Effect of phenobarbital on seizure frequency and mortality in childhood cerebral malaria: a randomised, controlled intervention study

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Summary

Background Seizures commonly complicate cerebral malaria and are associated with an increased risk of death and neurological sequelae. We undertook a randomised study to assess the efficacy of intramuscular phenobarbital in preventing seizures in childhood cerebral malaria.

Methods Children with cerebral malaria admitted to one hospital in Kilifi, Kenya, were randomly assigned a single intramuscular dose of phenobarbital (20 mg/kg) or identical placebo. Clinical tolerance was assessed at the start of the trial, with particular reference to respiratory depression and hypotension. Seizures were timed and recorded, and treated in a standard way. Plasma phenobarbital concentrations were measured. Analyses were by intention to treat.

Findings 440 children with cerebral malaria were admitted to the hospital; 100 were not recruited to the study. Of the remaining 340, 170 received phenobarbital and 170 placebo. The drug was adequately absorbed and well tolerated. Seizure frequency was significantly lower in the phenobarbital group than in the placebo group (18 [11%] vs 46 [27%]) children had three or more seizures of any duration; odds ratio 0.32 [95% CI 0.18–0.58]) but mortality was doubled (30 [18%] vs 14 [8%] deaths; 2.39 [1.28–4.64]). The frequency of respiratory arrest was higher in the phenobarbital group than in the placebo group, and mortality was greatly increased in children who received phenobarbital plus three or more doses of diazepam (odds ratio 31.7 [1.2–814]).

Interpretation In children with cerebral malaria, phenobarbital 20 mg/kg provides highly effective seizure prophylaxis but is associated with an unacceptable increase in mortality. Use of this dose cannot, therefore, be recommended.

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Introduction

Every year, more than one million children in sub-Saharan Africa die or are disabled as a result of cerebral malaria.1 Seizures complicate a high proportion of cases and are associated with an increased risk of death2 and neurological sequelae.3,4 The most common sequelae are hemiplegia, spastic quadriplegia, visual impairment, and epilepsy,5 but a much wider range of motor and cognitive impairments occurs. If anticonvulsant prophylaxis can lower the frequency of seizures complicating cerebral malaria, this benefit might in turn reduce the risk of death and neurological sequelae, and have an important impact on the educational potential of children in sub-Saharan Africa.

Phenobarbital has been used as an anticonvulsant for many years, and is highly effective in the treatment of both partial and generalised seizures.6 It is cheap and, unlike most anticonvulsant drugs used for seizure prophylaxis, widely available throughout Africa. It can be given by intramuscular injection, which is a further advantage, since intravenous therapy is not possible in many health facilities throughout the continent. The loading dose recommended for children is 10–20 mg/kg.7,8

There have been two previous studies of phenobarbital prophylaxis in cerebral malaria. In a small, randomised study on adults in Thailand, three of 24 patients treated with a single dose of phenobarbital (3.5 mg/kg) had seizures after admission to hospital, compared with 13 of 24 given placebo.9 However, in a pharmacokinetic study on Kenyan children with cerebral malaria,10 phenobarbital 10 mg/kg did not produce blood concentrations (15 mg/L and above) known to provide effective prophylaxis against febrile seizures.11,12

We undertook a randomised, placebo-controlled study to assess whether a single intramuscular dose of phenobarbital (20 mg/kg) given on admission to Kenyan children with cerebral malaria could lower the frequency of seizures complicating the clinical course in hospital. The safety and clinical tolerance of this dose were assessed at the start of the trial.

Methods

Study participants

The study took place at the Kenya Medical Research Institute (KEMRI) unit, at Kilifi District Hospital, on the coast of Kenya. The hospital serves a predominantly rural population, and about 3000 children are admitted to the 35-bed paediatric ward each year. Malaria transmission (of which over 95% is Plasmodium falciparum) occurs throughout the year, with peak transmission after the rainy seasons of April to May and October to November.13

The study was approved by the Kenyan National Ethical Committee. Informed, written consent was obtained from first-degree relatives in all cases.
440 children admitted with cerebral malaria

100 not recruited
63 consent refused
23 death imminent
14 insufficient staff available

340 randomised

170 assigned phenobarbital
8 met criteria for exclusion
30 died
9 lost to follow-up

170 assigned placebo
3 met criteria for exclusion
14 died
12 lost to follow-up

170 analysed for primary endpoint
(seizures)

170 analysed for primary endpoint
(seizures)

Figure 1: Trial profile

Eligible children were aged 9 months to 13 years and had cerebral malaria defined as unrousable coma (inability to localise a painful stimulus; Blantyre score 3 or less) in the presence of *Plasmodium falciparum* parasitaemia, detected by light microscopy. Children who had had seizures before admission were assessed a minimum of 30 min after the end of seizure activity. We excluded children who had pre-existing afebrile epilepsy or significant neurodevelopmental problems, those who had received treatment with phenobarbital or phenytoin during the current illness, and those found on lumbar puncture to have meningitis.

