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The Efficacy of Phenobarbital Given as Anti-Convulsant Prophylaxis in Children with Cerebral Malaria in Africa

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The Efficacy of Phenobarbital Given as Anti-Convulsant Prophylaxis in Children with Cerebral Malaria in Africa

Abstract
Background: Cerebral malaria is a severe neurological form of malaria that affects the central nervous system, is caused by Plasmodium falciparum parasitemia, and has a common complication of seizures and coma especially in children. In African children under the age of 5 it is the leading cause of death; over one million children in sub-Saharan Africa alone die or are disabled as a result of cerebral malaria annually. Seizures are a frequent complication of cerebral malaria and are associated with an increased risk of death and neurological sequelae including epilepsy, as well as a much broader range of motor and cognitive impairments. These impairments severely impact a child's lifelong educational and social potential. Phenobarbital is an effective anti-convulsant that both controls and prevents seizures, is widely available in resource poor countries and can be delivered in a single IM dose for ease of rapid delivery. The objective is to assess the efficacy of phenobarbital when given as anti-convulsant prophylaxis in children with cerebral malaria.

Methods: An exhaustive search of available medical literature was performed using CINAHL, MEDLINE, Cochrane Database, and the African Index Medicus. The search terms included “cerebral malaria”, “children”, “Phenobarbital”, “prophylaxis” and “seizure”. All full text articles in the English language were used. Meta-analysis and case studies were excluded. Three articles were chosen for review.

Results: Overall it was found in all the studies that the prophylactic use of phenobarbital (PB) in children with cerebral malaria decreased the number of prolonged seizures they had while in the acute stage of parasitemia. It was also found that malaria treatment with quinine does not potentiate or interact with the PB, and that PB does not prolong coma or delay the recovery of children with cerebral malaria, nor does PB have any long term negative cognitive effects in children. However, the dose and route of administration of PB in children remains a controversy. One study that suggested that PB 20mg/kg intramuscularly was effective, but the children in this study receiving treatment had a mortality rate double the control group, likely due to anti-convulsant polypharmacy. Another study recommended 10mg/kg IM dosing but it was found to not be effective in controlling seizures. One study showed that 15mg/kg intravenously was effective, and a parallel simulated study recommended that the same dose given IM would be just as effective, although there is no actual data to support this.

Conclusion: The use of phenobarbital as a prophylactic anti-convulsive in children that have cerebral malaria is an effective way of decreasing acute seizure activity and therefore reducing the risk of long term neurological sequelae in this population. Standardized dosing and route of administration of phenobarbital for this application have not yet been established however, and more randomized controlled trials need to be completed before recommendations can be made.

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Keywords
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The Efficacy of Phenobarbital Given as Anti-Convulsant Prophylaxis in Children with Cerebral Malaria in Africa

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A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
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Faculty Advisor: Mary Von, PA-C, MS, DFAAPA
Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD
Biography

Nikki McLeod is a native of Delaware and graduated from the University of New Hampshire where she majored in Outdoor Education and English, and first discovered her love of medicine as an EMT. After completion of her undergraduate degree, she moved to Lake Tahoe and worked as a professional ski patroller, taught in the Wilderness Studies Program at Lake Tahoe Community College, and was a climbing guide throughout the United States and abroad. Returning to New Hampshire, she worked in the Dartmouth Family Medicine Residency Program as a medical assistant and in the business office while pursuing coursework for PA school. She is married to Ben McLeod, who has graciously gone along for this adventure, and has two fabulous little boys, Liam and Campbell. The McLeod’s enjoy riding bikes, skiing, camping, traveling, and photography. She and her family plan to stay and enjoy Portland after graduation.
Abstract

Background: Cerebral malaria is a severe neurological form of malaria that affects the central nervous system, is caused by Plasmodium falciparum parasitemia, and has a common complication of seizures and coma especially in children. In African children under the age of 5 it is the leading cause of death; over one million children in sub-Saharan Africa alone die or are disabled as a result of cerebral malaria annually. Seizures are a frequent complication of cerebral malaria and are associated with an increased risk of death and neurological sequelae including epilepsy, as well as a much broader range of motor and cognitive impairments. These impairments severely impact a child’s lifelong educational and social potential. Phenobarbital is an effective anti-convulsant that both controls and prevents seizures, is widely available in resource poor countries and can be delivered in a single IM dose for ease of rapid delivery. The objective is to assess the efficacy of phenobarbital when given as anti-convulsant prophylaxis in children with cerebral malaria.

