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Review Article

Clinical Pharmacology of Phenytoin in Infants and Children

Gian Maria Pacifici*

Department of Pharmacology, University of Pisa, Italy

Abstract

Phenytoin is effective against all types of focal and tonic-clonic seizures but not absence seizures. In infants, the status epilepticus is treated with phenytoin intravenous loading dose 20 mg/kg followed by a maintenance dose of 2 mg/kg twice-daily or thrice-daily. In children, the treatment of tonic-clonic seizures is carried out with oral phenytoin and the status epilepticus is treated with intravenous phenytoin and in both treatments phenytoin dose varies according to the child age. Phenytoin is hydrolysed into hydroxyphenytoin and also a phenytoin catechol derivative is formed, the catalysts are several CYPs, and p-hydroxyphenytoin is conjugated with glucuronic acid. Phenytoin elimination half-life is 20.7 and 15.1 hours in newborns and infants, respectively, and in diseased children, aged 9 months to 13 years, phenytoin was co-administered with chloramphenicol or cefotaxime and phenytoin half-life is 23.7 and 15.4 hours when phenytoin is co-administered with chloramphenicol or cefotaxime, respectively. The treatment and trials with phenytoin have been extensively studied in infants and children and phenytoin interacts with drugs. Phenytoin penetrates into the cerebrospinal fluid and is transported into the human brain in significant amounts. Phenytoin freely crosses the human placenta and migrates into the breast-milk where achieves concentrations of few µg/ml. The aim of this study is to review the published data of phenytoin dosing, pharmacokinetics, treatment, and trials in infants and children, and phenytoin metabolism, interaction with drugs, penetration into the cerebrospinal fluid, transport into the human brain, placental transfer, and migration into the beast-milk.

***Corresponding author**

Gian Maria Pacifici, Department of Pharmacology,University of Pisa, Associate professor of Pharmacology, via Sant'Andrea 32, 56127 Pisa, Italy, Email: pacifici44@tiscali.it

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- Infants
- children

INTRODUCTION

Phenytoin is effective against all types of focal and tonic-clonic seizures but not absence seizures. Oral phenytoin is indicated for the control of focal-to-bilateral tonic-clonic seizures and the prevention and treatment of seizures occurring during or following neurosurgery. Parenteral phenytoin is indicated for the control of generalized tonic-clonic status epilepticus and the treatment of seizures occurring during neurosurgery. Parenteral phenytoin should only be used when oral phenytoin administration is not possible [1].

Pharmacological effects of phenytoin in the central nervous system

Phenytoin exerts antiseizure activity without causing general depression of the central nervous system. In toxic doses, it may produce excitatory signs and at lethal levels a type of decerebrate rigidity [1].

Mechanism of phenytoin action

Phenytoin limits the repetitive firing of action potentials evoked by a sustained depolarization of mouse spinal cord neurons maintained in-vitro. This effect is mediated by slowing of the rate of recovery of voltage-activated Na^+ channels from inactivation, an action that is both voltage (greater effect if membrane is depolarized) and use dependent. At therapeutic concentrations, the effects of Na^+ channels are selective, and no changes of spontaneous activity or response to iontophoretically applied γ-aminobutyric acid (GABA) or glutamate are detected. At concentrations of 5- to 10-fold higher, multiple effects of phenytoin are evident, including reduction of spontaneous activity and enhancement of responses to GABA; these effects may underline some of the unwanted toxicity associated with high levels of phenytoin [1].

Therapeutic uses of phenytoin

Use for epilepsy: Phenytoin is one of the more widely used antiseizure drugs; it is effective against focal and generalized tonic-clonic, focal-to-bilateral tonic-clonic, tonic-clonic of unknown onset (tonic-clonic), but not generalized absence seizures. Phenytoin preparations differ significantly in bioavailability and rate of absorption. In general, patients should consistently be treated with the same drug from a single manufacturer. However, if it becomes necessary to temporarily switch between products care, care should be taken to select a therapeutically equivalent product and patients should be monitored for loss of seizure control or onset of new seizures.

Other uses: Trigeminal and related neuralgias occasionally respond to phenytoin, but carbamazepine may be preferable [1]. Phenytoin controls acute neonatal seizures as effectively as phenobarbital, but phenytoin is seldom the first anticonvulsant used because of its very unpredictable half-life [2]. Monitor bradycardia, arrhythmias, and hypotension during infusion. Observe intravenous site for extravasation. Follow serum concentration closely: therapeutic range is 6 to 15 µg/ml in the first weeks of life, then 10 to 20 µg/ml due to changes in protein binding. Obtain initial trough concentration 48 hours after intravenous loading dose. Phenytoin is incompatible with: fat emulsion, amikacin, cefepime, ceftazidime, chloramphenicol, clindamycin, dobutamine, enalaprilat, fentanyl, heparin, hyaluronidase, hydrocortisone succinate, insulin, lidocaine, linezolid, methadone, micafungin, morphine, nitroglycerin, pentobarbital, potassium chloride, procainamide, propofol, sodium bicarbonate, and vitamin K1 [3].

