

REVIEW ARTICLE

A Systematic Review of the Pharmacokinetics of Antiepileptic Drugs in Neonates With Refractory Seizures

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BACKGROUND Neonatal seizures are associated with neurological sequelae and an increased risk of epilepsy later in life. Phenobarbital and phenytoin remain the antiepileptic drugs (AEDs) most commonly used to treat neonatal seizures, despite their suboptimal effectiveness and safety. As a result, other AEDs, such as levetiracetam and topiramate, are often used in neonates with refractory seizures, despite limited data and off-label use.

OBJECTIVES To systematically review published pharmacokinetic data for second-line AEDs used in neonates with seizures and to provide dosing recommendations for these agents in the neonatal population.

METHODS A literature search was conducted in PubMed (1949-May 2012), Medline (1950-May 2012), and Embase (1980-May 2012). Each study was ranked according to the quality of evidence it provided, based on the classification system developed by the US Preventive Services Task Force. Information extracted from each study included study design, number of subjects, gestational and postnatal age, AED dosage regimen, pharmacokinetic parameters, pharmacokinetic model, AED serum concentrations, and sampling times.

RESULTS Nineteen relevant pharmacokinetic studies involving a total of 8 different drugs were identified. No prospective, randomized, controlled studies (level I evidence) or nonrandomized controlled studies (level II-I evidence) were identified; 2 studies were prospective, nonrandomized, uncontrolled (cohort) studies (level II-2 evidence), 11 studies obtained evidence from multiple time series (level II-3 evidence), and 6 studies were case reports or descriptive studies (level III evidence).

CONCLUSIONS There are limited pharmacokinetic data for the use of carbamazepine, levetiracetam, lidocaine, paraldehyde, topiramate, valproic acid, and vigabatrin for neonates with seizures refractory to treatment with first-line antiepileptic agents. Further research is needed to elucidate target AED serum concentrations (if any) required to optimize effectiveness and minimize dose-related adverse effects in neonates.

INDEX TERMS anticonvulsants, antiepileptics, neonate, pharmacokinetics

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INTRODUCTION

Neonatal seizures are associated with neurological sequelae (including motor and cognitive deficits) and an increased risk of epilepsy later in life.¹ The estimated incidence of neonatal seizures ranges from 1 to 3.5 cases per 1000 live births in term neonates and from 58 to 132 cases per 1000 live births in premature infants (<38 weeks postconceptual age).² Despite the high incidence of seizures and potential

sequelae, there are currently no evidence-based guidelines for the management of neonatal seizures.³

Phenobarbital, phenytoin, and benzodiazepines remain the most common treatment modalities for treating neonatal seizures.⁴ However, a randomized controlled trial by Painter et al.⁵ comparing phenobarbital and phenytoin as first-line agents for seizures in neonates found that greater than 50% of neonates treated with either phenobarbital or phenytoin continued to have evidence of abnormal electrical activity. When both phenobar-

Table 1. US Preventative Services Task Force¹¹

Level of Evidence	Description
I	Evidence obtained from at least one properly randomized controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case-control analysis studies, preferably from more than one center or research group
II-3	Evidence obtained from multiple time series with or without the intervention or dramatic results in uncontrolled experiments
III	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees

bital and phenytoin were administered together, electrical control of seizures was achieved in only 60% of neonates. Furthermore, there is concern regarding possible adverse effects of phenobarbital and phenytoin on developing neuronal cells and proliferation of cortical neurons.⁶ As a result, other antiepileptic drugs (AEDs), such as levetiracetam and topiramate, are used in neonates with refractory seizures despite limited data and off-label use.^{3,7} The pharmacokinetics of AEDs in infants and children has been reviewed previously.⁸⁻¹⁰ However, the limited pharmacokinetic data regarding the administration of AEDs in neonates are provided in this review. Given the physiological differences in neonates (including but not limited to changes in gastric and intestinal pH, gastrointestinal motility, total body water-to-fat ratios, concentration and affinity of plasma binding proteins, drug metabolizing enzyme activity, and renal function), the pharmacokinetics of AEDs in this patient population are expected to vary profoundly.¹⁰ This paper systematically reviews the published pharmacokinetic data of second-line AEDs used in neonates with seizures and provides dosage recommendations for these agents in the neonatal population.

LITERATURE SEARCH

A literature search was conducted in PubMed (1949-2012), Medline (1950-May 2012), and Embase (1980-May 2012), using the following search terms: neonate or newborn, anticonvulsant or antiepileptic agent, and pharmacokinetics. The search was limited to articles published in English and using human subjects. Excluded were studies describing the pharmacokinetics of AEDs in neonates acquired from transplacental exposure and studies describing the pharmacokinetics of phenobarbital, phenytoin, or benzodiazepines

(first-line treatments). The reference lists of all relevant articles were manually searched for pertinent studies not identified in the electronic search.

Each study was ranked according to the quality of evidence it provided based on the classification system developed by the US Preventative Services Task Force (Table 1).¹¹ Information extracted from each study (where available) included study design, number of subjects, gestational and postnatal age, AED drug regimen (i.e., drug, dosage, route, duration), pharmacokinetic parameters (i.e., clearance and/or area under the concentration-time curve [AUC], volume of distribution, and elimination half-life), pharmacokinetic model, AED drug levels, and sampling times.

Nineteen relevant pharmacokinetic studies were identified. No prospective, randomized, controlled studies (level I evidence) or nonrandomized controlled studies (level II-1 evidence) were identified; 2 studies were prospective, nonrandomized, uncontrolled (cohort) studies (level II-2 evidence),^{25,26} 11 studies obtained evidence from multiple time series (level II-3 evidence),^{14-16,20,21,27,29,35,37,38,43} and 6 studies were case reports or descriptive studies (level III evidence).^{22,30,39-42} The pharmacokinetic parameters reported for the 19 studies (7 drugs) are summarized in Table 2.

