File ID	442692
Filename	V: Fosphenytoin does not prevent seizures or improve outcome in African children with acute non-traumatic coma

FOSPHENYTOIN DOES NOT PREVENT SEIZURES OR IMPROVE OUTCOME IN AFRICAN CHILDREN WITH ACUTE NON-TRAUMATIC COMA

Samson Gwer[1], Richard Idro[1,2], Gregory Fegan[1,3], Edwin Chengo[1], Ayub Mpoya[1], Esther Kivaya[1], Simon Ndirangu[1], Michael Kihara[1], Juliana Otieno[4], Bernhards R. Ogutu[5], Fenella Kirkham [6,7], Charles R. Newton [1,3, 7, 8]

INSTITUTIONAL AFFILIATION

1. Centre for Geographic Medicine Research, Kenya Medical Research Institute, Kilifi, Kenya

2. Department of Paediatrics and Child Health, Mulago Teaching Hospital, Makerere University, Kampala, Uganda

3. London School of Hygiene and Tropical Medicine, London, UK

4. Kondele Children's Hospital, Kisumu, Kenya

5. The Walter Reed Centre for Clinical Research, Kenya Medical Research Institute, Kisumu, Kenya

6. Department of Child Health, Southampton General Hospital, Southampton, UK

7. Neurosciences Unit, , University College London Institute of Child Health, UK

8. Department of Psychiatry, University of Oxford, UK

Corresponding Author:
Samson Gwer,
Kenya Medical Research Institute,
P.O. Box 1515, 80108, Kilifi, Kenya
E-mail: samgwer@gmail.com
Tel: +254 722 260437
Fax: +254 41 7522390

ABSTRACT

Background

Multiple seizures are associated with death and neurological sequalae in children presenting

with acute non-traumatic coma. Prevention of seizures may help improve outcome. We

conducted a double blind placebo randomized control trial of a single intramuscular (IM)

injection of fosphenytoin to prevent seizures and neurological sequelae in Kenyan children

admitted with acute encephalopathies.

Method

We conducted this study between December 2004 and March 2009 in Kilifi District Hospital,

at the rural coast of Kenya, and in Kondele Children's Hospital in western Kenya. We

recruited children aged between 9 months and 13 years, presenting with acute non-

traumatic coma (Blantyre Coma Score ≤ 2 persisting for at least 30 minutes even after

correction of hypoglycaemia or treatment of seizure). Study participants received either

intramuscular (IM) fosphenytoin or placebo after initial resuscitation at admission, in a

randomized double-blind design. The targeted sample size was 250 for each arm. We

primarily examined for differences in frequency of seizures during admission and gross

motor deficits at discharge.

Results

We recruited 173 children [median age 2.6 (IQR 1.7, 3.7) years] into the study; 110 had

cerebral malaria, 8 acute bacterial meningitis, and 55 encephalopathies of unknown

aetiology. Eighty five children received fosphenytoin and 88 placebo. Thirty three (39%)

children who received fosphenytoin had at least one seizure during study monitoring

compared to 32 (36%) children who received placebo (P = 0.73). Use of second-line AED for

seizure treatment during the study was greater (n=30) in the fosphenytoin group compared

to the placebo group (n=18; P = 0.03). Eighteen (21%) and 15 (17%) children died in the fosphenytoin and placebo arms respectively (p=0.5). Nine of 65 children (14%) in the fosphenytoin arm had gross motor deficits at discharge compared to 14 of 73 (19%) in the placebo arm (P=0.36). There was no difference in time to regaining full consciousness. The study was terminated early because of the slowing of recruitment from a reduction in the incidence of malaria and futility during the interim analysis.

Conclusion

A single IM injection of fosphenytoin did not prevent seizures or neurological deficits in children admitted with acute encephalopathies. Larger studies taking into consideration the different aetiologies and duration of illnesses may help clarify this finding.

BACKGROUND

Acute encephalopathies in children are associated with high mortality and significant neuro-cognitive sequelae among survivors (1, 2). Seizures are common in these encephalopathies and prolonged and multiple seizures are associated with poor outcome (3, 4). This could be due to neuronal damage by excitotoxins released by repeated neuronal firing, inadequate cerebral blood flow for metabolic demand in the context of impaired cerebral-vascular auto-regulation, aggravated intracranial hypertension, and abnormal respiration and aspiration of gastric contents during seizure episodes(5, 6). Alternatively, seizures may be a marker of neurological damage rather than the cause. If seizures do cause neuronal damage, prevention of their occurrence in this group of patients may reduce mortality and neuro-cognitive sequelae.

