

SODIUM VALPROATE AND COGNITIVE FUNCTIONING IN NORMAL VOLUNTEERS

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- 1 The effects of sodium valproate on the performance of a series of psychological tests and mood was studied.
- 2 Ten healthy male volunteers received sodium valproate and placebo, each for a period of 2 weeks, in a double-blind cross-over design. Dosage of sodium valproate was increased to 800 mg/day in the first week and to 1 g/day in the second week of treatment.
- 3 Psychological testing took place on three occasions, before and on completion of each of the two treatment periods.
- 4 The few significant differences between drug and placebo conditions indicated impairment on sodium valproate.
- 5 The findings are discussed in relation to those from a similarly designed study of the anticonvulsant phenytoin. Implications for epilepsy are also considered.

Introduction

Sodium valproate has been found to exert comparable control over certain seizure types as some of the more established anticonvulsants and has gained wide acceptance in the management of epilepsy (Parsonage & Caldwell, 1980). In addition, some authors have claimed it exerts a favourable influence on the cognitive state of patients with epilepsy. Following treatment with sodium valproate individuals have been variously described as being 'more alert', 'more active' and 'more co-operative' and the school performance of children with epilepsy has also been reported to improve (Völzke & Doose, 1973; Jeavons & Clarke, 1974; Haigh & Forsythe, 1975).

Systematic studies of the effect of sodium valproate on cognitive functioning and mood are few and their findings have not been entirely consistent. In keeping with the anecdotal reports above there are some investigations of treatment with this drug in epilepsy that show improvement (Harding, Pullan & Drasdo, 1980) although their psychological assessment was limited to a simple reaction time test. In contrast, Somerbeck *et al.* (1977) found 12 weeks of sodium valproate had a deleterious effect on the psychological test performance of patients with epilepsy in contrast with placebo. The authors commenting on their results stated that the drug 'had reduced psychomotor tempo and to a lesser degree visual spatial

analytic functions'. Sodium valproate, however, had been prescribed in addition to the patients existing regimens, individuals being prescribed a minimum of 3.2 different drugs and accordingly interpretation of their findings is contaminated by the possible influence of drug interactions.

In double-blind studies involving non-epileptic volunteers, Caille (1971) found 300 mg and 500 mg of sodium valproate a day for ten days had a beneficial influence on psychological test performance while 900 mg a day for 21 days had no effect, beneficial or otherwise. Investigations of single doses of this drug have reported no significant differences between sodium valproate and placebo administration on a variety of measures of cognitive and motor functions (Kugler & Laub, 1974; Boxer, Herzberg & Scott, 1976; Harding & Pullan, 1977).

Few conclusions can be drawn from these existing studies partly on account of the enormous variations between them regarding populations investigated, dosage and duration of treatment and the measures of mental functioning employed. In addition, interpretation of studies involving patients with epilepsy is often complicated because of changes occurring in other important variables suspected of influencing cognition such as seizure frequency (Seidenberg *et al.*, 1981) and the withdrawal of alternative anti-

convulsant medication (Thompson, in preparation). Considering the widespread use of sodium valproate in epilepsy it seems important to assess further its influence on cognitive functioning, in particular whether it does exert any beneficial effects as has been suggested. In an attempt to do this a preliminary investigation was undertaken involving its administration to healthy volunteers, and the use of psychological tests which covered a wide range of cognitive abilities, the results of which are presented here.

Methods

Subjects

Ten male medical and university students with a mean age of 26 (range 19–33) years took part in the study. Subjects had not received any regular medication in the past 12 months and were screened for possible blood and liver function abnormalities. Participants received a token payment on completion of the trial.

Design

Subjects were prescribed plain 200 mg sodium valproate tablets and identical placebo tablets, each for a period of 2 weeks in a double-blind cross-over design. Five subjects took the active compound in the first treatment period and the other five in the second. A 1 week wash-out interval was included between the two treatments during which time no medication was prescribed. The dosage of sodium valproate was increased from one to four tablets in the first 3 days of treatment (800 mg/day). Tablets were taken three times a day at mealtimes, two tablets being taken with the evening meal. In the second week an additional tablet was taken with the breakfast dose (1 g/day). Psychological testing took place on three occasions, before any treatment and at the end of each treatment, 3–4 h following the final (midday) dose. On completion of the second and third sessions a blood sample was taken to analyse serum valproic acid concentrations, blood and liver function and to check compliance.

Psychological tests

A series of psychological tests was used to assess cognitive functioning, which was the exception of the visual scanning tasks (2ii below), have been described in detail elsewhere (Thompson, Huppert & Trimble, 1981).

