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CASE REPORTS

Unexplained acute severe methaemoglobinaemia in a young adult

M. Falkenhahn[1], S. Kannan[1*] and M. O'Kane[2]

[1]Departments of Anaesthetics and [2]Clinical Chemistry, Altnagelvin Hospital, Glenshane Road, Londonderry BT47 1SB, UK

**Corresponding author: Department of Anaesthetics, Queen Elizabeth Hospital, Metchley Park Road, Edgbaston, Birmingham B15 2TH, UK*

This report describes the case of an otherwise healthy young adult female, who presented with a 12-h history of progressive bluish discolouration of lips and limbs. She denied ingesting or inhaling any drug or substance. A high Pa_{O_2} in the presence of 'cyanosis' and 'dark blood' led to suspicion of methaemoglobinaemia. Co-oximetry revealed the methaemoglobin level to be 47%. A urinary screen for drugs of abuse was negative and blood methaemoglobin reductase activity was within the normal range. The aetiology was traced to dapsone detected in the urine by gas chromatography/mass spectrometry. The therapeutic and diagnostic approach in such patients is discussed.

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Acute severe methaemoglobinaemia is an uncommon but potentially treatable disorder in which patients can present with dramatic signs and symptoms. Usually there is a history of some precipitating factor such as accidental or intentional ingestion of a drug or inhalation of certain substances. It is also well known that administration of certain medications can precipitate methaemoglobin (MetHb) formation in cases of overdose or even in normal doses if the patient is susceptible. We report the case of a young woman who presented with severe methaemoglobinaemia without any positive history.

Case report

A 29-yr-old female was referred by a general practitioner with a 12-h history of progressive bluish discoloration of limbs and lips, shortness of breath, several episodes of vomiting and pain in the anterior chest. She had consumed moderate quantities of alcohol the previous night at a pub. Apart from a history of taking two tablets of acetaminophen during the previous 24 h, she denied ingesting or inhaling any other drug. There was no past history suggestive of similar episodes or other illness, drug abuse, deep vein thrombosis or pulmonary embolism. She was a non-smoker. She was fully oriented, afebrile, anxious and had generalized cyanosis. The pulse rate was 145 beats min^{-1} and regular, the arterial pressure was 122/88 mm Hg and the jugular venous pressure was not raised. The respiratory rate was 35 bpm but the chest was clear to auscultation with normal heart sounds. Electrocardiogram, chest x-ray, full blood count, coagulation variables and serum biochemistry were normal. Arterial blood gas on 80% oxygen by mask showed pH 7.46, Pa_{O_2} 25 kPa, Pa_{CO_2} 2.7 kPa, HCO_3 15.3 mmol $litre^{-1}$, base excess—10 mmol $litre^{-1}$ and oxygen saturation of 98%. The pulse oximeter showed a haemoglobin saturation of 65% with a good pulse waveform. Blood alcohol, acetaminophen and salicylate were undetectable. Pulmonary embolism was suspected and heparin 10 000 units was given i.v. A computed tomography scan of the thorax to exclude pulmonary embolism and aortic dissection was normal. The patient was transferred to the intensive care unit and administered continuous positive airway pressure support by mask on 100% oxygen. During a repeat arterial blood gas sampling, it was noticed that the blood was dark coloured and the results showed a pH 7.46, P_{O_2} 70 kPa, P_{CO_2} 2 kPa, BE—10 mmol $litre^{-1}$, and oxygen saturation of 98%.

In view of the high Pa_{O_2} and the dark colour of the arterial blood, methaemoglobinaemia was suspected. Co-oximetry revealed MetHb levels to be 47%. Fifty milligrams of 1% methylene blue was given i.v. with 1 g of oral vitamin C. The MetHb levels ranged from 13.8 to 31% over the next 72 h and the patient required five additional doses of methylene blue 50 mg. In retrospect, there was no history of ingestion of fava beans or contact with aniline dyes. Red cell glucose-6-phosphate dehydrogenase levels were normal. A urinary

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screen for opiates, amphetamines, benzodiazepines, cocaine metabolites, barbiturates, cannabinoids and lysergic acid diethylamide was negative. Blood MetHb reductase activity was within the healthy population reference range. The patient was discharged to the ward on day 4 when the MetHb levels fell below 15% and she made an uneventful recovery. A basic extract of the urinary sample taken on day 3 was analysed by gas chromatography/mass spectrometry (Hewlett Packard 6890 series Gas Chromatograph and 5973 Mass Selective Detector). A peak with a retention time of 15.04 min under our operating conditions, gave a 97% match with the Pfleger MS Drug Spectral Library for dapsone. A smaller peak with a retention time of 10.81 min gave a 90% match with the Pfleger library for benzylbutylpthalate. This result suggested prior ingestion of dapsone although the patient denied that possibility. There was no history suggestive of either the patient or her immediate relatives taking dapsone for therapeutic reasons. There was no evidence of haemolysis or anaemia.

