Evaluation of phenytoin pharmacokinetics in neurotrauma patients

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ABSTRACT

Previous studies have suggested that drug metabolism may be altered in patients with severe neurotrauma. The purpose of this prospective study was to observe the alteration of phenytoin pharmacokinetic and the resulting drug plasma level among these patients.

Twenty patients with severe head injury (Glasgow Coma Scale≤8) requiring intravenous phenytoin were included in the study. Phenytoin sodium was diluted to a concentration of 25mg/ml and infused for 20 minutes at the rate of not faster than 25mg/min. Maintenance dose of phenytoin sodium was administered in the first day of head trauma and vital signs were monitored at hourly intervals while the patients remained in the neurosurgical intensive care unit. Blood samples were obtained for peak and trough concentrations. Free and total phenytoin levels were determined by both liquid chromatography and fluorescence polarization immunoassay (Éclair) of plasma samples after ultrafiltration and deproteinization respectively.

Based on the reported Km (Km = 5.4 mg/l), predicted population Vmax was calculated to be (7.3 ± 0.4 mg/kg/d) which was significantly lower than calculated individual Vmax (9.3 ± 3.2 mg/kg/d) (P=0.026). Moreover, significant differences was found between mean daily dose of phenytoin administered to patients (257 ± 4 mg/d) and calculated mean daily dose based on individual Vmax (479 ± 3 mg/d) (p=0.0015). Mean plasma concentrations determined by fluorescence polarization immunoassay (FPIA) (6.11 ± 2.9 mg/l) and HPLC method (5.78 ± 2.8 mg/l) were not statistically different

Metabolic rate increased non-proportionally with increase in phenytoin concentration, and as a result decrease in clearance. Significant alteration in the metabolism of phenytoin occurred after severe neurotrauma.

Based on our results, to keep phenytoin concentrations in the range of 10-20 mg/l, an increase in the phenytoin maintenance dose and more frequent monitoring of concentration is commonly required.

Keywords: Phenytoin, Pharmacokinetic, Free fraction, Neurotrauma

INTRODUCTION

Seizures after head injury are generally classified in two categories. Early seizures which occurs during the first week post brain injury and the late ones which are those occurring after the first week. (1,2)

Seizure exacerbates ischemia and greatly increases cerebral metabolic rate of oxygen ($CMRO_2$). Therefore, antiepileptic drugs are frequently initiated after severe neurotrauma to prevent post-traumatic seizures. (3,4). The use of drug therapy in this setting has been extensively studied. It has been reported that the use of phenytoin at therapeutic concentration is effective in the prevention of early post-traumatic seizures (5-7).

Phenytoin is the most commonly used anticonvulsant in the acute care setting because it is one of only a few agents available for parenteral administration. (4) It is also a good therapeutic choice for patients with neurotrauma due to non-sedating nature and good hemodynamic profile (8,9). It exhibits non-linear pharmacokinetic characteristic and requires frequent plasma monitoring and dose adjustment (1,2). One of the problems associated with administration of phenytoin in the critically ill patients is alteration of drug metabolism which makes it difficult to maintain the therapeutic drug concentration. It is suggested that maximum metabolic rate (Vmax) of phenytoin may change during initial therapy in critically ill head-trauma patients. Therefore it is often difficult to achieve therapeutic phenytoin concentration in patients with neurological trauma using recommended daily dosages (10).

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A variety of mechanisms have been proposed to explain this increased requirement. Stress related increase in hepatic metabolism, increase in clearance due to hypermetabolic or hypercatabolic state during head trauma, and increase in unbound Phenytoin concentration resulting in increased phenytoin clearance could be the reasons (11,12).
However, to the best of our knowledge, little data are available on phenytoin pharmacokinetic alteration in critically ill patients, where dosage recommendations and drug monitoring guidelines are based on preliminary data from stable patients receiving chronic phenytoin therapy or data from normal volunteers.
This prospective study was designed to determine the maximum metabolic rate of phenytoin (Vmax) among severe head trauma patients and the relationship between phenytoin clearance and phenytoin plasma concentration measured by HPLC and FPIA.

