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Pharmacokinetics and Pharmacodynamics of Levetiracetam in Neonatal Seizures: What We Still Need to Know

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Neonatal seizures affect 1 to 4 neonates per 1000 live births and are associated with increased mortality and neurological impairment. Currently, phenobarbital is recommended as the first-line treatment; however, its limited efficacy and serious safety concerns are significant drawbacks. Levetiracetam, a newer generation anti-seizure medication with minimal reported adverse effects, is commonly used off label for the treatment of neonatal seizures. Earlier studies showed limited efficacy of levetiracetam in neonatal seizures; however, these studies were limited by the lack of pharmacokinetic-pharmacodynamic data for larger doses (>60 mg/kg). The pharmacokinetics of levetiracetam differ in neonates compared to children and adults. In neonates, the volume of distribution of levetiracetam can exceed that in children and adults. By 7 days of postnatal age, the clearance approaches that of children, which also exceeds the clearance reported in adults. There are limited pharmacodynamic studies of levetiracetam in neonatal seizures. Because the pathophysiology of seizures and the treatment goals in neonates differ from those in children and adults, critical information on the pharmacodynamics of levetiracetam at larger doses is still needed to confirm its efficacy or lack thereof.

ABBREVIATIONS AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ASM, antiseizure medications; %CFB, percentage change from baseline; CrCl, creatinine clearance; CYP, cytochrome P450; EEG, electroencephalogram; FDA, US Food and Drug Administration; GA, gestational age; GABA, gamma-aminobutyric acid; ILAE, International League Against Epilepsy; LEV, levetiracetam; PNA, postnatal age; PK, pharmacokinetics; SV2A, synaptic vesicle glycoprotein 2A; Vd, volume of distribution

KEYWORDS antiseizure medications; children; levetiracetam; neonatal seizures; neonates; pharmacodynamics; pharmacokinetics

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Introduction

Seizures are the most common neurological dysfunction in neonates, affecting 1 to 4 neonates per 1000 live births.[1–4] Neonatal seizures are often an indication of some underlying disorders including hypoxic-ischemic encephalopathy, metabolic disturbances, and infection of the central nervous system.[1] While identifying and treating the cause of neonatal seizures are critical, seizures often require immediate attention because high seizure burden in neonates can lead to increased neurologic impairment and mortality.[5,6] As such, antiseizure medications (ASM) are initiated promptly to prevent further brain injury. Currently, phenobarbital is recommended as a first-line agent in neonatal seizures.[7] However, phenobarbital provides seizure control in fewer than half of the neonates.[8] Phenobarbital has been associated with major cognitive impairments in early developmental periods.[9,10] Due to the limited efficacy and serious safety concerns, another ASM, levetiracetam, is commonly used in neonates.

Levetiracetam improves seizure control and has an acceptable tolerability profile in children as young as 1 month old.[11,12] The dosing regimens of levetiracetam in children >1 month old were determined to achieve drug exposure that is similar to adults, largely by accounting for the pharmacokinetic differences due to well-described developmental changes.[11–13] However, the optimal dosing regimen of levetiracetam in neonates remain unknown. A recent randomized controlled trial concluded that levetiracetam was less efficacious than phenobarbital as a first-line agent for neonatal seizures but has better tolerability.[14] This study used a maximal levetiracetam dose of 60 mg/kg/day because it is the highest US Food and Drug Administration (FDA)-approved dose in any age group. Several retrospective studies reported that levetiracetam was at least as effective as phenobarbital as a first-line agent and had lower rates of adverse effects.[15–19] Though the evidence in the retrospective studies are not as rigorous as a randomized controlled trial, the wide range

of levetiracetam dosing (10–150 mg/kg/day) used in the retrospective studies may be a critical factor for the favorable levetiracetam efficacy, as a larger dose of levetiracetam has been associated with increased seizure control.[20] As the optimal use of levetiracetam in neonates remains elusive, this narrative review 1) evaluates the pharmacology, pharmacokinetics, and pharmacodynamics of levetiracetam, 2) discusses the evidence of levetiracetam use in neonatal seizures, and 3) discusses the information still needed to assess the efficacy and safety of levetiracetam in neonatal seizures.

Neonatal Seizures and Pharmacology of Levetiracetam

Neonates are more susceptible to seizures due to several age-related pathophysiologic factors.[9] For example, neonates have an increased number of N-methyl-D-aspartate (NMDA) receptors, resulting in a higher amount of neuronal glutamatergic excitatory signals.[21] Another type of glutamate receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, is also overexpressed in neonates. The immature AMPA receptors in neonates have enhanced calcium permeability, contributing to the increased neuronal excitability and other downstream signaling.[22] Additionally, neonates have an immature gamma-aminobutyric acid (GABA) neurotransmitter system. The activation of GABA receptors typically results in neuronal inhibition; however, the activation of GABA receptors of immature neurons may cause a neuronal membrane depolarization, rather than a hyperpolarization, leading to neuronal excitation.[23,24] Due to excess excitation and reduced inhibition of the immature neurons, neonates with insults to the central nervous system (CNS), such as hypoxic-ischemic encephalopathy and meningitis, have higher chances of seizures.[25]

