Unexpected outcome (positive or negative) including adverse drug reactions

Decreased milk drinking causing flecainide toxicity in an older child

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Flecainide is a class IC antiarrhythmic agent, used frequently in all age groups for the treatment of tachyarrhythmias. Flecainide blocks the voltage-gated sodium channel in the myocardium, leading to prolongation of depolarisation resulting in slowed conduction velocity. Within a paediatric population, flecainide is indicated primarily for supraventricular tachycardia resulting from atrioventricular nodal re-entry and accessory pathway mediated re-entry. It can be considered for use in patients with atrial tachycardia, fascicular ventricular tachycardia, benign right ventricular outflow tract tachycardia and paroxysmal atrial fibrillation. It is well documented to cause paradoxical proarrhythmia in children, with evidence that milk can reduce absorption in infants. The authors present the case of an older child whose flecainide levels were persistently subtherapeutic until he reduced his milk intake. At this time he developed symptoms of severe flecainide toxicity associated with increased levels.

BACKGROUND

Flecainide is a potentially toxic antiarrhythmic agent^{1–3} that requires therapeutic drug monitoring during use. Factors known to affect serum concentrations include weight and changes in diet. Our case represents an instance where serum levels were increased following a reduction in milk intake in an older child, with resultant toxicity. This effect has not been previously reported in this age group. We have therefore written the case up to remind medical practitioners of the potential influence of milk consumption⁴ on serum flecainide levels across the entire paediatric population, rather than just infants in whom it has previously been reported.

CASE PRESENTATION

An 11-month-old male infant was referred to cardiology for evaluation of a new onset murmur. A structurally normal heart was noted on echocardiography, a diagnosis of innocent murmur made, and he was discharged. He was subsequently seen aged 15 months for transient episodes of blueness to the lips and feet lasting about 20 min, but otherwise behaving normally and with no additional symptoms. In the presence of a normal echocardiogram

and ECG, a diagnosis of a benign form of acrocyanosis or Reynauds phenomenon was postulated. At the age of 5 years he presented acutely to the emergency department (ED) with palpitations, where he was assessed as being clinically stable. An ECG diagnosis of supraventricular tachycardia (SVT) was made. It did not respond to vagal manoeuvres, but was successfully terminated with a single dose of intravenous adenosine. He was followed up in cardiology clinic 2 weeks later, and noted to have normal heart sounds, a normal ECG and a normal echocardiogram. Treatment choices were explained to the family with a decision to start therapy dependant on symptom burden. He proceeded to have two further acute presentations with SVT, each requiring intravenous adenosine. His weight at this time was 21.5 kg, and he was commenced on flecainide 45 mg (2 mg/kg/dose) twice daily as maintenance antiarrhythmic. Flecainide is subject to routine therapeutic drug monitoring (TDM) at our institution, and a level was taken 3 weeks after initiation of therapy (354 micrograms/l, therapeutic range 200–1000 micrograms/l). He remained asymptomatic, and continued on this dose of flecainide until age 7 years (18 months after beginning medication), when he had another three episodes of SVT each

Table 1 Doses of flecainide and levels noted on routine therapeutic drug monitoring.

Date	Dose of flecainide	Dose of flecainide (mg/kg/day)	Flecainide level (micrograms/l)	Notes
06/11/07	45 mg twice daily	4.18	354	3 Weeks after dose commenced
04/09/08	45 mg twice daily	3.96	44	
23/05/09	45 mg twice daily	3.56	<50	
08/06/09	50 mg twice daily	3.96	83	Symptoms recurred
21/08/09	75 mg twice daily	5.72	279	
24/09/09	100 mg twice daily	7.60	122	
02/10/09	100 mg twice daily	7.60	124	
25/02/10	100 mg twice daily	7.38	576	Acute presentation with flecainide toxicity
22/03/10	75 mg twice daily	5.54	129	

requiring intravenous adenosine. Flecainide levels taken at this time were found to be <50 micrograms/l (table 1). The family insisted that there was good adherence with the medication, but did report that he tended to drink a lot of milk (more than 750 ml/day), frequently helping himself to milk from the fridge. Flecainide dose was increased to 50 mg twice daily, and TDM undertaken following this dose increase showed levels of 83 micrograms/l. He continued to have symptomatic SVT, and his dose was increased stepwise to 100 mg twice daily (7.6 mg/kg/day of flecainide). At this dose he was clinically asymptomatic, but with subtherapeutic TDM levels (122 micrograms/l). An ECG undertaken at this time continued to show no evidence of pre-excitation and there was a normal PR interval, normal QRS duration and QTc 430 milliseconds. Details of the doses and levels of flecainide are summarised in table 1. At each appointment advice was given regarding not drinking milk until at least 30 min after the dose of flecainide, and his adherence with the medication was asked about regularly and was always reported as good. Renal function was normal throughout this time, and there were not intercurrent illnesses of note or changes to the formulation of his medication.

