Controlled trial of sodium valproate in severe epilepsy

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Summary

In a double-blind crossover trial sodium valproate or placebo was added to the existing anticonvulsant treatment of 20 patients with chronic uncontrolled epilepsy. Sodium valproate 1200 mg/day significantly reduced the frequency of both tonic-clonic and minor seizures in these patients. Only mild and transient side effects occurred (drowsiness, ataxia, and nausea), and these may have been due to the effect of adding sodium valproate to existing phenobarbitone or phenytoin treatment. Further controlled trials are needed to assess more fully the efficacy of this drug in various types of epilepsy.

Introduction

Sodium valproate (sodium dipropylacetate, Epilim, Depakine) has been used as an antiepileptic drug in several European countries for several years and there have been many reports of its efficacy in most types of epilepsy.[1-3] All but one[4] of these reports, however, describe trials in which no attempt was made to control for observer bias by comparing the new drug with a placebo or an established antiepileptic drug. We thought that it was necessary to compare sodium valproate with a placebo to establish beyond doubt its antiepileptic effect. Because it is difficult to justify treating epileptic patients with a placebo alone, we chose to add either the active drug or a placebo on a double-blind crossover basis to the existing medication of patients with uncontrolled epilepsy.

Patients and methods

Twenty long-stay patients at the National Hospitals Special Centre for Epilepsy were studied (table I). The criterion for admission to the trial was that they should have chronic epilepsy that had not been satisfactorily controlled by various combinations of standard antiepileptic drugs. All had minor attacks, most of which were of psychomotor type or comprised alteration of consciousness. All but two (cases 5 and 6) had tonic-clonic fits at some time, though six other patients did not have this type of attack during the trial. In most cases the cause of the epilepsy had been established by clinical observation and repeated electroencephalograms.

The 20 patients were divided randomly into two groups of 10. One group was started on sodium valproate while the other received an identical placebo tablet. A run-in period allowed gradual introduction of the drug, but thereafter a fixed dose of 1200 mg/day was used throughout an eight-week assessment period (table II). Treatments were then crossed over gradually so that the risk of status epilepticus by sudden withdrawal of a possibly active drug was minimized. A second assessment period of eight weeks was then allowed. Neither the patients nor the assessing physician knew which treatment was being administered. Throughout the trial the patients' existing treatment was continued unchanged unless drowsiness occurred, in which case the dose of phenobarbitone or primidone was reduced.

We assessed the response to the drug by recording the major and minor fits that occurred each week of the trial. Although the staff in charge of the residential houses and work centres were trained in observing and recording fits, some fits, particularly minor ones, went unrecorded. This deficiency, however, should have occurred equally in the placebo and active drug treatment periods. Fits were assessed as two types: tonic-clonic seizures ("major" attacks); and all other types, including absence attacks, adversive attacks, and focal and psychomotor fits ("minor" attacks). To examine the possibility of drug interaction serum phenytoin and phenobarbitone levels were measured by enzyme immunoassay in seven patients before administration of sodium valproate and at the end of the assessment period in which the active drug had been used. Furthermore, tracer doses of ^{14}C-labelled phenytoin were given by mouth before and during sodium valproate treatment to measure the serum half life of the carbon label.[5]

Results

Control of fits—The effect of sodium valproate compared with placebo is shown in tables III and IV. These results were significantly in favour of sodium valproate (for major fits, $P<0.05$; for minor fits, $P<0.01$, using Wilcoxon signed-ranks test). The significance of the differences was confirmed by an analysis of variance. The frequency of major fits during valproate treatment was reduced to an average of 35% of the frequency on placebo. The corresponding reduction in minor fits was to 57% of the frequency on placebo.

Adverse effects—Thirteen patients showed signs of toxicity, comprising drowsiness, ataxia, and nausea (table III). These signs were usually mild and transient, however, and did not necessitate withdrawal of the test drug in any patient. In only three patients was it necessary to reduce the dose of primidone or phenobarbitone because of drowsiness, but in one of these it was discovered on breaking the code that the patient was receiving placebo at the time of drug reduction.

Interaction with phenobarbitone and phenytoin—Serum phenobarbitone levels measured in duplicate or triplicate showed a consistent rise in each of seven patients in whom the estimations were performed. The average increase was 27% (from 95 to 121 μmol/l (22 to 28 μg/ml)) with a range of 17-48%, and was statistically significant ($P<0.02$, Wilcoxon test). Serum phenytoin levels were measured in six patients, but no consistent change was observed. The serum half life of a tracer dose of phenytoin shortened in two patients and lengthened in five (not significant).

Discussion

Sodium valproate in a fixed dose of 1200 mg/day significantly reduced the frequency of both tonic-clonic and minor seizures when added to the existing treatment of 20 severely epileptic patients whose fits had proved difficult to control with the established drugs.

In three patients no response to sodium valproate was seen, and in three others the frequency of one type of seizure decreased while that of another increased. Apart from one patient who had an extensive right hemisphere lesion from a depressed skull fracture (case 15) these therapeutic failures occurred in patients with temporal lobe lesions. As 11 of our patients had this type of lesion firm conclusions about the response of different types of epilepsy cannot be drawn from our results, though Jeavons and Clark[6] have noted a poor response in patients with temporal lobe lesions.

