ORAL DOSING REQUIREMENTS FOR PHENYTOIN IN THE FIRST THREE MONTHS OF LIFE

Anita Cheng[2], Brenda Banwell[1], Simon Levin[2], Jamie A Seabrook[3], David Freeman[2], Michael Rieder[2]

[1]Department of Paediatrics, Neurology, The Hospital for Sick Children, University of Toronto, Toronto, Canada; [2]Department of Paediatrics, Physiology & Pharmacology and Medicine, University of Western Ontario, London, Canada; [3]Departments of Paediatrics and Sociology, The University of Western Ontario, Children's Health Research Institute, Children's Hospital, London Health Sciences Centre, London, Canada

Corresponding Author*: mrieder@uwo.ca*

ABSTRACT

Background
Historically, physicians have been reluctant to maintain infants on phenytoin (PHT) following initial stabilization with intravenous loading doses, as therapeutic blood levels are difficult to achieve with conventional oral doses, and there is concern that high doses will result in toxicity.

Objectives
To determine the oral dose of PHT required to achieve therapeutic blood concentrations, without clinical toxicity, in the first weeks of life.

Methods
Eight infants with seizures were treated with phenytoin from 2 weeks to 3 months of age. Total and free phenytoin concentrations, and urine phenytoin metabolite (p-hydroxyphenytoin) were measured every 2 weeks. Parents were asked to note seizure frequency and complete a questionnaire about possible side effects every 2 weeks.

Results
No infants had seizures and no clinical side effects were noted. Doses required to achieve therapeutic serum concentrations ranged from 10-20mg/kg/day, considerably higher than doses required in adults. Free phenytoin levels were 8-13% of total serum concentrations, similar to ratios reported in adults.

Conclusion
To achieve therapeutic serum phenytoin levels in infants, doses of 10-20 mg/kg/day are required. These higher doses can be safely administered without clinical toxicity.

Key Words: *Phenytoin, pharmacokinetics, drug safety, drug dosing*

Seizures in neonates are conventionally treated with either Phenytoin (PHT) or Phenobarbital (PB), although use of newer agents such as oxcarbamezepine, lamotrigine, or use of medications such as lidocaine has also been reported.[1-6] PB may cause significant behavioural side effects, including sedation or excitability, which compromises both the neurological examination and may interfere with normal feeding and sleep.[7,8] PHT is associated with fewer behavioural effects. However, physicians are reluctant to maintain infants on PHT following initial stabilization with intravenous loading doses because therapeutic blood levels are difficult to achieve with conventional oral doses and there is concern that high doses will result in toxicity. There are few studies of PHT pharmacokinetics in the neonatal age group, and thus dosing

requirements and PHT metabolism is not well established.[9-12]

Toxic effects of short-term PHT administration, including ataxia, sedation, and liver dysfunction have been well described, but are rare in infants.[7,9,10] Clinical experience suggests that most infants tolerate PHT well with no interference with feeding or level of alertness. The efficacy of PHT is well established for generalized seizures in children[9], and is identified as effective in the control of neonatal seizures.[13]

There is some evidence that high oral PHT doses are required to achieve therapeutic PHT levels in infants. Suzuki et al demonstrated that only 43% of infants had PHT concentrations within therapeutic range when dosed at the conventional 4-8mg/kg/day.[14] In this pilot study, we determined the oral dose of PHT required to achieve therapeutic blood concentrations in the first weeks of life, and evaluate clinical tolerability.

METHODS

Neonates were prospectively recruited from the Children's Hospital nursery and St. Joseph's Hospital Neonatal Intensive Care Units in London, Ontario.

For inclusion, infants were required to be born at term (>37 weeks gestation), to have presented with their first clinical seizure prior to 14 days of age, to have experienced more than one seizure, and to have been prescribed anticonvulsant therapy for at least 3 months (as determined by the treating neurologist based on clinical presentation and seizure severity). Infants born to women taking PHT during gestation, infants with liver disease, non-physiologic hyperbilirubinemia or renal disease, infants receiving parenteral nutrition, nasogastric tube feedings, or concomitant medications with known hepatic metabolism were excluded. These exclusions were based on the assumption that the aforementioned factors would alter drug metabolism. Infants requiring a second anticonvulsant due to inadequate seizure control (greater than 2 seizures despite therapeutic PHT levels) were to be excluded from further analyses.

Eligible infants were recruited consecutively over a twelve month period. One infant initially included in the study was subsequently excluded prior to any testing due to transfer to another institution, and a further child was enrolled.

