Indian J. Psychiat., 1993, 35(1), 54-57

COGNITIVE FUNCTIONING IN PATIENTS WITH COMPLEX ABSENCE FOLLOWING TREATMENT WITH SODIUM VALPROATE

SHOBINI L.RAO, P.SATISCHANDRA, M.GOURIE-DEVI

SUMMARY

The association of sodium valproate with cognitive functions was studied in 29 patients with complex absence seizures. Seventeen patients were on monotherapy and twelve on polypharmacy with sodium valproate. Cognitive functions assessed were attention, speech, visuo-special perception, memory and intelligence. Behavioral disturbances were also assessed. Two assessments were made six months apart; in the first assessment, attention and speech were adequate, while memory, visuo-spatial perception, and behavioral functioning were impaired. Intelligence was lower in the polypharmacy group, while other functions were similar. In the second assessment, intelligence and visual memory improved in the monotherapy group, while no changes were present in the polypharmacy group.

INTRODUCTION

Antiepleptic drug therapy is found to affect cognitive functioning (Vining, 1987). In normal volunteers, cognitive deficits in memory and information processing tasks were recorded in association with phenytoin, carbamazepine, sodium valproate, clobazam and clonazepam, fewer deficits being associated with sodium valproate, carbamazepine and clobazam (Trimble, 1987). Sodium valproate has been found to improve intellect, as patients become more alert and co-operative (Volzke & Doose, 1973). Better attention and school performance has been reported in children on sodium valproate (Jeavons & Clark, 1974), while reaction time has been reported as decreased in children and adolescents on sodium valproate (Harding et al, 1978). Valproate is associated with better behavioral and neuropsychological functioning compared with phenobarbital (Vining et al, 1987); in addition, in normal volunteers, it is associated with improved alertness (Betts et al, 1982). Contrary to these observations, there are a few reports that sodium valproate has a few adverse effects on cognitive functions. In normal volunteers, sodium valproate was associated with slowing down of mental processing speed which reached significance only when the demands of the task increased (Trimble, 1987). Addition of sodium valproate to drug resistant epileptics resulted in increased reaction time as well as increased time on tasks which required attention and had competing responses (Sommerbeck et al, 1977). As a monotherapy in high doses, it led to impairment of memory and auditory detection (Trimble & Thompson, 1983).

In view of the contradictory findings reported above, the present study was undertaken to evaluate the effect of sodium valproate on cognitive functioning in epileptic patients. It is increasingly felt that, in managing any patient with epilepsy, reduction in cognitive dysfunction and seizure frequency should be viewed together, without sacrificing one for another (Vining, 1987). In the present study, the association of sodium valproate with cognitive functioning was investigated by comparing two groups of patients. In the first group sodium valproate was used singly (monotherapy), whereas in the second group, it was used in conjunction with other antiepileptic drugs [AED] such as phenobarbitone, phenytoin, carbamazepine or benzodiazepines. By comparing its effect in isolation (monotherapy group) with its effect in interaction with other AEDs (polypharmacy group), the effect of sodium valproate on cognitive functioning in epileptics could be studied.

MATERIALS AND METHODS

Subjects

Twenty-nine patients, with complex absence as the predominant seizure type who were on monotherapy with sodium valproate (n=17) or on polypharmacy (i.e., phenobarbitone, phenytoin, carbamazepine & benzodiazepines) inclusive of sodium valproate (N=12) were included in the study. This sample was drawn from the Neurology out-patient service of the National Institute of Mental Health and Neurosciences (NIMHANS) between 1984-86 and formed the sample for a clinical drug trial on sodium valproate. Six patients in the monotherapy group and five patients in the polypharmacy group were males. Sample characteristics are shown in Table I.

Assessment Of Cognitive Functions

Two assessments were conducted, the initial after the commencement of sodium valproate and the second, six months later. The period of sodium valproate use before the first assessment varied from 1 to 23 months with a mean of 16 months in the monotherapy group. In the polypharmacy group, it ranged from 3-22 months, the mean being 17 months (Table I). The second assessment enabled evaluation of cognitive and behavioral functions associated with continued use of sodium valproate either as monotherapy or as a component of polypharmacy.

