CASE REPORT

A case of pseudocyanosis

Ruvan A I Ekanayaka

Institute of Cardiology,
National Hospital of Sri Lanka,
Colombo, Sri Lanka

Correspondence to

Dr Ruvan A I Ekanayaka,
ruvan_nishali.ekanayaka@
yahoo.com

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SUMMARY

Cyanosis is an ominous physical sign indicating significant cardiac or respiratory disease. However, bluish discolouration mimicking cyanosis could occur in methaemoglobinaemia. The clinical implications being very different, it is important that the aetiology of bluish discolouration of tissues is correctly identified. A case is reported where the antianginal agent nicorandil was identified as the most likely cause for methaemoglobinaemia.

BACKGROUND

Nicorandil is a common antianginal drug used in many countries. As it contains a nitrate moiety, it is theoretically possible to be an agent causing methaemoglobinaemia.

However, there is no report in the literature regarding this adverse effect in humans in therapeutic doses.

CASE PRESENTATION

A 75-year-old male patient on medication for chronic stable angina was brought in for consultation by his daughter, who was also a doctor, as she had noticed that the patient's fingernails had developed a bluish tinge. He had no acute symptoms and the physical examination was unremarkable except for the distinct bluish discolouration of the fingertips clearly discernible through the nails.

INVESTIGATIONS

Routine investigations including full haematological, renal and hepatic profiles were normal (table 1).

Contrast echocardiography was performed to exclude right-to-left shunting at the cardiac or pulmonary level. Pulse oximetry was normal. Cyanosis of cardiorespiratory causation being unlikely in this clinical scenario, the possibility of methaemoglobinaemia was considered.

The co-oximetry test was performed which read 8.7% (normal <1%).

DIFFERENTIAL DIAGNOSIS

The patient had no exposure to chemicals or dyes. Sources and items of food and drink had remained unchanged. He had not taken any medication without prescription for the past 2 months but was on multiple medications for his cardiac condition which included a large dose (120 mg daily) of isosorbide mononitrate (I.S.M.N.).

Nitrates are known to cause methaemoglobinaemia particularly in high doses. Nitrates are converted to nitrites in the gut by certain bacteria^{1 2} and also by hepatic metabolism.³ These nitrites are

a well-established cause of methaemoglobinaemia. Hence, the I.S.M.N. was thought to be the culprit agent and was omitted from the patient's prescription. One month later, the co-oximetry reading for methaemoglobin gave a value of 9.3%. Clearly, the oxidative process was continuing and the I.S.M.N. could not have been the causative agent. On review of his medication, it was found that he had continued to be medicated with nicorandil, which being nicotinamide nitrate, was theorised as being the potential cause for methaemoglobinaemia.

TREATMENT

No specific therapy was given. However, nicorandil was omitted from the drug regime.

OUTCOME AND FOLLOW-UP

Six weeks after omitting nicorandil, the methaemoglobin had decreased to 3.7% and the bluish discolouration was not perceptible.

DISCUSSION

Methaemoglobinaemia is a differential diagnosis to be considered when the physical examination suggests central cyanosis for which a cardiorespiratory cause is not evident. The term 'pseudocyanosis' has been used to describe the bluish tinge caused by methaemoglobinaemia,⁴ which term helps avoid confusion. True cyanosis is described as being a 'slate-blue-purple' hue whereas pseudocyanosis is 'brownish slate' but this distinction is not easy.⁴

