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Short report

Phenobarbitone in previously untreated epilepsy

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SUMMARY In a prospective study we used phenobarbitone to treat 13 new patients with epilepsy (eight adults and five children). Full seizure control was achieved in 11 patients and poor compliance was documented in one of the remaining two patients (in both of whom seizures were reduced by over 50%). Doses sufficient to give mean steady state plasma levels of more than 43 μmol/l (10 μg/ml) appeared to be associated with better seizure control than lower doses. No serious side effects were observed.

A variety of widely differing figures have been proposed as the therapeutic range of plasma phenobarbitone in epilepsy, such as 43–86 μmol/l (10–20 μg/ml),[1] 66–122 μmol/l (15–40 μg/ml),[2] and 43–302 μmol/l (10–70 μg/ml).[3] These figures have been based on reports that a mean level of 43 μmol/l (10 μg/ml) reduced the incidence of paroxysmal activity in the EEG by 90%,[4] that a level of 66 μmol/l (15 μg/ml) prevents febrile convulsions,[5] and from retrospective observations in well-controlled patients, rather than prospective studies correlating blood levels with seizure control in epilepsy.

We have studied the efficacy of phenobarbitone when it is used alone in newly diagnosed epilepsy. In addition, by selecting an initial dose which gave plasma levels at the lower end of the range(s) which have been suggested as effective, and monitoring levels frequently, we have attempted to determine the optimum dosage and plasma levels of phenobarbitone for this type of patient. When we began this investigation there was no published study of any anticonvulsant in previously untreated patients with epilepsy. This deficiency has since been made good in the case of phenytoin and carbamazepine.[6 7]

Patients and methods

Over a period of 15 months, when consent was obtained, all patients beginning treatment for epilepsy (excluding petit mal) were randomly allocated one of five anticonvulsants. Sixteen patients began with phenobarbitone but three failed to complete the study for reasons unrelated to the efficacy or side effects of the drug and these have not been included in the results.

The population studied comprised five children (all female, age range six to 14 years, mean age 10·6 years) and eight adults (six males and two females, age range 17 to 70 years, mean age 39·6 years). Of the 13 patients nine had generalised tonic-clonic seizures only and two had complex partial seizures only. One patient had partial seizures with simple and complex symptomatology (compound forms) and one patient suffered from both complex partial and secondary generalised seizures.

All patients had two or more seizures before treatment. During the six months immediately prior to treatment five patients had only one seizure, four patients had two seizures, and four patients had between three and 25 seizures each. The duration of epilepsy at the time treatment began ranged from three months to seven years. No adult had any additional neurological lesion, one child was educationally backward, and all were outpatients.

In our protocol we chose an initial dose range of 1·0–1·5 mg/kg for adult patients and 1·5–3·0 mg/kg for children. One adult was given a higher initial dosage (2 mg/kg) in error, but we decided not to reduce this. The patients were seen one week and three weeks after commencing treatment. Subsequently they were seen monthly until

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the end of the ninth month and three-monthly thereafter. At each visit the occurrence of seizures or side effects of treatment were noted and blood was drawn for determination of plasma phenobarbitone by GLC, using the method of Rogers *et al.*[8] Where any patient's seizures continued after treatment began (allowing time for steady state plasma levels to be attained) the dosage of phenobarbitone was increased. At the time of assessment the mean duration of follow up was 11 months (range 8–13 months). All our patients took phenobarbitone tablets, in two or three devided doses each day.

Results

Seizure control Of the 13 patients treated, 11 became free of seizures during the period of follow-up, and two had a marked (>50%) reduction in seizures.

Nine of the 11 who became seizure-free had no further seizures after treatment was initiated. Two patients (nos 10 and 11) had further seizures while on their initial dose of phenobarbitone, but had no further seizures during a long period (>6 months in both cases) using a slightly higher dosage. Both the patients with a >50% reduction in seizures had frequent attacks (13 in six months and six in six months) before treatment. One of these two considered herself so much improved after treatment began that she failed to follow dosage instructions and this was reflected in the blood levels observed (patient No 13).

Table *Doses, plasma levels, and outcome of treatment*

Patient no	*Age (yr)*	*Doses used (mg/kg)*	*Steady state plasma levels (μmol/l)*			*Outcome of treatment*
			Range	*Mean*	*SD±*	
1	34	1·1	43–73	53	11·0	Seizure free throughout
2	44	1·2–2·9*	60–142			
3	28	1·3	39–60	48	8·0	
4	61	1·4	43–103	64	20·0	
5	17	1·5	34–56	48	5·3	
6	22	2·0†	39–91	59	19·1	
7	14	1·6	26–52	39	8·4	
8	9	2·1	39–60	49	8·9	
9	6	2·6	56–89	66	7·9	
10	10	(a) 1·6	26–43	35	7·0	No seizures after dosage adjustment (a to b)
		(b) 1·9	30–52	44	8·2	
11	14	(a) 1·6	30–52	43	6·8	
		(b) 2·4	43–60	52	8·6	
12	41	1·0–1·75	52–86			Seizure frequency reduced (by >50%)
13	70	1·1–2·9‡	13–60			

*Seizure free from the outset; higher doses tried in an unsuccessful attempt to prevent occasional auras.
†Became pregnant during the study; plasma levels fell by approximately 40% after this.
‡Admits poor compliance.
Conversion: SI to traditional units—plasma phenobarbitone 1μmol/l≈0·23μg/ml

Seizure control in relation to type of epilepsy Of nine patients with generalised seizure only eight were free of seizures and one (with poor compliance) was improved. Of four patients with complex partial seizures three were seizure-free and one was improved.

Plasma levels and seizure control Of the nine patients who were free of seizures throughout the entire study, all but one (No 7) had mean plasma phenobarbitone levels >48 μmol/l.

