Deafness and biochemical imbalance after burns treatment with topical antibiotics in young children

Report of 6 cases

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SUMMARY Six children are described in whom deafness followed treatment of full thickness burns with topical antibiotic spray containing neomycin. 3 children developed hypocalcaemic tetany, and were shown to have a metabolic disorder involving hypocalcaemia, hypomagnesaemia, and hypokalaemia. The dangers of treating burns with topical ototoxic and nephrotoxic antibiotics are emphasised.

Six children were found to be deaf after investigation of their hearing following treatment of burns in Swindon. 3 of these children developed a syndrome of tetany associated with metabolic imbalance during treatment. All these children were treated similarly by exposure and topical antibiotic sprays containing the nephrotoxic and ototoxic antibiotics neomycin, bacitracin, polymyxin B, and colistin (polymyxin E).

Although users of these proprietary sprays are warned of potential side effects, including deafness and renal complications, we feel that the dangers of their topical use on burned surfaces are not sufficiently realised.

Case reports

Case 1. A boy of 16 months sustained scalds to 10% of his body surface. On day 32 of admission he developed tetany. Investigations at that time showed normal plasma sodium and albumin, but low potassium 2.88 mmol/l (mEq/l), calcium 1.75 mmol/l (7 mg/100 ml), magnesium 0.35 mmol/l (0.85 mg/100 ml), chloride 91.2 mmol/l (mEq/l), and a raised blood urea 16 mmol/l (96 mg/100 ml). He was given intravenous calcium gluconate and the tetany resolved, but returned on day 42 when further investigations showed hypocalcaemia, hypomagnesaemia, hypokalaemia, and hypochloraemia. Blood urea was then normal. Oral Ca and Mg supplements were then started. All blood chemistry was normal on day 49. He was referred again for

investigation of delayed speech development at 3½ years of age. Audiometry showed a severe bilateral hearing loss, more severe at high frequencies (Fig. 1).

Case 2. A boy, aged 16 months, was developing normally when he scalded 16% of his body surface. On day 18 of admission he was noted to have a hypokalaemic, hypochloraemic alkalosis (K 2.6, Cl 85, HCO₃ 33 mmol/l (mEq/l)). Oral K supplements were started, but on day 23 he developed carpopedal spasm. Plasma Ca was low (1.6

Fig. 1 Audiogram in Case 1. Free field audiometry.

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mmol/l; 6.4 mg/100 ml) as was Mg (0.4 mmol/l; 0.97 mg/100 ml). Plasma proteins normal; creatinine clearance 105.6 ml/min per 1.73 m^2 ; 24-hour urine clearance of Na 61 mmol, K 29.9 mmol, Cl 85 mmol. He was then started on oral Ca and MgCl_2 , but on day 30 had a further episode of tetany which resolved on intravenous calcium gluconate. All plasma values were normal 2 months after admission.

His hearing and eardrums were said to be normal 4 months after the scald, but at 8 months speech development had stopped. Audiometry showed a bilateral sensorineural deafness, which has become profound, necessitating special schooling.

Case 3. A boy of 14 months scalded 12% of his body surface. He was investigated for carpopedal spasm and lethargy 16 days after admission. Results showed Na 131 mmol/l, K 3.1 mmol/l, Cl 91 mmol/l, HCO_3 28 mmol/l, blood urea 4.9 mmol/l (6 mg/100 ml), Ca 1.5 mmol/l (6 mg/100 ml), Mg 0.35 mmol/l (2.4 mg/100 ml), PO_4 1.3 mmol/l (4 mg/100 ml). Plasma proteins normal; creatinine clearance 37.3 ml/min per 1.73 m^2 ; 24-hour urine output of Na 38.2 mmol, K 62.8 mmol, Cl 74.5 mmol, Ca 1.51 mmol (60 mg/24 h), Mg 1.25 mmol (30.4 mg/24 h), P 9.8 mmol (0.3 g/24 h), and urea 0.104 mol. He was started on oral Ca and Mg supplements, and plasma values for all electrolytes were normal for 46 days.

