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CASE REPORT

Methaemoglobinaemia following intravenous regional anaesthesia: Blue lips and brown blood

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Abstract

Methaemoglobinaemia is a rare complication of prilocaine, mainly affecting individuals with predisposing conditions or those receiving an unusually high dose. However, this case shows that a predetermined safe dose of prilocaine can still produce clinically significant symptoms. A healthy 20- year-old female presented with cyanosis, tachycardia and a low oxygen saturation with a distinctive brown-coloured arterial blood gas sample with raised methaemoglobin levels. She had undergone regional intravenous anaesthesiology of her right arm with prilocaine 1% 6 mg/kg (400 mg). The patient was not complaining of any symptoms. The diagnosis of prilocaine-induced methaemoglobinaemia was suspected and she was transferred to the intensive care unit for monitoring and respiratory support. In the absence of symptoms and in the context of spontaneously dropping methaemoglobin levels no other active treatment was initiated. She was discharged the following day in a good clinical condition.

Introduction

Methaemoglobinaemia has been widely recognised as a rare, reversible and serious complication following prilocaine use.[1] Prilocaine, an amide-type local anaesthetic, is one of the most frequently used local anaesthetics for intravenous regional anaesthesia (IVRA). In comparison with other amide-type local anaesthetics, it has a lower incidence of neurological and cardiac toxicity.[2] However, there is an increased risk for methaemoglobinaemia, especially when the dose exceeds the maximum of 500 mg.

Early recognition of methaemoglobinaemia can prevent potentially life-threatening complications such as rhythm disorders or circulatory arrest.[2] We therefore describe a case of methaemoglobinaemia following intravenous regional anaesthesiology of the arm (IVRA or Bier's block) using a safe therapeutic dose of prilocaine.

Case

The patient a 20-year-old otherwise healthy female, was admitted postoperatively to the plastic surgery department following an uncomplicated excision of a ganglionic cyst located on the right wrist. The anaesthetic technique (IVRA) was performed without incident using 400 mg (6 mg/kg) of intravenous prilocaine. The operation lasted for a total of 20 minutes. The pneumatic cuff was left inflated for a duration of 30 minutes after initial inflation. Later that evening she presented with significant refractory hypoxaemia at routine check-up. The patient was, however, asymptomatic. We encountered a cyanotic, pale woman, with a repeatedly measured peripheral oxygen saturation of 83%. She was calm, alert and had a respiratory rate of 16 breaths/min. Furthermore she had a regular tachycardia (127 beats/min) with a stable blood pressure (135/75 mmHg). Besides cyanosis of lips and nailbed, the further clinical evaluation was found to be normal. The arterial blood gas sample taken at 35% FiO_2 was brown coloured: pH: 7.39; PO_2: 5.9 kPa (10.0-13.3 kPa); PCO_2: 4.6 kPa (4.7-6.4 kPa); bicarbonate: 20.6 mmol/l (21.0-28.0 mmol/l); O_2 saturation: 82%; methaemoglobin level (metHb): 21.9% (0.0-1.5%). This raised the suspicion of prilocaine-induced methaemoglobinaemia. The patient was admitted to the intensive care unit for further monitoring and oxygen therapy. There was no sign of metabolic acidosis, anaemia, or kidney or liver disorders. In the course of several hours, the methaemoglobin levels dropped spontaneously to 4.4%. For this reason and in the absence of symptoms, intervention with methylene blue was withheld. She was discharged home the following morning in a good clinical condition.

Methaemoglobinaemia

Methaemoglobin, the oxidised form of haemoglobin, is unable to transport oxygen. Haemoglobin normally binds oxygen molecules to its haeme iron complexes (Fe^{2+}).[1] However, free oxygen radicals at tissue level can induce oxidation in a small percentage of the haemoglobin molecules (3%). In this process

the iron molecule loses one of its electrons to the oxygen radical and oxidises to ferric iron (Fe^{3+}) leading to methaemoglobin formation.[2] This not only results in a diminished functional haemoglobin capacity, but also increases the oxygen binding affinity of haemoglobin as the haeme binds more effectively to the oxygen molecule.[2] The body reduces this daily methaemoglobin production mainly (99%) using the cytochrome-b5-reductase enzyme (*figure 1*).[3] Disorders of this primary route can lead to a higher than physiological percentage of methaemoglobin. Percentages exceeding 10% are considered to be pathological and are usually accompanied by clinically significant symptoms.[4] Below 20% cyanosis is the major symptom. Between 30-50%, symptoms can include tachycardia, headaches and dyspnoea. Above 50% rhythm disorders and loss of consciousness can occur, whereas percentages of 70 and over are accompanied by multiorgan failure and even death.[4]

