*Paediatric and Perinatal Drug Therapy, 2005; 6 (3)*

# Phenytoin elimination in a child during hypothermia for traumatic brain injury

**Brian J Anderson**

*Department of Anaesthesiology, University of Auckland, Auckland, New Zealand*

Corresponding author

*Associate Professor B Anderson, PICU, Auckland Children's Hospital, Park Road, Auckland, New Zealand. Email: briana@adhb.govt.nz*

Background: **The aim of this study was to describe phenytoin pharmacokinetics in a child during hypothermic management of a traumatic brain injury.**

Methods: **Two children admitted to a paediatric intensive care unit with closed head injuries were given phenytoin prophylactically to prevent seizures. One child (1 y, 12 kg) who presented with a Glasgow Coma Score (GCS) of 7/15 underwent temp-erature reduction (33°C) for the first 24 h to reduce cerebral oedema and possible dysfunction. The second child (7 months, 8 kg) had an initial GCS of 10/15 and was maintained normothermic. Phenytoin time-concentration profiles from both children (15 observations) were available for analysis using non-linear mixed effects models (NONMEM). Estimates were standardised to a 70 kg person.**

Results: **Michaelis-Menten kinetics provided a better data fit than a one compartment first order elimination model. Parameter estimates were apparent volume of distribution ($V$) 67.6 l/70 kg, and Michaelis-Menten constant ($K_m$) 3 mg/l. The maximum rate of metabolism ($V_{max}$) at 37.3°C was 12.5 mg/h and decreased to 1.2 mg/h at 33°C.**

Conclusions: **Phenytoin elimination at a target concentration of 15 mg/l is reduced by 67% at 34°C compared to normothermia. Temperature is a large source of unexplained variability of phenytoin elimination and reinforces the continued need for therapeutic drug monitoring in order to limit exposure to a safe and effective range.**

Paed Perinatal Drug Ther 2005; 6: 133–138

*Keywords:* Phenytoin – pharmacokinetics – Michaelis-Menten – children – allometrics – hypothermia

## Introduction

The induction of hypothermia (33–34°C) within 8 h of traumatic brain injury (TBI) and its maintenance for 24 h is used in an effort to reduce cerebral oedema and preserve cerebral function[1-3]. This hypothermic state is achieved using cooling mattresses with the concomitant use of neuromuscular blocking drugs (NMBDs) to prevent shivering. Children with head trauma remain at risk of seizure activity during this phase of treatment and NMBDs mask signs of overt seizures. Seizures increase cerebral metabolic demands during a period when these should be kept minimal and anticonvulsant drugs such as phenytoin are commonly administered as prophylaxis[4,5].

Phenytoin is 90% bound to albumin in blood and is eliminated by hepatic hydroxylation (CYP2C9, CYP2C19). Elimination is dependent on unbound fraction and intrinsic clearance of the liver. The pharmacokinetics of phenytoin in adults and children has been described using Michaelis-Menten kinetics. The maximum rate of metabolism ($V_{max}$) and Michaelis-Menten constant ($K_m$) of a 70 kg adult male Caucasian were estimated to be 17.3 mg/h and 5.7 mg/l, respectively[6]. The $K_m$ for patients less than 15-years-old is 43% less than that of older patients. $V_{max}$ and $K_m$ vary unpredictably among individuals with a coefficient of variation of 10–20% and approximately 50% respectively[6]. Metabolism approaches adult levels within the first month of life[7,8]. $K_m$ but not $V_{max}$ has been shown to be age dependant, using a non-linear function of body weight to adjust for body size[6].

Body temperature has a profound effect on metabolic rate in all organisms[9]. Hypothermic techniques, involving temperature reduction to as low as 15°C, have been used in medicine for many years. Paediatric cardiac surgery, neurosurgery and the intensive care management of TBI all use hypothermia for cerebral protection. The effects of hypothermia uncomplicated by cardiopulmonary bypass on drug elimination are poorly documented. This current case report investigates the effect of hypothermia down to 33°C on phenytoin pharmacokinetics in a child. Phenytoin serum concentrations were available from routine therapeutic drug monitoring (TDM).