CARBAMAZEPINE

Carbamazepine prevents repetitive firing of action potentials in depolarized neurons by blocking frequency, use, and voltage-dependent sodium channels.¹² It is currently available only as an oral agent. An intravenous (IV) formulation has been developed and is being studied in phase III clinical trials. Carbamazepine is metabolized in the liver to carbamazepine 10,11-epoxide (carbamazepine epoxide).⁹ Conversion is mediated primarily by cytochrome (CYP) 3A4 (with minor metabolism

Table 2. Summary of Dosages and Pharmacokinetic Parameters

Drug	n	Dosage Studied		T_{max} (hr)*	Cp (mg/L)*	Vd (L/kg)*	CL (mL/min/kg)*	$T_{1/2}$ (hr)*
		LD (route)	MD (route)					
Carbamazepine	22	5-20 mg/kg (po)	9-21 mg/kg/day (po)	6.8 (2-16)	Cp _{max} : 6.7 (3.2-9.9) Cp _{ss} : 2.3-19.9	1.21 (0.64-2.5)	0.67 (0.09-0.85)	14.2 (4.7-60.2)
Levetiracetam	23	14.4-40 mg/kg (IV) 60 mg/kg (po)	- 30 mg/kg/day (po)	- NR	Cp _{max} : 55 (14.8-91.9) Cp _{ss} : 21 (11-31)	0.83 (0.37-1.26)	0.88 (0.43-2.89)	13.2 (3.2-21)
Lidocaine	120	1.5-2.2 mg/kg (IVF)	1-7 mg/kg/hr (IV)	-	Cp _{max} : NR Cp _{ss} : 5.74 (0.8-19)	3.1 (3-3.2)	13.4 (7.7-28)	5.3 (5.2-5.4)
Paraldehyde	9	150 mg/kg/hr × 3 hr (IVF)	-	-	Cp _{max} : 247 ± 23	1.73 (1.1-3.1)	2 (0.74-4.7)	10.2 (7.6-17.4)
Topiramate	13	5 mg/kg (po)	-	3.8 ± 2.2	Cp _{max} : 17.96 ± 4.2 Cp _{min} : 10.35 ± 2.5	NR	0.26 ± 0.08	35.6 ± 19.3
Valproic Acid	12	20-25 mg/kg (po) 20-30 mg/kg (pr) 10-25 mg/kg (IV)	10-20 mg/kg/day (po) 30 mg/kg/day (pr) -	1.5-3 NR -	Cp _{max} : NR 36.5 (35-38) 51.6 (35-78) Cp _{ss} : 27-61 (po)	0.29 (0.24-0.36)	0.32 (0.1-0.48)	21.7 (8.6-48.5)
Vigabatrin	6	125 mg (po)	250 mg/day (po)	2.1 (0.6-3.2)	14 (7.3-20.8)	NR	NR	7.5 (4.1-10.3)

Cp, concentration; CL, clearance; Cp_{max}, maximum concentration achieved; Cp_{min}, minimum concentration achieved; Cp_{ss}, steady-state concentration; NR, not reported; IV, intravenous; IVF, intravenous infusion; LD, loading dose; MD, maintenance dose; n, number of patients studied; po, oral administration; pr, rectal administration; PK, pharmacokinetic; T_{max}, time to reach maximum concentration; T_{1/2}, half life; Vd, volume of distribution

* Data are means ± SD or SEM (range)

by CYP1A2 and CYP2C8). The active epoxide metabolite is hydrolyzed to an inactive diol metabolite that is renally eliminated. Furthermore, carbamazepine is known to induce its own metabolism through the epoxide-diol pathway. This appears to be a dose-related mechanism with onset as early as 24 hours and time to completion ranging from 1 to 5 weeks. Steady-state concentrations are therefore lower than those predicted from single-dose studies.¹³

Level II-3 Evidence

Singh et al¹⁴ evaluated the pharmacokinetics of carbamazepine monotherapy (Tegretol syrup; Ciba-Geigy Corp., Summit, New Jersey) in 10 term neonates. A loading dose of carbamazepine (10 mg/kg) was administered via a nasogastric tube in 10 consecutive neonates experiencing two or more seizures. Serum drug concentrations were drawn at 1, 2, 4, 8, 12, and 24 hours following the loading dose in the first 5 neonates and at 4, 8, 12, 16, 20, and 24 hours in the latter 5 patients. The pharmacokinetic model used to describe the data not reported.

Carbamazepine serum concentrations reached "acceptable therapeutic range for older children (4-9.8 mg/L)" within 2 hours in the first 5 neonates and within 4 hours (the time of first measurement) in the latter 5 neonates. A reference for this therapeutic range was not provided. Peak concentrations were achieved 4 to 16 hours after the oral loading dose and ranged from 7.1 to 9.9 mg/L. The elimination half-life ranged from 9.6 to 60.2 hours (mean, 24.5 hours). Maintenance therapy was initiated 24 hours after the loading dose, with a 7 mg/kg dose administered orally every 8 hours in the first 5 neonates and a 5 mg/kg dose administered orally every 8 hours in the latter 5 neonates. Serum drug concentrations ranged from 7.0 to 19.9 mg/L in the first 15 days. A decrease in carbamazepine serum concentration of between 2.3 and 4.8 mg/L was noted between day 8 and day 15 of maintenance therapy. No information was provided regarding the timing of the serum concentrations in relation to the dose.

