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Brief Report

Lacosamide-induced atrial tachycardia in a child with hypoplastic left-heart syndrome: the importance of assessing additional proarrhythmic risks

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Abstract Antiepileptic medications have been reported to cause disturbances in cardiac conduction. Lacosamide decreases seizure burden by modulating sodium channels. Although it has been demonstrated to have few side effects, there have been reports of clinically significant cardiac conduction disturbances. We report the case of a child with hypoplastic left-heart syndrome and well-controlled multifocal atrial tachycardia who developed haemodynamically significant atrial tachycardia after receiving two doses of lacosamide.

Keywords: Lacosamide; atrial tachycardia; vimpat; flecainide

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LACOSAMIDE IS A NEWER ANTIEPILEPTIC DRUG composed of the functionalised amino-acid acetamido-N-benzyl-3-methoxypropionamide, which was approved for adjunctive therapy for partial onset seizures in epilepsy patients over 16 years of age.[1,2] Lacosamide has been demonstrated to achieve its antiepileptic effect by selectively enhancing slow inactivation of voltage-gated sodium channels and interfering with collapsin-response mediator protein 2, reducing the number of sodium channels that can be recruited for subsequent action potentials. Lacosamide has 100% oral bioavailability and is excreted by the kidneys with a half-life of ~13 hours.[3,4]

Early studies have shown that lacosamide has a favourable side effect profile with side effects including dyspepsia, dizziness, headache, nausea, and vomiting.[1,2] Cardiac effects are rare but have been documented in larger phase II trials as well as individual case reports and include atrioventricular block, atrial flutter/atrial fibrillation, and sinus node dysfunction.[5–11] We present the first reported case of atrial tachycardia in a child with congenital heart disease who received lacosamide for management of seizures.

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Case report

We present the case of a 3-year-old boy with a history of hypoplastic left-heart syndrome status post Norwood palliation in the first week of life and bidirectional Glenn palliation at 7 months of age. He had significant cardiac issues and comorbidities, resulting in hospitalisation for the bulk of his first 9 months of age. During this time, he had periods of multifocal atrial tachycardia that at times produced haemodynamic compromise. This arrhythmia was eventually well controlled with flecainide.

In addition to his congenital heart disease, this boy had developed cerebral palsy with subsequent epilepsy and developmental delay, eosinophilic oesophagitis, and jejunostomy tube dependence. His chronic antiepileptic therapy at the time of presentation included levetiracetam and clonazepam.

At the age of 3 years, the child presented to the emergency department after having a 15-minute generalised tonic-clonic seizure at home, having been seizure free for 2 years. Emergency medical services were notified and arrived on the scene at which point

