IN BRIEF

- The development of methaemoglobinaemia is a rare complication of local anaesthetic administration. In this condition the ability of haemoglobin to transport oxygen is impaired.
- Factors which may result in an increased susceptibility to the development of methemoglominaemia are highlighted.
- Some incongruities in the literature regarding the maximum safe dose of prilocaine are discussed.

Prilocaine induced methaemoglobinaemia in a medically compromised patient. Was this an inevitable consequence of the dose administered?

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Patient M, a 45-year old female, was admitted for extractions with local anaesthetic, sedation and monitoring. This was to be carried out on an in patient basis due to the patient's extensive medical history which included rheumatic heart disease, previous deep vein thrombosis and severe ulcerative colitis. Patient M also gave a history of allergy to penicillin and lignocaine. The procedure was completed without incident, local anaesthesia having been achieved using Citanest with Octapressin^{R} (prilocaine 30 mg/ml and felypressin 0.03 unit/ml 2 ml cartridge). However, on recovery Patient M's oxygen saturations dropped to 90% on air and although she had no symptoms, the levels could not be improved with supplemental oxygen. A diagnosis of methaemoglobinaemia (MetHb) was established, a rare complication associated with the administration of prilocaine. Patient M was transferred to the high dependency unit and was given methylthioninium chloride (methylene blue) intravenously. Her oxygen saturations quickly returned to normal and she was discharged the following day. This case highlights issues relating to the risk of developing MetHb, what is considered the maximum safe dose of prilocaine and some incongruities the authors feel exist in the literature.

INTRODUCTION

Methaemoglobinaemia (MetHb) is a rare complication of administration of the local anaesthetic prilocaine. However, it is probably under-recognised and it can result in significant morbidity and mortality.[1]

MetHb is an abnormal haemoglobin produced as a result of oxidation of the iron moiety changing normal ferrous haemoglobin to the ferric state. In this state the oxygen-binding properties of haemoglobin are inhibited. The body is subjected to continual production of MetHb due to various oxidant stresses. However, the levels of MetHb are normally kept below 1%, mainly due to the action of two enzyme systems:

- Diaphorase I (NADH- dependent reductase) 95%
- Diaphorase II (NADPH-dependent reductase) 5%.

The causes of methaemoglobinemia may be divided into three categories:

1. Compromised cellular defences against oxidant stress
2. Agents that inflict large oxidant stress
3. Predisposing conditions.

Each of these categories is outlined in more detail in Tables 1-3.[1,2]

MetHb may present with a variety of symptoms depending on the concentration of methaemoglobin (Table 4).[2,3]

The non-specific nature of the symptoms may make diagnosis difficult. Although pulse oximetry and arterial blood gas analysis may be useful, the diagnosis can only be confirmed by multiple wavelength co-oximetery.[2,4]

Pulse oximetry

Diagnostically pulse oximetry is unreliable; however, an abnormal value in an asymptomatic patient may suggest elevated MetHb. In patients with low-level MetHb it often reveals falsely low oxygen saturations while in patients with high-level MetHb it often reveals falsely high values oxygen saturations.

Arterial blood gas

Again, arterial blood gas analysis can be misleading as normal PaO2 concentrations are usually found on analysis. However, a normal arterial oxygen tensions in the presence of cyanosis or low oxygen saturations on pulse oximetery are highly suggestive of MetHb.

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Multiple wavelength co-oximetery

Co-oximeters measure the light absorption of blood at numerous ultraviolet wavelengths. Pulse oximeters measure ultraviolet absorption at only 2 wavelengths and can therefore only differentiate oxyhemoglobin from deoxyhemoglobin. Multiplewavelength co-oximeters can determine the amounts of oxyhaemoglobin, deoxyhaemoglobin, carboxyhaemoglobin, and methaemoglobin.

