Flecainide toxicity

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SUMMARY Flecainide toxicity occurred in an infant being treated for refractory atrioventricular re-entry tachycardia. Ventricular tachycardia developed when dextrose was substituted for milk feeds. We believe that milk was interfering with the absorption of flecainide, and so a high serum concentration developed when milk feeds were stopped.

Flecainide acetate is a comparatively new drug for the treatment of supraventricular and ventricular arrhythmias. Early clinical experience in infants and children has shown that it is effective and well tolerated.1 2

Case report

A baby boy was born at 34 weeks’ gestation after an apparently uncomplicated pregnancy. He was hydropic at birth, weighing 3100 g (>90th centile). Resuscitation with endotracheal intubation was required, and mechanical ventilation was continued for three days. After extubation he remained cyanosed and a hypertoxic test confirmed the presence of an appreciable right to left shunt. Standard investigations did not identify a cause for the hydrops fetalis, and he was referred for cardiological assessment.

On transfer to our hospital at 6 days of age he weighed 2100 g and was no longer hydropic. He...
The tachycardia appeared cyanosed on 30% oxygen, and was mildly tachypnoeic. There was a grade 2/6 mid systolic murmur, maximal at the left fourth intercostal space. The liver was palpable 3 cm, and the spleen 1 cm, below the costal margin.

The electrocardiogram showed sinus rhythm with no evidence of pre-excitation. A radiograph of the chest showed mild cardiomegaly. Cross sectional echocardiography identified an atrial septal defect, with dominant right to left shunting on contrast and Doppler examination.

The pulmonary venous connection was uncertain so cardiac catheterisation was carried out to exclude total anomalous pulmonary venous connection. A pulmonary arteriogram, however, did establish that the pulmonary veins connected normally to the left atrium. There was appreciable pulmonary hypertension and a right to left shunt at atrial level. It is likely that this was associated with persistent pulmonary hypertension of the newborn.

Cardiac catheterisation was complicated by an episode of supraventricular tachycardia. Direct current cardioversion restored sinus rhythm but several further episodes of tachycardia occurred during the next 24 hours. An electrocardiogram taken during an episode of tachycardia showed the features of atrioventricular re-entry tachycardia. The tachycardia was initially treated by direct current cardioversion and digitalisation, but as the episodes continued flecainide (0.5–2.0 mg/kg) was given intravenously. Oral flecainide was started at a dose of 2 mg/kg in divided doses, and increased while serum concentrations were closely monitored. There was a reduction in the frequency of the episodes of tachycardia as the oral dose of flecainide was increased over a period of two to three weeks. It was noted that a high dose of flecainide was required to gain control of the tachycardia and achieve adequate serum concentrations. The normal recommended dose of flecainide is 2–10 mg/kg in divided doses, but in this patient a total dose of 30 mg/kg did not completely control the tachycardia.

It was suspected that inadequate absorption might account for the poor clinical response, as the tachycardia responded consistently to flecainide given intravenously. To assess this, the serum flecainide concentration was measured two, five, and eight hours after 25 mg of flecainide had been given orally (table). The dose at the time was 25 mg every eight hours (30 mg/kg/day). As the serum concentrations were in the lower part of the reference range, the dose was increased further to 25 mg every six hours (40 mg/kg/day). This abolished the tachycardia for eight days, but there was concern about the high dose required.

It was considered possible that milk might be interfering with absorption of flecainide as there was no clinical evidence of malabsorption. This was evaluated by measuring serum flecainide concentrations before and after a 24 hour period of receiving 5% glucose feeds alone (see table). At the end of the 24 hour period he developed ventricular tachycardia. This was present intermittently for the next 60 minutes, but as the patient remained haemodynamically stable no additional treatment was given. The oral flecainide was stopped and milk feeds restarted.

The supraventricular tachycardia recurred 24 hours after the flecainide had been stopped. Treatment with a combination of digoxin and propranolol, and digoxin and disopyramide, was unsuccessful. Eventually he was given amiodarone orally (3 mg/kg three times daily) and when therapeutic serum concentrations were achieved the tachycardia was controlled. During six months of outpatient follow up, he has remained free of tachycardia.

