Complete Heart Block Secondary to Flecainide Toxicity: Is It Time for CYP2D6 Genotype Testing?

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Flecainide acetate is a Vaughan-Williams class IC antiarrhythmic drug prescribed for the treatment of supraventricular arrhythmias. It has a narrow therapeutic index and proarrhythmic effects even at therapeutic doses. Flecainide is metabolized by a CYP2D6 enzyme that exhibits polymorphism. In this case report, we present, to our best knowledge, the first case of toxicity contributed by genetic polymorphism in an infant. Our patient with recurrent supraventricular tachycardia was treated with a therapeutic dose of flecainide but developed heart block requiring extracorporeal membrane oxygenation support and subsequent treatment with lipid emulsion therapy. He was found to have supratherapeutic serum flecainide concentration, and gene testing revealed the patient to be an intermediate metabolizer. With this case report, we reinforce the importance of evaluating the CYP2D6 genotype before drug initiation in the neonatal population and recommend regular monitoring of serum flecainide levels and electrocardiograms in these patients.

CASE PRESENTATION

Our patient is a preterm Malay infant boy at 29 + 5/7 weeks’ gestation who developed tachycardia at day 18 of life with a heart rate (HR) of 300 beats per minute. An electrocardiogram (ECG) revealed supraventricular tachycardia (SVT). He was prescribed with oral propranolol (initial dose of 0.25 mg/kg per dose 3 times per day), and caffeine was discontinued. A transthoracic echocardiogram revealed only an atrial septal defect and patent foramen ovale. He remained stable until day 49 of life when he developed a recurrence of SVT. He was treated with intravenous adenosine (1 dose at 0.1 mg/kg per dose and 3 doses at 0.2 mg/kg per dose) and 2 doses of intravenous propranolol (0.05 mg/kg per dose). He was then converted from oral propranolol to oral flecainide (2 mg/kg per dose twice daily). An ECG 3 days later revealed sinus rhythm (HR of 132 beats per minute) with no evidence of QTc prolongation or Brugada sign. He was not on any medications that can...
potentially prolong QTc and was placed on continuous ECG monitoring.

On day 7 of flecainide therapy, he developed acute bradycardia (HR of 85 beats per minute). An ECG revealed heart block with widened QRS complex. He was transferred to the NICU and started on continuous positive airway pressure support. Although his initial oxygen saturations remained stable, they started to drop after 30 minutes. He became progressively bradycardic with an HR of 70 beats per minute and was subsequently intubated and ventilated. Endotracheal and intravenous adrenaline failed to improve the bradycardia. Repeat ECGs revealed complete heart block. An echocardiogram initially revealed normal cardiac contractility. Intravenous adrenaline (a maximum of 0.12 μg/kg per minute) and isoprenaline (1 μg/kg per minute) failed to improve the HR. Sodium bicarbonate (1 mmol/kg) was also given, but the HR did not improve. Transcutaneous pacing was attempted but was not successful. The patient was transferred to the cardiac catheterization laboratory, and transvenous pacing was performed with capture of his heartbeat. Fluoroscopic imaging at that time revealed poor cardiac contractility. This was confirmed on echocardiography. Chest compressions and venoarterial extracorporeal membrane oxygenation (ECMO) were initiated.

He was treated with intravenous calcium chloride for cardioprotection, and further sodium bicarbonate was administered for correction of metabolic acidosis. Because the clinical picture was consistent with flecainide toxicity, the serum flecainide level and extemporaneous flecainide suspension were sent for flecainide levels.

Serum electrolytes during the pericardiovascular collapse period were within normal ranges. Cardiac enzymes were not elevated, and an echocardiogram performed 12 hours later still revealed severely reduced and dyskinetic cardiac contractility. To treat for possible flecainide toxicity, intravenous lipemid emulsion (ILE) at 2 g/kg per day was given.