Levetiracetam exerts its action primarily by binding to the synaptic vesicle glycoprotein 2A (SV2A), interfering with the ability of the vesicle to release excitatory neurotransmitters in presynaptic neurons.[26] Many other antiseizure mechanisms of levetiracetam have also been reported.[27] Levetiracetam may block the potassium and voltage-dependent calcium channels, decreasing the synaptic transmission. It may also modulate the glutamatergic AMPA receptors on postsynaptic neurons, diminishing the excitatory current. The SV2A protein was found to be expressed in the postmortem human neocortex of neonates with a gestational age (GA) of 20 to 37 weeks, providing the evidence that the target of levetiracetam is present in neonates.[28] However, the expression of SV2A was reduced in premature neonates (62% of adult values at 20 weeks GA and 81% at 27–32 weeks GA) and approached adult values near term birth (94% at 37 weeks GA).[28] The differential expression of SV2A may suggest a reduced efficacy or a different exposure-response relationship of levetiracetam in premature neonates. In addition to targeting SV2A, levetiracetam may exert its antiseizure effect by inhibiting AMPA receptors, which are overexpressed during early postnatal periods. The activation of AMPA receptors has been found to play a crucial role in rodent model of neonatal hypoxia-induced seizures.[28] A higher concentration of levetiracetam may be needed to inhibit the overexpressed AMPA receptors, thereby increasing the antiseizure effect of levetiracetam. Although the exact mechanisms are unknown, levetiracetam likely exerts its effects in neonatal seizures by acting on multiple targets. Due to the several pathophysiologic factors unique to seizures in neonates, the target levetiracetam systemic exposure may be different in neonates compared to infants and children with seizures.

Pharmacokinetics of Levetiracetam in Adults. The pharmacokinetics of levetiracetam are highly favorable when compared with many other ASM. In adults, absorption of enteral levetiracetam is rapid (maximum plasma concentration achieved within 1 hour), complete (bioavailability approximately 100%), and minimally affected by food.[29] Levetiracetam has a short elimination half-life of 6 to 8 hours, achieving the steady state within 24 to 48 hours of initiating therapy.[29] Levetiracetam is minimally bound to plasma protein (<10%) and has a volume of distribution (Vd) of 0.5 to 0.7 L/kg, which is similar to that of the total body water.[29] The clearance of levetiracetam is estimated at 0.96 mL/min/kg. The kidneys are the primary drug eliminating organ where 66% of the drug is excreted unchanged in the urine with significant renal tubular reabsorption. The remaining levetiracetam is likely metabolized by Type B esterase expressed in red blood cells and other tissues, with the primary levetiracetam metabolite (inactive; ucb L057) accounting for 24% of elimination.[30] Consistently, metabolism of levetiracetam by the hepatic cytochrome P450 (CYP) enzyme system is found to be minimal.[29] As such, the pharmacokinetics of levetiracetam was not affected by hepatic impairment and concurrent use of CYP enzyme inducers such as phenytoin and phenobarbital.[31] Interestingly, a few studies found that CYP enzyme inducers such as phenytoin and phenobarbital may increase the clearance of levetiracetam (24%–64%), resulting in a lower plasma concentration.[32–35] The concentrations of the ucb L057 metabolite (from hydrolysis by Type B esterase) were similar between patients treated with and without enzyme inducers, suggesting that Type B esterase was not induced by the enzyme inducers.[36] It may be postulated that the induction of the CYP enzymes—despite their insignificant role in levetiracetam clearance—may significantly increase the contribution of CYP enzymes in overall levetiracetam clearance. On the other hand, because levetiracetam is primarily eliminated by the kidneys,

adjustment of the maintenance dose is necessary in patients with renal impairment. It is not surprising that elderly patients require reduced dosage to reach therapeutic ranges of concentration due to a gradual decline in renal function through age.

Pharmacokinetics of Levetiracetam in Children. A summary of pediatric levetiracetam pharmacokinetic studies is provided in Table 1. As children grow and mature, the changes in organ functions and body composition can lead to alterations in pharmacokinetics.[37] For levetiracetam, absorption in children appears to be similar to that in adults, where it is rapid and complete.[31] Consistently, the reported mean oral clearance values[38–44] (i.e., clearance divided by bioavailability; range: 0.69–2.18 mL/min/kg) from pediatric studies using the oral formulation are generally comparable with mean clearance values[45,46] (range: 1.33–1.49 mL/min/kg) determined from pediatric studies using the intravenous formulation (Table 1). This suggests that the bioavailability of levetiracetam in children is close to 100%. The weight-normalized Vd was found to be similar in adults and children (0.5–0.7 L/kg; Table 1). This suggests that the Vd of levetiracetam changes proportionally with the body weight in infants (>1 month) and children. The similarity in weight-normalized Vd in adults and children may imply that a comparable weight-based loading dose of levetiracetam will result in similar initial plasma concentrations in both adults and children. The weight-normalized clearance of levetiracetam was found to be higher in children. Specifically, the mean clearance values (1.4–1.5 mL/min/kg; SD: 0.4 mL/min/kg)[39,44] in children 2 months to 12 years of age are about 50% higher than that of an adult (mean [SD]: 0.96 [0.14] mL/min/kg).[31] This observation is likely because the drug-elimination organs mature at a faster rate than the rate of weight gain in younger children. The higher weight-normalized clearance in children suggests that larger doses of levetiracetam are needed in children to achieve steady-state plasma concentrations comparable with those in adults. The differences in weight-normalized clearance observed in children and adults are reflected in the dosing regimens in the levetiracetam product label: 25 to 30 mg/kg twice daily is recommended for partial onset seizures in children 6 months to 16 years, whereas 1500 mg twice daily is recommended for adults (i.e., 21 mg/kg twice daily for a 70-kg person).

