METHAEMOGLOBINAEOMIA INDUCED BY MAFFENIDE ACETATE IN CHILDREN

A report of two cases


SUMMARY

The local application of mafenide acetate (Sulfamylon, Winthrop) applied to extensive burn areas resulted in acute methaemoglobinemia.

Mafenide acetate (Sulfamylon, Winthrop) is a widely used topical agent in the treatment of burns. To our knowledge there have been no reports of methaemoglobinemia produced by this agent. We report two cases in which methaemoglobinemia is presumed to have developed after the topical application of mafenide acetate (Sulfamylon, Winthrop) to large burned areas.

CASE REPORT ONE

A 2-year-old, well-developed child was admitted after sustaining second and third degree burns of 50% of the body surface by hot oil. The child’s general condition was good, with stable vital signs. An i.v. infusion was commenced and 2 h after admission, the child was taken to the operating room for local treatment of the burned areas. Anaesthesia was induced with ketamine hydrochloride (Ketalar) and after a short period of surgical debridement, the burns were covered with mafenide acetate. In the recovery room, the child developed what was presumed to be cyanosis, but did not improve despite administration of oxygen. The trachea was intubated and the lungs were artificially ventilated (FiO₂ = 1.0). Blood taken for analysis of blood-gases, was chocolate-brown in colour (PaO₂ = 28.6 kPa; PaCO₂ = 5.5 kPa; pH = 7.35; oxygen saturation = 39% measured with an I.L. Co-oxymeter).

The child developed bradycardia and cardiopulmonary resuscitation was commenced. After 90 min of unsuccessful efforts, the patient was considered dead.

CASE REPORT TWO

A 2-year-old, well-developed child (15 kg) was admitted several hours after sustaining first and second degree burns of about 50% of the body surface by hot milk. The child was alert but irritable, and vital signs were normal. The patient was taken immediately to the operating room for treatment of the burned areas. Anaesthesia was induced with ketamine and was maintained with 50% nitrous oxide in oxygen, administered via a facemask from a non-rebreathing circuit. The procedure lasted about 15 min. The burns were dressed with mafenide acetate cream. Following this, the child became progressively cyanosed despite artificial ventilation of the lungs with 100% oxygen. Blood, taken for analysis of blood-gases, was chocolate-brown in colour (PaO₂ = 38.6 kPa; PaCO₂ = 4.9 kPa; pH = 7.29; oxygen saturation = 61.2% measured with an I.L. Co-oxymeter, a discrepancy of 38.6% from the expected value calculated using the Severinghaus slide rule (Severinghaus, 1966)). Nasotracheal intubation was performed. Despite apparently adequate ventilation with 100% oxygen, cardiac arrest occurred 5 min later.

Methylene blue 1 mg kg⁻¹ and ascorbic acid 1 g were given i.v. and the mafenide acetate cream was removed from the burned areas. After a few minutes sinus rhythm returned. Repeated doses of methylene blue to a total of 35 mg were given to treat recurrent episodes of abnormal skin colour. As soon as the child’s condition was stable, he was transferred to the intensive care unit, were the lungs were ventilated with a Bourns (L.S. 104) infant ventilator (FiO₂ = 1.0). Arterial blood-gas analysis showed PaO₂ = 41.9 kPa; PaCO₂ = 4.8 kPa; pH = 7.02; oxygen saturation was 90.8% (measured with the I.L. Co-oxymeter). There was no evidence of haemolysis, and the haemoglobin concentration was within normal limits, as was the serum concentration of bilirubin; the colour of the plasma was normal, and no reticulocytosis was present. The child was given 20 mmol of sodium bicarbonate to correct the acidaemia. Within
2 h $F_{10}$ was decreased to 0.4 and 6 h later to 0.21, with normal arterial blood-gas values; ventilation was then discontinued, and the next day the tracheal tube was removed.