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Conclusion: The use of phenobarbital as a prophylactic anti-convulsive in children that have cerebral malaria is an effective way of decreasing acute seizure activity and therefore reducing the risk of long term neurological sequelae in this population. Standardized dosing and route of administration of phenobarbital for this application have not yet been established however, and more randomized controlled trials need to be completed before recommendations can be made.

Keywords: Cerebral Malaria, Anti-convulsant Prophylaxis, Seizure, Children, Phenobarbital
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Figure 1: Epidemiology of malaria in Africa

List of Abbreviations

PB.................................................................Phenobarbital
CM.................................................................Cerebral Malaria
IV.................................................................Intravenous
OR.................................................................Odds Ratio
CI.................................................................Confidence Interval
WHO.........................................................World Health Organization

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Appendix A.........................................................Blantyre Coma Score
Efficacy of Phenobarbital as a Prophylactic Anti-Convulsive in African Children with Cerebral Malaria

BACKGROUND

Malaria is one of the most common parasitic diseases and a major public health problem worldwide, with the highest concentration of morbidity and mortality in Africa.¹ Cerebral malaria (CM) is a severe neurological form of malaria that affects the central nervous system, is caused by Plasmodium falciparum parasitemia, and has a common complication of seizures and coma especially in children. Children less than 5 years of age are particularly susceptible to developing cerebral malaria because of low immunity levels.² Over one million children in sub-Saharan Africa alone die or are disabled as a result of cerebral malaria annually, and 40% of all public health expenditure in Africa goes towards the prevention and treatment of malaria.³ Cerebral malaria is seen frequently, attributing to approximately 10-15% of all hospital admissions in sub-Saharan Africa⁴, but is not treated consistently. In this most endemic area of the world, it is important to assess what can be done to improve the outcomes for these children.

Seizures are a frequent complication of cerebral malaria and are associated with an increased risk of death and neurological sequelae such as hemiplegia, spastic quadriplegia, visual impairment, speech delay, and epilepsy as well as a much broader range of motor and cognitive impairment.⁵,⁶ These impairments severely impact a child’s lifelong educational and social potential. A recent study concluded that as many as 1 in 4 children who survive CM develop these long term neurological deficits.⁷
In sub-Saharan Africa, where over 80% of malaria cases and 90-95% of deaths worldwide occur, cerebral malaria accounts for an estimated 600,000 children under the age of 5 annually. Of these children, about 100,000 die, consistent with a mortality rate of almost 20%, and an additional 20,000 children experience long term neurological sequelae, particularly epilepsy.\textsuperscript{1,4,6-9} This number may be under reported due to lack of routine long term follow up, social pressure, and lack of resources. Epilepsy is still heavily stigmatized in African countries, as are most neurological and physical disorders.\textsuperscript{10} Therapies provided by traditional healers are the mainstay of treatment for many.\textsuperscript{11-13} Additionally, many people may not have been well educated on the signs, symptoms, and overall risks of their children developing cerebral malaria. The most frequently reported perceived causes of convulsions reported by respondents in a vignette study were phlegm, worm infections, mosquito bites, eating too much fatty or oily food, heat from the sun, and magico-religious causes.\textsuperscript{14} In fact, many studies done across sub-Saharan Africa show that spiritual forces dominate the perceived causes for children who have seizures.\textsuperscript{14} The lack of education and treatment by traditional healers has clearly decreased the timeliness of acute care needs and complicated the overall outcome of these children.

Phenobarbital is a barbituate that has been used since the early 1900s, it is the oldest and most widely used medication used to control seizures worldwide, and is a core medicine listed in the WHO Model List of Essential Medicines for developing countries. It is one of the longest acting anticonvulsant medications available, and per most recent data found online at www.Pharmacychecker.com, PB can be purchased in the United States for $.06 per pill, as opposed to diazepam at $.12 per pill or phenytoin at $.21 per
pill. In a follow up study aimed at assessing developmental outcomes in children who had received PB as an anticonvulsant prophylaxis in CM, it was found that PB showed no indication of producing long term negative cognitive effects. Additionally, PB does not potentiate or change the efficacy of concurrent quinine administration, necessary for the treatment of malaria.

