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REVIEW
DERLEME

Pharmacokinetic Variability of Antiepileptic Drugs in Neonates: A Narrative Review

Yenidoğanlarda Antiepileptik İlaçların Farmakokinetik Değişkenliği: Kapsamlı Bir İnceleme

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ABSTRACT

Neonatal seizures represent a significant clinical challenge with marked socioeconomic disparities in prevalence, ranging from 1-3 per 1,000 live births in high-income nations to 36-90 per 1,000 in low- and middle-income countries. Neonates present unique pharmacological challenges due to their rapidly changing physiology, requiring careful consideration in antiseizure drug administration. This paper presents a narrative review of existing literature analysing the pharmacokinetic variability of antiseizure drugs in neonates. This variability increases the risk of dose-related adverse reactions and highlights the critical importance of individualized dosing approaches. A comprehensive review of current literature was conducted across multiple electronic databases including PubMed, Embase, Cochrane Library and Medscape examining the pharmacokinetic properties of antiseizure medications in neonates, impact of physiological factors, therapeutic interventions, and long-term neurological consequences. Special attention was given to the effects of therapeutic hypothermia and other intensive care interventions on drug disposition. A total of 60 articles were included after screening 6331 studies and eliminating 6266 articles based on exclusion criteria. Neonatal physiology creates substantial pharmacokinetic variability in antiseizure drug disposition, with immature enzyme systems, altered protein binding, and developmental changes in clearance mechanisms. Therapeutic interventions, particularly hypothermia in hypoxic-ischemic encephalopathy, can substantially alter pharmacokinetic parameters and drug clearance. Animal studies suggest potential neurodevelopmental impacts of early antiseizure drug exposure, though establishing direct causality remains challenging due to the concurrent effects of seizures on brain development. The unique physiological characteristics of neonates necessitate an individualized approach to antiseizure drug dosing. The complex interplay between developmental factors, therapeutic interventions, and drug disposition highlights the importance of careful monitoring and dose adjustment based on patient-specific factors. Further research is needed to better understand the long-term neurodevelopmental implications of early antiseizure drug exposure.

Keywords: Antiseizure drugs, neonatal seizures, pharmacokinetics, newborn , variability

ÖZ

Yenidoğan nöbetleri, yüksek gelirli ülkelerde 1.000 canlı doğumda 1-3, düşük ve orta gelirli ülkelerde ise 1.000 canlı doğumda 36-90 arasında değişen yaygınlık oranları ile belirgin sosyoekonomik farklılıklar gösteren önemli bir klinik sorundur. Yenidoğanlar, hızla değişen fizyolojileri nedeniyle benzersiz farmakolojik zorluklar ortaya çıkarır ve antiepileptik ilaçların uygulanmasında dikkatli bir değerlendirme gerektirir. Bu makale, yenidoğanlarda antiepileptik ilaçların farmakokinetik değişkenliğini analiz eden mevcut literatürün anlatımsal bir incelemesini sunmaktadır. Bu değişkenlik, dozla ilişkili advers reaksiyon riskini artırır ve bireyselleştirilmiş dozlama yaklaşımlarının kritik önemini vurgular. PubMed, Embase, Cochrane Library ve Medscape gibi birçok elektronik veri tabanında, yenidoğanlarda antiepileptik ilaçların farmakokinetik özellikleri, fizyolojik faktörlerin etkisi, terapötik müdahaleler ve uzun vadeli nörolojik sonuçlar incelenerek mevcut literatürün kapsamlı bir incelemesi yapılmıştır. Terapötik hipotermi ve diğer yoğun bakım müdahalelerinin ilaç dağılımı üzerindeki etkilerine özel dikkat gösterilmiştir. 6331 çalışmayı taradıktan ve dışlama kriterlerine göre 6266 makaleyi eledikten sonra toplam 60 makale dahil edildi. Yenidoğan fizyolojisi, olgunlaşmamış enzim sistemleri, değişmiş protein bağlanması ve klirens mekanizmalarındaki gelişimsel değişiklikler nedeniyle antiepileptik ilaçların dağılımında önemli farmakokinetik değişkenlik yaratır. Terapötik müdahaleler, özellikle hipoksik-iskemik ensefalopatide hipotermi, farmakokinetik parametreleri ve ilaç klirensini önemli ölçüde değiştirebilir. Hayvan çalışmaları, erken antiepileptik ilaç maruziyetinin nörogelişimsel etkileri olabileceğini göstermektedir, ancak nöbetlerin beyin gelişimi üzerindeki eşzamanlı etkileri nedeniyle doğrudan nedensellik kurmak hala zordur. Yenidoğanların benzersiz fizyolojik özellikleri, antiepileptik ilaç dozlamasında bireyselleştirilmiş bir yaklaşım gerektirir. Gelişim faktörleri, terapötik müdahaleler ve ilaç dağılımı arasındaki karmaşık etkileşim, hasta özelinde faktörlere dayalı dikkatli izleme ve doz ayarlamasının önemini vurgulamaktadır. Erken antiepileptik ilaç maruziyetinin uzun vadeli nörogelişimsel etkilerini daha iyi anlamak için daha fazla araştırma gereklidir.