Attention was assessed using the components of spontaneous arousal, distractibility, fatiguability and perseveration. Speech was assessed in terms of the adequacy of expressive and receptive speech. Attention and speech were rated on a 5 point scale with 5 indicating adequate functioning. Visuo-spatial perception was assessed using the complex figure test, an adaptation of Rey-Osterich figure (Mukundan et al, 1979). Copying of this figure was

TABLE I: SAMPLE CHARACTERISTICS

Clinical Variable	MONOTHERAPY n=17 Mean	Range	Category	N	POLYPHARMACY n=12 Mean	Range	Category	N	Significance level
Age (Yrs)	11.6 (4.6)	5-22	≤ 12	11	16.0 (3.1)	12-22	≤ 12	2	p<0.001
			>12	6			>12	10	
Education (yrs of) schooling)	6.0 (3.4)	1-12	<10	14	7.3 (3.0)	0-10	<10	8	NS
			≥ 10	3			≥ 10	4	
Age of onset (Yrs)			≤ 10	13			<10	7	NS
			>10	4			>10	5	
Duration of seizures (yrs)			≤ 3	9			≤ 3	3	NS
			>3	8			>3	9	
Seizure Frequency		2-3/day	≤ 10/day	4		8-15/day	≤ 10/day	0	NS
Before Valproate use		50-100/day	>10/day	13		numerous	>10/day	12	
Duration (mths) of Valproate treatment	16.0 (6.4)	1-23	≤ 18	7	17.0 (5.6)	3-22	≤ 18	10	NS
			>18	5			>18	7	
Duration of seizure control with Valproate (mths)	12.6 (5.0)	5-20	≤ 12	7	8.8 (5.3)	1-18	≤ 12	9	NS
			>12	10			>12	3	
Co-existent seizure type Tonic-clonic				3				12	p<0.001
EEG			Normal	7			Normal	5	NS
			Abnormal	9			Abnormal	7	
Serum Level of Valproate	<50ug/ml			4				6	
	50-100ug/ml			9				5	NS
	>100ug/ml			2				1	

NB: In the monotherapy group, serum level was ascertained in 15 patients only. Significance levels refer to the X^2 test between the categories of patients in the two groups for each variable.

scored for its accuracy, the maximum score being 20. Immediate memory was assessed with digit forward and backward test, a subtest of the Binet Kamath test (Kamath, 1967). The number of digits recalled in either condition formed the score. Visual memory was tested using the complex figure test, wherein three repeated exposure recall sequences were followed by a delayed recall after 10 minutes. Mean accuracy of recall over the four trails formed the score, with the maximum score being 20. Verbal memory was tested by auditory presentation followed by recall of two story passages. For each passage three repeated exposure recall sequences were followed by a delayed recall after 10 minutes. Mean number of facts correctly recalled from both passages formed the score, the maximum score being 21. Intelligence was measured using the Binet Kamath test (Kamath, 1976).

Behavioral disturbances were rated by interviewing parents of patients using O'Connor's abbreviated rating scale (Goyette et al, 1978) and Achenbach rating scale for children below 16 years (Achenbach & Edelbrock, 1983). Adult patients were assessed using Bell's adjustment inventory (Bell, 1938). Behavioral disturbances were rated on a five point scale with 5 indicating adequate functioning.

RESULTS

The two groups were comparable with respect to most of the clinical variables known to affect cognitive functioning in epileptics (Table I). These include age of onset, seizure duration, seizure frequency, presence of EEG abnormalities, seizure free period prior to psychological assessment and serum level of the AED (Dodrill & Wilkus, 1978; Thompson & Trimble, 1982). Patients in the polypharmacy group were significantly older, the difference being four years. Tonic-clonic seizures as a co-existent seizure type was also present in a significantly larger number of patients in the polypharmacy group.

The performance of the monotherapy and polypharmacy groups in the first assessment are depicted in Table II. T test for uncorrelated means revealed that the two groups differed significantly in intelligence; the polypharmacy group being 17 I.Q. points below the monotherapy group. The two groups performed similarly on all other functions. A clinical profile of the mean scores reveal that in both groups attention and speech were adequate. Visuospatial perception was minimally impaired, i.e. 14-15/21 (maximum score). Immediate memory was moderately impaired. Visual and verbal memory were moderately impaired i.e., 8-9/20 (maximum score) and 10-12/21 (maximum score), respectively. Intelligence was in the normal range in the monotherapy group, but in the polypharmacy group, the mean I.Q. was below the normal range. Behavior functioning was minimally impaired in both groups, i.e. a mean rating near 4. Performance on the second assessment was compared with that on the first

Table II Mean and Standard deviation of the scores on the different tests for Monotherapy and Polypharmacy groups in the first assessment.

FUNCTION	MONOTHERAPY	POLYPHARMACY	t
Attention	4.8 (1.0)	4.7 (.9)	-.04
Speech	5.0 (0)	4.9 (.3)	1.29
Visuo-spatial perception	14.2 (5.6)	15.4 (4.4)	-.63
Immediate Memory Digit Forward	3.5 (1.8)	2.8 (1.4)	1.1
Immediate Memory: Digit Backward	1.7 (1.8)	2.1 (1.7)	-.5
Visual Memory	9.0 (4.0)	8.0 (3.2)	-.9
Verbal Memory	12.0 (6.1)	10.2 (5.7)	0.7
Intelligence	96.0 (15.6)	81.2 (22.4)	2.4*
Behavior	4.2 (1.1)	3.6 (1.3)	1.2

NB: Cell entries under the two groups are mean scores.
Standard deviation is given in brackets.
* P<0 .05

Table III Mean and Standard deviation of the scores on the different tests for Monotherapy and Polypharmacy groups in the I and II assessment.