**Design and procedures**

We calculated, assuming 90% power and a significance level of 5%, that a sample size of 320 children would be required to detect a 50% reduction (from 30% to 15%) in seizures occurring before recovery of consciousness in the phenobarbital-treated group. The seizure categories judged to be of particular clinical importance were: three or more seizures of any duration; any seizure lasting for 5 min or longer; and any episode of status epilepticus (defined as seizure activity lasting for 30 min or longer, or six or more seizures within a period of 2 h).

By means of a sequentially numbered register and as soon as possible after admission, children were randomly assigned a single intramuscular injection of phenobarbital 20 mg/kg (200 g/L), or the same volume (0·1 mL/kg) placebo. The placebo, 90% propylene glycol (the vehicle for parenteral preparations of phenobarbital), had the same viscosity and colour as the phenobarbital preparation. Numbered 5 mL ampoules of phenobarbital and placebo were prepared by the pharmacy department of Torbay Hospital, Torbay, UK. The code identifying drug and placebo was kept at Torbay Hospital, and therefore none of the clinical or scientific staff involved in the study knew which patients had received phenobarbital.

Since previous work had shown an increased frequency of seizures among younger children with cerebral malaria, randomisation was stratified into two age-groups (24 months or younger and above 24 months).

The clinical tolerance of phenobarbital 20 mg/kg was assessed at the start of the trial. 23 children were given the study drug (phenobarbital or placebo) by constant-rate intravenous infusion over 4 h instead of by intramuscular injection. The intravenous route was chosen because the infusion could have been stopped if any adverse events had occurred. As in the main study, the clinical investigators were unaware of which patients had received phenobarbital. Pulse, respiratory rate, blood pressure, and transcutaneous oxygen saturation were measured at baseline and every 30 min for 5 h. Blood was taken at the same times for measurement of phenobarbital concentration, and every 1 h for venous gas and lactate measurements. The trial was then unmasked for these 23 patients only, and the phenobarbital and placebo groups compared in terms of all clinical and biochemical findings.

Baseline blood samples were taken for quantitative parasite count, full blood count, measurement of glucose, electrolyte, and phenobarbital concentrations, blood gases, and blood culture. Further blood samples for phenobarbital measurements were taken from all patients at 1 h, 2 h, 4 h, 8 h, 12 h, 24 h, 36 h, and 48 h. Parasite counts were repeated every 8 h until discharge, death, or clearance of parasitaemia. Since intracranial hypertension is a feature of cerebral malaria, lumbar puncture was delayed until the neurological status of the child had improved, or was done post mortem for those who died. Cerebrospinal fluid was assessed by microscopy and culture, and all samples with a white-cell count of above 10 cells per µL were screened for antigens of *Haemophilus influenzae* and *Streptococcus pneumoniae*.

Children received antimalarial chemotherapy with a loading dose of intravenous quinine dihydrochloride (15 mg/kg), and subsequent doses of 10 mg/kg every 12 h. All children were treated with intravenous benzylpenicillin (60 mg/kg every 6 h) and chloramphenicol (25 mg/kg every 6 h) until the results of lumbar puncture were available. Intravenous fluids and blood were given as clinically indicated. Children with rectal temperatures above 38·5°C were treated with paracetamol (15 mg/kg per rectum every 6 h). Hypoglycaemia (blood glucose below 2·2 mmol/L) was corrected with a slow intravenous bolus of 0·5 g/kg dextrose. The number and duration of all seizures were recorded by means of timers preset to alarm at 5 min, 15 min, and 30 min. Seizures lasting for 5 min or longer were treated with diazepam 0·3 mg/kg, given as an intravenous injection over 2 min. After two doses of diazepam had been given without improvement, intramuscular paraldehyde 0·2 mL/kg was used as second-line therapy. Anticonvulsants were administered at 5 min, 15 min, 30 min, and 45 min if seizure activity persisted. Phenytoin 20 mg/kg was infused intravenously over 20 min if a child had received two doses of both diazepam and paraldehyde without resolution, or had experienced six or more seizures within 2 h. Vital signs (temperature, pulse, respiratory rate, transcutaneous oxygen saturation), Blantyre coma score, and blood glucose (BM Stix, Roche Diagnostics, Lewes, East Sussex, UK) were monitored every 4 h. Oxygen was available if required, but there were no facilities for artificial ventilation.