Rey et al¹⁵ evaluated the pharmacokinetic parameters of carbamazepine following administration of a single oral dose (15-20 mg/kg) of crushed carbamazepine tablets to 6 neonates (gestational age not reported). Serum drug concentrations were drawn over the next 48 hours after administration of the dose. Pharmacokinetic parameters were derived using a 1-compartment model. Peak serum carbamazepine concentrations were achieved 2.3 to 6.8 hours after administration of the single oral dose. Concentrations ranged from 5.8 to 9 mg/L.

The elimination half-life ranged from 4.7 to 11.3 hours (mean, 7.8 hours).

MacKintosh et al¹⁶ evaluated the pharmacokinetics of carbamazepine in 6 neonates following administration of a smaller single oral dose (5 mg/kg) of carbamazepine suspension (prepared by the pharmacy at the institution). Serum drug concentrations were drawn at 2, 4, 6, 8, and 12 hours following the one dose. The pharmacokinetic model used to describe the data was not reported.

Peak serum concentrations were achieved 2 to 12 hours following administration of the carbamazepine dose with concentrations ranging from 3.2 to 5.3 mg/L. The elimination half-life ranged from 7.2 to 14.5 hours (mean, 10.3 hours). Maintenance therapy was then initiated with a 5 mg/kg dose administered orally every 12 hours, with doses adjusted as necessary to maintain serum concentrations between 2.4 and 9.6 mg/L. Subsequent trough serum concentrations (12 hours after the preceding dose) were monitored 3 to 15 days after initiating therapy. Five of the 6 neonates attained trough carbamazepine serum concentrations within the targeted therapeutic range with doses ranging from 4.6 to 8.1 mg/kg/dose administered every 12 hours.

Dosage Considerations

In neonates, limitations to the use of carbamazepine include (1) lack of a parenteral formulation; (2) low activity of isoenzyme CYP 3A4 at birth, increasing to approximately 20% of adult values at 1 month of age (although whether this impacts effectiveness is unknown); (3) epoxide hydrolase enzymes not fully developed and functioning; and (4) reduced renal elimination (potentially decreasing clearance of carbamazepine and the epoxide metabolite).¹⁷

Given the above-described limitations, determining an "ideal" carbamazepine dose for neonates is difficult. Initial loading doses studied ranged from 5 to 20 mg/kg and maintenance doses from 5 to 8 mg/kg/dose administered every 8 to 12 hours (9-21 mg/kg/day), with wide variations in serum concentrations.¹⁴⁻¹⁶ Singh et al¹⁴ noted a decrease in serum carbamazepine concentrations ranging from 2.3 to 4.8 mg/L between days 8 and 15 of maintenance therapy, with a more gradual decline noted over the next 3 months of therapy (specific values not provided). Increases in drug metabolizing capacity, which generally occurs (in a term neonate) around 1 week of life, likely explain the significant drop in serum concentrations.¹⁸ The continual decline in serum concentrations is most likely due to both autoinduction and continued maturation of CYP P450 enzymes in the neonate. However, it is

important to note that for the neonatal population, the desired “reference range” for carbamazepine (defined as the range of drug concentrations specifying a lower limit below which a therapeutic response is unlikely to occur and an upper limit above which toxicity is likely to occur) is not known.¹⁹

Practitioners must also be aware of drug interactions with carbamazepine. Rey et al¹⁵ and MacKintosh et al¹⁶ reported a significantly shorter mean elimination half-life of carbamazepine in neonates (7.8 and 10.3 hours, respectively) than Singh et al¹⁴ did (24.5 hours). This may be explained by enzyme induction by interacting medications, primarily phenobarbital and phenytoin. Five of the 6 neonates studied by MacKintosh et al¹⁶ received phenobarbital and/or phenytoin prior to treatment with carbamazepine, while all 6 neonates studied by Rey et al¹⁵ were receiving concomitant phenobarbital therapy; the neonates studied by Singh et al¹⁴ were treated with carbamazepine monotherapy as a first-line agent.

LEVETIRACETAM

Levetiracetam is the active, water-soluble *S*-enantiomer of racemic pyrrolidine acetamide. It is believed to act by a nonconventional mechanism, binding to the synaptic vesicle protein within the brain.²¹ In the United States, levetiracetam is available both as an oral and as an IV agent. In Canada, it is currently available only in the oral form. Levetiracetam is not bound to plasma proteins.¹⁹ Unlike other AEDs that are metabolized, the metabolism of levetiracetam does not include the CYP P450 system. Two-thirds of the dose is eliminated unchanged in the urine while approximately one-third is hydrolyzed in the blood and various tissues into 3 inactive metabolites that are renally excreted.¹⁹

Level II-3 Evidence

Merhar et al²⁰ prospectively evaluated the pharmacokinetic of levetiracetam following the administration of a single IV loading dose in 19 neonates (both term and preterm). Three serum drug concentrations were collected in each patient (times not specified). A non-linear fixed effects model was used to analyze the pharmacokinetic data with a 2-compartment model with first order elimination used to describe the data. Individual Bayesian pharmacokinetic parameter estimates were then used to determine the pharmacokinetic parameters for each neonate. The loading dose of levetiracetam was chosen by the prescribing physician and ranged from 14.4 to 39.9 mg/kg. Peak serum concentrations (1 hour after the loading

dose) ranged from 14.8 to 91.9 mg/L (median, 39.8 mg/L). The median volume of distribution was 0.89 L/kg, median clearance 1.21 mL/min/kg and median elimination half-life 8.9 hours. Blonk et al²¹ evaluated the pharmacokinetics of levetiracetam in 2 neonates with seizures refractory to a total dose of 40 mg/kg of phenobarbital and 0.5 mg/kg of midazolam (total dose). Levetiracetam was administered by IV route at a dose of 20 mg/kg over 5 minutes. In case of continuing seizures, an additional 20 mg/kg dose of levetiracetam was administered approximately 10 minutes after the end of the first infusion. Serum concentrations were drawn at 5, 15, 20, 30, and 60 minutes and at 2, 4, 8, 12, 24, 36, 48, 60, and 78 hours after the start of infusion. A 3-compartment pharmacokinetic model was used to describe the data.

