The Effect of Carnitine on the Metabolism of Valproic Acid in Epileptic Patients

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SAKEMI, K., HAYASAKA, K., TAHARA, M., SANADA, Y. and TAKADA, G. *The Effect of Carnitine on the Metabolism of Valproic Acid in Epileptic Patients.* Tohoku J. Exp. Med., 1992, **167** (2), 89-92 — The half-life of valproic acid (VPA) was studied in 8 epileptic and severely mental retarded patients before and after one month of carnitine supplementation. Serum carnitine concentration was significantly decreased and VPA half-life was prolonged especially in adult patients before carnitine supplementation. After the treatment with carnitine, serum carnitine concentration was increased, and prolonged half-lives of VPA were corrected near to the normal range (from 12.2 ± 4.2 hr to 9.7 ± 2.2 hr; $p < 0.05$). Controlled state of epilepsy was unchanged during the short period of observation. ——— valproic acid; carnitine; epilepsy; pharmacokinetics

Valproic acid (VPA) has been widely used as an effective anticonvulsant for generalized as well as partial seizures, including prophylaxis of febrile convulsion (Wallance and Smith 1980). Nausea and vomiting are usually seen as side effects at the initiation of therapy, but transiently (Browne 1980; Committee on drug 1982). Other side effects are drowsiness, ataxia, tremor, thrombocytopenia, and hepatic dysfunction, including Reye-like syndrome (Gerber et al. 1979). Biochemical studies have shown hyperaminoacidemia, especially hyperglycinemia (Kochi et al. 1979; Hayasaka et al. 1980; Inuma et al. 1988), hyperammonemia, and hypocarnitinemia (Ohtani et al. 1982) in VPA-treated patients. Prolonged administration to rats caused an increase in enlarged and less functional mitochondria in liver (Hayasaka et al. 1986). Carnitine supplement has been reported to be effective in reducing the VPA associated hyperammonemia (Ohtani et al. 1982). Carnitine supplement may affect on the metabolism of VPA and we studied VPA half-life in patients before and after carnitine supplementation.

SUBJECTS AND METHODS

We studied 8 epileptic and severely mental retarded patients who were institutionalized in Akita Byoin National Sanatorium for the handicapped. They were treated with VPA and other anticonvulsants as described in Table 1. No patient had dysfunction of liver and

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TABLE 1. *Patient data*

Patient No.	Age (years)	Sex	VPA therapy		Other anticonvulsants
			Dose (mg/kg/day)	Duration (years)	
1	7	M	63	5.0	PB ^a , PHT, DZP
2	8	M	38	1.6	PB, CZP
3	13	M	26	8.8	CBZ
4	17	M	50	7.0	PB, PHT, ACE
5	19	F	31	6.3	PB, ACE
6	21	F	27	3.0	PB, PHT, CBZ, CZP
7	22	F	40	7.2	PHT, CZP, ACE
8	37	M	27	6.8	PB, CZP

^aPB, phenobarbital; PHT, phenytoin; DZP, diazepam; CZP, clonazepam; CBZ, carbamazepin; ACE, acetazolamide.

kidney. Mean dose of VPA was 37.8 mg/kg/day ranged from 26 to 63 mg/kg/day and mean duration of VPA therapy was 5.7 years ranged from 1.6 to 8.8 years. All anticonvulsants were maintained at their previous doses during the study. Total and free carnitine concentration in serum and VPA half-life were measured before and one month after supplement of DL-carnitine (40 mg/kg/day). Serum carnitine was assayed according to the method of Cederblad and Lindstedt (1972) and VPA was by fluorescence polarization immunoassay (TDX, Abbott). The log post-peak serum concentration-time curve after the last dose of VPA was fitted accurately to straight lines (Schobben et al. 1975) and pharmacokinetic parameters were calculated from the data using standard methods. The equation used was $t_{1/2} = 0.693/Ke$, where $t_{1/2}$ is the serum half-life of VPA and Ke is elimination rate constant. VPA and other anticonvulsants were administered at 7:00 and 19:00 and total VPA concentration in serum was measured three times between 13:00 and 18:00.

RESULTS

As shown in Table 2, the mean concentration of total and free carnitine in serum was significantly decreased in patients before carnitine supplement and simultaneously prolongation of VPA half-life was observed especially in adult patients. After carnitine supplement for one month, concentration of total and free carnitine in serum was significantly elevated and prolonged half-lives of VPA were shortened near to the normal range (from 12.2 ± 4.2 hr to 9.7 ± 2.2 hr; $p < 0.05$). Frequency of seizures in each patient was unchanged during two months of observation.

TABLE 2. VPA half-life and serum carnitine concentration before and after carnitine supplementation^a

Patient	Total carnitine (nmol/ml)		Free carnitine (nmol/ml)		VPA half-life (hr)		Frequency of seizure ^b (times/month)	
	Before	After	Before	After	Before	After	Before	After
1	10.9	73.6	5.2	55.8	6.8	6.3	27	26
2	20.4	56.0	16.4	37.9	9.1	8.0	15	13
3	24.5	74.9	15.5	47.4	9.2	9.5	2	2
4	23.7	57.1	13.9	43.8	16.2	12.1	16	12
5	43.9	55.0	34.1	46.5	18.1	12.6	0	0
6	55.0	60.3	34.0	52.7	8.6	8.3	10	13
7	19.4	48.6	14.9	35.2	15.0	9.2	0	0
8	21.7	56.6	15.0	43.3	14.8	11.3	5	4
Mean $\pm$ S.D.	27.4 $\pm$ 14.6	60.3 $\pm$ 9.2**	18.6 $\pm$ 10.1	45.3 $\pm$ 6.9**	12.2 $\pm$ 4.2	9.7 $\pm$ 2.2*		
Normal ^c range	49.0 $\pm$ 13.4		44.2 $\pm$ 12.2		9.5 $\pm$ 2.1 (adults) 9.2 $\pm$ 3.5 (children)			

^aDL-Carnitine was supplemented for one month at a dosage of 40 mg/kg/day.

^bClinical effect was estimated at two months after carnitine supplement.

^cNormal ranges of carnitine and half-life from Ohtani et al. (1982) and Redenbaugh et al. (1980).

* $p < 0.05$, ** $p < 0.01$, vs. before carnitine supplementation.

DISCUSSION

Administration of VPA decreased the concentration of total and free carnitine in serum as previously reported (Ohtani et al. 1982). Simultaneously, prolongation of VPA half-life was observed especially in adult patients and was corrected near to the normal range by carnitine supplement. VPA is metabolized mainly by glucuronidation and partly by several oxidative pathways including β -oxidation (Gugler and von Unruh 1980). Physiologically, carnitine has a significant role in the oxidation of long chain fatty acids, allowing long chain acyl-CoA esters to cross the mitochondrial membrane. A further role of carnitine may be to protect cells against toxic accumulation of acyl-CoA compounds of either endogenous or exogenous origin by trapping such acyl groups as carnitine esters, which may be excreted in urine. There was no change in urinary excretion of major oxidative metabolites of VPA under carnitine supplement (data not shown). Therefore, the effect of carnitine on VPA metabolism appears unrelated to β -oxidation of short chain fatty acid, VPA, but it might be related to promoting the excretion of toxic acyl-CoA compounds in urine and to improving the metabolism of VPA. VPA half-life is slightly shorter in children than that in adults (Redenbaugh et al. 1980). The glucuronidation of VPA in children may be more active than that in adults, resulting in less accumulation of acyl-CoA

compounds in children. Frequency of seizures in each patient was unchanged during two months of observation. Further cases should be studied for long term.

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