Many patients with angina pectoris are managed on medication regimes which include isosorbide dinitrates/mononitrates and/or nicorandil. However, methaemoglobinaemia has not been reported in this country with either agent. Theoretically, 2 mg/kg of I.S.M.N. is required to cause methaemoglobinaemia of any significance. Our patient was on 120 mg of I.S.M.N. which works out to this drug dosage. Some patients develop methaemoglobinaemia even with lower doses due to low cytochrome b5 reductase activity. Nicorandil and its metabolites may bind to haemoglobin leading to methaemoglobinaemia. Clinically evident bluish discolouration usually occurs only when the methaemoglobin is over 8–10%. At a 15% concentration, the pseudocyanosis becomes obvious. Increase in methaemoglobin to 40–60% leads to symptoms attributable to cerebral hypoxaemia. Dyspnoea at rest is a feature when methaemoglobin levels exceed 60%. A noteworthy feature is that pseudocyanosis *precedes* any degree of symptoms. Symptoms of methaemoglobinaemia are insignificant with levels less than 15% but even levels of 5–8% can give symptoms in the presence

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Table 1 Results of laboratory investigations

Haematology	
FBC	
WBC	8.3×10 ³ /μL
N	46%
L	47%
E	7%
RBC	4.43×10 ⁶ /μL
PLT	180×10 ³ /μL
HGB	12.9 g/dL
HCT	39.2%
MCV	88.5 fL
MCH	29.1 pg
MCHC	32.9 g/dL
Blood picture	
RBC	Normocytic, normochromic cells. No spherocytes, bite cells or fragments. No significant polychromasia
WCC	Neutrophils and lymphocytes are normal
PLT	Normal
Comment	This blood picture shows no features of active haemolysis
HPLC	
HbA	85.6%
HbA ₂	2.5% (NR 2.0–3.5%)
HbF	0.3%
Reticulocyte count	1.5%
Glucose 6 phosphate dehydrogenase assay	12.9 U/g Hb (NR 4.6–13.5)
Renal profile	
Serum urea	21 mg/dL
Serum creatinine	1.23 mg/dL
Serum uric acid	6.63 mg/dL
Serum calcium	8.2 mg/dL
Serum phosphorus inorganic	3.44 mg/dL
Serum sodium	132 mmol/L
Serum potassium	4.4 mmol/L
Serum chloride	98 mmol/L
Liver profile	
LDH	343 U/L
Serum bilirubin total	0.4 mg/dL
Serum bilirubin direct	0.1 mg/dL
Indirect bilirubin	0.3 mg/dL

E, eosinophil; FBC, full blood count; Hb, haemoglobin; HCT, haematocrit; HGB, haemoglobin; HPLC, high-performance liquid chromatography; L, lymphocyte; LDH, lactate dehydrogenase; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; N, neutrophil; PLT, platelet; RBC, red blood cells; WCC, white cell count.

of comorbidities such as anaemia, cardiovascular disease and lung pathology.

The therapeutic decision that needs to be made in this case is whether the patient could be given nitrates again. It is probably

the quality of life that would make a clinician reintroduce nitrates. This is a difficult decision but standard textbooks⁵ recommend reintroducing essential drugs in lower dosage. Experience with this patient indicates that individuals may respond differently to mononitrates and nicorandil with respect to methaemoglobin formation. There seems to be no literature available regarding this discrepancy in methaemoglobin formation.

As methaemoglobinaemia can occur several years after administration of nitrates, regular checks for pseudocyanosis are prudent.

It is of clinical relevance that the pulse oximetry in this patient gave a normal result. Pulse oximetry is said to be inaccurate when more than two varieties of haemoglobin coexist in the blood. In the presence of methaemoglobinaemia, the inaccuracy is towards overestimation of oxygen saturation.⁶ Thus, a high normal value on pulse oximetry in the presence of a bluish discolouration may suggest methaemoglobinaemia.

This case is of special interest as it could represent the first reported case of methaemoglobinaemia following the administration of therapeutic doses of nicorandil.

Learning points

- ▶ Methaemoglobinaemia must be considered in the differential diagnosis of blue discoloration of finger tips.
- ▶ Therapeutic agents may give rise to unexpected side effects which may appear after prolonged use.
- ▶ Nicorandil must be considered as a possible cause of methaemoglobinaemia.

Contributors RAIE diagnosed and managed the patient and wrote up the complete manuscript.

Competing interests None.

Patient consent Obtained.

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