# Pharmacokinetics and clinical effect of phenobarbital in children with severe falciparum malaria and convulsions

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***Aims*** Phenobarbital is commonly used to treat status epilepticus in resource-poor countries. Although a dose of 20 mg $kg^{-1}$ is recommended, this dose, administered intramuscularly (i.m.) for prophylaxis, is associated with an increase in mortality in children with cerebral malaria. We evaluated a 15-mg $kg^{-1}$ intravenous (i.v.) dose of phenobarbital to determine its pharmacokinetics and clinical effects in children with severe falciparum malaria and status epilepticus.

***Methods*** Twelve children (M/F: 11/1), aged 7–62 months, received a loading dose of phenobarbital (15 mg $kg^{-1}$) as an i.v. infusion over 20 min and maintenance dose of 5 mg $kg^{-1}$ at 24 and 48 h later. The duration of convulsions and their recurrence were recorded. Vital signs were monitored. Plasma and cerebrospinal fluid (CSF) phenobarbital concentrations were measured with an Abbott TDx FLx® fluorescence polarisation immunoassay analyser (Abbott Laboratories, Diagnostic Division, Abbott Park, IL, USA). Simulations were performed to predict the optimum dosage regimen that would maintain plasma phenobarbital concentrations between 15 and 20 mg $l^{-1}$ for 72 h.

***Results*** All the children achieved plasma concentrations above 15 mg $l^{-1}$ by the end of the infusion. Mean (95% confidence interval or median and range for $C_{max}$) pharmacokinetic parameters were: area under curve [AUC (0, ∞)]: 4259 (3169, 5448) mg $l^{-1}$.h, $t\frac{1}{2}$: 82.9 (62, 103) h, CL: 5.8 (4.4, 7.3) ml $kg^{-1}$ $h^{-1}$, $V_{ss}$: 0.8 (0.7, 0.9) l $kg^{-1}$, CSF: plasma phenobarbital concentration ratio: 0.7 (0.5, 0.8; $n$ = 6) and $C_{max}$: 19.9 (17.9–27.9) mg $l^{-1}$. Eight of the children had their convulsions controlled and none of them had recurrence of convulsions. Simulations suggested that a loading dose of 15 mg $kg^{-1}$ followed by two maintenance doses of 2.5 mg $kg^{-1}$ at 24 h and 48 h would maintain plasma phenobarbital concentrations between 16.4 and 20 mg $l^{-1}$ for 72 h.

***Conclusions*** Phenobarbital, given as an i.v. loading dose, 15 mg $kg^{-1}$, achieves maximum plasma concentrations of greater than 15 mg $l^{-1}$ with good clinical effect and no significant adverse events in children with severe falciparum malaria. A maintenance dose of 2.5 mg $kg^{-1}$ at 24 h and 48 h was predicted to be sufficient to maintain concentrations of 15–20 mg $l^{-1}$ for 72 h, and may be a suitable regimen for treatment of convulsions in these children.

*Keywords:* children, malaria, pharmacokinetics, phenobarbital, status epilepticus

## Introduction

Status epilepticus is common in children with cerebral malaria and is associated with a poor outcome [1]. In resource-poor countries, an anticonvulsant that controls seizures and prevents recurrence would be ideal. Diazepam is useful in status epilepticus, but it does not offer prophylaxis following single-dose administration [2], whereas multiple doses can cause respiratory depression [3]. Phenobarbital would be ideal for use in resource-poor countries, since it is cheap, readily available, fast-acting and can be administered i.m. at peripheral health facilities with few resources. At a dose of 10 mg $kg^{-1}$ i.m.,

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phenobarbital does not prevent seizures in children with cerebral malaria [4]. However, a dose of 20 mg $kg^{-1}$ i.m., producing plasma concentrations of 10–30 mg $l^{-1}$ reduces the number of seizures, but is associated with an increase in mortality, especially in those children who received diazepam [3].

The optimum dose of phenobarbital for the treatment and prophylaxis of seizures in children with cerebral malaria is still unknown. In this study, we examined the pharmacokinetics and clinical effects of phenobarbital following i.v. administration of a 15-mg $kg^{-1}$ loading dose and a 5-mg $kg^{-1}$ maintenance dose at 24 and 48 h in African children with severe falciparum malaria and status epilepticus.

