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Clinical and EEG response to anticonvulsants in neonatal seizures

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SUMMARY During a two year period prospective continuous electroencephalographic (EEG) monitoring of 275 infants identified seizure activity in 55 cases, 31 of whom were treated with anticonvulsant drugs on clinical grounds. EEG and clinical response was complete in only two and equivocal in another six. Clinical response with persistent EEG seizures occurred in 13 and neither clinical nor EEG response in 10. There was no significant improvement in the generally poor neurological outcome compared with that in 24 infants whose seizures were not treated because of limited or absent clinical manifestations. Background EEG abnormality (as an index of associated cerebral dysfunction) was a guide to potential lack of response to anticonvulsant drugs; it was also predictive of subsequent clinical outcome irrespective of treatment.

This study shows that commonly used anticonvulsant drugs (phenobarbitone, paraldehyde, phenytoin, and diazepam) have little effect on seizure control or neurological outcome in neonatal seizures associated with haemorrhagic, hypoxic, or ischaemic cerebral lesions. In view of the variable clinical appearance of EEG seizure activity, continuous EEG monitoring should be an essential feature of further study of neonatal anticonvulsant treatment.

Continuous electroencephalographic (EEG) monitoring has identified persistent EEG seizure activity in many infants in whom clinical signs are either undetected or may stop in response to treatment.[1 2] This raises the possibility that many such infants may be failing to receive optimal or adequate anticonvulsant treatment.

Before treatment for EEG detected seizures without clinical signs is contemplated, more critical evaluation of present neonatal anticonvulsant treatment is needed, particularly in view of the potential adverse effects.[3–7]

We have investigated this problem by analysing prospectively the effects of anticonvulsant treatment in all neonates treated for convulsions in our regional referral unit during a two year period. We specifically looked at the response of clinical and EEG seizure activity to anticonvulsant treatment and its association with later neurological outcome.

Patients and methods

During a two year period, 275 infants were recruited to a prospective evaluation of continuous EEG recording with the four channel Oxford Medilog monitor for the diagnosis of neonatal seizures.[2] The 55 infants in whom EEG seizure activity was diagnosed form the study group for this report.

During this time clinical seizures were treated initially with a single dose of one of several anticonvulsant drugs at the discretion of the clinician in the following sequence and dosage until response occurred: phenobarbitone (20 mg/kg intravenously); paraldehyde (0·3 ml/kg per rectum, or 1–3 ml/kg/hour of a 5% intravenous infusion in 5% dextrose); phenytoin (20 mg/kg intravenously); or diazepam (0·25 mg/kg intravenously). Plasma phenobarbitone concentrations were only measured for clinical reasons.

Decisions about the initiation, timing, and continuation of treatment were made independently by the neonatologists who were not given any results of EEG monitoring unless they specifically requested information about a particular child.

EEG recordings were made using the Oxford Medilog 4–24 continuous four channel monitor, according to the method described by Eyre *et al.*[1] Two channels were allocated to EEG, using silver/silver chloride electrodes applied with collodion in the F4–P4 and F3–P3 positions (impedances <5

kohms), one channel to electrocardiography and the fourth channel to either monitoring of respiration, or use as a time-event marker.

Each 24 hours of data was recorded on standard C–120 cassette tape and reviewed on the visual display unit of the Medilog system at 20 and 60 times the normal speed at scales of 1·5 and 3·0 cm/s. A compressed transcription for further analysis was made at 6 cm/minute, using a Siemens 8 Elema-Schonander ink jet recorder.

EEGs were analysed in relation to normal standards for gestational age established from previous studies using standard EEG recording[8–12] and also from our own study specifically for continuous four channel recording.[13]

Background EEG activity was categorised as either normal or abnormal; if the latter, they were allocated to one of the following categories:

1—Percentage of discontinuous activity/24 hours more than two SD above the gestational mean, but no other abnormality; this could be (a) transient (up to 24 hours only), or (b) sustained (more than 24 hours).

