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A POTENTIAL NEW THERAPY FOR FEBRILE SEIZURES*

PRELIMINARY REPORT ON DEVELOPMENT OF N-PHENYLBARBITONE

BY

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Febrile seizures occur commonly in infants and young children, and generally in response to fever caused by acute infections of the upper respiratory tract. The height of the fever is an important factor in aetiology, and the body temperature at the onset of the convulsion is a reliable measure of the febrile-seizure threshold (Millichap, 1959). Patients with a high threshold convulse only in response to fever of 41° C. (105.8° F.) or above, whereas those who are most susceptible have seizures with fever of 38.5° C. (101.3° F.) or below.

Conventional methods of treatment have been found inadequate. Phenobarbitone, administered intermittently at the time of febrile episodes and in combination with acetylsalicylic acid or continuously in repeated daily doses, failed to prevent recurrence of febrile seizures in 48% of 40 patients treated; phenytoin sodium given regularly and daily was entirely ineffective in seven patients. Tepid water-baths and other methods of hydrotherapy also were unsatisfactory (Millichap, Aledort, and Madsen, 1960).

The ideal therapy for febrile seizures should have both antipyretic and anticonvulsant effects in doses relatively non-toxic. Since seizures occur only at the time of an acute febrile illness, the action of the drug should be rapid in onset and allow intermittent administration so that necessity for continuous medication may be avoided. In the present study a new compound with potential activity against fever-induced seizures has been developed as the result of laboratory tests in animals. Its clinical efficacy has been demonstrated in preliminary trials.

Methods

Febrile seizures were induced in young Swiss albino mice by means of a microwave diathermy generator, according to a method described previously (Millichap, 1959). Drugs were tested for their ability (1) to retard the rate of rise of body temperature, (2) to raise the threshold convulsive temperature (temperature at the onset of clonus), and (3) to abolish the seizure. Various doses were employed and between 5 and 10 mice were treated at each dose level. Responses of test animals were compared with those of controls. The effects of

acetylsalicylic acid, phenobarbitone, and phenytoin sodium were examined initially so that the efficacy of new drugs could be compared with conventional methods of treatment and their potential clinical value assessed. The selection of new chemicals for testing was facilitated by preliminary observations of the activity of various classes of pharmacological agents against seizures induced experimentally (Millichap, 1958).

Results

Acetylsalicylic acid in oral doses of 10, 50, and 100 mg./kg. failed to retard the rate of temperature rise in mice and in toxic doses (600 mg./kg.) increased the severity of the febrile seizure. The inadequacy of acetylsalicylic acid in the prevention of febrile seizures may be explained in part by the failure of its antipyretic effect in the presence of a rising temperature. The ineffectiveness of phenytoin sodium against fever-induced seizures in children was observed also in animals; oral doses of 10, 20, and 50 mg./kg. exacerbated the clonic pattern. Phenobarbitone retarded the rate of rise in body temperature and prevented the febrile seizure, but large depressant doses were required; with smaller doses protection from seizures was incomplete but the threshold convulsive temperature was elevated.

Of 60 new chemicals tested, *N*-phenylbarbitone ("pyrictal") was the most potent anticonvulsant; its action was rapid in onset and toxicity was relatively low. In doses larger than those necessary for control of seizures in mice, hyperexcitability was the principal side-effect and, in contrast to phenobarbitone, sedation was of minimal degree; tremor and clonic movements were observed with sublethal doses of 600 mg./kg. Similar side-effects have been noted in other species, in acute and chronic toxicity studies performed by the Wellcome Research Laboratories, U.S.A. (E. J. deBeer, personal communication).

The chemical structure of *N*-phenylbarbitone and of phenobarbitone and the respective therapeutic indices are as follows:

The therapeutic index is a measure of the margin of safety and potential usefulness of a drug; it is obtained by dividing the dose which causes minimal signs of toxicity in 50% of animals (TD₅₀) by that which protects 50% of animals from the experimental seizure (ED₅₀).

Laboratory and clinical evaluations of *N*-phenylbarbitone and phenobarbitone are compared in the Table. Determinations of parallelism and estimates of relative potency and toxicity were made by the methods of Litchfield and Wilcoxon (1949). Dose-effect lines of the two drugs were parallel. The potency of anticonvulsant

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effect was not significantly different (potency ratio (1.45) $< f_{p.r.}$ (1.82)), but the neurotoxicity of phenobarbitone was three times that of *N*-phenylbarbitone (toxicity ratio: 3.1, with 95% confidence limits of 5.3 to 1.8).

