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Intraoperative cyanosis: a case of dapsone-induced methaemoglobinaemia

Intraoperative cyanosis is most commonly caused by hypoxaemia. The anaesthetist is required to perform a rapid series of diagnostic manoeuvres and take remedial action. Occasionally methaemoglobin, sulphaemoglobin, or haemoglobin M, undetected preoperatively, is the cause of the cyanosis. We report a case of methaemoglobinaemia secondary to dapsone ingestion that was diagnosed intraoperatively. Dapsone, a sulfone, is used therapeutically to treat leprosy and dermatitis herpetiformis. The differential diagnosis of cyanosis, and the origin and fate of methaemoglobin are discussed. In addition the diagnostic steps and the laboratory investigations required to make the diagnosis are listed.

Cyanosis is a sign for which the anaesthetist must be alert. Intraoperative cyanosis requires rapid and definitive diagnostic manoeuvres to rule out hypoxaemia prior to considering more exotic causes. The following case illustrates the course of such an investigation.

Case report

A 15-year-old boy from France, while attending an international church conference, developed periumbilical pain. After 48 hours the pain localized to the right lower quadrant and he was taken late at night to the emergency department. A diagnosis of appendicitis was made. Intravenous fluids were started and he was given metronidazole 500 mg, tobramycin 60 mg, meperidine 50 mg and dimenhydrinate 50 mg.

The patient gave a history of essential hypertension and

cigarette smoking. Allergies and the ingestion of any drug prior to admission were denied by the patient and his father.

Physical exam revealed a well hydrated 15-year-old boy whose skin appeared somewhat grey, with a BP of 180/70, a pulse of 96 and a temperature of 38.0°C. Abdominal examination was consistent with a diagnosis of acute appendicitis. The respiratory and cardiovascular systems were normal. The laboratory data were Hb 15.0 g·dl⁻¹, WBC 15.2 × 10³/dl, polymorphonuclear leukocytes 13.9 × 10³/dl with the serum electrolytes, BUN and creatinine all within normal limits.

The patient was brought to the operating room and prior to induction he received d-tubocurarine 3 mg and fentanyl 100 µg. A rapid-sequence induction technique was used. Following pre-oxygenation he was given thiopentone 250 mg and succinylcholine 100 mg. Anaesthesia was maintained with isoflurane one per cent, nitrous oxide 66 per cent, oxygen 33 per cent, and fentanyl 150 µg. At the time of intubation there was an increase in BP to 185/90 and pulse to 125 but these soon became steady at BP 130/80 pulse 80. The ventilator settings were: tidal volume 800 ml, rate nine per minute, with a peak inspiratory pressure of 14 cm H₂O.

Following incision of the skin the surgeon commented that the blood was "blue." The patient was then ventilated manually. The FiO₂ was increased to 1.0. The chest was auscultated and its movement observed. The correct position of the tube in the larynx was confirmed visually. The oxygen analyzer confirmed that 100 per cent oxygen was being delivered. The BP and pulse were unchanged. Arterial blood drawn for gas analysis was chocolate brown, with pH 7.39, PaCO₂ 37 mmHg and PaO₂ 438 mmHg. A tentative clinical diagnosis of methaemoglobinaemia was made. The appendectomy continued uneventfully, with an FiO₂ of 0.5. Methylene blue was not given because the BP and pulse were stable and the pH was normal.

The patient had an unremarkable postoperative course. Blood sent intraoperatively revealed methaemoglobin levels of 2.34 g·dl⁻¹, confirming the clinical diagnosis. Two days later the methaemoglobin level had fallen to 0.32 g·dl⁻¹. As the methaemoglobin disappeared so did the patient's grey complexion.

Key words

COMPLICATIONS: cyanosis; BLOOD: methaemoglobinaemia; ANAESTHETIC TECHNIQUES: general; PHARMACOLOGY: dapsone.

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Investigations undertaken postoperatively to determine the cause of the methaemoglobinaemia were: a G6PD screening test, an oxygen dissociation curve, 2,3-DPG levels and NADH reductase levels, all of which were normal. Also no Hb M nor other abnormal haemoglobins were detected by haemoglobin electrophoresis. All three of the patient's siblings had normal methaemoglobin levels.

A supplementary history was taken from the patient and his father. There had been no previous episodes of cyanosis or greyness but eventually the father admitted that the boy had ingested approximately ten "pep pills" (French proprietary medicine containing belladonna) and two 100 mg dapsone tablets the evening prior to admission to hospital. The dapsone had been supplied by a European physician who worked in Africa with the church groups. She had exhausted her supply of sulfa drugs which she normally used to treat diarrhoea and abdominal pain, and had substituted dapsone to treat the young man.

The patient made a satisfactory recovery and was discharged seven days postoperatively.