Diazepam is considered a first line anti-convulsant medication worldwide. While Diazepam is useful in status epilepticus, it does not offer any prophylactic benefit, particularly in a single dose administration. There is also a difference in diazepam efficacy seen in the comparison between patients with and without parasitaemia as a whole, potentially because patients with cerebral malaria have reduced plasma and CSF concentrations of histidine, an amino acid which is an important constituent of the GABA-A receptor that may influence benzodiazepine ligand binding. This could be a plausible explanation of diazepam's decreased binding affinity at the GABA-A receptors or its reduced clinical efficacy in patients with parasitaemia. Thus diazepam may be less efficacious in controlling seizures in children with malaria. It has been shown that PB is highly effective in treating status epilepticus without an increase in respiratory depression or hypotension. Buccal midazolam, intranasal lorazepam, IM paraldehyde, and rectal diazepam have also been studied as effective means for treatment and control of prolonged seizures but none have been studied as a prophylaxis, and the need for refrigeration with the lorazepam and paraldehyde make those options less feasible. Buccal midazolam is unattractive due to price, and the route of the diazepam administration has socially unacceptable associations. Previous findings in Kenyan
children also indicated that rectal absorption of parenteral diazepam is erratic and terminates less seizures than intravenous administration.17

METHODS

An exhaustive literature search was conducted using the MEDLINE, CINAHL, Cochrane Database, and the African Index Medicus. The search terms included “cerebral malaria”, “children”, “Phenobarbital”, “prophylaxis” and “seizure”. Only full text articles in the English language were used. Meta-analysis and case studies were not included. Subsequent examination of bibliographic entries in retrieved works provided additional studies for consideration. The results of the remaining studies were then compiled and examined.

Inclusion/Exclusion Criteria

Exclusion criteria included any study with adults and any study not done in Africa. Also excluded was any study that gave seizure prophylaxis other than PB while hospitalized, such as diazepam or phenytoin. All the studies examined here excluded children with a previous history of epilepsy and any child who had received any PB prior to admission. The population analyzed was hospitalized children living in endemic P. falciparum areas who received prophylactic PB versus those children who were not given any PB prophylaxis, and the outcomes measured included subsequent seizure activity, mortality rates in both groups, and the potential to develop long term neurological sequelae. All the studies reviewed defined children with CM as prostrate, in an unarousable coma (Blantyre score of 3 or less- see Appendix A for detailed explanation), and with P. falciparum parasitemia visible with light microscopy.21 Any study with
dosing or route variations of PB was included. Studies that gave additional treatment for cerebral malaria such as quinine sulfate, paracetamol, or antibiotics were included, as it has been shown that these polypharmacies are necessary for effective cerebral malaria treatment and do not decrease or potentiate the efficacy of the PB.\textsuperscript{22} There was no exclusion on the age of the article, as PB has been used for a century as an anticonvulsant, although the majority of the data collected was from the last decade.

**Critical Appraisal**

The studies were subsequently rated and assessed for quality using an original scoring criteria. Because there was only one randomized controlled study and a number of blinded but open trials, all articles were included for consideration despite a lower score. (see Table 1). A relative score representing quality and validity was assigned to each article. Higher scores were awarded for prospective and controlled investigations, and for large sample populations. Lower scores were earned by those with minimal effort to minimize confounding factors, and those with smaller experimental groups. The overall average age of the child participants in all of the studies examined in this review was 30 months of age. However, the age of participants ranged from approximately 9 months to 13 years of age in the three studies.

**RESULTS**

A total of 3 articles which met all of the inclusion criteria were examined in this review. The largest group studied consisted of 340 children with CM\textsuperscript{5}, and the smallest group consisted of 12\textsuperscript{16}. Each study defined CM in the same manner, a child with a Blantyre coma score of 3 or less with a positive malaria blood test. The shortest study
lasted only as long as the children were acutely hospitalized (a few days)\textsuperscript{16}, and the longest study participants were re-examined during a follow up period of three months\textsuperscript{5}. One study included in this review was a randomized, controlled trial, although not double blinded.\textsuperscript{5} One trial was an open label, non-randomized study\textsuperscript{16}, and one was a double blinded placebo controlled trial.\textsuperscript{22} All three studies compared African children who received PB prophylactically during an acute hospital admission for CM. All study participants had written informed parental consent for treatment.

