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Prophylactic phenobarbitone in young children with severe falciparum malaria: pharmacokinetics and clinical effects

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1 A method is described for the measurement of phenobarbitone (PB) by reversed phase high performance liquid chromatography (h.p.l.c.) from small samples of whole blood dried onto filter paper strips.

2 The disposition of PB given prophylactically to young children with severe malaria on parenteral quinine is contrasted with that in aparasitaemic Kenyan children on no antimalarial drugs. There were no differences in the disposition of PB between the two groups.

3 Peak blood PB concentrations were equal to or greater than 15 mg l^{-1} in 27% of the patients on quinine and 23% of those not on quinine; a concentration of 10 mg l^{-1} was achieved or exceeded by 100% and 92% of each group, respectively, and was maintained for 39 ± 24 h (mean ± s.d.), and 33 ± 21 h, respectively.

4 In an open, dose-finding study, the progress of young children with cerebral malaria given prophylactic PB (10 mg kg^{-1}), was contrasted with that of controls given no seizure prophylaxis.

5 The drug had no apparent effect on depth or duration of coma, but neither was the incidence of seizures reduced.

6 A controlled trial of prophylactic PB in young children with cerebral malaria is needed, but a larger dose than 10 mg kg^{-1} should be studied.

Keywords phenobarbitone pharmacokinetics severe malaria

Introduction

Mortality from cerebral malaria (CM) in children ranges from 10–40% (Warrell *et al.*, 1990), and the incidence of neurological sequelae is about 10% (Molyneux *et al.*, 1989). After admission to hospital about 60% of children with CM have seizures, and these have been shown to affect outcome adversely (Molyneux *et al.*, 1989). Phenobarbitone (PB) is a cheap anticonvulsant, is widely available in the tropics, and reduces the incidence of seizures in young adult Thai with CM (when given as a single i.m. prophylactic dose of 3.5 mg kg^{-1}; White *et al.*, 1988). Prophylactic PB has now been recommended for the treatment of CM (Phillips & Solomon, 1990; Warrell *et al.*, 1990), but its value in young children with the syndrome has not been established.

Before starting a double-blind trial of PB in this population we wanted to estimate the dose with optimal risk:benefit ratio. Our initial choice of 10 mg kg^{-1} was a compromise between the low blood concentration:dose ratio of PB in children (Brachet-Liermain *et al.*, 1975) and avoidance of adverse effects in a hospital where ventilatory support is not available. Furthermore, because of the possibility that quinine, the first-line drug for treatment of severe malaria might potentiate the effects of phenobarbitone (Boulos *et al.*, 1970; Riviere & Back, 1986; Suphakanawich & Thithapanda, 1987) we also wanted to exclude this potential pharmacokinetic interaction.

Methods

Both of the studies described below were approved by the Ethics Committee of the Kenya Medical Research Institute. The parents of the children gave written informed consent.

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Pharmacokinetic study

Patients A power calculation, based on data of Perucca *et al.* (1986), suggested that 12 patients would be required in each group to detect a 15% change in the C_{max} of PB and a 25% change in its AUC value (accepting an alpha error of 0.05 and a beta error of 0.1).

Malaria patients on quinine therapy (QN group) Patients were studied if they had cerebral malaria as indicated by unrousable coma (Warrell *et al.*, 1990), or were 'prostrate' (Pasvol *et al.*, 1991), or had had two or more seizures in the 24 h before admission. Patients were excluded if consent was refused or if PB had been given before admission.

Aparasitaemic patients (No QN group) Febrile (rectal temperature > 37.5° C), aparasitaemic patients admitted to the paediatric ward were eligible for study if they had a history of two or more convulsions within 24 h of admission. Exclusion criteria were as above.

Clinical care All patients were nursed in the KEMRI intensive care unit of the hospital, where they were weighed and venous access was obtained using teflon cannulae (one for i.v. fluid and drugs and one in the other arm for blood sampling). Blood was drawn for the measurement of glucose, a full blood count and blood culture. Hypoglycaemia was corrected with 50% w/v glucose solution (0.6 ml kg^{-1} body weight) and seizures of more than 5 min duration were treated with diazepam (0.3 mg kg^{-1} i.v.).