Anahtar Kelimeler: Antiepileptik ilaçlar, yenidoğan nöbetleri, farmakokinetik, yenidoğan, değişkenlik

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INTRODUCTION

Antiseizure medications are crucial for managing neonatal seizures, which can have severe consequences if left untreated. Neonatal seizure exhibits substantial socioeconomic variation in prevalence, ranging from 1-3 per 1,000 live births in high-income nations to 36-90 per 1,000 in low- and middle-income countries (1). Neonates present unique pharmacological challenges due to rapid physiological changes, leading to variability in drug disposition and increased risk of adverse reactions.

As per the recommendations of the Neonatal Task force by International League Against Epilepsy (ILAE). in 2023, phenobarbital is the primary antiseizure medication for neonatal seizures. Alternative options include phenytoin, levetiracetam, midazolam, with levetiracetam preferred for neonates with cardiac conditions. Sodium channel blockers are used for suspected channelopathies. For refractory seizures with unknown aetiology, a pyridoxine trial is warranted for neonates with clinical or EEG features of pyridoxine-dependent epilepsy (2).

Neonatal physiology differs significantly from older individuals, profoundly impacting drug disposition. Key variables include variations in distribution, clearance, protein binding, body composition, gastrointestinal function, and enzyme activity. The heightened total body water and altered protein binding in neonates can influence drug distribution, while immature hepatic and renal function impact metabolism, half-life, and elimination. Considering developmental measures such as gestational age, postnatal age, and weight is crucial when dosing antiseizure medications in this population. Special considerations are required in neonates large for their gestational age, where the weight based dosing ,body size metrics and dose capping can be complicated. Fluctuations in albumin and alpha1- acid glycoprotein levels during the neonatal stage can induce alterations in protein binding, which, in turn, influence the distribution and clearance of low-extraction drugs, including valproic acid (95%albumin bound). and carbamazepine (70-90% AAG bound) (3).

Different formulations of antiseizure medications influence their pharmacokinetic profiles. Extended-release formulations offer advantages including reduced dosing frequency and diminished peak-to- trough fluctuations. However, these formulations may not always be bioequivalent to immediate- release versions, potentially necessitating dosage adjustments.

Specific drug metabolising enzymes exhibit varied developmental trajectories during the fetal and neonatal stages. Enzymes like CYP3A7, SULT1A3/1A4 show peak expression during fetal life with activity diminishing over the first two years. CYP3A5, CYP2C19, SULT1A1 enzymes show a moderate increase postnatally, becoming more active later in pediatric period. CYP2D6, CYP3A4, CYP2C9, CYP1A2 enzymes displays modest ontogeny during the second or third trimester of pregnancy followed by another notable increase in phenotypic activity throughout infancy (61). In addition, Genetic polymorphisms in drug-metabolizing enzymes like CYP450 or UGT can cause significant variation in the rate of drug metabolism, clearance, bioavailability, overall efficacy, and adverse drug reactions (3).

Comorbidities like hepatic or renal impairment can further influence drug clearance and increase the risk of adverse reactions. Additionally, common neonatal intensive care interventions, including extracorporeal membrane oxygenation, hypothermia, and continuous renal replacement therapy, can significantly affect pharmacokinetics (2,4-9). The concurrent administration of multiple antiseizure medications to achieve adequate seizure control may increase the risk of drug-drug interactions. This risk is related to the ability of certain antiseizure drugs to modulate drug-metabolizing enzymes and the fact that many antiseizure drugs are substrates of the cytochrome P450 enzyme family. Valproic acid, phenobarbital, and phenytoin are notable for their high potential for DDIs due to their complex pharmacokinetic and metabolic pathways (3).