In the largest study by Crawley et al (2000)\textsuperscript{5}, a single PB dose of 20 mg/kg IM was used as anticonvulsant prophylaxis. Those results were compared with a pre-screened group of Kenyan children who were initially recruited to assess the clinical tolerance of PB 20mg/kg given by continuous IV infusion over a four hour time frame. There were 170 children from Kilifi District Hospital in both the treatment and control group. In this study, blood samples for PB measurements were taken from all patients at 1, 2, 4, 8, 12, 24, 36, and 48 hours. These samples were all sent to an independent lab in Nairobi, Kenya for analysis. Parasite counts were repeatedly taken every 8h until discharge, death, or parasitemia clearance. All the children in this study received antimalarial therapy in the form of IV quinine dihydrochloride, with a loading dose of 15mg/kg, and subsequent maintenance doses of 10mg/kg every 12h. IV fluids, blood transfusions, and treatment for hypoglycemia were given as clinically indicated and all vital signs were recorded. Any child with a fever above 38.5 C was treated with paracetamol (acetamenophen) 15mg/kg rectally every 6h. The number and duration of seizures were recorded at 5, 15, and 30 minutes. Seizures lasting longer than 5 minutes were treated with diazepam 0.3mg/kg IV injection, up to 2 doses, then changed to
paraldehyde 0.2mg/kg IM given every 5, 15, 30, and 45 minutes as needed. This study found that the median time to maximum blood concentration of PB was 4 hours. Concentrations were maintained above 15mg/L, within the optimal range of 10-30 mg/L, for at least 48 hours, which is considered effective for seizure prophylaxis.(1-18) The placebo and PB groups showed no difference in the median time to parasite clearance (p=0.21), and there was no difference in the groups in the time taken to recover consciousness (p=0.39). PB provided effective seizure prophylaxis, decreasing the frequency and duration of seizures by over 50% (95% CI). Fewer children who received the PB subsequently required further anticonvulsant medications (8.2% vs 15.9%, p=0.04, CI 95%). This study also had the result of the PB group with a doubled mortality rate of the placebo group. This was attributed by the authors to the fact that these children on admission were more deeply comatose, dehydrated, acidotic, and hypoglycemic than those who survived. The mean respiratory rate at 4 hours (also the median time to maximum PB concentrations) was much higher in those who died (57 vs 47, 95% CI). This was relevant because the majority of the children in this study who died did so from respiratory arrest (22 vs 11, OR 2:1, CI 95%, p=0.05). The main indicator for these deaths was the additional diazepam (3 or more doses) given for either pre-hospital treatment of seizures or for subsequent seizures after the PB had been given. The interaction between PB and diazepam was associated with increased risk of death ( CI 95%) with less than 3 doses of diazepam resulting in 15% mortality rate (OR 1.9, p=0.07) and with more than 3 doses of diazepam resulting in a 62% mortality rate (OR 31.7, p=0.001).
Winstanley et al (1992)\textsuperscript{22}, measured a single dose of PB given 10mg/kg IM specifically within two hours of admission. There were 14 Kenyan children from Kilifi District Hospital in the treatment group and 39 children in the control group in this study. These children were studied in two groups; one that looked at children with convulsions with CM as the treatment group, the other with children with convulsions (>2 in the 24 hours prior to admission) who were aparasitic as the control group. The children with CM were given appropriate anti-malarial treatment with quinine 20mg/kg IV loading dose followed by 10mg/kg maintenance doses every 12h. Patients were treated for fever and hypoglycemia under the same guidelines as the Crawley et al study. The aparasitic children were treated with appropriate antibiotics. All seizures over 5 minutes in duration were treated with diazepam 0.3mg/kg IV. Blood sampling for PB measurements was done at an interval of 0.5, 1, 1.5, 2, 4, 6, 12, 24, 48, 72, 96, 120, 144, and 168 hours after dosing. These samples were sent to the same lab in Nairobi as the Crawley et al study for analysis. The control group in this study received all the same therapy with the only exception being the single dose of PB. No follow up beyond hospital discharge was performed. Results from this study showed that the mean time to optimal PB blood concentrations in the treatment group of 4 hours vs. 3 hours in the control group was noted. An improvement in motor response score at a mean time of 21 hours after admission for the treatment group vs 22 hours in the control group. There was no difference in the groups in the incidence of seizures during admission (2.5 vs 1.5), or the incidence of neurological sequelae (2 vs 2). Mortality between the groups showed no real significance (2 (14) vs 9 (23)).
The third study by Kokwaro et al (2002)\textsuperscript{16} looked at the dose of PB in the same population at the Kilifi District Hospital in Kenya. A 15mg/kg dose of PB was given IV, infused over 20 minutes, followed by maintenance doses of 5mg/kg at 24 and 48h after the loading dose. Twelve children were in the treatment group—this study had no control group. Vital signs were recorded every 4 hours. Any seizure activity after the dose of PB was given was treated with diazepam, paraldehyde, or phenytoin. Blood samples for PB concentrations were collected at 10, 20, 25, 20, 40, and 60 minutes, and again at 2, 6, 12, 24, 36, 48, 54, 60, and 72 hours after the loading dose that were analyzed in house. All patients in this study were asked to come back for a three month follow up appointment. Results found that optimal PB blood concentrations (greater than 10mg/L) were achieved within 10 minutes of dosing, and maintained for at least 48 hours. This study also simulated a 2.5mg/kg maintenance dose of PB at 24 and 48 hours that appeared to show equal efficacy with 95% CI. Convulsions were controlled in 66\% of the treatment group, and there were no cases of neurological sequelae on follow up. There was no significant difference in biochemical measurements on admission between these children and those who received treatment and whose seizures were not controlled with PB.