Malaria was treated with parenteral quinine (20 mg kg^{-1} loading dose, followed by 10 mg kg^{-1} for 12 h thereafter, given i.m. or by i.v. infusion until drugs could be taken orally; Pasvol *et al.*, 1991). Aparasitaemic patients were treated with antibiotics appropriate to their diagnosis. Temperature was lowered in all patients by tepid sponging, fanning, and paracetamol (given rectally in those unable to take oral drug).

A single dose of PB (10 mg kg^{-1}; Gardenal sodium, May and Baker) was given by deep i.m. injection into the anterior thigh within 2 h of admission. At a later stage in the study, when blood drug concentration data were available and clinical experience with the drug had been obtained, the PB dose was increased to 15 mg kg^{-1}.

Blood sampling Blood (200 μl) for measurement of PB was drawn from the cannula pre-dose and at 0.5, 1.0, 1.5, 2, 4, 6, 12, 24, 48, 72, 96, 120, 144 and 168 h after dosing. The blood was mixed in lithium heparin tubes and aliquots (100 μl × 2) were transferred to filter paper as bands crossing the 2.5 × 8 cm strips. These were air dried and stored at room temperature, protected from direct sunlight.

Clinical efficacy study

Patients Patients were studied only if they had CM (Warrell *et al.*, 1990). The study was open and unrandomised. Children with CM admitted during recruitment for the above pharmacokinetic study entered the 'treatment group'; children with CM admitted after the pharmacokinetic study had closed entered the 'control group'.

Clinical care Children in the treatment group were given PB (10 mg kg^{-1}; Gardenal sodium, May and Baker) as a single i.m. injection, into the anterior thigh, within 2 h of admission. Children in the control group were given no seizure prophylaxis. Thereafter the management of both groups was identical, and was as described above. Children were examined neurologically every 6 h (when coma was assessed using a paediatric modification of the 'Glasgow coma scale'; Reilly *et al.*, 1988) until they could localise pain, and 12 hourly thereafter until discharge. Seizures of more than 5 min duration which occurred during admission were treated with i.v. diazepam (0.3 mg kg^{-1}).

Measurement

Materials Filter paper strips (Whatman chromatography paper grade 17) were a gift from Dr F. Churchill (CDC, Atlanta USA). Triethylamine (LR grade) was obtained from Fisons (Loughborough, UK). Orthophosphoric acid and methanol (both AnalaR grade) were obtained from BDH Chemicals (Poole, UK). Methanol was redistilled before use. Phenobarbitone sodium was obtained from Sigma (Poole, UK), and cyclobarbitone calcium (CB; internal standard) was a gift from Dr M. Feely (University of Leeds).

Chromatography PB was measured in Nairobi by the reversed-phase high performance liquid chromatographic method of Peaker *et al.* (1989), modified to allow measurement of the drug from filter paper-absorbed whole blood. Chromatography was performed using an Isochrom delivery system (Model No. A0099-314; Spectra Physics, San Jose, USA) equipped with a Rheodyne valve injector (fitted with a 50 μl loop) and connected to a stainless steel column (Ultrasphere ODS, 5 μm particle size, 15 cm × 4.6 mm i.d.; Beckman UK) preceded by a guard column (CN pre-column; Waters Ass., Milford, USA). The column effluent was monitored using a variable wavelength u.v. absorbance detector (model No. A0099-309a; Spectra Physics) set at 240 nm. The mobile phase comprised water/methanol (3:2 v/v) containing triethylamine (1%) adjusted to pH 7.5 with orthophosphoric acid and flowing at 2 ml min^{-1}.