Administration, distribution, metabolism and elimination of phenytoin

Phenytoin is available in two types of oral formulations that differ in their pharmacokinetics: rapid-release and extended-release forms. Once-daily dosing is possible only with the extended-release formulation, and due to differences in dissolution and other formulation-dependent factors, the plasma phenytoin level may change when converting from one formulation to another. Confusion also can arise because different formulations can include either phenytoin or phenytoin sodium. Therefore, comparable doses can be approximately by considering "phenytoin equivalents", but serum-level monitoring is also necessary to ensure therapeutic safety. When changing routes of administration from oral to intramuscular (or vice versa), appropriate dose adjustments and blood level monitoring are recommended. The pharmacokinetic characteristics of phenytoin are influenced markedly by its binding to serum protein, by the nonlinear of its elimination kinetics, and by its metabolism by hepatic CYPs. Phenytoin induces CYP2C9, CYP3A4, and CYP1A2 and phenytoin inhibits CYP2C9 and is metabolized by CYP2C9 and by CYP2C19. Phenytoin is extensively bound (90%), to serum protein, mainly albumin. Small variations in the percentage of phenytoin that is bound dramatically affect the absolute amount of free (active) drug. Some agents can compete with phenytoin for binding sites on plasma proteins and increase the free phenytoin plasma. However, the effect of free phenytoin is only short-lived and usually does not cause clinical complications unless inhibition of phenytoin metabolism also occurs. For example, valproate competes for protein-binding sites and inhibit phenytoin metabolism, resulting in marked and sustained increase in free phenytoin. Measurement of free rather than total phenytoin permits direct assessment of this potential problem in patient management. The rate of elimination of phenytoin varies as a function of its concentration (i.e., the rate is nonlinear). The elimination half-life of phenytoin ranges between 2 and 24 hours at plasma concentrations < 10 µg/ml. At low blood levels, metabolism follows first-order kinetics; as blood levels rise, the maximal limit of the liver to metabolize phenytoin is approached, and plasma concentration increases disproportionately as dosage is increased, even with small adjustment for levels near the therapeutic range. The majority (95%), of phenytoin is metabolized by CYP2C9 and to a lesser extent by CYP2C19. The principal metabolite is p-hydroxyphenytoin derivative which is inactive. Because its metabolism is saturable, other drugs that are metabolized by these CYP enzymes can inhibit the metabolism of phenytoin and increase its plasma concentration. Conversely, the degradation rate of other drugs that serve as substrates for these enzymes can be inhibited by phenytoin; one such drug is warfarin, and addition of phenytoin to a patient receiving warfarin can lead to blending disorders. Concurred administration of any drug metabolized by CYP2C9 can increase the plasma concentration of phenytoin by decreasing its rate of metabolism. Conversely, the degradation rate of other drugs that are substrates for these enzymes can be inhibited by phenytoin [1] (Figure 1 and Figure 2).

LITERATURE SEARCH

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "phenytoin dosing infants, children", "phenytoin metabolism", "phenytoin pharmacokinetics infants, children", "phenytoin treatment infants, children", "phenytoin trials infants, children", "phenytoin drug interactions", "phenytoin CSF", "phenytoin human brain", "phenytoin placental transfer", and "phenytoin breast-milk". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and Mangum [3], and The British National Formulary for Children [4] have been consulted.

RESULTS

Administration schedules of phenytoin to infants and children

Administration to infants [2]: A loading dose of 20 mg/kg of phenytoin given by intravenous infusion over 10 to 20 min (to prevent hypotension, arrhythmia, and pain at the injection site) will usually control acute status epilepticus in

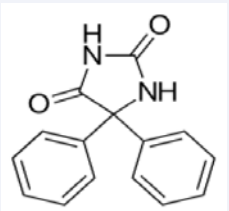

Figure 1 Phenytoin molecular structure (molecular weight = 252.268 grams/mole).

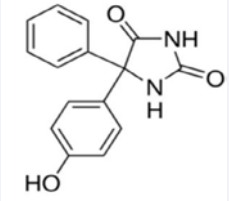

Figure 2 p-Hydroxyphenytoin molecular structure (molecular weight = 268.27 grams/mole).

the newborn. For infants older than this 18 mg/kg is the usual recommended dose. The optimum maintenance dose is variable but 2 mg/kg intravenously every 8 to 12 hours will usually maintain a therapeutic level in the first week of life, and the same maintenance dose usually works when given orally (at least in infants over 2 weeks old). Older infants may require 2 or 3 times as much as this (i.e., 10 to 20 mg/kg dally). Crystallization makes the intramuscular route unsatisfactory. The optimum plasma concentration is usually 10 to 20 μg/ml, but 20% less that this in the first 3 months of life because of reduced protein binding. Levels must be measured if phenytoin is given for more than 2 to 3 days in infants only a few months old.

Administration to children [4]:

Oral treatment of tonic-clonic seizures and focal seizures:

Children aged 1 month to 11 years. Give initially 1.5 to 2.5 mg/kg twice-daily, and then adjust the dose according to the response to 2.5 to 5 mg/kg twice-daily (maximum per dose = 7.5 mg/kg twice-daily), and the dose should also be adjusted according to plasma phenytoin concentration (maximum daily dose = 300 mg).