FUNCTION	MONOTHERAPY			POLYPHARMACY		
	Assesment			Assessment		
	I	II	t	I	II	t
Attention	4.8 (1.0)	4.8 (0.5)	-0.4	4.7 (0.9)	4.8 (0.6)	-0.3
Speech	5.0 (0)	5.0 (0)	0	4.9 (0.3)	5.0 (0)	-1.0
Visuo-spatial perception	14.2 (5.6)	14.5 (5.4)	-0.5	15.4 (4.4)	16.3 (5.3)	-1.2
Imm Memory Digit Forward	3.5 (1.8)	3.2 (1.8)	0.9	2.8 (1.4)	3.1 (1.3)	-0.9
Imm Memory Digit Backrd	1.7 (1.8)	2.2 (2.0)	-1.3	2.1 (1.7)	1.6 (1.0)	0.4
Visual Memory	9.0 (4.0)	11.0 (3.5)	-2.6*	8.0 (3.2)	7.1 (2.7)	0.5
Verbal Memory	12.0 (6.1)	13.1 (3.8)	-1.1	10.2 (5.7)	9.0 (4.6)	0.3
Intelligence	96.0 (15.6)	107 (17.5)	-3.6*	81.2 (22.4)	78.2 (18.0)	-0.4
Behavior	4.2 (1.1)	4.3 (0.9)	-0.4	3.6 (1.3)	3.1 (1.4)	0.7

NB: Cell entries under the two groups are mean scores.
Standard deviation is given in brackets.
* P<0 .05

using the t test for dependent means. Table III shows that performance did not differ between the first and second assessments on any of the functions in the polypharmacy group. In the monotherapy group, visual memory and intelligence had improved significantly in the second assessment, the gain in visual memory being small, though significant. The gain in intelligence is nearly 9 points and is substantial and significant. Performance on the other functions had not changed in the second assessment.

DISCUSSION

Sodium valproate administered as monotherapy in complex absence is associated with normal intellectual functioning. Administration in conjunction with other AEDs is associated with a below normal level of intellectual functioning. This poor intellectual functioning may be not entirely due to polypharmacy alone. The other significant clinical variables on which the two groups differed were age of the patient and co-existent type of seizures. The polypharmacy group was older, i.e. mean age of 16 years as compared to 11.6 years in the monotherapy group. However, as the I.Q. was scored on age appropriate norms, the age of the patient is unlikely to have influenced the I.Q. scores. The other significant difference was the presence of tonic-clonic seizures and the use of multiple anticonvulsant drugs in these patients.

Intellectual performance and other cognitive functions in epileptics are known to be affected by age of onset (O'Leary et al, 1981), duration of seizures (Lennox & Lennox, 1960), frequency of attacks (Dikmen & Matthews, 1977) and duration of seizure control (Virmani et al, 1973). In the present study, the two groups were comparable on all the above parameters (Table I). They were also comparable with regard to the presence of EEG abnormalities and serum level of sodium valproate. In view of this large homogeneity between the two groups, the differences in I.Q. may be attributed to the polypharmacy such as barbiturate and the presence of tonic-clonic seizures as the co-existent type. Further studies on a larger sample are required to separate these two influences on intelligence.

It is significant to note that the two groups are comparable on all other cognitive functions. In both groups the clinical profile indicates adequate attention and speech, but impaired visuo-spatial perception, immediate, visual and verbal memory. Behavior problems exist to a minimal extent in the nature of poor adjustment in the home sphere, irritability, stubbornness, moodiness and hyperactivity. Improved alertness has been associated with sodium valproate (Jeavons & Clark, 1974), which may explain the presence of adequate attention at the first assessment.

Slowing down of mental processing with increased task demands associated with sodium valproate (Trimble, 1987), cannot explain the deficits in visuo-spatial perception and memory functions present in both groups. As this slowing down would have a generalized effect on all cognitive functions, normal intellectual performance in the monotherapy group cannot be accounted for with this explanation.

The second assessment after six months indicated that continued use of sodium valproate was not associated with any improvement or worsening of cognitive or behavioral functions in the polypharmacy group. However, in the monotherapy group, it was associated with improvement of visual memory and intelligence; it is difficult to attribute this improvement to practice effects, as these effects are not group or function specific. Further studies with larger samples are required to clarify these preliminary observations regarding the effect of sodium valproate on cognitive functions in patients with complex absence seizures.