Extraction The filter paper strips were cut up, incubated in phosphate buffer (pH 7.5; 5 min) with added internal standard (CB 1.0 μg) and extracted into hexane/diethyl ether (1:1 v/v; 5 ml) by vortex mixing (30 s) in glass culture tubes (10 ml capacity). After centrifugation (2000 *g* for 10 min) and separation, the organic phase was transferred to a clean tube and evaporated to dryness under nitrogen (37° C). The residue was reconstituted in mobile phase (150 μl) and aliquots (50 μl) were injected into the chromatograph. Standard curve samples comprised drug-free blood to which was added PB (concentrations range 1–20 μg ml^{-1}); aliquots (100 μl) were then transferred to filter paper strips. Drug-free blood and standard curve samples were assayed in an identical manner to the unknowns in each run.

Assay validation Assay reproducibility was assessed within-day and day-to-day (over 6 weeks) using aliquots of drug-free blood spiked with PB (4 μg ml^{-1}; $n = 6$ for both assessments). Assay precision was further assessed by the determination of duplicate plasma samples ($n = 6$) in our own laboratory (where plasma absorbed onto filter paper strips was assayed) and a laboratory in the United Kingdom (where liquid plasma was assayed after storage at −20° C, and transferred packed in dry ice).

Calculations Values of C_{max} and rt_{max} were noted from the individual plasma PB data. AUC values were calculated using the linear trapezoidal rule and values of the terminal elimination half-life by log linear regression. In the pharmacokinetic study comparisons between the 'QN' and 'no QN' groups was by Student's *t*-test; in the clinical efficacy study comparisons between the 'treatment' and 'control' groups was by the chi-square test.

Results

Pharmacokinetic study

QN group Twelve patients with severe malaria fulfilled the entry criteria (seven with CM, three prostrate, and two with two or more seizures in the 24 h before admission; five of those with CM and all three of the prostrate children had also had two or more seizures in the previous 24 h). Parasitaemia ranged from 4,000–1,281,000 μl^{-1} (geometric mean 136,406 μl^{-1}); two patients were hypoglycaemic (blood glucose < 2.2 mmol l^{-1}) at entry. Eleven patients were given PB 10 mg kg^{-1} and one was given 15 mg kg^{-1}. Four out of 12 (33%) had taken chloroquine in the week before admission.

No QN group Thirteen aparasitaemic patients fulfilled the entry criteria. Working diagnoses were: febrile convulsions ($n = 5$), anoxic brain damage ($n = 2$), lung abscess ($n = 1$), viral hepatitis ($n = 1$), pneumonia ($n = 2$), bacterial meningitis with hydrocephalus ($n = 1$) and viral encephalitis ($n = 1$); the child with viral encephalitis died 5 days after admission. Seven out of thirteen (54%) had taken chloroquine in the week before admission. All patients were given PB 10 mg kg^{-1}.

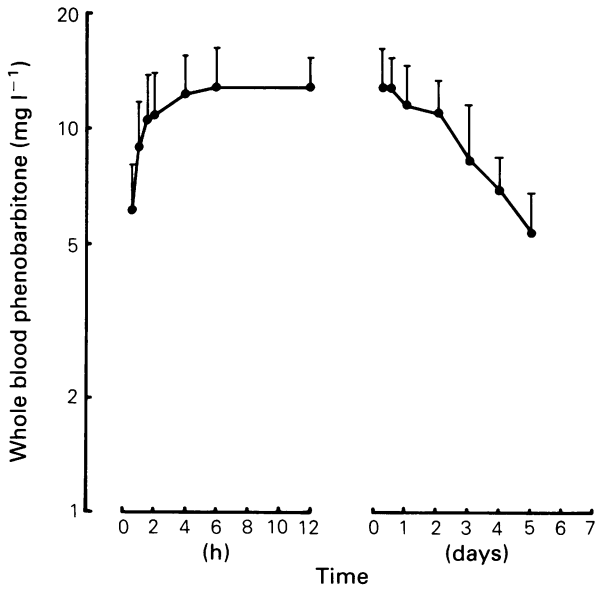

Figure 1 Mean (± s.d.) whole blood phenobarbitone concentrations in patients with severe malaria on parenteral quinine.