**Table 1 Serum flecainide concentrations**

<table>
<thead>
<tr>
<th>Dose of flecainide (mg)</th>
<th>Serum flecainide concentrations (μg/l) * after administration (hours)</th>
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<tbody>
<tr>
<td>25 mg Orally every eight hours (30 mg/kg/day) with milk feeds</td>
<td>2 5 8</td>
</tr>
<tr>
<td>25 mg Orally every six hours (40 mg/kg/day) with milk feeds</td>
<td>990— ——</td>
</tr>
<tr>
<td>25 mg Orally every six hours (40 mg/kg/day) dextrose feeds only for 24 hours</td>
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*Reference range 400–1000 μg/l.

**Discussion**

This case shows that milk may interfere with the absorption of flecainide given orally in early infancy, and it is possible for flecainide toxicity to occur on withdrawal of milk feeding. Clinical experience in the use of flecainide in the management of childhood tachyarrhythmias is increasing. There is, however, little information on its use in infancy. The pharmacology of flecainide has been studied in adults and extrapolation to infancy may not be accurate.

Flecainide has a proarrhythmic effect and this may occur within the ‘therapeutic range’.Ven-
Ventricular tachycardia has previously been noted with serum concentrations of greater than 1000 µg/l, and occasionally during intravenous administration. This patient developed ventricular tachycardia when a toxic serum flecainide concentration was achieved. It is likely that the ventricular tachycardia was a direct result of that serum concentration. The occurrence of ventricular tachycardia is of concern because of the association between sudden death and such arrhythmias.

Many cardiac units are using flecainide for first or second line treatment of supraventricular tachycardia, particularly in overt Wolff-Parkinson-White syndrome. Milk has not been reported to interfere with flecainide absorption in other children, but Wren and Campbell noted one patient (1 year old) who required a large oral dose (22.5 mg/kg/day) to achieve a therapeutic serum concentration. It is possible that this may be a common phenomenon and merits further investigation. It becomes of particular importance in early infancy when the diet is milk alone. We recommend that milk fed infants on high doses of flecainide should have the dose reduced when milk is reduced or stopped—for example, during an attack of gastroenteritis, or when weaning. Close monitoring of plasma concentrations is likely to be helpful in the management of such patients.

Phycomycotic abscesses in a preterm infant

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SUMMARY We report a case of neonatal infection with rhizopus, one of the Mucoraceae family. Human infection is rare but the mortality is high without prompt, correct treatment. The infant had a simultaneous candida septicemia secondary to colonisation of a central venous line. Serial C reactive protein estimations are valuable in monitoring treatment.

Fungal skin abscesses (usually caused by Candida spp) are common among preterm babies, especially those receiving intensive care. We describe an abscess caused by an unusual pathogen, rhizopus, which, although well documented as a cause of serious infection in immunocompromised adults and children has rarely been described in the newborn. The case also teaches an important lesson about the diagnosis and treatment of infection with multiple organisms.

References

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4 Morganroth J, Horowitz LN. Flecainide: its proarrhythmic effect and expected changes on the surface electrocardiogram. Am J Cardiol 1984;53:89–94B.

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Accepted 3 January 1989

Case report

A baby boy was born by emergency caesarean section (because of antepartum haemorrhage) at 26 weeks' gestation, weighing 1100 g. Mild respiratory distress syndrome was diagnosed and the baby was initially managed in headbox oxygen. On the fourth day of life he required positive pressure ventilation and was transferred to the neonatal intensive care unit at this hospital.

On arrival his blood glucose concentration was 28 mmol/l; /// he had a metabolic acidosis, and was clinically dehydrated. Despite prompt rehydration he developed acute renal failure due to tubular necrosis. Peritoneal dialysis was needed for nine days until his renal function recovered. During dialysis coagulase negative staphylococcal peritonitis developed, but he was successfully treated with a combination of parenteral and intraperitoneal vancomycin. A Broviac catheter for venous access was sited in the internal jugular vein.