After 16 hours of lipid emulsion therapy, arterial pulsatility returned. Both sinus rhythm and hemodynamic stability were also achieved. Although we had seen an improvement in cardiac function over the initial 24 hours, the infant subsequently developed recurrent SVT that required treatment with sotalol. The decision was made for decannulation. Because flecainide is metabolized by the CYP2D6 enzyme that exhibits polymorphism, a gene test was sent to determine the patient’s genotype. This test was only performed after a 2-week interval from the last blood transfusion. He was discharged with oral sotalol 2.8 mg/kg per day 3 times a day with no further runs of SVT. Because of prolonged cardiovascular collapse, he suffered from hypoxic-ischemic encephalopathy with extensive bilateral cystic encephalomalacia.

Investigations revealed a serum flecainide concentration of 1.7 μg/mL (normal range: 0.2−1.0 μg/mL) taken ~24 hours after the last dose and while he was on ECMO. The concentration of flecainide in the extemporaneous suspension was within range, and accidental overdose was ruled out after clarification with the nurses. The gene test revealed that the patient has a CYP2D6*10×2/*36 genotype that is predicted to have intermediate CYP2D6 enzyme activity.

**DISCUSSION**

Flecainide, a class IC antiarrhythmic drug, works by blocking fast-acting sodium channels to slow down depolarization in myocytes. It is an effective second-line agent for the treatment of refractory SVT in infants, but, in large doses, flecainide can lead to conduction disturbances such as widening of the QRS complex that can escalate into ventricular tachycardia and cardiovascular collapse. Most reported causes of toxicity in infants have been due to dosing errors. In our patient, we believe that flecainide toxicity was contributed by reduced metabolism secondary to an unfavorable genetic polymorphism.

CYP2D6 is a member of the cytochrome P450 gene family. Although it accounts for <2% of the total CYP450 liver enzyme content, CYP2D6 mediates metabolism in almost 25% of commonly used drugs (Table 1). Flecainide undergoes metabolism by CYP2D6, which exhibits polymorphism with >100 allelic variants being identified. CYP2D6 activity varies widely, and individuals can be classified into ultra, extensive, intermediate, and poor metabolizers. In ultra-metabolizers, faster metabolic clearance can potentially result in reduced effectiveness of flecainide, and these patients may need higher doses. In contrast, poor metabolizers may have an increased risk for drug interactions and adverse events from high drug concentrations and prolonged effects. Our patient was found to have a CYP2D6*10×2/*36 genotype, in which CYP2D6*10×2 was associated with reduced enzyme activity, whereas *36 was associated with no enzymatic function. The CYP2D6*10 mutation, associated with significantly reduced metabolic activity of ~60% of normal activity, has been identified in up to 43% of individuals in the Asian population. Furthermore, in infants, the CYP2D6 enzyme becomes active in hours or days and may only reach complete
TABLE 1 List of Commonly Used Drugs Metabolized by CYP2D6 (List Is Nonexhaustive)

<table>
<thead>
<tr>
<th>Drug Categories</th>
<th>Drugs</th>
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<tr>
<td>Antineoplastic agents</td>
<td>Tamoxifen</td>
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<tr>
<td>Antipsychotics</td>
<td>Clozapine, haloperidol, risperidone, zuclopenthixol, flupenthixol, aripiprazole, and fluvoxamine</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Propafenone, flecainide, and lidocaine</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Carvedilol, metoprolol, and propranolol</td>
</tr>
<tr>
<td>Opioids</td>
<td>Codeine, oxycodone, and tramadol</td>
</tr>
<tr>
<td>SSRIs and SNRs</td>
<td>Fluoxetine, paroxetine, venlafaxine, duloxetine, and sertraline</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Amitriptyline, nortriptyline, clomipramine, doxepin, imipramine, and atomoxetine</td>
</tr>
<tr>
<td>Prokinetic agent</td>
<td>Metoclopramide</td>
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<tr>
<td>Adrenergic agonist</td>
<td>Clonidine</td>
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<tr>
<td>S-HT2 receptor antagonist</td>
<td>Ondansetron</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Chlorpheniramine and diphenhydramine</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>Diltiazem</td>
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maturation after 1 year of life.3,16 Therefore, although our patient was treated with a literature-recommended dose of flecainide, the measured serum concentration of 1.7 μg/mL was supratherapeutic (therapeutic serum level of 0.2–1.0 μg/mL),4 probably because of drug accumulation from reduced metabolism secondary to genetic polymorphism and inherently reduced CYP2D6 enzyme activity. Authors of a genotyping study on 506 subjects conducted in Singapore found that the Chinese and Malay subjects exhibited approximately fivefold higher allele frequencies of *10 compared with the Indian subjects.17 The Royal Dutch Pharmacists Association Dutch Pharmacogenetics Working Group has thus evaluated therapeutic dose recommendations for flecainide on the basis of CYP2D6 genotypes and recommended a dose reduction by 25% for patients with intermediate CYP2D6 enzyme activity and 50% dose reduction for poor CYP2D6 enzyme activity.18 Because of patient heterogeneity, gene testing before flecainide initiation may be important to allow for appropriate dose initiation. However, in circumstances in which gene testing is not readily available, one potential strategy, albeit an unproven one, is to initiate patients at lower doses and monitor for efficacy and/or toxicity. We thus recommend flecainide levels to be performed for all patients and, if not, at least for patients at higher risk of toxicity (Table 2).