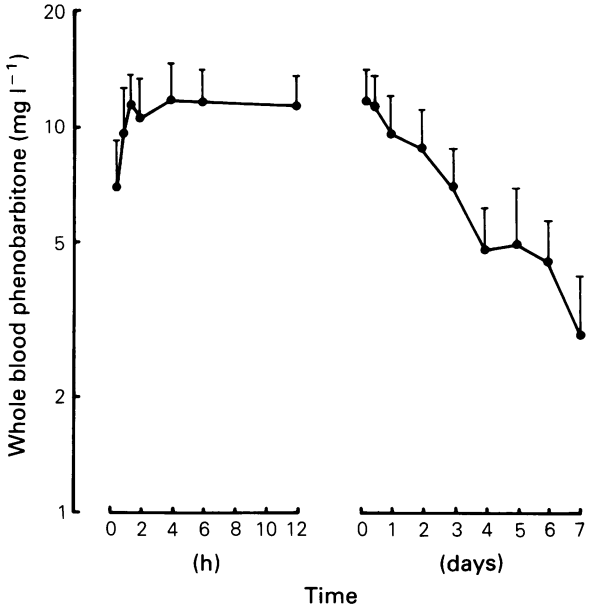

Figure 2 Mean (± s.d.) whole blood phenobarbitone concentrations in aparasitaemic patients on no antimalarial drugs.

Disposition of PB Figures 1 and 2 show mean plasma PB concentrations after PB 10 mg kg^{-1} in the two groups. Table 1 lists derived pharmacokinetic parameters. QN appeared to have no effect on the disposition of PB. Mean t_{max} values were 9 and 6 h in the 'QN' and 'no QN' groups, respectively. In those patients given PB 10 mg kg^{-1}, C_{max} exceeded 15 mg l^{-1} in 27% and 23% of patients in the 'QN' and 'no QN' groups, respectively. Similarly, in those patients given 10 mg kg^{-1}, peak PB concentrations exceeded 10 mg l^{-1} in 100% and 92% of patients, and this concentration was exceeded for 39 ± 24 h (mean ± s.d.) and 33 ± 21 h in the 'QN' and 'no QN' groups, respectively. Within the group of patients with severe malaria, there was no difference in PB disposition between those with cerebral malaria and the remainder.

Table 1 Pharmacokinetic parameters (mean ± s.d.) describing the fate of phenobarbitone in children with and without quinine therapy

	t_{max} (h)	C_{max} (mg l^{-1})	$t_{1/2}$ (h)	AUC (mg l^{-1} h)
No quinine ($n = 13$)	6 (4)	13.6 (2.3)	82.3 (23.2)	1551 (452)
Quinine therapy ($n = 12$)	9.5 (13.0)	13.6* (2.5)	85.8 (37.5)	1670* (461)
	NS	NS	NS	NS

*Excluding data from the one patient given PB 15 mg kg^{-1}.

Table 2 Admission variables of the children with cerebral malaria who entered the efficacy study

	Treatment group Phenobarbitone 10 mg kg^{-1} i.m.	*Control group No seizure prophylaxis*
n	14	39
Age (months)	43 ± 29	40 ± 22
Illness (days)	3.4 ± 1.9	3.9 ± 2.9
Number of fits in 24 h before admission	3.0 ± 3.9	2.6 ± 3.4
Rectal temperature (°C)	39.2 ± 1.0	39.0 ± 1.1
Blood glucose (mmol l^{-1})	4.3 ± 2.3	4.5 ± 2.3
Percentage hypoglycaemic (BS< 2.2 mmol l^{-1})	28.6	19.4
Parasites μl^{-1} range (geometric mean)	280–933,100 (34,368)	75–2,078,160 (92,638)

Figures are mean ± s.d. unless otherwise stated.

Table 3 Clinical progress after admission

	Treatment group Phenobarbitone 10 mg kg^{-1} i.m.	*Control group No seizure prophylaxis*
Number fitting after admission (%)	10 (71)	21 (54)
Number with fits >20 min duration (%)	1 (7)	2 (5)
Number of fits during admission*	2.5 ± 3.1	1.5 ± 2.2
Number of deaths (%)	2 (14)	9 (23)
Number of neurological sequelae (%)	2 (14)	2 (5)

* Mean ± s.d.; excluding fits of more than 20 min duration.