Pharmacokinetic variability in neonates presents characterization challenges due to complexities of conducting clinical studies in this population, including limited participant numbers, ethical considerations, and blood volume constraints. Population pharmacokinetics and modelling techniques help address data scarcity (3).

Therapeutic Hypothermia

A common intervention in neonates with hypoxic-ischemic encephalopathy which can significantly impact pharmacokinetic parameters. Hypothermia may decrease drug clearance and alter the volume of distribution by modulating intravascular blood volume, organ perfusion, and enzymatic metabolic processes. Studies have shown that phenobarbital clearance is reduced in cases of severe asphyxia and the application of therapeutic hypothermia, highlighting the importance of considering the underlying disease condition also when dosing medications in this patient population (10).

Long-term Neurological Consequences

Prolonged neonatal seizures can have significant long-term neurological consequences including cognitive deficits and increased epilepsy risk in over 30% of survivors (11). Hence, establishing direct causality between antiseizure drugs and developmental/cognitive problems is challenging, as early- onset epilepsy also contributes (12). Differentiating drug induced vs seizure induced neurological consequences is beyond the scope of this review, but therapeutic drug monitoring might benefit the treating physician in preventing overexposure through suitable dose adjustments.

Animal studies have shown that antiseizure drug exposure, especially phenobarbital, phenytoin and sodium valproate can increase neuron apoptosis and inhibit neurogenesis. Levetiracetam does not induce cell death. It is possible that these proapoptotic actions contribute to adverse outcomes observed in rats and cognitive impairment seen in humans following exposure to certain antiseizure medications during postnatal development (13-15).

A retrospective cohort study comparing phenobarbital to levetiracetam in infants assessed outcomes of cerebral palsy and neurodevelopmental outcomes at 24 months using the Bayley Scales of Infant Development (16). The study revealed a 2.3-fold increase in cerebral palsy exclusively with phenobarbital exposure. Assessment of motor, cognitive, and language performance using the Denver Assessment of Early Childhood at 12 months indicated negative effects of increased phenobarbital and levetiracetam exposure, specifically in motor domains. At 24 months, phenobarbital led to lower cognitive and motor skills (8-point and 9-point decreases on the Bayley Scales of Infant Development & BSID motor score respectively). In contrast, levetiracetam was linked to smaller decreases in cognitive and motor skills (2.2-point and 2.6-point decreases respectively), suggesting it may be a better option than phenobarbital (16). Moreover,A recent study comparing fosphenytoin to phenobarbital indicated that neonates treated with fosphenytoin demonstrated improved neurodevelopmental outcomes at 18-24 months compared to phenobarbital. But the small sample size was a major limitation (17).

The Early intervention and adherence to treatment protocols for neonatal seizures are associated with lower progression to status epilepticus, decreased morbidity, and shorter hospital stays (18). Studies on new antiseizure drugs in paediatric epilepsy have found cognitive functioning is often dose- dependently impaired, particularly with combination therapy. Identifying patients prone to cognitive issues early allows for gradual titration, as rapid titration risks neurological side effects (19).

METHODS - SEARCH STRATEGY

A comprehensive literature search was conducted for this narrative review across multiple electronic databases including PubMed, Embase, Cochrane Library and Medscape. The primary search terms were structured to identify literature on pharmacokinetic variability and antiseizure therapy in neonates. The search strategy combined Medical Subject Headings (MeSH). terms and free-text terms: ("pharmacokinetic" OR "pharmacokinetically" OR "pharmacokinetics"). AND ("variabilities" OR "variability" OR "variable"). AND ("anticonvulsants" OR "antiseizure" OR "antiepileptic drugs"). AND ("infant, newborn" OR "neonate" OR "neonatal").

Search strategy is depicted in **Figure 1**. The combined keyword search identified 65 articles published between 1976 and 2024 Articles were reviewed over a six-month period (January to June 2024), focusing on studies examining pharmacokinetic variability of individual antiseizure drugs in neonates. Additional relevant studies were identified through manual searching of reference lists from selected articles. 60 Relevant pharmacokinetic studies on neonates (0-28days). under antiseizure therapy were included in the final review.