A linear concentration-time profile was obtained, with a peak serum concentration of approximately 70 mg/L in each neonate following the administration of a total IV dose of 40 mg/kg of levetiracetam. Mean volume of distribution was 0.76 L/kg, mean clearance was 0.53 mL/min/kg, and mean elimination half-life was 17.5 hours. Both neonates required an additional dose of levetiracetam, 20 mg/kg, for continuing seizures 10 minutes after the end of the first infusion (total dose of 40 mg/kg). The clinical outcomes of the 2 neonates were not reported.

Level III Evidence

A case series described the pharmacokinetics of levetiracetam in 2 neonates who had received oral levetiracetam for the treatment of refractory seizures.²² A 42-week gestational neonate was administered a levetiracetam bolus (60 mg/kg) via an orogastric tube after phenobarbital and phenytoin failed to control the patient's seizures. Clinical and electroencephalographic (EEG) cessation of seizures were reported within 17 minutes of the levetiracetam bolus. The neonate was maintained on a dosage of 30 mg/kg/day. A trough concentration at discharge was 31 mg/L (the reference range in adults is 10-40 mg/L).¹⁹ A second neonate, born at 26 weeks gestation, developed seizures on day 5 of life. Levetiracetam was administered via orogastric tube at a dosage of 30 mg/kg/day following inadequate seizure control with fosphenytoin. A levetiracetam trough concentration 1 week after therapy was initiated was 11 mg/L. At 1 year of life, the infant remained seizure free on levetiracetam monotherapy and showed normal EEG results.

Dosage Considerations

The availability of an IV formulation (in the United States), excellent oral bioavailability (as

described in adults),¹⁹ lack of plasma protein binding, and CYP P450-independent metabolism make levetiracetam an attractive antiepileptic agent for use in neonates. Unfortunately, very little information has been published about the pharmacokinetics of levetiracetam in the neonatal population. Doses reported in the neonatal population range from loading doses of 15 to 60 mg/kg and maintenance dosages of 30 mg/kg/day, which are similar to the dosages used in infants and older children.²³ However, the increased volume of distribution of levetiracetam reported in neonates,²⁰ may indicate that neonates require a larger loading dosing than adults and older children. Furthermore, given the fact that renal function affects the rate of elimination of levetiracetam, the elimination half-life of levetiracetam would be expected to be prolonged in neonates and even further prolonged in preterm neonates, given their immature renal function. Further studies should be conducted to investigate the use levetiracetam in neonatal seizures in order to establish efficacy and safety and to help guide dosing.

LIDOCAINE

Lidocaine, an amide local anesthetic, has a concentration-dependent effect on seizures. At lower concentrations, lidocaine can effectively suppress clinical and electrographic manifestations of seizures. However, at higher concentrations, it may cause seizures. The mechanism mediating this "proconvulsant" effect is not completely understood.²⁴ When used for treating seizures, lidocaine is administered by continuous IV infusion due to its short half-life (90-100 minutes). Lidocaine is 60% to 80% bound to α_1 -acid glycoprotein. It is metabolized primarily by the liver (90%) into two active metabolites, monoethylglycinxyllidide and glycinxyllidide, which are excreted renally. These active metabolites are thought to contribute both to efficacy in terminating seizures as well as to toxicity in provoking seizures.¹⁹

Level II-2 Evidence

Hellstrom-Westas et al²⁵ prospectively studied 24 neonates (14 term and 10 preterm) with seizures refractory to phenobarbital. Twenty-one neonates had also received diazepam and/or phenytoin when treatment with phenobarbital alone had failed. Lidocaine treatment was initiated on postnatal days 0 to 16, with an IV loading dose of 1.5 to 2.2 mg/kg followed by an initial maintenance infusion of 4 to 6 mg/kg/hour. Blood concentrations of lidocaine and its active metabolites (monoethylglycinxyllidide and glycinxyllidide) were measured at 30 minutes and at 1, 2, 4, 8, 12, 24,

48 and 72 hours after initiation of the lidocaine infusion and was repeated every 24 hours during the infusion. The pharmacokinetic model used in the studies to describe the data was not reported.

The mean duration of the lidocaine infusion was 74.3 hours (range, 2-233 hours) in term infants and 105.2 hours (range, 22-144 hours) in preterm infants. Within 10 hours of infusion, mean lidocaine concentrations were above 6 mg/L, the upper limit of the reference range reported in adults (when it is used for antiarrhythmic therapy), and within 24 hours a significant accumulation of lidocaine (mean concentration, 19 mg/L) and monoethylglycinxyllidide (mean concentration, 9 mg/L) was noted. No significant difference in blood concentrations of lidocaine (or its active metabolites) was found between term and preterm neonates or between neonates who responded (seizures stopped) to the lidocaine infusion and those who had no anticonvulsant response. After the lidocaine infusion was discontinued, both lidocaine and its active metabolites were eliminated within 24 to 48 hours in all neonates. No other pharmacokinetic parameters were reported.

Rey et al²⁶ prospectively studied 13 neonates (8 term, 5 preterm) who began receiving lidocaine infusion after phenobarbital and diazepam therapy failed to control seizures. Lidocaine was infused at a rate of 4 mg/kg/hour on day 1 of therapy. The infusion rate was decreased by 1 mg/kg/hour per day and discontinued on day 5. Lidocaine plasma concentrations were monitored every 12 to 24 hours. The pharmacokinetic model used to describe the data was not reported.