Pharmacokinetics of Levetiracetam in Neonates. Neonates undergo drastic physiological changes during the first few weeks of life. As such, the pharmacokinetic characteristics of many drugs change rapidly as the neonate grows older. Neonates generally have a greater proportion of extracellular and total body water. Correspondingly, neonates (median GA 38–39 weeks; median postnatal age [PNA] 2 days) were found to have an increased Vd of levetiracetam, a highly water-soluble compound, compared with adults (0.89–0.98 vs 0.5–0.7 L/kg; Table 1).[47,48] A median Vd of 1.41 L/kg (range: 1.01–2.96 L/kg) was reported by Jenjirattithigarn et al,[49] though the small sample size (8 neonates) and lower mean GA (34.5 weeks) could account for the difference. Overall, a higher Vd may suggest the need for a higher weight-based dose to attain initial concentrations similar to those of adults.

The clearance of levetiracetam was found to increase significantly in neonates during the first week of life. A study conducted by Sharpe et al[48] examined the changes of levetiracetam clearance over a 7-day period in 18 neonates <7 days PNA with corrected GA between 37 and 41 weeks. They found that clearance nearly doubled from 0.7 mL/min/kg (SD: 0.27 mL/min/kg) to 1.31 mL/min/kg (SD: 0.35 mL/min/kg), approaching the value reported in older children.[48] Interestingly, the mean clearance at day 7 of levetiracetam use in these neonatal patients was higher than the clearance reported in adults (1.31 vs 0.96 mL/min/kg). The higher clearance of levetiracetam in term neonates were also reported in one other study (1.21 mL/min/kg).[47] Levetiracetam is primarily eliminated by the kidneys with significant tubular reabsorption, therefore the clearance of levetiracetam in neonates is likely affected by the maturation of kidneys. It may be speculated that their higher-than-adult clearance is a result of a reduced capacity for tubular reabsorption.[48] The concomitant use of phenobarbital in most neonates may also contribute to an increase in levetiracetam clearance. Enzyme-inducing drugs, such as phenobarbital and phenytoin, have been shown to increase the clearance of levetiracetam in children.[38,43,50] The inductive effects of phenobarbital and phenytoin on neonatal levetiracetam clearance are unstudied to our knowledge. Little is known about the activity of type B esterase, the enzyme responsible for levetiracetam metabolism, in neonates. Sharpe et al[48] observed a substantial increase in esterase activity between 12 and 36 hours, accounting for up to 30% of levetiracetam clearance by 36 hours of life. This relative contribution of metabolic clearance is similar to what is found in adults and older children. This may suggest that both renal and metabolic clearance of levetiracetam improve significantly during the first week of life, though the ability to accurately tease out the relative contribution of each route of elimination may be confounded by changes in the renal clearance of the metabolite during this time frame.

The rate and extent of levetiracetam oral absorption in neonates are mostly unknown because the neonatal pharmacokinetic studies used the intravenous formulation,[47–49] although its bioavailability in neonates is often assumed to be 100%. Also, the pharmacokinetics

Table 1. Summary of Levetiracetam Pharmacokinetics in Neonates and Pediatrics

References	Total N (% Male)	Age	Weight (kg)	Dose	Route	Volume of Distribution (Vd)*	Clearance (CL)†	Indication	Analytical and Sampling Method
Toublanc[38]	228 (52.6)	Median: 9.8 yr Range: 0.2–18 yr	Median: 32 Range: 6–89	Range: 10–40 mg/kg/day	Oral	$\frac{Vd}{F} = 21.4\ L \times \left(\frac{BW}{30\ kg}\right)^{0.898}$ (or 0.71 L/kg for a 30-kg child) CV: 19%	$\frac{CL}{F} = 2.18\ L/hr \times \left(\frac{BW}{30\ kg}\right)^{0.753} \times (1.22\ if\ EIAED)$ (or 1.211 mL/min/kg for a 30-kg child) CV: 19%	Partial-onset seizures	Gas chromatographic method with nitrogen-phosphorus detection; serial and sparse sampling
Pellock[39]	24 (62.5)	Mean: 9.4 yr SD: 2.2 yr	N/A	20 mg/kg single dose	Oral	Mean Vd/F: 0.72 L/kg SD: 0.12 L/kg	Mean CL/F: 1.43 mL/min/kg (or 0.0858 L/hr/kg) SD: 0.36 mL/min/kg	Partial-onset seizures	Validated gas chromatographic assays with nitrogen-phosphorous detection; serial sampling
Chhun[40]	170 (50.6)	Mean: 10.7 yr SD: 3.1 yr	Mean: 36.4 SD: 13.2	40 mg/kg/day	Oral	$\frac{Vd}{F} = 21.9\ L \times \left(\frac{BW}{33\ kg}\right)^{0.93}$ (or 0.66 L/kg for a 33-kg child) CV: 16.2%	$\frac{CL}{F} = 2.47\ L/hr \times \left(\frac{BW}{33\ kg}\right)^{0.89}$ (or 1.248 mL/min/kg for a 33-kg child) CV: 25.1%	Refractory epilepsy	High performance liquid chromatography by ultraviolet detection; sparse sampling
Fountain[41]	14 (57.1)	Mean: 10.2 yr SD: 2.2 yr	Mean: 35 SD: 12.2	20–60 mg/kg/day	Oral	N/A	Mean CL/F: 1.12 mL/min/kg (or 0.0672 L/hr/kg) SD: 0.19 mL/min/kg	Partial-onset seizures	Gas chromatographic assays with nitrogen–phosphorus detection; serial sampling
Tauzin[45]	194 (56.2)	Median: 8.9 yr Range: 0.04–18.9 yr)	Median: 26.8 Range: 2.8–95	Median: 35.1 mg/kg/day Range: 5–66.7 mg/kg/day	IV	$Vd = 80\ L \times \frac{BW}{26.8\ kg}$ (or 3.02 L/kg for a 27-kg child) CV: 88%	$CL = 2.4\ L/hr \times \left(\frac{BW}{26.8\ kg}\right)^{0.75}$ (or 1.493 mL/min/kg for a 27-kg child) CV: 46%	Unspecified	High-pressure liquid chromatography with ultraviolet detection; sparse sampling
Wang[42]	311 (51.4)	Mean: 6.34 yr Range: 0.5–14 yr	Mean: 25.2 Range: 5–70	Mean: 35.7 mg/kg/day Range: 5.1–62.5 mg/kg/day	Oral	Mean Vd/F = 12.1 L (or 0.48 L/kg for a 25-kg child) CV: 42.1%	$\frac{CL}{F} = 1.04\ L/hr \times \left(\frac{BW}{25\ kg}\right)^{0.567}$ (or 0.69 mL/min/kg for a 25-kg child) CV: 46.4%	Generalized, partial-onset, and undetermined epilepsy	High performance liquid chromatography; sparse sampling
Kim[46]	37 (48.6)	Median: 4.6 yr Range: 0.2–15 yr	Median: 18 Range: 3–87.5	20–30 mg/kg single dose	IV	$Vd = 8.55\ L \times \left(\frac{BW}{18\ kg}\right)^{0.87}$ (or 0.48 L/kg for an 18-kg child) CV: 22.4%	$CL = 1.44\ L/hr \times \left(\frac{BW}{18\ kg}\right)^{0.98}$ (or 1.33 mL/min/kg for an 18-kg child) CV: 16.4%	Acute, unprovoked seizures	High-performance liquid chromatography with tandem mass spectrometry; serial sampling

