

Behavioral and Cognitive Effects of Anticonvulsant Therapy

There are many potential adverse influences that may impact upon cognitive and behavioral problems of children who have epilepsy. These include inherited tendencies, the underlying epilepsy, associated brain pathology, and psychosocial factors. The role of anticonvulsant therapy in producing adverse neuropsychologic effects has, until recently, been largely ignored. Despite methodologic problems, the Committee on Drugs believes that there is now sufficient information to suggest that anti-epileptic therapy has an adverse influence on mental and behavioral functions. Physician awareness of these effects may significantly affect medical practice by influencing the initiation and termination of therapy, the selection of drugs, and approaches to the monitoring of side effects.

EFFECTS OF ANTICONVULSANT THERAPY

Behavioral

The reported incidence of behavioral disturbances in children who are taking phenobarbital has ranged from 9% to 75%.¹⁻³ Hyperactivity is the most commonly recognized disturbance; in addition, fussiness, lethargy, disturbed sleep (waking in the middle of the night), irritability, disobedience, stubbornness, and depressive symptoms occur frequently (Table).^{1,3,4} Barbiturate-induced behavior disturbance is not dose-related and usually appears in the first weeks and months of therapy. Some of the deterioration of fine motor functions and behavior associated with barbiturate administration may be transient; many abnormalities disappear after 1 year.⁵

Phenytoin intoxication is classically associated with the appearance of nystagmus, ataxia, dysarthria, and encephalopathy. Other side effects include extrapyramidal involuntary movements, an increased feeling of tiredness, errors in performance, and, possible, alterations of emotional state.^{6,7}

Adverse behavioral reactions associated with carbamazepine include difficulty in sleeping, agitation, irritability, and emotional lability—possibly occurring more frequently in patients with preexisting central nervous system (CNS) problems.⁸⁻¹⁰ A beneficial effect on mood and behavior has been suggested, possibly because this drug has a chemical resemblance to tricyclic antidepressants.^{7,8,11} However, because improvements have not been noted universally¹² and because they have occurred primarily in patients who switched from potentially intoxicating drugs (phenobarbital, primidone, and phenytoin⁷⁻¹¹), this claim requires additional supporting evidence.

Benzodiazepines are frequently associated with idiosyncratic behavioral disturbances: irritability, aggression, hyperactivity, disobedience, and anti-social activities. The incidence of these effects, especially in the pediatric population, may be as high as 50% with clonazepam therapy.¹³

Sodium valproate acts to increase the plasma concentration of phenobarbital through inhibition of barbiturate metabolism¹⁴ and may result in drowsiness. Volunteers receiving large initial daily doses of valproate appeared to be acutely intoxicated with drowsiness, decreased ability to concentrate, malaise, and speech difficulties.¹⁵ Other investigators¹⁶ found no change in attentiveness, ability to concentrate, activity level, disposition, attitude, and interest in a short placebo-controlled study.

Cognitive

Large doses of virtually all anticonvulsant medications can affect mental function. However, during the past decade, reports have been associated with cognitive impairment with therapeutic or supratherapeutic, but not necessarily toxic, anticonvulsant levels. Interpretation of these studies is difficult because (1) many patients were receiving polytherapy, (2) seizure frequency was variable, (3) potentially interfering psychosocial problems were present, and (4) the psychometric tests utilized differed widely among studies.

TABLE. Potential Adverse Behavioral and Cognitive Effects of Anticonvulsant Agents

Drug	Behavioral Effects	Cognitive Effects*
Phenobarbital (Luminal)	Hyperactivity, fussiness, lethargy, disturbed sleep, irritability, disobedience, stubbornness, depressive symptoms ¹⁻⁴	Deficits on neuropsychologic tests, impaired short-term memory and memory concentration tasks ^{3,11,22-26}
Phenytoin (Dilantin)	Unsteadiness, involuntary movements, tiredness, alteration of emotional state ^{6,7}	Deficits on neuropsychologic tests, impaired attention, problem solving and visuomotor tasks ^{7,27-29}
Carbamazepine (Tegretol)	Difficulty sleeping, agitation, irritability, emotional lability ⁸⁻¹⁰	Impaired task performance ²⁹
Clonazepam (Clonopin)	Irritability, aggression, hyperactivity, disobedience, antisocial activities ¹³	...
Valproic acid (Depakene)	Drowsiness (especially when used in combination with barbiturates) ^{14,15}	Minimal adverse effects on psychosocial tests ³¹

* Large doses of virtually all anticonvulsant medications can affect mental function. Effects with therapeutic or supratherapeutic, but not necessarily toxic, anticonvulsant levels are shown.

