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Comparison of Different Drug Combination Effect on Serum Levels of Phenobarbital, Phenytoin and Carbamazepine in Epileptic Patients

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Abstract: In this study serum levels of Phenytoin, Carbamazepine and Phenobarbital when used with sodium valproate as an enzyme inhibitor compared when they used as a single drug or in combination with each other. Blood samples from epileptic patients receiving Phenytoin, Carbamazepine and Phenobarbital as a single drug or the same dose of these drugs in combination with sodium valproate or other antiepileptic drugs given at least four weeks after initiation of therapy. Drug concentration was determined by HPLC. Mean serum levels of Phenobarbital when using in combination with sodium valproate was significantly ($p<0.05$) higher than those producing by the same dose (100 mg) of this drug as a single drug or when used with Phenytoin or Carbamazepine. In Carbamazepine plus sodium valproate treated patients serum levels of Phenytoin were more than in Carbamazepine plus Phenobarbital treated patients. Phenytoin level does not affected largely by the type of accompanied dugs. This study shows the importance of valproic acid in antiepileptic combination therapy and emphasis.

Key words: Valproic acid · Phenobarbital · Phenytoin · Carbamazepine · combined therapy of epilepsy

INTRODUCTION

Because antiepileptic drugs are frequently used together in pelotherapy, Knowledge of the major interactions between these drugs is of interest.

In general classic Antiepileptic drugs like Phenytoin, Carbamazepine, valproic acid and Phenobarbital exhibits a high potential for drug interaction, mostly because of their pharmacokinetic characteristics [1]. Several clinical trials indicate that Phenobarbital, Phenytoin Carbamazepine and sodium valproate have relatively equivalent efficacy in seizure prevention; but sodium valproate is varying in its effects on the metabolism of other antiepileptic drugs [2, 3].

Carbamazepine, Phenobarbital and Phenytoin are stimulators of cytochrome P_{450} enzymes, leading to enhanced metabolism and thus lower concentrations of other drugs [4]. Valproic acid causing cytochrome P_{450} enzyme inhibition leads to increased serum level of drugs, which concurrently administered with this drug [5].

This study compared serum concentrations of Phenobarbital, Phenytoin and Carbamazepine when using in combination with valproic acid or when used in combination with each others.

MATERIALS AND METHODS

Subjects: In this study serum levels of Carbamazepine, Phenobarbital or Phenytoin were measured when using as a single drug or in combination with sodium valproate or in combination with each other. Epileptic patients were from both genders, aged 20-63 years and the study performed over a period of two years. These patients were epileptics who referred for TDM of antiepileptic drugs to Rah Ahan hospital of Shahid Sadoughi University of medical science in Yazd.

Sample collection and processing: Blood samples were collected from patient's one hour before the next dose from epileptic patients at least two weeks after initiation of drug therapy to measure the steady state trough concentration. If antiepileptic drug type or dosage has to be altered, the plasma drugs level measured after an appropriate interval sufficient to allow a new steady state to obtain.

Analysis of samples: The serum was assayed for Phenobarbital, Carbamazepine or Phenytoin in the department of pharmacology using a modified HPLC technique. Briefly, Column: octadecylsilane 6*250 mm, Shimpack (Shimadzu, Japan), detector: UV at 230 nm, internal standard: clonidine, mobile phase: phosphate buffer pH =2.3, 50% methanol 40% and acetonitril 10% [6].

RESULTS

Phenobarbital: Figure 1 shows serum concentration of Phenobarbital (100 mg/day) when used as a single drug or in combination with other antiepileptic drugs. Serum levels of

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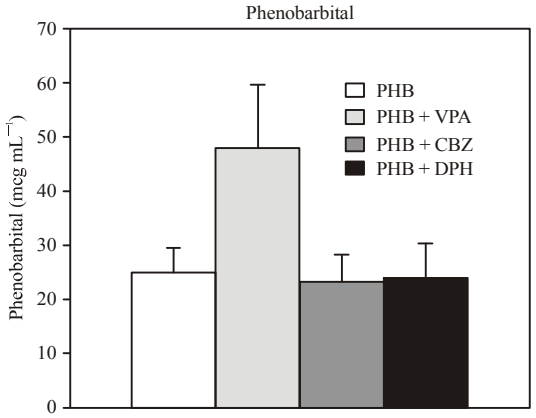

Fig. 1: Effect of different antiepileptic drug combination on serum concentration of Phenobarbital (PHB) in epileptic patients. Each bar represents Mean ± SEM of serum Phenobarbital concentrations. All patients were more than 14 years and receiving same dose of Phenobarbital (100 mg/day). Each patient received 100 mg/day of Phenobarbital alone (n=45) or in combination with sodium valproate (VPA, n=8), Carbamazepine (CBZ, n=22) or Phenytoin (DPH, n=12)

* Statistically significant at $p<0.05$ in comparison with other three groups using one way ANOVA.

f =4.854, Between group df = 3, within group df = 59 and total df = 62

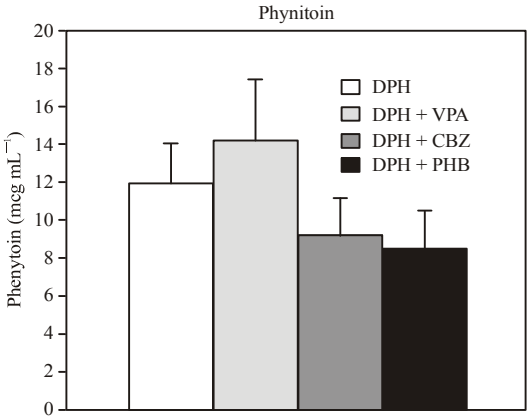

Fig. 2: Effect of different antiepileptic drug combination on serum concentrations of Phenytoin (DPH) in epileptic patients. Each patient received 300 mg/day of Phenytoin alone (n=20) or in combination with sodium valproate (VPA, n=4), Carbamazepine (CBZ, n=7) or Phenobarbital (PHB, n=9).