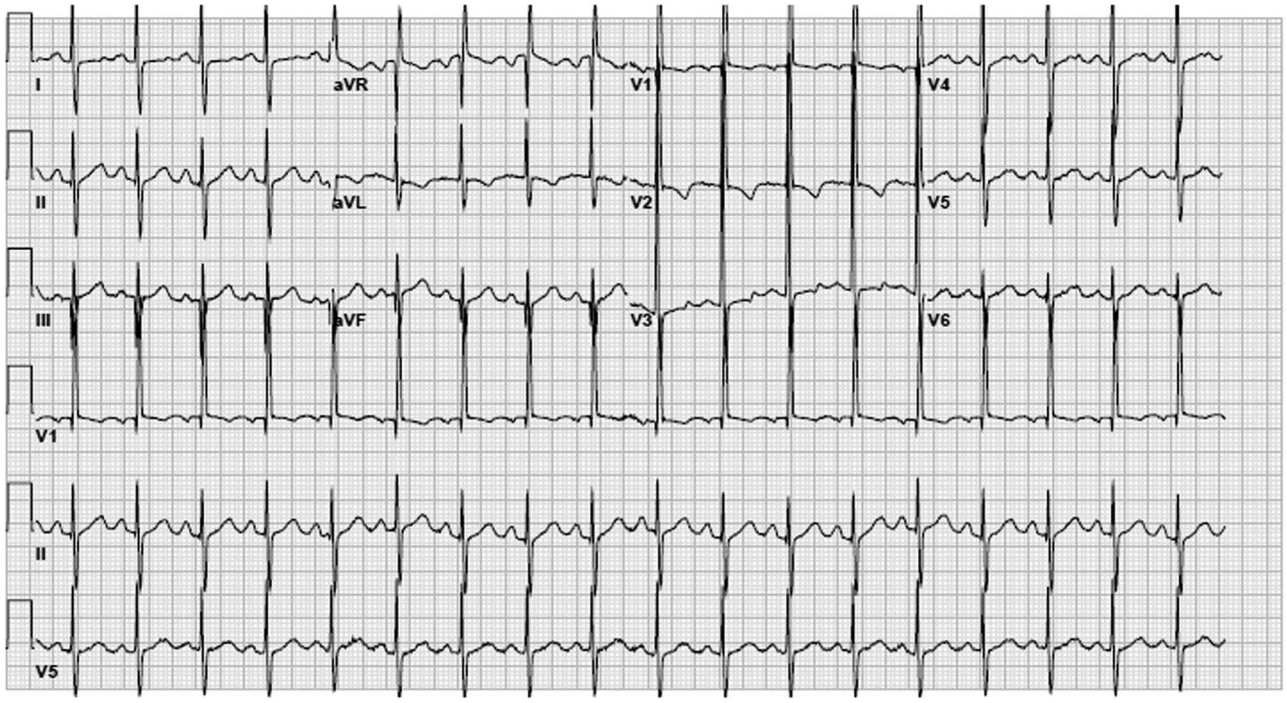

Figure 1.
Electrocardiogram obtained 2 weeks before presentation demonstration normal sinus rhythm.

the child was postictal but otherwise stable. On arrival to the emergency room, he had another generalised tonic-clonic seizure and was unresponsive with poor respiratory effort. Bag mask ventilation was initiated and intramuscular midazolam administered, as intravascular access could not be gained. This successfully terminated the generalised seizure. Within minutes of resolution, he began to have another generalised tonic-clonic seizure for which he received lorazepam and levetiracetam via intraosseus access. The seizures persisted, despite these interventions leading to intubation. A computed tomography scan of the brain was obtained that demonstrated no new abnormalities.

The child was then admitted to the intensive care unit where he was sedated, paralysed, and administered boluses of valproic acid and levetiracetam. Telemetry monitoring was initiated and demonstrated normal sinus rhythm with brief episodes of sinus tachycardia. An electrocardiogram performed at an outpatient cardiology visit 2 weeks before the current admission had also demonstrated normal sinus rhythm (Fig 1). Despite additional antiepileptic measures, long-term electroencephalographic monitoring continued to demonstrate subclinical seizure activity, and the decision was made to start lacosamide. The first 50 mg dose of lacosamide was administered 15 hours after the child's was presented to the emergency department, with this dose repeated roughly 4 hours later owing to persistence of seizure activity on electroencephalogram. A duration of 1 hour after the second dose of lacosamide – 20 hours after presentation to the emergency department – the child began to have wide complex tachycardia with haemodynamic compromise and was treated with a bolus dose of intravenous amiodarone, without termination of the tachycardia. The tachycardia rate was between 240 and 260, and demonstrated both 1:1 and 2:1 ventricular response. Review of his telemetry showed bursts of a narrow QRS complex tachycardia with gradual QRS widening during the nonsustained runs. This finding suggested conduction system disease, and thus treatment for possible flecainide toxicity was initiated with sodium bicarbonate, intralipids, and isoproterenol. A flecainide serum level was also drawn at this time. The amiodarone infusion was continued, and within 6 hours the multifocal atrial tachycardia persisted as salvos of irregular atrial tachycardia (Fig 2). The child was then electrically cardioverted with restoration of sinus rhythm noted on telemetry.