Children aged 12 to 17 years. Give initially 75 to 150 mg twice-daily, and then adjust the dose according to the response to 150 to 200 mg twice-daily (maximum per dose = 300 mg twice-daily) and the dose should also be adjusted according to the phenytoin plasma concentration.

Oral prevention and treatment of seizures during or following neurosurgery or severe head injury:

Children. Give initially 2.5 mg/kg twice-daily, and then adjust the dose according to the response up to 4 to 8 mg/kg daily, the dose should also adjusted according to the plasma phenytoin concentration (maximum daily dose = 300 mg).

Intravenous administration for the status epilepticus and acute symptomatic seizures associated with head trauma or neurosurgery:

Children aged 1 month to 11 years. Give: a loading dose of 20 mg/kg, and then (by slow intravenous injection or by intravenous infusion) give 2.5 to 5 mg/kg twice-daily.

Children aged 12 to 17 years. Give: a loading dose of 20 mg/kg, and then (by intravenous infusion or by slow intravenous injection) up to 100 mg thrice-daily or 4 times-daily.

METABOLISM OF PHENYTOIN

Phenytoin is primarily metabolized to the inactive hydroxyphenytoin and up to 90% of phenytoin is metabolized to p-hydroxyphenytoin and then glucuronidated and excreted into the urine. Hydroxyphenytoin can be converted to a catechol 3'-4'-di-hydroxyphenytoin by several CYPs. CYP2C19 is found to be the most effective catalyst of catechol formation; however, CYP2C9 and CYP3A4 may be responsible for the majority of the transformation because of their relative predominance in the liver. CYP3A5, CYP3A7, CYP2D6, and CYP2B6 are also shown to catalyse the catechol formation to some extent. p-Hydroxyphenytoin is glucuronidated by specifically UGT1A1, UGT1A4, UGT1A6, and UGT19. The glucuronidation of p-hydroxyphenytoin is stereoselective with UGT1A1 glucuronidating the S isomer

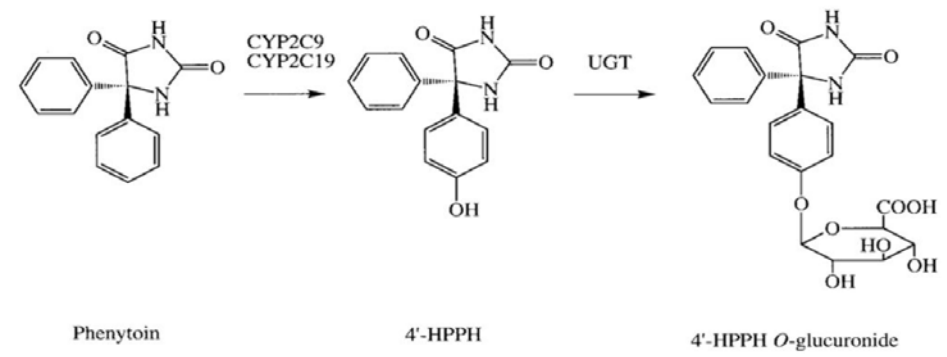

Figure 3 4'HPPH = p-hydroxyphenytoin. 4'HPPH O-glucuronide = p-hydroxyphenytoin-O-glucuronide.

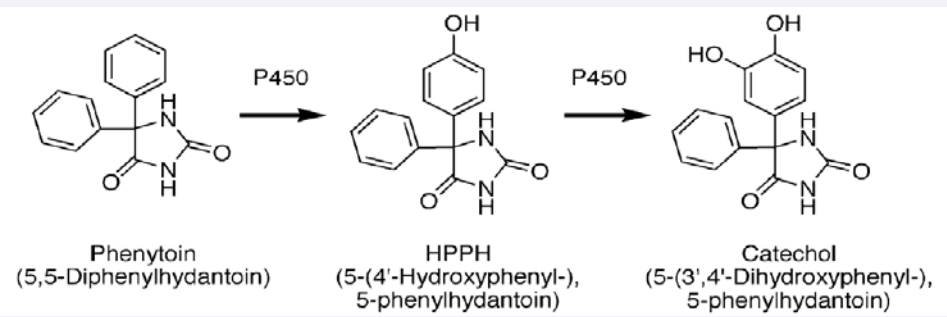

Figure 4 Metabolism of Phenytoin.

preferentially and UGT1A9 and UGT2B15 acting on the R isomer [5] (Figure 3 and Figure 4).

