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Original Article

Role of Intravenous Levetiracetam for Acute Seizure Management in Preterm Neonates

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ABSTRACT

BACKGROUND: Neonatal seizures are common in the first month of life and may impair neurodevelopmental outcome. Current antiepileptic drugs used in the treatment of neonatal seizures have limited efficacy and undesirable side effects. Intravenous levetiracetam is increasingly being used in the neonatal period to treat seizures. Presently, insufficient data about the efficacy and safety of intravenous levetiracetam in preterm neonates exist. **METHODS:** We retrospectively analyzed data from preterm neonates who were treated with intravenous levetiracetam at our institution between January 2007 and December 2011. Data were acquired from review of our institution's electronic medical record regarding patients who were treated with intravenous levetiracetam during the neonatal period (0 to 28 days) and were born at preterm gestation (<37 weeks). **RESULTS:** Twelve patients received a levetiracetam load of 25 to 50 mg/kg for neonatal seizures. Nine of 11 patients (82%) reached seizure cessation within 24 hours of receiving levetiracetam. No serious side effects were evident. Seven patients (59%) were discharged on oral levetiracetam alone, four patients (33%) were discharged on no oral antiepileptic drug, and one patient (8%) was discharged on levetiracetam and phenobarbital. Eleven of 12 patients were followed up to 6 months after receiving intravenous levetiracetam. Of these, six patients (55%) had achieved seizure freedom and been completely weaned off of all antiepileptic drugs. Three patients (27%) had achieved seizure freedom while still on oral levetiracetam. **CONCLUSIONS:** Intravenous levetiracetam appears to be efficacious for seizure management in preterm neonates.

Keywords: levetiracetam, treatment, seizures, seizure management, neonatal, neonates, preterm

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Introduction

Seizures affect one to four of 1000 live births in North America and are a major predictor of future adverse neurodevelopmental outcomes.[1,2] The incidence of seizures in preterm neonates is approximately 11 of 1000 live births, with clinical seizures occurring six times more often in preterm infants than term infants.[3] Few medications have been studied and approved to treat neonatal seizures, and none has shown superior efficacy over another. With a high incidence of seizures refractory to currently approved antiepileptic drugs, a pressing need exists for alternative treatment choices in preterm neonates. The most common causes of neonatal seizures are hypoxic ischemic encephalopathy, intracranial hemorrhages, central nervous system infections, cerebral infarctions, and metabolic disturbances.[1-3] The treatment of neonatal seizures often has limited efficacy and leads to deleterious adverse effects. The two antiepileptic drugs presently approved by the United States Food and Drug Administration (FDA) in the neonatal period—phenobarbital and phenytoin—demonstrate efficacy in less than 50% of cases and undesirable side effect profiles in major studies.[4-9] The benefits of alternative

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antiepileptic drugs are being recognized, and off-label use of antiepileptic drugs in children and neonates is increasing.[8-26] An imperative need to investigate the use of newer antiepileptic drugs in preterm neonates exists.[11-19]

Levetiracetam is a pyrrolidine derivative antiepileptic drug chemically different from all previous antiepileptic drugs, with linear pharmacokinetics, renal metabolism, and minimal protein binding.[10,12,27] Unlike phenobarbital, levetiracetam does not increase apoptosis in the developing brain in animal models.[10,28] Intravenous levetiracetam was approved by the FDA in August 2006 for use in patients older than 16 years of age. Oral levetiracetam was approved by the FDA in 2012 for use in partial-onset seizures in patients 1 month of age and older. Both intravenous and oral levetiracetam have been increasingly used off-label in pediatric and neonatal patients because of literature documenting efficacy and safety in adults, along with favorable reports in younger patients.[8-26] Here, we report on our experience with intravenous levetiracetam in the management of seizures in preterm neonates.

