

# Safety and efficacy of rectal compared with intramuscular quinine for the early treatment of moderately severe malaria in children: randomised clinical trial

Hubert Barennes, Tatiana Balima-Koussoubé, Nicolas Nagot, Jean-Christophe Charpentier, Eric Pussard

## Abstract

**Objective** To compare the safety and efficacy of quinine given by the rectal route with quinine given by the intramuscular route in children with moderately severe *Plasmodium falciparum* malaria.

**Design** Randomised, open, clinical trial.

**Setting** Health centre in Burkina Faso.

**Participants** 898 children with moderately severe *P falciparum* malaria who were unable to take oral treatment.

**Intervention** Rectal quinine (20 mg/kg diluted to 30 mg/ml in water solution) or intramuscular quinine (12.5 mg/kg) every 12 hours until oral quinine could be taken.

**Main outcome measures** Primary safety outcome was the presence of blood in stools and secondary safety outcome was diarrhoea. Primary efficacy outcome was early treatment failure and secondary efficacy outcomes were late clinical and parasitological failures, fever clearance time, and time to oral intake.

**Results** Blood in stools and diarrhoea were more common in children given quinine by the rectal route than by the intramuscular route (blood in stools: 5% *v* 1%, absolute difference 3.9%, 95% confidence interval 1.8% to 6.1%; diarrhoea: 5% *v* 1%, 3.5%, 1.3% to 5.7%). On anoscopy, inflammatory lesions (9/248, 3%) were associated with bloody striations in stools. Side effects of rectal quinine were rare and transitory. Local pain (90%), inflammation (79%), and transient impairment of mobility (15%) were observed with intramuscular quinine. Early treatment failure was higher in the rectal group (6% *v* 3%, absolute difference 3.0%, 95% confidence interval 0.2% to 5.9%). All except two children in each group had negative blood slide results at day 5. Fever recurrence at day 7 was higher in the intramuscular group (37/375 *v* 18/395, absolute difference 5.3%, 1.6% to 8.9%). Other efficacy outcomes (late clinical failure, late parasitological failure, fever clearance time, time to starting oral intake and rate of deterioration to severe malaria) did not differ.

**Conclusion** Quinine given through the rectal route has an acceptable safety profile and could be used in the early management of malaria in children in sub-Saharan Africa, halting progression to severe disease.

## Introduction

Most of the 1-2 million deaths from malaria each year, primarily of African children aged under 5 years, occur at home or at the first level of health care,<sup>1</sup> when intravenous infusion of quinine is often unsuitable. If oral treatment is not possible, quinine is usually given by the intramuscular route, although often unsafely.<sup>2</sup> The

rectal route is an alternative means of treating the early stages of severe malaria.<sup>3</sup> Preliminary studies support the use of rectal quinine.<sup>4-7</sup> We compared the safety and efficacy of rectal quinine compared with intramuscular quinine in children with moderately severe malaria.

## Methods

Our study was carried out in Hambdallaye Health Centre, Bobo-Dioulasso, Burkina Faso, from September 2001 to December 2002. In this malaria endemic area, isolates are fully sensitive to quinine.<sup>8</sup> We included children and young people aged 1 to 15 years with *Plasmodium falciparum* malaria who were unable to take oral treatment. We excluded children with a history of diarrhoea, current anal disease, or those who had received a traditional enema in the preceding week.

On enrolment we carried out a complete medical history and physical examination. Children were followed up twice daily for the first three days and then on days 5 and 7. We made home visits for missed appointments. During the second year of the study, we added an examination on day 14 (335 children) to look for delayed side effects.

The children were screened for eligibility criteria by a nurse at the health centre. A blood test for parasites was carried out by the study microscopist. Treatment was allocated according to a randomisation scheme kept sealed in an envelope until the patient was eligible and consent had been obtained.