(Table cont. on page 174)

Table 1. Summary of Levetiracetam Pharmacokinetics in Neonates and Pediatrics *(cont.)*

References	Total N (% Male)	Age	Weight (kg)	Dose	Route	Volume of Distribution (Vd)*	Clearance (CL)†	Indication	Analytical and Sampling Method
Pokorná[43]	56 (44.6)	Median: 3.91 yr Range: 0.1–18 yr	Median: 15.3 Range: 3.7–161	Median: 47.8 mg/kg/day Range: 4.8–72.7 mg/kg/day	Oral	$Vd\left(L/kg\right) = -0.0185 \times Age\left(in\ years\right) + 0.8351$ (or 0.76 L/kg for a 4-year-old child) CV: 33%	$\frac{CL}{F}\left(L/hr/kg\right) = -0.0038 \times Age\left(in\ years\right) + 0.1464$ (or 2.18 mL/min/kg for a 4-year-old child) CL/F increased by 49% when valproate was use concurrently. CV: 43%	Epilepsy or non-epileptic seizures	High performance liquid chromatography with tandem mass spectrometry; sparse sampling
Glauser[44]	13 (53.8)	Mean: 1.66 yr SD: 1.2 yr	Mean: 10.2 SD: 3.4	20 mg/kg single dose	Oral	Mean Vd/F: 0.63 L/kg SD: 0.08 L/kg	Mean CL/F: 1.46 mL/min/kg (or 0.0876 L/hr/kg) SD: 0.42 mL/min/kg	Any form of epilepsy	Validated gas chromatographic assays with nitrogen-phosphorous detection; serial sampling
Merhar[47]	18 (56)	Median GA: 38 wk (range: 35–41 wk) Median PNA: 2 days (range: 0–32 days)	Median: 2 Range: 2–4.4	14–30 mg/kg bolus	IV	Median Vd: 0.89 L/kg Range: 0.37–1.26 L/kg	Median CL: 1.21 mL/min/kg (or 0.0726 L/hr/kg) Range: 0.47–2.89 mL/min/kg	Clinical or electrographic seizure	Liquid chromatography-electrospray tandem mass spectrometry; sparse sampling
Sharpe[48]	18 (50)	Corrected GA: 37–41 wk PNA: 1–5 days	2.5–4.7	20 or 40 mg/kg bolus followed by 5–10 mg/kg/day	IV	Median Vd = 0.98 L/kg Range: 0.81–1.24 L/kg	$CL = 0.97mL/min/kg \times \left(\frac{PNA}{5days}\right)^{0.399}$ (or 0.0582 L/hr/kg for a 5-day-old child) CV: 27%–38%	Persistent seizures after 20 mg/kg of phenobarbital	Liquid chromatography-tandem mass spectrometry; sparse sampling
Jenjirattithigarn[49]	8 (62.5)	Mean GA: 34.5 wk Range: 24–40 wk Mean PNA: 9.2 days Range: 0–24 days	Mean: 3.2 Range: 2.6–4.2	40 mg/kg single dose	IV	Median Vd: 1.41 L/kg Range: 1.01–2.96 L/kg	Median CL: 1.56 mL/min/kg (or 0.0936 L/hr/kg) Range: 0.81–3.24 mL/min/kg	Neonatal seizures	Liquid chromatography-tandem mass spectrometry; serial sampling

CV, coefficient of variation; GA, gestational age; IV, intravenous; N/A, not available; PNA, postnatal age

* Oral volume of distribution is reported as V/F.
† Oral clearance is reported as CL/F.

of levetiracetam in premature neonates is largely unknown. Renal function in premature neonates varies among those with different birth weight and gestational age.[51] Specifically, renal function at birth is lower among those with a lower birth weight; renal function after birth improves faster in neonates with older gestational age. This suggests that optimal maintenance dose of levetiracetam may depend on their prematurity, and dose adjustment may be needed over time.