**DISCUSSION**

Upon reviewing these studies, it seems apparent that using PB as a prophylactic anticonvulsant in children with CM is an effective way of reducing subsequent seizures, possibly ensuring a more rapid recovery from a comatose state and a way to decrease mortality as long as precautions are taken when additional anticonvulsant medications are given. No evidence was found that PB prolonged coma.\textsuperscript{23} Diazepam, phenytoin, and
midazolam are newer, more effective medications, some with a decreased risk of respiratory depression, that are considered to be first line treatment in Africa for these patients. These medications are not always available because of their overall worldwide supply, cost, and their route of administration may not be socially acceptable. PB has been around since the early 1900s, is widely available worldwide, and is considered a cheap, safe, long-acting medication with excellent bioavailability after IM administration to be given for seizures, and accordingly is used most often in malaria endemic regions. In CM, children tend to have prolonged seizures that are associated with an increased risk of death and long term neurological sequelae.

The efficacy of PB as a prophylactic anti-convulsant in patients with CM is apparent, but potentially based solely on its dose and route of administration. IV administration is the most rapid way to bring blood concentrations of PB up to optimal levels to reduce further seizure activity. However, in many places worldwide this route may be hampered by lack of supplies, time, or qualified staff. IM administration is the most simple form, and at a dose of 20mg/kg it proved very effective. In a simulated profile, it was suggested that a 15mg/kg IM dose would also be effective. A 10mg/kg IM dose was found not to be effective and although in Thailand one study by White et al found a smaller dose of 3.5kg/mg effective, those results did not translate over to a pediatric sub-Saharan Africa population which is possibly due to the difference in the pathophysiology of CM between children and adults. Additionally of interest, PB was not found to potentiate or change the efficacy of quinine absorption in children with CM, or vice versa. In a different study based on traumatic brain injuries, it was shown that the use of prophylactic anti-epileptic drugs were effective at preventing early and immediate
provoked seizures when used briefly at the outset of the initial trauma, which could be applied to those children with acute cerebral malaria.

