A diagnostic blood methaemoglobin level should be obtained.

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Key terms: amyl nitrite; cyanosis; convulsions; methaemoglobinaemia

Fitting is frequently seen in accident and emergency (A&E); common causes include hypoglycaemia, epilepsy, alcohol withdrawal or

excess, infection (including meningitis, encephalitis, or childhood febrile fits), head injury, hypoxia, and intracranial pathology.¹

Methaemoglobinaemia is usually described as an uncommon cause of cyanosis in patients presenting to the A&E department,²⁻⁵ but has also been reported to cause chest pain^{4,6} or coma.⁶⁻⁸ We report a case of methaemoglobinaemia presenting with recurrent fits.

Case report

A 31 year old male was brought to the A&E department by ambulance after being found on a pavement having repeated convulsions. The fits were described as recurrent, lasting approximately two minutes each with three-minute intervals, during which time he was unresponsive to voice or pain. He was unaccompanied and no other history was available.

On arrival he was in status epilepticus. Only the upper half of his body was convulsing, with

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violent clonic movements. There was bruising to his forehead, and large irregular old keloid scars to his chest, abdomen, and forearms. Between fits his Glasgow coma scale score was 3. He was maintaining an airway, was not cyanosed, and he had an irregular ventilatory rate of between 10 and 12 breaths per minute. He was haemodynamically stable with a regular pulse of 130 beats/min and a blood pressure of 117/65 mm Hg. Pupils were equal at 2 mm and reactive to light, but the fundi could not be seen clearly. All limbs had equal tone with reduced but equal reflexes.

Peripheral oxygen saturation was 92% with FiO_2 of 0.4. Normal investigations included cervical spine and chest x rays, full blood count, clotting screen, urea and electrolytes, blood glucose, liver function tests, serum calcium, and paracetamol and salicylate levels. Creatine kinase was slightly raised at 231 (normal <195). His ECG showed sinus tachycardia.

Old records revealed a past history of attendances at the A&E department for analgesic overdoses. He was hepatitis B positive, for which he was taking interferon, and also had a history of asthma for which he took salbutamol and Becotide inhalers. As a teenager he also suffered from gigantism.

Fentanyl, propofol, and suxamethonium were given to facilitate intubation and ventilation for a cerebral computerised tomography scan, which was normal. A stomach washout released a smell of bleach.

In the intensive therapy unit (ITU) a large difference between PaO_2 and peripheral saturation was noted (table 1). Other results included $\text{pH} = 7.36$, $\text{PCO}_2 = 4.8$ kPa (36.7 mm Hg), and $\text{HCO}_3^- = 2.76$ kPa (21 mm Hg). On insertion of a central venous pressure line it was noted that the patient's blood remained a chocolate brown colour on being exposed to air.

These findings suggested methaemoglobinemia induced by a probable drug overdose. Methaemoglobin levels of 16% were recorded and 200 mg methylene blue was given intravenously. A dramatic response was noted, with peripheral oxygen saturations rising to 99% with FiO_2 of 0.5. PaO_2 remained high at 22.6 kPa (172 mm Hg), $\text{pH} = 7.42$, $\text{PCO}_2 = 4.2$ kPa (32 mm Hg), and $\text{HCO}_3^- = 2.76$ kPa (21 mm Hg).

The patient was extubated and transferred from ITU to a medical ward within 12 hours of admission. On the ward he remained well and fit-free. Before being medically discharged the next day he admitted to having taken an unknown amount of amyl nitrite "Poppers", but refused to divulge any other drugs he may have taken.