Discussion

Cyanosis may be peripheral or central. Peripheral cyanosis is due to reduced flow in the extremities, with subsequent desaturation. It is characteristically seen in the nailbeds and the nose. The arterial blood will be red. Central cyanosis is observed in the mucous membranes of the mouth, the lips and the conjunctiva. The arterial blood will not be red. In the preceding case cyanosis was clearly seen in the operative field in the abdomen.

The differential diagnosis of cyanosis is given in Table I. The most common cause of intraoperative cyanosis is hypoxaemia. Causes of hypoxaemia during anaesthesia are listed in Table II.

It is generally accepted that cyanosis is apparent in the skin and mucous membranes when there is $5 \text{ g} \cdot \text{dl}^{-1}$ of deoxyhaemoglobin present.¹ The fact that cyanosis is

TABLE I Differential diagnosis of cyanosis

<i>Deoxyhaemoglobin</i>
hypoxaemia
polycythaemia
Hb with increased P_{50}
<i>Methaemoglobinaemia</i>
Congenital
- enzyme deficiency
- cytochrome b_5 deficiency
- haemoglobin M
Acquired
- toxic
<i>Sulphaemoglobinaemia</i>

TABLE II Causes of hypoxaemia during anaesthesia

<i>Reduced PAO_2</i>
decreased FiO_2
decreased alveolar ventilation
<i>Normal PAO_2</i>
diffusion defect - rare
anatomic shunt
ventilation-perfusion inequalities
increased venous desaturation - e.g., decreased cardiac output, malignant hyperthermia

neither a sensitive nor a reliable sign^{2,3} of hypoxaemia does not lessen the anaesthetist's responsibility to determine as rapidly as possible that he is delivering adequate amounts of oxygen to the patient. Very quickly the flowmeters, oxygen monitor and integrity of the circuit can be checked when cyanosis is recognized. The patient should be taken off the ventilator and ventilated manually while checking the spirometer, inspiratory pressures, and observing and auscultating the chest bilaterally. The endotracheal tube's correct position must also be verified. The blood pressure, pulse and temperature of the patient should be measured. If all of the preceding investigations are normal, only ventilation-perfusion inequalities, anatomic shunts and diffusion defects remain as possible causes of hypoxaemia. The next step in the investigation is direct measurement of the arterial PaO_2 .

There are two other causes of deoxyhaemoglobin in excess of $5 \text{ g} \cdot \text{dl}^{-1}$. The first, polycythaemia, can be determined with reference to the patient's preoperative haemoglobin. The second, and much rarer cause, is a low affinity haemoglobin. These haemoglobin mutants have oxygen dissociation curves shifted to the right, e.g., Hb Kansas has a P_{50} of 70. This form of cyanosis should be noticeable preoperatively.⁴

Methaemoglobin is the haemoglobin molecule with the haeme moiety in the oxidized or ferric state. Normally less than $0.15 \text{ g} \cdot \text{dl}^{-1}$ of haemoglobin is in this form and when methaemoglobin levels rise to 1.5 to $2.0 \text{ g} \cdot \text{dl}^{-1}$ cyanosis can be detected clinically. Patients are often described as having a greyish hue and the arterial blood is chocolate brown in colour.⁴ Symptoms do not usually occur until levels are above $4 \text{ g} \cdot \text{dl}^{-1}$.

To prevent accumulation of spontaneously occurring methaemoglobin there are two enzymatic systems *in vivo* which are capable of reducing the methaemoglobin to haemoglobin:

- 1 NADH-methaemoglobin reductase. This enzyme transfers an electron from NADH to the haeme using cytochrome b_5 as an electron carrier (Figure (A)).
- 2 NADPH-methaemoglobin reductase. This enzyme transfers an electron from NADPH to the haeme but *in vivo*

FIGURE Enzymatic systems for the reduction of methaemoglobin to haemoglobin. (A) NADH-methaemoglobin reductase pathway – this pathway is the primary *in vivo* route for the reduction of methaemoglobin. (B) NADPH-methaemoglobin reductase pathway – this pathway requires an exogenous electron carrier such as methylene blue.

has no electron carrier. If methylene blue is added to the system it acts as an electron carrier and the methaemoglobin is rapidly reduced (Figure (B)).

