Epilepsy Research (2008) **82**, 215–218

journal homepage: www.elsevier.com/locate/epilepsyres

SHORT COMMUNICATION

Response to diazepam in children with malaria induced seizures

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Received 15 April 2008; received in revised form 31 July 2008; accepted 10 August 2008
Available online 19 September 2008

KEYWORDS
Anticonvulsants;
Benzodiazepine receptor;
Diazepam;
Malaria;
Seizures;
Children

Summary Malaria infection reduces the binding capacity of benzodiazepine receptors in mice. We studied the efficacy of diazepam terminating seizures in children with falciparum malaria. Diazepam stopped seizures in fewer patients with malaria parasitaemia ($\chi^2 = 3.93$, $P = 0.047$) and those with clinical diagnosis of malaria ($\chi^2 = 9.84$, $P = 0.002$) compared to those without. However malaria was not identified as an independent risk factor for diazepam's failure to stop seizures in children.

Introduction

Acute seizures are common in many children presenting to sub-Saharan African health facilities (Idro et al., 2008; Ogutu et al., 2002). In these facilities, diazepam is used as the standard antiepileptic drug (AED) to stop acute seizures and status epilepticus in children, due to its rapid action, low expense and wide availability (Mpimbaza et al., 2008; Ogutu et al., 2002). Falciparum malaria is a common cause of acute seizures in children admitted to hospital (Waruiru et al., 1996) and its metabolic and circulatory complications may affect the action of drugs. About a third of patients with malaria and seizures have cerebral malaria (Asindi et al., 1993).

While falciparum malaria does not appear to alter the pharmacokinetics of diazepam (Ogutu et al., 2002), *Plasmodium berghei* infection in mice significantly decreases the binding capacity of Gamma-aminobutyric acid-A (GABA-A) receptors to which benzodiazepines bind (Kokwaro et al., 1997). Similar studies on effect of malaria on benzodiazepine receptors have not been reported in humans.

We assessed the efficacy of intravenous diazepam which is the preferred route of diazepam administration (Ogutu et

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0920-1211
doi:10.1016/j.eplepsyres.2008.08.002

al., 2002), in treatment of acute seizures in children with falciparum malaria.

Methods

Study population

The notes of children presenting to the pediatric ward of Kilifi District Hospital, Kenya with acute convulsions between 1st March 2000 and 28th February 2007 were retrospectively evaluated. During this period the clinical and laboratory features were recorded systematically on standard proformas. These children were from Kilifi district—a malaria endemic area where individuals are exposed to a range of <1—120 infectious bites per year (Mbogo et al., 2003). However the clinical presentation of malaria is dependent on factors such as age level of transmission and immunity of the patient (Mwangi et al., 2005; Reyburn et al., 2005).

Malaria was considered to be the primary diagnosis if the child had fever and peripheral parasitaemia, without any other cause of the fever found. Information retrieved on the children with convulsions included; age, sex, weight, AED, dose, time of AED administration, number and type of seizures, time the seizures started and stopped, history of seizures, clinical diagnosis, conscious level for patients with cerebral malaria as defined by a Blantyre Coma Scale of $\leq$2 (Molyneux et al., 1989), oxygen saturation and falciparum malaria parasitaemia (detected in blood slides stained with 10% Giemsa).

All children who were given AEDs for acute convulsions were identified. Children with inadequate/missing information or who had not been given any AED (seizures lasted <5 min and aborted spontaneously) were excluded.

Either intravenous (IV) diazepam (0.3 mg/kg) or intramuscular (IM) paraldehyde (0.4 ml/kg) was used as first line treatment, usually dependent upon the availability of venous access. In the event of refractory seizures, a repeat dose of either drug could be given. If the seizure did not stop, then second line IV phenobarbital (15 mg/kg) or IV phenytoin (18 mg/kg) and eventually the third line (thiopental; 4 mg/kg) were given, according to the hospital protocol (Ogutu et al., 2002) based on ILAE guidelines (1993).

Diazepam was considered to be effective if it stopped the convulsion in less than 15 min with no recurrence (Qureshi et al., 2002). The point in the treatment protocol at which the seizure was terminated as well as factors such as respiratory depression (defined as low oxygen saturation <92% following drug administration) and the effect of malaria as the clinical diagnosis, on the efficacy of AEDs were evaluated.

Statistical analysis

The data were entered and tabulated in *Microsoft Visual Fox-Pro* 6.0 (Microsoft Corporation) and analysed with Stata (version 9; Stata Corp, College Station, TX, USA). Measures of association were done using Pearson's Chi-square test. We performed a univariate analysis of the various risk factors (history of seizures, seizure duration and malaria as an underlying condition) and stratified for possible confounders such as age and sex. A multiple logistic regression was performed adjusting for history of seizures, age, sex, seizure duration and malaria as an underlying condition.