No additional doses of lacosamide were administered, and seizure control was achieved by increasing the levetiracetam dose and adding zonisamide. Inotropic and amiodarone infusions were successfully discontinued by day 3 of hospitalisation and the child was extubated. Flecainide was held for 2 weeks after he was presented, but the initial levels returned normal at 0.19 mcg/ml (normal range 0.2–1.0 mcg/ml), leading to resumption of flecainide. The child was discharged home on hospital day 23 of hospitalisation

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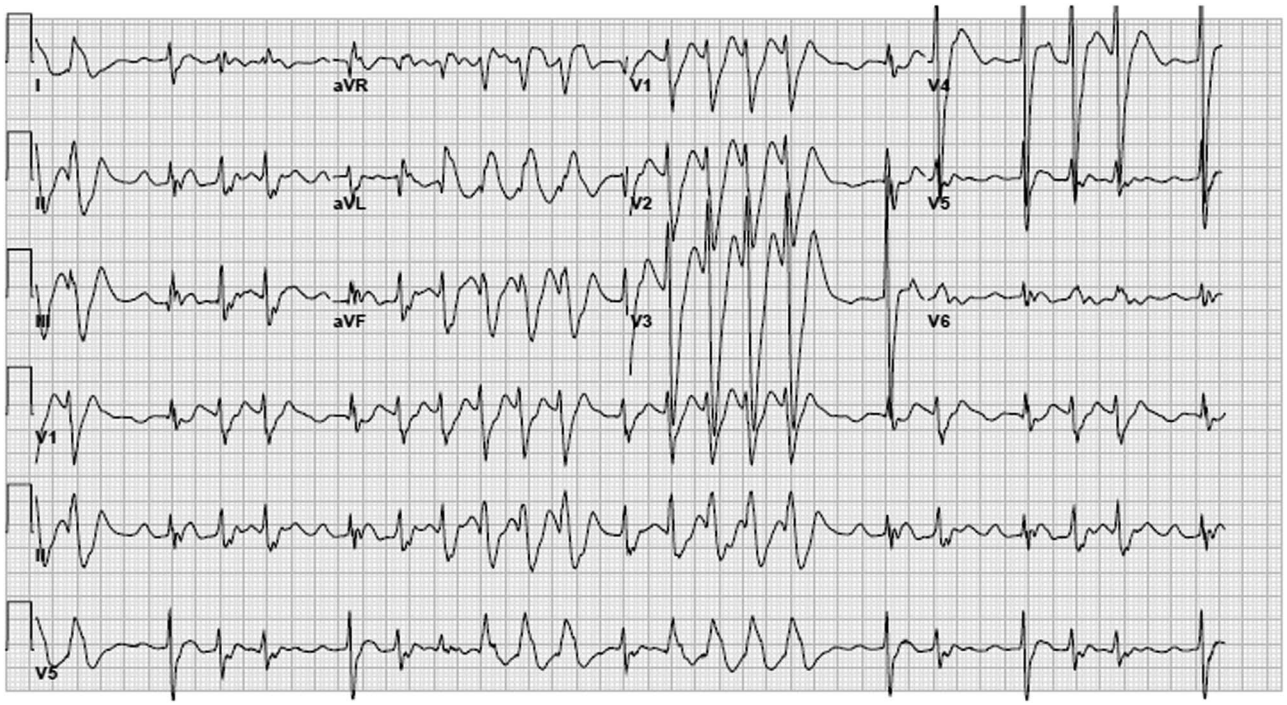

Figure 2.
Electrocardiogram obtained during the episode of tachycardia, demonstrating a wide complex tachycardia.

with no further atrial or ventricular arrhythmias after day 1. At subsequent follow-up, he remained in sinus rhythm without arrhythmias.