The articles included in this review reflect a broad variety of research methods in less than optimal conditions, and their results are of variable quality. Limitations in these studies were numerous, mostly because of the small study sizes and lack of randomized controlled trials with significant data. In terms of global representation, only three studies from sub-Saharan Africa were used. It would be ideal to include more studies from Asia, India, and South and Central America to compare dosing recommendations and efficacy of PB worldwide. Practitioners who lack blood for transfusions, IV access, laboratory supplies to test for parasitemia, quinine, antibiotics, or dextrose solution for the correction of low blood counts, dehydration, infection, or hypoglycemia, would find that prophylactic treatment with PB would prove moot, which is frequently the case in developing countries where even basic medical care is often unavailable. Additional treatment with other anti-convulsant medications becomes a major problem because many healthcare facilities do not have the appropriate equipment to monitor or treat patients for respiratory distress.

The onset of illness to the time of treatment also plays a critical factor in the efficacy of PB and overall outcome of these patients. Only one study addressed this problem directly, but did not make any further recommendations regarding prompt treatment after recognizing the patient was severely ill. Children have a very brief interlude between the time when CM symptoms first present to the time of coma, on average only 1-2 days. This problem will continue to be a major issue in developing countries due to difficulty accessing medical care, physically and financially. In addition,
appropriate and adequate nursing care is crucial to the successful outcomes of children with CM as nurses are often the first line component of assessment and pre-hospital treatment. This subjective factor is an important step in the treatment process, and is variable at best. It is estimated that only 24% of children under the age of 5 that present with a fever to hospitals in Africa receive anti-malarial treatment, even when 40% of all hospital admissions for children are for malaria. A recent statistic analysis reports that worldwide malaria morbidity and mortality is under-represented, and in many sub-Saharan African countries the overall death rate in children under 5 has been rising since 1999. Though this review is limited by the fact that a countless number of confounding and modifying factors are present when studying a process such as CM progression and prophylactic convulsion treatment in children, it does help to elucidate many of the topics that remain to be studied with regard to the overall health of children with CM worldwide. Complicating effects are the variability in which CM manifests in children overall. Some children experience severe anemia or hypoglycemia, and some do not. The effects of variables concerning each child’s overall nutritional status or home environment, which contribute greatly to their cognitive status, is nearly impossible to track. As an example, another common cause of seizures in African children is helminthes infection, due to lack of proper footwear, adequate food preparation, or poor hygiene. These variables may mask the benefits of the PB prophylaxis, limiting conclusions that might be drawn about its benefits. Additional confounding effects of these studies were lack of a true placebo group in the Kokwaro et al trial, so no comparisons between a treatment and control group could be made, the data collected was minimal. The White et al study did not differentiate the data in terms of age, so it is
impossible to extrapolate if the PB dose given was suitable or helpful for children, and no data was collected for children under 5 years of age, the most susceptible age group for developing CM.

Ethical issues were problematic in this review. There is a known interaction between PB and diazepam that causes respiratory depression, and an increased risk of death.\(^5\) The only clinical significance between the groups in admission or laboratory findings was the mean respiratory rate because the majority of the children in this study who died did so from respiratory arrest. However in many of the studies, diazepam was given to children who experienced further convulsions after receiving PB prophylaxis, even in a hospital who did not have the means to provide any respiratory support or resuscitation. It would be beneficial to have a study done at a facility that has proper equipment to assess the true mortality rates of these children when all the necessary lifesaving resources are available. The laboratory in Nairobi where all but one of the blood samples from these studies was processed at is another ethical debate. It is difficult to know if any of the samples were contaminated or changed during their transport time, over an 8 hour drive, from the coast to Nairobi. It would be best to have a more specialized in-house lab team that could process blood samples for future studies to provide the purest and most timely results.

Social stigmas and delay or lack of proper treatment due to cultural beliefs contribute to the dilemma of children receiving adequate care for CM. The perceived causes of seizures among sub-Saharan Africans are dominantly magico-religious causes, and many reports across sub-Saharan Africa emphasized use of traditional healers as the primary source of treatment for convulsions, rather than modern medical care.\(^13\) Studies
have shown that even among urban-dwelling Africans with epilepsy, up to 70 percent use
traditional medicines. In rural regions, the population has less education and limited
access to modern care possibly elevating this figure even further. Because concerns about
supernatural causes of convulsions are evident, epilepsy is still heavily stigmatized in
African countries. The negative impact is evident on extended family members, too. Families with a child suffering from epilepsy may go to great lengths to prevent the
development of recurrent seizures in their other family members because in addition to
their superstitions, they may believe that epilepsy is also contagious. Relating outcomes
to timely help-seeking and malaria prevention needs to incorporate local relevance into
the design and implementation of local program strategies.