Treatment varies depending of the concentration of MetHb present. Clinical recognition is paramount, as patients may have non-specific symptoms. Any offending oxidising agent should be removed and the patient administered supplemental oxygen. An asymptomatic patient with MetHb levels of less than 20% may require only observation. Otherwise an intravenous solution of 1% methylthioninium chloride (methylene blue) in a dose of 1 mg/kg is the first line treatment and is very effective. In the few patients resistant to this treatment hyperbaric oxygen therapy or packed RBC exchange transfusions may be necessary.[2]

Table 1 Compromised cellular defences against oxidant stress[1]

Compromised cellular defences against oxidant stress
• Children younger than four months may have underdeveloped protective mechanisms. GI infections may cause a build-up of systemic oxidants by an overgrowth of gut bacteria
• Congenital lack of protective cellular capabilities includes those with the following: - Diaphorase I deficiency (congenital MetHb). - Haemoglobin M disease

Table 2 Agents inflicting oxidant stress[1,2]

Examples of agents inflicting oxidant stress	
Nitrates	**Paracetamol**
Paraquat	Sulfonamide antibiotics
Silver nitrate	Antimalarials
Industrial salts	Dapsone
Nitrous oxide	Sodium valporate
Aniline dyes and inks	Benzocaine
Mothballs	Lidocaine
Industrial solvents	**Prilocaine**
Fungicide (copper sulfate)	Nitroglycerin
Nitrates	**Fentanyl**

CLINICAL CASE

Patient M, a 45-year-old female, was admitted for an upper dental clearance and removal of a lower premolar (11, 12, 17, 21, 25, 27 and 45) with local anaesthetic, sedation and monitoring.

The patient had an extensive past medical history which included rheumatic heart disease, previous deep vein thrombosis and severe ulcerative colitis which had resulted in a colectomy and ileostomy being undertaken. A Hickman line for supplemental total parenteral nutrition was *in situ*.

Patient M also gave a history of allergy to penicillin and lignocaine. Although the allergy to penicillin appeared to be a true allergy we were suspicious that the reported reaction to lignocaine had actually been due an intravascular injection as the only symptoms the patient had experienced were palpitations. Mrs M's medication currently comprised warfarin, cocodamol and total parental nutrition.

On admission she had a blood pressure of 94/62 mm hg, pulse rate of 90 bpm, temperature of 36.3°C and her weight was 43 kg. Preoperatively, a full blood picture, electrolytes and urea and echocardiograph were all within normal limits. However, from the patient's previous nutritional records we were aware that she was sideropenic and suffered from micronutrient deficiencies (most notably vitamin K and vitamin C).

The procedure was undertaken in theatre with a consultant anaesthetist present. Initially 300 mg of clindamycin (Dalacin C^{R} clindamycin 150 mg/ml) was given intravenously as infective endocarditis prophylaxis. Patient M was then sedated using 4 mg of midazolam (Hypnovel^{R} midazolam 2 mg/ml, given incrementally) and 50 mcg of fentanyl (1 ml 50 mcg/ml), both drugs were given intravenously. Patient M was subsequently administered 5.25 cartridges of Citanest and Octapressin^{R} (3% prilocaine 30 mg/ml and felypressin 0.003 unit/ml 2 ml cartridge), representing 10.5 ml of local anaesthetic solution or 315 mg of prilocaine. This was administered as inferior alveolar, greater palatine, nasopalatine and long buccal nerve blocks along with local infiltrations. The final 1.25 cartridges were given via interligamentary injection. The procedure was completed without event.

On recovery Patient M's oxygen saturations dropped to 90% on air and although she had no symptoms, the levels could not be improved with supplemental oxygen. At this stage an arterial blood sample was taken and revealed methaemoglobin levels of 11-14 %, (normal = 1%). Patient M was transferred to the high dependency unit where she was given 43 mg of methylthioninium chloride (methyl blue) intravenously. Her oxygen saturations quickly returned to normal and she was discharged the following day.