Attempts to circumvent some of these confounding variables have led to investigations of anticonvulsant effects on cognitive function in nonepileptic adult volunteers. These studies have identified deficits in psychologic test performance with therapeutic and subtherapeutic serum levels of barbiturates^{17,18} and phenytoin^{19,20} and less marked impairments with therapeutic levels of sodium valproate.²¹ Thus, these short-term toxicity studies support the theory that there may be a causal relationship between anticonvulsant use and psychologic impairment.

A more difficult question is the extent to which cognitive function in the epileptic patient may be adversely influenced by an anticonvulsant, even though "therapeutic" concentrations are maintained. Several studies have been performed in epileptic patients in order to assess the effect of barbiturates on cognitive function. Thompson and Trimble²² reported deficits in psychologic test performance in adults with high serum concentrations, although decrements in performance also occurred at lower serum concentrations. These authors noted that documentation of diminished psychologic test performance might be overlooked in standard outpatient interviews because more exacting tests were required. MacLeod et al²³ have shown that phenobarbital selectively impairs short-term memory function with lower test scores associated with higher serum phenobarbital concentrations. In a double-blind, placebo-controlled, randomized febrile seizure study in toddlers, Camfield et al³ reported that phenobarbital seemed to have an adverse effect on memory concentration tasks despite the fact that no serum levels were in the toxic range. These memory effects were not associated with a difference in the mean IQ scores between children treated with phenobarbital and those

treated with placebo. However, declining general comprehension scores in children receiving phenobarbital for longer periods did suggest that treatment for greater than 8 to 12 months might eventually affect IQ scores.

Additional data supporting the proposal that barbiturates affect mental function are derived from reports monitoring changes after drug withdrawal and drug crossover studies.^{11,24,25} Vining et al,²⁶ using a double-blind crossover protocol, compared the effects of phenobarbital and valproate in epileptic children. Despite the exclusion of children who had previously been adversely affected by phenobarbital and those who showed obvious behavioral manifestations, the authors reported significantly poorer performances on neuropsychologic tests in patients who were receiving barbiturates. These results were not related to differences in either the frequency of seizures or variations from recommended serum anticonvulsant levels. Furthermore, neither specially designed questionnaires nor physical examinations showed evidence of the psychologic changes readily apparent on validated psychometric testing.

Psychometric studies have also been used to evaluate epileptic patients receiving phenytoin. Dodrill²⁷ compared patients with high serum phenytoin levels (greater than 30 $\mu\text{g}/\text{ml}$) with a group of patients with lower levels (mean, 17 $\mu\text{g}/\text{mL}$); the toxic group tended to do worse on all measures, especially those involving motor activities. In a double-blind crossover study comparing 4-month trials with phenytoin and carbamazepine therapy, Troupin and Dodrill⁷ showed that carbamazepine therapy resulted in fewer errors on tasks involving attention and problem-solving as well as improvement in mood. Recently, Andrewes et al²⁸ have compared the effects of phenytoin and carba-

mazepine into two groups of patients who were matched for age and IQ and who were similar with respect to seizure type and frequency and duration of treatment. The carbamazepine-treated group performed better on multiple memory tests as well as on a visuomotor task. Studies in children with seizure disorders have also demonstrated that phenobarbital therapy interferes with attentional abilities more than carbamazepine therapy.²⁹ However, results also suggested that carbamazepine therapy did have some effect on task performance.

Sodium valproate has been less intensively studied. Valproate added to preexisting therapy had no effect on paired associate learning tasks,³⁰ and its use produced minimal adverse effects in patients performing a series of psychologic tests.³¹

SUMMARY

Behavioral disturbances associated with the use of anticonvulsant therapy may be readily apparent and easily diagnosed. They are most commonly reported with the use of barbiturates and usually include hyperactivity, disturbed sleep, irritability, and emotional lability. But, subtle behavioral disturbances may also adversely affect performance and learning. Behavioral changes resulting from therapy with barbiturates and benzodiazepines tend to be idiosyncratic as opposed to the dose-related effects seen with phenytoin and valproate therapy. Carbamazepine and valproate can affect mood and behavior negatively, but, generally, this occurs less frequently than when several other anticonvulsants are used; this is especially true in patients without CNS damage.