The causes of these disorders can be classified as congenital or acquired. Congenital methaemoglobinaemia is rare and can be divided into three subtypes.[3] Types I and II are both consequences of an expression disorder in the cytochrome-b5-reductase enzyme.[3,5] Haemoglobin-M-methaemoglobinaemia is the result of a mutation in the globin chain that inhibits the reduction of the iron haeme complex.[3] Acquired methaemoglobinaemia, the most common form of this condition, is induced by free oxygen radicals.[3] These radicals, released during the metabolism of methaemoglobin-inducing substances, oversaturate the cytochrome-B5-reductase enzyme (*figure 1*).[3] Patients with a cardiopulmonary history, oxidative substance use (*table 1*) or other predisposing factors, such as anaemia, liver of kidney function disorders, acidosis or infants (<6 months of age), are more prone to developing methaemoglobinaemia.

Table 1. Possible oxidative agents

Nitrates	Paracetamol
Herbicides/ fungicides	Sulphonamides
	Industrial solvents
Silver nitrate	Antimalarials
Industrial salts	Dapsone
Nitrous oxide	Sodium valproate
Aniline dyes	Benzocaine
	Fentanyl
Mothballs	Lidocaine
Copper sulphate	Prilocaine

Adapted from Adams et al.[4]

Diagnostic regimen and treatment

Methaemoglobinaemia should be considered in any patient with a low peripheral oxygen saturation and a brown discoloration of the arterial blood gas sample; this analysis forms the cornerstone of the diagnostics. Pulse oximetry is unreliable due to disturbances in the absorption rate; methaemoglobin absorbs wavelengths of 660 nm and 940 nm (deoxyhaemoglobin and oxyhaemoglobin, respectively).[6] The fastest effective treatment of symptomatic methaemoglobinaemia consists of cessation of the causative substance and administration of 1-2 mg/kg methylene blue. This can then be repeated after one hour for a maximum of three doses or 7 mg/kg.[8] Methylene blue is converted to leuko-methylene via the NADPH-methaemoglobin-reductase enzyme which then reduces methaemoglobin to functional haemoglobin. Contraindications for methylene blue are G6PD deficiency because of dysfunction of the NADPH-enzyme causing haemolysis. Furthermore serotonergic substance use is a contraindication in that methylene blue inhibits the function of the enzyme monoamine-oxidase potentially leading to serotonergic syndrome.[7]

Treatment can then be substituted with 1-2 mg/kg ascorbic acid intravenously: a non-enzymatic antioxidant that is also able to reduce methaemoglobin at a relatively slower rate.[7] Additional treatment with replacement transfusion or hyperbaric oxygen should be considered if, after re-valuation, no clinical improvement is seen.[7]

The Biers block

The Biers block (1908) is an anaesthetic technique that utilises a double pneumatic cuff after exsanguination by elevation and bandaging of the limb to ensure that the injected anaesthetic substance does not reach the systemic circulation. This pneumatic isolation is continued for at least 30 minutes after administration of the anaesthetic substance. Portioned de-cuffing at the end of the procedure prevents systemic toxicity. However, minimal prilocaine leakage from the tissue into the circulation can cause some degree of methaemoglobin production.[2] Prilocaine is, next to lidocaine, one of the most frequently used anaesthetics for IVRA. Both are evenly effective but prilocaine has been shown to have less toxicity-related symptoms.[2] Prilocaine metabolism in the liver, however, produces the metabolite O-toluidine, a known inducer of methaemoglobin.[1]

Research has shown that a dose of 600 mg of prilocaine is needed to reach a clinically significant level of methaemoglobin.[8] Therefore, in the Netherlands, a maximum dose of 500 mg is maintained. National guidelines for IVRA suggest 40-50 ml of 0.5% prilocaine.[9] However, manufacturer guidelines for prilocaine state that the dose/percentage can be modified to fit the surgical procedure within the limits of the maximum dose of 500 mg.[10]