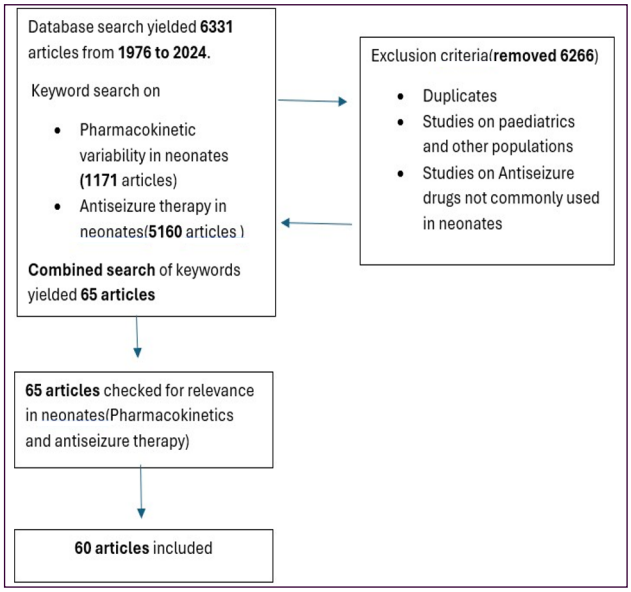

Figure 1. Search strategy for literature review

Phenobarbital Pharmacokinetics

Phenobarbital is a commonly used antiseizure agent in neonates due to its effectiveness and availability in intravenous formulations. Phenobarbital should initially be given at 20 mg/kg intravenously, followed by a maintenance dose of 5 mg/kg/day, either IV or orally. Studies showed a 40% response after the first dose, and giving more IV phenobarbital helped control seizures in both term and preterm neonates (20). It is lipophilic, with a relatively long half-life, which can be advantageous in the treatment of neonatal seizures (9). However, the physicochemical properties of phenobarbital, such as its high protein binding and potential for interactions with other drugs, can also contribute to the variability in its pharmacokinetics and efficacy (9, 21).

In neonates, phenobarbital has reduced oral bioavailability and a longer elimination half-life compared to older children and adults. Therefore, a low dose per kilogram (dose/kg). is recommended during the neonatal period. The dose requirement decreases with increasing age, especially in children also taking valproic acid, which inhibits phenobarbital metabolism (22).

Phenobarbital clearance is reduced in severe asphyxia and therapeutic hypothermia (10). While CYP2C19 metabolism may be suppressed by hypothermia, dose adjustments are typically not required (22-24). However, conflicting recommendations exist regarding second loading doses during therapeutic hypothermia (20). Additionally, factors that may impact renal or hepatic elimination in neonatal encephalopathy could potentially affect phenobarbital metabolism.

In children on renal replacement therapy (RRT), age did not affect phenobarbital dosing recommendations, but higher loading and maintenance doses were needed. In the study by Céline Thibault on neonates undergoing ECMO therapy, phenobarbital clearance was lower but volume of distribution (Vd). estimates was higher. The higher Vd was consistent with a prior study in neonates on extracorporeal membrane oxygenation (ECMO), likely due to factors like fluid resuscitation and inflammation (25).

Recent ILAE guidelines recommend monitoring plasma levels of phenobarbital during maintenance (2). While phenobarbital remains the first-line treatment for neonatal seizures, its use is associated with concerns about potential adverse effects on the developing nervous system (21,26,27). Preclinical studies have shown that early-life exposure to phenobarbital can disrupt synaptic development and induce neuronal apoptosis, which may lead to long-term neurodevelopmental consequences (21,27).

Phenytoin Pharmacokinetics

Phenytoin has a narrow therapeutic index (10±20 mg/l), which becomes even narrower during the neonatal period (6±14 mg/l). Infants and young children often require higher doses of phenytoin per kilogram body weight to achieve therapeutic plasma levels compared to adults, likely due to differences in drug clearance (28,29). An initial loading dose of 20mg/kg phenytoin equivalent is administered over 30 minutes, succeeded by a maintenance regimen of 5 mg/kg/day, administered intravenously or orally in two divided doses (20). The bioavailability of phenytoin in newborns and infants remains controversial (30,31). Additionally, due to non-linear pharmacokinetic elimination, small changes in doses can result in significant variations in serum concentrations. During infancy, impaired protein binding contributes to the pharmacokinetic variability of phenytoin (28,31). At higher concentrations, saturation of protein binding occurs. The protein binding of phenytoin is 90%, and hence in the presence of hypoalbuminemia, concomitant drug administration or renal impairment, lower therapeutic concentrations must be targeted to avoid drug toxicity. Phenytoin clearance may be reduced in patients with decreased activity of CYP2C9 variants, increasing their susceptibility to dose-related side effects (32). Analogous to phenobarbital, experimental evidence suggests that phenytoin may induce apoptotic neurodegeneration (20).