## Methods

The study was approved by the Kenya Medical Research Institute (KEMRI) ethics Committee, and carried out at the KEMRI/Wellcome Trust high dependency Unit at the Kilifi District Hospital on the Kenyan Coast.

### *Subjects*

Children were recruited into the study if they: (i) were aged between 6 months and 13 years, (ii) had signs of severe malaria (prostration, deep breathing and coma [5]), (iii) had status epilepticus defined as a prolonged convulsion lasting ≥ 15 min, which did not respond to 2 doses of diazepam given 5 min apart or a single dose of paraldehyde and diazepam given 5 min apart, or three or more short convulsions lasting less than 5 min, in 2 h. A parent or guardian gave written informed consent for children to participate. Children were recruited with intent to treat. They were excluded if they had a history of epilepsy and had received phenobarbital prior to admission to hospital, or if the pre-dose sample contained detectable phenobarbital.

### *Study protocol*

This was an open-label non-randomised study. A clinical history was taken and physical examination performed on all of the children on admission. Venous access was obtained by inserting Teflon cannulae (Jelco™, Ethicon S.p.A, Italy), one for i.v. administration of fluids and drugs, and another in the opposite arm for blood sampling. Blood (6 ml) was drawn for a quantitative parasite count, blood culture, measurement of blood glucose, electrolytes, total plasma proteins, albumin and a differential blood count. A portion of the blood was centrifuged (1500 *g*; 3 min) and plasma was stored at −20 °C until assayed for pre-dose phenobarbital concentrations. The clinical management of the patients has been described elsewhere [2].

A specifically designed proforma was used to record the characteristics of the convulsions (number, type, duration, lowest oxygen saturation and blood glucose during the convulsion) and a 5-min postictal evaluation of the level of consciousness, respiratory rate and transcutaneous oxygen saturation. Convulsions were first treated with diazepam or paraldehyde [2] and then with phenobarbital as a second line anticonvulsant.

Phenobarbital sodium (Laboratory & Allied Ltd, Nairobi, Kenya; 15 mg $kg^{-1}$) was infused over 20 min followed by a maintenance dose of 5 mg $kg^{-1}$ at 24 and for 48 h after the loading dose. Children who did not respond to phenobarbital were treated with phenytoin (Faulding Pharmaceuticals Plc., Queensway Royal, Lemington Spa, Warwickshire, UK), diluted with normal saline to a final concentration of 8 mg $ml^{-1}$ and infused over 20 min. Status epilepticus not terminated by phenobarbital and phenytoin, was treated with thiopentone (Rotecmidica GmbH, Trittau, Germany), administered as 4 mg $kg^{-1}$ bolus over 30 s, followed by a maintenance dose (4 mg $kg^{-1}$ $h^{-1}$) infused over 2 h under close medical supervision. If a child had recurrence of convulsions within the 24 h observation period after stopping phenobarbital, a daily maintenance dose at 5 mg $kg^{-1}$ was restarted and the child discharged home on the same maintenance dose of phenobarbital but given orally.

### *Blood and CSF sampling*

Blood samples (0.4 ml) were taken at 10, 20, 25, 30, 40, 60 min, and 2, 6, 12, 24, 36, 48, 54, 60 and 72 h after the loading dose. Another 0.4 ml was taken 5 min after administration of the maintenance dose at 24 and 48 h. The cannula was flushed with 1 ml sterile heparinisted (20 i.u. $ml^{-1}$) normal saline after each sample collection. Residual saline in the cannula was removed before each sample was withdrawn. The blood was collected in lithium heparin tubes and centrifuged immediately (1500 ***g***; 3 min) at room temperature. Plasma was stored in polyvinyl vials at −20 °C until analysis for phenobarbital. An additional blood sample (1.5 ml) obtained 0.3 h post-phenobarbital loading dose was used to obtain plasma for the determination of unbound phenobarbital. An aliquot (1 ml) was placed in a Centrifree® micropartition filter unit (Amicon Inc., Beverly, MA, USA) and centrifuged at 4 °C (1500 ***g***; 15 min) to obtain plasma water. An aliquot of CSF (100 μl) was also collected and stored at −20 °C in those patients who underwent lumbar puncture (to exclude central nervous system infections) after administration of phenobarbital. In the latter patients, phenobarbital was measured in the CSF and in a concomitant plasma sample.