Patients who are symptomatic with methaemoglobinemia can be treated with intravenous methylene blue. The initial dose should be 1 mg·kg⁻¹ over five minutes. If no effect is seen in 30 to 60 minutes a repeat dose of 2 mg·kg⁻¹ may be given. NADPH is required as an electron donor for methylene blue to be converted to leukomethylene blue and in turn reduce the methaemoglobin (Figure (B)). Therefore methaemoglobinemia patients who have a deficiency of glucose-6-phosphate dehydrogenase (G6PD) are unaffected by methylene blue. In addition methylene blue may initiate a haemolytic episode in G6PD-deficient individuals further embarrassing their oxygen carrying capacity.¹⁴

Methaemoglobinemia causing cyanosis can be either congenital or acquired. Congenital methaemoglobinemia, which is rare, can be of three forms. A haemoglobinopathy in which an amino acid substitution in the haemoglobin molecule creates an environment in which the haeme molecule is preferentially oxidized. The modified haemoglobin is called haemoglobin M. A deficiency of the NADH-reductase enzyme allowing the

accumulation of spontaneously occurring methaemoglobin or the recently described⁷ deficiency of cytochrome b₅ which cripples the NADH-reductase system by not providing an electron carrier. These patients are described as being more blue than sick.^{4,8}

Acquired methaemoglobinemia is the common form. Many chemical compounds and therapeutic agents are known to directly or indirectly oxidize the haeme moiety. An abbreviated list of the common problem agents is given in Table III. The therapeutic agents commonly incriminated and encountered in anaesthetic practice are prilocaine, benzocaine, amyl nitrite, nitroglycerine, phenacetin and sulfonamides.^{6,9}

Dapsone, which appears to have been the cause of the methaemoglobinemia in this case, is a sulfone used to treat leprosy and dermatitis herpetiformis and is well known to produce a dose related methaemoglobinemia. The dose administered (200 mg) is well above the dose which would produce methaemoglobinemia.¹⁰⁻¹³

Sulphaemoglobinemia is the final cause of cyanosis. It is a green pigmented molecule with a sulfur atom incorporated in the porphyrin ring. It results from irreversible oxidation of haemoglobin by drugs or chemicals. Many of the agents listed in Table III have this potential. It is not understood why reversible methaemoglobin is formed in some instances and irreversible sulphaemo-

TABLE III Agents implicated in acquired methaemoglobinemia

Direct oxidants	
<i>Therapeutic agents</i>	<i>Domestic and industrial agents</i>
Amyl nitrite	Well water high in nitrogen
Ethyl nitrite	Food high in nitrates
Sodium nitrite	Nitrous gases (arc welders, silo fillers)
Ammonium nitrate	Corning extract
Silver nitrate	Potassium chlorate
Bismuth subnitrate	
Nitroglycerine	
Quinones	
Indirect agents	
<i>Sulfonamides</i>	<i>Miscellaneous compounds</i>
Sulfamethazone	Acetanilid
Sulfanilamide	Aminobenzenes
Sulfapyridine	Aminophenol
Sulfathiazole	Benzocaine
Protosil	Nitrobenzenes
	Nitrotoluenes
	Phenacetin
<i>Aniline Dyes</i>	
Diaper marking ink	Phenazopyridine (pyridium)
Dyed blankets	Phenylenediamine
Laundry markings	Prilocaine
Freshly dyed shoes	Resorcin
Red wax crayons	Toluenediamine
	Trinitrotoluene

globin in others. Patients with sulphaemoglobinaemia can be profoundly cyanosed but have minimal dyspnoea. This is because cyanosis can be detected at a blood level of $0.5 \text{ g} \cdot \text{dl}^{-1}$, lower than methaemoglobin ($1.5\text{--}2.0 \text{ g} \cdot \text{dl}^{-1}$) or deoxyhaemoglobin ($5.0 \text{ g} \cdot \text{dl}^{-1}$),⁴ and in addition, sulphaemoglobin moves the P_{50} of the oxygen-dissociation curve to the right, enhancing oxygen delivery to the tissues.¹⁵ The arterial blood is described as having a mauve or lavender hue.⁴

When cyanosis is diagnosed intraoperatively the anaesthetist must act quickly and decisively. A rapid set of manoeuvres must be performed to rule out hypoxaemia. A clear understanding of the differential diagnosis of cyanosis in conjunction with several laboratory tests should then reveal the more exotic causes such as methaemoglobinaemia.

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Résumé

La cyanose intraopératoire est le plus souvent provoquée par l'hypoxémie. L'anesthésiste est demandé d'accomplir rapidement une série de manoeuvres diagnostiques afin d'y remédier. Occasionnellement la méthémoglobine, la sulfhémoglobine ou l'hémoglobine M, non détecté en période préopératoire est la cause de cyanose. On rapporte le cas d'une méthémoglobinémie secondaire à l'ingestion de dapsone ayant été diagnostiquée en période opératoire. Le dapsone, un sulfone, est utilisé afin de traiter la lèpre et la dermatite herpétiforme. Le diagnostic différentiel de la cyanose ainsi que l'origine et le sort de la méthémoglobine sont discutés. En plus les manoeuvres diagnostiques et l'investigation du laboratoire requis pour confirmer le diagnostic sont énumérées.