## Case report 1

A 1 year old 12 kg child was an unrestrained back seat passenger in a motor vehicle collision. The child was found by ambulance staff in a ditch beside the road 10 m from the car. Three other car occupants died in the accident. On arrival at the district general hospital the child was noted to have a Glasgow Coma Score (GCS) of 7/15 with intact vital signs. The child was sedated with diazepam (100 mcg/kg/h) and morphine (20 mcg/kg/h) and electively intubated (propofol 20 mg, pancuronium 2 mg) and ventilated before transport to a paediatric intensive care unit (PICU) at a tertiary children's hospital. Computed tomography (CT) revealed an isolated head injury consistent with diffuse axonal injury. The intracranial pressure from a monitor sited in the subdural space was 10-14 mmHg. Intravenous phenytoin 250 mg (20.8 mg/kg) over 1 h, followed by 40 mg 8 hourly was administered for 40 h. A noradrenaline infusion (0.05 mcg/kg/min) was used to maintain a cerebral perfusion pressure greater than 60 mmHg. The child was cooled to 33°C for 24 h and then allowed to passively rewarm (Figure 1a). Temperature was measured at the tympanic membrane. Neuromuscular blockade was maintained with pancuronium 1 mg prn. Rewarming over 6 h occurred without any intracranial pressure elevation; sedation and NMBDs were ceased. The child was extubated after 42 h and was noted to be crying and moving her left side purposefully. She had weakness of her right arm and leg that was resolving on discharge to the hospital ward at 72 h. Blood chemistry, hepatic transaminases and serum creatinine and albumin (39 g/l) were normal throughout her PICU stay. Antibiotics were not required during her management.

## Case report 2

A 7 month, 8 kg infant restrained in a back child seat was involved in a motor vehicle collision. The front seat passenger died on impact, but the driver and infant were cut free of the wreckage and survived to hospital. The infant's GCS was reported as 10/15 on arrival at hospital. The infant was electively intubated (propofol 25 mg, pancuronium 1 mg) for a CT of the head, neck, chest and abdomen. Sedation was maintained with diazepam (100 mcg/kg/h) and morphine (20–30 mcg/kg/h). The infant suffered left sided rib fractures with underlying lung contusion and a diffuse axonal injury with a 2 mm depressed skull fracture in left fronto-parietal bone and blood was present in the cerebral ventricles. The infant was admitted to PICU where she was maintained normothermic, given intravenous phenytoin 160 mg (20 mg/kg) over 1 h, and weaned from artificial ventilation within 6 h. At extubation she had spontaneous eye opening, full purposeful power in all limbs and was crying. She was discharged to the ward after 38 h. Blood chemistry, hepatic transaminases, albumin (40 g/l) and serum creatinine were normal throughout her PICU stay. Antibiotics were not required for her management.

## Pharmacokinetic modelling

Total phenytoin serum concentration measurements were assayed using fluorescence polarisation immunoassay (TDx, Abbott Laboratories, North Chicago, IL, USA) in the hours following sample collection and were reported in mg/L.

Parameter estimates ($V_{max}$, V) were obtained using a non-linear mixed effects model (NONMEM)[10]. A proportional term (Err) characterised the residual unknown variability. Convergence criterion was 3 significant digits. A Compaq Digital Fortran Version 6.6A compiler with Intel Celeron 333 MHz CPU (Intel Corp., Santa Clara, CA) under MS Windows XP (Microsoft Corp., Seattle,