1. *Memory* Twenty pictures (photographed from a variety of magazines) and 20 words were displayed as slides at the beginning of each session. One minute, and again 1 h, following the presentation of the last

stimulus in each set, subjects were asked to recall as many of the items as they could remember. On completion of the measure of delayed recall, a yes/no recognition test was administered in which the 20 original slides were presented in a random order with 20 new slides. A different set of stimuli and recognition distractors were used on the three testing sessions.

2. *Concentrations* (i) *The Stroop test*: The version used consisted of three cards. The task was to read the colour words (red, green, blue) on the first card (I) and to name the colour of the rectangles (red, green, blue) on the second card (II) as quickly as possible. On the third card (III) the colour words (red, green, blue) were written in coloured ink (red, green, blue) never congruent with the word, for example the word green would be written in blue or red ink. The subject was required to name the colour of the words as quickly as possible. Adequate performance on this last card requires considerable concentration to avoid the preferred response of reading the word. The difference in the time taken to complete cards II and III and the number of errors made on card III were recorded.

(ii) *Visual scanning*: The time needed by subjects to cancel a target digit from a page of random numbers was recorded in two conditions (a) performed alone and (b) in the presence of an auditory distracting task. In the second task a tape recording, which consisted of spoken letters of the alphabet interspersed with numbers, was played to the subjects who had to respond whenever they heard a number by repeating it aloud. The time to complete the visual scanning task in the two conditions was used as the measure of performance, errors being infrequently made.

3. *Perceptual speed* The minimum exposure duration at which subjects could recognise pictures of objects and words flashed onto a screen in a masking paradigm was used as the measure of speed of perceptual registration.

4. *Decision making* The speed of responses to simple questions about the colour of an object (Is it red?) or more difficult ones about category membership (Is it a living thing?) was recorded. Stimuli were presented as slides, the exposure of which activated a msec digital timer, which was deactivated when the subject made a response. Forty trials were administered, 20 concerning colour and 20 category. The median reaction time for each question type was calculated.

A measure was also made of the visuo-motor component of the above task, that is, the time to respond to light onset when no further decision was required.

5. *Motor speed* Tapping rate between two metal plates with the dominant and non-dominant hand was used as a measure of simple manual movements.

6. *Subjective ratings of mood* The mood of the subject at the time of testing was assessed using Lishman's (1972) adaptation of McNair & Lorr's (1964) Mood Adjective Check List (MACL). This version of the MACL consisted of 24 adjectives descriptive of different mood states each to be rated on a four point intensity scale. The scores for eight adjectives were summed to give a rating for depression and the scores for four adjectives each were summed to give ratings for anxiety, fatigue, activity and aggression respectively.

Results

Statistical analysis

Paired *t*-tests using two-tailed confidence limits were performed on the psychological test scores in the sodium valproate and placebo sessions. Data

obtained from the MACL were analysed non-parametrically with Wilcoxon T tests.

The relationship between test performance and serum valproic acid concentrations was investigated using Spearman Rank correlations. The performance measure used was the difference between the scores on the drug and placebo sessions for each subject.

Means and standard deviations in the sodium valproate and placebo sessions, together with the results of the statistical analysis are presented in Table 1.

1. Memory

No statistically significant treatment effects were observed on any of the measures of memory, neither was there any consistent trend toward impaired or improved performance on the active drug.

2. Concentration

On the visual scanning tasks subjects took longer to scan for target digits when the task was performed alone and in conjunction with the auditory distracting task but the difference between the treatments was

Table 1 Means and s.d. of test scores following the administration of placebo and sodium valproate.

<i>Psychological measures</i>	<i>Placebo</i>		<i>Sodium valproate</i>		<i>t</i>
	<i>Mean</i>	<i>s.d.</i>	<i>Mean</i>	<i>s.d.</i>	
<i>Memory</i>					
<i>Pictures:</i>					
Immediate recall	12.0	1.6	12.0	2.7	-
Delayed recall	11.9	2.4	10.7	3.6	1.3
Recognition (max = 40)	39.7	0.7	39.7	0.9	-
<i>Words:</i>					
Immediate recall	8.1	2.9	7.4	3.2	0.8
Delayed recall	6.3	2.7	6.4	2.0	-0.1
Recognition (max = 40)	31.0	4.2	30.6	3.0	0.4
<i>Concentration</i>					
<i>Stroop</i>					
Naming speed III-II	9.9	6.0	11.9	9.9	-1.3
Errors	0.7	1.3	1.7	2.2	-1.5
<i>Visual scanning</i>					
Alone (s)	43.8	4.6	47.2	7.7	-1.9
With auditory task (s)	47.5	7.5	51.3	6.2	-1.8
<i>Perceptual speed (s)</i>					
For words	0.046	0.012	0.050	0.016	-1.5
For pictures	0.058	0.009	0.060	0.010	-0.5
<i>Decision making (s)</i>					
For colour	0.507	0.071	0.552	0.096	-2.4*
For category	0.644	0.076	0.692	0.095	-3.7†
Visuo-motor Response	0.216	0.028	0.233	0.046	-1.9
<i>Motor speed</i>					
Dominant hand	87.2	8.9	84.2	9.2	2.0
Non-dominant hand	70.8	10.9	70.8	12.7	-

* $P < 0.05$, † $P < 0.01$

not significant. On the Stroop test no significant changes in test scores were recorded.

