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Congenital methaemoglobinaemia detected by preoperative pulse oximetry

Methaemoglobinaemia is an unusual cause of cyanosis whether it is congenital or acquired. Hence, the diagnosis may not be immediately obvious and appropriate treatment may be delayed. The case described shows that it should be considered when pulse oximetry and arterial blood gas analysis appear to give conflicting results. A healthy 24-yr-old woman was found to have a pulse oximeter reading of 82% prior to induction of anaesthesia for minor surgery. Clinical examination confirmed cyanosis but no other abnormality was detected. She had no important medical history and was not receiving any medications. Arterial blood gas analysis with the patient breathing air showed PaO_2 12.03 kPa (90 mmHg). Co-oximeter analysis of this sample revealed a methaemoglobin content of 13.4% and she was subsequently found to have congenital methaemoglobin reductase deficiency. Anaesthesia was induced and maintained with incremental doses of propofol and fentanyl. A spontaneously breathing technique with oxygen in nitrous oxide was employed uneventfully. No specific treatment for methaemoglobinaemia was given. Perioperative pulse oximetry is one of the major advances in patient monitoring in recent years but unexpected results should not be accepted uncritically. A knowledge of the working principles of oximetry is essential to enable appropriate management in the presence of dyshaemoglobins.

La méthémoglobémie est une cause rare de cyanose congénitale ou acquise. Le diagnostic peut ne pas être immédiatement manifeste et son traitement peut être retardé. Cette observation

montre qu'il faut y penser quand l'oxymétrie pulsée et les gaz du sang artériel semblent se contredire. L'oxymétrie pulsée d'une femme de 24 ans bien portante indique 82% de saturation avant l'induction de l'anesthésie pour une chirurgie mineure. L'examen clinique confirme la cyanose mais on ne détecte pas d'autre anomalies. L'anamnèse est sans particularité et la patiente ne reçoit aucun médicament. Lorsque la patiente respire de l'air, l'analyse des gaz du sang artériel montre une PaO_2 de 12,03 kPa (90 mmHg). L'analyse au co-oxymètre de l'échantillon révèle un contenu en méthémoglobine de 13,4%. Par la suite, on diagnostique une déficience congénitale de la méthémoglobine réductase. L'anesthésie est induite et entretenue avec des doses répétées de propofol et de fentanyl. Une technique de respiration spontanée avec de l'oxygène dans du protoxyde d'azote est utilisée sans incident. On n'administre pas de traitement spécifique pour la méthémoglobémie. Ces dernières années, l'oxymétrie pulsée péroperatoire a représenté un des progrès majeur du monitoring mais des résultats inattendus ne doivent pas être acceptés sans discernement. Une connaissance des principes de l'oxymétrie est essentielle pour une conduite appropriée en présence d'une dyshémoglobémie.

Key words

BLOOD: methaemoglobinaemia;
COMPLICATIONS: cyanosis;
MEASUREMENT TECHNIQUES: pulse oximetry;
MONITORING: oxygen.

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Pulse oximetry is now widely regarded as part of minimal monitoring prior to induction of anaesthesia to provide a continuous estimate of arterial oxygen saturation (SpO_2).¹ The universal adoption of this practice may, on occasion, reveal some surprising abnormalities. Many factors are known to interfere with these devices and they are not without limitations.²⁻³ A patient with asymptomatic cyanosis is described, whose abnormality was detected in the anaesthetic room by pulse oximetry. This was subsequently found to be due to congenital methaemoglobinaemia secondary to methaemoglobin reductase deficiency.

Case report

A 24-yr-old 51 kg Caucasian woman presented for evacuation of retained products of conception. Six years previously she had undergone a Caesarean section under general anaesthetic, and a year later had had a termination of pregnancy also under general anaesthetic. Both

these anaesthetics were conducted without incident but in neither case had pulse oximetry been used. Her past medical history was otherwise unremarkable. She admitted to smoking up to 20 cigarettes a day but she had not taken any recent medications, prescribed or otherwise.

A preoperative full blood count estimated her haemoglobin at $15.3 \text{ g} \cdot \text{dl}^{-1}$ with a haematocrit of 0.448 and MCV 84.2 fl. Anaesthetic preoperative assessment was performed in a gloomy side room on the gynaecology ward and failed to reveal any abnormality. No premedication was prescribed.