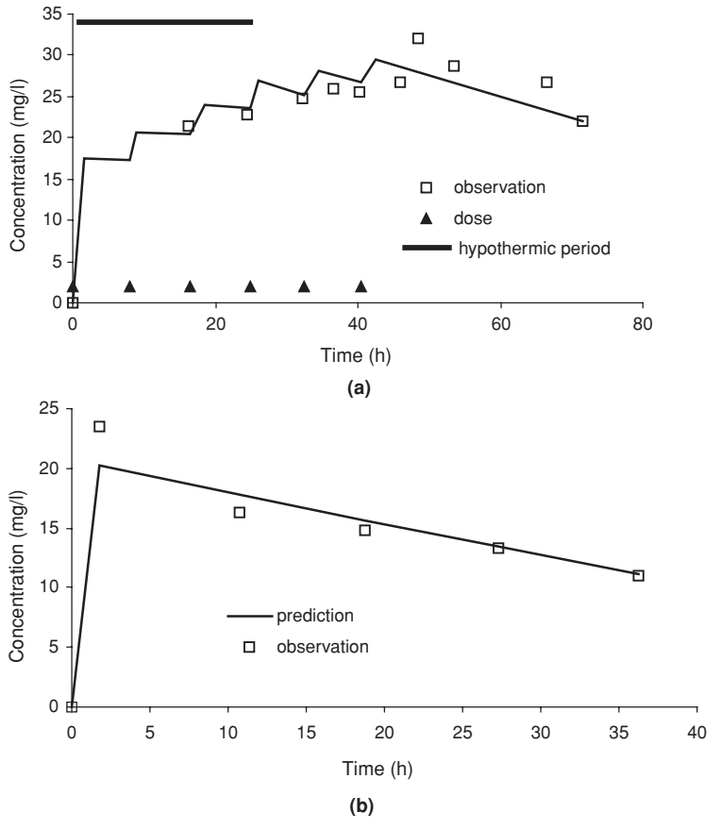


**Figure 1** Time-concentration profiles and individual predictions. (1a) the infant managed with hypothermia. The hypothermic period and timing of phenytoin doses are also shown. (1b) the infant managed with normothermia.

WA) was used to compile and execute NONMEM. Both a one compartment first order elimination model and a Michaelis-Menten (mixed order elimination) model were fitted to the data.

The parameter values were standardised for a body weight of 70 kg using an allometric model[11,12].

$$P_i = P_{std} \times (W_i / W_{std})^{PWR}$$

where $P_i$ is the parameter in the $i$th individual, $W_i$ is the weight in the $i$th individual and $P_{std}$ is the parameter in an individual with a weight $W_{std}$ of 70 kg. This standardisation has a strong theoretical and empirical basis and allows comparison of neonatal parameter estimates with those reported for adults. The PWR exponent was ¾ for clearance and 1 for distribution volume[13–15].

Covariate analysis included exponential and linear models to investigate the effect of temperature on $V_{max}$ e.g.

$$V_{max} = (V_{maxstd} \, x \, (Wt/70)^{0.75}) \times (1+Const \times EXP\ (-(Temp-37) \, x \, F_{temp})) \text{ mg/h}$$

$$V_{max} = (V_{maxstd} \, x \, (Wt/70)^{0.75}) \times (1+Const \times (Temp-37)) \text{ mg/h}$$

where $V_{maxstd}$ is the estimate for Michaelis–Menten maximum rate of metabolism ($V_{max}$) at 37°C, standardised to a 70 kg person using allometric models; Temp is tympanic membrane temperature, $F_{temp}$ is a scaling factor applied to temperature and Const is a constant.

The quality of fit of the pharmacokinetic model to the data was judged by NONMEM's objective function and by visual examination of plots of observed versus predicted concentrations. Models were nested and a decrease in the objective function was referred to the Chi-squared distribution to assess significance e.g. an objective function change (OBJ) of 3.84 is significant at $\alpha$=0.05.

## Results

Total phenytoin time-concentration profiles from both children (15 observations) were available for analysis. Michaelis-Menten kinetics provided a better data fit than a one compartment first order elimination model. It was not possible to estimate the $K_m$ because this was considerably less than that of the lowest measured concentration. An estimate from the literature of 3 mg/l was used for this parameter[6, 16]. Parameter estimates are

**Table 1** Parameter estimates for linear and exponential models. SE is the standard error of the estimate

| | Linear Model | | Exponential Model | |
|---|---|---|---|---|
| | **Estimate** | **SE (%)** | **Estimate** | **SE (%)** |
| V l/70kg | 67.6 | 2.9 | 67.6 | 2.9 |
| $V_{maxstd}$ mg/h | 11.7 | 9.6 | 21.7 | 7.7 |
| $K_m$ mg/l | 3 FIX | 0 | 3 FIX | 0 |
| Const | 0.221 | 2.4 | -0.562 | 10.0 |
| $F_{temp}$ | – | – | 0.133 | 18.9 |
| Err | 0.078 | 8.8 | 0.078 | 8.8 |