In sub-Saharan Africa, the most common causes of acute non-traumatic encephalopathies are cerebral malaria (CM), acute bacterial meningitis (ABM) and viral encephalitides (7, 8). In CM, up to 80% of children present with a history of seizures and 60% have seizures during admission (3). A placebo controlled trial of phenobarbital (a single intramuscular (IM) injection of 20mg/Kg) as a prophylactic anti-epileptic drug (AED) in children with CM showed more than 50% reduction in the incidence of seizures in those who received phenobarbital, with a trend towards decrease in neurological sequelae (9). However, the mortality was more than double in those given phenobarbital, probably due to respiratory depression in unventilated children. Fosphenytoin is an effective anti-epileptic drug, has minimal cardio-respiratory depression, and since it is water soluble, can be given intramuscularly (IM), a useful characteristic in resource poor regions. Fosphenytoin has been used for the prevention of seizures in traumatic brain injury and in other neurosurgery patients(10). In a

preliminary pharmacokinetic study among children with severe falciparum malaria, IM fosphenytoin (18 PE/Kg) rapidly (5-20 minutes) achieved plasma unbound phenytoin concentrations within the therapeutic range and controlled status epilepticus in 64% of patients (11). In a second study in a similar group of patients, the median time to peak unbound phenytoin concentration after a single dose of I.M fosphenytoin (18 PE/Kg) was observed to be 4 hours(12). Pharmacokinetic modeling indicated that 20 mg PE/kg of I.M. fosphenytoin would provide prolonged therapeutic concentrations without toxicity. Only 30% of the children had clinical seizures compared to the expected 60% and no significant cardio-respiratory depression was noted. These initial studies supported the basis for greater examination of fosphenytoin for prevention of seizures in children with acute non-traumatic coma.

We conducted a double blind randomized control trial (ISRCTN11862726) to examine the effectiveness of a single IM injection of fosphenytoin (20 PE/Kg) in preventing seizures and improving outcome in children presenting with acute non-traumatic coma.

METHODS

Children (aged 9 months to 10 years) who were admitted with an acute encephalopathy were randomized to receive either a single I.M. injection of fosphenytoin (20 PE/Kg) or placebo (normal saline). The null hypotheses were that fosphenytoin did not have an effect on the frequency of seizures or on the prevalence of seizures, abnormal motor posturing, and neurological sequelae. The study was approved by the Kenya Medical Research Institute Ethics Review Committee (ERC).

Setting

We conducted this study at the high dependency units (HDU) of Kilifi District Hospital (KDH) and Kondele Children's Hospital (KCH). KDH is situated in the rural coast of Kenya in an area of stable malaria transmission. It has a 35-bed Paediatric unit that admits over 5000 children annually and is supported by a 7-bed HDU. KCH is a referral hospital serving Nyanza Province, a region in the west of Kenya of mostly stable malaria transmission. The hospital has a 62-bed Paediatric ward with a 7-bed HDU annexed to it.

Study Population

We recruited children aged between the age of 9 months and 13 years who were not able to localize a painful stimulus (Blantyre Coma Score (BCS) ≤ 2) even 30 minutes after treatment of a seizure or correction of hypoglycaemia. The BCS is a simple score of coma status, based on assessment of motor, verbal and eye opening, and preferred in malaria endemic areas because it better predicts outcome in children with falciparum malaria, and has better inter-observer agreement among health workers in this setting compared to the other coma scales (13). We did not consider children below the age of nine months because at that development stage they cannot localize painful stimuli, a key criterion in our assessment of coma. We excluded children with a history of epilepsy, significant developmental delay, traumatic brain injury, sickle cell disease or who had received phenytoin for treatment of seizures before presentation.

Study Duration

We started enrollment of patients in December 2004 at KDH, and in March 2008 at KCH following an application to add a second site in consideration of the low rate of recruitment at the initial site. The study was interrupted twice; between April 2006 and January 2007 and

in July 2008, due to expiry of the study drug and difficulty in replenishing. From 2007, recruitment of children with CM in KDH was done on alternate weeks to accommodate another trial (ISRCTN50258054) on severe malaria. The study was terminated on 31st March 2009 on expiry of the third batch of study drug supplies in consideration of the slow recruitment rate even after including a second site and the unlikely possibilities of observing effect and achieving the targeted sample size over the remaining duration of 9 months.