Methods

Infants were eligible for inclusion if they were born at preterm gestational age (<37 weeks) and received their first dose of intravenous levetiracetam during the neonatal period (0 to 28 days of age). A retrospective electronic medical record review was conducted on all patients who met inclusion criteria between January 2007 and December 2011 at our institution. This study was approved by our institutional review board.

Data collection

Clinical data were obtained through review of neonatologist and pediatrician progress notes, pediatric neurologist exams, and nursing notes. Electroencephalographic data were reviewed by one of our pediatric neurologists. Levetiracetam dosages were determined by one of our pediatric neurologists on a case-by-case basis.

Variables collected included patients' gender, race, gestational age, birth weight, Apgar scores, seizure etiology, seizure type, indication for initiation of intravenous levetiracetam, loading and maintenance doses of levetiracetam, prior antiepileptic drugs used, response to treatment, adverse events during or after infusion, discharge medications, and well child follow-up visits at 2, 4, and 6 months.

Objectives

Our primary objective was to assess response to treatment based on clinical and/or electroencephalographic chart documentation. This included response at 24 hours after loading dose of levetiracetam and time until complete seizure cessation while on maintenance dosing. Secondary objectives included indication for initiation of levetiracetam, adverse events, and prevalence of seizure freedom at well child follow-up visits.

Results

We retrospectively analyzed 12 preterm neonates who had been treated with intravenous levetiracetam at our institution. The following variables were taken into consideration (Table).

Demographics

There were eight females (67%) and four males (33%). Among them, five were white, five were Hispanic, and two were black. Gestational ages ranged from 23.3 to 36 weeks, with a mean of 32.39 ± 4.3 weeks. Birth weights ranged from 0.62 to 2.96 kg, with a mean of 1.98 ± 0.692 kg. One-minute Apgar scores ranged from 0 to 9, with a mean of 2.75 ± 2.83, and 5-minute Apgar scores ranged from 0 to 9, with a mean of 4.67 ± 2.96.

Seizure etiology and seizure types

Five patients (42%) had a primary underlying diagnosis of hypoxic ischemic encephalopathy, three (25%) had hemorrhages, three (25%) had an unknown seizure etiology, and one (8%) presented with herpes simplex virus encephalitis. Imaging data were used to help determine seizure etiology.

TABLE.
Seizure management in preterm neonates

Patients	EGA/Sex	Birth Weight (kg)	Apgar 1 min/5 min	Etiology of SZ	Indication for LEV Use	Route	Loading Dose (mg/kg)	Response to LEV at 24 h	Adverse Events
1	33.4/F	2.258	5/8	HSV meningoencephalitis	Initially LD with LEV	IV	50	Yes	None
2	24.2/M	0.62	4/7	Unknown	Continued SZ on PB	IV	25	Yes	None
3	34.2/F	2.067	9/9	Hemorrhage	Initially LD with LEV	IV	50	Yes	None
4	34/F	2.42	1/3	HIE	Continued SZ on PB	IV	50	Yes	None
5	31/M	2.051	1/1	Hemorrhage	Continued SZ on PB	IV	50	No	None
6	35/M	2.081	5/7	Unknown	Initially LD with LEV	IV	50	Yes	None
7	34.3/F	2.554	2/6	Hemorrhage	Continued SZ on PB	IV	50	Yes	None
8	36/M	2.21	0/0	HIE	Continued SZ on PB	IV	50	No	None
9	35.2/F	2.96	0/4	HIE	Continued SZ on PB	IV	25	Yes	None
10	23.3/M	0.65	5/6	Unknown	Continued SZ on PB	IV	25	Yes	None
11	36/F	1.9	1/4	HIE	Switch from PB	IV	25	N/A	None
12	32.1/F	2.03	0/1	HIE	Continued SZ on PB	IV	25	Yes	None

Abbreviations:
EGA = Estimated gestational age
F = Female
HIE = Hypoxic ischemic encephalopathy
HSV = Herpes simplex virus
IV = Intravenous
LD = Loading dose
LEV = Levetiracetam
M = Male
PB = Phenobarbital
SZ = Seizures