Fosphenytoin is a water-soluble prodrug of phenytoin that can be administered intravenously, providing a more stable and predictable pharmacokinetic profile compared to phenytoin in neonates. However, fosphenytoin still exhibits similar variability in absorption, distribution, and metabolism as phenytoin due to the unique physiology of neonates (5,7,8). Fosphenytoin may be preferred over phenytoin due to a potentially lower risk of adverse effects, easier and safer intravenous administration (33). Fosphenytoin is associated with a lower risk of cardiovascular adverse effects compared to phenytoin, but neonates may still experience complications such as hypotension and arrhythmias.

Levetiracetam Pharmacokinetics

Levetiracetam is safe and effective in paediatric epilepsy, due to its easy titrability and fewer drug interactions. According to the ILAE, levetiracetam should be administered with an initial intravenous loading dose of 40 mg/kg, followed by a subsequent intravenous loading dose of 20 mg/kg if necessary. The maintenance dosage is 40-60 mg/kg/day, administered intravenously or orally in three divided doses. In a study focusing on neonates, the initial cumulative levetiracetam dosage varied between 50 and 100 mg/kg. A separate study on infants with hypoxic-ischemic encephalopathy reported mean total and maintenance levetiracetam doses of 63 and 65 mg/kg/day, respectively (20).

Drug clearance is the most significant parameter to be considered in dosing levetiracetam. Conflicting results on neonatal drug clearance were identified. A study on 18 neonates found that levetiracetam clearance increases significantly during the week of life in neonates with the simultaneous decrease in the mean half-life over the same period (34,35). This means that to maintain therapeutic levels, more frequent dosing may be needed for neonates than in older children and adults.

A population pharmacokinetic model developed for neonates with seizures based on 44 measured concentrations from 20 neonates demonstrated that creatinine clearance (CRCL). and total body weight influence the disposition of levetiracetam, which in turn impacts the dosing strategy required to maintain a target concentration range of 6-20 mg/L when administering this anticonvulsant once daily (36). They also noted that clearance was higher than that predicted based on physiological characteristics. This study did not find any alteration in disposition in infants managed with therapeutic hypothermia (36).

Other studies conclude that neonates have lower clearance, higher volume of distribution, and a longer half-life compared to adults. Small sample sizes and interindividual variability were major limitations (35,37).

The lower clearance and longer half-life in neonates raise concerns about potential toxicity. While we found no reported adverse effects on vital signs, urine output, or hepatic and renal function, even at higher doses, close monitoring for potential toxicity is crucial, especially in neonates with impaired renal function (38). Close monitoring is advised in patients under CRRT therapy (39).

Levetiracetam is not appreciably protein bound and the metabolism is mainly through metabolic pathways such as hydrolysis of acetamide group and not liver CYP 450. Thus, pharmacokinetic interactions with other drugs are unlikely. However, monitoring therapy is recommended when concomitant seizure medications like carbamazepine, phenobarbital are used (40,41).

Overall, neonates require different dosing regimens than adults to maintain therapeutic levels of levetiracetam. A Study by Venkatesan et al suggests that higher loading doses may be necessary (38). and that by Sharpe et al indicates that more frequent dosing is needed (34). Higher cumulative loading doses were reported in neonates undergoing ECMO therapy (42).

Levetiracetam when compared to phenobarbital in neonates had better safety profile. But it requires further investigations in larger sample populations, as other studies comparing the adverse events found no significant differences in both groups (43,44).