* Statistically not significant at $p<0.05$ in comparison with other three groups using one way ANOVA. f =1.024, Between group df = 3, within group df = 36 and total df = 39

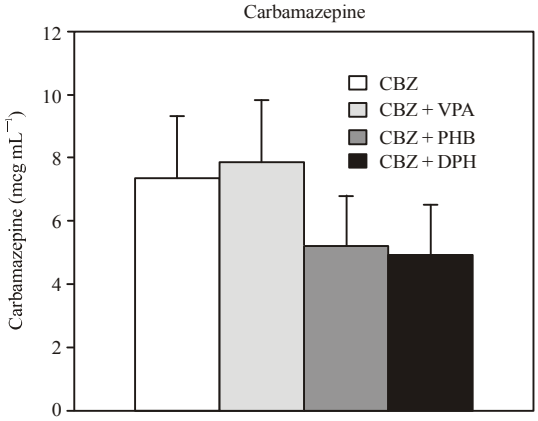

Fig. 3: Effect of different antiepileptic drug combination on serum concentrations of Carbamazepine (CBZ) in epileptic patients. Each patient received 600 mg/day of Carbamazepine alone (n=24) or in combination with sodium valproate (VPA, n=8), Phenobarbital (PHB, n=20) Or Phenytoin (DPH, n= 14).

* Statistically significant at $p<0.05$ in comparison with other three groups using one way ANOVA.

f = 3.878, Between group df = 3, within group df = 62 and total df = 65

Phenobarbital when used in combination with sodium valproate (41.5±5) were about two folds more than serum levels of this drug when used as a single drug (27±3.2) or when used in combination with Carbamazepine or Phenytoin. Carbamazepine or Phenytoin co administration had not any significant effect on Phenobarbital serum concentration.

Phenytoin: As shown in Fig. 2 serum levels of Phenytoin (300 mg/day) when used in combination with sodium valproate (14.42±0.28) were more than serum levels of this drug when used as a single drug (12.8±1.63) or when used in combination with Carbamazepine or Phenobarbital, but this difference were not statistically significant. Serum levels of Phenytoin in combination with sodium valproate were about 40 percent more than serum concentration of this drug when used in combination with Phenobarbital.

Carbamazepine: Serum levels of Carbamazepine (600 mg/day) when used as single drugs or in combination with other antiepileptic drugs in our study were statistically significant ($p<0.05$). Serum levels of Carbamazepine in combination with Phenytoin were less than Carbamazepine concentration when used with other drugs. Mean serum level of Carbamazepine in combination with Phenytoin was 5.8±0.12 and when used as a single drug was 7.34±012 (Fig. 3).

DISCUSSION

In this study concurrent administration of sodium valproate with Phenobarbital caused about 50 percent increase in serum Phenobarbital concentration. Effect of sodium valproate co administration on serum levels of Phenytoin was not statistically significant but Serum levels of Carbamazepine in combination with different antiepileptic combination which is used in this study were statistically significant ($p<0.05$).

Valproate primarily inhibits drugs metabolized by cyp2c9 including Phenytoin and Phenobarbital. The principal cytochrome p450 responsible for Phenobarbital metabolism is cyp2c9 and the majority (95%) of Phenytoin also is metabolized principally in the hepatic endoplasmic reticulum and mainly by the cytochrome p450 isoform Cyp2c9/10 [7].

Another aspect of valproate interaction with Phenobarbital is the acidification of urine by valproate enhances reabsorbtion of Phenobarbital, which is also acidic. This phenomenon also resulting increases in the half-life of Phenobarbital and leads to increase in its concentration [5]. This causes higher increase in concentrations of Phenobarbital in comparison with Phenytoin, which observed in our study. Same results also reported by Fukuka and coworkers which was showed significant differences in Phenobarbital concentration as a single drug or in combination with valproic acid, Phenytoin or Carbamazepine [8] in other studies also the correction of Phenobarbital dose co administered with valproic acid is emphasized [9].

In our study serum concentration of Phenytoin as a single drug or in combination with valproic acid, Phenobarbital or Carbamazepine were not statistically significant same results also reported by Riva and coworkers [10] But Mamia and Coworkers studies indicated elevation of serum free Phenytoin by valproic acid [11]. When applying valproate with Phenytoin free Phenytoin concentration may be increased more than total Phenytoin and in our study design only we determined total Phenytoin serum concentration [12, 13].

Interaction between Phenobarbital and other drugs usually involve induction of the hepatic microsomal enzyme system by Phenobarbital [6]. In our study also Phenobarbital decreased serum concentration of Carbamazepine and Phenytoin but its effect on Carbamazepine concentration were more profound. Ramsay and coworkers also reported higher concentrations of Carbamazepine in combination with valproic acid comparing with Carbamazepine serum levels when used as a single drug [14]. Other studies also indicating inhibition of Carbamazepine metabolism by valproic acid [15]. The ratio of Carbamazepine-epoxide active metabolite of Carbamazepine may also affected by enzyme-inducer drugs such as Phenobarbital and Phenytoin [16, 17].

This study emphasizes the importance of valproic acid effect on the serum concentration of other antiepileptic drugs. In this regards the effect of valproic acid on Phenobarbital is more important.

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