All patients were neurologically examined at the time of discharge from hospital. All patients were asked to return 3 months later for full neurodevelopmental assessment.

Serial blood samples were taken from all patients for phenobarbital assay. Whole-blood phenobarbital concentrations were measured in Nairobi, Kenya, by reverse-phase high-performance liquid chromatography. Patients in whom no phenobarbital was detected in the blood samples taken at 1 h, 2 h, and 4 h were assumed to have received placebo. Correct assignation was verified at the end of the study when the code had been broken. We derived pharmacokinetic variables (maximum concentration, time to maximum concentration, and area under the concentration/time curve [AUC 0–12]) after every ten profiles on patients who had received phenobarbital. Since there was very little variability in the data, with no significant change in the mean derived pharmacokinetic profiles as numbers increased, we decided that profiles on 50 patients would provide a good representation of the phenobarbital group as a whole. In this way, we avoided the cost and time of assaying samples from all 170 children who received phenobarbital.
Demographic and Clinical Features

The placebo and phenobarbital groups were matched in terms of most clinical and laboratory variables (table 1). 28% of the children (49 placebo, 45 phenobarbital), had previously had a febrile illness complicated by seizures. During the current illness, a significantly higher proportion of children assigned placebo had had seizures before admission (table 1; p=0.04). The difference in the proportions of children who had been given a dose of diazepam during the 6 h before admission was not, however, significant (43 [25%] placebo, 32 [19%] phenobarbital; p=0.19).

Clinical tolerance

Among the 23 children (ten phenobarbital, 13 placebo) assessed for clinical tolerance, baseline clinical and biochemical characteristics were similar in both groups (p>0.40 for all comparisons). There were no significant differences between the groups in the mean change between baseline and 5 h or baseline and maximum or minimum values for any of the variables measured (p=0.07 for fall in lactate 0–5 h and maximum rise in pH, p=0.10 for all other comparisons).

Pharmacokinetics

Whole-blood concentrations of phenobarbital obtained by intramuscular injection and intravenous infusion of 20 mg/kg are shown in figure 2. Intramuscular injection (n=50) resulted in a median maximum concentration of 25.6 mg/L (IQR 23.6–30.2). Median time to maximum concentration was 4.0 h (2.0–12.0). Concentrations were maintained above 15 mg/L, which is within the range (10–30 mg/L) thought to provide effective seizure prophylaxis for at least 48 h. The mean AUC0–12 after intramuscular injection was 250 mg h L–1 (95% CI 232–268). Maximum phenobarbital concentrations were slightly lower in eight children who died than in 42 survivors (median 25.1 [range 15.3–33.1] vs 26.6 [10.0–44.9] mg/L). There were no significant differences in pharmacokinetic variables between survivors and those who died (p>0.4 for all comparisons), but numbers are small.

For technical reasons, we could obtain pharmacokinetic profiles on only four of the ten children.
who had received phenobarbital by intravenous infusion. The mean AUC$_{0-12}$ after intravenous infusion was 196.2 mg h L$^{-1}$ (95% CI 154.1–238.4). The difference in AUC$_{0-12}$ between the intravenous and intramuscular routes of administration was of borderline statistical significance (p=0.05).

**Outcomes**

213 (63%) of the 340 patients achieved parasite clearance before discharge or death. The placebo and phenobarbital groups did not differ in the median time to parasite clearance (40.0 [IQR 31.5–52.8] vs 45.7 [30.6–63.0] h; p=0.21). There was no difference between the groups in the time taken to recover consciousness (the ability to localise a painful stimulus; figure 3, p=0.39, log-rank test).

Phenobarbital provided effective seizure prophylaxis, decreasing the frequency and duration of seizures by over 50% (table 2). Multivariate logistic regression analysis, with allowance for the slight excess of children in the placebo group who had a history of seizures before admission, did not affect this finding. Significantly fewer children assigned phenobarbital than of those assigned placebo subsequently required treatment with phenytoin (14/170 [8.2%] vs 27/170 [15.9%], p=0.04).

