

Benzocaine-induced methaemoglobinaemia: a case study

Stefan Bittmann, Carsten Krüger

Abstract

Benzocaine is a widely used topical anaesthetic and has been reported to cause toxic methaemoglobinaemia in otherwise healthy individuals with no predisposing risk factors. We report a rare case of benzocaine-induced methaemoglobinaemia following adeno-tonsillectomy in a 5-year-old girl. Topical benzocaine was applied orally for relief of postoperative wound pain on the 8th postoperative day. Two hours after application generalized cyanosis, mild dyspnoea and some degree of agitation developed. The methaemoglobin level was 38.5%. Treatment with methylene blue was initiated immediately. Symptoms completely disappeared four hours after initiation of methylene blue therapy. The further course was uneventful. Therefore, all health personnel should be aware that topical anaesthetics after surgery can induce methaemoglobinaemia in children, even after a prolonged interval and especially when applied on wound surfaces.

Key words: Benzocaine ■ Children's nursing ■ Methaemoglobinaemia ■ Topical anaesthetic ■ Post-operative care

(AQ1: please insert a brief introductory paragraph explaining what methaemoglobinaemia is, including when it usually occurs, the indications, risks, and treatment)

More than 100 years ago, congenital methaemoglobinaemia was first reported in an Amish kindred (AQ2: please provide reference). Soon after, toxic methaemoglobinaemia due to numerous agents, including therapeutic drugs, was reported (AQ3: please provide reference). Methaemoglobinaemia due to the use of topical anaesthetics is an uncommon, but important complication in adults as well as in children. Benzocaine, a widely used topical anaesthetic, has been reported several times to cause methaemoglobinaemia in otherwise healthy individuals with no predisposing risk factors (AQ4: please provide reference). Typically this complication occurs when benzocaine is used to achieve topical anaesthesia of the skin and mucous membranes during and after endoscopic and surgical procedures, either immediately or after a short interval only.

This article describes a rare case of methaemoglobinaemia

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in a 5-year-old female patient induced by topical application of benzocaine which was administered 8 days after adeno-tonsillectomy. (AQ5: please provide year of incident, and location if possible). Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

Case report

A 5-year-old female patient had an adeno-tonsillectomy performed at the Ear, Nose and Throat Department of a neighbouring hospital. One day after operation, she was discharged from hospital with normal progress in healing, but still some throat pain due to the operation. She was admitted to our paediatric department on the 4th postoperative day for relief of her persistent wound pain, and due to a refusal to eat and drink properly. Physical examination showed a well-healing operation site, covered with fibrinous membranes, but no signs of local infection or bleeding. Apart from a mild degree of dehydration, no further abnormalities were noted. Vital signs were stable (temperature 37.1°C, blood pressure 100/64 mmHg, pulse rate 81/min, respiration rate 25/min). Full blood picture and blood chemistry were normal; C-reactive protein was 41.4 mg/L.

Besides starting intravenous fluid treatment and analgesia, enteral nutrition with fluids and soft foods was initiated. As progress was slow, topical benzocaine was applied orally as a powder preparation once on the 8th postoperative day. Two hours after application, the girl developed a marked change in skin colour with bluish skin, mild dyspnoea and some agitation (Figure 1). Lethargy was not present; no other symptoms were apparent. Anaemia from late bleeding was excluded immediately: temperature, respiration rate, pulse and blood pressure were normal. Oxygen saturation ran at 95%. Because toxic methaemoglobinaemia was suspected, methaemoglobin blood concentration was measured immediately, which was markedly elevated at 38.5%. Family history was negative for congenital or toxic methaemoglobinaemia.

The patient was treated with supplemental oxygen and 1% methylene blue (1 mg/kg) intravenously. Four hours after application of the topical benzocaine powder, symptoms had completely disappeared. Methaemoglobin concentration was <1% at this stage. The further course and healing process was uneventful, and the child was discharged home in good condition after 6 days in our hospital. An emergency card with regard to her risk of toxic methaemoglobinaemia was issued. No further episodes have occurred so far, and the child's development has been normal.

Discussion

In normal erythrocytes, methaemoglobin is present at a level of 1–2%. Methaemoglobin is continuously formed in red blood cells and is readily reduced to deoxyhaemoglobin by the nicotinamide adenine dinucleotide-dependent methaemoglobin reductase enzyme. Methaemoglobinaemia results from oxidation of ferrous to ferric iron in haemoglobin. In addition to a functional anaemia, methaemoglobinaemia causes the O₂-binding affinity of the remaining O₂ sites in the haemoglobin tetramer to increase, essentially shifting the oxyhaemoglobin dissociation curve to the left and decreasing oxygen delivery. Methaemoglobinaemia may be either congenital due to defects in enzyme activity, or acquired, with the acquired form being more common.

Many chemical agents, food ingredients and drugs can cause methaemoglobinaemia. In clinical practice, pharmacologic agents are the most frequent cause. The drugs most often implicated are nitrates, inhaled nitric oxide, nitroprusside, topical silver nitrate, silver sulfadiazine, dapsone, sulfonamides, antimalarials, flutamide and phenacetin. Topical anaesthetics such as prilocaine, lidocaine and benzocaine have also been reported to cause methaemoglobinaemia (Feiner et al, 2009; Kreshak et al, 2009; Lin et al, 2009; Mintzer et al, 2009; Mohorovic et al, 2009; Ozdogan et al, 2010).