The cytochrome P-450 is the most effective catalyst of hydroxyphenytoin oxidation to the catechol metabolite and is also associated with the highest levels of covalent adduct formation. CYPs 3A4, 3A5, 3A7, 2C9*1, and 2C9*2 also catalyse bioactivation of hydroxyphenytoin, but to a lesser extent. The CYP2C19 and other forms of 2C and 3A subfamilies may be targets as well as catalysts of drug-protein formation from phenytoin [6]. Phenytoin plasma concentrations and CYP2C9, CYP2C19, and ABCB1 genetic polymorphism are analysed. Initial phenytoin concentrations are higher than expected (69 µg/ml); normal range: 10 to 20 µg/ml, and the patient is homozygous for the CYP2C9*2 allele, heterozygous for the CYP2C19*4 allele and homozygous for the 3435C and 1236C ABCB1 alleles. The association of these genes with phenytoin-induced adverse-effects is documented in adult population. These genetic polymorphisms cause phenytoin plasma concentrations and toxicity [7]. It was explored the possible influence of CYP2C9 (*2, *3 and IVS8-109 A>T), CYP2C19 (*2, *3 and *17), and ABCB1 (1236C>T, 2677G>A/T and 3435C>T) on phenytoin plasma concentrations in 64 Mexican Mestizo patients with epilepsy currently treated with phenytoin in mono- (N = 25), and poly-therapy (N = 39). Genotype and allele frequencies of these variants were also estimated in 300 Mexican Mestizo healthy volunteers. Linear regression models are used to assess associations between the dependent variables (phenytoin plasma concentration and dose-corrected phenytoin concentration) with independent variables (CYP2C9, CYP2C19 and ABCB1 genotypes, ABCB1 haplotypes, age, sex, weight, and poly-therapy). In multivariate models, CYP2C9 IVS8-109 T was significantly associated with higher phenytoin plasma concentrations (P-value = 0.03). Moreover, this allele is more frequent in the supra-therapeutic group as compared with the subtherapeutic group (0.13 versus 0.03, respectively; P-value = 0.05, Fisher's exact test). Results suggest that CYP2C9 IVS8-109 T allele may decrease CYP2C9 enzymatic activity on phenytoin [8]. The CYP2C9 genetic polymorphisms (particularly the *3 allele) are associated with high risk of epileptic patients developing phenytoin-induced neurological toxicity [9]. The percentage increase in free phenytoin concentration by undernourishment, CYP2C9 allelic variants, and undernourishment CYP2C9 allelic variants are 127%, 290%, and 472%, respectively, compared to well-nourished patients with the wild-type CYP2C9 genotype group. The contribution of undernourishment and genetic factors (CYP2C9 allelic variant) for developing phenytoin toxicity was calculated to have an odds ratio of 37.3 (P-value < 0.0001). Undernourishment and variant CYP2C9 alleles elevate free phenytoin concentrations individually and in combination show additive effects [10].

PHARMACOKINETICS OF PHENYTOIN IN INFANTS

Loughnan et al. [11], studied the pharmacokinetics of phenytoin in newborns and infants and phenytoin was administered intravenously at a dose of 8 mg/kg once-daily (Table 1).

This table shows that the distribution volume of phenytoin is similar to the water volume and the elimination half-life of phenytoin is longer in newborns than in infants.

This Table 2 shows that the distribution volume of phenytoin in preterm infants is similar to that of term newborns and there is a remarkable interindividual variability in the elimination half-life of phenytoin in preterm infants. The elimination half-life of phenytoin is longer in preterm infants than in term newborns but because of the wide variability of elimination half-life of phenytoin and the little number of cases of preterm infants the difference is not significant when the phenytoin elimination half-life is compared between preterm infants that of newborns.

PHARMACOKINETICS OF PHENYTOIN IN CHILDREN

Ogutu et al. [12], investigated the pharmacokinetics of phenytoin in 15 children, aged 9 months to 13 years, and a single intramuscular phenytoin dose of 18 mg/kg was administered. Phenytoin was co-administered with chloramphenicol at a dose of 25 mg/kg 4 times-daily or with cefotaxime at a dose of 25 mg/kg thrice-daily and both treatments lasted 72 hours.

Table 1: Pharmacokinetic parameters of phenytoin which are obtained in 6 newborns and 7 infants. Figures are the minimum, maximum, mean, and ±SD, by Loughnan et al. [11].

Value	Postnatal age	Distribution volume (L/kg)	Elimination half-life (h)
Newborns (N = 6)			
Minimum	2.0 days	0.71	6.8
Maximum	4.0 days	1.02	41.9
Mean	2.8 days	0.80	20.7
SD	±0.4 days	±0.26	±11.6
Infants (N = 7)			
Minimum	2.0 weeks	0.53	4.6
Maximum	96 weeks	1.04	15.1
Mean	30.9 weeks	0.73	7.6
SD	±14.2 weeks	±0.18	±3.5
*Distribution volume newborns versus infants P-value = 0.6782			
*Elimination half-life newborns versus infants P-value 0.0455			
*Student t test for unpaired data.			

Table 2: Pharmacokinetic parameters of phenytoin which are obtained in 4 preterm infants. Figures are the minimum, maximum, mean, and ±SD, by Loughnan et al. [11].

