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Enteral Nutrition and Phenytoin Administration in Head Trauma Patients

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ABSTRACT

Background: Seizure is common after head trauma and neurosurgery. Phenytoin is the most common anti-convulsant drug used in epileptic patients and for prevention of seizure in patients with head trauma and stroke. This drug has unique pharmacokinetic and pharmacodynamic characteristics. Phenytoin administration along with enteral nutrition in ICU patients may be accompanied by decreased phenytoin absorption and inadequate therapeutic concentration. The present study was performed to assess the effect of enteral nutrition on the pharmacokinetic therapeutic parameters of phenytoin given to our patients.

Materials and Methods: In a clinical trial, the study group was divided into two groups of 15 patients each. After obtaining steady-state phenytoin serum concentration, two blood samples were obtained from each patient on 2 consecutive days and then analyzed. The mean was assessed on the basis of serum albumin level of the patient. Clearance and maximum metabolic capacity were also calculated.

Results: Serum phenytoin level was below the therapeutic range (10- 20 mg/l) in 70% of patients in group 1 and was higher than the therapeutic range in 70% of patients in group 2 who received oral phenytoin (by dissolving in water) 2h after enteral nutrition. Mean phenytoin concentration was 6.3 ± 4 mg/l and 24.7 ± 9.4 mg/l in group 1 and group 2, respectively.

Conclusion: We found oral phenytoin administration with enteral nutrition (gavage solutions) to result in a significant decrease in absorption and blood concentration of phenytoin. We recommend administration of phenytoin with water only.

In addition, monitoring of phenytoin serum concentration is necessary for assessment of therapeutic concentration and prevention of side effects. (Tanaffos 2008; 7(3): 59-62)

Key words: Enteral nutrition, Phenytoin, Head trauma

INTRODUCTION

Seizure is common after head trauma and brain surgery. Status epilepticus may occur and has a

mortality rate estimated to be about 22% (1). Post-traumatic seizure aggravates the patient's condition by increasing intracranial pressure and cerebral metabolism and threatens the patient's health (2). Therefore, administration of anticonvulsant drugs for prophylaxis is important (1). Phenytoin is still administered as the most common anticonvulsant

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drug. Proper treatment necessitates drug dose adjustment for each individual patient (3). Metabolism of phenytoin is via liver enzymes and is capacity-limited meaning that, by increasing plasma concentration of the drug, its clearance is decreased. In other words, if maintenance dose of the drug increases, plasma phenytoin concentration will also increase resulting in imbalance difficulty of phenytoin concentration (4). Genetic factors cause extensive inter-individual variability for metabolizing phenytoin (3). An appropriate therapeutic serum concentration for phenytoin is 10-20 mg/l. Signs of CNS toxicity occur with serum concentrations higher than 20 mg/l.

Co-administration of phenytoin and enteral nutrition may be accompanied by decreased absorption of phenytoin, insufficient therapeutic concentration of the drug and seizure (5). Numerous studies have been performed for assessment of absorption of oral phenytoin when co-administered with enteral nutrition. These studies reported a significant decrease in phenytoin absorption (1, 6-8). However, some studies showed opposite results (9, 10). Cook et al. showed that co-administration of phenytoin capsules and food had no effect on its bioavailability (11). Furthermore, some recommended that phenytoin be administered with food to decrease gastrointestinal side effects (12).

There is no standard gavage solution in our country; thus, foods like cooked meat, egg, yogurt, milk and honey are blended manually by the hospital staff. With regard to the narrow therapeutic index of phenytoin (13) and necessity of therapeutic drug monitoring (TDM) in patients who use this drug, we decided to measure serum level and clearance of phenytoin and assess the effect of gavage solutions on pharmacokinetic characteristics of phenytoin in patients hospitalized for head injury.

MATERIALS AND METHODS

A clinical trial was performed on 30 patients who were hospitalized for head injury at Shahid Bahonar hospital, Kerman in 2006. The patients had acute cerebral injury and were over 18 years old. All of them had $GCS \leq 10$ with no history of epilepsy, liver or renal failure (liver enzymes were within the normal range, creatinine clearance > 25 ml/min) and had not received medications affecting phenytoin metabolism. Moreover, they did not have a previous history of CNS disorders like epilepsy. Confidence interval was 95%, power of study was 80%, and based on previous same studies (3,5,10,14) standard deviation of phenytoin concentration in two groups was 8.8, and d (expected difference, between two groups) was 9.