 

*Clinical measurements*

Heart rate, blood pressure, respiratory rate, transcutaneous oxygen saturation and level of consciousness were recorded at the time of each blood sample. In addition, the number, duration and pattern of convulsions were recorded. Temperature, pulse, level of consciousness (Blantyre coma score and Adelaide coma score [6] and papillary light reaction) were monitored every 4 h. Some children had middle cerebral artery blood flow measurements performed. Hypotension was defined as a mean blood pressure of less than 50 mmHg, respiratory depression as a respiratory rate of less than 20 breaths $min^{-1}$, transcutaneous oxygen saturation of less than 96%, and bradycardia as a heart rate of less than 80 beats $min^{-1}$. All patients were requested to come for review three months after discharge to monitor the development of any neurological sequelae (convulsions, hearing loss, speech disorders, behavioural disorders, paraparesis, paraplegia and blindness).

*Clinical outcome definitions*

A prolonged convulsion was considered terminated if it stopped within 30 min from the start of phenobarbital infusion. Convulsions were considered to be controlled if patients did not require another anticonvulsant for 24 h after phenobarbital administration.

*Analytical procedures and pharmacokinetic analysis*

Plasma phenobarbital concentrations were determined in 50 µl plasma using the Abbott TDx FLx® fluorescence polarisation immunoassay analyser (Abbott Laboratories, Diagnostics Division, Abbott Park, IL, USA). Calibration curves were prepared using the phenobarbital calibrators supplied by the manufacturer, with concentrations of 0, 5, 10, 20, 40 and 80 mg $l^{-1}$. Quality control (QC) samples at low (LQC), medium (MQC) and high (HQC) concentrations spanning the calibration curve range, were assayed together with the patient samples. At least one of the QC samples was included in each run. The target (range) concentrations for the QC samples were 15.0 (13.5–16.5), 30.0 (27.0–33.0) and 50.0 (45.0–55.0) mg $l^{-1}$ for the LQC, MQC and HQC samples, respectively. The limit of detection for phenobarbital was 1.1 mg $l^{-1}$. Between-run coefficients of variation (CV) were 0.98% ($n = 5$), 1.10% ($n = 6$) and 2.16% ($n = 4$) for the LQC, MQC and HQC samples, respectively. Accuracy values for the same QC samples were 3.84%, 0.87% and 3.85%, respectively. The assay is reported to be specific for phenobarbital, with minimal cross-reactivity with the major metabolite of phenobarbital, p-hydroxyphenobarbital.

The area under the plasma phenobarbital concentration-time curve (AUC), total body clearance (CL), steady state volume of distribution ($V_{ss}$) and elimination half-life were determined by noncompartmental analysis using the pharmacokinetic programme TopFit [7]. Maximum plasma phenobarbital concentration ($C_{max}$) achieved after the loading dose and the corresponding time ($t_{max}$) were noted directly. We used the mean estimated pharmacokinetic parameters to simulate the dosage regimen that would maintain concentrations between 15 and 20 mg $1^{-1}$ for 72 h. For the simulations, a one-compartment model with slow i.v. input and first order elimination was used. The loading dose was taken to be 15 mg $kg^{-1}$, and maintenance doses varied from 1.8 to 5.0 mg $kg^{-1}$, which covers the range previously used in paediatric patients administered phenobarbital i.v [8–13].

*Statistical analysis*

Pharmacokinetic parameters (except $C_{max}$ and $t_{max}$) were expressed as the means and the corresponding 95% confidence intervals (CI), calculated with CIA software [14]. $C_{max}$ and the corresponding $t_{max}$ were expressed as medians (range).

## Results

Twelve children (11 males, one female), median age 25 months (range: 7–62 months) with mean body weight of 10.7 kg (95% CI: 9.6–11.7 kg) were recruited into the study. The mean (95% CI) biochemical measurements on admission were: albumin 31.4 (27.2, 35.6) g $l^{-1}$, total plasma proteins 60 (56.9, 63.1) g $l^{-1}$, haemoglobin 5.9 (4.6, 7.2) g $dl^{-1}$, creatinine 56.0 (39.0, 73.0) µmol $l^{-1}$, blood glucose 5.1 (3.96, 6.30) mmol $l^{-1}$ and blood pH 7.34 (7.27, 7.40). These values were typical for children suffering from cerebral malaria [2].

