DOES HEAD INJURY ALTER CEREBROSPINAL FLUID PHENYTOIN LEVEL? A Clinicopharmacological Study

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SUMMARY :

Forty craniocerebral trauma patients who were hospitalized for observation or surgical intervention were administered phenytoin for anticonvulsant prophylaxis. Blood and cerebrospinal fluid samples were taken on the eighth day of medication and pheytoin levels were determined with the aim of searching for a possible correlation between the severity of trauma and cerebrospinal fluid phenytoin level. Glasgow Coma Scale scores of the patients ranged from 4 to 15. Twenty-eight patients had traumatic lesions on computed tomographic scans. Early posttraumatic epilepsy was not observed. No significant association was noted between the severity of trauma, resulting pathological changes, and cerebrospinal fluid phenytoin levels.

KEY WORDS :

Anticonvulsant prophylaxis, Head Injury, Phenytoin.

The controversy over prophylactic use and effectiveness of antiepileptics in craniocerebral trauma has not yet been resolved. There are both advocates (13,22,27,29) and opponents (17,20,28,30) of such a procedure. On the other hand, prophylactic or intraoperative diphenylhydantoin (phenytoin, DPH) has been successful in reducing seizures seen after craniotomies performed for non-traumatic pathologies (16,24,25).

Plasma and cerebrospinal fluid (CSF) concentrations of phenytoin are well studied. Plasma phenytoin level is the sum of the bound and free fractions of the drug; 90 % of the plasma pheytoin is bound to plasma proteins, mostly to the albumin fraction (9,10). Under normal circumstances the CSF/plasma ratio of phenytoin is about 1/10 (6,9,23) and brain levels in man are 5 to 10 fold the CSF value.

The anatomical basis of the blood brain barrier is considered to be the tight junctions of the cerebrovascular endothelium (5). Trauma is expected to cause damage to this barrier and consequent changes in the CSF phenytoin levels may also be expected. The primary purposes of this study are to find out if such a change occurs, and if it occurs, to search for a possible correlation between the severity of the trauma and CSF phenytoin levels.

MATERIALS AND METHODS

Forty patients who experienced craniocerebral trauma and were hospitalized in our clinic between January and November 1987 were included in the study.

The ages of the 40 patients (34 males, 6 females) ranged from 2 to 65 years. None of the patients in our series had prior head injury or epilepsy.

The criteria for hospitalization were either definite indication for surgery (e.g. intracranial hematoma or depression fracture) or blunt trauma requiring close observation because of either amnesia or loss of consciousness. Each patient was evaluated according to the initial neurological examination and Glasgow Coma Scale (GCS) values were noted. Routine skull x-rays and computed tomographic (CT) scans were performed. Seventeen patients were operated and 23 were treated conservatively. CT findings are outlined in Table 1.

Patients are grouped according to severity of trauma, and presence of traumatic lesion on CT scan. Severity of trauma is judged by Glasgow Coma Scale (GCS) scores and three groups are defined: 12 patients with GCS scores of 15, 19 patients with GCS

Table : 1 CT Findings In 40 Head Injury Patients

	Number of Patients
Normal	10
Subdural hematoma	8
Epidural hematoma	5
Brain edema	5
Edema+Subarachnoid hemorrhage	3
Contusion	3
Intracerebral hematoma	2
Pneumocephalus	1
Subdural hematoma+Edema+Subarachnoid Hemorrhage	1
Edema+Basal fracture+Pneumocephalus	1
Subdural hematoma+Pneumocephalus	1

scores of 14-10, and 9 patients with GCS scores of9-5. Twenty-eight patients had traumatic lesion/s on CT scans, and 12 patients had normal CT scans.

Adults were initially. administered 900 mg oral phenytoin (diphenylhydantoine sodium, Embil İlaç Sanayii Ltd. Şti., İstanbul, Turkey) followed by 300 mg phenytoin daily. Children were given three times the regular dose (5 mg/kg) the first day, followed by 5 mg/kg dose daily (8). Comatose patients received the same dose through a nasogastric tube.

In the morning of the eighth day of medication simultaneous blood and CSF samples were taken for determination of phenytoin levels. Serum and CSF phenytoin levels were calculated by an Immuno Chemistry Analyser II and using phenytoin reagents (Beckman Instruments, Inc., Fullerton, Calfiornia, USA). The ratio of serum phenytoin level to CSF phenytoin level (S/CSF pheytoin) was determined. This ratio is considered a direct indicator of blood brain barrier penetration of phenytoin.

CSF phenytoin values and S/SCF pneytoin values in each group defined above were compared statistically.

RESULTS

Post traumatic epilepsy and mortality was not observed in this patient group.

Average blood phenytoin level was 9.26 μg/ml. Eleven patients had serum pheytoin values in the therapeutic range of 10-20 μg/ml. 3 patients (7.5 %) had values considered to be toxic, and in one patient who showed clinical signs of toxicity (serum phenytoin 34.1 μg/ml, CSF phenytoin 12.5 μg/ml) phenytoin was discontinued.

