

Phenobarbitone dosage in neonatal convulsions

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SUMMARY In order to find the optimal dosage schedule of phenobarbitone for neonatal convulsions, four groups of patients were studied. Twelve infants (group 1) received a mean phenobarbitone dose of 9.5 mg/kg a day given intramuscularly for 3 days followed by 5.8 mg/kg a day given intramuscularly and then orally. Six infants (group 2) received a mean intravenous loading dose of 9.5 mg/kg followed by 6.8 mg/kg a day given intramuscularly or orally. Nine infants (group 3) received a mean loading dose of 14.9 mg/kg intravenously followed by a maintenance dose of 5.9 mg/kg a day. Thirteen patients (group 4) received a mean intramuscular loading dose of 15.2 mg/kg followed by 5.9 mg/kg a day. Blood samples were taken regularly and phenobarbitone levels were determined by gas liquid chromatography. A mean intravenous or intramuscular loading dose of 15 mg/kg of phenobarbitone safely achieved therapeutic levels within 2 hours of injection and high therapeutic levels were maintained with a dose of 6 mg/kg a day.

Despite the fact that phenobarbitone has been in clinical use since 1912 and is widely regarded as the drug of choice for the management of convulsions in the neonate, recommended dosage schedules have varied widely.¹⁻⁵ Few authors provide pharmacokinetic data to support their recommendations and even in the well-researched studies of Jalling⁶ and Painter *et al.*⁷ dosage recommendations have been unsatisfactory either because of difficulty in predicting dose serum level relationships or because of excessively high mean blood levels. In this paper we reported the results of systematic studies of phenobarbitone dosage in the convulsing neonate with resultant recommendations for the appropriate use of phenobarbitone in this age group.

Patients and methods

The patients were divided into four groups receiving varying dosage regimens as follows:

Group 1. Twelve infants aged between 1 and 5 (mean 3.5) days whose birthweights were between 2000 and 3905 (mean 3145) g received a mean dose of 9.5 mg/kg a day given intramuscularly in two divided doses for 3 days. The dose was then reduced to a mean of 5.8 mg/kg a day given intramuscularly or orally. The aetiology of the seizures was: birth hypoxia 2; subarachnoid haemorrhage 1; Poland syndrome 1; ventricular septal defect and cerebral embolism 1; idiopathic 7*.

Group 2. Six infants aged between 1 and 25 (mean 10.2) days and weighing between 1650 and 3580 (mean 3053) g received a mean loading dose of 9.5 mg/kg intravenously followed by a mean maintenance dose of 6.8 mg/kg a day given intramuscularly for at least the first 6 doses and then orally or intramuscularly. The first maintenance dose was given 12 hours after the end of the infusion. The aetiology of the seizures was: birth hypoxia 2; hydrocephalus and congenital heart disease 1; prematurity and intracranial haemorrhage 1; recurrent hypoxia due to tracheo-oesophageal fistula 1; idiopathic 1*.

Group 3. Nine patients aged between 1 and 18 (mean 5.1) days and weighing between 1650 and 3980 (mean 3066) g received a mean loading dose of 14.9 mg/kg intravenously followed by a mean maintenance dose of 5.9 mg/kg a day given intramuscularly or orally in two divided doses. The aetiology of the seizures was: birth hypoxia 3; birth trauma and hypocalcaemia 2; congenital heart disease 2 (one with hypoparathyroidism and one with intracranial haemorrhage); intracranial haemorrhage 1; idiopathic 1*.

Group 4. Thirteen patients aged between 1 and 22 (mean 5.5) days and weighing between 1520 and 4085 (mean 2891) g received a mean loading dose of 15.2 mg/kg given intramuscularly followed by a mean maintenance dose of 5.9 mg/kg a day given

*Further clinical details are available on request.

orally or intramuscularly in two divided doses starting 12 hours after the loading dose. The aetiology of the seizures was: birth hypoxia 3; prematurity and sepsis 1; meningitis 1; cerebro-hepato-renal syndrome 1; chromosome defect 1; intracranial haemorrhage 1; congenital heart disease and hydrocephalus 1; congenital ascites, hypocalcaemia, and ventricular tachycardia 1; congenital hemiparesis 1; idiopathic 2*.

Patients were in neonatal intensive care units at the time of the study. Blood samples were collected at regular intervals by heel prick, venous, or arterial sampling. During intravenous infusions of phenobarbitone, the heart and respiratory rate were carefully monitored. Apart from drowsiness, no deleterious effects were noted. Plasma phenobarbitone levels were measured in batches by gas liquid chromatography using an adaptation of the method of Kallberg *et al.*^{8,9} and employing 0.1 ml aliquots of frozen plasma. The coefficient of variation of the assay was 4.2% at an actual concentration of 5 µg/ml (20 µmol/l) and 5.4% at 20 µg/ml (80 µmol/l).

