RESEARCH ARTICLE

Do total concentrations of phenytoin predict free concentrations in Malaysian pediatric patients?

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Phenytoin is the highly protein-bound drug. Its free fraction represents the pharmacologically active portion of administered medication. This study is to determine the relationship between estimated free concentrations and measured total phenytoin concentrations, and to estimate phenytoin pharmacokinetic parameters (V_{max} and K_m). There were 52 steady-state phenytoin concentrations from 52 pediatric patients with hypoalbuminemia. Sheiner-Tozers equation was used to estimate free concentration (C_{fest}) of phenytoin. of 52 steady state total phenytoin concentrations, 11.5%, 25%, 63.5% were found toxic, therapeutic and subtherapeutic respectively, of 52 free concentrations, 21.2%, 28.8%, 50% were found toxic, therapeutic and subtherapeutic respectively. 5 patients (9.7%) had toxic free levels (>2 µg/ml) when simultaneously measured total levels were therapeutic (<20 µg/ml). The Mean ± SD for K_m and V_{max} in 47 patients were 4.495 ± 3.508 mg/L and 9.049 ± 5.357 mg/kg/day but the mean of K_m and V_{max} for those 5 patients were 6.18±1.749 mg/L and 5.352 ± 2.085 mg/kg/day. There was a correlation between free concentration and total concentrations (r^2 = 0.83). The authors observed that there was correlation between free and total phenytoin concentrations even with an increased variability in protein binding observed in patients. Free phenytoin concentration estimation and monitoring requires further investigation.

Keywords: *Phenytoin, Hypoalbuminemia, Pediatric, Sheiner-Tozers equation, Malaysian.*

INTRODUCTION

Phenytoin is one of the greatly prescribed anti-epileptic drugs for prophylaxis of seizures in the pediatric unit. When a phenytoin level is available, methods based on the Michaelis-Menten equation can be used to estimate the suitable dose [1]. Careful monitoring of phenytoin concentrations is necessitated because of the narrow therapeutic index of phenytoin to prevent intoxication or insufficient treatment of seizures. However, small changes in phenytoin dose may greatly disproportionate changes in phenytoin serum concentration [2]. In addition to its nonlinear kinetics, the pharmacokinetics of phenytoin is influenced by potential interactions with other anti-epileptic drugs with enzyme-inducing capacity (carbamazepine and phenobarbital) or plasma protein displacement drug (valproic acid). Most patients are seizure-free with total phenytoin concentrations of 5 µg/ml, and in clinical practice maintenance of total serum phenytoin concentrations between 10-20µg/ml is desirable [3]. This commonly needs incremental adjustments in the phenytoin maintenance regime [4, 5]. Phenytoin is highly protein-bound and its free fraction represents the pharmacologically active portion. The therapeutic range of the free-phenytoin serum concentration is about 10% of the total phenytoin serum concentration [6, 7]. In the presence of hypoalbuminemia, both the ratio of free/total phenytoin concentration and the total phenytoin concentration may be changed. When free levels are high, phenytoin toxicity will be result in symptoms such as diplopia, nystagmus, ataxia, cardiac arrhythmias or death [8-12]. The aim of this retrospective data collection was to determine the relationship between estimated free concentrations (C_{fest}) and measured total phenytoin concentrations (C_t) and to estimate phenytoin pharmacokinetic parameters [maximum metabolic rate (V_{max}) and Michaelis–Menten constant (K_m)].

METHODS

Data Collection

Patient data were collected for three years (2006-08) from Therapeutic Drug Monitoring (TDM) service at Penang General Hospital (PGH)

in Penang, Malaysia. In this study, all the hypoalbuminic pediatric patients (age <17 years) with documented epilepsy diagnosis and taking phenytoin in monotherapy were enrolled. Briefly, exclusion criteria were patients with laboratory evidence of renal or hepatic disease, patients taking any concurrent medication known to interfere with phenytoin pharmacokinetics, and those patients with inaccurately documented dosage and sampling histories. Data collection included demographic data (age, gender, race and total body weight), phenytoin dosing history (total daily phenytoin dose, time of last phenytoin dose intake and dosing schedule), total phenytoin serum concentration, sampling time and laboratory data (potassium level, sodium level, serum creatinine and serum albumin). The Clinical Research Committee (CRC) and National Institutes of Health (NIH) approved study.