Mortality among children assigned phenobarbital was more than double that of the placebo group (table 2). Of the 44 children who died, 30 were in the phenobarbital group, compared with 14 in the placebo group (odds ratio 2.39 [95% CI 1.28–4.46], p=0.01). Use of multivariate logistic regression analysis showed that this difference could not be accounted for by minor imbalances in risk factors between the groups. Median time from drug administration to death was 22.5 h (range 0.4–92.7) for children in the phenobarbital group and 24.2 h (0.4–66.7) for those in the placebo group (p=0.72). Kaplan-Meier curves, comparing overall survival in the two groups, are shown in figure 3.

Children who died were, on admission, more deeply comatose and significantly more dehydrated, acidotic, and hypoglycaemic than those who survived (p<0.01 for all variables). Among children who died, mean admission respiratory rate was higher in the placebo group than in the phenobarbital group (57 [95% CI 50–64] vs 41 [41–52], p=0.03). However, respiratory rate at 4 h (median time to maximum phenobarbital concentration) was similar for the two groups (47 [41–43] vs 48 [43–53], p=0.76). There were no other significant differences between the groups in admission clinical or laboratory characteristics.

33 children had a respiratory arrest (cessation of breathing in the presence of normal cardiac function) during their clinical course in hospital; of these 30 died. Of the 33 who had a respiratory arrest, 22 had received phenobarbital and 11 placebo (odds ratio 2.1 [95%CI 1.0–4.5], p=0.05). In analyses according to total diazepam dose (in four categories; this total included doses given in the 6 h before admission, plus all doses given in hospital), the odds of death for children treated with phenobarbital rose from 0.2 for those given fewer than three doses of diazepam to 1.7 for those given three...
We found that a single intramuscular dose of phenobarbital or placebo, and diazepam category (fewer than three doses/three or more doses) was then examined by logistic regression and the likelihood ratio test. Diazepam category alone was not significantly associated with an increased risk of death (odds ratio 0·55 [0·07–4·48], p=0·5). The interaction between diazepam category and drug group (phenobarbital or placebo) was, however, associated with a greatly increased risk of death (16·5 [1·3–215], p=0·03). The likelihood ratio test, comparing the logistic regression models with and without the interaction term, was significant (p=0·015) and, after adjustment for the interaction between drug group and diazepam category, the effect of phenobarbital on death became nonsignificant (odds ratio 1·92 [0·94–3·91], p=0·07). Table 3 compares the difference in mortality between the phenobarbital and placebo groups after fewer than three and three or more doses of diazepam. The excess mortality in the phenobarbital group may be partly accounted for by the interaction between phenobarbital and multiple (three or more) doses of diazepam. This suggestion is consistent with the hypothesis that the increased mortality is due to respiratory depression.

51 (17%) children had neurological sequelae at discharge from hospital. Although the proportion of children with sequelae was lower in the phenobarbital group than in the placebo group (table 2), the difference was of borderline significance (p=0·06). Of 275 children seen 3 months after discharge, 24 (9%) had persistent sequelae (table 2). Of these, six children (one phenobarbital, five placebo) who were blind, with spastic quadriplegia and global developmental delay, were judged to have severe sequelae. The remaining 18 children (eight phenobarbital, ten placebo) had one or more of hemiplegia, epilepsy, ataxia, visual impairment, delayed speech.

Discussion

There are many reasons why anticonvulsant prophylaxis is likely to be beneficial in childhood cerebral malaria. There is clinical and experimental evidence that long-duration, uncontrolled seizure activity can damage the brain.21,22 Seizures complicating cerebral malaria are associated with an increased risk of neurological sequelae,3–5 and survivors can have substantial cognitive problems.

Experimental evidence suggests that phenobarbital can prevent structural damage resulting from uncontrolled seizure activity within the developing brain.21,22 We found that a single intramuscular dose of phenobarbital was effective in preventing seizures in children with cerebral malaria. We emphasise, however, that the clinical conditions of this study, with rapid treatment and close observation of all children with seizures, are very different from those that prevail in many hospitals throughout Africa. Inadequate staffing and paucity of drugs and equipment mean that children may have seizures for many hours without adequate treatment, so increasing the attendant morbidity and mortality.

In this study, the unacceptable price of effective seizure prophylaxis was the doubling of mortality in the phenobarbital group. The most plausible explanation is that phenobarbital-induced respiratory depression precipitated respiratory arrest in a group of children who were critically dependent on their respiratory drive (and for whom ventilatory support was not available). This hypothesis is supported by the findings that respiratory arrest was more likely in the phenobarbital group, and that mortality was higher among children treated with both phenobarbital and several doses of diazepam. This was, however, a post-hoc analysis on a very small number of patients (of the 16 “excess deaths” in the phenobarbital group, only five of these children received three or more doses of diazepam), and should, therefore, be interpreted with caution. Children who continue to have seizures despite phenobarbital prophylaxis represent a subgroup with particularly refractory cerebral pathology, and may be unusually susceptible to further sedation. The apparent reduction in neurological sequelae among children treated with phenobarbital may reflect the higher mortality in that group; those who died might, had they survived, have had a high frequency of sequelae.

