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Cardiac Dysfunction Associated with Lacosamide in a Premature Infant with Hypoxic Ischemic Encephalopathy: A Case Report

Trassanee Chatmethakul, MD[1,2] Amy H. Stanford, MD[2] Danielle R. Rios, MD, MS[2]
Adrianne R. Bischoff, MD[2] Theresa Czech, MD[3] Patrick J. McNamara, MB BCh, MRCPCH, FASE[2,4]

[1] Department of Pediatrics, Neonatal-Perinatal Medicine Section, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma
[2] Division of Neonatology, Department of Pediatrics, University of Iowa, Iowa City, Iowa
[3] Pediatric Neurology Division, Department of Pediatrics, University of Iowa, Iowa City, Iowa
[4] Department of Internal Medicine, University of Iowa, Iowa City, Iowa

Address for correspondence Patrick J. McNamara, MB BCh, MRCPCH, FASE, Division of Neonatology, Department of Pediatrics, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242 (e-mail: patrick-mcnamara@uiowa.edu).

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Abstract

Lacosamide (Vimpat Harris FRC Corporation, 2022 UCB, Inc. Smyrna, GA 30080) is an antiseizure medication, which acts through blockage of voltage-gated neuronal sodium channels. Its recent implementation in the neonatal population has been extrapolated from adult and pediatric data suggesting a favorable safety profile. Of note, preterm infants have unique developmental characteristics that may predispose them to increased risk of adverse reactions. We present a case of a preterm neonate who developed left ventricular dysfunction coinciding with the initiation of lacosamide.

Keywords
- cardiac dysfunction
- antiseizure medication
- preterm infant
- lacosamide

Case Presentation

A 34 weeks' gestation female infant was born at a primary care hospital following an emergency cesarean section for decreased fetal movement and poor biophysical profile. Apgar scores were 0 at 1, 5, and 10 minutes, 1 at 15 minutes, 3 at 20 minutes, and 4 at 25 minutes. The modified SARNAT exam was consistent with severe hypoxic ischemic encephalopathy (HIE) for which prompted transfer to a level IV neonatal intensive care unit for therapeutic hypothermia. Laboratory evaluation showed no evidence of renal impairment (serum creatinine 1 mg/dL with urine output 3.4 mL/kg/d).[1–4] Baseline electrocardiogram and renal ultrasound were unremarkable. On admission, there was clinical and echocardiography evidence of acute pulmonary arterial hypertension and severe right ventricular (RV) dysfunction. These findings had resolved by postnatal day 2, after treatment with inhaled nitric oxide and myocardial inotropic support (►**Table 1**).

Her hospital course, however, was complicated by refractory status epilepticus for which lacosamide was added as adjunctive therapy. Thereafter, continuous electroencephalogram monitoring showed improvement in frequency and duration of the seizure activity. Treatment was gradually titrated to a maximum dose of 9 mg/kg/d over 72 hours. Within 24 hours of reaching the maximum dose of lacosamide, the infant developed persistent systemic hypertension (systolic blood pressure [SBP] 85–111 mm Hg, diastolic blood pressure [DBP] 58–76 mm Hg [$>95^{th}$ percentile blood pressure for 34 weeks' postmenstrual age])[5] for which targeted neonatal echocardiography (TnECHO) was

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Table 1 Clinical course and echocardiographic data