Pharmacokinetic Analysis

The Sheiner-Tozer equation was used to estimate the free concentration (C_{fest}) of phenytoin from steady-state dosing. Sheiner and Tozer [13] described a patient with phenytoin toxicity in the setting of hypoalbuminemia (1.8g/dL) and proposed a correction formula based on serum albumin concentrations.

$$C_{adjusted} = C_{reported} / (0.25 \text{ serum} \times \text{albumin}) + 0.1$$

$$C_{fest} = C_{adjusted} \times 0.1$$

Phenytoin pharmacokinetic parameters (V_{max}) and (K_m) were estimated using Vozeh-Sheiner method (orbit graph). This method can estimate the pharmacokinetic parameters of phenytoin (V_{max}) and (K_m) by using one dose and one concentration and this is a good advantage for this method [14].

Statistical Analysis

Data are expressed as means ± standard deviation (SD). Linear regression statistical test was used to shows the correlation between estimated free phenytoin concentration and total phenytoin concentration.

RESULTS

Fifty-nine epileptic patients with hypoalbuminemia receiving phenytoin in monotherapy were screened, but eventually only 52 were enrolled. Seven patients had exclusion criteria: three patients had clinical or laboratory evidence of hepatic or renal disease, two patients were taking concurrent medication other than anti-epileptic drugs, two patients had inaccurately documented sampling histories.

We identified 52 patients in whom albumin and total phenytoin concentrations were simultaneously measured. The age of the patients averaged 9.8±5.6 yrs (range 7 months to 16.6 yrs), Race (25 Malay, 18 Chinese, and 9 Indian) and Gender (23 male / 29 female). The mean serum albumin concentration was 2.8±0.6 g/dl (range of 1.4-3.4 g/dl). Severe hypoalbuminemia (<2.5 g/dl) was present in 25 patients (48%), moderate hypoalbuminemia (2.6–3 g/dl) in 13 (25%), mild hypoalbuminemia (3.1–3.5 g/dl) in 14 (27%) (Table1).

Table 1. Demographic information, findings and laboratory measures for the sample patients

No. of patients	52 patients	
Gender (Male/Female)	(23/29)	(44% / 56%)
Age (years)	(9.8±5.6yr)[a]	(7months -16.6yr)[b]
Race Malay	25pts	(48%)
Chinese	18pts	(34%)
Indian	9pts	(18%)
S. albumin conc. (g/dl)	(2.8±0.6 g/dl)[a]	(1.4-3.4 g/dl)[b]
S. albumin <2.5 g/dl	25pts	(48%)
S. albumin 2.6–3 g/dl	13pts	(25%)
S. albumin 3.1–3.5 g/dl	14pts	(27%)

[a] Values expressed as mean ± SD, [b] Range

Study observed that there was correlation ($r^2 = 0.83$) between free and total phenytoin concentrations and this correlation is strong (Figure 1). A negative correlation was observed between albumin and free phenytoin fraction, demonstrating that lower serum albumins were associated with higher free fractions. Interestingly, the binding ratio observed with a serum albumin<3.5 g/dl was elevated to 0.16 (16% free phenytoin).

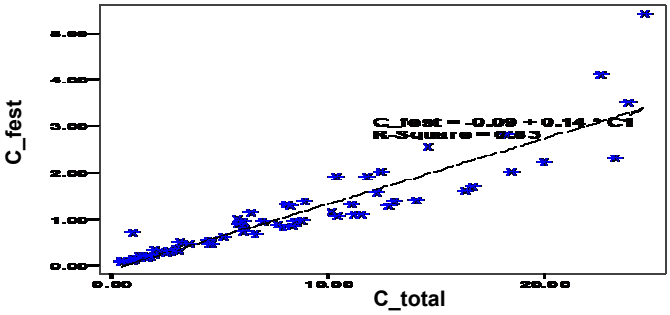

Figure 1: Scatter plot of free vs. total serum phenytoin concentrations in 52 patients