After arrival in the anaesthetic room continuous pulse oximetry and electrocardiographic (EEG) monitoring (Hewlett Packard 78352A) were instituted before induction of anaesthesia. The SpO_2 recorded varied between 80–84%. The patient's pulse rate was $80 \text{ beats} \cdot \text{min}^{-1}$, blood pressure 100/70 mmHg and the ECG appearance (lead II) was normal. Oxygenation using 100% oxygen via a tight-fitting mask and coaxial Lack circuit failed to raise the SpO_2 . The pulse oximeter was checked on members of staff on whom it gave normal readings. With the benefit of knowing the SpO_2 the patient now looked cyanosed. On direct enquiry she admitted to having always had a "dusky" appearance but again denied any cardiovascular or respiratory symptoms. Repeat examination at this time failed to reveal any heart murmurs or other signs of a right to left shunt or pulmonary pathology.

The operation was postponed and a 12-lead ECG and chest radiograph ordered. A blood gas sample was taken from the patient's radial artery after she had been breathing room air for ten minutes. This showed pH 7.45, PaCO_2 4.34 kPa (33 mmHg), PaO_2 12.03 kPa (90 mmHg), SaO_2 97.2% (Radiometer ABL 330). These results were somewhat surprising considering the patient's appearance and rather venous looking nature of the blood gas sample. The remains of this sample were sent for co-oximeter analysis (Instrumentation Laboratories Inc., Lexington, Massachusetts; Model IL 482). Results: methaemoglobin 13.4%, carboxyhaemoglobin 1.0%. Both the chest radiograph and 12-lead ECG were within normal limits.

It was decided to proceed with surgery as planned, avoiding any drugs that could exacerbate her methaemoglobinaemia. Anaesthesia was induced with propofol 150 mg and fentanyl 75 μg . A spontaneously breathing technique was employed with an inhaled gas mixture of 50% nitrous oxide in oxygen via a circle system and face mask. Increments of propofol to a total dose of 250 mg were given to maintain anaesthesia. Oxytocin, 5 units, was given after cervical dilatation. The procedure lasted about 15 min and was uneventful. Throughout the operation her SpO_2 remained between 80–84%. The patient made a rapid recovery and was discharged the following

day with an outpatient appointment for the haematology clinic.

At the clinic the patient revealed that her 34-yr-old brother had been diagnosed as having "a hole in the heart" as a small baby. Despite his bluish colour he had led an active life without any medical intervention or follow up. Her other three siblings were all of normal appearance. A repeat methaemoglobin concentration was 14.2%. Her methaemoglobin reductase concentration was 2.5 EU at 30°C (normal range 12.2–21 EU at 30°C). These results were consistent with a diagnosis of congenital methaemoglobin reductase deficiency. Her brother was subsequently found to have a methaemoglobin concentration of 10%.

Discussion

A pulse oximeter reading of 82% in an asymptomatic individual breathing room air with a PaO_2 of 12.03 kPa (90 mmHg) was a surprising finding. This alerted us to the possible presence of an abnormal haemoglobin which may have affected the accuracy of the pulse oximeter. The effects of methaemoglobin on SpO_2 with varying amounts of oxyhaemoglobin and reduced haemoglobin have been studied in dogs by Barker *et al.*⁴ At 660 nm methaemoglobin has a similar absorbance to reduced haemoglobin, at 940 nm methaemoglobin adds to both the absorbances of reduced and oxyhaemoglobin but has a quantitatively smaller effect. Hence, in the presence of small quantities of methaemoglobin the effect on the ratio of absorbances is interpreted as an increase in reduced haemoglobin and displayed as a decrease in SpO_2 . At increasing concentrations of methaemoglobin (30–35% of total haemoglobin) absorbance is increased at both wavelengths which tends to drive the ratio of absorbances towards unity. A ratio of 1.0 is interpreted by the calibration algorithm as a saturation of between 80–85%. Under these conditions the pulse oximeter unfortunately provides no useful information on the actual haemoglobin saturation. The overall effect is that with increasing concentrations of methaemoglobin the SpO_2 will gradually decrease to 80–85% and remain there regardless of the actual haemoglobin saturation. Hence, at low actual saturations the SpO_2 will be an overestimate. Co-oximeters such as the IL 482 are functionally different from pulse oximeters in that they measure absorbances at four different wavelengths of light *in vitro*.⁵ This enables them to distinguish accurately between oxyhaemoglobin, reduced haemoglobin, carboxyhaemoglobin and methaemoglobin.