3. Perceptual speed

No significant influence of sodium valproate was observed on the measures of perceptual speed.

4. Decision making

Subjects took significantly longer to answer questions about colour ($P < 0.05$) and category membership ($P < 0.01$) after sodium valproate in comparison with placebo but no significant difference between the treatments was recorded on the visuo-motor component of the task.

5. Motor speed

No statistically significant differences were found between drug and placebo for tapping rate with either the dominant or non-dominant hand.

6. Subjective ratings

No significant influence of sodium valproate was found on the MACL.

Serum levels

The mean valproic acid serum level of the ten subjects was $452.3 \mu\text{mol/l}$ with a range of $265\text{--}806 \mu\text{mol/l}$, a value that falls within the therapeutic range of this compound (Eadie & Tyrer, 1980). No significant correlations were observed between psychological test performance and individual valproic acid concentrations.

Discussion

Sodium valproate, taken daily for 2 weeks, did not have any beneficial effect on the psychological test performance of healthy volunteers. Indeed the two significant differences observed between the drug and placebo treatments indicated a detrimental influence of this compound, with subjects taking longer to make decisions about pictures of objects. These impairments occurred at a mean valproic acid serum concentration which fell within the therapeutic range for the treatment of epilepsy. No significant correlations were found between test scores and individual valproic acid levels, and no significant differences in subjective ratings of mood were recorded between the treatments.

This apparent mild slowing in the execution of certain tasks in association with sodium valproate seems at variance with the reports made by Harding *et*

al. (1980) of shortened reaction times following the administration of this drug. The measure these authors employed was a simple reaction time test, and in the present study no effect of the drug was observed on a comparable measure—the visuo motor component of the decision making task. It was only when the decisions required by the subject became more difficult that significant slowing of responses was recorded, and it is possible that in the past the detrimental effects of sodium valproate have been overlooked because the tasks employed have been undemanding. In addition studies by Harding *et al.* (1980) involved patients with epilepsy; while it is difficult to extrapolate from a study of normal volunteers to clinical practice, the variables of seizure severity and frequency contaminates patient studies and may have influenced their results. Discrepancies between our findings and those of Caille (1970) possibly reflect the comparatively high dosage employed in the present study. Caille (1970) reported beneficial effects of sodium valproate on cognitive functioning in association with 300 mg and 500 mg daily doses but he did not find such effects maintained on a 900 mg daily regimen. Our results are much more in keeping with those of Sommerbeck *et al.* (1977) who also reported slowing on a reaction time test and on several other psychological tests where speed was the measure of performance when patients were treated with sodium valproate in comparison with placebo. Unfortunately, as noted earlier, interpretation of their findings is confounded by the possible interaction between sodium valproate and the patients existing anticonvulsant medications.

These results with sodium valproate should be viewed in the context of a similarly designed study using the same psychological tests in which 300 mg/day of phenytoin was given to a different group of volunteers (Thompson *et al.*, 1981). In this, impairment on the active drug was far more widespread than was observed here for sodium valproate, although the mean phenytoin serum level of the subjects was in clinical terms, subtherapeutic. On the psychological measures employed in both studies, deficits on the active drug were noted on six indices of performance in the phenytoin trial compared with only two in this sodium valproate trial. Prolonged decision making for colour and category judgements was common to both drugs but, in addition, phenytoin was associated with a decrease in tapping rate with the dominant hand, an increase in errors on the Stroop test and impaired retention on the immediate recall test for words and the delayed recall test for pictures. Furthermore, correlations with serum phenytoin levels were noted for the measures of picture recall, perceptual speed and colour decision making, the higher the serum concentration of the drug the greater the deleterious effect. With regard to mood subjects also rated themselves as feeling signifi-

cantly more fatigued while taking phenytoin in comparison with placebo.