Pharmacodynamics of Levetiracetam in Adults and Children

The dose-response and exposure-response relationship of levetiracetam have been reported in adults and children with partial onset seizures. In 4 double-blind placebo-controlled trials, Snoeck and Stockis[52] found that both the placebo and levetiracetam reduced seizure frequency over a period of 16 to 24 weeks in adult refractory epileptic patients with partial onset seizures who received levetiracetam therapy as an add-on treatment.[52] They found that 59% patients who received placebo had a lower number of seizures compared with baseline. The proportion of improving patients was approximately 75% among those who received levetiracetam treatment. The proportion of improving patients increased slightly (from 72% to 77%) with increasing daily levetiracetam dose (from 1 g/day to 3 g/day). Rhee et al[53] evaluated the effect of levetiracetam dose and concentration on seizure occurrence among adult patients who received levetiracetam with or without other ASM. They reported that among patients receiving 500 to 3000 mg of daily levetiracetam dose, 34% to 71% of patients were seizure free. However, a higher total daily dose and plasma concentration were not associated with a higher proportion of seizure-free patients. They suggested that the seizure response to levetiracetam may be all-or-none, where patients with seizures that are not controlled after titrating to 2 g/day may require a change of ASM with a different mechanism of action. Based on the dose-response relationship evaluated in the abovementioned studies by Snoeck and Stockis[52] and Rhee et al,[53] larger doses of levetiracetam did not provide a clear benefit in adult patients with partial onset seizures.

Dose-response relationship is valuable for determining optimal dose of drugs with relatively low pharmacokinetic variability. For drugs with large interpatient pharmacokinetic variability, the same dose may result in different exposures (trough concentration, area under the concentration-time curve [AUC], or average concentration) in different patients. In such cases, exposure-response relationship is more informative to help individualize dosing regimen. Similarly, exposure-response relationship is more helpful to determine optimal dosing in patients who have different physiological variables, such as children and patients with organ dysfunction. In a recent study, Mehrotra et al[54] performed exposure-response analyses of add-on ASM including levetiracetam for treatment of partial onset seizures, using adult and pediatric phase 3 clinical trial datasets available at the FDA. They found that in adults and children >4 years of age, the relationship between the levetiracetam average plasma concentration and the percentage change from baseline (%CFB) in seizure frequency could be described using a log-linear model. The baseline seizure frequency was determined over an 8- to 12-week period prior to levetiracetam use, and the %CFB was calculated based on the weekly seizure frequency during levetiracetam treatment period. In this model, the %CFB was −45%, −52%, −58%, −64%, and −67% when the average concentration was 0 mg/L (placebo), 10 mg/L, 20 mg/L, 30 mg/L, and 40 mg/L, respectively. They found that the effect of levetiracetam on the %CFB did not differ between adults and children ($p = 0.25$).

Schoemaker et al[55] performed PK/PD modeling on levetiracetam in adults and children using datasets from placebo-controlled phase 3 clinical trials, where levetiracetam was used as add-on treatment for refractory partial onset seizures. They also found that the levetiracetam concentration-effect relationship was similar in adults and children >4 years of age. In this study, they reported that adult and pediatric patients who receive levetiracetam were generally divided into 2 populations: placebo-like population (66%) and responder population (34%). The placebo-like population had a 15% reduction in daily seizure frequency following levetiracetam treatment. Such reduction in seizure frequency was similar to patients who were randomized to the placebo group. In the responder population, a higher levetiracetam concentration was associated with greater reduction in seizure frequency (up to a maximum of 96% reduction), and a levetiracetam concentration of 31.4 mg/L would reduce the seizure frequency by 48% (half of the maximum levetiracetam effect). The authors reported that there was no significant difference in the relationship between levetiracetam concentration and the reduction of seizure frequency in adults and children.

The analyses of clinical trial data from both Mehrotra et al[54] and Schoemaker et al[55] showed that the concentration-effect relationship of levetiracetam is similar in adults and children >4 years old. To achieve a similar antiseizure effect, dosing of levetiracetam in children can be derived by accounting for the pharmacokinetic differences between children and adults. This is consistent with the findings reported by Pellock et al[13] that show similarity in pathophysiology of partial onset seizures in adults and children down to 2 years of age. In May 2020, at the Epilepsy Foundation Research Roundtable for Epilepsy, researchers further showed that in patients 1 month to <2 years of age, the partial onset seizure characteristics and symptoms, the features of electroencephalogram, the progression of disease, and the response to ASM were similar to children >2 years of age.[54] Consistently, a randomized, placebo-controlled trial demonstrated the efficacy of levetiracetam in children with partial onset seizures as young as 1 month old.[11] Extrapolating the efficacy of ASM for partial onset seizures from adults to children and infants can help avoid additional dose-finding studies in young children. In general, studies to assess pharmacokinetics and safety in the extrapolated

population are still needed. Although the concentration-effect relationship of levetiracetam has been determined in adults and children with partial onset seizures, the therapeutic range is not well-defined due to large patient-to-patient variability.[56,57] Also, as reported by Schoemaker et al,[55] the concentration-effect relationship may only be observed among responders and not in nonresponders. As such, therapeutic drug monitoring for levetiracetam is not performed routinely in clinical practice.