Table 1: Pharmacokinetic parameters, variability and special considerations of antiseizure medications in neonates

Drug	Half-Life (hours)	Clearance (mL/min/kg)	Volume of Distribution (L/kg)	Protein Binding (%)	Special Considerations
Phenobarbital	• 45-409 hours (22)	• Reduced in severe asphyxia and therapeutic hypothermia	• 0.85±0.059 L/kg(59) Higher in ECMO therapy	• 36-43% (60)	• Longer elimination half-life vs older children;CYP2C19 metabolism • Higher doses needed in RRT • Dose-dependent side effects: • CNS: drowsiness, ataxia, vertigo, cognitive impairment • Respiratory depression
Phenytoin	• 6.9-194 hours (28,30)	• Reduced in CYP2C9 poor metabolizers • Age-related changes due to enzyme maturation affecting clearance (3)	• GA 27-30 weeks: 1.2±0.11 • L/kg GA 31-36 weeks: 1.17±0.21 L/kg GA • ≥37 weeks: 1.22±0.21 L/kg (30)	• 61-91% (30)	• Narrow therapeutic index in neonates • Non-linear pharmacokinetics • Higher doses/kg needed vs adults • Dose-dependent side effects:Concentration-dependent neurological toxicity • Drug-induced seizures • Pharmacogenetic variability (CYP2C9 & CYP2C19)
Levetiracetam	• Day 1: 18.5 hours • Day 7: 9.1 hours (34)	• Day 1: 0.7 mL/min/kg • Day 7: 1.33 mL/min/kg (34) • Influenced by postnatal age and body weight (3)	• 1.01±0.13 • L/kg(range: 0.81- • 1.24 L/kg) (34) • Higher than adults • Weight-based effect on volume of distribution (3)	• <10% • Not appreciably protein bound (41)	• 50% dose reduction in CRRT • Influenced by creatinine clearance • Dose-dependent ADRs: CNS depression: gait incoordination, fatigue, dizziness • Somnolence, feeding difficulty- Mild apnea and bradycardia
Carbamazepine	• 8.7-24.5 hours (48,51)	• Altered due to immature liver enzymes	• Neonates: 1.52±0.5 L/kg (51)	• Lower binding affinity vs older patients	• Peak levels: 4-16h post- administration • Monitor 10,11-epoxide metabolite • Dose-dependent ADRs:Neurological: ataxia, dizziness, sedation, hypotonia • Respiratory depression • Psychiatric: anxiety, depression • Hematological: leukopenia, thrombocytopenia • Hepatotoxicity, hyponatremia (SIADH) • Sinus tachycardia (in overdose)
Midazolam	• Neonates: 4-12 hours • Average: 6.3 hours (range: 2.6-17.7 • hours) (55) • Seriously ill neonates: 6.5-12 hours	• 1.8 mL/min/kg(range: 0.7-6.7 mL/min/kg) (55)	• 1.1 L/kg(similar to adults) (55)	• Primarily albumin (80% of adult albumin levels)	• Clearance proportional to birth weight • Higher clearance after 39 weeks gestation • CYP3A4/5 metabolism • Dose-dependent ADRs:Gastrointestinal: vomiting • Respiratory depression, hypotension Hypothermia, paradoxical reactions • Neonates: Cognitive/behavioral issues, neuronal injury, seizure-like movements(IV bolus)

*Abbreviations: GA = Gestational Age; CNS = Central Nervous System; ECMO = Extracorporeal Membrane Oxygenation; RRT = Renal Replacement Therapy; CRRT = Continuous Renal Replacement Therapy; ADR = Adverse Drug Reaction; SIADH = Syndrome of Inappropriate Antidiuretic Hormone Secretion

Carbamazepine Pharmacokinetics

Carbamazepine is proposed as the drug of choice in benign familial neonatal seizures (45). Neonatal epilepsy linked to KCNQ2 or SCN2A ion channel disorders demonstrates favourable responses to sodium-channel blockers including carbamazepine.

Autoinduction-related pharmacokinetic variability has been a well-recognized challenge with carbamazepine, potentially leading to suboptimal dosing and toxicity (21,26,46). Oxcarbazepine, an orally administered alternative to carbamazepine, may be safer to use owing to its more favourable characteristics regarding enzyme induction (47).

Carbamazepine exhibits significant pharmacokinetic variability in neonates compared to adults, posing unique challenges in neonatal treatment. Studies like those by Singh et al highlight a considerably shorter elimination half-life in neonates, necessitating different dosing regimens (48,49). This variation is attributed to the immature liver enzyme activity and altered drug clearance mechanisms (50).

A one-compartment pharmacokinetic model by Rey et al in neonates identified peak concentrations ranging from 3.14 to 10 mcg/ml at 2 and 9 hours post-administration, while study by Singh et al showed peak levels attained between 4 to 16 hours post-administration (48,51). Levels declined sharply around 8 to 15 days and then slowly over the subsequent 3 months (48).