$V_{maxstd}$ is the estimate for Micahaelis-Menten maximum rate of metabolism ($V_{max}$) at 37°C, standardised to a 70 kg person using allometric models; Temp is tympanic membrane temperature, $F_{temp}$ is a factor applied to temperature and *Const* is a constant. *Err* is a proportional term that characterises the residual unknown variability.

shown in Table 1. Inter-individual variability from the two individuals was minimal and set to 0. Time-concentration profile and individual estimates for the infant managed with hypothermia are shown in Figure 1a. Apparent volume of distribution ($V$) was 67.6 l/70 kg. Introduction of a function to describe temperature effects reduced the objective function by 12.437. The maximum rate of metabolism ($V_{max}$) at 37.3°C was 12.5 mg/h and decreased to 1.2 mg/h at 33°C. Linear and exponential functions both adequately described the relationship between $V_{max}$ and temperature, but there were no observations made between temperature extremes that allowed one function to gain ascendancy over the other (Figure 2). Interpolation of Figure 2 suggests a $V_{max}$ of approximately 4 mg/h at 34°C. If a target concentration of 15 mg/l is assumed, then phenytoin elimination is 3.3 l/h/70 kg at 34°C compared to 9.9 l/h/70 kg at 37°C – a reduction of 67% at 34°C.

## Discussion

The apparent volume of distribution of 67.6 l/70 kg is similar to that previously reported[17] of 70 l/70 kg (CV 23%). The $V_{max}$ and $K_m$ of a 70 kg Caucasian adult male were estimated to be 17.3 mg/h and 5.7 mg/l, respectively[6]. A $K_m$ of 2.41 mg/l and a lower $V_{max}$ of 13.5 mg/h has been reported in Japanese adults[16] (60 kg); attributable to reduced CYP2C9 activity. The estimate for the current reported individual of 12.5 at 37.3°C is consistent with these reports. The elimination clearance (a first order process) of phenytoin was reduced by 67% in 14 adults (15–73 yr) with TBI at 34°C compared to the same individuals at normothermia[18], similar to the current observation using Michaelis-Menton kinetics based on two individuals. The large reduction in $V_{max}$ at 33°C observed in this current study is due to decreased metabolism at lower body temperature. There may be a small contribution to the increase in $V_{max}$ due to a progressive increase in systemic phenytoin clearance during therapy in critically ill patients[19]. This apparently increasing clearance may be a consequence of changes in protein binding, induction of metabolism, or the influence of stress on hepatic metabolic capacity[20]. Noradrenaline reduces splanchnic perfusion but is unlikely to effect elimination of a "capacity limited" drug. Other medications used during treatment were unlikely to effect phenytoin elimination.

Size has considerable impact on the estimation and interpretation of pharmacokinetic parameters in children[11, 12] and is often unaccounted for in paediatric pharmacokinetic and neonatal

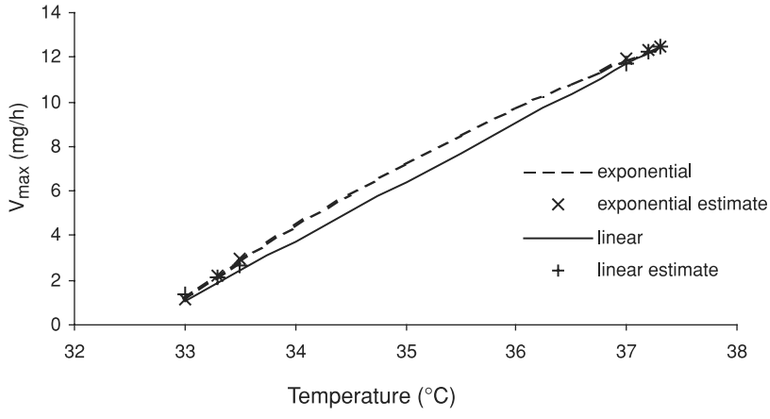


**Figure 2** Linear and exponential functions described the relationship between $V_{max}$ and temperature (°C). Both functions were adequate. There were few observations made between temperature extremes.

