Kinetics of CSF Phenytoin in Children

G. Koren, Z. Barzilay, E. Schachar, N. Brand, S. Danee, H. Halkin and S.M. MacLeod

SUMMARY: The efficacy of intravenous phenytoin for the treatment of status epilepticus is related to the rapid entry of phenytoin into brain parenchyma. There is no information concerning the correlation between phenytoin serum and CSF concentrations in children, and the application of CSF data to clinical use. We report 7 children (2-11 yrs) who were treated or exposed to phenytoin in doses between 10.5-230 mg/kg. Lumbar puncture was performed 9 times in 6 of the patients. In one patient, an intraventricular catheter permitted successive assessment of CSF phenytoin concentrations. The ratio of CSF/serum phenytoin concentrations was 0.16 ± 0.08, with gradual increase over the first 8 hours as the serum phenytoin concentration decreased. There was good correlation between therapeutic outcome and CSF phenytoin levels higher than 2 mcg/ml. In one patient the coma state secondary to phenytoin intoxication was associated with high CSF concentration (6 mcg/ml).

RÉSUMÉ: L'efficacité du phenytoin intraiveneux dans le traitement du status épilepticus est en rapport avec l'entrée rapide du phenytoin dans le parenchyme cérébral. Il n'existe pas de données sur la corrélation entre les taux sériques de phenytoin et ceux dans le LCR chez les enfants ni sur la valeur clinique des taux dans le LCR. Nous rapportons l'étude de 7 enfants (2-11 ans) traités ou exposés au phenytoin à des doses de 10.5-230 mg/kg. Neuf ponctions lombaires furent faites chez 6 des patients. Un patient qui possédait un catheter intraventriculaire a pu également être étudié. Le rapport LCR/serum des concentrations de phenytoin était de 0.16 ± 0.08, avec une augmentation graduelle pendant les premières 8 heures alors que la concentration sérique décroissait. Il y a une bonne corrélation entre les résultats thérapeutiques et des concentrations liquidiennes dépassant 2 mcg/ml. Chez un patient, l'état de coma secondaire à une intoxication au phenytoin s'accompagnait de concentrations de 6 mcg/ml dans le LCR.

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The efficacy of intravenous phenytoin for the treatment of status epilepticus has been established in adults (Cranford et al., 1979; Wilder et al., 1977) as well as in neonates (Laughman et al., 1977; Painter et al., 1978) and children (McWilliams et al., 1958). The rapid entry of phenytoin into brain parenchyma shown in animal studies may account for the rapid onset of phenytoin effect in controlling seizures (Kutt et al., 1968; Louis et al., 1968).

Good correlation has been shown between serum phenytoin concentrations and the therapeutic outcome. The range of 5-20 mcg/ml has been defined as the optimal therapeutic concentration (Buchthal et al., 1960). However, there are only a few studies concerned with the correlation between phenytoin serum and cerebrospinal fluids (CSF) concentrations. Lund (1972) demonstrated that phenytoin CSF levels are equal to the serum unbound levels of the drug. Vajda (1974) found that the CSF/plasma ratio for phenytoin was 0.12 ± 0.04. Wilder (1977) reported CSF phenytoin data for 6 adult patients, showing a gradual increase in CSF phenytoin concentrations over 50 minutes as the serum concentrations decreased, with a parallel decrease of the serum/CSF phenytoin ratio. Wilder suggested passive entry as the mechanism for phenytoin penetration into the CSF and concluded that there is no correlation between CSF phenytoin concentrations and seizure control.

Since no data have been published concerning CSF phenytoin concentrations in the pediatric age group and its correlation with the clinical outcome, we reviewed our data from 7 children who received or were exposed to phenytoin and had a subsequent CSF measurement carried out.

Material and Methods

Six of the 7 patients (age range 2-11 yrs) were treated with intravenous phenytoin either for established convulsions (patients A-D) or as a preventive measure after head trauma with coma (patients E-F). One patient (G) accidentally swallowed 3g (230 mg/kg) of phenytoin, and was deeply comatose on admission. There was no evidence for liver or kidney disease that might be expected to change the metabolism of phenytoin. None of the patients had received other drugs prior to the administration of phenytoin. Phenytoin was administered intravenously (Patients A-E) in doses between 10.5-20 mg/kg (mean ± S.D. = 13.9 ± 3.7) of body weight at a rate not exceeding 90 mg per minute. Blood pressure and electrocardiogram were monitored during the infusion. Lumbar puncture was performed 9 times on 6 of 7 patients and CSF specimens were obtained.