Value	Gestational age (week)	Body-weight (grams)	Postnatal age (day)	Distribution volume (L/kg)	Elimination half-life (h)
Minimum	26.0	760	2	0.57	15.6
Maximum	36.0	2,950	18	1.00	160
Mean	32.0	1,614	7.4	0.80	75.4
SD	±1.6	±498	±3.0	±0.22	±64.5
*Distribution volume preterm infants versus term newborns P-value = 1.0000					
*Elimination half-life preterm infants versus term newborns P-value = 0.1189					
* Student t test for unpaired data.					

Table 3: Pharmacokinetic parameters of phenytoin which are obtained in 15 children and phenytoin was co-administered with chloramphenicol or with cefotaxime. Figures are the mean ±SD or the mean and (range), by Ogutu et al. [12].

Parameter	Chloramphenicol group	Cefotaxime group	95% CI of difference between means
$AUC_{0-\infty}$ total (µg/ml*h)	841±426 (N = 11)	563±225 (N = 8)	-634, 65.3
$AUC_{0-\infty}$ unbound (µg/ml*h)	58.5±24.2 (N = 7)	47.6±9.4 (N = 6)	-35.0, 11.4
Fraction unbound	0.06±0.03 (N = 7)	0.09±0.04 (N = 6)	-001, 0.07
Elimination half-life (h)	23.7±9.1 (N = 10)	15.4±2.8 (N = 9)	-1.71, 14.99
CSF to plasma ratio of phenytoin	0.21 (0.14 – 0.40) N = 12	0.22 (0.01 – 0.41) N = 10	-0.08, 0.10
Peak conc. total (µg/ml)	15.0 (7.5 – 34.6) N = 15	14.4 (8.3 – 34.9) N = 9	-5.0, 6.6
Peak conc. unbound (µg/ml)	1.12 (0.6 – 1.8) N = 12	1.28 (0.96 – 1.95) N = 10	-0.5, 0.04
Tmax (h)	4.0 (0.33 – 12.0) N = 15	4.0 (0.33 – 12.0) N = 13	-2.0, 3.7
CSF = cerebrospinal fluid. Tmax = time to reach the phenytoin peak concentration. CI = confidence interval.			

This Table 3 shows that phenytoin is tightly bound to plasma protein, is slowly absorbed following intramuscular dosing, is slowly cleared from the body, the cerebrospinal fluid to plasma ratio of phenytoin is 0.20 suggesting that phenytoin penetrates into the cerebrospinal fluid is significant amounts, the co-administration of chloramphenicol increases the elimination half-life of phenytoin compared to children who received cefotaxime but in these two groups of children the elimination half-life of phenytoin is not significantly different, and there is a remarkable interindividual variability in pharmacokinetic parameters. This variability may be accounted by the wide variability in child age, disease, and concomitant therapy. The comparison of phenytoin elimination half-life between children and infants (for infants see tables 1 and 2), is difficult because the wide variability in child age, disease, and concomitant therapy.

TREATMENT OF INFANTS AND CHILDREN WITH PHENYTOIN

In the first 2 years of life, intravenous administration of phenytoin is useful for status epilepticus but oral treatment is poorly effective with difficulty to achieve appropriate and stable therapeutic plasma concentrations and with frequent adverse-effects [13]. Phenobarbital and phenytoin are equally but incompletely effective as anticonvulsants in neonates. With either drug given alone, the seizures were controlled in fewer than half of neonates [14]. Following a phenytoin loading dose of 18 mg/kg, blood levels were sub-therapeutic in 22% children therapeutic in 62% children and supra-therapeutic in 16% children. After a loading dose of 20 mg/kg, the percentages were 15, 59, and 26, respectively [15]. Intravenous phenytoin and intramuscular fosphenytoin demonstrate that the efficacy, safety, and pharmacokinetics of these drugs are similar in 5- to 18-year-old children [16]. In status epilepticus, phenytoin dose should be adjusted according to plasma concentrations to avoid overdosage and paradoxical inefficacy [17]. Fifteen infants and children were treated with phenytoin for status epilepticus. They received doses of 31.5 mg/kg in the first 24 hours, 18.5 mg/kg on the second day and 11 mg/kg on the third day and this treatment controls seizures [18].

TRIALS WITH PHENYTOIN IN INFANTS AND CHILDREN

A trial showed that intravenous phenytoin and fosphenytoin are the current recommended first-choice second-line drug treatments in infants aged 6 months and older infants with seizures [19]. The efficacy of levetiracetam is similar to phenytoin as second line of antiseizure medication for paediatric convulsive seizures [20]. Levetiracetam is more effective than phenytoin for seizure control in children with status epilepticus, and it is safe and effective as a second-line therapy [21]. A randomised controlled trial showed that levetiracetam and phenytoin are effective in children with convulsive status epilepticus in whom benzodiazepines have failed [22]. Levetiracetam is not superior to phenytoin for second-line management of paediatric convulsive status epilepticus [23]. Although levetiracetam is not significantly superior to phenytoin the safety profiles and comparative ease of levetiracetam administration suggest that levetiracetam is an appropriate alternative to phenytoin as

the first-choice second-line anticonvulsant in the treatment of paediatric convulsive status epilepticus [24]. Prophylactic phenytoin is efficacy in preventing early posttraumatic seizures in children with moderate to severe blunt head injury [25].