Average CSF phenytoin level was 3.43 μg/ml. Five patients had values below 1 μg/ml, two between 4-5 μg/ml, one between 5-6 μg/ml, seven patients equal to or more than 7 μg/ml. Average CSF phenytoin levels in each group defined above are outlined in Table 2. The differences between groups are not statistically significant.

Table 2 : Average Cerebrospinal Fluid Phenytoin Values and Serum/CSF Phenytoin Values In Different Patient Groups

	Number of Patients	CSF Phenytoin (μg/ml)	Serum/CSF Phenytoin Value
GCS Score			
5- 9	9	3.97±1.11	2.69±0.27
10-14	19	3.52±0.65	3.15±0.45
15	12	3.84±0.65	2.90±0.31
		p>0.05	p>0.05
CT Finding			
Normal	12	3.86±0.92	2.90±0.24
Pathologic	28	3.20±0.37	3.00±0.31
		p>0.05	p>0.05

The overall serum/CSF phenytoin value is 2.69/1. Average values of serum/CSF phenytoin in each group defined above are given in Table 2. The differences between groups are not statistically significant.

DISCUSSION

Posttraumatic epilepsy occurs either early or late after the trauma. Early epilepsy refers to the fits seen during the first two weeks following the trauma. Seizures encountered after this time are considered as late epilepsy (20,27).

The incidence of posttraumatic epilepsy is extremely variable. Late epilepsy in the civilian population is reported as 7.1 % and 10.9 % (1,30). Respectively the figure rises to 15 % in patients with nonmissile depressed skull fractures (10). Early seizures are seen in 30 to 60 % of patients with subdural and intracerebral hematomas (11). Caveness in his study among males from the Korean campaign found that 42.1 % of the missile injured and 16.4 % of the nonmissile injured men had epilepsy (7). Annegers reports 2.1 % early epilepsy in a group of 2747 head trauma patients (1).

Although the seriousness of posttraumatic epilepsy is reflected in the above figures, the issue of anticonvulsant prophylaxis is not settled. The ambi-

guity among neurosurgeons is best exemplified in a survey where 60 % of the board certified neurosurgeons said that they administer anticonvulsant prophylaxis whereas 34 % of the neurosurgeons were uncertain of the indications. Furthermore there was not a consensus about choice of drug, dosage and duration of therapy (18).

Inhibition of phenytoin absorbtion in patients on nasogastric tube feeding was shown in a study in which 10 patients receiving DPH 300 mg daily had a mean phenytoin value of 2.59μg/ml. DPH level rose to 10.22μg/ml after nasogastric feeding was stopped. Conversely in 10 patients receiving DPH 300 mg daily and having a stabilized phenytoin concentration of 9.8μg/ml, the value dropped to 2.72μg/ml in seven days during which nasogactric feeding continued (2). Our results do not cerrelate with the above findings. We had to feed nine patients through nasograstric tube. And they had GCS scores between 4-9. The mean blood phenytoin value for this group was 11.02μg/ml which was even higher than the patients with better GCS scores who received phenytoin orally. In addition, the highest blood phenytoin value in the series (34.1μg/ml) was found in a patient with a GCS score of 5. She was completely unconscious and received all phenytoin through the nasogastric tube.

In many controlled studies (14,29) the correlation between plasma concentration and central effects of phenytoin has been observed. A similar relationship between plasma and brain concentrations has been demonstrated (26).

The free portion of phenytoin is generally accepted as the pharmacologically effective portion capable of diffusing across the biological membranes (12,21).

Pregnancy, liver and renal disease, drugs such as valproic acid, diazoxide, salicylic acid and phenylbutazone displace phenytoin from its plasma protein binding sites (19) thus causing an increase in the free portion. Such a situation was very well documented in a study of ten comatose head trauma patients (3). Although the total phenytoin value was 6.8$\pm$1.8μg/ml in these patients, the free phenytoin value was within the therapeutic range of 1 to 2μg/ml. Hypoalbuminemia was postulated as the probable cause of this situation and attention was drawn to the hazards of unnecessary dosage increases in such conditions.

All these examples illustrate that plasma levels do not always correlate with central effects of the drug in contrast to what has been mentioned previously. Our study originated from the idea that blood-brain permeability changes produced by craniocerebral trauma (4) may result in a similar misleading conclusions.

Our results show a general reduction in blood/CSF ratio, around 2,5-3.0/1.0, but this does not enable us to state that the severity of the craniocerebral trauma and the resulting pathological changes correlate with serum/CSF phenytoin rations (Table 2). It has been our policy to start anticonvulsant prophylaxis in head injury patients even with simple depressed skull fractures without any neurological deficit. As a result of this practice we lack a control group not receiving anticonvulsant prophylaxis, which was a drawback for our study.

In our series severity of trauma and resulting pethological changes in the brain did not cause significant changes in the CSF phenytoin values. Therefore the magnitude of craniocerebral trauma does not seem to be a parameter in determining individual phenytoin requirements.

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