

Randomised controlled trials of phenobarbitone and valproate in febrile convulsions

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SUMMARY Results from British trials of phenobarbitone and valproate for the prophylactic treatment of febrile convulsions were pooled and analysed on an intention to treat basis. The overall odds ratio for phenobarbitone was 0.8 and for valproate 1.42. Neither result was significant. Neither treatment can be recommended in the light of experience.

Controlled trials of drug treatment are usually pragmatic studies of treatment practice, and analysis should then be on an intention to treat basis. The question being asked is whether the intention to treat a population of children with febrile fits with anticonvulsants reduces the risk of recurrence relative to that in a control group. Many trials have excluded children from analysis who did not take their medication through either poor adherence to instructions or side effects. Analysis on this basis answers the question of whether risk of recurrence is reduced in quite a selected population which is difficult to define in advance.

Analysis on an intention to treat basis demands that children are analysed with the group to which they were originally allocated. Invariably some children are lost to follow up and available resources make this difficult to overcome. An assumption is usually made in the analysis that no bias has been introduced through this happening. Studies have shown apparently conflicting results. This is often due to small study groups either exaggerating or overlooking clinical benefit due to the play of chance. Pooled analysis leaves less to the play of chance by increasing the study population size. The method used is similar to that used in multicentre trials. Within centre differences between study and control groups become within study differences that are estimated and then pooled. An overall odds ratio (relative risk) is provided. This is the risk of recurrence in the treatment group relative to controls. An odds ratio of unity thus will signify no difference. An odds ratio of less than unity suggests some treatment benefit; greater than unity no benefit. When the odds ratio and its 95% confidence interval lie entirely to one side of unity the result is significant at $p < 0.05$.

The method assumes data from all trials are available. None must be omitted because they showed negative results and were therefore unpublished. The method does not assume that one trial is directly comparable with another, but does assume the true odds ratio to be the same for each.

Method

Statistical analysis was identical to that used by Collins *et al.*¹ Six British trials of phenobarbitone^{2 3 5-8} were identified and four of valproate.^{4 6-8} The table summarises data from the trials.

Trials were identified through a computerised literature search. Those unpublished were identified by writing to all members of the British Paediatric Neurology Association and paediatricians known to have participated in such work.

Children were reallocated to the groups to which they were originally assigned before reanalysis of data. Details were usually available from the paper itself or clarification was sought from the authors. Data in all but one paper can be confirmed.⁷

Results

The numbers in each trial and recurrences in each study group are summarised in the table. The pooled analysis of the phenobarbitone and valproate trials is summarised in the figure.

For phenobarbitone the odds ratio varied from 0.42⁶ to 2.07⁷: in two it was less than unity and in four greater. The overall odds ratio for the 535 children was 0.8 (95% confidence interval: 0.53 to 1.20) a non-significant result. Sixty six of the 296 (22%) treated children had recurrences compared with 58 of 236 (25%) controls.

Table Characteristics of randomised controlled British trials of phenobarbitone or valproate, or both, in febrile convulsions

Study (reference)	Age on entry	Follow up period	No of patients followed up		No of recurrent febrile convulsions	
			Treated	Control	Treated	Control
Phenobarbitone trials						
²	6 months-3 years	6 months	88	73	10	14
³	6 months-4 years	6 months	51	10	14	2
⁵	<24 months	12 months	50	45	10	15
⁶	6-18 months	Mean of 13.5 months	23	21	4	7
⁷	6-42 months	24 months	43	27	16	6
⁸	6-72 months	Mean of 30 months	41	60	12	14
Overall			296	236	66	58
Valproate trials						
⁴	6 months-6 years	12 months	30	28	8	9
⁶	6 months-6 years	Mean of 13.5 months	20	21	1	7
⁷	6 months-6 years	24 months	45	27	20	6
⁸	6 months-6 years	Mean of 30 months	50	60	20	14
Overall			145	136	49	36

Plasma drug concentrations were measured in each trial except that of Bacon *et al*⁵ which measured salivary concentrations.

With valproate the odds ratio varied from 0.11⁶ to 2.8,⁷ in two it was less than unity and in two greater. The overall odds ratio was 1.42 (95% confidence interval: 0.85 to 2.36), also a non-significant result. Forty nine of 145 (34%) treated children had recurrences compared with 36 of 136 (26%) controls.

Discussion

Only the British experience has been considered as the logistic problems in identifying unpublished trials showing negative results on a world basis seemed insurmountable. The analysis shows well how small study groups serve to exaggerate benefits or drawbacks of treatment. All the trials have been too small for paediatricians to use their findings with confidence.

Pooled analysis of the British experience fails to show any overall value in deciding to treat children who have febrile convulsions with anticonvulsants. The results do suggest that phenobarbitone might prevent as many as half the recurrences but they establish that any benefit from valproate is likely to be unacceptably small.

The overall risk of recurrence is 26%. If the odds ratio of 0.8 for phenobarbitone trials were significant one would have to give anticoagulants to 100 children to stop five having a recurrence.

With side effects reported in up to 40% of the treated group it must be concluded that prophylactic treatment for febrile convulsions cannot be recommended. Alternative methods of treatment must be assessed such as the administration of rectal diazepam in those particularly at risk of recurrence. Meanwhile clear advice to parents on the first aid management of a seizure and how to gain access to medical care remain most important.

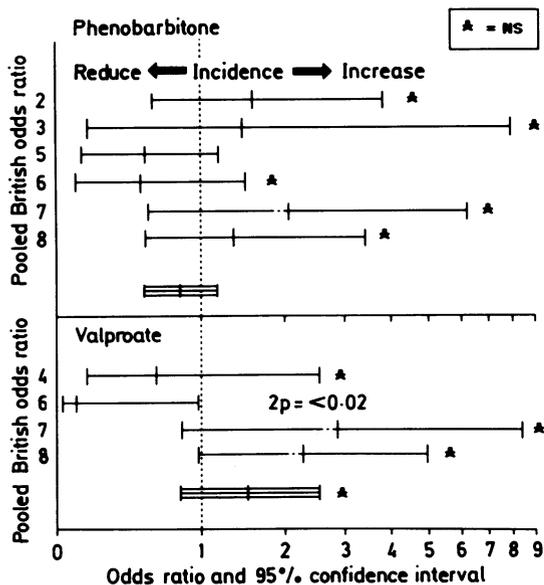


Figure Pooled odds ratio of recurrent fit in randomised controlled trials of phenobarbitone and valproate, with 95% confidence limits.

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