Case 4. A boy scalded 15% of his body surface at 13 months of age. Apart from a brief episode of otitis media treated with penicillin, his progress in hospital was uneventful. He failed to make any progress with speech, and audiometry 14 months after the scald showed a 55–66 dB high tone loss bilaterally (Fig. 2).

Case 5. A boy aged 8 months sustained scalds of 22% of his body. His hearing had been previously assessed as normal at 6 months. He failed to develop speech, and 21 months after the scald had a severe hearing deficit. He now requires special schooling.

Case 6. A boy of 14 months scalded 10% of his body surface. He was found to have poor speech on attending play-school, and audiometry 26 months after the scald showed a severe hearing loss, more severe at high frequency (Fig. 3).

Discussion

A summary of the clinical features of the 6 cases is given in the Table. Treatment of all cases was similar. After assessment of the extent of the burn, and sedation or analgesia, the child was barrier

nursed with the burn exposed. Where the area of the burn exceeded 10% of the body surface, fluids were replaced intravenously with plasma and dextrose saline. Otherwise, liberal oral fluids were given.

Topical antibiotics were applied 4-hourly by nursing staff, while unhealed and nongrafted surfaces were exposed (usually 3 weeks). No record was made of the amount of spray used, but it was reported to be up to one full container per day. For all but the most recent case (Case 3) the antibiotic was Disbiotic (Avlex). This contains neomycin sulphate 500 000 U (735 g), colistin (polymyxin E) 300 000 U, zinc bacitracin 37 000 U. In Case 3, the antibiotic was Dispray (Avlex): neomycin sulphate 650 000 U

Fig. 2 Audiogram in Case 4. Free field audiometry.

Fig. 3 Audiogram in Case 6. Free field audiometry.

Table Clinical features of 6 reported cases

Case no.	Age at scald (m)	Percent body surface	Treatment	Complications	Deafness
1	16	10	Oral fluids; CaCl ₂ , MgCl ₂ , KCl	Pyrexia, diarrhoea, tachycardia; low Ca, Mg, K, Cl, alkalosis, high urea; grafted	High tone, progressive; 6/12 after scald
2	16	16	IV fluids; CaCl ₂ , MgCl ₂ , KCl	Pyrexia, diarrhoea; low Ca, Mg, K, Cl; alkalosis; grafted	Progressive; 4/12 after scald
3	14	10	IV fluids, CaCl ₂ , MgCl ₂ , KCl	Pyrexia; low Ca, Mg, K, Cl; low creatinine clearance	? normal at 2/12; deaf at 10/12 after scald
4	13	15	IV fluids	Pyrexia; grafted; ? otitis media	High tone loss from time of scald
5	8	22	IV fluids	Pyrexia; grafted	High tone loss 26/12 after scald
6	14	10	Oral fluids	Pyrexia; grafted	High tone loss 16/12 after scald

(955 g), polymyxin B 165 000 U, zinc bacitracin 10 000 U. The change in the routine antibiotic used took place in 1973.

The nephrotoxic and ototoxic effects of neomycin are well described (Meuwissen and Robinson, 1967; *British Medical Journal*, 1969; Vinnicombe and Stamey, 1969; Appel and New, 1977). Polymyxin is known to be nephrotoxic (Jawetz, 1961; Vinnicombe and Stamey, 1969; Appel and New 1977), and colistin shares the toxic effects of the polymyxins, being indistinguishable from polymyxin E. Colistin has been said to cause partial deafness at very high plasma levels (Meuwissen and Robinson, 1967) but this has not been commonly reported. Experimentally, polymyxin B has caused cochlear damage in guinea pigs (Kohonen and Tarkkanen, 1961). Topically the polymyxins are said not to be absorbed (Vinnicombe and Stamey, 1966), but if given parenterally have been incriminated in a syndrome of hyponatraemia, hypokalaemia, hypochloraemia, and hypocalcaemia (Rodriguez *et al.*, 1970) as well as in reduced glomerular filtration rate, and azotaemia. Bacitracin is known to be nephrotoxic, causing azotaemia when given parenterally, but is not absorbed when applied topically (Jawetz, 1961).