Clinical efficacy study

Patients Fourteen children with CM entered the 'treatment group' (six of whom also entered the pharmacokinetic study), and 39 entered the 'control group' (Table 2).

Clinical progress Figure 3 shows the change in motor response score (Reilly *et al.*, 1988) of individual patients between admission and 6 h thereafter (when drug concentration was at, or close to, C_{max} in those who had received PB). Motor score improved in 29% of the treatment group and 26% of the control group; was unchanged in 36% and 51%, respectively; worsened in 7% and 8% respectively; and was not available (because the child died, or the data were not recorded) in 29% and 13%, respectively. Excluding those who died, the time taken for children to localise pain (motor response score = 4; Reilly *et al.*, 1988) was 21 ± 19 h (mean ± s.d.; range 6–60 h) in the treatment group, and 22 ± 14 h (range 6–60 h) in the control group. There was no difference between the groups in the incidence of seizures (total or those lasting more than 20 min), number of seizures during admission or incidence of neurological sequelae (Table 3). While mortality appeared to be lower in those given PB (Table 3), the difference was not significant.

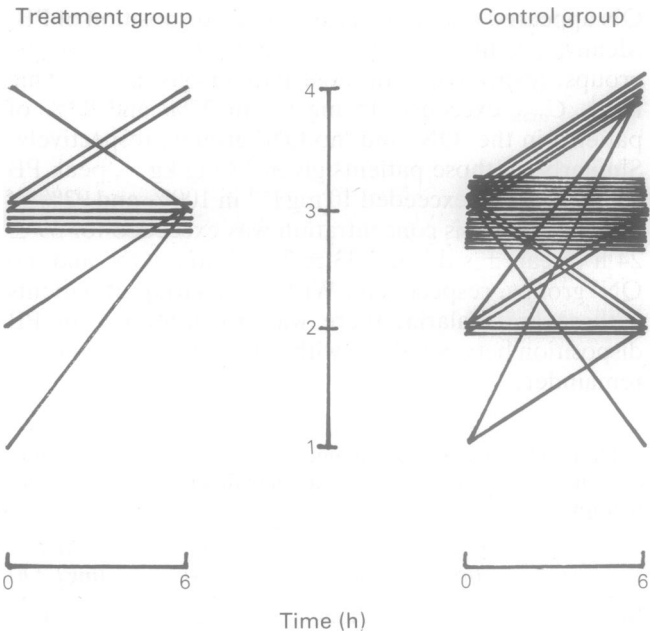

Figure 3 Changes in motor response to pain between admission (0 h) and 6 h thereafter in children with cerebral malaria given either prophylactic phenobarbitone ('treatment group'; n = 10), or no seizure prophylaxis ('control group'; n = 33). (The scale indicates the best motor response to painful pressure on the sternum: 1 = no response; 2 = extension to pain; 3 = flexion to pain; 4 = localisation of pain. Reilly *et al.*, 1988.)

Assay validation

PB and CB were resolved to baseline and were free of interference from intrinsic ligands and from the following drugs: QN, chloroquine, amodiaquine and desethylamodiaquine. Calibration curves were linear within the range 1.0–20 mg l^{-1}. The lowest measurable concentration of PB from 100 μl of filter paper-absorbed blood was 250 ng ml^{-1} (which at 0.01 AUFS produced a deflection > × 4 background noise). The coefficients of variation for the assay were 9.7% within-day and 13.1% between-day. The difference between results from duplicate samples of plasma assayed in our laboratory and the laboratory in the UK was 8.0 ± 2.3%.