2—Excess discontinuity as in category 1, plus one or more of the following: asynchrony, asymmetry, prolonged interburst interval duration (more than two SD above the gestational mean), low amplitude; this could be (a) transient (up to 24 hours only), or (b) sustained (more than 24 hours).

3—Maximal background depression with no discernible electrical activity for more than one hour; (a) as the culmination of a sequence of progressive deterioration of activity with steadily increasing interburst intervals and decreasing burst duration and amplitude, or (b) as an established finding at the first recording.

The efficacy of anticonvulsant drugs in suppressing both clinical and EEG seizure activity was assessed by allocating the response of treated infants into one of the following groups:

Complete response: immediate and sustained cessation of EEG and clinical seizures;

Equivocal response: delayed response (within six hours); poorly sustained response (recurrence within 24 hours);

Persistence of EEG seizure activity after cessation of clinical signs;

No EEG or clinical response. These responses were also evaluated in relation to the postmenstrual age, main aetiological associations, and to the background EEG activity of the infants.

The prognostic importance of these responses was assessed by comparing the clinical neurological outcome in infants in each of the above groups. This assessment was based on examination at discharge from the unit using a standardised form,[14] and at intervals between six and 24 months using the Griffiths's mental development scales[15] and items from Amiel-Tison and Grenier,[16] and Touwen.[17] Infants were then allocated to one of four groups: normal outcome, transient changes in tone but no other abnormality,[18] major neurological abnormality (cerebral palsy or mental retardation, or both), or death.

Comparison was made between the main clinical associations and later outcome of the treated and untreated infants. This was particularly related to background EEG abnormality, which (as a sensitive index of cerebral dysfunction) may permit closer comparison of infants with equivalent degrees of neurological compromise. For this purpose background activity was classed as normal or abnormal. Abnormal background activity was further subclassified as moderately abnormal (categories 1a, 1b, and 2a) or showing major abnormality (categories 2b, 3a, and 3b).

Results

Of the 55 infants with EEG seizures, 31 were treated with anticonvulsant drugs; 30 of these had clinical signs. Twenty four were not treated, only two of whom had clinical signs.

RESPONSE OF EEG AND CLINICAL SEIZURES TO ANTICONVULSANT DRUGS

Of the 31 infants treated, a complete response was found in only two, and another six had an equivocal response. Thirteen had cessation of clinical signs but persistent EEG seizures, and the remaining 10 showed neither EEG nor clinical response.

Responses of individual anticonvulsants (table 1)

Phenobarbitone was used as the first drug of choice in all 31 infants, but achieved complete EEG and clinical response in only two. Equivocal EEG and clinical responses were found in another two infants, and a further six showed apparent clinical response with persistent EEG seizures. The commonest finding, however, was a complete lack of EEG or clinical response and this occurred in the remaining 21 infants treated with phenobarbitone. Only one of these infants had a plasma phenobarbitone concentration below the therapeutic range.

No subsequent anticonvulsant drug produced complete EEG and clinical response. Paraldehyde was used in 15 infants, four of whom had equivocal EEG and clinical responses, two showed clinical response with EEG persistence, and nine had neither EEG nor clinical response. Phenytoin was given to six infants of whom one showed a clinical response with EEG persistence, and the other five

had neither EEG nor clinical response. Diazepam was given to seven infants, of whom four showed a clinical response with EEG persistence; the remaining three showed neither EEG nor clinical response. Pyridoxine was also given without EEG or clinical effect to all infants with persistent clinical seizures.

Anticonvulsant response and background EEG activity (table 2)

Of the eight infants with complete or equivocal responses, five had background EEG activity that was either normal or showed only excessive discontinuity as an isolated abnormality. In contrast, of the 23 infants with unresponsive EEG seizures with or without clinical response, only four had the above features while the remaining 19 had more severe abnormalities.