ACKNOWLEDGMENT

We are grateful to Reckitt and Coleman for financial assistance and to Ms. Ruby Joseph, Research Assistant, for help in data collection. We gratefully acknowledge the assistance of Mr. D.K. Subbakrishna, Associate Professor of Biostatistics, NIMHANS, in statistical analysis.

REFERENCES

Achenbach, T.M. & Edelbrock, C. (1983) *Manual for the child behavior check-list and revised child behavior profile*. USA: Queen City Printers Inc.

Bell, H.M. (1938) *Bell's Adjustment Inventory*. Stanford: Stanford University Press.

Betts, T.A., Crowe & Alford, C. (1982) Psychotropic effects of sodium valproate. *British Journal of Clinical Practice*, 18, 145-46.

Dikmen, S. & Matthews, C.G. (1977) Effect of major motor seizure frequency upon cognitive - intellectual functions in adults. *Epilepsia*, 18, 21-29.

Dodrill, C.B. & Wilkus, R.J. (1978) Neuropsychological correlates of the EEG in epileptics III. Generalized nonepileptiform abnormalities. *Epilepsia*, 19, 453-62.

Fedio, P. & Mirsky, A.F. (1969) Selective intellectual deficits in children with temporal lobe or centrencephalic epilepsy. *Neuropsychologia*, 7, 287-300.

Giordani, B., Berent, S., Sackellares, J.C., Rourke, D., Seidenberg, M., O'Leary, D.S., Dreifuss, F.E. & Boll T.J. (1985) Intelligence test performance of patients with partial and generalized seizures. *Epilepsia*, 26, 37-42.

Goyette, C.H., Conners, C.K. & Ulrich, R.F. (1978) Normative data on Revised Parents and Teacher Rating Scales. *Journal of Abnormal Child Psychology*, 6, 221-36.

Harding, G.F.A., Herrick, C.E. & Jeavons, P.M. (1978) A controlled study of the effect of sodium valproate on photosensitive epilepsy and its prognosis. *Epilepsia*, 19, 555-65.

Jeavons, R.M. & Clark, J.E. (1974) Sodium valproate in the treatment of epilepsy. *British Medical Journal*, 2, 584-86.

Kamath, V.V. (1967) *Measuring Intelligence of Indian Children*. Bombay: Oxford University Press.

Klove, H. & Matthews, C.G. (1966) Psychometric and adaptive abilities in epilepsy with different aetiology. *Epilepsia*, 7, 330-38.

Mukundan, C.R., Murthy, H.N., & Hemalatha, M. (1979) *Battery of tests of learning and memory function for assessing temporal lobe involvement*. Paper presented at the 10th All India Convention of Clinical Psychologists at NIMHANS, Bangalore.

O'Leary, D.S., Seidenberg, M., Berent, S. & Boll, T.J. (1981) Effect of age of onset of tonic-clonic seizures on neuropsychological performance in children. *Epilepsia*, 22, 197-204.

Sommerbeck, K.W., Theilgaard, A., Rasmussen, K.E., Lohren, V., Gram, L. & Wulff, K. (1977) Valproate sodium: evaluation of so called psychotropic effect. *Epilepsia*, 18, 159-66.

Thompson, P.J. & Trimble, M.R. (1982) Anticonvulsant drug and Cognitive Function. *Epilepsia*, 23, 531-44.

Trimble, M.R. (1987) Anticonvulsant drugs and cognitive function: A review of the literature. *Epilepsia*, 28, 535-45.

Trimble, M.R. & Thompson, P.J. (1983) Anticonvulsant drugs, cognitive functions and behavior. *Epilepsia*, 555-63.

Vining, E.P.G. (1987) Cognitive dysfunction associated with antiepileptic drug therapy. *Epilepsia*, 28, 518-22.

Vining, E.P.G., Mellits, E.D. & Dorsen, M.M. (1987) Psychological and behavioral effects of antiepileptic drugs in children. A double blind comparison between phenobarbital and valproic acid. *Pediatrics*, 80, 165-74.

Virmani, V., Juneja, S. & Chawla, H.M. (1973) Disturbance of cognitive functions in epileptic patients. *Annals of Indian Academy of Medical Sciences*, 9, 181-187.

Volzke, E. & Doose, H. (1973) Dipropsatetae in the treatment of epilepsy. *Epilepsia*, 14, 185-93.

Shobini L.Rao *, *Associate Professor of Clinical Psychology; P.Satischandra, Associate Professor of Neurology; M.Gourie-Devi, Professor of Neurology, National Institute of Mental Health and Neuro Sciences, Bangalore - 560 029.*

*Correspondence