our study confirmed the efficacy of intrarectal quinine in the management of severe malaria.

Pooling data from similar studies allowed us to reach a sample size close to that suggested by Eisenhut [1]. Pooling the Nigerian and Ugandan data revealed an interesting but non-statistically significant trend toward higher mortality in the intravenous quinine group, compared with the rectal quinine group (15.4% [14 of 91 patients] vs. 8.4% [8 of 95 patients]; \( P = .1 \)). Furthermore, pooling data from similar studies in which intravenous quinine was administered to 327 patients in the same hospital from 2003 through 2007 [4, 6, 7] showed a trend of lower mortality in the intrarectal quinine group (8.4% [8 of 95 patients] vs. 15.9% [37 of 232 patients]; \( P = .07 \)) [7, 8].

However, we believe that the debate should focus on another topic. Less than 20% of deaths come to the attention of any formal health care system [8]. Therefore, hospital-based trials investigating severe malaria are affected by a survival bias, because only children who survive and seek care in a hospital can be evaluated. In our comparison of the 2 treatment modes, we noted that intravenous quinine is available only at hospitals and that intrarectal quinine could be available at the village level. Therefore, rectal quinine could be administered early, at the onset of illness, with a mean of 3.5 days before reaching the hospital [4]. In these situations, rectal quinine is likely to save more lives than intravenous quinine. Indeed, a study comparing the 2 routes should be performed at the community level, not at the hospital level.

Eisenhut [1] also commented on the need to focus on comparison of safety, convenience, and cost implications. However, a study performed since his review [9] provide this information. We previously evaluated drug tolerance among 898 patients in a randomized study in Burkina Faso; the feasibility and acceptability of treatment at the community level have recently been evaluated in Niger, Mali, and Senegal [10–12].

We acknowledge the comments by Eisenhut [1]; however, our results highlight the important role that rectal quinine could play as early treatment in settings where there are often insurmountable challenges associated with transferring patients to medical centers that are better equipped to handle such cases.

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Jane Achan,1 Hubert Barennes,2 Justus Byarugaba,1 and James K. Tumwine1

1Department of Pediatrics and Child Health, Makerere University, Kampala, Central Uganda; and 2Institut Francophone de Medecine Tropicale, Vientiane, Laos

Reference


Michael Eisenhut
Luton & Dunstable Hospital National Health Service Foundation Trust, Luton, United Kingdom

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Reply to Eisenhut

To the Editor—Eisenhut [1] underlined the importance of the equivalence trial design for the comparison of rectal quinine treatment with other quinine applications. Very few cerebral malaria studies have been able to enroll a sufficient number of patients to answer the primary outcome of mortality among patients, and most studies have focused on secondary outcomes. Analysis of mortality can only be realized through costly multicenter studies, which are beyond the reach of many clinicians working in resource-constrained countries.

Although quinine remains the main treatment for severe malaria in Africa, alternative and simple techniques, such as the rectal route, have received little support. Since the first publications by Barennes in 1989 and 1994 [2, 3], only 2 randomized studies evaluating rectal quinine for the treatment of cerebral malaria have been performed [4, 5]. We acknowledge that our recent study [4] had insufficient power to demonstrate equivalence between the 2 treatment groups; nonetheless,
Tigecycline for Acinetobacter baumannii Infection: Other Considerations

To the Editor—In the 15 February 2008 issue of Clinical Infectious Diseases, Anthony et al. [1] published a retrospective study that included 18 patients who had serious infections due to multidrug-resistant, gram-negative microorganisms and who were treated with tigecycline. They found that Acinetobacter baumannii isolates with pretherapy MICs of tigecycline of $\geq$2 mg/L were associated with higher mortality rates and suggested that, if susceptibility data allow it, therapy with $\beta$-lactams or carbapenems should be used instead of tigecycline.

We agree with the authors that more formal comparative data related to tigecycline use—in addition to use for approved indications (i.e., treatment of skin, skin-structure, and intra-abdominal infections)—are needed. However, in our opinion, the authors omitted several points that deserve consideration.

With regard to tigecycline susceptibility tests, Sahm et al. [2] found that the MIC$_{50}$ of tigecycline for Acinetobacter species is 2-fold higher with Etest than it is with broth-based methods, and MIC$_{90}$s were never lower when determined with the Etest than with broth-based methods. Therefore, we believe that Anthony et al. [1] should have used broth-based methods to determine susceptibility, at least for isolates with an MIC of tigecycline of $\geq$2 mg/L, before concluding that the intermediate susceptibility (MIC, 3 mg/L) was associated with poor clinical outcomes.

In addition, the authors did not mention whether patients who were infected with tigecycline-intermediate isolates had received previous antibiotics. The overexpression of the AdeABC multidrug efflux pump, which is the mechanism of tigecycline-resistant in Acinetobacter species, can be up-regulated with previous use of other antibiotics (e.g., fluoroquinolones and aminoglycosides), which are frequently administered to patients with serious infection [3, 4]. The authors state that all the patients who were infected with A. baumannii that had intermediate susceptibility to tigecycline died of infection (i.e., they had an infection-related death). Three of these patients had a diagnosis of ventilator-associated pneumonia, and the remaining patient had mediastinitis. Several considerations should be taken into account.

First, no score (e.g., APACHE II or Mortality Probability Model II) was used to measure the severity of illness in patients who did or did not have a positive clinical response. Second, the mean length of hospital stay before receipt of the first dose of tigecycline was higher for patients who died (58.5 vs. 16.8 days; $P = .054$, by the Wilcoxon rank sum test), thus increasing the probability of infection with multidrug-resistant, gram-negative microorganisms [5]. In fact, the rate of infection with imipenem-resistant A. baumannii was higher among patients who died than among those who survived (100% and 33%, respectively; $P = .0381$, by 1-tailed Fisher’s exact test); by itself, imipenem-resistant A. baumannii infection is a predictor of mortality [6]. Third, the 95% CI for mortality in the A. baumannii group indicates that the real mortality rate could be between 4.6% and 75%. In summary, establishment of the relationship between mortality and the susceptibility of A. baumannii to tigecycline deserves a more complex analysis.

Finally, in contrast to the authors’ advice, we note that one of the main reasons to use tigecycline at our hospitals is to reduce use of carbapenems (e.g., for treatment of nosocomial peritonitis or surgical site infection), with the aim of preserving and, in some cases, recovering lost susceptibilities (e.g., for multidrug-resistant Pseudomonas aeruginosa). With regard to off-label use of tigecycline (e.g., for ventilator-associated pneumonia), physicians must evaluate the benefits and risks of use of this antibiotic for indications that still lack rigorous scientific support.

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D. Curcio and F. Fernández
Sanatorio San José, Infectología Institucional SRL, Capital Federal, Argentina

References


Reprints or correspondence: Dr. James Tumwine, Paediatrics and Child Health, Makerere University Medical School, PO Box 7072, Kampala 256, Central Uganda (jturnwine@imulu.com).

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