Results

A total of 1653 children aged 0—12.9 years, admitted during the 7-year period were given AED to stop acute seizures, of whom 1189 (72%) had adequate information recorded in the notes and proforma. Malaria was the most common underlying condition, occurring in 566 (48%) of children of whom 239 (42%) had cerebral malaria.

First line AEDs stopped seizures in 298 (25%) of all patients. Diazepam terminated seizures in fewer patients with *P. falciparum* parasitaemia compared to those without parasitemia ($\chi^2 = 3.93$, $P = 0.047$) (Table 1). Diazepam also stopped seizures in less children with a primary diagnosis of malaria compared to those without malaria (40% vs. 62%, $\chi^2 = 9.84$, $P = 0.002$). However the level of parasitaemia did not influence the outcome and malaria was not an independent risk factor for the lack of termination of seizures (Table 2). Furthermore diazepam was not significantly associated with more episodes of respiratory depression in children with malaria compared to those without malaria (3.7% vs 1.1%, Fishers Exact Test = 0.189).

Discussion

This study showed that diazepam is less efficacious in stopping seizures in children with falciaprum malaria. However, after adjusting for risk factors, the effect of malaria was not statistically significant (Table 2). In a study conducted in Uganda by Mpimbaza et al. (2008) the authors have shown that rectal diazepam is less effective in terminating convulsions in children with malaria. This result is in agreement with previous findings in Kenyan children which indicated that rectal absorption of parenteral diazepam is erratic and terminates less seizures than intravenous administration (Ogutu et al., 2002). Intramuscular paraldehyde does not act on benzodiazepine receptors; it is however used as an alternative first line drug to IV diazepam.

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 (Mturi et al., 2003), and this may influence benzodiazepine ligand binding (Wieland et al., 1992). This could be a plausible explanation to diazepam's decreased binding affinity at the GABA-A receptors (Kokwaro et al., 1997) or its reduced clinical efficacy in patients with parasitaemia.

The effect of diazepam on respiration also depends upon the integrity of the benzodiazepine receptors (Braestrup et

Table 1 Treatment outcome of children given diazepam to stop acute seizures

	Number given diazepam, $N = 200$	Number (%) in whom seizures stopped
Patients without *P. falciparum* parasitaemia	53	32 (60%)
Patients with *P. falciparum* parasitaemia	147	69 (47%)
Patients with *P. falciparum* parasitaemia and clinical diagnosis of malaria	109	44 (40%)

Table 2 Multiple logistic regression analysis of factors associated with termination of seizures

	Seizures stopped, $N = 298$	Adjusted odds ratio	95% Confidence interval (CI)	P-value
Drug: (termination of seizures)		0.32	0.18—0.56	<0.001*
Diazepam vs.	103			
Paraldehyde	195			
Sex: female	139	1.53	0.90—2.61	0.129
History of seizures		1.10	0.57—2.10	0.767
Yes	199			
No	67			
Missing	32			
Length of seizure after drug administration				
<5 min[a]				
5—15 min	142	0.82	0.40—1.67	0.586
>15 min	39	0.13	0.06—0.29	<0.001*
Age				
0—6 months[a]				
6—12 months	44	0.57	0.20—1.65	0.308
1—3 years	52	0.54	0.18—1.62	0.275
3—6 years	136	0.64	0.24—1.69	0.370
6—13 years	26	2.41	0.51—11.3	0.262
Malaria: Yes	126	0.79	0.44—1.42	0.447

[a] This refers to the baseline group in the different categories.
* Represents a significant P-value.

al., 1982). The incidence of respiratory depression in this study is lower than that previously reported (Norris et al., 1999; Prensky et al., 1967) and may reflect the decreased receptor sensitivity in malaria patients. However there were insufficient numbers to determine if this occurred significantly less frequently in children with malaria.

The difference in diazepam efficacy is not only seen in the comparison between the malaria group versus the non-malaria group but those patients with and without parasitaemia as a whole. Thus diazepam may be less efficacious in controlling seizures in children with malaria. However a randomized trial is needed to clarify these findings and to elucidate the effect of malaria on benzodiazepine receptors in humans.

Acknowledgements

We thank the ICT department staff at KEMRI/Wellcome Trust Research Programme, Tony Kazungu, Rachel Odhiambo and Monica Omondi for providing online patient database and the archives staff (Josphine Kazungu and Ramos Kazungu) for their assistance in retrieving patient files used in this audit. Professor Charles Newton is funded by the Wellcome Trust, UK and Professor Kokwaro supported by a Research Capacity Strengthening Grant from WHO (MIM/TDR). We thank the Director of KEMRI for permission to publish this paper.

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