Patients and methods

Twenty adult head trauma patients who were admitted to a neurosurgical intensive care unit and required phenytoin for the seizure prophylactic treatment were enrolled in the study.
Patients with severe head injury were included if they were over 18 years and had a Glasgow Coma Scale (GCS) of less than 8.
The protocol was approved by the Institutional Review Board at Tehran University of Medical Sciences.
Patients with bradycardia (heart rate<60), second or third degree heart block, clinically significant hypotension, hepatic or renal disease (total bilirubin > 3mg/dl and/or ALT>120µg/l and/or serum creatinine >2 mg/dl) were excluded.
By history taking, subjects who had received phenytoin or any other medications known to interfere with phenytoin protein binding or metabolism before admission to the hospital, and patients who required concomitant valporic acid, phenobarbital, sulfonamides or theophyline were excluded from the study.

Drug administration and blood sampling

Phenytoin sodium (50mg/ml in 40% propylene glycol and 10% ethanol, Daru Pakhsh) was diluted in normal saline to a concentration of 25mg/ml. All intravenous doses were infused for 20 minutes at the rate of not faster than 25mg/min. Maintenance dose of phenytoin sodium was administered in first day of head trauma and vital signs were monitored at hourly intervals while patients remained in the neurosurgical intensive care unit.
Blood samples (48 h after initiation of intravenous phenytoin therapy) were obtained from forearm vein of the patients at 30 minutes after the end of infusion for peak concentration and 30 minutes before the next dose for trough concentrations. Venous blood samples (5ml) were collected in heparinized tube and centrifuged at room temperature for 15 minutes at 3000/min to obtain plasma. An aliquot of plasma was filtered through suitable ultrafilter (Amicon centrifree, cut of =5000 Dalton) for preparation of free fraction.

Drug assay

Extraction of plasma samples for total phenytoin was performed by deproteinization of samples with the same volume of acetonitrile. A 50µl of either deproteinized supernatant or ultrafiltrate was injected onto the HPLC column for determination of total plasma and free phenytoin concentration respectively.
Plasma sample concentrations were determined according to the reported method (13) with slight modifications as follows:
Analysis was performed using a 600E high pressure pump, a 486 UV spectrophotometer, a 746 data module (all from waters). The samples were introduced to a Techsphere C8 column (3µm, 150 X 4.6mm) through a rheodyne 7725 injector fitted by a 50µL loop. Acetonitrile: Water (73.4:26.6, pH=2.5) was used as eluent with a flow rate of 1.4ml/min and the eluate was monitored at 210 nm. Column temperature was maintained at 30 ^{o}C during the assays.
Total plasma phenytoin was also determined by Fluorescence Polarization Immuno Assay method (Merck VITALAB Éclair) according to the manufacturer instruction.

Pharmacokinetic and statistical analysis

The rate limiting enzymatic reaction contributing to phenytoin elimination follows typical Michaelis– Menten kinetics in which the rate of reaction could be calculated as:

$$(S)(F)(Dose/t) = V_{max} \times Cpss / K_m + Cpss$$

Where V_{max} (mg/day) is the maximum metabolic rate, K_m (mg/l) is the substrate concentration with a value of the plasma concentration at which the rate of metabolism will be one- half of V_{max} (22), F=1 is phenytoin bioavailability and S=0.92 shows sodium salt factor.
The magnitude of difference between the predicted and calculated Vmax was correlated with the variables such as Glasgow Coma Scale , plasma albumin concentration , age , race and weight.(14)

RESULTS AND DISCUSSION

Twenty adult critically ill head trauma patients (12 men & 8 women) were enrolled in the study.