Discussion

Mortality from severe falciparum malaria in children is high; for CM it remains 10–40% (Warrell *et al.*, 1990). In addition, neurological sequelae including hemiparesis, aphasia and cortical blindness were seen in 12% of the survivors in a recent series of paediatric patients with CM (Brewster *et al.*, 1990). Mortality and morbidity are both associated with seizures, especially if prolonged (Brewster *et al.*, 1990; Molyneux *et al.*, 1989), and seizures can cause aspiration, itself a cause of morbidity and mortality (Warrell *et al.*, 1982). Furthermore, seizures

increase intracranial pressure and this may persist for some time after clinical and electrical features have ceased (Minns & Brown, 1978). Newton *et al.* (1991) have recently demonstrated raised opening lumbar pressures in children with CM, and it is likely that prolonged seizures exacerbate raised intracranial pressure, increasing the risk of tentorial herniation. One aim in the therapy of severe malaria should therefore be effective anticonvulsant prophylaxis.

Prophylactic PB is attractive because it is practicable, widely available and cheap. However, although its efficacy has been demonstrated in Thailand (White *et al.*, 1988) the population studied comprised mainly young adults. The value of prophylactic PB in young children with severe malaria has not been established, and the optimal dose is unknown. We felt that the surprisingly small PB dose effective in Thai patients with CM (3.5 mg kg^{-1}; White *et al.*, 1988) was unlikely to achieve concentrations in the accepted therapeutic range (Faero *et al.*, 1972; Hvidberg & Dam, 1976; Jalling, 1974). Consequently, we opted for a higher dose. However, we were concerned to avoid worsening of coma, since ventilatory support is unavailable in our hospital. We chose to study 10 mg kg^{-1} initially, but latterly because of the apparent therapeutic failure of this dose we changed to 15 mg kg^{-1}.

Although PB is eliminated partly unchanged, about 40–60% is metabolised in the liver, mainly to para-hydroxyphenobarbitone which is pharmacologically inactive (Kallberg *et al.*, 1975; Lous, 1966; Ravn-Jonsen *et al.*, 1969). Though less potent than quinidine, QN has been shown to be an inhibitor of mixed function oxidase activity in animals, both *in vitro* and *in vivo* (Riviere & Back, 1986), and inhibits barbiturate metabolism (Suphakanawich & Thithapanda, 1987) and prolongs barbiturate sleeping time (Boulos *et al.*, 1970). Although evidence of clinically-relevant hepatic enzyme inhibition by QN in man is sparse, we wanted to exclude the possibility of potentiation of the effects of PB by QN. To do this we adapted an existing method for the assay of PB to allow sample storage on filter paper strips, which is more convenient in a tropical setting. We then used the method to study the disposition of the drug in two groups of seriously ill children—those with malaria on QN therapy, and aparasitaemic children on no antimalarial drugs.

QN had no apparent effect on the disposition of PB. The two groups of patients were as comparable as was possible, given that all patients with clinical malaria require prompt antimalarial therapy. Plasma concentrations of PB observed in the present study were similar to those reported by Brachet-Liermain *et al.* (1975), and Hvidberg and Dam (1976). The therapeutic plasma concentration range of PB in childhood CM is unknown, but 15–30 mg l^{-1} is required to prevent febrile convulsions (Faero *et al.*, 1972). Like Brachet-Liermain *et al.* (1975), we found that PB 10 mg kg^{-1} failed to achieve sustained therapeutic concentrations in the majority of patients. It is therefore perhaps not surprising that the clinical study of the drug showed a lack of effect on depth and duration of coma or on the incidence of seizures. The efficacy of PB 3.5 mg kg^{-1} in young adult Thai with CM (White *et al.*, 1988) is at variance with our findings, but the explanation may rest in differences of the pathophysiology of CM between adults and children (Newton *et al.*, 1991).

The present study of clinical efficacy was 'open' and unrandomised and, although the patients were comparable on entry and were managed identically, its results must be interpreted with caution. The benefits and risks of prophylactic PB in young children with CM must now be assessed in a controlled trial. Knowing the disposition of PB in this population and reassured that QN does not potentiate PB, and that PB 10 mg kg^{-1} i.m. neither prolongs nor deepens coma, we propose a study using 15 mg kg^{-1}. Until the results of such a trial are available, the prophylactic use of PB for young children with CM is premature.

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