Of 52 steady state total phenytoin concentrations, 11.5%, 25%, 63.5% were found toxic, therapeutic and subtherapeutic respectively, Of 52 free concentrations, 21.2%, 28.8%, 50% were found toxic, therapeutic and subtherapeutic respectively. Five patients (9.8%) had a free phenytoin levels above the therapeutic range (>2 µg/L) with total phenytoin levels in the therapeutic range (<20 µg/L). The Mean ±SD for K_m in 5 patients were higher than in 47 patients, but Mean ±SD for V_{max} for those 5 patients were lower than in 47 patients (Table 2).

Table 2. V_{max} and K_m value of phenytoin in pediatric patients with hypoalbuminemia in 52 patients

Phenytoin free conc.	V_{max} (mg/kg/day)	K_m (mg/L)
5 patients Toxic	5.352±2.085	6.18±1.749
47 patients Therapeutic	9.044±5.357	4.495±3.50

DISCUSSION

This study differs from other pharmacokinetic studies of phenytoin in that: A) It is the first pharmacokinetic study on phenytoin in pediatric patients with hypoalbuminemia; B) It is the first study in which the V_{max} and K_m estimated for patient had toxic free concentrations despite total concentrations within the therapeutic range.

Our observations suggest that total phenytoin concentrations are inappropriate for directing therapy in pediatric patients and that free concentrations should be routinely monitored. We observed that the strong correlation between free and total phenytoin concentrations (r^2= 0.83) in these pediatric and the result is similar to that previously reported in the adult literature (r^2=0.84) [15], but it is slightly higher than that previously reported in the children literature (r^2=0.795) [16]. Hypoalbuminemia < 3.5g/dL was found to particularly affect binding ratios, increasing them to 0.16 and yielding a much greater fraction of unbound phenytoin. This result was significantly different from the expected free/total phenytoin ratio in patients with normal albumin levels of 0.10 (10% free phenytoin).

Hypoalbuminemia is common in children admitted to the pediatric unit. The mean serum albumin concentration in our patients was 2.8 g/dL near to that reported by other researchers. Durward and coworkers [17] reported a mean serum albumin of 3.0 g/dL in 134 critically ill children admitted to a pediatric unit. Hypoalbuminemia is a well-described risk factor for elevated free phenytoin concentrations.

This study found that five of our patients (9.8%) had elevated free concentrations despite total concentrations within the therapeutic range; this result similar to the other study [16] reported that six patients (10%) among 60 patients had elevated free concentrations despite total concentrations within the therapeutic level.

The values of V_{max} and K_m for phenytoin determined in our study slightly difference than those reported in other populations (Table3). The difference between phenytoin pharmacokinetic parameters in this studies and our study probably based on interethnic differences, age differences, and albumin level differences.

CONCLUSION

In conclusion this study found that the correlation between total and free phenytoin concentration is strong for free concentration of phenytoin less than 2 µg/ml. Total phenytoin concentrations are frequently unreliable for directing therapy in the pediatric unit. Considering our findings, we recommend that free phenytoin concentrations be regularly measured in critically ill children, particularly when adjusting phenytoin doses. If free levels are unavailable, the clinician should be alerted to potentially altered phenytoin binding when serum albumin concentrations are < 3.5 g/dl.

Table 3. Population pharmacokinetics of total phenytoin showing ethnic and age variations in V_{max} and K_m

Ethnic	Age	V_{max} (mg/kg/day)	K_m (mg/L)	Author (reference)
Japanese	2.7 – 71 yrs	5.4	2.4	Yukawa et al. 1990 [18]
Malaysian	9 – 60yrs	7.3	3.7	Ismail et al. 1994 [19]
Saudi	> 16yrs	8	6.5	Abduljabbar et al. 1999 [20]
Caucasian	0.5 – 16	8.25-13.95	5.69-6.82	Bauer et al. 1983 [21]

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