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LACK OF HEPATIC ENZYME INDUCING EFFECT OF SODIUM VALPROATE

Many of the drugs prescribed for the major epilepsies, e.g. phenytoin and phenobarbitone, are potent inducers of hepatic microsomal enzymes. This property is responsible for a number of drug interactions (Richens, 1977) and for altering the metabolism of various endogenous substances. The latter may account for certain chronic adverse effects such as anticonvulsant osteomalacia and folate deficiency (Richens & Rowe, 1970; Maxwell, Hunter, Stewart, Ardeman & Williams, 1972). The most recently introduced antiepileptic drug, sodium valproate, has been shown not to induce liver enzymes in rats (Jordan, Shillingford & Steed, 1976). The present study was designed to evaluate this property in humans.

Eight adult subjects who were considered to require antiepileptic drug therapy because of recurrent fits of recent onset were studied on two occasions, one immediately before starting sodium valproate therapy and the second after at least 3 months (mean 4 months) of regular treatment with this drug. None of the subjects had been previously treated with antiepileptic drugs, and none had taken any other drugs known to induce liver enzymes for at least 6 months prior to the study. Sodium valproate was administered as sole drug therapy during the period of the study. The daily dose was 600–800 mg in divided doses. The subjects were admitted to hospital for 3 days on both occasions and the following indirect indices of liver enzyme induction were measured: (i) serum antipyrine half-life, using the analytical method described by van Boxtel, Wilson, Lindgren & Sjöqvist (1976), and calculating the half-life by the method of least squares regression; (ii)

Table 1 Plasma antipyrine half-life and urinary D-glucaric acid excretion in eight patients before and during sodium valproate therapy

Subject	*Age (years)*	*Sex*	*Daily dose of sodium valproate (mg)*	*Serum valproic acid concentration* (μmol/l)*	*[1]Antipyrine half-life (h)*		*[2]D-glucaric acid excretion (μmol/24 h)*	
					Before	*During*	*Before*	*During*
1	19	F	600	515	11.4	10.4	10.3	10.6
2	51	F	600	316	5.7	5.9	+	10.5
3	45	F	800	689	12.4	14.1	19.3	11.6
4	22	F	800	476	13.9	11.0	4.7	9.1
5	37	M	600	364	14.1	15.1	3.0	4.5
6	33	M	600	424	7.3	7.4	11.4	7.4
7	22	M	800	441	18.1	14.7	1.1	11.9
8	32	M	800	511	14.7	13.4	16.5	19.0
Mean	35.3			491	12.2	11.5	9.5	10.6
s.d.	11.7			112	4.0	3.5	6.5	4.2
					NS		NS	

*mean of two samples, + no sample
*7 μmol/l = 1 μg/ml
[1]Normal range 7–19 h; [2]Normal range < 20 μmol/24 h

urinary D-glucaric acid excretion measured in a single 24 h urine collection according to the method of Latham (1974). Serum valproic acid concentration was measured by the gas chromatographic method of Schultz & Toseland (1977) on samples taken approximately 3 h after the administration of the morning dose.

The results were analysed using Student's two tailed *t*-test for paired samples (Table 1). There was no significant change in the mean antipyrine half-life or D-glucaric acid excretion during sodium valproate administration. Routine liver function tests performed at the end of the study showed no abnormality.

These results indicate that sodium valproate does not induce liver enzymes in the dose administered to our patients. This property may make it a safer antiepileptic drug for long-term use than traditional drugs with potent enzyme inducing effects.

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