Association of anticonvulsant response and clinical neurological outcome (table 3)

Both infants who responded completely to anticonvulsant drugs had no subsequent persistent abnormality. Of 19 infants who showed equivocal responses or persistent EEG seizures after clinical response, two had a completely normal outcome and one had only transient dystonia, but three had

Table 1 *Responses of 31 infants to specific anticonvulsant drugs (59 doses)*

Response	*Anticonvulsant drug*				*Total No*
	Phenobarbitone (n=31)	*Paraldehyde (n=15)*	*Phenytoin (n=6)*	*Diazepam (n=7)*	
Complete EEG and clinical	2	0	0	0	2
Equivocal	2	4	0	0	6
No clinical, persistent EEG	6	2	1	4	13
No response	21	9	5	3	38

Table 2 *Response to anticonvulsant drugs in 31 patients with background EEG activity*

Response	*Background EEG activity*							*Total No*
	Normal	*Abnormal*						
		1		*2*		*3*		
		a	*b*	*a*	*b*	*a*	*b*	
Complete EEG plus clinical	0	2	0	0	0	0	0	2
Equivocal EEG plus clinical	2	0	1	0	2	1	0	6
No clinical, persistent EEG	0	0	2	2	2	6	1	13
No response	0	0	2	0	0	5	3	10

Table 3 *Response to anticonvulsant treatment and clinical response in 31 patients*

Response	*Clinical neurological outcome*				*Total No*
	Normal (n=2)	*Dystonia (n=3)*	*Major abnormality (n=6)*	*Death (n=20)*	
Complete EEG and clinical	0	2	0	0	2
Equivocal	1	0	1	4	6
No clinical, persistent EEG	1	1	2	9	13
No response	0	0	3	7	10

major neurological abnormalities and the remaining 13 died. Of 10 infants who showed no EEG or clinical responses, seven died, and the three survivors all had major neurological abnormalities.

COMPARISON OF TREATED AND UNTREATED INFANTS (TABLE 4)

The 31 treated and 24 untreated infants differed in several respects. The treated group, with the exception of one infant, had clinical signs and EEG seizures. The exception was a baby boy who was paralysed for ventilation and was treated after a specific request for EEG data from his clinician. In the untreated group only two infants had clinical seizures, and these were not treated because they rapidly resolved. The treated group were also generally more mature (table 4).

Clinical neurological outcome did not differ significantly between the treated and untreated group. The incidence of normal outcome and major abnormality in survivors was similar (table 5). There were more infants with transient dystonia in the untreated group, which also had a lower mortality.

In an attempt to compare the two groups further, infants were subdivided by background EEG appearances so that those with roughly equivalent degrees of cerebral functional disturbance could be compared. All 27 infants with severe background EEG abnormalities (categories 2b and 3), of whom 20 were treated and seven were not untreated, either died or survived with major neurological abnormalities. Nineteen had lesser degrees of background abnormality, but there was no significant difference in outcome between the eight infants who were treated and the 11 who were not.

Outcome in the nine infants who had normal

Table 4 *Comparison of 31 infants treated with anticonvulsant drugs and 24 not so treated*

	Treated with anticonvulsant drugs (n=31)	*Not treated with anticonvulsant drugs (n=24)*	*Total No*
Clinical seizures:			
Present	30	2	32
Absent	1	22	23
Postmenstrual age (weeks):			
<32	8	14	22
32–37	9	5	14
>37	14	5	19
Neurological outcome:			
Normal	2	2	4
Dystonia	3	5	8
Major abnormality	6	7	13
Death	20	10	30

Table 5 *Correlation of clinical neurological outcome and presence of background EEG activity in 55 infants*

Background EEG activity	*Clinical neurological outcome*				*Total No*
	Normal (n=4)	*Dystonia (n=8)*	*Major abnormality (n=13)*	*Dead (n=30)*	
Normal:					
Treated	1	—	—	1	2
Untreated	2	3	2	—	7
Abnormal: moderate (Types 1a, 1b, 2a)					
Treated	1	3	1	4	9
Untreated	—	2	1	7	10
Abnormal: major (Types 2b, 3a, 3b)					
Treated	—	—	5	15	20
Untreated	—	—	4	3	7

background EEG activity was more difficult to compare as only two of these were treated, one of whom died and the other who was abnormal. Of the seven untreated infants, two had a normal outcome, three showed only transient dystonia, and the other two survived with major neurological abnormalities.