Efficacy of Levetiracetam in Neonatal Seizures

The evidence of efficacy and pharmacodynamics of levetiracetam in neonatal seizures remain scarce. A nice review of levetiracetam in neonatal seizures by Mruk et al[58] has been previously published in this journal. More recently, the Neonatal Task Force of the International League Against Epilepsy (ILAE) conducted a systematic literature review (up to June 2020) of neonatal seizure management.[7] It is recommended that phenobarbital should be used as the first-line ASM, and levetiracetam may be considered as a second-line agent.[7] Levetiracetam may be the preferred second-line agent in neonates with cardiac disorders.[7] Table 2 includes a summary of the efficacy, effectiveness, and safety of levetiracetam in neonatal seizures. The recommendation by the ILAE Task Force regarding the levetiracetam use was primarily supported by a recent randomized controlled, phase 2b clinical trial. In the trial (NEOLEV2), levetiracetam and phenobarbital were compared as first-line agents for neonatal seizures confirmed by continuous electroencephalogram (EEG).[14] Study neonates were either treated with an initial dose of 40 to 60 mg/kg of levetiracetam or 20 to 40 mg/kg of phenobarbital. Phenobarbital was found to be more efficacious in 24-hour seizure freedom when compared with levetiracetam (80% vs 28%, $p < 0.001$). However, a slight improvement (7.5%) in seizure control was observed when levetiracetam was increased from 40 mg/kg to 60 mg/kg. The initial loading dose of 40 mg/kg of levetiracetam was determined to achieve a trough of >20 mg/L in majority of neonates.[48] This target concentration was based on therapeutic concentration of levetiracetam determined from adult and pediatric populations. However, the target concentration remains unknown for complete seizure control in neonates. A dose-ranging study may be needed to determine whether levetiracetam is truly ineffective in neonatal seizures or if larger doses may produce favorable outcomes. In fact, the investigators of NEOLEV2 are conducting a dose escalation study (NCT05610085) that will examine the efficacy and safety of levetiracetam in doses from 60 mg/kg to a maximum dose of 150 mg/kg. Furthermore, given the large variability in neonatal pharmacokinetics, determining the concentration-response relationship, rather than dose-response relationship, would be most helpful in finding optimal dosing regimens for levetiracetam in neonatal seizures.

Unlike the NEOLEV2 trial, other studies that evaluated the effectiveness of levetiracetam in neonatal seizures were observational trials (Table 2). These studies included varying study outcome measures and dosing regimens, with most loading doses being less than 60 mg/kg.[14,17–19,59–65] The achievement of seizure freedom ranged from 26% to 57% among neonates who received levetiracetam as the first-line ASM for varying duration (Table 2). Rao et al[62] reported that levetiracetam, as opposed to phenobarbital, as the first-line ASM may shorten the time to reach seizure freedom (adjusted hazard ratio: 2.57, $p = 0.01$). Due to the nature of the retrospective observational study design, these studies are limited by the risk of bias.

Some evidence has suggested that larger doses of levetiracetam (>60 mg/kg) may be needed in neonatal seizures. A retrospective cohort study by Verwoerd et al[66] examined the use of levetiracetam (50–100 mg/kg loading dose) and phenobarbital (20 mg/kg) as a first-line treatment for neonatal seizures. They found that levetiracetam and phenobarbital resulted in similar percentage of patients (63%–65%) having a sustained seizure burden <10% (<6 minutes of electrographic seizure per 1-hour period). The use of phenobarbital as the first-line agent resulted in a larger absolute reduction in average seizure burden (−24.3 vs −14.2 min/hr) an hour before and after the treatment. Conversely, the use of levetiracetam as the first-line agent led to a shorter average time to achieve seizure freedom (15 vs 21 hours). It should be noted that this study only included 25 neonates and the results were not statistically significant. However, initial cumulative bolus doses of levetiracetam up to 100 mg/kg were found to be well tolerated. This is consistent with the safety profile reported by Venkatesan et al,[20] who reported no adverse side effects in cumulative bolus doses of levetiracetam up to 120 mg/kg for the treatment of seizures in neonatal hypoxic-ischemic encephalopathy. In addition to the dosing of levetiracetam, the effectiveness of levetiracetam for neonatal seizures may be affected by the prior use of benzodiazepine. A retrospective cohort study by Wagner et al[67] found that, as compared with neonates without prior benzodiazepine exposure, neonates with prior benzodiazepine exposure had a higher seizure resolution rate when treated with phenobarbital but a lower seizure resolution rate when treated with levetiracetam. This finding may be a result of pharmacodynamic interactions; however, the differential response may also stem from differences in disease severity between those who did and did not receive benzodiazepine treatment. It should also be noted that, like phenobarbital, prolonged benzodiazepine exposure (>7 days) is associated with negative neurodevelopment outcomes.[68]

Table 2. Efficacy, Effectiveness, and Safety of Levetiracetam Used as First- or Non-First-Line Agent for Neonatal Seizures