Table 1 PaO_2 and peripheral saturation with varying FiO_2

	FiO_2	
	0.9	0.5
Pulse oximetry saturation	85%	79%
PaO_2	>400 mm Hg (>52.6 kPa)	150 mm Hg (19.7 kPa)

Table 2 Agents causing methaemoglobinaemia^{6 13}

Agent	Source/use
Anaesthetics prilocaine benzocaine lignocaine	caudal, epidural topical, lubricants topical, local
Antiseptic/antibacterials para-aminosalicylic acid dapsona	tuberculosis therapy antimalarial, leprosy, dermatological treatment
sulfanilamide phenazopyridine sulphathiazole primaquine	vaginal antibacterial genitourinary analgesic/antiseptic ophthalmic ointment antimalarial
Analgesic/antipyretics acetanilide	over the counter (OTC) combination
phenacetin	OTC combination
Nitrates/nitrites sodium nitrite bismuth subnitrite amyl nitrite	food preservative OTC antidiarrhoeal, astringents cyanide therapy, vasodilator, abused inhalant
butyl nitrite	air freshener, abused inhalant ("Rush")
glyceryl trinitrate silver nitrate nitrate salts	coronary vasodilator topical burn therapy fertilizer, contaminated water, food
Miscellaneous aminophenol aniline compounds	photographic developer dyes, inks, crayons, paints, polishes
chlorate salts metoclopramide nitrobenzene compounds	match heads antiemetic solvents polishes, dyes
nitrogen dioxide resorcin trinitrotoluene (TNT)	inhalation in silo fillers fungicidal ointment explosive

Discussion

Methaemoglobinemia is a rare condition resulting from the altered molecular structure and reduced oxygen carrying capacity of the haemoglobin molecule due to the formation of methaemoglobin. Methaemoglobin is produced when haemoglobin in the ferrous (Fe^{2+}) state is oxidised to the ferric (Fe^{3+}) molecule.

The iron in deoxyhaemoglobin is in the ferrous form (Fe^{2+}), allowing oxygen to bind avidly to it. The iron in oxyhaemoglobin remains in a ferric low spin state due to a partial transfer of an electron from the iron to the oxygen.⁹ When haemoglobin unloads its oxygen, the ferrous state of iron is restored; however, during deoxygenation, a small portion of oxygen leaves haemoglobin as a superoxide (O_2^-) radical, thus leaving the iron in a ferric state (methaemoglobin).⁹ Although methaemoglobin is continuously formed in erythrocytes, normal concentrations are maintained at a level of 1% or less¹⁰ by the simultaneous reduction of iron to the ferrous state (Fe^{2+}) by red cell enzymes, most important of which is the methaemoglobin NADH-cytochrome b5 reductase system.⁹ A second enzyme system which is probably responsible for only 5% of methaemoglobin reduction and is not essential under physiological conditions is the NADPH-methaemoglobin reductase system, which uses NADPH from the pentose phosphate shunt to reduce flavin, which in turn reduces methaemoglobin.⁹ This enzyme system reduces methaemoglobin rapidly in the

presence of an artificial electron carrier such as methylene blue, but has no physiological substance in the erythrocyte that may provide the same role as methylene blue.⁹

Methaemoglobinaemia may be congenital or acquired. Congenital methaemoglobinaemia can either be due to an abnormal haemoglobin molecule with specific amino acid substitutions in the α or β subunits, resulting in an altered haemoglobin structure and increased exposure of iron to the risk of oxidation to the ferric state, or to deficiency in the NADH-cytochrome b5 reductase system.⁹

Acquired methaemoglobinaemia is the most common form of methaemoglobinaemia and follows exposure to drugs or toxins which, by a poorly understood mechanism, result in the oxidation of iron to the ferric state (table 2). Most commonly these include nitrites, nitrates (which are converted by bacteria to nitrites), and aniline dyes.⁶

It is known that infants are more susceptible to acquired methaemoglobinaemia because concentrations of NADH-cytochrome b5 reductase are as low as 50% in the newborn⁹ and slowly rise until 4 months of age.^{6,11,12}