Mean lidocaine concentrations in preterm and term neonates 24 hours after the start of the 4 mg/kg/hour infusion were 8.2 mg/L (3-10.5 mg/L) and 4.5 mg/L (2.8-7 mg/L), respectively. Assuming steady-state was achieved at least 24 hours after the start of infusion (based on a lidocaine elimination half-life of 3.16 hours, previously reported following subcutaneous administration of lidocaine in 4 neonates),²⁴ clearance was calculated for each infusion rate in both preterm and term neonates. Clearance was significantly lower in preterm neonates for all dose rates. In both term and preterm infants, lidocaine clearance increased with decreased infusion rates, suggesting lidocaine elimination is a saturable process.

Level II-3 Evidence

Malingre et al²⁷ studied 20 neonates treated with IV lidocaine following inadequate seizure control with phenobarbital (with or without a benzodiazepine). An IV loading dose of lidocaine 2 mg/kg was administered over 10 minutes, followed by a

continuous infusion of 6 mg/kg/hour for 12 hours, 4 mg/kg/hour for 12 hours, and 2 mg/kg/hour for 12 hours. Plasma samples were drawn at 8, 12, 24, 36, 50, and 72 hours after the start of the infusion. A 1-compartment model was used to describe the data.

Thirteen neonates (65%) had lidocaine plasma concentrations greater than 9 mg/L at some point during the infusion (time not-specified). Plasma concentrations above 9 mg/L have been associated with cardiac toxicity in adult patients.²⁸ The mean clearance and volume of distribution of lidocaine were estimated to be 10.7 mL/min/kg and 3.2 L/kg, respectively.

In a second phase of their study, Malingre et al²⁷ developed a new lidocaine infusion regimen to reduce the risk of toxicity in neonates. The modified lidocaine infusion regimen (2 mg/kg IV loading dose over 10 minutes, followed by a continuous IV infusion of 6 mg/kg/hour for 6 hours, 4 mg/kg/hour for 12 hours, and 2 mg/kg/hour for 12 hours) was then administered to 15 neonates. The new regimen resulted in lidocaine plasma concentrations less than 9 mg/L in 11 of the 16 neonates (73%). Five neonates (3 preterm, gestational age 27-33 weeks) continued to have plasma concentrations greater than 9 mg/L. Cardiac toxicity was not observed with either regimen.

In an attempt to reduce the risk of lidocaine toxicity in preterm neonates, Van den Broek et al²⁹ developed a new lidocaine infusion regimen for term and preterm neonates by using population pharmacokinetic modeling and simulation. Van den Broek et al used the infusion regimen previously described by Malingre et al²⁷ in 46 neonates (including 18 preterm neonates) within 10 days of birth. Plasma lidocaine concentrations were collected after completion of the initial lidocaine loading dose (2 mg/kg), during the dose-reduction steps, and in cases of (suspected) toxicity. These concentrations were then used to create a pharmacokinetic model able to predict individual and population lidocaine concentration-time profiles for neonates with different body weights and maturation progress.

The dosing strategy developed consists of an initial bolus dose of 2 mg/kg (administered over 10 minutes), followed by a body weight-based infusion over 4 hours, with different doses for different weight categories (0.8-1.5 kg, 5 mg/kg/hour over 4 hours; 1.6-2.5 kg, 6 mg/kg/hour over 4 hours; 2.6-4.5 kg, 7 mg/kg/hour over 4 hours). After the 4-hour infusion was completed, the infusion is reduced to half the initial infusion rate for 6 hours and then further reduced by half for an additional 12 hours.

Using the dosage regimen described by Malingre et al²⁷, 31% of neonates had lidocaine plasma

concentrations of >9 mg/L following the 6-hour infusion. Using this new dosing strategy, the median concentration achieved at the end of the 4-hour infusion was 6.1 mg/L with only 2.4% of the simulated individual plasma concentrations greater than 9 mg/L. Prospective validation of this infusion regimen is currently under study.

Level III Evidence

Wallin et al³⁰ published a case series of 3 neonates with refractory seizures treated with IV lidocaine for 3 days, 3 weeks, and 3 months, respectively. One term neonate, 2 days postnatal age, receiving lidocaine infusion (6.8 mg/kg/hour for the first 12 hours) after phenobarbital and diazepam failed to control seizures. Within 12 hours, plasma concentrations of lidocaine and monoethylglycincxylylidide were 13.6 mg/L and 2.6 mg/L, respectively; glycincxylylidide was not detected until 36 hours after the infusion was started. After the lidocaine infusion was stopped after 3 days of treatment, the estimated plasma half-life of lidocaine and monoethylglycincxylylidide was 5.2 hours and 28.4 hours, respectively. Similarly, the second case report describes a term neonate successfully treated with IV lidocaine for 3 weeks (average daily dosage: 2 mg/kg/hour). The plasma concentration of lidocaine after 1 week of infusion was 1.6 mg/L. Plasma concentrations were not reported for the third neonate. Two infants (treated for 3 weeks and 3 months, respectively) experienced repeated seizures when the lidocaine dose was decreased (in an attempt to wean from the lidocaine infusion). The authors speculated that these seizures were due to the accumulation of monoethylglycincxylylidide and glycincxylylidide, which increased the excitability of the nervous system while the inhibitory effect of the parent compound was reduced.³⁰

Dosage Considerations

There are pharmacokinetic data to support the use of lidocaine infusions in neonates with refractory seizures; however, significant concern exists regarding the toxicities of lidocaine. In neonates, the volume of distribution and unbound fraction of lidocaine are expected to be greater than in adults given the reduced concentration of plasma proteins in neonates. Lower glomerular filtration rates will result in decreased renal clearance of lidocaine and its active metabolites, thereby increasing the risk of toxicity when used for prolonged periods in neonates.³¹ As such, the lidocaine infusion regimen proposed by Malingre et al²⁷ is not recommended for use in premature neonates, based on poor response and high lidocaine plasma concentrations reported in the four preterm neonates (gestational

age, 27-33 weeks). The infusion regimen proposed by Van den Broek et al²⁹ is promising but requires validation before it can be recommended (Table 2).