References	Study Design	Total N (% Male)	Age	Weight (kg)	Primary Outcome (Monitored By)	Dose	Concomitant or Prior ASM	Efficacy/ Effectiveness	Safety
Sharpe[14]	Randomized controlled trial	First-line: 64 (48) Second-line (after PB): 6 (unspecified)	Mean GA: 39.3 wk SD: 1.3 wk PNA: <14 days	Birth weight, mean: 3.33 SD: 0.55	Complete seizure freedom for 24 hr (cEEG)	LD 40–60 mg/kg MD 10 mg/kg every 8 hr	None (n = 64); after PB (n = 6)	First-line: 28% Second-line: 17%	4 of 64 experienced grade 4 or 5 unspecified AE or SAE*
Thibault[59]	Retrospective	First-line: 22 (45) Second-line (after PB): 7 (unspecified)	Median GA: 38 wk IQR: 37–39 wk PNA: ≤30 days	Birth weight, median: 3.1 IQR: 2.3–3.5	Seizure cessation within 72 hr (cEEG)	Initial dose: median: 30 mg/kg IQR: 20–40 mg/kg Total 72-hr dose: median: 45 IQR: 30–51 mg/kg	Concomitant MDZ (9%), ketamine (27%) with first-line LEV	First-line: 55% Second-line: 30%	No AE reported
Kurtom[60]	Retrospective	61 (77)	Mean GA: 24.6 weeks Range: 22–28 wk PNA: unspecified	Birth weight, mean: 0.67 Range: 0.43–0.91	Seizure cessation at 12–24 hr (EEG)	LD: 40–80 mg/kg MD: 40–80 mg/kg/day	None	First-line: 26%	No AE reported
Han[61]	Retrospective	37 (49)	Mean GA: 31.5 wk SD: 1.9 wk PNA: ≤28 days	Birth weight, mean: 1.84 SD: 0.10	Seizure cessation for 7 days (cEEG)	LD: 40–60 mg/kg MD: 20–30 mg/kg twice daily	None	First-line: 57%	No AE observed
Rao[62]	Retrospective	20 (70)	Median GA: 39 wk IQR: 37.5–40.4 wk PNA: unspecified	Birth weight, median: 3.12 IQR: 2.84–3.46	Time to seizure freedom (cEEG)	LD: 20–30 mg/kg MD: 35–60 mg/kg/day	None	First-line: shorter interval to seizure freedom in LEV compared with PB; hazard ratio = 2.58, p = 0.007	No AE reported
Glass[63]	Prospective observational	611 (63)	Range: GA <28 wk to GA <37 wk PNA: unspecified	Not reported	Seizure cessation after initial dose (cEEG)	Not specified	Not reported	First-line: 42%	No AE reported
Yau[64]	Retrospective	12 (50)	Mean GA: 34.9 wk Range: 24–40 wk PNA: 0–19 days	Not reported	Seizure cessation after 24 and 72 hr (EEG)	LD: 7:5–20 mg/kg MD: 5–60 mg/kg/day	After PB, MDZ, and/or THI	Non-first-line: 58% by 24 hr 75% by 72 hr	No AE observed
Rakshasbhuvankar[65]	Retrospective	8 (62.5)	Mean GA: 34 wk Range: 22–37 wk PNA: unspecified	Not reported	>80% seizure reduction (aEEG)	LD: 5–10 mg/kg MD: 10–35 mg/kg/day	After PB, PHT, MDZ, and/or CZP	Non-first-line: 75%	No AE observed

(Table cont. on page 178)

Table 2. Efficacy, Effectiveness, and Safety of Levetiracetam Used as First- or Non-First-Line Agent for Neonatal Seizures *(cont.)*

References	Study Design	Total N (% Male)	Age	Weight (kg)	Primary Outcome (Monitored By)	Dose	Concomitant or Prior ASM	Efficacy/ Effectiveness	Safety
Khan[18]	Retrospective	12 (42)	Mean GA: 32.4 wk SD: 4.3 wk PNA ≤28 days	Birth weight, mean: 1.98 SD: 0.69	Seizure cessation at 24 hr (EEG)	LD: 25–50 mg/kg MD: 25 mg/kg twice daily	After PB (n = 9); none (n = 3)	First- or non-first-line: 82%	No AE observed
Khan[19]	Retrospective	22 (45)	Mean GA: 39.3 wk SD: 1.0 wk PNA ≤28 days	Birth weight, mean: 3.42 SD: 0.57	Seizure cessation at various time points (EEG)	LD: 10–50 mg/kg MD: 20–75 mg/kg/day	After PB, PHT, LOR, and/or MDZ; none (n = 3)	First- or non-first-line: 64% by 24 hr 100% by 48 hr	One patient experienced irritability
Abend[17]	Retrospective	23 (48)	Mean GA: 38.7 wk SD: 1.7 wk PNA: 14 days SD: 13 days	Not reported	>50% seizure reduction within 24 hr (cEEG)	LD: 5–22 mg/kg MD: 10–80 mg/kg/day	After PB, PHT, and/or TPM; none (n = 4)	First-line (n=4): 25% Non-first-line: 37%	No AE observed

AE, adverse event; ASM, antiseizure medications; cEEG, continuous EEG; CZP, clonazepam; EEG, electroencephalogram; GA, gestational age; LD, loading dose; LEV, levetiracetam; LOR, lorazepam; MD, maintenance dose; MDZ, midazolam; PB, phenobarbital; PNA, postnatal age; PHT, phenytoin; SAE, serious AE; THI, thiopental; TPM, topiramate

* Less serious AEs such as hypotension, respiratory suppression, and requirement for pressor support were reported to be less common in LEV than PB.