Informed parental consent was obtained from all families, and the study was approved by the Review Board for Health Sciences Research Involving Human Subjects at the University of Western Ontario.

All patients received loading doses of PHT (20mg/kg) intravenously at the onset of seizures. Subsequent PHT dose adjustments were made according to a predetermined protocol (initial maintenance dose 10mg/kg/day, and 25% increase or decrease in dose based on serum levels and current weight). All infants were given phenytoin 25mg/mL suspension in a twice daily oral regimen.

Parents completed a questionnaire every two weeks about possible PHT side effects (rash, irritability, drowsiness, and poor feeding), intercurrent illness, seizure frequency and medication compliance.

Heel prick blood samples (2mL) were collected every two weeks for three months (6 visits per patient). Samples were analyzed for total serum trough PHT, trough free PHT, liver enzymes (aspartate transaminase, alkaline phosphatase), serum urea, creatinine, bilirubin and albumin. Samples were collected prior to the morning dose of PHT. A total of 48 samples from 8 patients (6 samples per patient) were obtained for total serum PHT level and biochemistry. A total of 36 samples were available for serum free PHT analysis. Twelve free PHT levels could not be measured due to insufficient sample volumes.

Urine samples were collected in an adhesive plastic urinary bag every two weeks on the morning of the blood sample. Urinary PHT metabolite (p-OH-PHT) concentrations were analyzed in 100µL aliquots by reverse phase high performance liquid chromatography (HPLC) following solid phase extraction on C18 micro columns. Thirty-nine samples were available for analysis. Nine samples leaked in transport.

Chromatography of all urine extracts was performed on a Spherisorb C8 (5u) column (10cm x 0.32 cm ID) heated to 50ºC. The mobile phase was 35% MeOH/H_2O adjusted to a final pH of 3.5 with phosphoric acid. Flow rate was maintained 0.5mL/min and the column effluent monitored at

210 nm. Quantization of PHT and its metabolite (p-OH-PHT) was performed automatically by external standardization based on peak areas.

Random samples of each patient's commercial suspension of PHT 25mg/mL were analyzed to ensure that the appropriate concentration of PHT was present. Parents were instructed at the onset of the study on the importance of shaking the PHT bottle prior to administration.

RESULTS

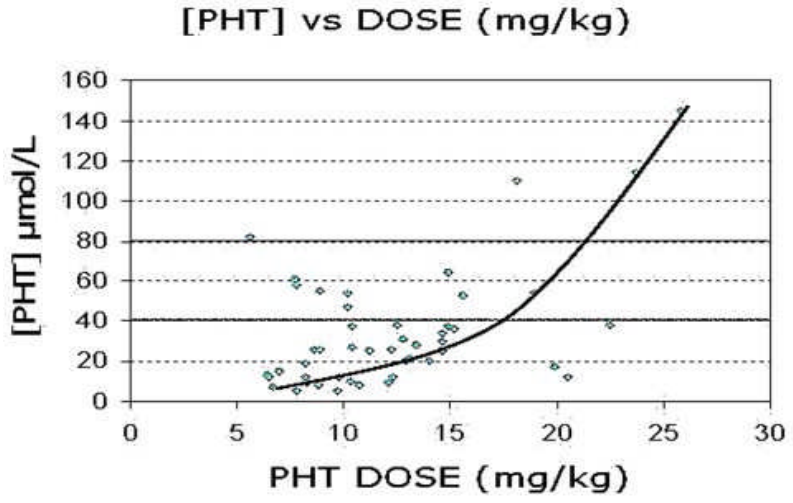
Eight neonates with more than two seizures in the first 14 days of life were identified. Three were diagnosed with hypoxic-ischemic encephalopathy; one had grey matter heterotopia evident on neuroimaging; two patients had meningitis; one patient had hypoglycemia; and one patient had seizures for which no cause was identified. Several patients had a single dose of PB at the onset of seizure, but none received subsequent doses. All infants were on oral PHT monotherapy at the time of their enrolment (14 days of age).

Parents uniformly felt PHT was well tolerated. None of the infants developed rash or excessive drowsiness and impaired feeding was not reported. No infant had a seizure during the 12 weeks of study, and thus all were maintained on PHT monotherapy. One child had seizures when PHT was weaned after 3 months.