Discussion

We present the case of a 3-year-old boy with congenital heart disease who had an episode of wide complex tachycardia, consistent with atrial tachycardia with intraventricular conduction delay, after receiving two doses of lacosamide for seizure control. This is the first report of any cardiac effects of this antiepileptic medication in the paediatric population and the first report of a wide complex tachycardia secondary to lacosamide. Previous reports of cardiac effects of lacosamide describe prolongation of the PR and QRS intervals on electrocardiogram, atrioventricular block, atrial flutter/atrial fibrillation, and sinus node dysfunction.[5–11] Although it cannot be said with absolute certainty that the arrhythmia was subsequent to lacosamide, the timing of the arrhythmia and the lack of recurrence after cessation of lacosamide makes the association very likely.

It is plausible that the administration of lacosamide in conjunction with flecainide was the substrate for the atrial arrhythmia in this current case. Flecainide, a class IC antiarrhythmic, exerts its antiarrhythmic effects by blocking sodium channels, particularly the $NA_V1.5$ sodium ion channel encoded by the SCN5A gene.[12] Thus, the addition of lacosamide may have led to flecainide toxicity and sodium channel blockade to the extent that it precipitated the atrial arrhythmia. Flecainide has been documented to induce wide complex tachycardia consistent with supraventricular tachycardia with aberrancy.[13,14] Flecainide's slowing of intracardiac conduction seems to be secondary to its slow unbinding from sodium channels, particularly in diastole. Because of this, refractoriness is increased and leads to a decrease in intracardiac conduction in the cardiac tissue at all extremes of heart rate.[15]

Other sodium channel-blocking antiepileptics, such as lamotrigine and carbamazepine, have also been found to infrequently have effects on cardiac conduction, although usually clinically insignificant. In a majority of instances, the effects are greater in those with already present atrioventricular conduction defects.[16] This double hit phenomenon seems to hold true with lacosamide as well as most previous reports of cardiac effects were in patients who had comorbidities that may have predisposed them to conduction disturbances. Diabetes mellitus, panhypopituitarism, acute lymphocytic leukemia, and hypothyroidism were present in previously reported cases.[7,9,10] In the present case, the child had a history of congenital heart disease and had undergone palliative procedures that put him at a higher risk for developing arrhythmias. In addition, the child had a history of multifocal atrial tachycardia, which had developed in the postoperative period and had been successfully managed medically. His antiarrhythmic

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regimen of flecainide, which was continued while lacosamide was administered, may have also put him at additional risk.

This case highlights the importance of considering potential proarrhythmic interactions between medications before starting lacosamide, particularly with respect to other sodium channel blockers. It is also necessary to weigh the risks posed by the patient's previous medical history and arrhythmia burden as this may place them at higher risk for clinically significant cardiac conduction disturbances secondary to lacosamide. An electrocardiogram should always be obtained before initiating lacosamide and repeated as needed if there is any concern for symptoms associated with atrioventricular block or dysrhythmias. Appropriate dosing is also of utmost importance as this child received two 50 mg doses of lacosamide within hours of each other. This dose has been shown to be appropriate for those 17 years of age or older, although the initial dose for children between 3 and 16 years of age is 1 mg/kg daily divided over two doses. The dose can then be increased by 1 mg/kg daily up to a max of 10 mg/kg daily.[17] For the current patient, weighing 14 kg, the recommended initial dose is much lower than the administered dose.

Conclusion

Lacosamide is a newer antiepileptic that enhances the slow inactivation of sodium channels. Approved for adjunct use in epilepsy patients over 16 years of age, there is limited data on the paediatric population, and therefore caution should be used in this population. Close monitoring for cardiac conduction disturbances that include prolongation of the PR interval, prolongation of the QRS, atrioventricular conduction delay, atrial fibrillation/atrial flutter, sinus node dysfunction, and now atrial tachycardia is necessary.

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Conflicts of Interest

None.

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