INTERACTION OF PHENYTOIN WITH DRUGS

Phenytoin is an inducer of cytochrome CYP3A4 and quetiapine is a substrate of this enzyme. Phenytoin co-administered with quetiapine results in a significant reduction in quetiapine blood and yielding a lack of quetiapine efficacy [26]. Warfarin and phenytoin combination requires discontinuation of therapeutic-dose phenytoin secondary to possible purple glove syndrome [27]. Co-administration of phenytoin with posaconazole significantly reduces posaconazole exposure and increases plasma phenytoin levels and this drug combination should be avoided [28]. A drug interaction between phenytoin and efavirenz results in lower efavirenz plasma concentrations and elevated phenytoin levels [29]. Liver CYPs stimulation by phenytoin enhances the elimination half-life of dexamethasone reducing the dexamethasone steroidal effect [30]. The total amounts of dexamethasone administered during the 24 hour period ranges from 16 to 150 mg. The average serum phenytoin concentration is 17.28±3.49 μg/ml in patients receiving both drugs, as compared to 12.48±3.52 μg/ml in patients receiving only phenytoin (P-value < 0.001). Thus serum phenytoin concentrations should be monitored in patients receiving concurrent dexamethasone therapy [31]. Following the co-administration of phenytoin with dexamethasone, the subtherapeutic phenytoin concentration decreases by a diminished phenytoin absorption-rate and increased phenytoin metabolism [32]. The Vmax values of phenytoin (mg/kg daily) are 16.1 without allopurinol, and 12.4 and 10.9 with allopurinol given at doses of 150 and 200 mg/day, respectively, whereas those for Km remained relatively constant 3.9 to 4.9 μg/ml, thus allopurinol inhibits the hepatic metabolism of phenytoin [33]. A study suggests that tricyclic antidepressants inhibit both CYP2D6 and CYP2C19 and the interaction between tricyclic antidepressants and phenytoin involves inhibition of CYP2C19-catalyzed phenytoin increasing phenytoin blood concentration of p-hydroxylation [34]. The addition of phenytoin to mirtazapine results in a mean decrease of the $AUC_{0\text{-}24h}$ from 576±104 to 305±81.6 ng/ml and a mean decrease of peak concentration from 69.7±17.5 to 46.9±10.9 ng/ml of phenytoin. These effects are due to an induction of CYP3A which reduces phenytoin disposition [35].

PENETRATION OF PHENYTOIN INTO THE CEREBROSPINAL FLUID (CSF)

The ratio of CSF to serum phenytoin concentrations is 0.16±0.08 with gradual increase over the first 8 hours as the serum phenytoin concentration decreases. There is a good correlation between therapeutic outcome and CSF phenytoin levels [36]. A phenytoin dose of 750 mg daily provides therapeutic human plasma and CSF concentrations [37].

TRANSPORT OF PHENYTOIN INTO THE HUMAN BRAIN

Phenytoin loading dose of 20 mg/kg was infused at a rate of 50 mg/min followed by a maintenance dose 5 mg/kg. The median phenytoin concentration in brain was found to be significantly decreased (64.8%), in aneurysmal subarachnoid haemorrhage group (3.78 μg/gram) as compared to control brain (10.73 μg/gram), P-value = 0.010. Similarly, median phenytoin brain concentration as fraction of plasma was significantly decreased in aneurysmal subarachnoid haemorrhage group (36.72%), compared to that of control brain (89.55%), P-value = 0.003 [38]. The kinetic profiles of phenytoin for the frontal cortex and hippocampus were indistinguishable suggesting that phenytoin distribution in the brain is not brain region specific [39]. An investigation performed with microanalysis in the human brain revealed that, at steady-state concentration, the extracellular fluid of phenytoin concentration correlates closely to unbound serum concentrations and no differences are observed between different sites within the brain [40]. A good correlation was found between the plasma and brain concentrations of phenytoin. Similarly, a good correlation was found between the plasma and cerebrospinal concentrations of phenytoin [41]. Under usual clinical circumstances, human brain accumulates phenytoin against a concentration gradient; the accumulative process may be due to binding of phenytoin to tissue proteins and phospholipids [42].

TRANSFER OF PHENYTOIN ACROSS THE HUMAN PLACENTA

The placental transfer of phenytoin and its metabolites: p-hydroxy-phenytoin, and p-hydroxy-phenytoin-glucuronide, was studied in term placental lobules perfused single pass in both maternal and fetal circuits. The ratios of clearance of phenytoin and these metabolites are 1.08±0.03, 0.52±0.02 and 0.12±0.01, respectively, suggesting that phenytoin freely crosses the human placenta whereas the transfer-rate of phenytoin metabolites is lower than that of phenytoin [43]. In six full-term newborn infants born to epileptic mothers, the cord-to-maternal concentration ratio of phenytoin is 1.71±0.23 [44].