At the age of 8 years 3 months, he became acutely unwell. During a physical education lesson he felt unwell, and subsequently became limp and apnoeic, requiring first aid including mouth to mouth resuscitation. By the time the ambulance arrived, he was breathing but remained floppy, and as consciousness returned he was noted to be agitated and confused, with increased tone and extensor posturing. He received intravenous lorazepam (0.1 mg/kg) in the ED in order to control the level of agitation. In addition to the routine management, he underwent an ECG (figure 1) that showed no significant arrhythmia, but there was significant broadening of QRS duration to 160 milliseconds and QT prolongation (QTc 520 milliseconds) consistent with flecainide toxicity.

Flecainide levels taken at 18 h postdose were found to be 576 micrograms/l. No specific treatment was given but he made a good improvement by withholding subsequent flecainide doses.

Following resolution of symptoms, he had a normal exercise tolerance test, and was subsequently discharged on a decreased dose of 75 mg twice daily (5.54 mg/kg/day). Discussion with the family did not reveal any changes in adherence (which was always reported to be good), or any accidental or deliberate overdose, but they did note that he had reduced his milk drinking considerably before the episode. Symptoms have since remained well controlled apart from two short and self-correcting episodes which occurred around the time he was changed from liquid solution to tablets.

INVESTIGATIONS

See text.

OUTCOME AND FOLLOW-UP

Definitive treatment for SVT is offered routinely at our institution to patients over 25 kg often allowing the patient and family to consider the risks of intervention against medical therapy and or symptom burden. Our patient underwent an electrophysiological study under general anaesthesia at the age of 9 years and 3 months. A concealed left-sided accessory pathway was found to be the cause of arrhythmia and successfully treated with transcatheter radiofrequency ablation. At 6 months, he has been symptom free and no longer requires medication.

DISCUSSION

Oral flecainide is a well used and largely effective therapy for tachyarrhythmia. In a paediatric population flecainide has been shown to be effective in 78% of patients.³ Despite its efficacy, there is a risk of arrhythmias, estimated at 6.9–7.4% of patients.^{2,3} These risks are managed by use of TDM and assessment of ECG changes in clinic, but intra and interpatient variability make initial and ongoing dosing challenging. These difficulties, as well as the danger of toxicity are demonstrated in this case.

Alterations in flecainide levels have been related to consumption of milk in neonates and infants,⁴ as well as age,⁵ sex,⁵ serum creatinine concentration⁵ and cytochrome p450

Figure 1 ECG taken by paramedic team attending acute collapse. Shows broadening of QRS complexes to 0.16 milliseconds and QT prolongation (QTc 520 milliseconds) consistent with flecainide toxicity.

2D6 genotype.⁵ A model using the latter four factors in adult Japanese patients reduced the unexplained variability in clearance from 32.9% to 17.8%, but comparable studies in children have not been published. The reports relating to oral milk intake have shown that in infants flecainide levels may be reduced by milk drinking,⁴ but to our knowledge this is the first report of an older child potentially having such an effect. We feel this highlights the importance of a dietary history in patients who have persistently low flecainide levels, as well as advice not to suddenly change the volume of milk drunk once a stable dose has been achieved (in addition to the advice about timing of milk drinking with respect to flecainide doses).

We acknowledge that there are several factors that could explain the symptoms of flecainide toxicity temporally associated with increased flecainide levels, including sudden improvement in adherence and overdose (deliberate or accidental). In this case we feel that suddenly improved adherence and overdose are unlikely. This is partly based on the good therapeutic relationship between the cardiology team and the family. Possibilities such as these were directly raised in family discussions following the acute episode, but were not considered possible by them. There have also not been any other concerns about the families understanding of the condition, attendance at clinics, or ability to care of the child that would have increased the cardiology teams concern in these regards. However, we do acknowledge that assessment of adherence can be very difficult and the lack of formal data regarding adherence such as repeat prescription frequency data is a limitation of this report. However, we remain concerned that it was the decrease in milk drinking that significantly affected the flecainide levels in this child, causing a life-threatening arrhythmia.

Learning points

- ▶ Flecainide is a potent antiarrhythmic agent with significant potential for adverse side effects in the paediatric population.
- ▶ Numerous factors have been identified that can affect bioavailability of the drug meaning that therapeutic drug monitoring is essential.
- ▶ At all age's dietary intake, particularly milk ingestion, can affect serum levels of flecainide.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Thompson B, Mangat J, Barton C, Hawcutt DB. Decreased milk drinking causing flecainide toxicity in an older child. *BMJ Case Reports* 2012;10.1136/bcr.02.2012.5810, Published XXX

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