Clinical cyanosis is said to become apparent when the reduced haemoglobin concentration is $>5 \text{ g} \cdot \text{dl}^{-1}$. Methaemoglobin is able to produce detectable cyanosis at a lower concentration of about $1.5 \text{ g} \cdot \text{dl}^{-1}$.⁶ Our patient

had a methaemoglobin concentration of $2.05 \text{ g} \cdot \text{dl}^{-1}$ ($15.3 \text{ g} \cdot \text{dl}^{-1} \times 13.4\%$). Methaemoglobin is an oxidation product of haemoglobin formed *in vivo* at a slow predictable rate when haem loses an electron as a superoxide radical is displaced.⁷ This oxidation of haemoglobin from ferrous to ferric form leaves it incapable of transporting oxygen. To regain its oxygen-carrying capacity the oxidized ferric haemoglobin is immediately reduced by nicotinamide adenine dinucleotide (NADH) methaemoglobin reductase (cytochrome b5 reductase) to ferrous haemoglobin within the red cell.⁸ The capacity of the red cell to reduce the methaemoglobin exceeds the spontaneous rate of haemoglobin oxidation by several hundred-fold. Therefore, usually, less than 1% of total haemoglobin is present in the ferric or methaemoglobin form.⁹

For abnormal amounts of methaemoglobin to be present one of the following must occur:

- (a) Greatly increased production of methaemoglobin overwhelming the reducing capacity of the red cell. This occurs in acquired or drug-induced methaemoglobinaemia. Some agents such as nitrites, nitrates, chlorates and nitric oxide are direct oxidizing agents, others such as sulphonamides, primaquine, aniline dyes, prilocaine and benzocaine seem to act through indirect mechanisms.
- (b) An abnormal globin moiety which makes methaemoglobin resistant to metabolic reduction (haemoglobin M).
- (c) Decreased breakdown of methaemoglobin due to deficiency in the reducing mechanism of the red cell (NADH-methaemoglobin reductase deficiency).

This last mechanism was the cause of methaemoglobinaemia in our patient. It is an hereditary condition with an autosomal recessive mode of transmission. It is more prevalent in certain racial and ethnic groups such as Eskimos, American Indians, Puerto Ricans and Mediterraneans; in other racial groups it is rare and tends to occur sporadically.⁹ Affected individuals are homozygous for the abnormal gene; however, the carrier or heterozygous state is characterised by an intermediate level of enzyme activity and hence an increased susceptibility to the effects of oxidant drugs and chemicals.¹⁰

The only clinical feature of this disorder is cyanosis, usually present from birth without any accompanying features. These individuals have been described as "more blue than sick." Untreated individuals usually have methaemoglobin concentrations between 15–30%. The effect of partial oxidation of one haem group in the haemoglobin tetramer increases the oxygen affinity of the remaining haem groups. This causes the oxygen dissociation curve to be shifted to the left. Sometimes, as in our patient, this causes a mild compensatory erythrocytosis. Severe methaemoglobinaemia (>50%) usually

only occurs with the acquired form. Symptoms range from exertional dyspnoea and headache to lethargy and stupor with increasing concentrations. The lethal concentration for adults is probably greater than 70%.¹¹

Infants (<6 mo) are more prone than adults to the acquired form of methaemoglobinaemia. This has been demonstrated with lidocaine-prilocaine cream (EMLA).¹² It is thought to be due to the limited capacity of methaemoglobin reductase in early infancy, associated with the increased susceptibility of haemoglobin F to oxidation. The presence of acidosis, hyperchloraemia and partially deoxygenated haemoglobin worsens the tendency to form methaemoglobin.¹³

Treatment of congenital methaemoglobinaemia is only usually required for cosmetic purposes and consists either of oral methylene blue or ascorbic acid. Methylene blue can also be given intravenously ($1 \text{ mg} \cdot \text{kg}^{-1}$) as an acute treatment for methaemoglobinaemia. It acts as an exogenous electron acceptor and is converted to leukomethylene blue, which rapidly reduces methaemoglobin nonenzymatically.¹¹ We decided not to treat our patient with intravenous methylene blue as it was felt that she had sufficient oxygen-carrying capacity and it also interferes with pulse oximetry.¹⁴

Pulse oximeters are a major advance in the perioperative monitoring of patients. However, an understanding of their working principle is essential when unexpected results are displayed, to avoid inappropriate and potentially dangerous interventions. Hence, in the presence of dyshaemoglobins, arterial blood gas analysis should be used in conjunction with co-oximeter readings, rather than depending on pulse oximetry to indicate adequate patient oxygenation.

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