Results

The plasma levels of phenobarbitone achieved by the various therapeutic regimens are plotted in Figs 1 to 4. Fig. 5 is a graph of mean levels achieved in groups 1-4.

In group 1, infants achieved a mean plasma level at 24 hours of 7.5 µg/ml (30 µmol/l) with a range of 5.5 to 11.5 µg/ml (22 to 46 µmol/l). At 72 hours, the mean level was 21 µg/ml (84 µmol/l) and the range 13.5 to 28 µg/ml (54 to 112 µmol/l). By the end of the first week values were similar and declined slowly thereafter. Thus all infants had achieved levels above 10 µg/ml (40 µmol/l) by 72 hours but only one had risen above this level by 24 hours.

In group 2, the mean intravenous infusion of 9.5 mg/kg produced a mean plasma level of 9 µg/ml (36 µmol/l). There was no significant decline in

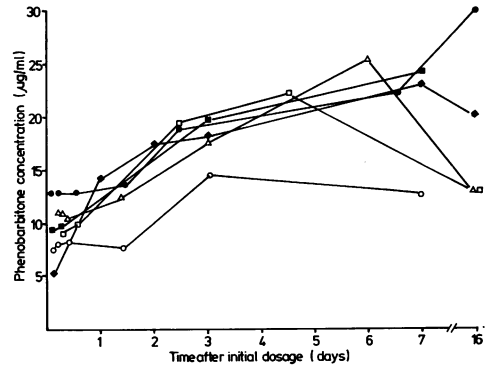


Fig. 2 Serum phenobarbitone concentrations in 6 infants of group 2.

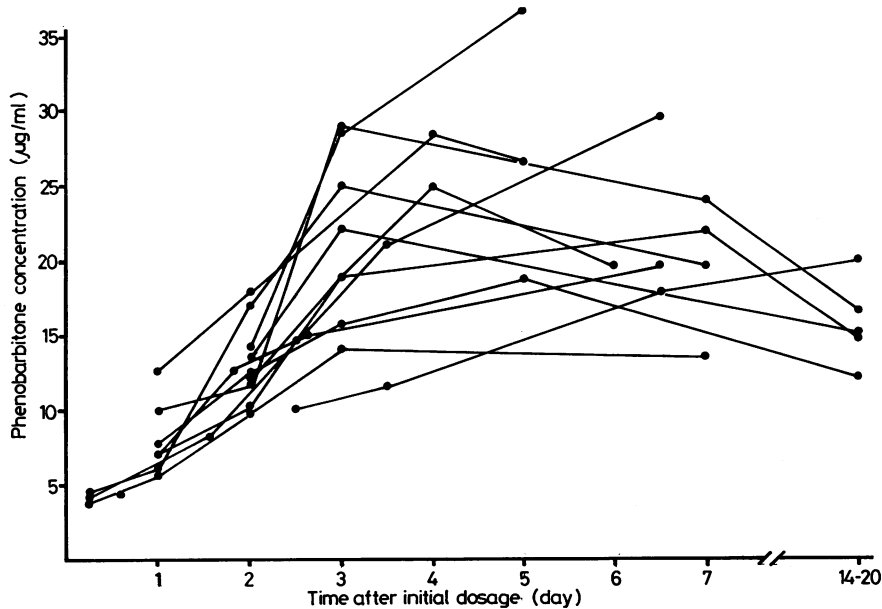


Fig. 1 Serum phenobarbitone concentrations in 12 infants of group 1.

plasma level at 12 hours. The mean plasma level was 19 $\mu\text{g/ml}$ by 72 hours (76 $\mu\text{mol/l}$) and 20.6 $\mu\text{g/ml}$ (82 $\mu\text{mol/l}$) in 4 cases at one week.

Group 3 patients achieved a mean level of 16.5 $\mu\text{g/ml}$ (66 $\mu\text{mol/l}$) within 2 hours and 17.1 $\mu\text{g/ml}$ (68 $\mu\text{mol/l}$) within 12 hours of the mean intravenous loading dose of 14.9 mg/kg; the level reached 21.9 $\mu\text{g/ml}$ (88 $\mu\text{mol/l}$) at 7 days and was well maintained at 14 days on the maintenance dose of 5.9 mg/kg.