DIAGNOSIS

The diagnosis of methaemoglobinaemia begins with the history of exposure to an implicated substance, and the characteristic cyanosis is not relieved by high concentrations of oxygen.⁶ In our case, a history was unavailable, and the patient was not centrally or peripherally cyanosed. The decreased pulse oximetry oxygen saturation reflected the similarity between the absorption characteristics of methaemoglobin and deoxyhaemoglobin.¹⁴ A high P_{aO_2} of 52.6 kPa (400 mm Hg) with high oxygen therapy reflected the accumulation of oxygen in plasma. Laboratory-calculated oxygen saturation measurements on arterial blood gases are based on the partial pressure of dissolved oxygen and assume that no abnormal haemoglobin is present. Therefore laboratory oxygen saturations are often higher than those measured with pulse oximetry.⁶ Characteristic of methaemoglobinaemia is the dark "chocolate brown" colour of blood which, unlike deoxygenated haemoglobin, does not turn bright red in the presence of oxygen but remains brownish due to the haemoglobin molecule's inability to accept oxygen.¹⁰

It has been proposed that the symptoms of methaemoglobinaemia are a result of the decreased oxygen carrying capacity of the blood. It is well documented that with concentrations between 20% and 45%, dyspnoea, fatigue, lethargy, and headache are common. Alterations in levels of consciousness, and respiratory depression are seen with concentrations between 45% and 55%, and at levels approaching 70%, circulatory collapse, cardiac dysrhythmias, seizures, and death are likely.^{4,6,10} It is important, however, to treat each case individually according to the clinical severity (for example, level of consciousness, dyspnoea, myocardial ischaemia), as some patients have died^{15,16} or, as in the case above, have had severe

symptoms¹⁷ with methaemoglobin levels of less than 35%, while other patients have recovered with levels above 80%.^{7,8,18} Our patient only had levels of 16% and the convulsions were possibly due to hypoxia rather than to direct neurological toxicity.

TREATMENT

Treatment of methaemoglobinaemia begins with securing the airway, giving high flow oxygen therapy in order to saturate existing haemoglobin, and removing the offending agent, which may require removal of clothes, skin decontamination, emetics, or gastric lavage.^{4,6}

Pharmacological treatment relies principally on methylene blue given intravenously at a dose of 1–2 mg/kg in the form of a 1% solution over a period of five minutes. This dose can be given hourly if the symptoms are not relieved; however, the total dose should not exceed 7 mg/kg. Although treatment with methylene blue is recommended for methaemoglobin levels of 30% or more, treatment at a lower level is recommended in the presence of underlying anaemia, symptoms of hypoxia, another accompanying poisoning such as carbon monoxide or cyanide poisoning during fire exposure,¹⁹ or if usage of more than one drug has occurred.⁶

Unresponsiveness to two doses of methylene blue treatment must raise the possibility of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, reducing hexose monophosphate shunt activity and therefore the availability of NADPH, or perhaps NADPH reductase deficiency.¹⁰ In fact, the administration of methylene blue to patients who are deficient in G-6-PD may aggravate methaemoglobinaemia and increase the risk of haemolytic anaemia.⁹

Other forms of treatment that may be considered include ascorbic acid, which, although very slow, reduces methaemoglobin, or an exchange transfusion if methaemoglobin levels in the blood remain high and the patient is symptomatic.⁹

CONCLUSION

Although methaemoglobinaemia is a rare cause of cyanosis, it may present in the absence of cyanosis. There may not be a suggestive history, and symptoms or signs of hypoxia may be subtle. In the absence of cyanosis, a low oxygen saturation measured on pulse oximetry that fails to improve with oxygen treatment, the presence of "chocolate brown" blood that does not change on exposure to air, and a high P_{aO_2} in arterial blood during oxygen therapy should support a diagnosis. A diagnostic blood methaemoglobin level should be obtained. Methylene blue is the treatment of choice.

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ADVANCED LIFE SUPPORT GROUP

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The contact person for all these courses is: Ms J Antrobus, Advanced Life Support Group, Second Floor, The Dock Office, Trafford Road, Salford Quays, Manchester M5 2XB. Tel 0161 877 1999; Fax 0161 877 1666