Safety of Levetiracetam in Neonates. Most neonates who received levetiracetam did not experience adverse events; less than 5% experienced mild adverse events such as irritability and somnolence (Table 2).[7,19,47] Additionally, levetiracetam is associated with less adverse events when compared with phenobarbital. In the NEOLEV2 trial, Sharpe et al[14] reported that neonates who received phenobarbital experienced more serious adverse events, such as hypotension, respiratory suppression, sedation, and requirement for pressor support. Similarly, in a retrospective cohort study Bättig et al[15] found that 25% of 75 neonates given phenobarbital experienced serious adverse events; however, only one out of 33 neonates (3%) treated with levetiracetam experienced such effects. Furthermore, the safety of short-term and long-term phenobarbital use has been a concern because it has been shown to induce neuronal apoptosis in animal models and depress cognitive performance in children.[69,70] In animal models, single-dose and repeated dosing (over 36 hours) of phenobarbital and phenobarbital/midazolam combination at therapeutically relevant concentrations resulted in significant apoptotic neurodegeneration in the neonatal brains.[69,71] It is unclear whether the results from animal studies are translatable to human neonates following 1 to 2 weeks of phenobarbital exposure. Given the clinical data suggesting a correlation between phenobarbital and long-term negative neurodevelopment consequences, there is a need to explore other safer options. In contrast, levetiracetam has not shown such detrimental effects.[72] These highlighted studies demonstrate the promising safety profile of levetiracetam in neonates. However, it is important to note that many studies lack safety data or fail to analyze the data in a standardized manner.[7] There is a need for future studies to include long-term safety data in a systemic manner, especially in this vulnerable population.

Discussion and Future Directions

More effective and safe treatments of neonatal seizures are desperately needed. Despite the unfavorable levetiracetam treatment outcomes in the NEOLEV2 trial, critical information such as the pharmacodynamics (concentration-effect relationship) of levetiracetam in larger doses is still needed to confirm its efficacy or lack thereof. Levetiracetam has been shown to be safe and effective in children; however, most pharmacokinetic and pharmacodynamic data of levetiracetam in pediatrics are from children with partial onset seizures. Furthermore, the pathophysiology of seizures in neonates are different from that in children and adults. The treatment goals for neonatal seizures are also different from those for seizures in children and adults. In children with partial onset seizures, the desired clinical outcome for ASM treatment is typically a reduction in seizure frequency over a period of time. ASM treatment is usually long-term and may be discontinued if the child remains seizure free for two years on monotherapy. In neonates, most neonatal seizures are acute provoked seizures, and the primary goal is to achieve complete control of seizures within 1 to 2 days of starting ASM

treatment. A loading dose of the first line ASM is given initially, and an additional loading dose may be used if seizure activity persists after 30 minutes. Maintenance doses follow the loading doses, and a second-line agent may be added if the first-line agent fails.[5] The ASM may be discontinued after 72 hours of seizure freedom, prior to hospital discharge.[7,73]

To achieve complete seizure control within a short amount of time (1–2 days) in neonatal seizures, the target levetiracetam concentration may differ from that targeted for children with partial onset seizures. In children 4 to 15 years of age with partial onset seizures, the therapeutic dose of 60 mg/kg/day resulted in the average levetiracetam plasma concentration of 33 mg/L (IQR: 29–36 mg/L).[54] This plasma levetiracetam concentration range observed in children is similar to that found in adult patients with partial onset seizures (mean: 32.3 mg/L; IQR: 30–35 mg/L) and those with status epilepticus (mean: 25.8 mg/L; range: 19.4–49.2 mg/L) who responded to levetiracetam therapy.[54,57] This plasma concentration range may not be enough for complete seizure control in neonatal seizures. The effective concentration of levetiracetam may also differ when other ASM are used concomitantly. Additionally, the differential expression of the molecular target of levetiracetam SV2A in neonates with different gestational age may further contribute to the variability in levetiracetam treatment response.[28]

Further pharmacokinetic and pharmacodynamic information are needed for levetiracetam in neonates to individualize the optimal dosing regimen. As the pharmacokinetics of neonates undergo dramatic changes during the first few weeks of life, optimal dosing of levetiracetam may vary significantly for neonates with different ages and/or body weights. For example, the clearance of levetiracetam in neonates nearly doubles during the first week of life, which may result in significantly different plasma concentrations if the same dosing regimen is used. Approaches like physiologically based pharmacokinetic modeling may offer invaluable insights on how the intertwined relationship among age (gestational and postnatal), weight, and organ growth and maturation may affect the distribution and elimination of levetiracetam. Furthermore, the optimal dosing regimen for levetiracetam in neonatal seizures is determined by the target plasma concentrations, which could differ from those used in levetiracetam therapy for seizures in children and adults. As such, it is necessary to determine the relationship between the levetiracetam plasma concentration and its antiseizure effect in neonatal seizures. The use of video EEG monitoring to measure seizure burden and qualify seizure freedom may further allow the quantification of the concentration-effect relationship. Long-term neurodevelopmental effects of levetiracetam vs phenobarbital should also be evaluated. This may further demonstrate the significance of drug selection in the early neonatal period. In conclusion, the additional information on levetiracetam may help determine whether it is a safer first-line alternative for treating neonatal seizures.

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