Group 4 patients achieved a mean level of 14.2 $\mu\text{g/ml}$ (56 $\mu\text{mol/l}$) at 2 hours and 15.2 $\mu\text{g/ml}$ (66 $\mu\text{mol/l}$) at 12 hours after the mean intramuscular loading dose of 15.2 mg/kg. On the maintenance dose of 5.9 mg/kg a day, the plasma levels averaged

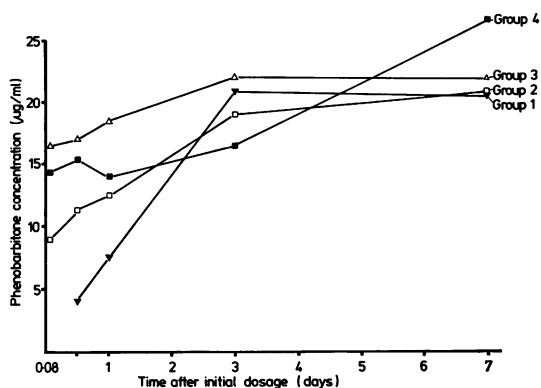


Fig. 5. Mean serum phenobarbitone concentrations at given times are plotted for each of the groups 1-4.

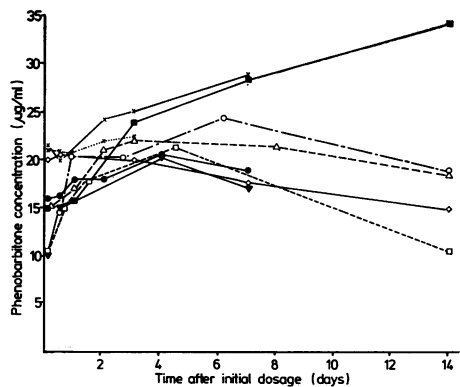


Fig. 3 Serum phenobarbitone concentrations in 9 infants of group 3.

Table Mean time to achieve seizure control

Group	Mean time to reach therapeutic levels (hours)	Mean level at 7 days ($\mu\text{g/ml}$)	Mean time to stopping fits (hours)
1	38	21	60
2	30	20.6	27
3	<2	21.9	8
4	<2	26.5	32

26.5 $\mu\text{g/ml}$ (106 $\mu\text{mol/l}$) at 7 days. One patient developed a toxic level of 75.5 $\mu\text{g/ml}$ (302 $\mu\text{mol/l}$) at one week.

Discussion

Pharmacokinetic parameters were not investigated. Values for the elimination half-life of phenobarbitone have been reported by Jalling,⁶ Painter *et al.*,⁷ Pitlick *et al.*,¹⁰ Boreus *et al.*,¹¹ and more recently by Duffy *et al.*¹² and Fischer *et al.*¹³ The elimination half-life was of the order of 104 hours after 2 weeks of treatment and decreased to about 45 hours after 4 weeks in one study.⁷ In Duffy's study the half-life declined from 112 hours at 5 days to 70 hours at over 7 days (Duffy, 1981, personal communication). The elimination half-life is shorter in preterm dysmature infants.¹⁴ The volume of distribution of the drug is between 0.71 and 0.97 litres per kg in both term and preterm infants.^{6, 10}

The recommended therapeutic range for phenobarbitone in older individuals is 10-25 $\mu\text{g/ml}$ (40-100 $\mu\text{mol/l}$). This range is based on studies of patients with chronic seizure disorders¹⁵ and there have been few attempts to correlate serum levels with seizure control in patients with seizures of very

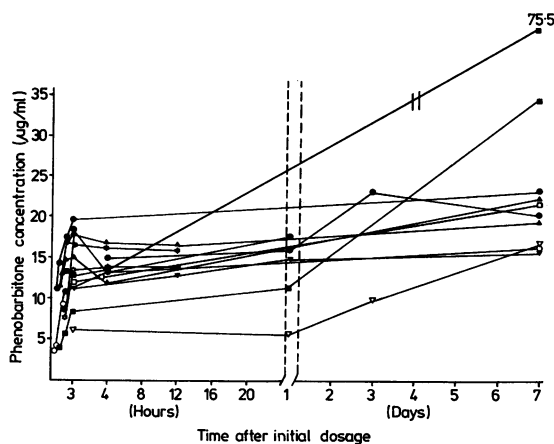


Fig. 4 Serum phenobarbitone concentrations in 13 patients of group 4.

recent onset. The assumption was made that the therapeutic range is the same in both clinical situations. Jalling⁶ studied a small number of neonates and found that convulsions ceased at serum levels between 12 and 30 $\mu\text{g/ml}$ (48 and 120 $\mu\text{mol/l}$). As expected, there was a group of convulsing patients whose seizures could not be controlled despite the achievement of levels in this range. It is unknown what effect the lower plasma protein binding of phenobarbitone in the neonate has on the therapeutic range for the drug in this age group.¹⁶

Recently Lockman *et al.*¹⁷ have reported studies in the neonate suggesting that a serum level of at least 16.9 $\mu\text{g/ml}$ was necessary to control neonatal seizures. None of the patients in the controlled group had a blood level below 16.9 $\mu\text{g/ml}$ (67.6 $\mu\text{mol/l}$) whereas those with uncontrolled seizures had levels well above and below this level. Since there were more than twice as many uncontrolled patients as controlled, their series was clearly weighted by the inclusion of an unusual number of refractory cases. In our experience some patients have been controlled at plasma levels between 7 and 15 $\mu\text{g/ml}$ (28 and 60 $\mu\text{mol/l}$). Jalling⁶ reported similar results to our own. Further study is needed to define the lower level of the therapeutic range in the neonate.

