

Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Acute life-threatening methaemoglobinaemia following ingestion of chloroquine

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Summary

A 25 year old man was rushed to the emergency department when he was found unconscious in his room after taking two chloroquine tablets (600 mg base) for fever prescribed by local practitioner. On examination, the patient was unconscious and deep cyanosis was present on lips, tongue, oral cavity, nail beds and finger tips. Subsequent laboratory investigation revealed methaemoglobin level of 54%. Diagnosis of chloroquine-induced methaemoglobinaemia was made and methylene blue (1 mg/kg) was administered. The patient improved dramatically and was discharged following day.

BACKGROUND

Methaemoglobinaemia is characterised by increased quantities of haemoglobin in which iron of heme is oxidised to ferric (Fe^{3+}) form. Methaemoglobin has a very high affinity for oxygen and virtually no oxygen is delivered to the tissues. Levels >50–60% are often fatal. The condition may arise as a result of a genetic defect in red blood cell metabolism or haemoglobin structure, or it may be acquired following exposure to various oxidant drugs or toxins. Dapsone, local anesthetics, antimalarials, phenacetin and nitrates are the most common drugs causing methaemoglobinaemia, also growing number of drugs are being implicated in its causation.

CASE PRESENTATION

A 25-year-old male without any history of chronic illness with average built and fair coloured skin was rushed to the emergency department when he was found unconscious in his room after taking two chloroquine tablets (600 mg base) for fever from a local practitioner. The patient was unconscious, his pulse rate was 96/min, blood pressure 128/70 mm Hg, respiratory rate 28/min, and temperature 98.4°F. Deep cyanosis was present on lips, tongue, oral cavity, nail beds and finger tips. The patient responded to painful stimulus only. There were no signs of meningeal irritation. His chest was clear, no rhonchi or crepts were present and intensity of breath sounds was equal on both the sides. Cardiovascular examination was also within normal limits with normal first and second heart sounds. No murmurs were audible and there was no clubbing of digits.

The profound cyanosis of patient persisted despite administration of 100% oxygen, at the time of presentation, his oxygen saturation was 88% by pulse oxymetry.

INVESTIGATIONS

Arterial blood gas analysis revealed pH of 7.4, pO_2 315 mm Hg, pCO_2 35 mm Hg, oxygen saturation (calculated)

by blood gas analysis was 98%. The arterial blood was chocolate-brown in colour.

The presence of cyanosis with history of drug intake, absence of other apparent cause of cyanosis, persistence of deep cyanosis despite oxygen therapy, characteristic colour of blood, unexpectedly high value of pO_2 in the presence of deep cyanosis and difference of more than five between oxygen saturation by blood gas analysis and pulse oxymetry (saturation gap) prompted us to think about methaemoglobinaemia. Methaemoglobin levels were performed and they came out to be 54%.

TREATMENT

Injection methylene blue 60 mg (1 mg/kg) was given intravenously over 10 min and within 15–20 min patient's cyanosis started improving and he started to regain consciousness.

OUTCOME AND FOLLOW-UP

He was discharged from the hospital next day in stable condition.

DISCUSSION

Haemoglobin consists of a tetramer of globin polypeptide; each globin chain enfolds a single heme moiety, consisting of protoporphyrin IX ring complexed with a single iron atom in ferrous state (Fe^{2+}). Each heme moiety can bind a single oxygen molecule; a molecule of haemoglobin can transport upto four oxygen molecules. Removal of an electron from a reduced iron atom (oxidation: Fe^{2+} to Fe^{3+}) produces the methaemoglobin which has very high oxygen affinity and virtually no oxygen is delivered to the tissues. This causes oxyhemoglobin curve to shift to the left.¹ Under physiologic circumstances methaemoglobin is continuously produced as a result of the oxidising effect of oxygen; however, it is rapidly converted back to haemoglobin, predominantly by NADH dependent

methaemoglobin reductase. As a result, methaemoglobin levels are normally less than 2%.² Five g/dl of deoxyhaemoglobin is required to produce cyanosis, but because of the spectrographic properties of methaemoglobin, the latter compound produces visible skin discoloration at a level of only 1.5 g/dl.¹