Neonates appear to exhibit lower binding affinity for carbamazepine (CBZ). compared to older patients, while the binding of carbamazepine-epoxide (CBZ-E). remains similar. This suggests that the therapeutic range of total CBZ concentrations in neonates may differ from that in adults, but can be confirmed with further clinical studies (52). For infants, children, and adolescents receiving oral carbamazepine, it is recommended to measure serum levels of the 10,11-carbamazepine epoxide metabolite in cases where drug toxicity is suspected, even if the serum carbamazepine concentration is within the therapeutic range (53).

Midazolam Pharmacokinetics

Midazolam, a benzodiazepine, has rapid onset and short duration of action. In healthy neonates, the half-life is 3.3-fold longer and clearance is 3.7-fold smaller, while the volume of distribution is similar compared to adults (54).

Midazolam is metabolized by CYP3A4 and CYP3A5 enzymes, whose activities increase in the liver during the first weeks of life, leading to a lower metabolic rate in neonates. Due to the immaturity of hepatic cytochrome P450 3A4 activity, preterm infants exhibit markedly reduced midazolam clearance compared to older children. Concomitant administration of phenobarbital significantly elevated midazolam clearance. If phenobarbital is replaced by non-CYP3A inducers as the primary anticonvulsant, a 50% reduction in the midazolam maintenance dose may be warranted to prevent excessive exposure during the initial days after birth (56).

Population studies have found that midazolam clearance and volume of distribution are directly proportional to birth weight, with gestational age being a significant factor. Neonates born after 39 weeks gestation demonstrate 1.6 times higher clearance rates (57,58).

Neonatal pharmacokinetics of midazolam are affected by disease states, as multiple organ failure reduces clearance and mechanical ventilation prolongs half-life. Furthermore, extracorporeal membrane oxygenation (ECMO). therapy significantly alters midazolam's half-life, clearance, and volume of distribution (54). In term neonates diagnosed with hypoxic-ischemic encephalopathy receiving therapeutic hypothermia, studies have shown that this intervention does not significantly impact the clearance of phenobarbital or midazolam.

Drug interactions observed included one with indomethacin where exposure to indomethacin and its apparent effects on midazolam clearance suggested that alterations in drug disposition may arise from a patent ductus arteriosus or the direct impacts of indomethacin on hemodynamic or renal function (55).

These findings underscore the complexity of midazolam pharmacokinetics in neonates and the need for individualized dosing strategies based on factors such as gestational age, birth weight, disease state, and treatment modalities.

CONCLUSION

Antiseizure drug therapy in neonates represents one of the most challenging areas in paediatric pharmacotherapy, where the developing brain is uniquely vulnerable to both seizure-related injury and drug-induced neurotoxicity, creating critical needs for precision in therapeutic decision-making.

Substantial pharmacokinetic variability stems from physiological and developmental factors unique to neonates, compounded by distinct drug profiles and under-recognition of adverse reactions in NICUs. This highlights urgent needs for sophisticated drug therapy optimization approaches.

Key clinical implications emerge from this analysis. Firstly, Individualized dosing is essential, as standard weight-based approaches fail to account for profound pharmacokinetic variability. Second, Therapeutic drug monitoring should become routine practice, particularly for phenobarbital and phenytoin with narrow therapeutic windows. Lastly, Intensive care interventions including hypothermia, ECMO, and renal replacement

therapy significantly alter pharmacokinetics and require proactive dose adjustments.

Emerging evidence suggests levetiracetam potentially offers superior long-term safety compared to phenobarbital. However, phenobarbital remains ILAE-recommended first-line therapy due to superior seizure control efficacy, creating tension between immediate management and long-term neurodevelopmental considerations. Distinguishing medication effects from seizure-related injury requires further investigation.

Advanced quantitative methodologies, particularly physiologically-based pharmacokinetic modeling and population analysis, offer promising pathways forward. These approaches capture effects of age, organ development, and concomitant therapies on drug disposition, enabling precise exposure prediction and dosing individualization. Emerging technologies including dried blood spot sampling further enhance intervention precision.

The field must prioritize individualized therapy protocols considering patient characteristics, drug interactions, and long-term outcomes. Success requires a paradigm shift toward precision medicine that recognizes complex interplay between developmental physiology, disease pathology, and drug disposition in this vulnerable population.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

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