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EFFECTS OF COADMINISTERED ANTIEPILEPTIC DRUGS ON FREE FRACTIONS OF PHENOBARBITAL AND VALPROIC ACID IN EPILEPTIC CHILDREN

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INDEXING WORDS

phenobarbital; valproic acid; polypharmacy, free fraction; serum albumin

SYNOPSIS

The free fractions of phenobarbital and valproic acid were determined in 198 epileptic children. The total and free phenobarbital concentrations were 15.83 ± 5.59 μg/ml and 8.27 ± 2.81 μg/ml in PB monopharmacy, while those in PB polypharmacy with five drugs were 39.73 ± 14.41 μg/ml and 21 ± 6.61 μg/ml, respectively. The free fraction of phenobarbital was 51.32 ± 3.92% in PB monopharmacy, while that in PB polypharmacy with five drugs was 54 ± 2.94%. The serum albumin concentrations were 4.43 ± 0.21 g/dl in PB monopharmacy and 4.10 ± 0.28 g/dl in PB polypharmacy with five drugs. The total, free valproic acid concentration and free fraction were 95.66 ± 28.57 μg/ml, 11.75 ± 7.95 μg/ml and 11.28 ± 3.93% in VPA monopharmacy, while those in VPA polypharmacy with three drugs were 80.31 ± 22.93 μg/ml, 7.47 ± 2.43 μg/ml and 9.19 ± 1.30%. The serum albumin concentrations were 4.38 ± 0.26

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g/ml in VPA monopharmacy, and 3.87 ± 0.05 g/dl in VPA polypharmacy with five drugs. The serum albumin concnetration significantly decreased with number of coadministered drugs in PB polypharmacy and VPA polypharmacy.

INTRODUCTION

Since seizure treatment has included monitoring of the concentrations of antiepileptic drugs in blood, clinical management of epilepsy has been much improved. Antiepileptic drugs bind to different degrees with plasma proteins, mainly albumin, and only the unbound antiepileptic drugs can reach the active sites in the central nervous system from the plasma. Therefore, the concentration of free antiepileptic drugs in plasma should correlate better with the efficacy and toxicity of the medication than with total drug concentrations. Protein binding of antiepileptic drugs can be influenced by the plasma albumin concentration, total drug concentration and interaction with other antiepileptic drugs. Patsalos et al[9] and Kapetanovic et al[6] reported that valproic acid significantly displaced phenobarbital from the plasma protein binding site in vitro and in vivo. On the other hand, the addition of phenobarbital, carbamazepine and phenytoin to valproic acid caused no significant changes in the free fraction of valproic acid, because it binds more tightly to human serum albumin than other protein bound anticonvulsants.[8] However, there have been few studies dealing with the effects of coadministration of one or more additional antiepileptic drugs on free fractions in epileptic children under chronic anticonvulsive therapy.

The present study deals with the effects of coadministration of antiepileptic drugs, in which an increased number of coadministered epileptic drugs results in decreased serum albumin concentration.

PATIENTS AND METHODS

The subjects in this study were 198 epileptic outpatients at the Department of Pediatrics of Kobe University Hospital. The patients were treated with phenobarbital alone (n=57), phenobarbital combined with other antiepileptic drugs (n=60), valproic acid alone (n=36) or valproic acid combined with other antiepilep-

tic drugs (n=48), as shown in Table 1. PB polypharmacy consisted of 17 cases of coadministration of one drug (PB polypharmacy with two drugs), 29 cases of coadministration of two drugs (PB polypharmacy with three drugs), 11 cases of coadministration of three drugs (PB polypharmacy with four drugs), and 3 cases of coadministration of four drugs (PB polypharmacy with five drugs). VPA polypharmacy consisted of 15 cases of coadministration of one drug (VPA polypharmacy with two drugs), 17 cases of coadministration of two drugs (VPA polypharmacy with three drugs), 12 cases of coadminstration of three drugs (VPA polypharmacy with four drugs) and 3 cases of coadministration of four or five drugs (VPA polypharmacy with five or six drugs). Antiepileptic drugs were not changed for at least 2 months prior to the determination of blood concentration. They were given twice a day regularly. The doses of