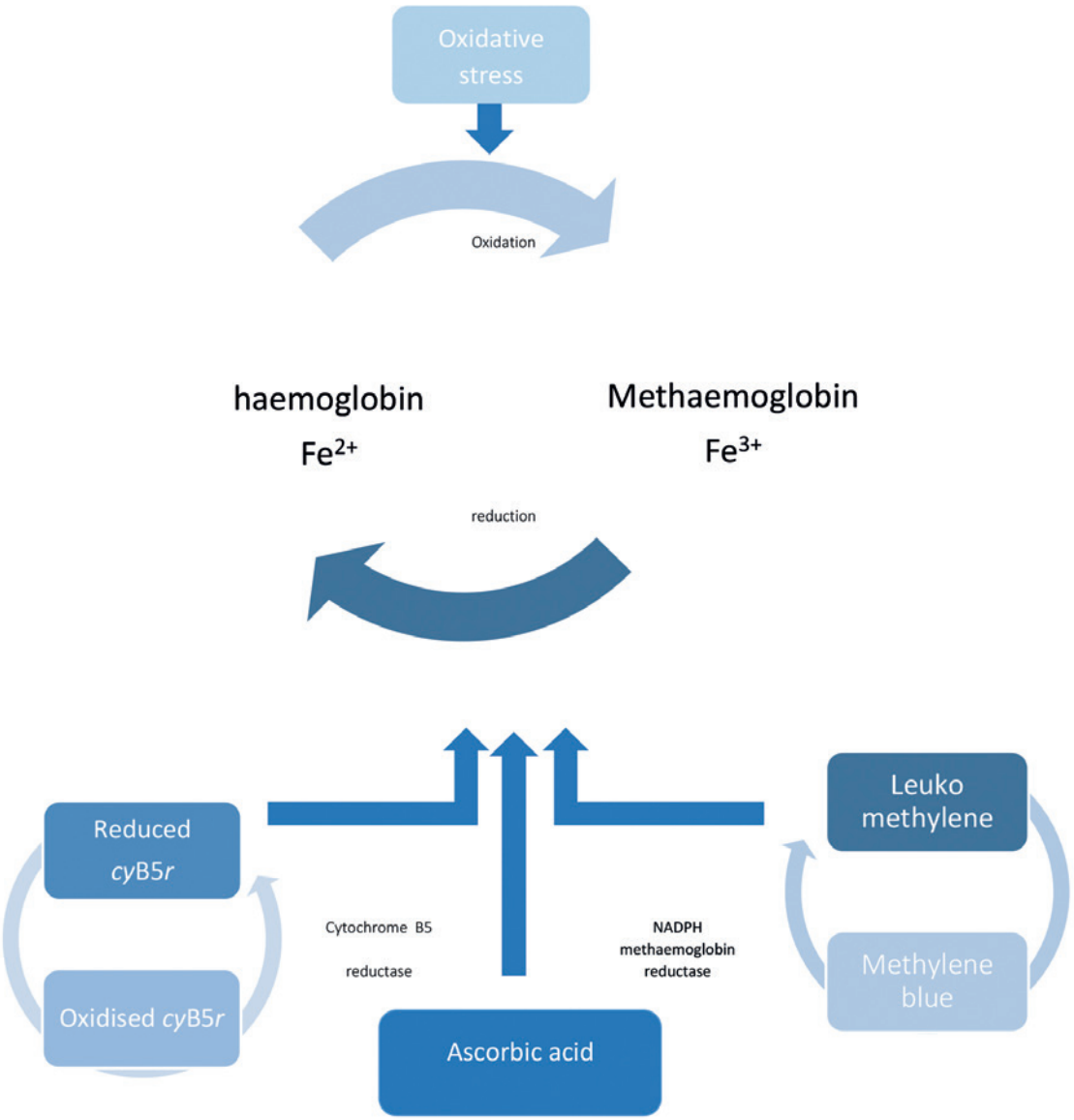

Figure 1. Oxidation and reduction of methaemoglobin
Adapted from Kuiper-Prins et al.[5], with permission

Earlier research has shown that the level of methaemoglobin produced reaches a peak concentration averaging 7.6% (max. 12%) 155 minutes after cuff deflation.[11] After this period the level steadily begins to drop, indicating a safe use of prilocaine for IVRA. Furthermore, Bartholomew's study, focusing on 45,000 Bier blocks using prilocaine in the United Kingdom, showed no indication for serious complications or mortality.[12] However, it should be of note that 75% of the reporting departments used a dose of 3 mg/kg, which corresponds to a far lower maximum dose.

Discussion

Why our patient developed methaemoglobinaemia is unclear. During the operation she received a total dose of 400 mg prilocaine, (6 mg/kg) a dose below the allowed maximum. The cuff stayed inflated for a duration of 30 minutes prior to sequential deflation. She had no prior history of congenital methaemoglobinaemia, had no record of prescribed or not prescribed medication use and a G6PD deficiency was verbally excluded. Interpersonal variability in metabolism is, therefore, the most probable cause of methaemoglobinaemia development following a safe dose of prilocaine.

Conclusion

Following intravenous anaesthesia using a safe therapeutic dose of prilocaine, the formation of clinically significant methaemoglobinaemia should still be considered. The arterial blood gas analysis not only confirms the diagnosis, but combined with the clinical symptoms poses the guideline for initiating therapy.

Disclosures

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Written informed consent was obtained from the patient for the publication of this case report.

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