The understudy patients were randomly divided into two groups. Group 1 received phenytoin with gavage solution/enteral nutrition and group 2 received the drug at least 2h after gavage and phenytoin was dissolved in water and administered to patients by a nasogastric (NG) feeding tube. One week after initiation of oral phenytoin, 2 venous blood samples (immediately before administration of next dose of the drug) were obtained in 2 consecutive days (7 and 8 days after giving the maximum dose) (4). The blood samples were transferred into heparinized tubes and after centrifugation the separated plasma was kept at -20°C . Then the samples were analyzed by high-performance liquid chromatography (HPLC) method (Waters Model, USA, C18 column, UV detector) (15) and phenytoin concentration was measured. Factors like age, weight, gender and serum albumin level were recorded during sampling days. Phenytoin administration was performed by attending physicians and the primary maximum dose of 15mg/kg IV and then oral capsules 100 mg every 8h.

Mean serum level of phenytoin was measured in 2 consecutive days and corrected on the basis of serum albumin level using following formula (4):

$$\text{True phenytoin concentration} = \frac{\text{Patients' phenytoin concentration}}{\left[0.9 \times \frac{\text{Patient' s Serum Albumin}}{4.4 \text{ mg/dl}}\right] + 0.1}$$

Because of special characteristic of phenytoin metabolism (capacity-limited metabolism) and based on Michaelis Menten equation (K_m), maximum metabolic capacity (V_m) for administered phenytoin in the study patients was calculated for phenytoin capsules using the following formula (4):

$$V_m = \frac{(S.F.Dose / \tau)(K_m + C)}{C}$$

($F=1$, $S=0.92$ and $K_m=4\text{mg/l}$)

Finally, true clearance of phenytoin was calculated in two groups using the following formula (4):

$$CL_{\text{phenytoin}} = \frac{V_m}{K_m + C}$$

RESULTS

Nine patients in group 1 and 11 in group 2 were males. The mean age of patients was 36.2 ± 15 yrs and 35.8 ± 13.9 in group 1 and group 2, respectively. Other parameters are shown in Table 1. Seventy percent of the patients in group 1 had sub-therapeutic concentrations of phenytoin.

Table 1. Comparison of serum phenytoin level, clearance and V_m between the two groups

Variable	Group 1	Group 2	P-Value
Serum phenytoin concentration (mg/l)	6.3 ± 4	24.7 ± 9.4	<0.001
V_m (mg/d)	509.5 ± 113.8	333.2 ± 39.4	<0.001
Cl (L/d)	58.2 ± 28.7	13 ± 5.9	<0.001

DISCUSSION

There are more than 100 different formulations for enteral nutrition. Most formulations are semi-synthetic and other additives like vitamins and minerals are also added (12). Unfortunately, there are no standard gavage preparations in our country and regular foods are used for patients with no additives.

Studies performed on interaction of enteral nutrition with phenytoin have used standard commercially available solutions. The exact mechanism of this interaction is not well known but it seems that absorption of phenytoin is related to electrolytes or proteins of these enteral nutrition solutions; drug binding to NG tube and alteration in gastric pH result in decreased absorption and precipitation of the drug (5).

In our study, drug concentration was significantly lower in group 1 than those of group 2 (6.3 ± 4 mg/l, vs. 24.7 ± 9.4 mg/l respectively, $p < 0.001$). As expected, clearance of phenytoin in group 1 was higher than group 2 ($p < 0.001$).

In a study performed on 22 patients with head trauma in 1998, corrected level of phenytoin based on serum albumin level was 19.8 ± 6.4 mg/ml and 11.7 ± 7.9 mcg/ml in patients who had received phenytoin with gavage and those who had received the drug one hour after receiving standard gavage, respectively ($p < 0.05$) (14).

Another study which was performed to assess interaction of oral phenytoin with standard gavage solutions, showed decreased concentration of phenytoin accompanied by an unknown mechanism and this increased the incidence of seizure (16).

The recommended dosage of phenytoin to prevent seizure is 15 mg/kg IV and then maintenance dose of 5-7 mg/kg/d (17). An appropriate therapeutic concentration for phenytoin is 10-20 mg/l (4). Phenytoin is still used as the most common anti-convulsant drug in epileptic, head trauma and stroke patients in the ICU to prevent seizure. This drug has

unique pharmacokinetic and pharmacodynamic characteristics (3). In our study, phenytoin was administered with steady-state dose of 300 mg/day for all patients via gavage. Thus, significant difference in serum level of phenytoin between the two groups who were matched by age, weight and other characteristics can be only due to interaction of phenytoin with gavage solutions. Corrected concentration of phenytoin based on serum albumin level in 70% of patients in group 1 was < 10 mg/l and >20 mg/l in 70% of patients in group 2 which is not appropriate.