The three primary causes for the development of methaemoglobinaemia are: (1) an inherited autosomal recessive enzymatic deficiency of nicotinamide adenine dinucleotide (NADH) methaemoglobin reductase.^{3,4} This enzyme reduces the ferric iron in methaemoglobin. With a decrease in the amount of NADH methaemoglobin reductase, patients are unable to rapidly convert Methaemoglobin to normal haemoglobin. (2) Haemoglobin M disease, an inherited autosomal dominant trait, can cause significant elevations in methaemoglobin.^{3,4} (3) The most frequent cause of methaemoglobinaemia is exposure to chemical compounds or drugs.^{4,5} Dapsone, local anesthetics, antimalarials, phenacetin and nitrates are the most common drugs causing methaemoglobinaemia although growing number of drugs are being implicated in its causation. This patient of ours needs to be investigated for heterozygous form of methaemoglobin reductase deficiency but unfortunately, this investigation is not performed at our centre. Methaemoglobinaemia due to chloroquine administration has been rarely reported in the literature. We identified only four studies that have reported on this rare phenomenon.⁶⁻⁹

The definitive diagnostic test for methaemoglobinaemia is multiple-wavelength co-oximetry. Because multiple wavelength co-oximetry is not universally available, emergency physicians must be aware of clinical findings and other laboratory values suggesting methemoglobinaemia. Clinical findings include cyanosis that is unresponsive to oxygen and cyanosis in the presence of normal (calculated) oxygen saturation. Although pulse oximeter readings are inaccurate in this circumstance, oximeter saturation values that deviate substantially from the clinical picture may suggest the diagnosis.¹⁰ In addition, if the difference between the calculated oxygen saturation from a standard blood gas machine and the reading from a pulse oximeter is greater than 5%, it is likely that the patient has abnormal haemoglobin, this difference between oxygen saturation from blood gas machine and from pulse oxymetry is known as saturation gap. We also suspected methaemoglobinaemia in our patient on the basis of cyanosis not responding to oxygen, falsely high saturation despite presence of cyanosis and presence of saturation gap of >5%.

Injection methylene blue intravenously in a dose 1–2 mg/kg (0.1–0.2 ml/kg of 1% solution) over 3 to 5 min is the treatment of choice, 15–30 ml fluid flush should be given after injection.^{11,12} Methylene blue acts as a cofactor for the enzyme NADPH methaemoglobin reductase. Electrons are transferred from NADPH to methylene blue, which leads to a reduction of the heme iron in the form of deoxyhaemoglobin. Methylene blue should not be administered to patients with severe glucose-6-phosphate

dehydrogenase deficiency. Side effects of methylene blue include bluish skin discoloration (complicating the assessment of cyanosis), haemolysis, gastrointestinal distress, bladder irritation and ironically, methaemoglobinaemia (particularly in doses above 7 mg/kg). The patient presented above responded promptly to methylene blue in dose 1 mg/kg.

Dextrose may be given because the major source of NADH in the red blood cells is the catabolism of sugar through glycolysis. Dextrose is also necessary to form NADPH through the hexose monophosphate shunt, which is necessary for methylene blue to be effective.¹³

Learning points

- ▶ In patients with normal cardiovascular and respiratory function, methaemoglobinaemia should be considered as a cause of cyanosis in patients taking antimalarials.
- ▶ Cyanosis that is unresponsive to 100% oxygen inhalation and cyanosis in the presence of normal (calculated) oxygen saturation strongly suggests methaemoglobinaemia.
- ▶ The present case represents an uncommon association between chloroquine and methaemoglobinaemia which was successfully managed by administration of methylene blue.

Competing interests None.

Patient consent Obtained.

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