Liver and renal function tests were normal for 7 of the 8 patients on all occasions. One patient had a mild, transient rise in serum AST which resolved on repeat testing two weeks later. Serum bilirubin, albumin and electrolytes were normal in all infants. One male infant had hypoglycaemia as part of his primary diagnosis unrelated to PHT administration.

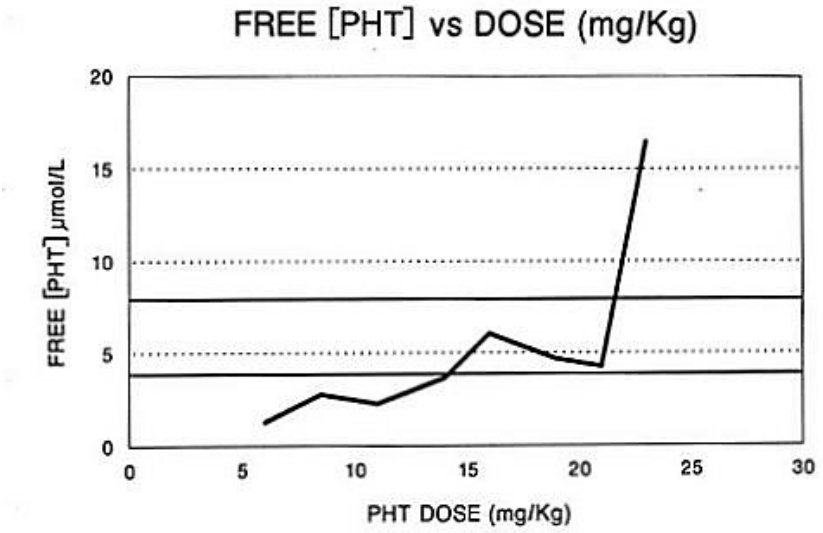
The relationship between PHT dose (mg/kg/day) and serum total PHT level (µmol/L) is shown in Figure 1. Doses of 10-20 mg/kg/day were needed to achieve levels between 40-80 µmol/L. Data obtained at two weeks of age were excluded as two patients were not yet at steady state. Free PHT concentrations (µmol/L) are compared to PHT dose (mg/kg/day) in Figure 2. Free PHT levels were well within the therapeutic range (4-8 µmol/L) at doses between 15-20mg/kg/day but rose dramatically at doses greater than 20mg/kg/day.Free PHT concentrations were compared to total PHT concentrations at each two week interval. Free PHT remained between 8-13% of total PHT. There was no correlation between oral PHT dose and urinary PHT metabolite (p-OH-PHT) concentrations. A consistently low urinary concentration was found, even at high PHT doses (see Figure 3).

FIG. 1 Total serum Phenytoin (PHT) concentration vs. Phenytoin does (mg/kg/day)



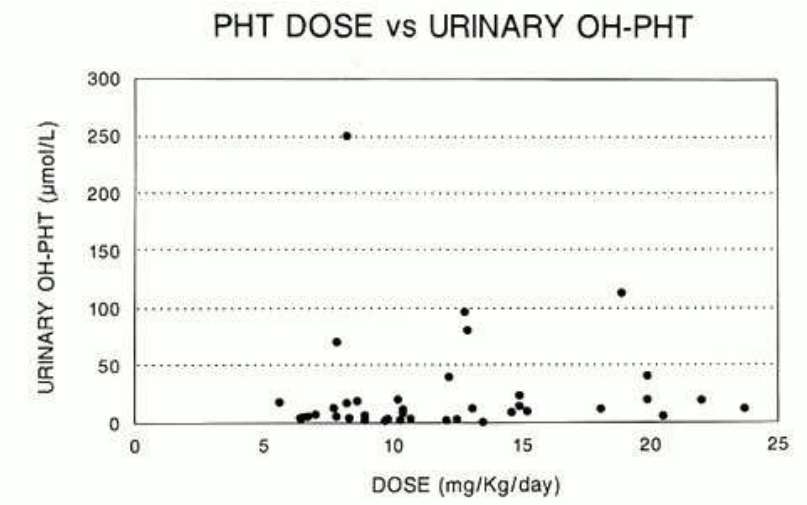
Note: Lines at 40 and 80µmol indicate therapeutic range in our laboratory. Each point represents an individual patient value.

FIG. 2 Mean Serum free Phenytoin (PHT) levels vs. Phenytoin dose



Note: Lines at 4 and 8 µmol indicate therapeutic range for free Phenytoin concentration in our laboratory.