**DISCUSSION**

Methaemoglobinaemia is a disturbance in which haemoglobin is oxidized from the ferrous to the ferric form (Wintrobe, 1968). This condition may result from a congenital deficiency (Gibson and Harrison, 1974; Ronald, Gabel and Bunn, 1974) of NADH-Diaphorase (Joseph, 1962; Jaffé and Heller, 1964) or a toxic reaction to various drugs or substances which oxidize the haemoglobin directly in the circulation. A combination of these two factors may occur (Williams et al., 1972). A large number of substances have been found to cause methaemoglobinaemia (Bodansky, 1951), including aniline dyes (Gräubarth et al., 1945), benzocaine (Peterson, 1960; Bloch, 1965), prilocaine (Smith and Olson, 1973), lignocaine (Burne and Daught, 1964), nitrates (Kaiffer et al., 1972), nitrates (Kaiffer et al., 1972), phenacetin (Easly and Condon, 1974), acetanilide (Finch, 1948), carrot juice (Keatine et al., 1973), and sulphones and sulphonamides (Finch, 1948), to which group mafenide acetate belongs.

The major clinical feature, and sometimes the only symptom, is cyanosis (Ronald, Gabel and Bunn, 1974). If the concentration of methaemoglobin exceeds 60% there may be cardiovascular collapse and circulatory arrest (Williams et al., 1972). The typical sign is chocolate-brown coloration (Williams et al., 1972). Specific therapy consists of 1% methylene blue dye solution 1 mg kg$^{-1}$ (Wintrobe, 1968; Cartwright, 1974) and may be repeated up to 7 mg kg$^{-1}$ (Joseph, 1962; Cartwright, 1974), and ascorbic acid 1–3 g, both administered as an i.v. bolus (Williams et al., 1972). Mafenide acetate U.S.P. (Sulfamylon cream, Winthrop) is widely used for the treatment of burns. The drug is absorbed rapidly from the burn surface, and peak plasma concentrations are reached in 2 or 4 h. Mafenide and its metabolite, para-carboxybenzene sulphonamide, inhibits carbonic anhydrase which may result in metabolic acidosis (Goodman and Gilman, 1975). There may be allergic manifestations such as rash, itching and facial oedema.

Although we had no opportunity to perform spectroscopic examination of the blood, the diagnosis of methaemoglobinaemia was suggested in our two patients by:

(1) Dark chocolate-brown coloration did not change after reoxygenation in vitro.

(2) Saturation (measured by the I.L. Co-oxymeter) in the two patients was very low, although the $PaO_2$ was in excess of 14 kPa and the carboxyhaemoglobin concentration was normal.

(3) The fast clinical and laboratory improvement following treatment with methylene blue and vitamin C.

The fact that no other drugs were administered, and that no other product was applied on the burned area, made us consider that the methaemoglobinaemia described in our two cases was produced by the mafenide acetate. The surviving child underwent a later uneventful anaesthetic in which ketamine hydrochloride was the only agent used.

Both children came from small Arab villages in the Galilee area, where family intermarriage is common. This raises the question of an hereditary predisposition to drug-induced methaemoglobinaemia. Another possibility is that children may have deficiency in methaemoglobin reducing enzyme (Williams et al., 1972), and may be more sensitive to this preparation.

The examination of glucose-6-phosphate-dehydrogenase in the second patient and in the parents of the child showed normal values, and this may exclude the possibility of a family deficiency.

These two cases strongly suggest that in infants and in young children there might be a NADH-diaphorase deficiency and that more precautions should be taken when drugs capable of causing methaemoglobinaemia are used.

**ACKNOWLEDGEMENT**

We wish to express our thanks to Mr D. Edelman, C.R.T.T., I.R.I.T., of the I.C.U. staff, for his very helpful advice.

**REFERENCES**


METHAEMOGLOBINAEMIA INDUCED BY MAFENIDE ACETATE


METHEMOGLOBINEMIE PROVOQUEE PAR LE MAFENIDE ACETATE

*Rapport de deux cas*

RESUME

Deux cas de methemoglobinemie aigue provoques par l'application locale de mafenide acetate (Sulfamylon, Winthrop) chez deux enfants atteints de brulures etendues sont rapportes.

HERVORRUFUNG VON METHAMOGLOBINAMIE DURCH Mafenidazetat bei Kindern

ZUSAMMENFASSUNG

Die lokale Anwendung von Mafenidazetat (Sulfamylon, Winthrop) bei grossen Brandwunden führte zu akuter Methämoglobinämie.

METHEMOGLOBINEMIA INDUCIDA POR Mafenide Acetato en Ninos

*Reporte de dos casos*

SUMARIO

Reportamos dos casos en los cuales la aplicación local de mafenide acetato (Sulfamylon, Winthrop) en extensas quemaduras, produjo severa methemoglobinemia aguda.