These results suggest that while the acute administration of sodium valproate had adverse effects on certain measures of cognitive function they were noticeably less than seen in another study following phenytoin. Although the observed decrements in the present investigation may well reflect only transient impairment of functioning, evidence from other work, especially involving phenytoin, suggests that this is not the case, adverse effects having been recorded with more prolonged use (Dodrill, 1975; Dodrill & Troupin, 1977; Trimble & Corbett, 1980) and, conversely, improvements following its withdrawal (Rosen, 1968; Nolte *et al.*, 1980; Thompson, in preparation). Thus while the majority of reports of sodium valproate mentioned earlier, especially if anecdotal impressions are included, suggest a beneficial effect of this drug in patients with epilepsy it is possible these observed improvements may be an indirect consequence of other variables such as better seizure control or withdrawal of other medications which had previously been exerting a detrimental influence, rather than to an independent psycho-

tropic effect *per se*. However, further patient studies are clearly indicated. In healthy volunteers disturbances of mood and cognition are not expected at the outset and thus improvements are probably difficult to achieve. In patients, where deficits in cognitive functioning are not uncommon (Dikmen, 1980), changes may be more readily observed and possible psychotropic effects measured. If sodium valproate, when given chronically, is found to have less adverse effects on mental abilities and mood than some of the more established anticonvulsants as suggested from these volunteer studies, it would offer advantages for the management of epilepsy particularly in the treatment of children, where even subtle impairments of mental function may have a damaging effect on academic attainment.

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References

- BOXER, C.M., HERZBERG, J.L. & SCOTT, D.F. (1976). Has sodium valproate hypnotic effects? *Epilepsia*, **17**, 367-370.
- CAILLE, E.J. (1971). Effets du traitement par le dipropyl-acetamide sur la vigilance, la perception, les capacités de décision et le sommeil de jeunes adultes normaux. *Psychologie Medicale*, **6**, 791-796.
- DIKMEN, S. (1980). Neuropsychological aspects of epilepsy. In *A Multidisciplinary Handbook of Epilepsy* ed. Herman, B.P., pp 36-73. Springfield, Illinois: Charles C. Thomas.
- DODRILL, C.B. (1975). Diphenylhydantoin serum levels, toxicity and neuropsychological test performance in patients with epilepsy. *Epilepsia*, **16**, 593-600.
- DODRILL, C.B. & TROUPIN, A.S. (1977). Psychotropic effects of carbamazepine in epilepsy: a double-blind comparison with phenytoin. *Neurology*, **27**, 1023-1028.
- EADIE, M.J. & TYRER, J.H. (1980). *Anticonvulsant therapy: pharmacological basis of practise*. London: Churchill Livingstone.
- HAIGH, D. & FORSYTHE, W.I. (1975). The treatment of childhood epilepsy with sodium valproate. *Dev. Med. Child. Neurol.*, **17**, 743-748.
- HARDING, G.F.A. & PULLAN, J.J. (1977). The effect of sodium valproate on the E.E.G., the photosensitive range, the CNV and reaction time. *Electroenceph. clin. Neurophysiol.*, **43**, 465.
- HARDING, G.F.A., PULLAN, J.J. & DRASDO, N. (1980). The effect of sodium valproate and other anticonvulsants on performance in children and adolescents. In *The place of sodium valproate in the treatment of epilepsy*, Royal Society of Medicine Series, no. 30, eds. Parsonage, M.J. & Caldwell, A.D.S. pp 61-71. London: Royal Society of Medicine and Academic Press.
- JEAUVONS, P.M. & CLARKE, J.E. (1974). Sodium valproate in the treatment of epilepsy. *Br. med. J.*, **2**, 584-586.
- KUGLER, J. & LAUB, M. (1974). Vigilanzbestimmungen und psychoexperimentelle Testuntersuchungen nach einmaliger Ergenyl-injektion. In *Epilepsien- behandlungsgrundsätze und Spezielle Therapie mit Ergenyl*, ed. Kugler, J. pp 49-58. Dusseldorf: Labaz-Erfolg durch Forschung.
- LISHMAN, W.A. (1972). Selective factors in memory: Part 2, Affective disorders. *Psychol. Med.*, **2**, 248-253.
- MCNAIR, D.M. & LORR, M. (1964). An analysis of mood in neurotics. *J. Abnorm. Soc. Psychol.*, **69**, 620-627.
- NOLTE, R., WETZEL, B., BRUGMANN, G.A. & BRINZINGER, I. (1980). Effects of phenytoin monotherapy and primidone monotherapy on mental performance in children. In *Antiepileptic Therapy; Advances in Drug Monitoring*, eds. Johanesson, S.I., Morselli, P.L., Pippenger, D., Richens, A., Schmidt, D. & Meinardi, H., pp 81-88. New York: Raven Press.
- PARSONAGE, M.J. & CALDWELL, A.D.S. (1980). *The place of sodium valproate in the treatment of epilepsy*. Royal Society of Medicine Series no. 30. London: Royal Society of Medicine and Academic Press.
- ROSEN, J.A. (1968). Dilantin dementia. *Trans. Am. Neurol. Ass.*, **93**, 273.
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