PARALDEHYDE

Paraldehyde, a polymer of acetaldehyde, has been used historically as a sedative-hypnotic and for refractory seizure control, but its exact mechanism of action is unclear.³² It is primarily metabolized via the CYP P450 system and is partially excreted through the lungs.³³ Paraldehyde is available as an IV solution (AFT Pharmaceuticals Ltd., Auckland, New Zealand); however, IV paraldehyde is not commonly used to treat neonatal seizures. Serious adverse effects, including pulmonary edema, pulmonary hemorrhage, and hypotension have been reported in older children after IV administration of paraldehyde.³⁴ In North America, paraldehyde is administered primarily rectally to treat refractory seizures, despite limited evidence to support this practice.

Level II-3 Evidence

One trial describing the pharmacokinetics of IV paraldehyde in the treatment of neonatal seizures was identified.³⁵ Nine term neonates with status epilepticus (defined as repeated clonic or tonic convulsions lasting longer than 1 hour) refractory to phenobarbital and phenytoin were given paraldehyde IV infusion (150 mg/kg/hr) for 3 hours. Blood samples were collected prior to initiation of therapy, hourly during the infusion, and at 1, 3, 6, 9, 21, 33, and 45 hours after completion of the infusion. A 1-compartment pharmacokinetic model was used to describe the data. Mean peak paraldehyde concentration achieved was 247 mg/L, mean volume of distribution was 1.73 L/kg, mean clearance was 0.121 L/hr/kg, and mean elimination half-life was 10.2 hours.

Dosage Considerations

The pharmacokinetic data for IV paraldehyde are limited in neonates with refractory seizures. Furthermore, concern regarding significant adverse effects of IV paraldehyde in older children limits its use. No pharmacokinetic data regarding rectal paraldehyde in neonates are available to help guide dosing.^{34,36}

TOPIRAMATE

Topiramate is an AED with multiple mechanisms of action, including glutamate receptor inhibition and sodium blockade. It is currently available only as an oral formulation. Topiramate is not highly protein bound and exhibits a linear

relationship between dose and serum concentration. Approximately 70% of the drug is eliminated unchanged in the urine.^{19,37}

Level II-3 Evidence

One trial investigating the pharmacokinetics of topiramate in neonates was identified.³⁷ In that study, 13 full-term neonates with hypoxic ischemic encephalopathy were randomized to receive either deep (30-33°C) or mild (33-34°C) hypothermia. Topiramate was administered to all neonates via orogastric tube as enteric-coated granules mixed with water at a dose of 5 mg/kg once per day for the first 3 days of life. Seven of the 13 neonates received concomitant treatment with phenobarbital. Topiramate plasma concentrations were evaluated for the first 9 patients after 48 hours of hypothermia, before the third dose of topiramate was administered (at 48 hours) and over the next 24 hours. The final 4 patients had topiramate plasma concentrations drawn at the beginning of hypothermia (at 0 hours) and over the next 72 hours. A noncompartmental pharmacokinetic model was used to describe the data.

Topiramate plasma concentrations were within the stated "reference range" of 5 to 20 mg/L in 11 of the 13 neonates who were cooled for 72 hours. This reference range was extrapolated from adult data.¹⁹ Peak plasma concentrations were achieved at 3.8 ± 2.2 hours after oral topiramate administration and ranged from 15.38 to 19.87 mg/L. The mean volume of distribution was not reported. The mean clearance was 0.26 mL/min/kg, and the mean elimination half-life was 35.6 ± 19.3 hours. The pharmacokinetic parameters between the neonates treated with deep and mild hypothermia did not differ significantly. Neonates who were treated with phenobarbital (an enzyme inducer) had a significantly lower minimum plasma concentration (C_{pmin}) than those given topiramate alone ($p=0.032$); however, none of the other pharmacokinetic parameters differed significantly.

Dosage Considerations

Limited pharmacokinetic data are currently available to guide the dosage regimen of topiramate in neonatal seizures. The dosage regimen used by Filippi et al³⁷ (topiramate 5 mg/kg orally once daily) achieved plasma concentrations within the commonly reported reference range of 5 to 20 mg/L. This dose regimen, however, was developed arbitrarily with the purpose of rapidly achieving "therapeutic" plasma concentrations for a short period of time (3 days) in this select patient population. Given the long half-life (35.6 hours) of topiramate in that study, it would be expected

that steady-state topiramate concentrations would be much higher than the values achieved in this study. Data for the pharmacokinetics of topiramate in normothermic neonates are limited to newborns of mothers treated with topiramate. Further pharmacokinetic studies investigating the dosing of topiramate in neonates in normothermic conditions, over a longer period of time are needed before we can make dosing recommendations.

VALPROIC ACID

The mechanism of action of valproic acid (Depakene syrup) is not completely understood. It acts on a variety of targets, including sodium channel blockade, increased γ -aminobutyric acid (GABA) function, and modulation of *N*-methyl-D-aspartate (NMDA) receptors.^{10,19} Valproic acid is available both as an oral and an IV agent. Like phenytoin, valproic acid is highly (90%-95%) protein bound (primarily to albumin). However, the protein binding of valproic acid is saturable, resulting in a nonlinear increase in free drug concentration with dose escalation, and, in patient populations with lower concentrations of serum binding proteins,¹⁹ valproic acid is primarily metabolized in the liver by β -oxidation (30%) and glucuronidation (40%). Its metabolites are excreted renally.