The pharmacokinetic parameters are shown in Table 1. All the children had achieved a plasma phenobarbital concentration of greater than 10 mg $l^{-1}$ within 10 min, and peak concentrations of more than 15 mg $l^{-1}$ were maintained for 24 h before the first maintenance dose. After administration of the second maintenance dose at 48 h, peak concentrations exceeded 20 mg $l^{-1}$ (Figure 1).

Simulations indicated that a loading dose of 15 mg $kg^{-1}$, followed by two maintenance doses of 2.5 mg $kg^{-1}$ administered at 24 h and 48 h would maintain concentration between 15 and 20 mg $l^{-1}$ for 72 h (Figure 1), which would be sufficient for anticonvulsant prophylaxis.

Only one child had an episode of hypoxia after phenobarbital administration and this occurred at 20 min after the start of infusion and 10 min postictal. The child

**Table 1** Pharmacokinetic parameters for phenobarbital following administration of intravenous phenobarbital (15 mg kg$^{-1}$ over 20 min followed by a 5-mg kg$^{-1}$ maintenance dose at 24 and 48 h) in children with severe malaria and status epilepticus.

| *Parameter* | *Number of children* | *Mean (95% CI) or median (range)‡* |
|---|---|---|
| CL (ml h$^{-1}$ kg $^{-1}$) | 8 | 5.8 (4.4, 7.3) |
| $V_{ss}$(1 kg$^{-1}$) | 8 | 0.79 (0.67, 0.90) |
| AUC (0,∞) (μg ml$^{-1}$ h) | 8 | 4259 (3169, 5448) |
| Fraction unbound ($f_u$) | 11 | 0.48 (0.40, 0.56) |
| CSF:plasma phenobarbital ratio | 7 | 0.66 (0.54, 0.78) |
| $C_{max}$ (μg ml$^{-1}$)‡ | 8 | 19.9 (17.9–27.9) |
| $t_{max}$ (h)‡ | 8 | 0.33 (0.33–2.0) |

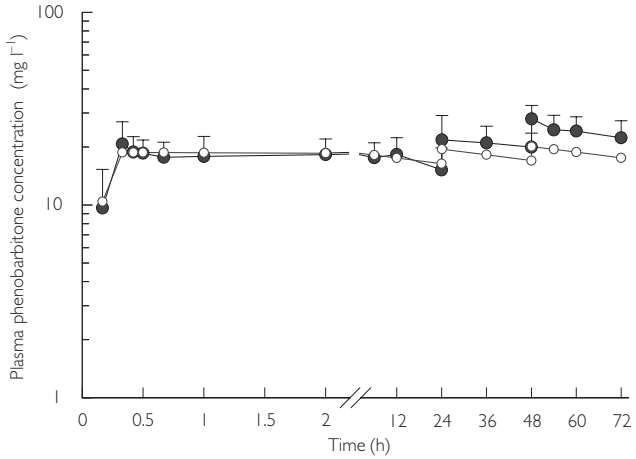


**Figure 1** Measured (closed circles; $n$ = 12) and simulated (open circles) plasma phenobarbital concentrations (mg 1$^{-1}$) following administration of intravenous phenobarbital (a 15-mg kg$^{-1}$ loading dose infused over 20 min followed by 5 mg kg$^{-1}$ maintenance dose at 24 and 48 h (measured) or a 2.5-mg kg$^{-1}$ (simulated) maintenance dose at 24 and 48 h, in children with severe malaria and status epilepticus.

was hypoxic (oxygen saturation 94%), hypothermic (rectal temperature 35.2 °C) and acidotic (with a base deficit of −16.7) before phenobarbital administration. None of the children had respiratory depression or marked changes in blood pressure, heart rate or middle cerebral artery blood flow.