CONCLUSION

WHO has recently implemented two programs; the Global Malaria Programme
and the Roll Back Malaria initiative in Africa, to help prevent, more rapidly and correctly
assess, and ultimately help cure malaria. Both programs hold promise in collecting more
detailed information and getting more definitive education and treatment options out to
communities and medical personnel. Ultimately, more randomized controlled studies
using PB specifically in a single IM dose need to be completed to provide a better
understanding of its overall risk versus benefit in prophylactically reducing seizures in
children with CM to determine its efficacy in the easiest, most cost-effective
administration in developing countries. The current standard of care entails treating each
child as individual circumstances warrant and mostly focuses on anti-malarial treatment
as a priority. However, based on the studies reviewed here, the evidence points to the
overall benefit of using PB as anti-convulsant prophylaxis, especially when seen in the incidence of helping to prevent long term neurological sequelae. This improved treatment could positively affect the lives of millions of children not just in Africa, but worldwide.
REFERENCES


**Table 1 – Matrix of Reviewed Literature**

<table>
<thead>
<tr>
<th>Author and Study Type</th>
<th>Patients/Population</th>
<th>Comparison</th>
<th>Outcome(s)</th>
<th>Validity-Original Scoring</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crawley et. al (2000) Randomized Controlled Study</td>
<td>340 children in tropical Africa; 170 in treatment group, 170 in control group</td>
<td>Children given Phenobarbital during acute episode of cerebral malaria vs. no Phenobarbital.</td>
<td>Phenobarbital use at 20mg/kg IM proved effective prophylaxis. Doubled mortality of patients in the treatment group however, possibly due to dosing and polypharmacy.</td>
<td>4/5</td>
<td>Study was not double blinded. Safe and effective dosing of Phenobarbital needs to be addressed as well as administration of drug.</td>
</tr>
<tr>
<td>Kokwaro, et. al (2002) Open label non-randomized study</td>
<td>12 children in tropical Africa; no control group.</td>
<td>No real comparison group.</td>
<td>Phenobarbital use in 15mg/kg IV dose proved effective at seizure prophylaxis, simulated IM dose may also work.</td>
<td>3/5</td>
<td>Study was not randomized, or double blinded. H &amp; P screening only for participants. Very small treatment group, larger more complete studies needed, but a good start at narrowing down dosing and route.</td>
</tr>
<tr>
<td>Winstanley, et. al (1992) Open label non-randomized study</td>
<td>14 children in tropical Africa in treatment group, 39 children in control group.</td>
<td>Children given Phenobarbital during acute episode of cerebral malaria vs. no seizure prophylaxis.</td>
<td>PB use in 10mg/kg IM dose proved to be ineffective, treatment changed to 15mg/kg mid-study.</td>
<td>3/5</td>
<td>Study was not randomized or double blinded. Small treatment group and control group, larger more complete studies needed. Study showed that QS did not potentiate any Phenobarbital activity, and that dosing was too low at 10mg/kg.</td>
</tr>
</tbody>
</table>
Figure 1: Malaria distribution in Africa, courtesy of MARA/ARMA
Appendix A: Blantyre Coma Scale

The following coma scale – the “Blantyre coma scale” – is modified from the widely used Glasgow coma scale (1974), is applicable to children, including those who have not learned to speak.

**Best motor response:**
- Localizes painful stimulus: 2
- Withdraws limb from pain: 1
- Nonspecific or absent response: 0

**Verbal response:**
- Appropriate cry: 2
- Moan or inappropriate cry: 1
- None: 0

**Eye movements:**
- Directed (e.g., follows mother’s face): 1
- Not directed: 0

**Score:**

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>0–5</td>
</tr>
</tbody>
</table>

A state of unrousable coma is reached at a score of <3. This scale can be used repeatedly to assess improvement or deterioration.

\(a\) Rub knuckles on patient’s sternum.
\(b\) Firm pressure on thumbnail bed with horizontal pencil