Standard Care

On admission, patients underwent initial resuscitation to manage their airway, breathing and circulation according to standard guidelines(14). Hypoglycaemia (blood sugar < 2.5mmol/L) was treated with 10% dextrose (5mls/Kg) and fever managed with paracetamol or ibuprofen. Children who had seizures lasting at least 5 minutes even after correction of hypoglycaemia received intravenous diazepam (0.3mg/Kg) and intramuscular paraldehyde (0.4mls/Kg) as first line anticonvulsants. Second line agents were intravenous phenobarbital (15mg/Kg initial dose and 2.5-5mg/Kg/day maintenance dose for at least 3 days) and sodium valproate (25mg/Kg). Intravenous thiopental (0.4mg/Kg) or midazolam (initial dose 0.3mg/Kg and maintenance 0.1mg/Kg/hour) was given if the seizures were refractory to second line anticonvulsants. Initial laboratory investigations were blood glucose, giemsa film for malaria parasitaemia, full blood count, sodium and potassium levels, creatinine, blood gas analysis and blood culture. A lumbar puncture was done when the patient was stable. All children received parenteral anti-malarial (quinine) and antimicrobial (benzyl-penicillin and chloramphenicol) therapy until otherwise guided by the results of three initial 8 hourly malaria microscopy results, and blood, urine and CSF culture results. Vital signs were

routinely monitored and recorded every four hours. Mechanical ventilatory support was not available other than bag and mask ventilation during resuscitation.

Study Procedures

After initial resuscitation and upon obtaining informed consent, the study drug (0.4ml/Kg) was administered intramuscularly on the upper lateral aspect of the right thigh. The site of injection was marked by a circle using a black marker pen to observe for local reactions. Thenceforth, vital signs were measured and documented every 10 to 20 minutes for the next 4 hours, after which the rate of monitoring was staggered to 2 hourly for four hours and then 4 hourly until discharge from the HDU. Plasma sample collected at the time of clinical and laboratory review 4 hours after administration of the study drug, and CSF samples collected at LP, were stored at -70ºC until assayed for total phenytoin concentrations. The assay method has been described before with 0.5µg/ml being the lowest measurable concentration which could be distinguished from 0(11).

Continuous electroencephalographic (EEG) monitoring was done on alternate recruitment over the initial 72 hours of observation or until the child regained consciousness, whichever was earlier. Episodes of clinical seizure episodes and abnormal motor posturing, anticonvulsant drug administration, clinical details of cardio-respiratory status, and other significant clinical events were documented on the study case report form (CRF) until the patient regained full consciousness. Adverse events (AE) were observed for and serious adverse events (SAE) reported to the Data and Safety Monitoring Board (DSMB) and the ERC within 24 hours of occurrence. An event was considered serious if it resulted in death, was life threatening, caused persistent or significant disability, or resulted in the prolongation of hospitalization. At discharge, neurological deficits were examined for and cognitive

assessment using evoked response potentials (ERP) was done. Clinical review and ERP assessment was repeated at 3 months after discharge.

Treatment Allocation and Blinding

Allocation to an intervention arm was facilitated by randomization in blocks of 50. The drug ampoules containing either fosphenytoin 250 PE (50 PE/ml) or placebo (5mls of 0.9% saline) were numbered from 1 to 500 based on this randomization. The list linking the study number to the intervention arm was retained by the DSMB. To ensure double blinding, the interventions, both colourless liquids, were presented in identical ampoules and were both administered at 0.4mls/Kg.