Intravenous diazepam is the drug of first choice for the immediate treatment of status epilepticus, because of its ease of administration and rapid onset of action.4 This drug is highly lipid soluble and is rapidly distributed to cerebral tissue and lipid stores. After repeated administration, redistribution ceases as tissue stores equilibrate, and further doses result in high, persistent concentrations within the brain, and the consequent risk of sudden respiratory arrest and hypotension. In contrast, two controlled studies have shown that phenobarbital, is highly effective in the treatment of status epilepticus, with no associated increase in respiratory depression or hypotension.21,22 A retrospective review of children with refractory status epilepticus, who had been treated with phenobarbital (30–120 mg/kg),23 showed a striking lack of respiratory depression. Published case reports suggest that the combination of phenobarbital and diazepam may result in respiratory depression and hypotension,24,25 and this study documents an increase in mortality resulting from concomitant use of the two drugs.

Other drug interactions should be considered, since all children were treated with quinine, benzylpenicillin, chloramphenicol, and, in most cases, paracetamol. Winstanley and colleagues10 found that, in children with severe malaria, intravenous quinine did not affect the disposition of intramuscular phenobarbital. We know of no evidence that benzylpenicillin, chloramphenicol, or paracetamol may interfere with the action of phenobarbital.

Is there a dose of phenobarbital that is both safe and effective in childhood cerebral malaria? Phenobarbital is said to provide effective seizure prophylaxis at plasma concentrations of between 10 and 30 mg/L. Plasma concentrations may, however, vary widely between individuals given the same dose,26 a finding confirmed in this study. In addition, phenobarbital has a pKa of 7·2, and changes in body pH therefore affect the distribution and excretion of the drug. If the pH of the blood is lower than that of the brain, the gradient will

<table>
<thead>
<tr>
<th>Diazepam doses</th>
<th>Placebo</th>
<th>Phenobarbital</th>
<th>Odds ratio (95% CI)</th>
<th>p</th>
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<tr>
<td>&lt;3 doses</td>
<td>13/150 (9%)</td>
<td>25/162 (15%)</td>
<td>1·9 (0·9–3·9)</td>
<td>0·07</td>
</tr>
<tr>
<td>≥3 doses</td>
<td>1/20 (5%)</td>
<td>5/8 (62%)</td>
<td>31·7 (1·2–814)</td>
<td>0·001</td>
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Table 3: Mortality in phenobarbital and placebo groups, according to number of doses of diazepam or more doses (p=0·004 for unequal odds). The relation between death and the interaction between drug group (phenobarbital or placebo) and diazepam category (fewer than three doses/three or more doses) was then examined by logistic regression and the likelihood ratio test.
favour movement of phenobarbital into the brain. Status epilepticus disrupts the blood-brain barrier, increasing cerebral uptake of phenobarbital even further. The relation between plasma concentration and effect in cerebral malaria could be different from that in other disorders without generalised cerebral pathology. Effective anticonvulsant prophylaxis might result from plasma concentrations of phenobarbital generally judged subtherapeutic. Phenobarbital 3.5 mg/kg provided effective seizure prophylaxis in adults with cerebral malaria. Phenobarbital 10 mg/kg, in a larger study, might prove effective in childhood cerebral malaria, despite blood concentrations below the "therapeutic" cut-off of 15 mg/L.

Other therapeutic options, such as magnesium sulphate, should be explored in children with cerebral malaria. Once a drug that is both safe and effective has been found, the next step would be to establish, in a sufficiently large study, whether seizure prophylaxis can lower the frequency of neurological sequelae complicating this devastating disease.

Contributors
Jane Crawley was responsible for trial design and coordination, clinical care of patients, data reduction, and statistical analysis. Catherine Waruiru, Sadik Mithwani, and Isiah Mwangi were responsible for clinical care of patients and data collection. William Winstanley was responsible for phenobarbital assays and calculation of derived pharmacokinetic data. David Ouma was responsible for phenobarbital assays. Peter Wynstanley was involved in trial design, pharmacokinetics, and clinical tolerance. Timothy Peto was trial monitor and gave statistical advice. Kevin Marsh was involved in trial design, clinical care of patients, and data collection. Jane Crawley prepared the paper, which was then critically appraised by all the other investigators.

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