Level II-3 Evidence

Gal et al³⁸ evaluated the pharmacokinetics of valproic acid administered orally to 6 neonates with prolonged, intractable seizures, who were unresponsive to phenobarbital used in conjunction with at least one other anticonvulsant (phenytoin, lorazepam, and/or paraldehyde). A loading dose of valproic acid (20-25 mg/kg) was administered via nasogastric tube, and serum valproic acid concentrations (both total and free) were measured 4 times over a 12-hour period. Pharmacokinetic parameters were derived using a 1-compartment model.

Peak concentrations (C_{max}) were not reported, whereas time to peak concentration (T_{max}) was stated to have occurred within 2 to 3 hours of the initial oral dose. Large interpatient differences were noted in the volume of distribution, apparent oral clearance, and elimination half-life of both total (0.36-0.46 L/kg, 5.5-28.9 mL/hr/kg, and 8.6-36.3 hours, respectively) and free (1.41-2.44 L/kg, 42-252 mL/hr/kg, and 6.7-14.5 hours, respectively) valproic acid concentration. The free fraction ranged from 11.3% to 31.6% (mean, 19.2%) with the free fraction increasing with total serum valproic acid concentrations. All patients were given a maintenance dose of 5 to 10 mg/kg valproic acid every 12

hours until individualized pharmacokinetic calculations allowed for dose adjustments to attain a targeted trough concentration between 40 and 50 mg/L. Valproic acid controlled seizures in 5 of the 6 neonates, with trough concentrations reported between 26 and 60 mg/L. Although serum ammonia levels were elevated in all 6 of the neonates treated with valproic acid, hyperammonemia led to the discontinuation of valproic acid in 3 (50%) of the neonates.

Level III Evidence

Steinberg et al³⁹ reported two case studies in which rectal valproic acid successfully terminated refractory neonatal seizures. Total serum concentrations of 35 and 38 mg/L were attained after rectal administration of valproic acid syrup in doses of 20 mg/kg and 30 mg/kg, respectively. The relation of these concentrations to the timing of the dose was not specified.

Irvine-Meek et al⁴⁰ described the pharmacokinetic parameters of valproic acid following the administration of a single oral dose (7.5 mg/kg) of valproic acid syrup in a 24-day old neonate. Pharmacokinetic parameters were derived using a 1-compartment model. The volume of distribution was 0.28 L/kg, apparent oral clearance 0.18 mL/min/kg, and elimination half-life 17.2 hours.

Last, Alfonso et al⁴¹ published two additional case studies in which 2 neonates with seizures refractory to phenobarbital and phenytoin were treated with IV valproic acid. Serum valproic acid concentrations were measured 15 minutes and 2.5 hours following a 30-minute loading dose infusion. Each 1 mg/kg IV valproic acid increased the 15-minute and 2.5-hour postinfusion total serum valproic acid concentrations by 4 and 3 mg/L, respectively. The calculated volume of distribution and clearance of valproic acid were 0.245 L/kg and 25 mL/hr/kg, respectively.

Dosage Considerations

Limited pharmacokinetic data are currently available to guide dosages of IV and/or rectal administration of valproic acid in neonatal seizures. Initial loading doses studied ranged from 20 to 25 mg/kg (oral), 20 to 30 mg/kg (rectal), and 10 to 25 mg/kg (IV); maintenance dosages ranged from 5 to 10 mg/kg/dose (oral) and 15 mg/kg/dose (rectal) administered every 12 hours, with wide variations in serum concentrations. Like other AEDs, dosing must be based on patient response (efficacy and safety) and not on valproic acid concentrations as the "therapeutic range" for valproic acid in neonates is unknown. Further studies are required

Table 3. Summary of Advantages, Disadvantages, and Dosing Guidelines and Considerations

AED	Route of Administration	Advantages	Disadvantages	Dosage Guidelines and Considerations
Carbamazepine	Oral	3 (level II-3) PK studies to help guide dosing	No IV formulation; Autoinduction (challenging to dose); Drug interactions (e.g., with phenytoin, phenobarbital)	LD: 5-20 mg/kg; MD: 5-8 mg/kg/dose every 8-12 hr (9-21 mg/kg/day); Because of cytochrome P450 enzyme maturation and autoinduction (peak effect 8 to 15 days after initiation) as neonates age, dosage increases will be necessary over the first 3 months of therapy to maintain target serum concentrations
Levetiracetam	Oral IV (US)	Available as an IV agent (US); 100% bioavailability; No protein binding; CYP P450- independent metabolism; No drug interactions (e.g., phenytoin, phenobarbital)	Limited PK data in neonates to guide dosing	LD: 40-60 mg/kg; MD: 30 mg/kg/day; Requires dosage adjustment in renal failure
Lidocaine	IV Infusion	Multiple PK studies in neonates to help guide dosing (e.g., 2 level II-2, 2 level II-3, and 1 level III study);	Significant toxicities associated with prolonged infusions/high serum concentrations (e.g., CNS, seizures; CVS, arrhythmias)	Dosage: 2 mg/kg (infused over 10 min), followed immediately by infusion based on the following weight categories: 0.8-1.5 kg: 5 mg/kg/hr for 4 hr, then 2.5 mg/kg/hr for 6 hr, then 1.25 mg/kg/hr for 12 hr; 1.6-2.5 kg: 6 mg/kg/hr for 4 hr, then 3 mg/kg/hr for 6 hr, then 1.5 mg/kg/hour for 12 hr; 2.6-4.5 kg: 7 mg/kg/hour for 4 hr, then 3.5 mg/kg/hr for 6 hr, then 1.75 mg/kg/hr for 12 hr; Avoid using for prolonged periods; there is an increased risk of toxicity because of decreased renal elimination of lidocaine and its active metabolites

Table 3. Summary of Advantages, Disadvantages, and Dosing Guidelines and Considerations (cont.)