In patient E, who suffered from coma secondary to head injury, an intraventricular catheter for continuous monitoring of intracranial pressure permitted successive assessment of CSF phenytoin concentrations. Serum specimens were obtained at the time of the CSF collection. All serum and CSF specimens were assayed for phenytoin by gas chromatography (9).

Results

Historical data and patient characteristics are listed in Table 1. CSF and serum concentrations are shown in Table 2.

In all the epileptic patients treated intravenously (A-D), convulsions ceased within 6 minutes after phenytoin administration.

From the Divisions of Pediatriac ICU and Clinical Pharmacology, The "Sheba" Medical Center, Tel Hashomer, Israel and The Division of Clinical Pharmacology, The Hospital for Sick Children, Toronto, Canada.

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Reprint requests to: Dr. Gideon Koren, The Division of Clinical Pharmacology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8.

TABLE 1: Historical data and patient characteristics

Patient	Age (yr)	Diagnosis	Weight (kg)	Phenytoin dosage mg/kg body weight	Mode of administration
A	11	Grand mal Epilepsy	30	20	I.V.
B	6	Grand mal Epilepsy	28	14.3	I.V.
C	1⁹⁄₁₂	Grand mal Epilepsy	10	10	I.V.
D	10	Grand mal Epilepsy	28	14	I.V.
E	7⁹⁄₁₂	Post traumatic coma	24	15.	I.V.
F	6	Post traumatic coma	25	10	I.V.
G	2³⁄₁₂	Accidental intoxication	13	230	P.O.

TABLE 2: CSF and serum phenytoin concentrations in relation to time after administration.

Patient	Phenytoin serum concentration (mcg/ml)	Phenytoin CSF concentration (mcg/ml)	CSF/serum ratio	Time after phenytoin injection (hrs)	Therapeutic success
A	12.1	2.1	0.17	2	Yes
B	35.8	2.72	0.07	0.33	Yes
C	7.8	2.2	0.28	6	Yes
D	15	2.8	0.19	5	Yes
E	20.4	1.7	0.08	0.66	*
	17.5	3	0.17	1	
	12.1	2.6	0.215	5	
	10.3	2.3	0.223	8	
	8.5	2.1	0.245	24	
F	12.3	2.4	0.20	0.66	*
	8	0	0.0	20	
G	45	6	0.11	2	*

* No convulsions

Their serum concentrations were within the therapeutic range in the first 6 hours after the injection. Their CSF phenytoin concentrations were all higher than 2 mcg/ml (2.1-2.8).

Figure 1 is a plot of the serum and CSF phenytoin concentrations of patient E, showing a gradual increase in CSF concentration, reciprocal to the biphasic decrease in serum phenytoin levels during distribution and elimination phases. The concentration ratio of CSF/serum phenytoin was between 0.-0.28 (mean ± S.D. = 0.16 ± 0.08). Over the first 8 hours after the phenytoin administration, there was a significant positive correlation between this ratio and time (Fig. 2) ($r = 0.61$, $p<0.05$).

Discussion

Our data indicate that CSF concentrations of phenytoin increase with time, as was previously shown by Wilder et al. (1977). This phenomenon is consistent with the two compartment kinetic model (Laughman et al., 1976), in which phenytoin is distributed from a central compartment (blood) into a peripheral compartment (CSF). The concentration ratio of CSF/serum phenytoin closely resembled the unbound/total serum phenytoin ration (Lund, 1972), and suggests that free phenytoin passively enters the CSF (Wilder et al., 1977). However, the increased CSF/serum ratio over time suggests accumulation of free phenytoin in the CSF against concentration gradient, without allowing equilibration between CSF and serum unbound phenytoin.

Brain penetration of phenytoin after intravenous administration is rapid, and parenchymal concentration tends to exceed serum levels within 20-60 minutes after infusion (Wilder et al., 1977; Kutt et al., 1968).