Table 1 Baseline Patient Characteristics

Patient number	Age (year)	Gender (M/F)	Weight (Kg)	S cr. (mg/dL)	GCS	Diagnosis	Outcome
1	55	M	80	0.6	5	Frontal contusion	D/C
2	50	F	70	0.7	6	Trauma-lateral ventricle hemorrhage	D/C
3	32	M	65	1.1	7	Trauma- epidural bleeding	D/C
4	18	M	62	0.8	4	MVA-ventricle hemorrhage	D/C
5	20	M	60	1.1	6	MVA-subdural hemorrhage	D/C
6	40	M	65	1.2	5	Trauma-epidural bleeding	D/C
7	55	M	63	1.3	5	Trauma intraparanchymal hemorrhage	D/C
8	55	M	60	1.3	5	Trauma-subdural bleeding	D/C
9	18	M	65	0.8	7	Trauma-closed-head injury	D/C
10	60	M	60	0.6	5	Skull fracture	D/C
11	52	F	65	1.0	4	Trauma intraparanchymal hemorrhage	D/C
12	53	F	70	1.3	8	Trauma- epidural bleeding	D/C
13	55	F	60	0.9	4	Trauma intraparanchymal hemorrhage	D/C
14	45	F	65	1.0	5	Frontal contusion	D/C
15	41	M	65	0.9	7	Trauma-lateral ventricle hemorrhage	D/C
16	24	M	65	0.8	8	Trauma- epidural bleeding	D/C
17	33	M	65	1.2	6	Skull fracture	D/C
18	50	F	60	0.8	5	MVA-subdural hemorrhage	D/C
19	45	F	65	1.1	5	Trauma-subdural bleeding	D/C
20	50	F	70	1.1	6	Trauma-closed-head injury	D/C
Mean	42.2		64.7	1.0	5.6		
SD	14.0		4.8	0.2	1.3		

Scr: serum creatinine, GCS: Glasgow Coma Scale, MVA: motor vehicle accident, D/C: discharged

Table 2. Total and free phenytoin concentration, and predicted and actual Vmax

Patient no.	Peak Conc* (mg/l)	Trough Conc* (mg/l)	Peak Conc** (mg/l)	Trough Conc** (mg/l)	Free Peak Conc^{+} (mg/l)	Free trough Conc^{+} (mg/l)	Pred. V_{max} (mg/kg/day)	Actual V_{max} (mg/kg/day)
1	0.8	0.4	0.77	0.53	0.1	0.007	5.6	17.8
2	1.2	0.5	0.85	0.51	0.1	0.007	7.2	19.3
3	3.7	1.7	3.51	1.5	0.2	0.1	7.5	9
4	4.2	1.9	4.1	2	0.6	0.3	7.2	8.6
5	11.8	2.3	10.65	2.18	0.3	0.2	7.5	8.6
6	3.8	1.5	3.56	1.34	0.2	0.1	7.5	8.9
7	5.9	2.1	5.53	1.9	0.4	0.1	7.44	8.7
8	7.1	2.8	6.92	2.95	0.7	0.3	7.5	8.5
9	12.5	4.1	11.87	4	0.5	0.3	7.5	7.7
10	8.5	3.1	8.59	3.12	0.9	0.7	7.5	8.5
11	5.2	2.1	4.85	2.1	0.4	0.2	7.5	7.5
12	7.3	2.4	7.05	2.48	0.4	0.3	7.5	7.4
13	6.2	2.1	5.95	2.68	0.1	0.006	7.49	7.4
14	3.4	1.3	3.34	1.12	0.1	0.007	7	9.3
15	5.6	2.1	5.2	2.21	0.55	0.1	7.5	7.3
16	5.5	1.9	5.18	1.73	0.55	0.2	7.5	7.4
17	6.1	2.3	5.37	2.2	0.3	0.1	7.4	9
18	8	3.3	7.6	3.13	0.3	0.1	7.5	9.7
19	6.3	2.2	5.84	2.5	1	0.58	7.5	6.8
20	9.1	3.1	8.9	2.4	1.1	0.2	7.4	7.9
Mean	6.0	2.1	5.6	2.1	0.4	0.2	7.3	9.3
SD	3.0	0.9	2.8	0.9	0.3	0.2	0.4	3.4

*Peak and trough concentration measured by FPIA

**Peak and trough concentration measured by HPLC

+ Free peak and trough concentration measured by HPLC

Table 3. Comparison of administered and calculated (based on actual Vmax) doses and other parameters for patients with head trauma

