

PAPERS AND ORIGINALS

Successful prophylaxis against febrile convulsions with valproic acid or phenobarbitone

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Summary and conclusions

A total of 184 six-month periods were analysed during which feverish illnesses occurred in children aged 6-42 months with a history of a febrile convulsion. Fits occurred in 34 out of 100 such periods when no treatment was being given, in six out of 45 periods when the serum phenobarbitone concentration was 69.0 $\mu\text{mol/l}$ (1.6 mg/100 ml) or more, and in five out of 39 periods when the plasma valproic acid concentration was 416.4 $\mu\text{mol/l}$ (6.0 mg/100 ml) or more. Thus in adequate dosage both phenobarbitone and valproic acid were significantly better than no treatment in preventing febrile convulsions ($p < 0.02$). The two drugs were of comparable efficacy.

It is concluded that with improved compliance valproic acid, which is relatively free from side effects, might be an effective prophylactic agent against febrile convulsions.

Introduction

Repeated febrile convulsions make a severe fit with the accompanying possibility of neurological damage more likely.¹ The incidence of later spontaneous seizures rises if many febrile convulsions have occurred.²⁻⁴ Girls who have further episodes after an initial unilateral fit are likely to have learning difficulties.⁵ Prevention of febrile convulsions is therefore desirable, and is of particular relevance in children with factors carrying a high risk of recurrence.^{6, 7}

Barbiturates are reportedly either successful⁸⁻¹¹ or unsuccessful¹² as prophylactic agents. It has been further suggested

that valproic acid is as effective as phenobarbitone.¹³ In none of these studies, however, was the efficacy of the drug related to the presence of the necessary stimulus—namely, fever. We have therefore examined the incidence of recurrence of fits in children aged 6-42 months who were receiving either continuous valproic acid or phenobarbitone or no treatment at the time of a feverish illness.

Patients and methods

We studied 121 children (64 boys, 57 girls) who had had their first convulsions during a feverish illness of 38°C or more. They had been admitted consecutively to the five paediatric units in Cardiff and Newport between April and December 1976. Children were considered to be at increased risk of a further convulsion if at least one of the following factors was present: age under 19 months; neurological state other than normal; seizures in parents or siblings; and initial convulsion other than single, completely generalised, and lasting under 30 minutes. Parents of such children were advised alternately to give phenobarbitone or valproic acid. The other children were prescribed sequentially either phenobarbitone, valproic acid, or no treatment.

Even after explaining to parents the likelihood of subsequent fits some did not accept the need for treatment, and many children with at least one risk factor did not receive anticonvulsants. In effect, those given phenobarbitone, valproic acid, and no treatment at times of feverish illnesses were comparable for risk factors. Initially 48 children were given valproic acid 20-30 mg/kg body weight daily, 46 phenobarbitone 4-5 mg/kg daily, and 27 no treatment. Blood anticonvulsant concentrations were measured routinely two to three weeks after beginning treatment and six-monthly thereafter; they were measured more often if fits recurred or side effects were noted. We aimed to achieve a serum phenobarbitone concentration of 69.0 $\mu\text{mol/l}$ (1.6 mg/100 ml) or more and a plasma valproic acid concentration of 416.4 $\mu\text{mol/l}$ (6.0 mg/100 ml) or more. Of the 121 children, 117 were followed up for at least 24 months, during which all episodes of fever and all fits were recorded.

Fever was deemed to have occurred if the parents gave a history of either a definite illness requiring intervention by a general practitioner or a temperature of at least 38°C. Minor upper respiratory tract infections were discounted. We compared the anticonvulsants both against each other and against no treatment; recordings were made during the six-month periods when feverish illnesses occurred in children aged 6-42 months who were either taking no treatment or

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had the optimal concentration of valproic acid ($\geq 416.4 \mu\text{mol/l}$) or phenobarbitone ($\geq 69.0 \mu\text{mol/l}$) in the blood.