FIG. 3 Urine hydroxyl-phenytoin (OH-PHT) vs. Phenytoin dose



DISCUSSION

We were unable to find any prospective study that has examined oral PHT requirements in infants as they progress through the first three months of life. Our study was not designed to determine detailed pharmacokinetics of PHT[15-17], but, to prospectively determine dose requirements and to ensure that the anticipated increased requirements resulted in therapeutic and efficacious serum total and free PHT levels.

Phenytoin was first introduced as an anticonvulsant in 1938 by Merrit and Putnam[18]. Although several authors have studied PHT pharmacokinetics, these studies predominantly included infants greater than 5 months of

age.[11,12,15,16,18-20] Physicians have been reluctant to use PHT in neonates because of difficulty obtaining adequate blood levels on conventionally recommended doses (5.0-7.5 mg/kg/day).

PHT is a somewhat unique drug in that, over the usual range of concentrations used in clinical care, it exhibits near-zero order or non-linear saturable kinetics. Cytochrome P450 mixed function oxidase metabolizes PHT in the liver, and once this enzyme is saturated, a small increase in dose results in a disproportionately large rise in serum PHT level. The Michaelis-Menton equation is used to describe non-linear kinetics and can be modified to be.[14]

$$R_0 = \frac{V_{max.} \times C_{ss}}{K_m + C_{ss}}$$

Where R_0 = the rate of drug administration (mg/kg/day)
V_{max} = the maximum rate of metabolism (or elimination)
C_{ss}= the plasma PHT concentration (µmol/L) at steady state

Several factors are known to influence the K_m and V_{max} of PHT. Inter-individual variability in K_m and V_{max} vary widely.[19] Liver failure will decrease V_{max}, while concomitant use of medications known to induce cytochrome P450 metabolism (e.g. PB) will increase $V_{max.}$[8] Relatively large liver volume has been proposed to directly correlate with $V_{max.}$[21-23] Neonates have large liver to body weight ratios and this has been a proposed explanation for the increased dose requirements in this age group.[21] Hyperbilirubinemia has been shown to influence PHT binding to albumin.[20,24] Renal failure increases PHT toxicity, as uremia is felt to inhibit plasma PHT protein binding, resulting in increased free PHT levels.[8,25] Nasogastric tube feeding has been shown to influence PHT absorption by increasing gastrointestinal transit time and thus decreasing the time available for absorption. Our exclusion criteria were based on the assumption that the above factors would alter drug metabolism. Premature infants are known to have different liver metabolism; in utero exposure to maternal anticonvulsants might well induce the P450 enzyme in the infant; and similarly, a second anticonvulsant would alter metabolism of PHT.

This study has shown that 10-20mg/kg/day are needed to achieve therapeutic PHT levels in infants throughout the first three months of life. Toxicity was not reported, and seizure control was obtained in all children. Free PHT was found to represent 8-13% of the total serum levels, which is consistent with values reported in adults.[12,21] These results dispel the concern that therapeutic PHT levels may mask toxic free PHT levels.

The urinary p-OH-PHT assays showed that as oral PHT doses increased, the urine PHT metabolite concentration did not increase. Ninety-five percent of PHT is excreted as its metabolite in the urine, which suggests that increased metabolism was not the reason for increased dose requirements. However, a single sample may not reflect the true excretion rate, and 24 hour urine collection would be required for more complete analysis. Collection of 24 hour urine samples from diapered infants, however, is prohibitive. Al Za'abi et al investigated the enteral bioavailability of PHT in adults and infants, and found no kinetic differences based on body weight alone. Postnatal age was an independent factor that affected drug clearance.[26] Further studies are needed to clarify whether the higher doses of PHT required in infants reflects poor absorption, or increased hepatic metabolism. With the emergence of newer anticonvulsants, many of which have limited safety data in the neonatal population, the role of PHT requires re-evaluation. Prospective comparative trials are required, as it remains possible that established medications such as PHT may still have therapeutic advantages in selected patient populations, and in countries unable to afford more expensive medications.

Acknowledgements
This study was supported by a grant form the London Health Sciences Centre Internal Development Fund.

Dr. Rieder holds the CIHR-GSK Chair in Paediatric Clinical Pharmacology at the University of Western Ontario.