Neomycin administered orally has been shown to have nephrotoxic and ototoxic effects in certain conditions in adults, in hepatic failure (Last and Sherlock, 1960) and after laparotomy (Greenberg and Momary, 1965; Ruben and Daly, 1968), and audiotoxic effects in children (Zelenka *et al.*, 1966). Similarly ototoxic effects have been reported after rectal irrigation (Fields, 1964) and wound irrigation (Kelly *et al.*, 1969).

Topically, neomycin has been incriminated in ototoxicity when absorption was aided by dimethylsulphoxide (Herd *et al.*, 1967) in a 6-year-old girl, and inhalation by aerosol has been shown to cause hearing loss in children (Fuller, 1960). Parenteral administration has been well documented as a cause of acute tubular necrosis and subsequent deafness (De Beuklaer *et al.*, 1971) and there has been a previous report of topical neomycin contained in bacitracin and polymyxin (Polybactrin) spray causing deafness in a severely burned (80%) 5-year-old child (Stewart, 1966). Typically, deafness has been progressive and irreversible, starting with a high tone loss. Presentation may be delayed for some months after exposure to the neomycin (Meuwissen and Robinson, 1967; Herd, 1967; Kelly *et al.*, 1969).

The syndrome of hypokalaemia, hypomagnesaemia, and hypochloraemic alkalosis has been described in adults on gentamicin therapy for pulmonary tuberculosis by Holmes *et al.* (1970). They found raised aldosterone levels in their patients, and ascribed this to a hyperaldosteronism consequent on the antibiotic. 2 further adult patients were described by Bar *et al.* (1975) who developed hypomagnesaemia and hypocalcaemia on high dose gentamicin therapy. There was high urinary magnesium and potassium loss and low parathormone levels. Gentamicin-induced magnesuria and kaluria was suggested as the initial problem with a consequent hypomagnesaemia, hypocalcaemia, and hypokalaemia. In these cases the aldosterone levels were normal. The biochemical abnormalities were slow to resolve (8 and 15 weeks respectively).

The biochemical findings in our patients were similar to those in the gentamicin patients, and, of the antibiotics present in the antibiotic sprays, neomycin is similarly an aminoglycoside. Urinary potassium loss was raised in Case 3 and was likely to be so in the face of low plasma potassium levels in Case 2. Case 3 was the only patient in whom urinary magnesium loss was measured, the loss probably being excessive as magnesuria usually stops in the face of hypomagnesaemia. Calcium loss was normal in Case 3. In all patients the abnormalities were slow to resolve, and were refractory to initial calcium replacement, all requiring magnesium replacement. The mechanism remains obscure, but is most simply explained by an interference in renal magnesium and potassium reabsorption, with the hypocalcaemia resulting from the hypomagnesaemia.

The delay in diagnosing deafness may well have been due to the delayed and progressive nature of the lesion. There is strong supporting evidence in Case 3 where hearing was followed up prospectively. Speech upsets may be easily explained immediately after a prolonged and painful hospital stay, particularly at such a sensitive period of speech development. However, the prolonged delay in speech eventually alerted parents to the possibility of deafness.

There is still doubt as to why these particular patients suffered such complications, although other children were treated similarly between 1965 and 1976. Age at burn (8–16 months) may have been critical, being the earliest age at which significant burns are likely in the exploring toddler. All affected infants were boys. Over the period where complete records are available (1974–76), boys outnumbered girls in hospital admissions for burns by 37 to 23.

The surface area of the scalds was considerable (10–22%) and all had full thickness burns. Absorption was thus made more likely. Renal perfusion may well have been compromised by fluid loss from the burned surface, and in Cases 1 and 2 by some diarrhoea. Oliguria was noted in Case 2, high blood urea in Case 1, and reduced creatinine clearance in Case 3. Ultimately the blood urea was normal in all cases in which it was measured. Poor renal function at the time of initial treatment probably enhanced the ototoxicity of the neomycin, and the nephrotoxicity of neomycin may have hindered excretion of the drug.

Follow-up of other infants treated by this burns regimen is continuing, but deafness in other children may have been missed. Where similar treatment has been the practice, it is suggested that audiometry be performed on all children who have had more than trivial burns or scalds.

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