MIGRATION OF PHENYTOIN INTO THE BREAST-MILK

Two lactating women were taking phenytoin at a dose of 300 mg daily. In a woman the concentration of phenytoin in the breast-milk ranges from 1.2 to 2.2 μg/ml at various times on days 4 to 6 postpartum. In the other woman the phenytoin concentration ranges from 1.0 to 2.6 μg/ml on days 1 to 4 postpartum and was 1.3 μg/ml on day 33 postpartum [45]. In a woman taking phenytoin 500 mg daily in 2 divided doses, the breast-milk concentration of phenytoin was 0.58 μg/ml 3 hours after the morning dose and 0.26 μg/ml 1 hour before the evening dose [46]. Phenytoin concentration was measured in the breast-milk of 5 women. In a woman taking 100 mg daily of phenytoin, the breast-milk concentration is 0.76 μg/ml 3 days postpartum. In 4 other women taking 300 mg daily of phenytoin, the breast-milk concentrations on several occasions mostly during the first week postpartum ranges from 0.41 to 1.3 μg/ml. Most of the levels were in the range of 0.5 to 0.6 μg/ml [47]. Phenytoin excretion into human breast-milk was studied in six nursing women with epilepsy. The average ratio between the AUC plasma to breast-milk is 0.13. There is a good (r = 0.97), correlation between the mean plasma and breast-milk concentrations of phenytoin, and

an even better relation (r = 0.99), between the AUC for phenytoin in plasma and the mean breast-milk concentration. The ratio between unconjugated and conjugated p-hydroxyphenytoin in plasma to breast-milk is 0.08 and 0.09, respectively [48].

DISCUSSION

Phenytoin is effective against all types of focal and tonic-clonic seizures but not absence seizures. Oral phenytoin is indicated for the control of focal-to-bilateral tonic-clonic seizures and for the prevention and treatment of seizures occurring during or following neurosurgery. Parenteral phenytoin in indicated for the control of generalized tonic-clonic status epilepticus and the treatment of seizures occurring during neurosurgery [1]. In newborns, the status epilepticus is treated with intravenous phenytoin loading dose of 20 mg/kg followed by a maintenance dose of 2 mg/kg twice-daily or thrice-daily and in older infants the loading dose is 18 mg/kg [2]. In children, the treatment of tonic-clonic seizures and focal seizures consists in an oral phenytoin and the status epilepticus, the seizures associated with head trauma, or neurosurgery are treated with phenytoin intravenously and the dose varies according to the child age for these treatments [4]. The metabolism of phenytoin has been extensively studied [5-10]. Phenytoin is primary metabolized to the inactive hydroxyphenytoin up to 90% of phenytoin and p-hydroxyphenytoin is the mean metabolite which is glucuronidated. Hydroxyphenytoin is converted into the catechol 3'-4'-di-hydroxyphenytoin by several CYPs. CYP2C19 is the most effective catalyst of catechol formation however CYP2C9 and CYP3A4 are responsible for the majority of the transformation because of their predominance in the liver. p-Hydroxyphenytoin is conjugated to glucuronic acid by various UGT enzymes and phenytoin and its metabolites are excreted in the urine. The glucuronidation of p-hydroxyphenytoin is stereoselective with UGTA1 glucuronidating the S isomer preferentially and UGT1A9 and UGT2B15 acting on the R isomer [5]. CYPs are the most effective catalyst of hydroxyphenytoin catechol and CYP 3A4, 3A5, 2C9*1, and 2C9*2 catalyse the bioactivation of hydroxyphenytoin but at lesser extent [6]. The metabolic-rate of phenytoin, the formation-rate of adverse-effects, the phenytoin plasma concentration, and the therapeutic effect of phenytoin vary according to the polymorphic CYP2C9, CYP2C19, and the ABCB1 gene [7, 8]. CYP2C9 genetic polymorphism (particularly the *3 allele) cause neurologic toxicity in epileptic patients treated with phenytoin [9]. The percentage increase in free phenytoin concentration by undernourishment, CYP2C9 allelic variants, and undernourishment CYP2C9 allelic variants are 127%; 290%, and 472%, respectively, compared to well-nourished patients with the wild-type CYP2C9 genotype group. The contribution of undernourishment and gene factors (CYP2C9 allelic variant) for developing phenytoin toxicity was calculated to have an odds ratio of 37.3 (P-value < 0.0001) [10]. The pharmacokinetics of phenytoin were studied in 6 newborns and in 7 infants and the elimination half-life of phenytoin is 20.7 and 7.6 hours (P-value = 0.0455), in newborns and infants, respectively, and it is 75.4 hours in 4 preterm infants [11]. Phenytoin is cleared from the body by renal route and metabolism and both elimination pathways increase with infant maturation. Phenytoin was administered intramuscularly to 15 diseased children, aged 3 months to 13 years, and phenytoin was co-administered with chloramphenicol or with cefotaxime. Phenytoin is slowly absorbed following intramuscular administration as the time to reach the peak concentration of phenytoin is 4 hours. The elimination half-life is 23.7 and 15.4 hours in children who were co-treated with chloramphenicol or cefotaxime, respectively [12]. The treatment with phenytoin has been studied in infants and children [13-18]. Intravenous phenytoin is more effective than oral phenytoin in treating status epilepticus in infants [13], and phenobarbital or phenytoin control seizures in fewer than half of infants [14]. A phenytoin loading dose of 20 mg/kg is more effective than a loading dose of 18 mg/kg in controlling seizures in children [15], intravenous phenytoin and intramuscular fosphenytoin are equally effective in controlling childhood seizures [16], the phenytoin dose should be adjusted according to the plasma concentration in order to optimize the treatment of status epilepticus [17], and seizures are controlled with 31.5, 18.5, and 11 mg/kg of phenytoin in the first, second, and third day, respectively, of treatment [18]. The trials with phenytoin have been conducted in infants and children [19-25]. Intravenous phenytoin and fosphenytoin are the first-choice second-line treatment of seizures in young and older infants [19], levetiracetam and phenytoin are similarly effective in controlling the statue epilepticus in children [20-24], and prophylactic phenytoin is efficacy in preventing posttraumatic seizures in children with moderate to severe blunt head injury [25]. The interaction of phenytoin with drugs has been extensively studied [26-35]. Phenytoin reduces the quetiapine blood concentration as phenytoin is an inducer of CYP3A4 and quetiapine is metabolized by this enzyme [26], warfarin combined with phenytoin causes purple glove syndrome [27], the co-administration of phenytoin with posaconazole reduces posaconazole exposure and increase phenytoin plasma concentration [28], phenytoin decreases the plasma level of efavirenz [29], phenytoin stimulates hepatic CYPs thus enhancing the elimination half-life of dexamethasone [30], phenytoin plasma concentration is decreased when phenytoin is combined with dexamethasome [31], as dexamethasone reduces the phenytoin absorption-rate [32]. Allopurinol inhibits the hepatic metabolism of phenytoin [33], tricyclic antidepressants inhibit both CYP2D6 and CYP2C19, phenytoin is metabolized by CYP2C19 thus tricyclic antidepressants increase phenytoin exposure [34], and mirtazapine decreases phenytoin exposure [35]. Phenytoin penetrates into the cerebrospinal fluid, the ratio of phenytoin concentration in the cerebrospinal fluid to serum ratio is 0.16 [36], and a phenytoin dose of 750 mg daily provides therapeutic concentration in the cerebrospinal fluid [37]. The transport of phenytoin into the human brain has been investigated [38-41]. The transport of phenytoin is decreased in aneurysmal subarachnoid haemorrhage compared to control brain [38], phenytoin distributes in the frontal cortex and hippocampus is similar amounts suggesting that phenytoin distribution is not brain region specific [39], the concentration of phenytoin in the brain extracellular fluid correlates with the unbound phenytoin serum concentration [40], there is a good correlation between the concentration of phenytoin in plasma and brain [41], and human brain accumulates phenytoin against a concentration gradient as phenytoin binds to brain protein and phospholipids [42]. The transfer of phenytoin across the human placenta was studied in-vitro using the placental perfusion [43], and *in-vivo* in women at term of pregnancy [44], and phenytoin