The suspicion that there may be a causal relationship between anticonvulsant therapy and impairment of cognitive skills in nonintoxicated patients is gaining increasing support. Neuropsychologic studies in acutely exposed normal volunteers, studies in epileptic patients receiving monotherapy, and crossover studies between drugs have incriminated barbiturates and hydantoin drugs. Memory/cognitive dysfunction, although affected to a greater extent with higher drug dosages, has been reported with levels within the therapeutic range. Thus, serum drug levels cannot be considered good predictors of which patients will have subtle side effects. Carbamazepine and valproate seem to be relatively free of many adverse neuropsychologic effects, although additional studies need to be performed.

The complete separation of seizure effects from drug effects remains an ongoing goal. Similarly, in comparative studies to date, the issues of whether the differences between the drugs are due to nega-

tive effects of one or positive psychotropic effects of the other, or both, are not adequately addressed. In addition, because current physician office procedures do not detect subtle mental impairments, more sensitive techniques are needed to assess potential cognitive and behavioral side effects of medications.

RECOMMENDATIONS

In view of accumulating evidence indicating that anticonvulsant therapy may have detrimental effects on behavior and cognition, the Committee on Drugs makes the following recommendations: (1) Physicians should have an understanding of the natural history of seizure disorders, especially knowledge of when to initiate and when to discontinue medications. For example, febrile seizures may not require treatment,³² nor may a first, unprovoked seizure.^{33,34} In addition, in a child who remains seizure-free, medication should perhaps be used for no longer than 2 to 4 years.³⁵⁻³⁷ (2) When an antiepileptic medication is required, the physician must consider the specificity of the drug for the seizure type, as well as the drug's potential side effects. Thus, the relative influence of each anticonvulsant agent on behavioral and cognitive function should be considered, along with all other potential adverse effects, when selecting a medication. (3) If anticonvulsant therapy is initiated, the physician should give careful attention to reports from parents and teachers as well as office observations of cognitive function, mood, and behavior during follow-up visits. (4) If significant behavioral or cognitive changes appear and no alternative explanations are readily available, the physician must consider the possibility that anticonvulsant therapy might be responsible and perhaps the dose should be reduced or the medication should be changed. (5) A brief, readily administered, sensitive neuropsychologic screening test capable of detecting subtle intellectual and behavioral side effects should be developed. (6) Finally, the need for the performance of studies designed to evaluate and compare behavioral and cognitive effects of anticonvulsant therapy in children should be recognized and supported.