Discussion

Although widely used in clinical practice, the efficacy of anticonvulsant drugs in the newborn has never been assessed by controlled trials.[19] In this study we found that the response of neonatal seizures to anticonvulsant drugs was disappointing, and this was especially apparent when the results of continuous EEG monitoring were taken into account. This unexpectedly poor response could be due to population bias in that most of our infants were preterm with major haemorrhagic or ischaemic lesions, and the infants born at full term with hypoxic-ischaemic encephalopathy were largely referrals from other units and thus already preselected for severity.

Poor response to anticonvulsant drugs may be either an intrinsic feature of such lesions in infants of particular states of maturity, or be related to the specific treatment regimen used. The relative importance of these factors, however, is difficult to assess because of the limited understanding of mechanisms determining seizure generation and control in the newborn.[19–22] Previous studies have produced conflicting reports of the benefit of high dose barbiturate treatment to long term outcome.[23 24] Our own findings suggest that phenobarbitone, used as initial treatment in conventional dosage in all infants, was of little or no benefit to most of those treated. None of the other agents were any more effective, but were only used in the more refractory cases and not as initial treatment. A comparative study of alternative sequences of drugs used in the present regimen might determine whether paraldehyde, phenytoin, or diazepam was more effective as drug of first choice. If these proved equally ineffective, alternatives might be sought among anticonvulsant drugs already in established use in older subjects.

Another surprising feature of this study was the absence of any significant difference in neurological outcome in infants with EEG seizures whether treated or not treated with anticonvulsant drugs. Interpretation of this finding must be done with caution because the untreated infants were not recruited and randomised as a formal control group. In particular, they consisted almost entirely of infants without clinical manifestations of EEG seizure activity. Nevertheless, even if different pathophysiological mechanisms cause EEG seizures, with and without clinical manifestations, we have shown elsewhere[2] that they are equally associated with important cerebral lesions. Background EEG activity is an acknowledged index of the degree of cerebral dysfunction,[8–13] even in the presence of commonly used anticonvulsant drugs within the therapeutic range[25 26]; it may thus be of value in comparing treated and untreated infants with equivalent degrees of cerebral dysfunction and help to compensate for imbalances between the groups. In this way we have at least shown that those with extremely abnormal background EEG activity had an equally poor neurological outcome, irrespective of whether they received anticonvulsant drugs, and that those with moderately abnormal background activity derived no clear benefit from treatment.

The effect of anticonvulsant drugs on outcome was more difficult to assess in the nine infants with normal background activity, which is usually associated with normal outcome.[2 8–12] There may be some grounds for concern at the finding of major neurological abnormality in two of seven untreated infants, despite this comparatively favourable prognostic feature. Further study of a larger number of cases may identify a potential advantage to treatment in this group.

On the basis of these findings, the nature and severity of the underlying cerebral lesions seem to be the main determinants of both the frequency and duration of associated seizure activity and the subsequent neurological outcome of the infant. Its implications for neonatal practice suggest that more critical review is needed of both clinical and nonclinical seizures, of the balance between anticipated benefits of the use of anticonvulsant drugs, and their recognised adverse effects, particularly in infants with established cerebral lesions.

Further research may thus optimally be aimed at management of the primary lesion, including assessment of new agents for limiting its progress, such as glutamate antagonists,[27] rather than undertaking exhaustive comparative studies of available anticonvulsant drugs. In any further study, the use of continuous EEG monitoring for accurate diagnosis of seizures and their response to treatment would be essential.

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