Analysis

Sample size determination of 250 in each study arm was based on ability to detect a 50% reduction (from 27 to 13.5%) in patients with at least one seizure, lasting not shorter than 5 minutes, allowing for a 20% loss to follow up and 90% power at the conventional 5% significance level. We recorded the study data on paper based CRFs which were then double-entered onto a Visual Foxpro ^{TM} (version 9, x) database. We analysed the data using Intercooled STATA (version 11.0, StataCorp LP, Texas USA). We examined for any significant differences in the baseline clinical and laboratory parameters between the two study sites before pooling the data. We analysed the data by intention-to-treat. The primary outcome variables were the number and prevalence of clinical seizures lasting at least 5 minutes, and the prevalence of neuro-cognitive sequelae at 3 months review. The secondary outcome variables were the prevalence of seizures of any duration, the prevalence of seizures detected by EEG monitoring, the prevalence of abnormal motor posturing, the prevalence of neuro-cognitive sequelae at discharge, mortality by discharge, the frequency of hypotension

and respiratory depression, and the prevalence of neuro-cognitive deficits at discharge and at 3 months after admission. We examined plasma and CSF phenytoin concentrations to explore the relationship between phenytoin concentrations and prevalence of seizures. We examined differences between the two arms using Chi square test and Fisher's exact test for categorical variables, and unpaired T test or Wilcoxon rank-sum test for continuous variables, the appropriateness of test being guided by the distribution of the data. We described the association between the study drugs and the outcomes using odds ratios (OR) and 95% confidence intervals (95% CI).
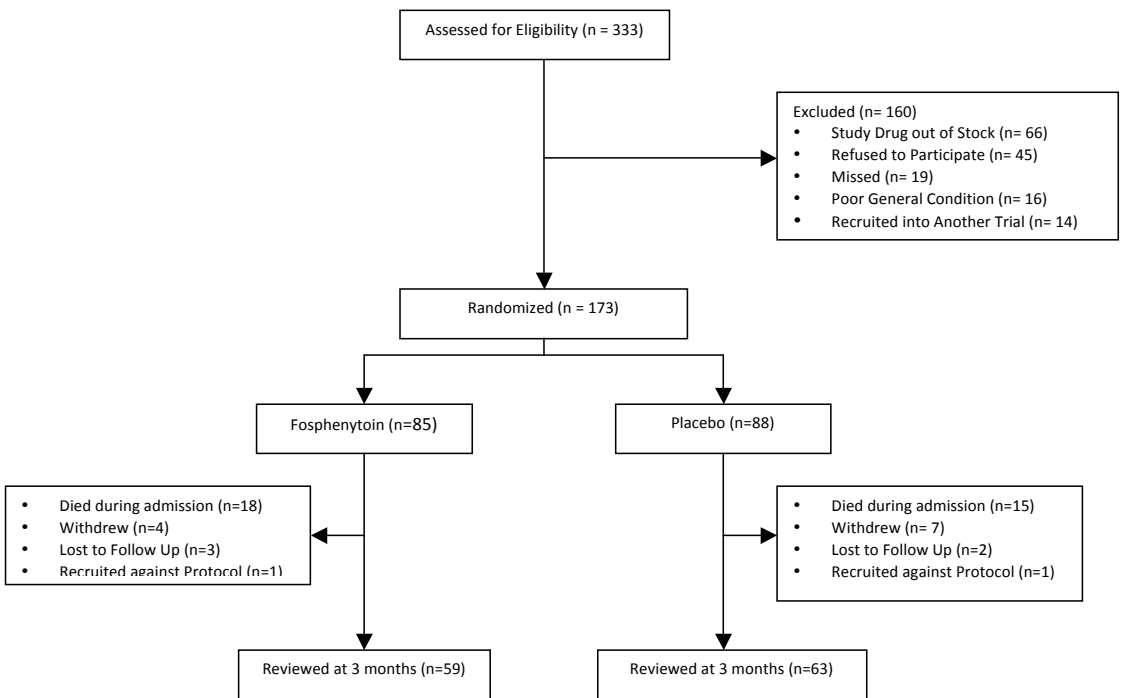
RESULTS

Figure 1: Study Flow chart. Children who were recruited against protocol were not followed up at 3 months or 2 years.

Over the study period, we recruited 173 children out of an eligible 333 children (Figure 1);
158 at the Kilifi site and 15 at the Kisumu site. They were of median age 2.6 (IQR 1.7, 3.7)
years and 72 were female. One hundred and ten (64%) children had cerebral malaria, 55
(32%) had encephalopathies of unknown aetiology (EUA), and 8 (5%) had acute bacterial
meningitis. Children with ABM and EUA had greater mortality than those with CM
(Supplementary Table 1). Children with EUA were also more likely to have neurological
deficits at discharge compared to those with CM. Eighty five (49%) children received
fosphenytoin and 88 (51%) received placebo. Baseline characteristics were similar across the
two study arms (Table 1).