AED	Route of Administration	Advantages	Disadvantages	Dosage Guidelines and Considerations
Paraldehyde	IV Rectal	Partially excreted via the lungs (excretion not limited in neonates)	IV route is associated with significant adverse effects (pulmonary edema, pulmonary hemorrhage, hypotension); Rectal route: no PK studies in neonates	IV paraldehyde should not be used to treat refractory neonatal seizures given the risk of significant adverse effects; No data to guide PR dosages in neonates
Topiramate	Oral		No IV formulation currently available; PK data in neonates are limited to neonates being cooled	Neonates receiving therapeutic hypothermia: 5 mg/kg once daily; No data to guide dosing in normothermic neonates or neonates receiving therapeutic hypothermia for more than 3 days
Valproic acid	Oral PR IV (US)	Multiple routes of administration	Saturable protein binding; Associated with fatal hepatotoxicity and hyperammonemia; Children <2 years of age are at increased risk; Limited PK data to guide IV/PR dosages of valproic acid in neonates	Loading dose: 20 to 25 mg/kg (po) 20 to 30 mg/kg (pr) 10 to 25 mg/kg (IV); Maintenance dose: 5-10 mg/kg/dose every 12 hr (po) 15 mg/kg/dose every 12 hr (pr); Liver function and ammonia levels must be monitored; Enzyme-inducing medications (e.g., phenobarbital, phenytoin) should be discontinued while administering valproic acid (to minimize risk of hepatotoxicity)
Vigabatrin	Oral	Wide therapeutic index; Not protein bound; Not metabolized	No IV formulation; Limited PK data in neonates; 50% efficacy when used for refractory neonatal seizures	Insufficient data to recommend dosage guidelines for neonates

AED, antiepileptic drug; CNS, central nervous system; CVS, cardiovascular system; IV, intravenous; LD, loading dose; MD, maintenance dose; PK, pharmacokinetic; PR, rectal route

to determine the optimal oral, rectal and IV dosing of valproic acid in the neonatal population.

VIGABATRIN

Vigabatrin, a selective inhibitor of GABA transaminase, increases GABA (a major inhibitory neurotransmitter) concentrations in the central nervous system. It is administered orally as a racemic mixture of two enantiomers, *S*(+) and *R*(-); only the *S*(+) enantiomer is pharmacologically active.¹⁹ Vigabatrin is not protein bound and exhibits linear kinetics. It is not metabolized and is primarily excreted unchanged in urine.

Level II-3 Evidence

A single study reported the pharmacokinetics of vigabatrin in neonates with uncontrolled seizures.⁴² Six neonates (15 to 26 days postnatal) were given a single 125-mg dose of racemic vigabatrin orally. Blood samples were collected before and at 0.5, 1, 2, 3, 6, 9, 12, and 24 hours after the first dose. Oral vigabatrin was then continued at 125 mg twice daily, for 5 days. Blood samples were drawn prior to and 1 hour after the morning dose. The pharmacokinetic model used to describe the data was not reported.

With respect to the *S*(+) enantiomer, the absorption of vigabatrin (based on a 50 mg/kg dose) administered orally to neonates was comparable to the values previously obtained in infants and children.⁴³ The mean C_{max} and T_{max} were 14 mg/L and 2.1 hours, respectively.⁴² The AUC or total drug exposure, however, appeared higher in neonates (142.6 ± 44.0 mg/L/hr), and the elimination half-life appeared longer (7.5 ± 2.1 hours). This can be explained by the reduced renal function of neonates compared to infants and older children. On repeated dosing however, no accumulation of either enantiomer occurred.

Dosage Considerations

The pharmacokinetic profile of vigabatrin (low plasma protein binding, linear kinetics, eliminated unchanged in the kidney) along with its wide therapeutic index make vigabatrin a potentially desirable agent for use in treating refractory neonatal seizures. The study by Vauzelle-Kervroedan et al⁴² demonstrated similar pharmacokinetic parameters for the active *S*(+) enantiomer of vigabatrin in neonates, as previously reported in infants and older children,⁴³ suggesting a similar dosing regimen (vigabatrin, 125 mg orally twice daily for 5 days) can be used in the neonatal population. However, further study regarding

vigabatrin's effectiveness in neonatal seizures is required.

SUMMARY

Table 3 summarizes the overall advantages and disadvantages of each of the 7 second-line AEDs that have pharmacokinetic data in neonates and provides dosing considerations and guidelines for use in neonates. In summary, the pharmacokinetics of AEDs are impacted by age.¹ While seizures occur more often in the neonatal period than at any other time in life,² there are limited pharmacokinetic data to guide the dosages for AEDs in this population. The available pharmacokinetic data are derived primarily from small, nonrandomized, noncontrolled trials, case studies, and retrospective reviews. This information is difficult to apply in clinical practice as limited data are provided (about the patient, how the drug was administered, the timing of drug levels, the clinical outcome, and other data). Many of the studies include both term and preterm neonates, who differ in their physiological development and ability to eliminate drugs, accounting for some of the variability in the reported pharmacokinetic parameters.

The neonate, whether term or preterm, is rapidly developing during the first month of life. Administering drug dosages at steady state likely does not occur for many of the AEDs, given the neonate's rapid and ongoing organ development.⁴⁴ As a result, the neonatal patient receiving AEDs must be continually monitored and drug doses adjusted based on clinical parameters and physiological development. While established reference ranges of AEDs do not necessarily apply to the neonate, therapeutic drug monitoring may be useful in guiding dosage adjustments and in cases of suspected toxicities. Further research in this area is needed to elucidate the target serum concentration of AEDs in neonates in order to optimize effectiveness and minimize dose-related adverse effects.

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ABBREVIATIONS AED, antiepileptic drug; AUC, area under the concentration-time curve

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