Tinnitus in a patient with beta-thalassaemia intermedia on long-term treatment with desferrioxamine

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Summary  
A woman with beta-thalassaemia intermedia, and iron overload following many years' treatment with oral iron, was treated with subcutaneous desferrioxamine. During the course of this treatment she developed tinnitus, which was considered to be a rare complication of the use of this chelating agent. The mechanism of this effect is not understood.

Introduction  
Long-term subcutaneous administration of desferrioxamine (DF) (Ciba-Geigy) is now a widely accepted method of treating chronic iron overload (Modell and Beck, 1974; Hussain et al., 1976; Propper et al., 1977; Modell, 1979; Pippard et al., 1977). Apart from local skin reactions related to the site of injection, no major side effects have been observed in reported patients who have been treated in this manner (Modell, 1979).

A patient with beta-thalassaemia intermedia is now described in whom the occurrence of disabling and (so far) irreversible tinnitus, led to withdrawal of DF as a means of treating her iron overload.

Case report  
A female aged 43 years, was referred to Hope Hospital in June 1978 with a 6-month history of exertional dyspnoea, tiredness and limb paraesthesiae. She had had 2 previous episodes of jaundice. The first, which occurred when she was 18 years of age, lasted 2 weeks and was preceded by anorexia and vomiting, and was thought to be infective hepatitis. The second occurred in 1970 and was accompanied by mild lower abdominal pain. Although she remained off work for one week, she remained 'well': the cause of this jaundice, observed by her local GP, is obscure.

She was known to be anaemic during each of her 3 pregnancies, during which time she had variously received many courses of parenteral iron, but only 2 units of whole blood. Since the birth of her first child (now aged 23 years) she had been taking oral iron almost continuously for poorly responsive anaemia. Two previous bone marrow aspirations had been performed at local hospitals in the past, but no definitive diagnosis had been made.

On examination, she was a slight, pale woman with fair hair and blue eyes, she weighed 54 kg and her height was 158 cm. There was a fine pigmentation around the face, but she was not jaundiced. Body hair was normally distributed. The pulse was regular and there were no signs of heart failure. Blood pressure was 110/60 mmHg. Neurological examination was normal.

Investigations revealed a Hb of 8.5 g/dl, the film showing considerable hypochromia and microcytosis; erythroid hyperplasia and numerous sideroblasts were present in the marrow. Other haematological indices were as follows: serum iron 30 μmol/l, TIBC 45 μmol/l, serum ferritin 760 μg/l, (n.r. 160 μg/l); folate 6.8 ng/l, B12 235 ng/l; direct Coombs' test negative and serum haptoglobin undetectable; urine contained no haemosiderin. Haemoglobin electrophoresis revealed 80% Hb A₂ and 2.3% Hb F, suggesting beta-thalassaemia intermedia.

Liver biopsy showed preservation of lobular architecture, with marked iron accumulation within hepatocytes and Kupffer's cells. Cholecystogram was normal, and tests of pituitary, thyroid and adrenal function were within normal limits. Hb₃Ag was not detected in serum. Computerized axial tomography revealed dense liver and spleen, compatible with siderosis (Morris et al., 1978).

She was admitted for treatment with DF in October 1978 in view of her gross tissue iron...
overload, and initially dose-response curves were established to determine an effective dose of DF. Marked excretion of urinary and faecal iron was achieved (with oral ascorbic acid, one g/day) and a plateau in iron excretion was obtained at a dose of 5 – 6 g DF/day. It was decided to opt for a dose of 4 g DF/day administered subcutaneously in order to keep the infusion volume within practical limits.

She was discharged 18 days later with an infusion pump for domiciliary use; however, alternate day therapy (4 g) which became necessary in view of some local skin irritation, allowed her to continue use of DF by the subcutaneous route.