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REFERENCES

1. Wolf SM, Forsythe A: Behavior disturbance, phenobarbital, and febrile seizures. *Pediatrics* 1978;61:728-731
2. Thorn I: A controlled study of prophylactic long term treatment of febrile convulsions with phenobarbital. *Acta Neurol Scand [Suppl]* 1975;60:67-73
3. Camfield CS, Chaplin S, Doyle A-B, et al: Side effects of phenobarbital in toddlers; behavioral and cognitive aspects. *J Pediatr* 1979;95:361-365
4. Ferrari M, Barbas G, Matthews WS: Psychological and behavioral disturbance among epileptic children treated with barbiturate anticonvulsants. *Am J Psychiatry* 1983;140:112-113
5. Hellstrom B, Barlach-Christoffersen M: Influence of phenobarbital on the psychomotor development and behavior in preschool children with convulsions. *Neuropadiatrie* 1980;11:151-160
6. Chadwick D, Reynolds EH, Marsden CD: Anticonvulsant-induced dyskinesias: A comparison with dyskinesias induced by neuroleptics. *J Neurol Neurosurg Psychiatry* 1976;39:1210-1218
7. Troupin AS, Dodrill CB: Carbamazepine: A double blind comparison with phenytoin. *Neurology* 1977;27:511-519
8. Dalby MA: Behavioral effects of carbamazepine. *Adv Neurol* 1975;11:331-344
9. Silverstein FS, Parrish MA, Johnston MV: Adverse behavioral reactions in children treated with carbamazepine. *J Pediatr* 1982;101:785-787
10. Steinbrecher W: Therapie zerebraler Anfallsformen mit Tegretol. *Med Welt* 1966;25:1381-1385
11. Schain RJ, Ward JW, Guthrie D: Carbamazepine as an anticonvulsant in children. *Neurology* 1977;27:476-480
12. Rett A: Tegretol therapy of epileptic children, in Wink CAS (ed): *Tegretol in Epilepsy*. Manchester, England, C. Nichols, 1972, pp 12-15
13. Browne TR: Clonazepam: A review of a new anticonvulsant drug. *Arch Neurol* 1976;33:326-332
14. Kapetanovic I, Kuperberg HJ, Porter RJ, et al: Valproic acid-phenobarbital interaction: A systemic study using stable isotopically labeled phenobarbital in an epileptic patient, in Johannessen SI, Morselli PL, Pippenger CE, Richens A, Schmidt D, Meinardi H (eds): *Antiepileptic Therapy: Advances in Drug Monitoring*. New York, Raven Press, 1980, pp 373-380
15. Bowdle TA, Patel IH, Wilensky AJ, et al: Hepatic failure from valproic acid, Letter to the Editor. *N Engl J Med* 1979;301:435-436
16. Sonnen AEH, Zelveler WH, Bruens JH: A double-blind study of the influence of dipropylacetate on behavior. *Acta Neurol Scand [Suppl]* 1975;60:43-47
17. Hutt SJ, Jackson PM, Belsham AB, et al: Perceptual-motor behavior in relation to blood phenobarbitone level: A preliminary report. *Dev Med Child Neurol* 1968;10:626-632
18. Houghton GW, Latham AN, Richens A: Difference in the central actions of phenytoin and phenobarbitone in man, measured by critical flicker fusion threshold. *Eur J Clin Pharmacol* 1973;6:57-60
19. Idstrom CM, Schalling D, Carlquist V, et al: Acute effects of diphenylhydantoin in relation to plasma levels: Behavioral and psychophysiological studies. *Psychol Med* 1972;2:111-120
20. Thompson PJ, Huppert FA, Trimble MR: Phenytoin and cognitive function: Effects on normal volunteers and implications for epilepsy. *Br J Clin Psychol* 1981;20:155-162
21. Thompson PJ, Trimble MR: Sodium valproate and cognitive functioning in normal volunteers. *Br J Clin Pharmacol* 1981;12:819-824
22. Thompson PJ, Trimble MR: Anticonvulsant serum levels: Relationship to impairments of cognitive functioning. *J Neurol Neurosurg Psychiatry* 1983;46:227-233
23. MacLeod CM, Dekaban AS, Hunt E: Memory impairment in epileptic patients: Selective effects of phenobarbitone concentration. *Science* 1978;202:1102-1104
24. Oxley J, Richens A, Wadsworth J: Improvement in memory function in epileptic patients following a reduction in serum phenobarbitone levels, in *Abstracts. Eleventh Epilepsy International Symposium*, Florence, Italy 1979
25. Thompson PJ, Trimble MR: Anticonvulsant drugs and cognitive functions. *Epilepsia* 1982;23:531-544
26. Vining EPG, Mellitus ED, Cataldo MF, et al: Effects of phenobarbital and sodium valproate on neuropsychological function and behavior. *Ann Neurol* 1983;14:360
27. Dodrill CB: Diphenylhydantoin serum levels, toxicity, and neuropsychological performance in patients with epilepsy. *Epilepsia* 1975;16:593-600
28. Andrewes DG, Tomlinson L, Elwes RDC, et al: The influence of carbamazepine and phenytoin on memory and other aspects of cognitive functions in new referrals with epilepsy. *Acta Neurol Scand [Suppl 99]* 1983;69:23-30
29. Schain RJ, Shields WD, Dreisbach M: Carbamazepine and cognitive function. Abstract. Presented at the American Epilepsy Society Annual Meeting, Washington, DC, Sept 26-30, 1983
30. Sommerbeck KW, Theilgaard A, Rasmussen KE, et al: Valproate sodium: Evaluation of so-called psychotropic effect: A controlled study. *Epilepsia* 1977;18:159-167
31. Trimble MR, Thompson PJ: Sodium valproate and cognitive function. *Epilepsia* 1984;25(Suppl 1):S60-S64.
32. Consensus Statement NIH: Febrile seizures: Long-term management of children with fever-associated seizures. *Pediatrics* 1980;66:1009-1012
33. Hauser WA, Anderson VE, Lowenson RB, et al: Seizure recurrence after a first unprovoked seizure. *N Engl J Med* 1982;307:522-528
34. Hirtz DG, Ellenberg JH, Nelson KB: The risk of recurrence of nonfebrile seizures in children. *Neurology* 1984;34:637-641
35. Shinnar S, Vining EPG, Mellits ED, et al: Discontinuing antiepileptic medication in children with epilepsy after two years without seizures: A prospective study. *N Engl J Med*, in press, 1985
36. Emerson R, D'Souza BJ, Vining EPG, et al: Stopping medication in children with epilepsy: Predictors of outcome. *N Engl J Med* 1981;304:1125-1129
37. Thurston JH, Thurston DL, Hixon BB, et al: Prognosis in childhood epilepsy: Additional follow-up of 148 children 15 to 23 years after withdrawal of anticonvulsant therapy. *N Engl J Med* 1982;306:831-836

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