Results

A total of 184 six-month periods in 108 children were suitable for analysis. During these, fits occurred on six occasions in four children with optimal serum phenobarbitone concentrations, on five occasions in five children with optimal plasma valproic acid concentrations, and on 34 occasions in 24 children taking no treatment (table). Each agent

Incidences of febrile convulsions during prophylaxis and no treatment in children aged 6-42 months studied for 184 six-month periods. Results expressed as numbers of periods in which fever occurred

Prophylaxis	Fits	No fits	
Phenobarbitone (serum concentration $\geq 69.0 \mu\text{mol/l}$)	6	39	} $\chi^2 = 6.61$; $p < 0.02$
None	34	66	
Valproic acid (serum concentration $\geq 416.4 \mu\text{mol/l}$)	5	34	} $\chi^2 = 6.15$; $p < 0.02$

Conversion: SI to traditional units—Phenobarbitone: $1 \mu\text{mol/l} \approx 0.023 \text{ mg/100 ml}$. Valproic acid: $1 \mu\text{mol/l} \approx 0.014 \text{ mg/100 ml}$.

was significantly better than no treatment in preventing fits when these children became feverish ($p < 0.02$). The relative efficacies of the two drugs were comparable.

Children whose blood phenobarbitone or valproic acid concentrations were less than optimal also had a lower incidence of convulsions than those taking no treatment. Fits occurred with fever during eight out of 58 six-month periods in such children taking phenobarbitone and during six out of 35 six-month periods in those taking valproic acid.

Discussion

Our findings show that both phenobarbitone and valproic acid significantly reduce the likelihood of further convulsions when vulnerable children become feverish. Not only is this medically desirable but it removes the inevitable panic seen in parents of children who convulse.^{14 15} That children given theoretically "suboptimal" dosages had an incidence of convulsions closer to that in children given "optimal" dosage than to that in untreated children differs from other reports.^{8 9 11} It might be explained by greater diligence with ancillary measures such as antipyretics and cooling in those whose parents were complying to some extent than in those whose parents completely failed to comply.

Undesirable effects of phenobarbitone on behaviour have been documented in almost all investigations of its use for febrile convulsions.^{12 16 17} In our study parents reported deterioration in at least one aspect of behaviour significantly more often after phenobarbitone than after valproic acid.¹⁸

Compliance with long-term anticonvulsant regimens is generally poor^{11 12} and varied in our study also. Interestingly, despite a higher reported incidence of side effects from phenobarbitone compliance was significantly better, especially in the

manual classes, when phenobarbitone rather than valproic acid was prescribed (personal paper delivered at the Epilepsy International symposium, Vancouver, 1978). Better education about the long-term outlook if fits persist and knowing that recurrences can be prevented by suitable anticonvulsants might lead to better compliance.

We conclude that valproic acid may be an effective prophylactic agent against febrile convulsions and is relatively free from side effects.

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ONE HUNDRED YEARS AGO There has been much controversy from time to time as to the propriety to a patient using again a prescription, after the occasion for which the medical attendant gave it and received a fee. Such a question would be hardly likely to arise in the case of a very large form of prescription, of which the *National* gives the following account. According to that journal, a medical man of Chalons being sent for to a case in a neighbouring village, forgot to take his memorandum-book with him. Apparently, elementary education is not enforced in that part of the world; for, when the doctor asked for pen, ink, and paper to write a prescription, nothing of the kind was forthcoming, nor could writing materials of any description whatever be obtained in the neighbourhood. Tired of waiting, the doctor seized a piece of charcoal, and wrote a prescription

on the barn-door of the farm where the patient lived. The relations, however, of the sick man naturally found themselves unable to read what had been ordered for his benefit, and thus another difficulty arose. At last, the bright idea struck them of taking the door off the hinges, and sending it bodily to the druggist. This was accordingly done, and the pharmacist in the neighbourhood was considerably astonished by the apparition of a cart stopping at his establishment, laden with a huge door. It was impossible to take this novel form of prescription into the shop; so, realising the situation, he propped it up on the pavement, read the formula, and returned the door with the medicine ordered, of course taking proper precautions that, should the *ordonnance* require repetition, he would not again need to see the original prescription. (*British Medical Journal*, 1880.)