	Day 1	Day 2	Day 7	Day 9	Day 12	Day 16
LV function						
EF (%)	61	64	42	49	53	63
GLS (%)	N/A	N/A	−11.3	−10.4	−11.7	−11.9
LVO (mL/kg/min)	96	176	188	185	165	167
RV function						
TAPSE (mm)	7.2	9.5	7.4	8.1	8.0	9.0
FAC	0.26	0.43	0.37	0.51	0.48	0.48
RVO (mL/kg/min)	60	102	215	214	203	188
RVSp using TR jet (mm Hg)	51 mm Hg + RAp	62 mm Hg + RAp	Incomplete TR jet	Incomplete TR jet	Incomplete TR jet	Incomplete TR jet
Eccentricity Index in systole	1.3	1.24	1.1	1.02	1.08	0.94
Ductal shunt	Bidirectional	Bidirectional	Closed	Closed	Closed	Closed
Atrial shunt	Bidirectional	Bidirectional	Bidirectional	Left to right	Left to right	Left to right
Cardiovascular medications	iNO 20 ppm Epinephrine 0.05 µg/kg/min Vasopressin 1.6 milliunits/kg/min	iNO 20 ppm Epinephrine weaned off on day 2	None	Milrinone 0.66 µg/kg/min	Milrinone 0.66 µg/kg/min	Milrinone 0.66 µg/kg/min
Therapeutic hypothermia	Yes	Yes	No	No	No	No
Antiseizure medications	Single dose (20 mg/kg/dose) phenobarbital IV	Maintenance phenobarbital 5 mg/kg/day Fosphenytoin 20 mg/kg/dose ×2 doses on DOL 1 and 2 Midazolam infusion 90 µg/kg/min	Lacosamide Phenobarbital Midazolam infusion weaning	Phenobarbital Levetiracetam	Phenobarbital Levetiracetam	Phenobarbital Levetiracetam

EF, ejection fraction by Simpson's biplane; FAC, fractional area change; GLS, Global longitudinal strain; IV, intravenous; LV, left ventricle; LVO, left ventricular output; Rap, Right atrial pressure; RV, right ventricle; RVO, right ventricular output; RVSp, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