Discussion

Methaemoglobinaemia is a condition in which an abnormal proportion of the iron in the haem moiety of haemoglobin is oxidized to the ferric state leading to impaired oxygen transport and 'anaemic hypoxia'. The initial presentation of methaemoglobinaemia may cause diagnostic confusion because of the 'low' oxygen saturation on the pulse oximeter in favour of the 'cyanosis'. Standard pulse oximeters give spuriously low readings in the presence of excess methaemoglobin. The pulse waveform is not disturbed as long as peripheral circulation is maintained. All this can lead to performance of unnecessary investigations and administration of certain potentially hazardous drugs. In our patient, the results of the first arterial blood gas done in the ward to assess the severity of hypoxaemia might have aroused suspicion but it was felt that the patient had clinically deteriorated (become more blue) in the interval between arterial puncture and the availability of the results. The 'normal' oxygen saturation on the blood gas analysis and tachycardia along with tachypnoea diverted the attention to other possibilities. Most arterial blood gas analysers calculate the oxygen saturation based on the Pa_{O_2} and hence give 'false high' values in such cases. The dark coloured blood with a high Pa_{O_2} from the second blood gas analysis in the intensive care unit led to the suspicion of methaemoglobinaemia.

Clinical features of methaemoglobinaemia depend on the MetHb levels in blood. The discolouration of blood and appearance of cyanosis manifests when the MetHb levels reach 15–20%. Levels between 20–45% are associated with dyspnoea, lethargy, dizziness and headaches. MetHb levels above 45% are usually associated with impaired consciousness and levels above 55% can cause seizures, coma and cardiac arrhythmias. Although the lethal concentration for adults is considered to be >70%, survival has been reported with levels as high as 83%.[1]

Methaemoglobinaemia can be caused either by a genetic defect in red cell metabolism or haemoglobin structure, or acquired by a variety of drugs and toxins. About forty substances have been implicated in causing this condition, the most prominent being dapsone, nitrates, prilocaine, antimalarials, sulphonamides and dyes. Domestic causes of acquired methaemoglobinaemia include ingestion of food and water high in nitrites and nitrates,[2] inhalation of room odourizers containing butyl nitrite, exposure to aniline dyes in dyed blankets, laundry markings, freshly dyed shoes, red wax crayons[3] and cleaning solution.[4] Most contain some form of nitrates. Methylene blue when given in doses of over 15 mg kg^{-1} can itself cause methaemoglobinaemia and haemolysis but the MetHb levels rarely exceed 8%.[5] One important differential diagnosis for methaemoglobinaemia is sulphaemoglobinaemia. Sulphaemoglobin can be detected by most standard co-oximeters. Once the diagnosis is established, all the possible causes of methaemoglobinaemia should be considered. Information from the patient's relatives may prove beneficial. Apart from the potential-offending agents, a search should be made for other substances of abuse, which can be co-ingested. Where appropriate, methaemoglobin reductase activity should be measured.

There have been a number of reports of methaemoglobinaemia because of dapsone.[5–8] In all the cases, there was a history of ingestion of the drug. Dapsone is almost completely absorbed from the gastrointestinal tract and undergoes entero-hepatic circulation.[6] The plasma elimination half-life of dapsone is reported to vary from 10 to 80 h and is dose dependent. Renal excretion of unchanged dapsone is limited to approximately 20% of the administered dose. Dapsone is used in the treatment of leprosy and certain skin conditions. This patient did not have any skin lesions. The urine sample results taken on day 3 and the long duration of the methaemoglobinaemia in spite of treatment with methylene blue favoured dapsone as the offending agent. As for the source of dapsone, it is possible that the patient was given dapsone under the guise of 'ecstasy' tablets along with the alcohol. Benzyl butylphthalate is one of the plasticizers present widely in various household substances. Although there is a risk of chronic toxicity, acute toxicity is not known in humans.

This report describes a case of severe methaemoglobaemia without any positive history. The aetiology was traced to the possible ingestion of dapsone, which was detected in the urine by gas chromatography/mass spectrometry.

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