Table 1 Anticonvulsants given to patients

Phenobarbital			
Monopharmacy	57 cases		
Polypharmacy	60 cases		
Two drugs 17 cases;		PB + VPA	5
		PB + CBZ	10
		PB + other	2
Three drugs 29 cases;		PB + VPA + CBZ	13
		PB + CBZ + PHT	8
		PB + others	8
Four drugs 11 cases;		PB + VPA + CBZ + CZP	3
		PB + VPA + CBZ + AZA	2
		PB + others	6
Five drugs 3 cases			
Valproic acid			
Monopharmacy	34 cases		
Polypharmacy	47 cases		
Two drugs 15 cases;		VPA + CBZ	9
		VPA + PB	4
Three drugs 17 cases;		VPA + PB + CBZ	8
		VPA + PB + PHT	3
		VPA + CBZ + other	3
		VPA + PB p other	2
		VPA + others	1
Four drugs 12 cases;		VPA + PB + CBZ + other	6
		VPA + PB + PHT + other	2
		VPA + others	4
Five drugs 2 cases			
Six drugs 1 cases			

PB: phenobarbital, PHT: phenytoin, VPA: valproic acid, CZP: clonazepam, CBZ: carbamazepine, AZA: acetazolamide.

anticonvulsants given to patients were 2.0 - 5.0 mg/kg for phenobarbital and 15 - 40 mg/kg for valproic acid. Antiepileptic drugs other than phenobarbital and valproic acid were given in the therapeutic range of serum concentration. There were no patients with hepatic disease or renal failure in this study. Venipuncture was performed precisely 2 hrs after the medicine had been taken at breakfast, to exclude the influence of free fatty acid level in serum. Three milliliters of venous blood was collected in a polypropylene syringe and the serum was separated at room temperature. One milliliter of the serum was, as soon as possible, centrifuged for 15 min at 1,400 g at room temperature, using Free-Level™ system I (Syva), to obtain unbound antiepileptic drugs.[2, 3, 7, 12] The drugs were assayed by an enzyme immunoassay technique (EMIT, Syva, Palo Alto, CA). The serum albumin concentration was determined by electrophoresis. The data were analysed by Student's t-test.

RESULTS

Effect of coadministered drugs on free fraction of phenobarbital

The age of patients with PB monopharmacy was significantly lower than that of the patients with PB polypharmacy with three drugs, and lower than that of the patients with PB polypharmacy with five drugs, as shown in Table 2. The maintenance doses of phenobarbital were not different in these five groups, and ranged from 2.98 ± 0.79 mg/kg to 3.10 ± 1 mg/kg. The total phenobarbital concentration significantly increased with the number of coadministered drugs, from 15.83 ± 5.59 μg/ml in PB monopharmacy to 39.73 ± 14.41 μg/ml in PB polypharmacy with five drugs. The free phenobarbital concentration also increased from 8.27 ± 2.81 μg/ml in PB monopharmacy to 21 ± 6.61 μg/ml in PB polypharmacy with five drugs. The free fraction of phenobarbital increased from 51.32 ± 3.92% in PB monopharmacy to 54.32 ± 4.43% in PB polypharmacy with four drugs. The serum albumin concnetration decreased from 4.43 ± 0.21 g/dl in PB monopharmacy to 4.10 ± 0.28 g/dl in PB polypharmacy with five drugs. The increased free fraction of phenobarbital with the number of coadministered drugs not only resulted from reduced protein binding,[4] but also from reduced serum albumin concentration.[10, 12, 13]

Table 2 Effect of coadministered drugs on free fractions of phenobarbital

No of drugs	No of cases	Age (yrs)	Dose (mg/kg)	Total (μg/ml)	Free (μg/ml)	Free fraction (%)	Albumin (g/dl)
1	57	8.98 ± 5.89	3.03 ± 0.73	15.83 ± 5.59	8.27 ± 2.81	51.32 ± 3.92	4.43 ± 0.21
2	17	10.94 ± 4.56	2.98 ± 0.79	19.53 ± 5.61	10.14 ± 2.86	52.84 ± 3.19	4.38 ± 0.18
3	29	12.15 ± 6.23	2.93 ± 0.85	24.83 ± 6.52	12.93 ± 3.44	52.31 ± 5.89	4.30 ± 0.24
4	11	7.25 ± 4.09	3.10 ± 1.00	20.82 ± 7.60	10.86 ± 3.87	54.32 ± 4.43	4.17 ± 0.35
5	3	15.67 ± 1.70	2.98 ± 0.90	39.73 ± 14.41	21.00 ± 6.61	54.00 ± 2.94	4.10 ± 0.28