REFERENCES

1. Rennie J, Boyland G. Neonatal Seizures and their Treatment. Curr Opin Neurol 2003;16:177–81.
2. Bassan H, Bental Y, Shany E, et al. Neonatal seizures: dilemmas in workup and management. Pediatr Neurol 2008 Jun;38(6):415-21.
3. Silverstein FS, Ferriero DM. Off-label use of antiepileptic drugs for the treatment of neonatal seizures. Pediatr Neurol 2008 Aug;39(2):77-9.
4. Rennie J, Boyland G. Treatment of Neonatal Seizures. Arch Dis Child Fetal Neonatal Ed 2007;92:F148–F150.
5. Carmo K, Barr P. Drug treatment of neonatal seizures by neonatologists and paediatric neurologists. J Paediatr Child Hlth 2005;41:313–6.
6. Barth A, Shen J, et al. Neonatal Seizures: Multicenter Variability in Current Treatment Practices. Pediatr Neurol 2007;37:85-90.
7. Herranz J, Armijo J, Arteaga R. Clinical Side Effects of Phenobarbital, Primidone, Phenytoin, Carbamazepine and Valproate during Monotherapy in Children. Epilepsia 1988;29:794-804.
8. Katzung B. Basic and Clinical Pharmacology, Third Edition. Appelton and Lange, Norwalk, Connecticut, 264-266, 1987.
9. Sicca F, Contaldo A, Rey E, Dula O. Phenytoin administration in the newborn and infant. Brain & Development 2000;22:35-40.
10. Neubauer D, Novosel-Sever M. Phenytoin treatment in the newborn and infant. Brain & Development Mar 2001;23(1):75.
11. Albani M, Wernicke I. Oral Phenytoin in Infancy: Dose requirement, Absorption, and Elimination. Pediatric Pharmacology 1983;3:229-236.
12. Albani M. An Effective Dose Schedule for Phenytoin Treatment of Status Epilepticus in Infancy and Childhood. Neuropaediatrics 1977;286-292.
13. Painter MJ, Scher MS, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. New Engl J Med 1999 Aug 12;341(7):485-9.
14. Suzuki Y, Mimaki T, Cox S, Koepke J, Hayes J, Walson P. Phenytoin age-ose-concentration relationship in children. Therapeut Drug Monitor Apr 1994;16(2):145-50.
15. Loughan PM, Greenwald A, Purton WW, Arandi J, Watters G, Neims A. Pharmacokinetic Observations of Phenytoin Disposition in the Newborn and Young Infant. Arch Dis Child 1977;52;302-9.
16. Rane A, Wilson J. Clinical Pharmacokinetics in Infants and Children. Clin Pharmacokinet 1976;1:2-24.
17. Malik S, Painter M, Venkataramanan R, Alvin J. Phenytoin and Phenobarbital Stable Isotope Studies in Neonates. Pediatric Neurology 2003;29:376-80.
18. Merrit H, Putnam T. A New Series of Anticonvulsant Drugs Tested By Experiments on Animals. Arch Neurol Psychiat 1938;39:1003-15.
19. Borofsky L, Lois S, Kutt H. Diphenylhydantoin in Children. Pharmacology and Efficacy. Neurol 1973;23:967-72.
20. Chiba K, Ishizaki T, Miura H, Minagawa K. Michaelis-Menton Pharmacokinetics of Diphenylhydantoin and Application in the Pediatric Age Patient. J Pediat 1980;96(3),479-84.
21. Rane A, Lunde P, Jallings B, Yaffe S, Sjoqvist F. Plasma Protein Binding of Diphenylhydantoin in Normal and Hyperbilirubinemic Infants. J Pediat 1971;78(5):877-82.
22. Bauer L, Blouin R. Phenytoin Michaelis-Menton Pharmacokinetics in Caucasian Pediatric Patients. Clin Pharmacokinet 1983;8:545-9.
23. Bach B, Hansen J, Kampmann J. Disposition of Antipyrine and Phenytoin Correlated with Age and Liver Volume in Man. Clin Pharmacokinet 1981;6:389-96.
24. Blain P, Mucklow J, Bacon C, Rawlins M. Pharmacokinetics of Phenytoin in Children. Br J Clin Pharmac 1981;12:659-61.
25. Fredhom B, Rane A, Persson B. Diphenylhydantoin Binding to Proteins in Plasma and It's Dependence on Free Fatty Acid and Bilirubin Concentration in Dogs and Newborn Infants. Pediat Res 1975;9:26-30.
26. Al Za'abi M, Lanner A, Xiaonian X, Donovan T, Charles B. Application of Routine Monitoring Data for Determination of the Population Pharmacokinetics and Enteral Bioavailability of Phenytoin in Neonates and Infants With Seizures. Ther Drug Monit 2006;28:793–9.