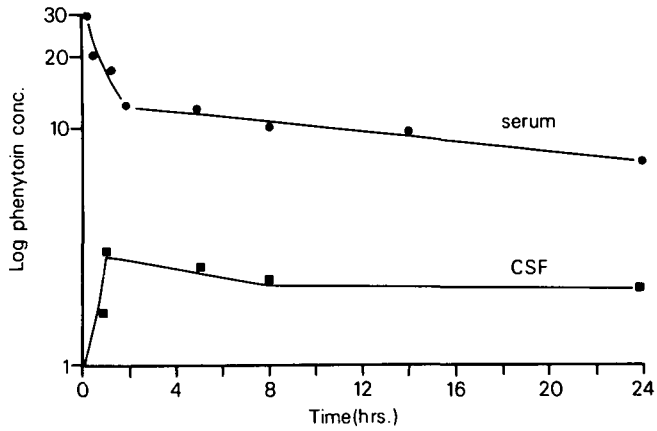

Figure 1 — Serum and CSF phenytoin concentrations of patient E in relation to time after injection. The CSF level remains stable despite a decrease in serum level.

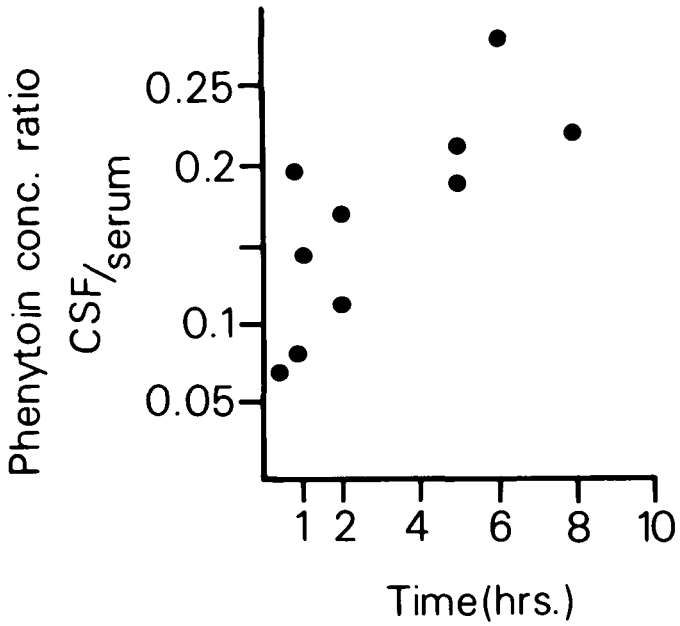

Figure 2 — Ratio of CSF/serum phenytoin concentration in relation to the time of administration in the 7 patients. The ratio increases significantly during the first 8 hours ($r = 0.61$, $p<0.05$, $y = 0.14 + 0.1x$).

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Since the ratio between free/total serum phenytoin tends to remain stable, and there is good correlation between serum levels and therapeutic or toxic effects (Kutt et al., 1964), one might expect good correlation between CSF phenytoin levels and clinical outcome. Indeed, in the 4 epileptic children treated with I.V. phenytoin, CSF phenytoin levels were higher than 2 mcg/mg, with concomitant serum levels in the therapeutic range.

Patient G swallowed an excessive amount of phenytoin (230 mg per kg body wt). Coma, secondary to phenytoin intoxication, correlated with the high CSF concentration of the drug (6 mcg/ml).

Our data contradict Wilder's assumption that CSF phenytoin concentrations do not correlate with seizure control. His CSF assessments were performed on six patients who underwent pneumoencephalography. There are no details available indicating whether these patients suffered from convulsions while receiving phenytoin, nor was there any record of seizure activity after the phenytoin infusion. Moreover, in Wilder's series, phenytoin CSF concentrations ranged from 0.26-2.1 mcg/ml, lower than those in the epileptic children treated by us (2.1-2.8 mcg/ml). Our data suggest that phenytoin CSF levels higher than 2 mcg/ml are associated with good therapeutic outcome in children.

In conclusion, CSF data may give a better idea on the real concentration of phenytoin near its target organ, thus correlating better than serum concentrations with the clinical outcome.

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