There is no specific antidote for flecainide toxicity, but various modes of treatment modalities have been proposed. One of them is ILE therapy. The theory proposes that ILE expands the lipid phase of plasma and creates a “lipid sink,” in which lipophilic drugs may diffuse into and be sequestered away.19,20 Reported ILE regimens vary in the literature,21 and there is no well-defined dose, especially in infants. Given that the maximum safe dose of ILE is unknown,21 we chose a physiologic dose of 2 g/kg per day in our case. ILE was chosen as our next choice of therapy because use of ILE is ubiquitous in most ICUs for total parental nutrition and its safety has been well described.22–24 Other treatments include the use of sodium bicarbonate and ECMO in patients with cardiac arrest, cardiogenic shock, or pulseless electrical activity. The use of sodium bicarbonate has also been proposed because it can theoretically be used to overcome sodium blockade by displacing flecainide from its receptor sites to reverse the action of sodium channel blockade.7,25 Alkalization also converts flecainide to its inactive nonionized form.7,25 Indeed, in several studies, researchers have reported successful treatment with the use of sodium bicarbonate.6,7,25 Our patient was effectively treated with ECMO, which is consistent with other published case reports,26,27 revealing that ECMO can be an effective means for restoring circulation and allowing drug clearance.

Because flecainide has a narrow therapeutic index and the toxicity can be life-threatening, our case report highlights the importance of gene testing for flecainide in infants when this drug is being considered.28 However, gene testing can be expensive and may not be universally available. It is currently not standard care in many centers. In our practice, the test needs to be sent out to an external laboratory, and it takes 7 to 10 working days for results. Furthermore, this test should not be done within 2 weeks of any blood transfusion, which is often required by critically ill patients. Therefore, it may not be practical to wait for the results before starting this drug for patients who require it urgently. Other limitations of the genotype testing include uncertainty toward

<table>
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<th>TABLE 2 Patients at Higher Risk of Flecainide Toxicity</th>
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<tr>
<td>Infants (≤ 12 mo of age), especially premature infants</td>
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<tr>
<td>Known slow metabolizers</td>
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<tr>
<td>Those requiring higher than the recommended dosing of 2–3 mg/kg/dose</td>
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genotype-phenotype, gene-concentration, and gene-dose relationships. Because CYP2D6 can be involved in the metabolism of up to 25% of commonly used drugs (eg, codeine, fluoxetine, and ondansetron), further studies on the impact of CYP2D6-dependent metabolism of drugs in a larger number of pediatric patients are warranted.

**CONCLUSIONS**

As illustrated in our case, because of genetic polymorphism in the metabolism of flecainide by CYP2D6, toxicity can still occur even at therapeutic doses. An evaluation of a patient’s CYP2D6 genotype should be considered before dosing flecainide in infants. In addition, regular monitoring of serum flecainide levels and ECG should be strongly recommended for all patients on long-term flecainide to monitor for efficacy and toxicity.

**ABBREVIATIONS**

ECG: electrocardiogram  
ECMO: extracorporeal membrane oxygenation  
HR: heart rate  
ILE: intravenous lipid emulsion  
SVT: supraventricular tachycardia

**REFERENCES**


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26. Reynolds JC, Judge BS. Successful treatment of flecainide-induced cardiac