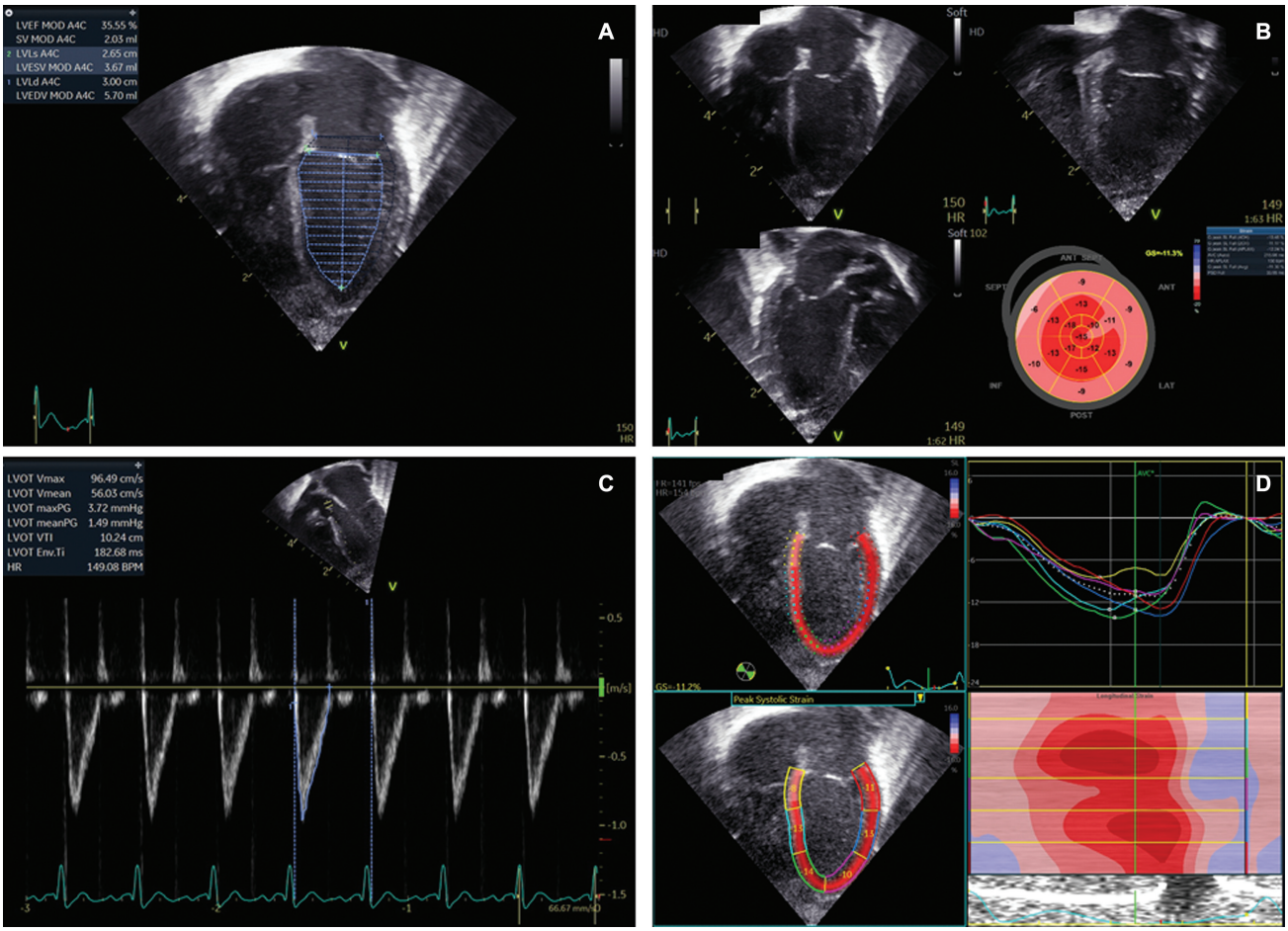

Fig. 1 Echocardiography imaging on postnatal day 7 demonstrating decreased ejection fraction (**A**) with a preserved left ventricular output (**C**). Echocardiographic strain imaging (myocardial deformation analysis) demonstrating decreased systolic function (Global longitudinal strain [GLS] = −11.3%) (**B, D**).

obtained. TnECHO revealed impaired left ventricular (LV) systolic and diastolic performance (►**Fig. 1**; ►**Table 1**). Continuous milrinone infusion was initiated for cardiovascular support; however, 48-hour follow-up assessment with TnECHO continued to demonstrate severe LV systolic dysfunction.

Due to the temporal relationship of initiation/dose escalation of lacosamide and onset of cardiac dysfunction, and lack of alternative explanatory cause, lacosamide was discontinued and replaced with levetiracetam. Serial follow-up with TnECHOs were performed 24, 96, and 192 hours after discontinuation of lacosamide. There was a marginal improvement in LV systolic function by 96 hours; however, by 192 hours, complete resolution was noted. LV function remained normal following discontinuation of milrinone. The infant remained hemodynamically stable without recurrence of systemic hypertension and was discharged home with no cardiovascular medications.

Discussion

Recent evidence of a potential neuroprotective effect of lacosamide in animal experimental models suggest it to be a candidate for seizure control in neonates with HIE.[6] Through blockage of voltage-gated sodium channels, lacosamide may predispose to cardiac arrythmias. Moreover, it also has been shown that at the cellular level, alteration of cardiac sodium current may play important roles in mechanical dysfunction of the myocardium.[7] Case reports have also suggested impaired, but reversible, cardiac excitation, and contraction in adults and a dose-dependent response with higher rates of toxicity and mortality seen with dose escalation or when used in combination with other sodium channel blockers.[8,9] Although there are currently no published data on the effect of lacosamide on neonatal cardiac function, concomitant use with phenobarbital and fosphenytoin could also negatively impact heart function.[10,11] Regardless, it is important to note that the temporal relationship between lacosamide initiation and LV dysfunction was striking; however, it is not possible to exclude a synergistic negative effect of concurrent anticonvulsant use. The impact on RV systolic performance is unknown. In addition, normalization of LV function following cessation of treatment lends supports to the possibility of causation. It is not clear whether the mechanism relates to a direct effect on the myocardium or represents an independent effect of increased LV afterload secondary to systemic hypertension and elevated systemic vascular resistance.

Conclusion

This case highlights the susceptibility of premature infants to cardiac dysfunction following lacosamide administration. While it is not possibly to assign causality on the basis of a single case report, clinicians should consider a possible contributary effect of lacosamide in patients with new-onset LV systolic dysfunction; therefore, caution is advised using this medication and especially in patients with known LV dysfunction. Cautious use, strict monitoring, and pharmacokinetic investigation are warranted in neonates.

Conflict of Interest
None declared

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