Because sodium valproate or placebo were added to existing treatment we cannot say whether the anticonvulsant effect

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TABLE I—*Details of patients included in trial*

Case No.	Age and sex	Type of epilepsy	Drug Treatment (mg/day)				
			Phenytoin	Phenobarbitone	Primidone	Carbamazepine	Others
1	22 M	Temporal lobe	400	180			Chlordiazepoxide 10
2	24 M	„ „	300	180			
3	40 M	„ „	300	180			Diazepam 6
4	29 M	„ „	200		750		Diazepam 15
5	28 F	„ „	300	120			
6	34 M	„ „	300	180			
7	38 F	„ „	400	180		800	
8	19 M	„ „	250	150		600	
9	23 M	„ „	300		1000	400	Ethosuximide 750
10	54 M	„ „	300		1000	400	Diazepam 6
11	20 M	„ „		150	1500		Sulthiame 200
12	21 M	Focal motor	200		750	400	
13	41 M	„ „	400		1500		
14	21 M	Focal motor (post-trauma)	300		1000		Pheneturide 400
15	28 M	Focal motor (post-trauma)	200		1000	600	
16	29 M	Idiopathic	300	60	750		Ethosuximide 1500
17	37 F	„		180	750		
18	28 M	„	300		1000		Diazepam 4, pheneturide 600
19	24 M	Petit mal variant	300		1000		Ethosuximide 750
20	29 M	Uncertain	300		1000		

TABLE II—*Dosage scheme used in trial. Each tablet of sodium valproate contained 200 mg of the drug*

Week	Group 1	Group 2
1	Sodium valproate 400 mg/day	Placebo 2 tablets/day
2	Sodium valproate 800 mg/day	Placebo 4 tablets/day
3-10	Sodium valproate 1200 mg/day	Placebo 6 tablets/day
11	Sodium valproate 800 mg/day, placebo 2 tablets/day	Placebo 4 tablets/day, sodium valproate 400 mg/day
12	Sodium valproate 400 mg/day, placebo 4 tablets/day	Placebo 2 tablets/day, sodium valproate 800 mg/day
13-20	Placebo 6 tablets/day	Sodium valproate 1200 mg/day

TABLE III—*Response and adverse effects to sodium valproate treatment*

Case No	No of fits in 8-week assessment period				Adverse effects on valproate
	Placebo		Valproate		
	Major	Other	Major	Other	
1	5	37	0	5	Initial drowsiness
2	0	52	0	22	
3	9	63	0	41	
4	6	2	0	4	Initial drowsiness and nausea
5	0	25	0	32	Initial drowsiness and nausea
6	0	29	0	20	Transient ataxia
7	5	15	0	10	Initial drowsiness and nausea
8	0	52	3	25	Transient ataxia
9	6	19	5	17	Initial drowsiness
10	1	12	0	14	Initial drowsiness and nausea
11	5	7	6	8	Initial drowsiness and nausea
12	0	9	0	8	
13	0	65	0	30	
14	0	52	0	22	
15	0	6	1	11	
16	7	17	0	1	Initial drowsiness*
17	0	54	0	31	†
18	0	27	0	15	Initial drowsiness
19	4	36	2	13	Initial nausea
20	7	5	2	5	Initial drowsiness and ataxia‡
Total	55	584	19	334	

*Phenobarbitone discontinued during valproate treatment.
†Phenobarbitone reduced during placebo treatment.
‡Primidone reduced during valproate treatment.

TABLE IV—*Summary of response to sodium valproate*

Type of fit	Better	Unchanged	Worse
Major	9	8	3
Minor	14	1	5
Combined	16	0	4

that we have shown was the result of a pharmacological action of sodium valproate itself or of an increase in the serum concentration of phenobarbitone. In the seven patients whose phenobarbitone levels were measured a rise was seen at the end of the eight-week assessment period, though the average increase was only 27%. Similar observations have been made in three patients by Schobben *et al.*[7] This rise may well explain the initial drowsiness and ataxia which often occurs when adding sodium valproate to existing phenobarbitone or primidone treatment; this was seen in 12 of our patients. If the dose of phenobarbitone or primidone is reduced the toxic symptoms abate rapidly. In contrast, sodium valproate had little effect on phenytoin metabolism in the patients in whom this was studied. No consistent change in serum phenytoin levels or half lives was seen.

The dose of sodium valproate used in this trial was not large; the plasma levels of valproate found in four patients in whom they were measured ranged from 237-475 μmol/l (34-68 μg/ml) and were within the range expected from a dose of 1200 mg/day. A "therapeutic range" of 350-700 μmol/l (50-100 μg/ml) has been cited by Schobben *et al*,[7] though no prospective studies have been performed to establish such a range.

The patients selected for this trial had severe epilepsy that had responded inadequately to various combinations of established drugs. The useful therapeutic effect that was produced by sodium valproate in these patients is therefore promising. Further controlled trials are necessary, however; firstly, to establish the part played by concurrent phenobarbitone or primidone treatment in the therapeutic response to valproate; and, secondly, to compare its efficacy with other established drugs used for the various types of epilepsy.

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