Thus, oral phenytoin should be administered separately from gavage solutions. With narrow-therapeutic index drugs like phenytoin, therapeutic drug monitoring should be performed.

REFERENCES

1. Kitchen D, Smith D. Problems with phenytoin administration in neurology/neurosurgery ITU patients receiving enteral feeding. *Seizure* 2001; 10 (4): 265- 8.
2. Young KD, Okada PJ, Sokolove PE, Palchak MJ, Panacek EA, Baren JM, et al. A randomized, double-blinded, placebo-controlled trial of phenytoin for the prevention of early posttraumatic seizures in children with moderate to severe blunt head injury. *Ann Emerg Med* 2004; 43 (4): 435- 46.
3. Deleu D, Aarons L, Ahmed IA. Estimation of population pharmacokinetic parameters of free-phenytoin in adult epileptic patients. *Arch Med Res* 2005; 36 (1): 49- 53. Erratum in: *Arch Med Res* 2005; 36 (2): 186.
4. Winter ME. Phenytoin. In: Winter ME. Basic clinical pharmacokinetics. 4th ed. Philadelphia: Lippincott Williams and Wilkins 2004: 321- 61.
5. Burstein AH, Cox DS, Mistry B, Eddington ND. Phenytoin pharmacokinetics following oral administration of phenytoin suspension and fosphenytoin solution to rats. *Epilepsy Res* 1999; 34 (2-3): 129- 33. Erratum in: *Epilepsy Res* 1999; 36 (1): 83.
6. Au Yeung SC, Ensom MH. Phenytoin and enteral feedings: does evidence support an interaction? *Ann Pharmacother* 2000; 34 (7-8): 896- 905.
7. O'Hagan M, Wallace SJ. Enteral formula feeds interfere with phenytoin absorption. *Brain Dev* 1994; 16 (2): 165- 7.
8. Fleisher D, Sheth N, Kou JH. Phenytoin interaction with enteral feedings administered through nasogastric tubes. *JPEN J Parenter Enteral Nutr* 1990; 14 (5): 513- 6.
9. Gilbert S, Hatton J, Magnuson B. How to minimise interaction between phenytoin and enteral feeding: two approaches. *Nutr Clin Pract* 1996 ; 11(1) : 28-31.
10. Nishimura LY, Armstrong EP, Plezia PM, Iacono RP. Influence of enteral feedings on phenytoin sodium absorption from capsules. *Drug Intell Clin Pharm* 1988; 22 (2): 130- 3.
11. Cook J, Randinitis E, Wilder BJ. Effect of food on the bioavailability of 100-mg dilantin Kapseals. *Neurology* 2001; 57 (4): 698- 700.
12. Rollins CJ, Huckleberry Y, Cauley P. Adult enteral nutrition. In: Koda-Kimble MA. Applied therapeutics the clinical use of drugs. 8th ed. Philadelphia, 2005.
13. Wilder BJ, Leppik I, Hietpas TJ, Cloyd JC, Randinitis EJ, Cook J. Effect of food on absorption of Dilantin Kapseals and Mylan extended phenytoin sodium capsules. *Neurology* 2001; 57 (4): 582- 9.
14. Faraji B, Yu PP. Serum phenytoin levels of patients on gastrostomy tube feeding. *J Neurosci Nurs* 1998; 30 (1): 55- 9.
15. Patil KM, Bodhankar SL. Simultaneous determination of lamotrigine, phenobarbitone, carbamazepine and phenytoin in human serum by high-performance liquid chromatography. *J Pharm Biomed Anal* 2005; 39 (1-2): 181- 6.
16. Au Yeung SC, Ensom MH. Phenytoin and enteral feedings: does evidence support an interaction? *Ann Pharmacother* 2000; 34(7-8): 896-905.
17. Boucher BA, Rodman JH, Jaresko GS, Rasmussen SN, Watridge CB, Fabian TC. Phenytoin pharmacokinetics in critically ill trauma patients. *Clin Pharmacol Ther* 1988; 44 (6): 675- 83.