studies[21]. A great many physiological, structural and time related variables scale predictably within and between species with weight exponents of ¾, 1 and 1/4 respectively[15]. These "¼ power models" were used in this current study rather than centred weight, or some other function of weight, because the "¼ power models" have sound biological principles. Fractal geometry has been used to mathematically explain this phenomenon[13,14]. The "¾ power law" for metabolic rates was derived from a general model that describes how essential materials are transported through space-filled fractal networks of branching tubes[13,14]. These design principles are independent of detailed dynamics and explicit models and should apply to virtually all organisms.

The pharmacokinetics of phenytoin are significantly affected by age, but $V_{max}$ changes are compatible with size effects. Out of the neonatal age range, $V_{max}$ in children can be predicted from adult values based on a power function of weight; the estimate of the power function is reported[6,17] as 0.6 and as 0.737. The impact of these different exponents over the human weight range 10–100 kg is minimal[11] when compared to 0.75 (¾) and is consistent with the "¼ power models".

Hypothermia decreases clearance of propanolol[22], rocuronium[23], remifentanil[24], propofol[25], nitroglycerine[26] and pentobarbital[27]. These temperature effects on clearance are not always disentangled from those effects on distribution volumes or concomitant bypass circuitry and the relationship between temperature and clearance remains undefined in humans for these drugs.

Temperature had a dramatic effect on phenytoin elimination in this current case report, beyond the increased phenytoin clearance observed in critically ill patients on therapy after a few days. This $V_{max}$ reduction during hypothermia must be factored into dosing and emphasises the need for TDM in such clinical scenarios. TDM has proved invaluable in rationalising the use of phenytoin. Because of wide inter-individual variation and non-linear kinetics, it is difficult to establish an optimum maintenance dose for this drug. Individualising dose using Bayesian forecasting resulted in improved seizure control in 10 of the 11 patients (91%) receiving phenytoin[28]. Others have reported similar success in children and adults[29,30]. Target concentration intervention based on population analyses are not yet possible in a cohort of hypothermic paediatric patients until further covariate analyses quantifies hypothermic effect and its variability[31].

## Financial support

Support was provided solely from institutional and/or departmental sources.

## References

1. Marion DW, Obrist WD, Carlier PM, Penrod LE, Darby JM. The use of moderate therapeutic hypothermia for patients with severe head injuries: a preliminary report. J Neurosurg 1993; 79: 354-362.
2. Clifton GL, Allen S, Barrodale P *et al.* A phase II study of moderate hypothermia in severe brain injury. J Neurotrauma 1993; 10:263-267.
3. Shiozaki T, Sugimoto H, Taneda M *et al.* Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. J Neurosurg 1993; 79:363-368.
4. Temkin NR, Dikmen SS, Wilensky AJ *et al.* A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med 1990; 323:497-502.
5. The role of antiseizure prophylaxis following head injury. Brain Trauma Foundation. J Neurotrauma 1996; 13:731-734.
6. Grasela TH, Sheiner LB, Rambeck B *et al.* Steady-state pharmacokinetics of phenytoin from routinely collected patient data. Clin Pharmacokinet 1983; 8:355-364.
7. Battino D, Estienne M, Avanzini G. Clinical pharmacokinetics of antiepileptic drugs in paediatric patients. Part II. Phenytoin, carbamazepine, sulthiame, lamotrigine, vigabatrin, oxcarbazepine and felbamate. Clin Pharmacokinet 1995; 29: 341-369.
8. Leff RD, Fischer LJ, Roberts RJ. Phenytoin metabolism in infants following intravenous and oral administration. Dev Pharmacol Ther 1986; 9:217-223.
9. Gillooly JF, Brown JH, West GB, Savage VM, Charnov EL. Effects of size and temperature on metabolic rate. Science 2001; 293:2248-2251.
10. Beal SL, Sheiner LB, Boeckmann A. Nonmem User's Guide. San Francisco: Division of Pharmacology, University of California, 1999.
11. Holford NHG. A size standard for pharmacokinetics. Clin Pharmacokinet 1996; 30:329-332.
12. Anderson BJ, Meakin GH. Scaling for size: some implications for paediatric anaesthesia dosing. Paediatr Anaesth 2002; 12:205-219.
13. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. Science 1997; 276:122-126.
14. West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science 1999; 284: 1677-1679.
15. Peters HP. Chapter 4. Physiological correlates of size. In: Beck E, Birks HJB, Conner EF, eds. The Ecological Implications of Body Size. Cambridge: Cambridge University Press, 1983:48-53.
16. Yukawa E, Higuchi S, Aoyama T. Population pharmacokinetics of phenytoin from routine clinical data in Japan: an update. Chem Pharmaceut Bull 1990; 38:1973-1976.
17. Vozeh S, Uematsu T, Aarons L *et al.* Intravenous phenytoin loading in patients after neurosurgery and in status epilepticus. A population pharmacokinetic study. Clin Pharmacokinet 1988; 14:122-128.