DISCUSSION

This case highlights issues relating to the risk of developing MetHb, what is considered the maximum safe dose of prilocaine and some incongruities the authors feel exist in the literature. It must be stressed however that the administration of prilocaine, or indeed any local anesthetic, is generally a very safe procedure and that the development of MetHb is very rare.

The British National Formulary (BNF)[5] gives the maximum safe dose of prilocaine as 400 mg (approx 6.5 cartridges of Citanest^{R}) and for children over six months it recommends a dose of 5 mg/kg. For prilocaine used with the vasoconstrictor felypressin (Citanest with Octapressin^{R}) it recommends that 300 mg (five cartridges) should not be exceeded. It further suggests that the dose be reduced in the elderly or debilitated and those with renal impairment.

Our patient was administered 5.25 cartridges of Citanest with Octapressin^{R} (315 mg of prilocaine). The final 1.25 cartridges were given via interligamentary injection. It could be argued that there should have been a reduction in dose

given our patient's medical history and weight, and the use of oxidising agents such as fentanyl and paracetamol. However, it is arguable that a significant amount of the last 1.25 cartridges which were delivered interligamentally was actually aspirated.

In addition, the recommended maximum dose is not universal throughout the literature. Scully and Cawson's *Medical problems in dentistry*[6] concurs with the BNF with regards to the maximum safe dose of plain prilocaine ie 400 mg or approximately 6.5 cartridges. However, it is in discord regarding the maximum safe dose of prilocaine with felypressin stating the maximum dose to be 600 mg which approximates to ten cartridges.

Furthermore the advice given by the American Food and Drug Administration (FDA)[7] is also that 600 mg is the maximum safe dose of prilocaine in a normal healthy individual. This advice does not change when a vasoconstrictor is used, although the vasoconstrictor used in North America is adrenaline rather than felypressin. With regards to the BNF recommendations the authors are at a loss to explain why the maximum dose of prilocaine allowable decreases when felypressin is used. We assume this relates to the maximum safe dose of felypressin but have been unable to confirm this assumption.

Interestingly, the FDA has changed its advice[7] to state that although the development of MetHb is generally dose related it may occur at any dose in susceptible individuals. The BNF advice still only states that 'if used in high doses, methaemoglobinaemia may occur'. The FDA also now recommends that for any individual who weighs less than 70 kg the dose should be weight-related and calculated using values of 4 mg/kg, rather than the usual dose of 8 mg/kg (600 mg maximum dose). If we had been following the FDA recommendations the maximum safe dose for this patient would have been only 172 mg (approx 2.8 cartridges). Furthermore in the textbook *Pain and anxiety control for the conscious dental patient*[8] the maximum dose is stated as 6.0 mg/kg, which in this case would have limited the dose to under four cartridges.

We would like to highlight the importance of considering factors which may predispose to the development of MetHb when deciding upon an appropriate dose of prilocaine. Factors which may require the dose of prilocaine to be reduced include extremes of age and the patient's medical condition. We would also suggest that in patients who are underweight the dose needs to be reduced. The importance of the use of additional oxidising agents, such as fentanyl and paracetamol, in the development of MetHb is difficult to assess but probably play a minor role.

We feel that there may be grounds to reconsider the guidelines for the maximum safe dose of prilocaine, taking into account the different recommendations available; albeit that this may greatly limit the number of teeth that can be removed at any one visit.

Table 3 Predisposing condition[1]

Conditions predisposing to Methaeoglobinaemia	
Anaemia	Liver impairment
Acidosis	Renal impairment
Cardiopulmonary disorders	Extremes of age

Table 4 Symptoms associated with Methaemoglobinaemia[2,3]

% MetHb	Symptoms
<10%	Asymptomatic
10-20%	Cyanosis
20-30%	Headache Light-headedness Weakness Anxiety Tachycardia
30-50%	Dizziness Fatigue Confusion Increasing tachycardia
50-70%	Arrthythmias Acidosis Coma Seizures
>70%	Death

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