Table 1: Clinical features at admission

	Fosphenytoin	Placebo	P value
Age (Median)	2.6 (IQR 1.7,3.7)	2.6 (IQR 1.8, 3.6)	0.77*
Sex			
Male	52	49	
Female	33	39	0.46
History of Seizures in Previous Illness			
Children with History of Seizures at Presentation	83	86	1.0
Duration of Unconsciousness by the Time of Admission (Median)	4(IQR 2,8)	3(IQR 2,6)	0.08*
Coma Status; Blantyre Coma Score			
0	16	15	
1	30	41	
2	39	32	0.31
Received 1st line AED prior to study drug	31	35	0.66
Received 2nd line AED prior to study drug	6	8	0.62
Diagnosis			
Cerebral Malaria	54	56	
Unknown Encephalopathy	27	28	
Acute Bacterial Meningitis	4	4	0.999

*Kruskal Wallis equality of population test

Table 1: Summary of clinical features at admission of patients recruited into the study. There
were no significant differences between the two study groups.

Children who received fosphenytoin had a 4 hour median plasma phenytoin concentration of 16.8 (IQR 13.0, 19.0) µg/ml compared to insignificant concentrations; 0.2 (IQR 0.0, 0.3) µg/ml, in those who received placebo (P <0.01). Two of the children who received fosphenytoin had 4 hour phenytoin plasma concentrations below the therapeutic value of 10 µg/ml; 9.4 µg/ml and 3.2 µg/ml. Lumbar puncture was done at varied times after administration of the study drug depending on the clinical progress of the patient. Children who received fosphenytoin had a median CSF phenytoin concentration of 2.1 (IQR 1.6, 2.6) µg/ml compared to 0.1(IQR 0.0, 0.3) µg/ml in those who received placebo (P <0.01).

Seizures, anti-epileptic drug use and abnormal motor posturing

The majority (n=108; 62%) of the children did not suffer any seizures after administration of the study drug. Thirty three (39%) children who received fosphenytoin suffered at least one seizure after administration of the study drug compared to 32 (36%) children who received placebo (P = 0.73). In children with CM (n=110), there was no difference in the prevalence of seizures between the fosphenytoin (35%; n=54) and the placebo (38%; n=56) (P = 0.80) arms of the study. Amongst all the children who suffered seizures, those who received fosphenytoin had median number of seizures of 4 (IQR 2, 9) compared to 5 (IQR 2, 9) in those who received placebo (P = 0.67). Twenty one children who received fosphenytoin and 25 who received placebo underwent continuous EEG monitoring. Six (29%) of the children who received fosphenytoin were noted to have seizures on EEG compared to 10 (40%) of the children who received placebo (P =0.42). Overall, there were no differences in frequency or prevalence of clinical seizures between the two study arms (Table 2). Use of first line AED for treatment of seizures during the duration of study monitoring was also similar between the two study arms (Table 2).

Outcome

Nine children (14%; n=65) in the fosphenytoin arm of the study were found to have motor deficits at discharge compared to 14 (19%; n=73) in the placebo arm (P =0.36). In children with CM, 46 children (11%) in the fosphenytoin arm had gross motor deficits at discharge compared to 48 (19%) in the placebo arm (P = 0.28). Thirty three children died during the study; 18 (21%) were in the fosphenytoin arm and 15 (17%) in the placebo arm of the study (P = 0.49). There were no differences in outcome between the two study groups. There were no differences between the two arms of the study in time to localize painful stimulus and in time to regain full consciousness (Table 3). On assessment at 3 months, 7 children in the fosphenytoin arm and 9 children in the placebo arm were lost to follow up. At this assessment, 10 children in the fosphenytoin arm were found to have persistent motor deficits (n=59) compared to 12 children in the placebo arm (n=63) (P =0.76) (Table 4).

Table 3: Assessment at Discharge

	Fosphenytoin (n=85)	Placebo (n=88)	P value
Died	18 (21%)	15 (17%)	0.489
Sequelae	9 (13%; n = 67)	14 (19%;n = 73)	0.359†
Time to localize pain (hrs)*	18(8,28)	14(6,33)	0.378†
Time to regain full consciousness (hrs)*	21.5(15.5,32.5)	24(10,48)	0.875

Differences in proportions examined using the chi square test, * Time to localize painful stimulus and time to regain full consciousness considered only for those who survived without motor neurological deficits and presented as median(inter-quartile range), † Kruskal Wallis equality of population test

Table 3: There were no differences between the two study groups in those who died, those who suffered neurological sequalae, and in time to regain consciousness.