18. Iida Y, Nishi S, Asada A. Effect of mild therapeutic hypothermia on phenytoin pharmacokinetics. Ther Drug Monit 2001; 23:192-197.
19. Boucher BA, Rodman JH, Jaresko GS *et al.* Phenytoin pharmacokinetics in critically ill trauma patients. Clin Pharmacol Ther 1988; 44: 675-683.
20. Markowsky SJ, Skaar DJ, Christie JM, Eyer SD, Ehresman DJ. Phenytoin protein binding and dosage requirements during acute and convalescent phases following brain injury. Ann Pharmacother 1996; 30:443-448.
21. Anderson B. Disentangling PK-PD in neonates. Arch Dis Child Fetal Neonatal Ed 2004; 89:F3-4.
22. McAllister RG, Jr, Bourne DW, Tan TG *et al.* Effects of hypothermia on propranolol kinetics. Clin Pharmacol Ther 1979; 25:1-7.
23. Beaufort AM, Wierda JM, Belopavlovic M *et al.* The influence of hypothermia (surface cooling) on the time-course of action and on the pharmacokinetics of rocuronium in humans. Eur J Anaesthesiol Suppl 1995; 11:95-106.
24. Russell D, Royston D, Rees PH, Gupta SK, Kenny GN. Effect of temperature and cardiopulmonary bypass on the pharmacokinetics of remifentanil. Br J Anaesth 1997; 79:456-459.
25. Leslie K, Sessler DI, Bjorksten AR, Moayeri A. Mild hypothermia alters propofol pharmacokinetics and increases the duration of action of atracurium. Anesth Analg 1995; 80:1007-1014.
26. Booth BP, Brien JF, Marks GS, *et al.* The effects of hypothermic and normothermic cardiopulmonary bypass on glyceryl trinitrate activity. Anesth Analg 1994; 78:848-856.
27. Schaible DH, Cupit GC, Swedlow DB, Rocci ML, Jr. High-dose pentobarbital pharmacokinetics in hypothermic brain-injured children. J Pediatr 1982; 100:655-660.
28. Botha J, Bobat RA, Moosa A, Miller R. Therapeutic drug monitoring in a paediatric epilepsy clinic. South African Med J 1990; 19 77:511-514.
29. Yukawa E, Higuchi S, Aoyama T. Phenytoin dosage adjustment method using population clearance. Chem Pharmaceut Bull 1990; 38: 510-512.
30. Yukawa E, Higuchi S, Aoyama T. One-point feedback control method for phenytoin dosage adjustment. J Pharmacy Pharmacol 1991; 43: 499-503.
31. Holford NHG. Target Concentration Intervention: Beyond Y2K. Br J Clin Pharmacol 1999; 48:9-13.

Paper PPDT– 0124, *Accepted for publication:* 17 February 2005
*Published Online:* 24 March 2005
doi:10.1185/146300905X3933