Laboratory and Clinical Evaluation of N-Phenylbarbitone Compared with Phenobarbitone

Evaluation	<i>N</i> -Phenylbarbitone	Phenobarbitone
Laboratory:		
Anticonvulsant ED ₅₀	150 mg./kg. (112-200)*	103 mg./kg. (61-173)
Neurotoxic TD ₅₀	190 mg./kg. (152-238)	61 mg./kg. (37-100)
Antipyretic activity	18%	1.6%
Test rate of rise	5.0 $\pm$ 0.27° F./min.†	6.59° F./min.
Control rate of rise	6.1 $\pm$ 0.35° F./min.	6.70° F./min.
t, df, P	2.43, 12, <0.05	
Time of maximal effect	1½ hours	3 hours
Clinical:		
Febrile seizure control	100% (12)‡	52% (40)‡

* 95% confidence limits.

† Mean $\pm$ standard error.

‡ Difference significant: $\chi^2=6.7$, $P<0.01$. No. of patients shown in parentheses.

Antipyretic effects were expressed as the percentage retardation of rate of rise of body temperature. The effect of *N*-phenylbarbitone was significant in non-toxic doses (150 mg./kg.), whereas phenobarbitone was inactive at a toxic dose level (50 mg./kg.). In contrast to *N*-phenylbarbitone, the antipyretic effect of phenobarbitone was irregular and a satisfactory dose-response curve was not obtained.

Clinical Evaluation

Anticonvulsant activity of *N*-phenylbarbitone was evaluated in 20 institutionalized patients with major, minor, or combined seizures previously uncontrolled by conventional anti-epileptic drugs. The average daily dose administered orally was 17 mg./kg. A reduction in the incidence of seizures of 75% or more was obtained in 8 out of 15 patients with major seizures and in 9 out of 10 patients whose seizures were minor in type. Myoclonic, opisthotonic, and absence seizures were controlled more effectively than the tonic or tonic-clonic pattern, and a combination of phenytoin sodium and *N*-phenylbarbitone was necessary for satisfactory treatment of major epilepsies.

Antipyretic activity of *N*-phenylbarbitone was determined in infants and children with fever greater than 38.3° C. (101° F.). The average single dose administered orally was 23 mg./kg. and the range was 14-30 mg./kg. A fall in body temperature was recorded within one hour in 75% of 71 children treated with *N*-phenylbarbitone and in 31% of a control group of 16 children who received no antipyretic therapy for the same period of time. A response to the drug was obtained in a significant proportion of patients ($\chi^2=9.0$, $P<0.01$).

The combined antipyretic and anticonvulsant properties of *N*-phenylbarbitone were examined in infants and children with fever and a previous history of febrile seizures. The drug was administered orally at the onset of acute infection in doses of 20 mg./kg. Febrile seizures did not occur in 12 patients treated with *N*-phenylbarbitone, whereas the incidence of recurrence was 48% in 40 patients who received phenobarbitone.

In febrile children treated intermittently no side-effects were observed. Of epileptic patients who received the drug continuously, one was restless, one was anorexic, and one was sedated. Drowsiness was increased transiently in four patients who were treated with *N*-phenylbarbitone in addition to phenobarbitone and phenytoin sodium.

Summary and Comment

The ideal therapy for the prevention of febrile seizures is an anticonvulsant which acts also as an antipyretic and inhibits heat production during the initial and pyrogenic stage of a febrile illness. It should elevate the febrile seizure threshold and prevent a rise in body temperature above the threshold convulsive temperature for the individual patient.

Conventional methods of treatment have been found inadequate. Acetylsalicylic acid facilitates heat loss in a febrile patient but has no effect on heat production; the optimum antipyretic effect is obtained when the administration of the drug coincides with the expected defervescence of the fever (Goodman and Gilman, 1955). Phenobarbitone is relatively ineffective as an anticonvulsant in the febrile patient.

N-phenylbarbitone has been developed as a specific therapy for febrile seizures. The efficacy has been demonstrated in laboratory and clinical tests.

In contrast to acetylsalicylic acid, *N*-phenylbarbitone retards the rise of body temperature during the induction of fever in animals, and compared with phenobarbitone it is equally effective in the prevention of experimental febrile seizures, has only one-third the toxicity, and is antipyretic in non-depressant doses. In epileptic patients, clonic, opisthotonic, and absence seizures are responsive, but the major tonic pattern is not well controlled.

To be accepted for general use, the new compound must prove superior in efficacy and less toxic than the therapy employed at present. The results of initial trials of *N*-phenylbarbitone in children with fever and seizures are encouraging and further evaluation of its clinical efficacy against febrile seizures, hyperpyrexia, and minor epilepsies seems warranted.

N-phenylbarbitone (pyrictal) and other new chemicals were synthesized and supplied by Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N.Y. The drug was developed at the Departments of Paediatrics and Pharmacology, Albert Einstein College of Medicine, and the Bronx Municipal Hospital Center, New York City. I am indebted to Dr. Bernard I. Kramer for his supervision of the trials of the drug in patients with fever and febrile seizures, to Dr. Richard C. Cooke and Dr. Philip R. Dodge for permission to conduct trials at the Myles Standish State School, Taunton, Mass., and to Dr. Alfred Gilman for his interest and encouragement.

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