Table 4: Assessment at 3 months

	Fosphenytoin	Placebo	P value
Lost to follow-up/Withdrew	7 (11%; 66)	9 (13%; 72)	0.728
Persistent Neurological deficits	10 (17%; n=59)	12 (19%; n=63)	0.763

Table 4: A summary of assessment at 3 months clinical

Serious Adverse Events

Ten (12%) children in the fosphenytoin group suffered respiratory depression compared to 13 (15%) children in the placebo arm (P=0.56). Twenty nine children suffered hypotension during the study monitoring; 15 in the fosphenytoin group and 14 in the placebo group (P =0.75). Only two children were observed to have bradycardia; both were in the placebo arm of the study. Two children in the fosphenytoin arm had local reactions at the site of injection; one a swelling and the second, induration.

DISCUSSION

In this study, we investigated the efficacy of a single IM injection of fosphenytoin to prevent seizures in children presenting with acute non-traumatic coma. We observed no significant and consistent differences between the two study arms in the prevalence and frequency of seizures, AED use, time to localize painful stimuli or to regain full consciousness, neurological deficits at discharge, and mortality.

We have previously examined the pharmacokinetics of IM fosphenytoin in a similar but smaller group of children (11). We observed rapid attainment of therapeutic range plasma phenytoin levels and better seizure control compared to intravenous (IV) fosphenytoin and IV phenytoin(11). Except for one child, all the children who received fosphenytoin and were assayed attained plasma phenytoin levels within the appropriate therapeutic range. Thus, it is unlikely that the lack of efficacy of fosphenytoin was due to inadequate therapeutic concentration. Our initial study was specifically on children with CM. Falciparum malaria is known to be epileptogenic. Over the study period we observed an unprecedented drop in malaria transmission in the study area with consequent decrease in malaria coma admissions(15). The aetiological profile of the children we recruited reflected a greater

proportion than previously observed of non-malarial coma, a group with less seizure burden and greater mortality compared to CM.

Forty two percent of the children recruited into the study received at least one AED during resuscitation before administration of the study drug. Lack of initial seizure control in acute encephalopathies begets more seizures and conversely seizure treatment helps prevents more seizures. Thus, efficient seizure treatment during initial emergency resuscitation could have diminished the apparent effect of prophylactic AED. A combination of these factors could have contributed to our not observing an effect of the active arm on prevention of seizures and neurological sequelae. It could also be that a single dose of IM fosphenytoin given to this group of patients is not optimal for prevention of seizures and neurological sequelae, perhaps because the underlying mechanisms or factors prolonging seizures in trauma and non-traumatic encephalopathies are different.

The role of fosphenytoin in seizure prophylaxis among TBI and neurosurgery patients is well established in developed country settings (10). In our setting, fosphenytoin is an attractive choice for seizure prophylaxis among children with acute non-traumatic coma since it is water soluble and can be administered IM, an important consideration in resource poor settings. Further, it causes minimal cardio-respiratory depression, a beneficial characteristic for settings like ours with no capacity for routine sedation and mechanical ventilation. Indeed we demonstrated no difference in occurrence of cardio-respiratory depression between the active arm and the placebo arm. Thus, although not efficacious for prevention of seizures, it is a relatively safe AED and may have utility in treatment of status epilepticus.

The short shelf life and the current complicated supply process may inhibit the use of fosphenytoin in sub-Saharan Africa and other resource poor settings even if it is shown to be

effective. However, these logistical obstacles can be surmounted and it is still crucial to understand the role of fosphenytoin in seizure prophylaxis and treatment in children with acute non-traumatic coma through larger studies. A study design that allows for waiver of consent in the initial emergency period may allow for administration of prophylactic AED during initial resuscitation. The ethical issues surrounding such a design would need to be clarified considering that such a study would be placebo controlled and fosphenytoin has potential, albeit minimal, for cardio-respiratory depression. Larger studies would also allow for adequate examination of seizure prevention taking into account the different aetiologies and the onset of illness. Novel AEDs with minimal adverse effects such as leviracetam could also be explored.

There appears to be no apparent benefit in using single IM injection of fosphenytoin for seizure prophylaxis in children with acute non-traumatic coma in a setting where optimal seizure treatment is possible.