Our patient with toxic methaemoglobinaemia developed her symptoms several days after adeno-tonsillectomy. The only drug which the child received and which could cause methaemoglobinaemia, was topically applied benzocaine. The short time interval between application and development of symptoms favours a causal relationship. It should be noted that it took about 2 hours until the first symptoms developed. Usually symptoms occur within 30–60 minutes. The delay may be explained by the fact that the dose was applied as powder, and that the absorption through the healing mucous membranes was probably delayed.

Initial diagnosis of methaemoglobinaemia is based on clinical findings and a history of application of potentially causative agents. Generalized cyanosis is out of proportion to respiratory status and, as was the case in our patient, does not improve with oxygen therapy (AQ6: please confirm - in the case being discussed, cyanosis did not improve with oxygen therapy?). The symptoms and signs of methaemoglobinaemia generally correlate to the amount of abnormal haemoglobin present. Normally, 5 g/dl of methaemoglobin produce cyanosis, but already 1.5 g/dl of methaemoglobin can produce noticeable cyanosis. Clinical symptoms are lacking with methaemoglobin levels under 10%. Concentrations of 10–15% produce visible cyanosis unresponsive to oxygen therapy, and blood may appear burgundy brown in colour. Concentrations above 20% result in symptoms related to tissue hypoxia and include anxiety, fatigue, dyspnoea, lethargy, tachycardia, headache and syncope. As levels exceed 50%, oxygen delivery suffers and results in marked dyspnoea, metabolic acidosis, dysrhythmia, and lethargy, progressing to stupor, coma, and convulsions. Death has been reported at levels above 70%, and may be due to arrhythmia, circulatory failure, or neurologic compromise (Lim and Tan, 2009; Vallurupalli et



Figure 1. Blue skin appearance in a 5-year-old child 2 hours after application of topical benzocaine

al, 2009). In our patient, methaemoglobin blood level was 38.5%. Cyanosis and dyspnoea were present, but lethargy was absent.

As regards therapy, removal of the offending agent is important in the asymptomatic or mildly symptomatic individual. Most cases resolve within 24–36 hours after the metabolism of the offending drug (Vallurupalli et al, 2009). The half-life of methaemoglobin itself is 55 minutes (Gharahbaghian et al, 2009). General supportive measures like oxygen supplementation are indicated, especially if methaemoglobin levels are above 30%, since lower levels are usually tolerated well (Raza and Kumar, 2009).

Specific treatment consists of intravenous application of 1% methylene blue in severe cases. This acts as a reducing agent via the nicotinamide adenine dinucleotide phosphate (NADPH) methaemoglobin reductase pathway, converts ferric iron back to the ferrous state and restores the oxygen-carrying capacity of haemoglobin. Cyanosis resolves within 15–30 minutes. Marked reduction in the methaemoglobin concentration, usually by 50%, is seen within 30–60 minutes (Raza and Kumar, 2009; Vallurupalli et al, 2009). This could be demonstrated in our case as well, as after 4 hours methaemoglobin was <1%. Methylene blue itself has oxidizing properties at higher doses, with toxic effects appearing in doses over 7 mg/kg (Thomas et al, 2009; Vallurupalli et al, 2009). Thus it is important not to exceed a dose of 1–2 mg/kg. Hyperbaric oxygen and exchange transfusion may be used, especially in patients with leukocyte G6PD deficiency who do not respond to methylene blue (Raza and Kumar, 2009).

Benzocaine is available in spray form, throat lozenges, powder and liquid and gel preparations. Predisposing factors for benzocaine-induced methaemoglobinaemia are not known. No identifiable factor is evident. The toxic effects of benzocaine may be due to a toxic metabolite, an N-hydroxy derivative that has an aniline group incorporated in its

structure and possesses oxidizing properties. Differences in absorption and metabolism of benzocaine may explain the variability of benzocaine-induced methaemoglobinemia (Lim and Tan, 2009).

Some cases are reported in literature concentrating on entry of benzocaine into the bloodstream due to mucosal damage as a contributing factor (Tobias and Ramachandran, 2009). Absorption of benzocaine through broken skin, mucosa, or the gastrointestinal tract is believed to be the main route of systemic access, like in our case. The long time interval between operation and administration of the drug should be noted, though, and supports recommendations to carefully consider the need for using this agent in patients, even after longer intervals between operation and application. Rectal fissures, oropharyngeal abrasions and erosions, gastritis, eczematous skin and respiratory mucosa have also been proposed as contributing to enhanced systemic absorption (AQ7: please provide reference). Increased systemic exposure seems to play a major role (AQ8: please provide reference). Benzocaine has been found to produce symptomatic cyanosis and methaemoglobinemia at 15 mg/kg body weight in infants and at 150–300 mg in adults (AQ9: please provide reference). Topical anaesthetics are rapidly absorbed into the circulation through denuded skin and mucous membranes, especially when the mucosa is inflamed or disrupted. Topical application over inflamed or broken skin and mucous membranes should be avoided if possible.

Conclusion

Benzocaine and other local anaesthetics are widely used for topical anaesthesia in a variety of procedures, including endotracheal intubation, bronchoscopy, upper and lower gastro-intestinal tract endoscopy, nasogastric tube placement, and minor surgery. Benzocaine-induced methaemoglobinemia can be fatal and is unpredictable: therefore, physicians using the drug should be aware of this severe, albeit rare side effect and should reconsider its frequent use. Methylene blue should be readily available in medical institutions where topical anaesthetics are frequently used. BJN

Conflict of interest: none

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KEY POINTS

- AQ10: please provide a list of 4 or 5 key points, summarising the main points of the article