The two patients who became seizure-free after an increase in dosage had mean plasma levels on their initial dosage of 34 and 43 μmol/l. After the increase in dosage (when seizure free) their mean plasma levels were 44 and 52 μmol/l respectively.

The patient who complied poorly had a plasma level of 60 μmol/l on one occasion. Despite the prescription of doses up to 2·9 mg/kg all her other plasma levels were only in the range 13–43 μmol/l. The other patient who is improved (No 12) has had no seizure during three months between the last dosage adjustment and the time of assessment. During this time on a daily dose of 1·75 mg/kg, his plasma levels have been in the range 69–86 μmol/l. With lower doses of phenobarbitone (1·0–1·6 mg/kg) his blood levels were between 52 and 73 μmol/l and his seizures were much reduced.

Relationship of plasma levels to phenobarbitone dosage The doses of phenobarbitone used and plasma levels observed throughout the study are shown in the table. The relationship between mean steady state plasma levels and phenobarbitone dosage is illustrated for both adults and children in the figure (B).

Side effects No serious side effects were observed. Several patients reported sedation on commencing treatment but this was mild and transient (seven to 14 days). One adult (No 12) reports some mild sedation with a daily dose of 1·75 mg/kg (levels 69–86 μmol/l). The parents of all five children were asked to enquire from teachers concerning performance at school. One child was reported to have improved dramatically and none were noted to have disimproved during treatment.

Discussion

We feel that the results obtained with phenobarbitone in previously untreated epilepsy were very satisfactory. It appears that in such patients a

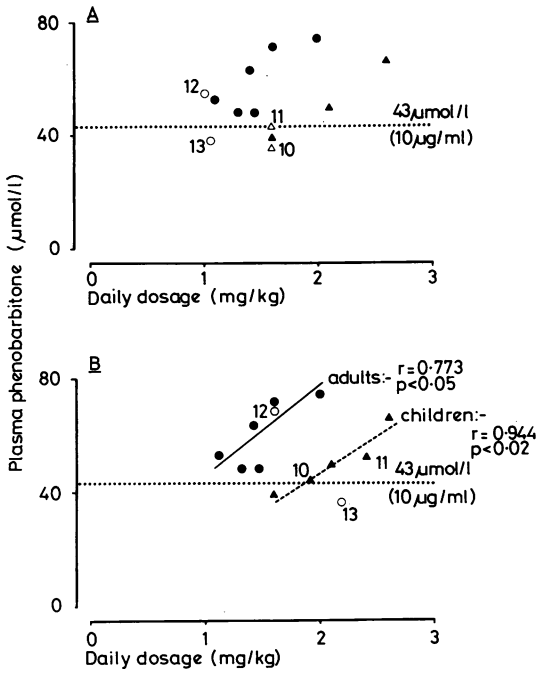

Figure *Daily phenobarbitone dosage and mean plasma levels of all patients; initially (A) and after dosage was adjusted in five patients (B). Adults: ● seizure free, ○ with seizures. Children: ▲ seizure free, △ with seizures. The four patients identified by number are: The children who became seizure-free after an increase in dosage—10 and 11. The adult with a mean level >43 μmol/l who continued to have seizures—12. The non compliant (adult) patient (who was not included when we calculated the coefficient of correlation)—13.*

success rate of 85–90% can be obtained with monotherapy, using phenobarbitone, phenytoin,[6 7 9] or carbamazepine.[6 7 10]

We cannot claim to have defined clearly a figure for the lower end of the range of plasma phenobarbitone levels which will provide full suppression of seizures in newly diagnosed patients. It may be that, as is the case with phenytoin and carbamazepine,[6 7 9 10] blood levels well below those which are usually optimum in severe and long-standing epilepsy may be consistent with full control in many new patients. However, we note that of nine patients who had mean plasma levels of 48 μmol/l or greater following the introduction of treatment, only one had any further seizures. On the other hand three of the four patients with mean plasma levels less than 44 μmol/l on their initial dose had further seizures. Furthermore two of these three later became free of seizures following a small increase in dosage (and plasma levels), while in the remaining patient adequate levels were not attained, owing to poor compliance. We would now recommend an initial dosage of phenobarbitone sufficient to produce steady state levels in the range 50–65 μmol/l. This would be approximately 1·5 mg/kg for an adult and between 2·5 and 3·0 mg/kg in the child over 6 years.

Our results are in accord with previous observations on the relationship of plasma phenobarbitone levels to dosage in both adults[11 12] and children.[13] It appears reasonable to assume that if we had used a minimum initial dosage of 2·5 mg/kg for the children they might all have been fully controlled from the outset. In addition to showing that there is little individual variation in the relationship of plasma level to phenobarbitone dosage (once age is taken into account) our results also show that plasma levels in the individual patient remain remarkably constant during prolonged treatment. We believe that during monotherapy measurement of phenobarbitone plasma levels is unnecessary except where compliance is in doubt. This may constitute an advantage of phenobarbitone over phenytoin as an initial treatment in epilepsy.

From an examination of the literature we conclude that the efficacy of phenobarbitone in complex partial (temporal lobe) seizures has not been adequately studied. As we only studied four patients with this type of epilepsy we cannot reach any firm conclusions, but we are forced to question the previous view that temporal lobe seizures "do not respond to and may be made worse by phenobarbitone."[11] Our total number of patients was small and most of them had mild epilepsy. Relatively low doses of phenobarbitone were effective for these new patients and it is probably because of this that we did not encounter serious side effects. One of us is studying further patients, including those with more severe epilepsy, in an attempt to define an optimum range of phenobarbitone dosage and plasma levels in epilepsy.

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