Patient number	Ad. Dose* (mg/day)	Cl (L/day)	T1/2 (day)	Vd** (L/kg)	Calc. MD (mg/day)+
1	200	230	0.16	0.63	1137
2	200	216	0.14	0.62	1078
3	250	65	0.45	0.65	465
4	250	56	0.5	0.63	424
5	375	32	0.83	0.64	413
6	250	64	0.45	0.64	458
7	300	50	0.57	0.59	435
8	300	41	0.65	0.8	407
9	375	29	1.00	0.63	400
10	300	32	0.85	0.87	358
11	250	48	0.60	0.70	388
12	300	41	0.77	0.65	405
13	250	39	0.70	0.65	351
14	250	69	0.43	0.64	478
15	250	44	0.66	0.63	374
16	250	45	0.65	0.65	381
17	300	55	0.54	0.64	465
18	300	39	0.74	0.65	376
19	250	39	0.74	0.93	354
20	300	39	0.80	0.67	442
Mean	273.7	65.0	0.60	0.70	481.4
SD	47.5	56.9	0.20	0.10	224.2

*Administered daily dose
**Calculated Volume of distrbution for phenytoin
+ Calculated maintenance dose based on actual Vmax

Patients' demographics data are listed in table 1. Total and free phenytoin concentration measured by FPIA (Eclair-Merck) and HPLC, predicted and actual Vmax and other results are provided in table 2. Administered dose and calculated maintenance dose (based on actual Vmax) are reported in table 3.

The actual Vmax of our patients showed a wide range (442 to 1424 mg/day) which is in good agreement with previously reported studies (15,16). This high interindividual variability could be explained by high haemodynamic and stress related metabolic changes in head trauma patients. Interestingly, actual mean Vmax (611.4 ± 269.8 mg/day) was higher than mean predicted Vmax (475.4 ± 24.5 mg/day) and this difference was statistically significant (P=0.02). This finding could explain why phenytoin serum concentrations were lower than therapeutic level in most of the patients.

In report (17) Km and Vm ranged from 1.5 to 5.8 mg/l and 275 to 585 mg/day in epileptic patients respectively. In another study, a wide range of variability in Km and Vmax values was reported in a heterogeneous population. These variability's were related to age, race, and weight (14).

A significant difference between adjusted dose based on actual Vmax, and administered dose for our patients in intensive care unite was found (p=0.0015). These results were consistent with those of previous studies indicating that administration of higher doses of phenytoin is necessary to achieve therapeutic plasma concentration in patients with neurological injuries. (1,2). Several mechanism have been proposed to explain this finding, including increased unbound phenytoin concentrations resulting in increase free phenytoin clearance, (18), increased in total phenytoin clearance due to drug interaction (19), and stress – related increase in hepatic metabolism (9). An increase in free phenytoin concentration observed in our study as well as increased Vmax could explain the higher doses that was required in our patients.

Among the patients who received equal doses of phenytoin (about 50% of all), phenytoin serum concentrations ranged from minimum of 0.77mg/l to maximum of 11.8mg/l indicating that phenytoin doses correlates poorly with serum drug concentration which could be a consequence of different Vmax and Km among different groups of patients. These interindividual differences are explained by limitation in drug metabolism, variation of Vmax, and plasma albumin concentration, as well as trauma severity score (14).

Under normal condition about 90% of phenytoin is primarily bound to serum albumin and the unbound fraction is 10%, thus, the proposed therapeutic unbound concentration would be 1-2 mg/l (20). It has also been noted that the binding of phenytoin to albumin is commonly altered in the critically ill patients (21). Bauer and Co-workers (2) found that although patients with head trauma had statistically sub-therapeutic total phenytoin concentration, free concentration remains in therapeutic levels. Our results demonstrated that although mean free fraction of phenytoin was about 10% of the total phenytoin concentration, subjects had sub-therapeutic free as well as sub-therapeutic total phenytoin concentration. This finding may suggest that more than one mechanism is involved in this phenomenon. Added to increased unbound plasma concentration as a result of decrease in plasma proteins, increased total clearance due to drug interaction (10,11) and increase in hepatic metabolism might be involved in this complex phenomenon (4).

CONCLUSION

Although the exact mechanism of the increased clearance of phenytoin in head trauma patients is unknown, it is clear that maintenance of phenytoin concentrations in the range of 10-20 mg/l commonly required incremental increase in the phenytoin maintenance dose and more frequent monitoring of concentration in these patients during the first 7-14 days of therapy. It seems the usual reported half-life for phenytoin (22 hours) is not a constant value.

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