Convulsions were controlled in 66% (8/12) of the 12 children and there were no cases of neurological sequelae on follow up. There were no significant differences in biochemical measurements on admission between those children in whom convulsions were controlled and those who did not respond to treatment with phenobarbital. One child who later died had numerous convulsions prior to hospitalisation and a total of 24 convulsions while on the ward of which eight were after phenobarbital administration. The convulsions lasted less than 5 min and were accompanied by posturing (hyperextension) and at times assumed an opisthotonic position. The child had hyperaemic retinal disc and later developed retinal haemorrhages with loss of optic disc margins in both eyes. He also had bilateral lung crackles. His haemoglobin (Hb) dropped from 5.6 to 4.7 g dl$^{-1}$ within 12 h and he was transfused with whole blood. About 25 h after admission and 23 h after phenobarbital infusion, he had respiratory failure with elevated blood pressure (132/90 mmHg) but otherwise normal cardiovascular status (pulse 197 min$^{-1}$ and oxygen saturation 97%). However, 30 min later he suffered a cardiac arrest. The cause of respiratory failure could have been multifactorial as the child had positive signs of intracranial hypertension and intractable seizures.

## Discussion

We have shown that a 15-mg kg$^{-1}$ loading dose of phenobarbital, followed by two maintenance doses of 5 mg kg$^{-1}$ achieve the expected therapeutic plasma concentrations of 10–30 mg l$^{-1}$ in children with severe falciparum malaria and status epilepticus. All the children achieved plasma phenobarbital concentrations of greater than 10 mg l$^{-1}$ within 10 min after the loading dose, and peak phenobarbital plasma concentrations of greater than 15 mg l$^{-1}$. Mean clearance, steady state volume of distribution, fraction unbound and CSF:plasma ratio were comparable to reported values in paediatric patients [11, 15–17], whereas the mean elimination half-life was comparable to values previously reported in children with severe malaria [4].

The pharmacokinetics and clinical effects of i.m. phenobarbital administered for seizure prophylaxis have been studied previously in children with severe malaria. At a dose of 10 mg kg$^{-1}$ maximum plasma phenobarbital concentrations greater than 15 mg l$^{-1}$ were attained in few patients and the incidence of seizures was not reduced compared with controls given no phenobarbital [4]. In a second study, at a higher (20 mg kg$^{-1}$) i.m. dose, maximum concentrations of approximately 25 mg l$^{-1}$ were achieved in most patients, and the incidence of seizures was significantly lower on the phenobarbital group. However, mortality was also higher in phenobarbital treated patients compared to the control group given placebo [3].

In the present study, phenobarbital was administered i.v. for control of seizures. Median peak concentrations were approximately 20 mg l$^{-1}$, but following administration of the second maintenance dose, peak concentrations were approximately 25 mg l$^{-1}$. Although the i.v. regimen was well tolerated by all patients in the present study and all the seizures were controlled, peak concentrations were too high in some patients following administration of the second maintenance dose.


 

From the present and the two previous studies in children with severe malaria, it appears that a regimen that would achieve and maintain phenobarbital concentrations at approximately 20 mg $l^{-1}$ might be effective for seizure control or prophylaxis, and also be associated with few adverse effects. With pharmacokinetic parameters derived in the present study, we determined that 15 mg $kg^{-1}$ i.v. loading dose followed by a maintenance dose of 2.5 mg $kg^{-1}$ at 24 h and 48 h would achieve and maintain plasma phenobarbital concentrations at approximately 20 mg $l^{-1}$ for 72 h. Previously reported plasma phenobarbital concentrations following i.m. administration [3, 4] with simulated profiles based on slow i.v. infusions of identical doses indicated close agreement, suggesting that the proposed regimen would achieve adequate and broadly similar plasma phenobarbital concentrations following administration by either route. After correction for differences on body surface area, the maintenance dose of 2.5 mg $kg^{-1}$ calculated for children in this study is equivalent to the recommended maintenance dose of 100 mg for adults [18]. For a 70-kg adult, this is 1.43 mg $kg^{-1}$. The reason why the dose for children, expressed as mg $kg^{-1}$, is higher than the adult dose is because clearance is proportional to surface area, and the latter expressed per kilogram increases disproportionately with a decrease in weight [18].

In conclusion, we have shown that a 15-mg $kg^{-1}$ loading dose achieves peak plasma phenobarbital concentrations within the range that appears to be effective in seizure control in children with severe malaria. This dose followed by a maintenance dose of 2.5 mg $kg^{-1}$ at 24 and 48 h would achieve and maintain concentrations at approximately 20 mg $l^{-1}$ for 72 h. Larger controlled studies are needed to evaluate effectiveness (seizure control or prevention) and safety of this regimen following both i.v and i.m. administration.

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