In the absence of firmer data, we elected at the start of these studies in 1975 to regard a range of 10–25 $\mu\text{g/ml}$ (40–100 $\mu\text{mol/l}$) as likely to be effective and non-toxic for the convulsing neonate and attempted to design dosage schedules that would result in the rapid achievement and maintenance of such levels with reliability.

In a preliminary study of 6 infants given the often recommended dosage of 6 mg/kg a day, we showed that only one infant achieved therapeutic levels by 72 hours. We therefore studied varying but higher dosage levels in groups 1 to 4 of the current series.

Although group 1 patients had all achieved therapeutic serum levels by 72 hours, most of them had subtherapeutic levels at 24 hours. Once achieved, serum levels were well maintained on the maintenance dose. In group 2, a mean intravenous loading dose of 9.5 mg/kg achieved serum levels close to the lower end of the therapeutic range. The mean loading dose of 15 mg/kg given either intravenously as in group 3 or intramuscularly as in group 4 achieved excellent therapeutic levels, almost immediately in group 3, and within 4 hours in group 4 (confirming the work of Jalling⁶). The levels were well maintained on the maintenance dosage of about 6 mg/kg a day for the duration of the study. Because of the occasional finding of unexpectedly high levels we recommend that a serum level should be taken on days 3 and 7 to estimate progress.

In line with the observations of Volpe² no serious side effects occurred. Many babies appeared lethargic and heavily sedated but it was often difficult to separate the effects of the anticonvulsant from those of the underlying disorder. One infant who had suffered hypoxic seizures secondary to inhalation of gastric contents secondary to an H-type tracheo-oesophageal fistula had a further episode of inhalation within a few hours of an intravenous loading dose of phenobarbitone. He suffered no serious sequelae and made a complete recovery after corrective surgery. No infant required artificial respiration as a result of phenobarbitone administration, although several were on respirators before institution of treatment with phenobarbitone. Because of the impossibility of separating the serious sequelae of the underlying condition from those of the phenobarbitone administration *per se*, it is difficult to evaluate the long-term effects of the drug itself on cerebral function and maternal-infant bonding.

Against the apparently mild adverse effects of phenobarbitone must be balanced the serious effects of status epilepticus or frequent seizures on the patient's ultimate neurological outcome.¹⁸ Experimental studies in the baboon have shown the damaging effects of convulsive status even in the presence of adequate oxygenation.¹⁹ Wasterlain²⁰ has demonstrated significant disturbances in the brain growth of immature rats subject to comparatively minor seizure states. It is possible that some of the serious sequelae of neonatal seizure states would be preventable by earlier and more vigorous treatment of the convulsions.

We therefore recommend that infants subject to frequently recurring or continuous seizures be treated with an intravenous dose of phenobarbitone of 15 mg/kg as soon as appropriate investigations for the numerous causes of neonatal convulsions are under way. In our experience, the suggested regimen of Rose and Lombroso²¹ of infusions of dextrose, calcium, and magnesium followed by an anticonvulsant is rarely appropriate. Although hypoglycaemia and hypocalcaemia must always be rapidly excluded, they are now fairly rare causes of neonatal convulsion.

If convulsions are not so frequent, an intramuscular loading dose of 15 mg/kg may be more practical. In either case, the maintenance dosage of 6 mg/kg a day may be begun 12 hours after the loading dose. Serum anticonvulsant levels should be obtained on day 3 and day 7 of therapy. If convulsions have not stopped within an hour of an intravenous loading dose or within 2 hours of an intramuscular loading dose, a further dose of 5 mg/kg of phenobarbitone might be considered or other anticonvulsants introduced. We are not able

to suggest the duration of treatment on the basis of the present study.

The currently recommended regimen appears to have advantages over that of Painter *et al.*⁷ in that the frequent very high and possibly toxic serum levels achieved in that study were rarely seen by us. We disagree with Jalling⁶ that it is difficult to construct rational maintenance dose schedules but agree that optimal dosage must be monitored by serum level estimations. Our results confirm that the rapid achievement of therapeutic levels results in earlier control of serial seizures in the newborn as shown by the shorter mean time to achieve seizure control in the groups given intravenous and high intramuscular loading doses. The possibility that the higher pulse levels created by the intravenous loading route may have advantages over the intramuscular route is currently being investigated in our unit.

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