freely crosses the human placenta. The migration of phenytoin into the breast-milk has been extensively studied [45-48], and following phenytoin therapeutic dosing phenytoin concentration in the breast-milk is of few µg/ml.

In conclusion, phenytoin is effective against all types of focal and tonic-clonic seizures but not absence seizures. Oral phenytoin is indicated for the control of focal-to-bilateral tonic-clonic seizures and intravenous phenytoin is used in the control of generalized tonic-clonic status epilepticus and the treatment of seizure occurring during neurosurgery. The status epilepticus in infants is treated with an intravenous loading dose of 20 mg/kg followed by a maintenance dose of 2 mg/kg. In children, the tonic-clonic and focal seizures are treated with oral phenytoin and the status epilepticus, the seizures associated with head trauma, or neurosurgery are treated with intravenous phenytoin and in these treatments phenytoin dose varies according to the child age. Phenytoin is extensively metabolized by several CYPs, the mean metabolites are p-hydroxyphenytoin and a catechol derivative and p-hydroxyphenytoin is glucuronidated. The elimination half-life of phenytoin is 20.7 and 7.6 hours in newborns and infants, respectively. Phenytoin is cleared from the body by metabolism and renal route and both elimination pathways increase with infant maturation. In diseased children who were treated with phenytoin co-administered with either chloramphenicol or cefotaxime, the elimination half-life is 23.7 and 15.4 hours in children co-treated with chloramphenicol and cefotaxime, respectively. The treatment and trials with phenytoin have been extensively studied and phenytoin interacts with different drugs. Phenytoin penetrates into the cerebrospinal fluid in significant amounts and this dug is transported into the human brain. Phenytoin freely crosses the human placenta and migrates into the beast-milk where reaches a concentration of few µg/ml following phenytoin therapeutic treatment in lactating women. The aim of this study is to review the clinical pharmacology of phenytoin in infants and children.

CONFLICT OF INTERESTS

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria. This article is a review and drugs have not been administered to men or animals.

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