When next seen as an out-patient 14 days later, she complained of 'pounding in the ears', a symptom she had complained of previously and which was thought to be due to anaemia. She was seen again 7 and 13 days later, when she felt 'improved'. It was at a subsequent review 6 weeks later that she specifically complained of 'buzzing' in the ears, especially during the night, and she was started on oral pyridoxine 50 mg daily. Despite this, the buzzing persisted and so she herself stopped the DF infusion. Her aural symptoms regressed completely over the next 3 weeks and when seen one week later, no hearing loss was detected, and DF was restarted at a dose of 4 g on alternate days. The tinnitus gradually returned but was 'less severe than before' 6 weeks later.

However, one week later, she again abandoned DF infusions because of 'tiredness and weakness' and increasingly persistent buzzing in the ears. An ENT examination was negative and she was referred for formal audiometric testing to the University Department of Audiology. This examination likewise revealed no detectable hearing loss or cochlear dysfunction. The tinnitus persists and is still distressing for her especially when the environment is quiet. Treatment is now based on regular, limited venesections (250 ml) per week, and approximately 3 litres of blood have been removed in this way. Her haemoglobin remains between 9 – 10 g/ml.

Discussion

This patient received oral iron over nearly 25 years for a ‘non-responsive iron-deficiency type anaemia’ which was apparently due to β-thalassaemia intermedia. On referral, she was found to have marked iron overload and was considered for DF treatment which was thought to be preferable to long-term venesection. This report is concerned with the development of tinnitus during that course of treatment and which, although difficult to prove, seems likely to have been caused by direct exposure to the drug. The cessation of symptoms when the drug was stopped, and their return after further DF therapy, strongly suggests a drug-related effect. She was not taking any medication before DF and ascorbic acid therapy was commenced and, subsequently, only pyridoxine was added. There was no evidence of renal impairment (creatinine clearances: 70 – 90 ml/min) and no history at all of previous ear disease. The total dose administered, which was approximately 350 g over 6 months at a dose of 4 g on alternate days, is comparable to other reported long-term schedules (Modell and Beck, 1974; Propper et al., 1977; Pippard et al., 1977; Hussain et al., 1977).

The mechanism of this presumed toxicity is unknown. DF treatment, in general, is not associated with serious or continuing symptoms. Some vaso-motor-like symptoms may appear soon after the commencement of i.v. infusion of DF (Modell, 1979) but are transient; the development of cataracts in a 10-year-old boy who received 750 mg DF by i.m. injection for 9 months has also been reported (Modell, 1979), but other reactions and complications are poorly documented (Modell, 1979). No chronic side effects, and particularly no neurological damage, have been previously reported with subcutaneous injections, or are known to the authors personally. It is possible that accumulation of high concentrations of drug within the cochlea owing to the very slow rate of removal of perilymph could be responsible for the damage observed in this patient, and thus be similar to that brought about by diuretics and 8-amino-glycosides (Hybels, 1979). In this respect, the recent use of DF-containing red cell ghosts, which may allow delivery of drug to specific sites of iron storage, may render this kind of side effect avoidable in the future (Green, Lamon and Curran, 1980). However, in view of the uncertainty concerning mechanisms of inner ear toxicity, a rational explanation for the occurrence of tinnitus in this one patient is difficult to conceive.

The dose-response curve obtained in this patient, as in a few other reported patients, plateaued at a fairly high concentration of DF (5 – 6 g/day). However, 4 g/day was taken to be a reasonable dose which, furthermore, could be dissolved in a suitable volume for subcutaneous infusion. Local irritation and thickening of the subdermal tissues of abdominal wall and thighs at the site of infusion occurred but, on alternate day treatment, was found to be well tolerated. This dose secured effective mobilization of iron, both in urine and also in faeces. Indeed, the data emphasize the marked faecal losses in addition to urinary losses. Combined faecal and urinary loss should therefore be measured in assessing the effect of DF therapy in any patient, if only to find the lowest effective dose required for long-term administration.

The prognosis for this patient must be guarded;
so far, she has shown no improvement. She is somewhat older than the majority of patients described with this form of treatment and, in most cases, 2 g/day may be the most suitable dosage for effective iron mobilization (Propper et al., 1977; Hussain et al., 1977). Until more information is available on the mechanism of this particular reaction, it would be advisable to caution about the use of doses exceeding 2 g/day for middle-aged or older patients in whom continuous DF therapy is contemplated.

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References
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