Acknowledgement

REFERENCES

1.   Pelkonen T, Roine I, Monteiro L, Correia M, Pitkaranta A, Bernardino L, et al. Risk factors for death and severe neurological sequelae in childhood bacterial meningitis in sub-Saharan Africa. Clin Infect Dis. 2009 Apr 15;48(8):1107-10.

2.   Birbeck GL, Molyneux ME, Kaplan PW, Seydel KB, Chimalizeni YF, Kawaza K, et al. Blantyre Malaria Project Epilepsy Study (BMPES) of neurological outcomes in retinopathy-positive paediatric cerebral malaria survivors: a prospective cohort study. Lancet Neurol. 2010 Dec;9(12):1173-81.

3.   Crawley J, Smith S, Kirkham F, Muthinji P, Waruiru C, Marsh K. Seizures and status epilepticus in childhood cerebral malaria. Qjm. 1996 Aug;89(8):591-7.

4.   Idro R, Carter JA, Fegan G, Neville BG, Newton CR. Risk factors for persisting neurological and cognitive impairments following cerebral malaria. Arch Dis Child. 2006 Feb;91(2):142-8.

5.   Newton CR, Krishna S. Severe falciparum malaria in children: current understanding of pathophysiology and supportive treatment. Pharmacol Ther. 1998 Jul;79(1):1-53.

6.   Mishra SK, Newton CR. Diagnosis and management of the neurological complications of falciparum malaria. Nat Rev Neurol. 2009 Apr;5(4):189-98.

7.   Ibekwe RC, Ibekwe MU, Onwe OE, Nnebe-Agumadu UH, Ibe BC. Non-traumatic childhood coma in Ebonyi State University Teaching Hospital, Abakaliki, South Eastern Nigeria. Niger J Clin Pract. Jan-Mar;14(1):43-6.

8.   Anga G, Barnabas R, Kaminiel O, Tefuarani N, Vince J, Ripa P, et al. The aetiology, clinical presentations and outcome of febrile encephalopathy in children in Papua New Guinea. Ann Trop Paediatr.30(2):109-18.

9.   Crawley J, Waruiru C, Mithwani S, Mwangi I, Watkins W, Ouma D, et al. Effect of phenobarbital on seizure frequency and mortality in childhood cerebral malaria: a randomised, controlled intervention study. Lancet. 2000 Feb 26;355(9205):701-6.

10.   Boucher BA, Feler CA, Dean JC, Michie DD, Tipton BK, Smith KR, Jr., et al. The safety, tolerability, and pharmacokinetics of fosphenytoin after intramuscular and intravenous administration in neurosurgery patients. Pharmacotherapy. 1996 Jul-Aug;16(4):638-45.

11.   Ogutu BR, Newton CR, Muchohi SN, Otieno GO, Edwards G, Watkins WM, et al. Pharmacokinetics and clinical effects of phenytoin and fosphenytoin in children with severe malaria and status epilepticus. Br J Clin Pharmacol. 2003 Jul;56(1):112-9.

12.   Ogutu BR, Newton CR, Muchohi SN, Otieno GO, Kokwaro GO. Phenytoin pharmacokinetics and clinical effects in African children following fosphenytoin and chloramphenicol coadministration. Br J Clin Pharmacol. 2002 Dec;54(6):635-42.

13.   Newton CR, Chokwe T, Schellenberg JA, Winstanley PA, Forster D, Peshu N, et al. Coma scales for children with severe falciparum malaria. Trans R Soc Trop Med Hyg. 1997 Mar-Apr;91(2):161-5.

14.   WHO. Pocket book of hospital care for children - guidelines for the management of common illnesses with limited resources. Geneva: WHO; 2005.

15.   O'Meara WP, Bejon P, Mwangi TW, Okiro EA, Peshu N, Snow RW, et al. Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. Lancet. 2008 Nov 1;372(9649):1555-62.

SUPPLEMENTARY MATERIAL

Supplementary Table 1: Diagnosis versus Outcomes

Diagnosis	Seizure Prevalence	Died	Neurological Sequelae
Cerebral Malaria (n=110)	40 (36%)	16 (15%)	14 (13%)
ABM (n=9)	1 (11%)	6 (67%)	0
Unknown Encephalopathy (n=54)	22 (41%)	11 (20%)	9 (17%)