* P<0.01, ** P<0.025, *** P<0.05

Table 3 Effect of coadministered drugs on free fractions of valproic acid

No of drugs	No of cases	Age (yrs)	Dose (mg/kg)	Total (μg/ml)	Free (μg/ml)	Free fraction (%)	Albumin (g/ml)
1	34	7.76 ± 3.38	21.62 ± 5.84	95.66 ± 28.57	11.75 ± 7.95	11.28 ± 3.93	4.38 ± 0.26
2	15	9.00 ± 4.20	22.63 ± 6.06	83.54 ± 19.17	7.39 ± 3.01	8.47 ± 1.96	4.44 ± 0.20
3	17	12.24 ± 5.77	23.45 ± 6.17	80.31 ± 22.93	7.47 ± 2.43	9.19 ± 1.30	4.35 ± 0.22
4	12	7.85 ± 4.70	33.05 ± 8.97	82.67 ± 18.47	8.78 ± 3.56	10.23 ± 3.33	4.29 ± 0.38
5	3	12.67 ± 2.62	34.07 ± 3.67	80.33 ± 2.64	9.27 ± 2.08	10.70 ± 1.28	3.87 ± 0.05

* P<0.01, ** P<0.025, *** P<0.05

Effect of coadministered drugs on free fraction of valproic acid

There was no significant difference in the age in these five groups, as shown in Table 3. Maintenance doses of valproic acid significantly increase with the number of coadministered drugs. The total valproic acid concentration of VPA monopharmacy was significantly higher than that of VPA polypharmacy with three drugs. The free valproic acid concentration of VPA monopharmacy was significantly higher than that of VPA polypharmacy with two or three drugs, as shown in Table 3. These results indicate that coadministered drugs induce the biotransformation of valproic acid. The free fraction of VPA monopharmacy was significantly higher than that of VPA polypharmacy with two or three drugs, but serum albumin concentration in these three groups did not vary. The result may be due to the induction of biotransformation of valproic acid by coadministered drugs. On the other hand, the free fraction of VPA polypharmacy with five or six drugs was significantly higher than that of VPA polypharmacy with two drugs, depending on lower serum albumin concentration in VPA polypharmacy with five or six drugs.

Serum albumin concentration in VPA polypharmacy also decreased with the number of coadministered drugs.

DISCUSSION

Antiepileptic drugs are frequently administered in combination, creating the possibility of pharmacodynamic and pharmacokinetic interactions. In the clinically important pharmacokinetic drug interactions, hepatic microsomal enzyme induction of coadministered drugs is the proven or presumed mechanism for decreases in serum concentration of the original antiepileptic drug in most cases, although a few of the decreases may be due to reduced protein binding. On the other hand, inhibition of hepatic metabolism is the proven or presumed mechanism for increases in serum concentration of the original antiepileptic drug.[1)] The total valproic acid concentration decreases when carbamazepine, phenobarbital, phenytoin or primidone is coadministered.[11)] On the other hand, the total phenobarbital concentration increases when methsuximide, phenytoin or valproic acid is coadministered.[12)] In our study, the total and free phenobarbital concentration in serum

increased with the number of coadministered drugs, with no difference in dosing rate. These results suggest that drugs coadministered with phenobarbital may inhibit hepatic metabolism. The increased free fraction was mainly dependent on the reduced serum albumin concentration from the coadministered drugs, in our study. On the toxities of antiepileptic drugs, a lot of neurological, hematological, allbergic and hormonal side effects have been reported, while decreased serum albumin concentration due to antiepileptic drugs in combination has not been reported. However, the authors were not able to clarify the mechanism of hypoalbuminemia.

In our study, the total and free concentration of valproic acid was significantly lower in VPA polypharmacy than in VPA monopharmacy, as reported previously.[11, 12] The serum albumin concentration of VPA polypharmacy with more than five drugs was significantly lower than those of other groups. The free fracttion of valproic acid mainly depended on the number of coadministered drugs when the serum albumin concentration did not differ in the five groups. When serum albumin concentration was different in the five groups, the free fraction depended on the number of coadministered drugs and serum albumin concentration. Patel and Levy reported that the unbound fraction of valproic acid was not affected by anticonvulsants (phenytoin, phenobarbital and carbamazepine).[8] According to Yu, when daily doses of sodium valproate ranging from 29 to 73 mg/kg/day, with or without coadministration of antiepileptic drugs were administered per OS, the unbound fraction ranged from 10.32 to 48.39%.[5] Our previous study also indicated that the free fraction of valproic acid was dependent more on the total valproic acid concentration than on the serum albumin concentration, when the total valproic acid concentration was above 80 μg/ml in VPA monopharmacy.[12] These results suggest that the free fraction of valproic acid is affected by a lot of factors.

In conclusion, our study demonstrated that serum albumin concentration decreases with the number of coadministered antiepileptic drugs, and influences the free fractions of phenobarbital and valproic acid.

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