## Drug administration and laboratory tests

For both the rectal and intramuscular routes we used the intravenous form of quinine gluconate (Quinimax, containing 96% quinine, 2.5% quinidine, and 0.67% cinchonin and cinchonidin; Sanofi-Synthelabo, Gentilly, France). The intramuscular dose (12.5 mg/kg of quinine base) was administered in the gluteal muscle. The rectal dose (20 mg/kg of quinine base) was prepared by dilution of quinine gluconate in water to obtain a 30 mg/ml solution. The children were observed for one hour after drug administration and received a further half dose if the drug was expelled during this period.<sup>9</sup> The drug was administered (maximum of six times) under medical supervision every 12 hours until the patient was able to swallow tablets. Quinine was then given orally (8 mg/kg, every eight hours) to complete a seven day course.

We prepared Giemsa stained thick and thin films from blood obtained from the children by finger prick at enrolment and on days 3, 5, 7, and 14. A routine

Centre MURAZ,  
01BP390  
Bobo-Dioulasso,  
Burkina Faso  
Hubert Barennes  
*epidemiologist*  
Tatiana  
Balima-Koussoubé  
*general practitioner*  
Nicolas Nagot  
*epidemiologist*

Methodology and  
Research Centre,  
Cernay les Reims,  
France

Jean-Christophe  
Charpentier  
*statistician*

Hôpital du Kremlin  
Bicêtre, Service de  
Pharmacologie,  
France

Eric Pussard  
*pharmacologist*

Correspondence to:  
H Barennes, Institut  
de la francophonie  
pour la médecine  
tropicale, BP 9519  
Vientiane, Lao  
People's Democratic  
Republic  
hubert.barennes@  
auf.org

BMJ 2006;332:1055-7



This is an abridged version: the full version is on [bmj.com](http://bmj.com)

**Table 1** Safety outcomes observed in children with malaria after administration of intramuscular or rectal quinine

Outcomes	Rectal group (n=450)	% (95% CI)	Intramuscular group (n=448)	% (95% CI)
Rectal side effects:				
Presence of blood in stools*	21	5 (3 to 7)	3	1 (0 to 1)
Blood in stools	4	1 (0 to 2)	0	0
Blood striation†	17	4 (2 to 5)	3	1 (0 to 1)
At least one abnormal stool‡	357	79 (76 to 83)	50	11 (8 to 14)
Soft stools	105	23 (19 to 27)	24	5 (3 to 7)
Liquid stools (<3 per day)	105	23 (19 to 27)	23	5 (3 to 7)
Diarrhoea (≥3 stools per day)§	21	5 (3 to 6)	5	1 (0 to 2)
Mucoid stools	296	66 (61 to 70)	22	5 (3 to 7)
Painful anal sphincter contraction and tenesmus	46	10 (7 to 13)	2	0.4 (0 to 1)
Isolated painful anal sphincter contraction	19	4 (2 to 6)	1	0.2 (0 to 1)
Isolated tenesmus	10	2 (1 to 4)	1	0.2 (0 to 1)
Anal pruritus	2	0.4 (0 to 1)	1	0.2 (0 to 1)
Intramuscular side effects:				
Local inflammation of gluteus muscle	0		355	79 (75 to 83)
Impaired mobility	0		68	15 (12 to 18)
Decreased hip mobility	0		9	2 (0 to 3)
Leg paraesthesia	0		1	0.2 (0 to 1)
Pain during or after administration¶	9	2 (0 to 3)	404	90 (87 to 92)
Abscess	1	0.2 (0 to 1)	2	0.4 (0 to 1)

\*Absolute difference 3.9% (95% confidence interval 2% to 6%), P<0.001.

†Absolute difference 3.1% (1% to 5%), P=0.001.

‡Absolute difference 68.1% (62% to 75%), P<0.001.

§Absolute difference 3.5% (1% to 6%), P=0.001.

¶Intramuscular v rectal: absolute difference 88.1% (85% to 91%), P<0.001.

anoscopic examination was carried out before treatment and on days 3, 5, and 7 for the first 240 children in each group. Parasitological examinations and bacteriological culture were carried out on mucoid, bloody, or diarrhoeal stools.

### Outcome measures

The primary safety outcome was the presence of blood in stools and the secondary safety outcome was the onset of diarrhoea (more than three stools per day).

We used early treatment failure as the primary efficacy outcome, and the five secondary efficacy outcomes of late clinical failure and late parasitological failure according to standard World Health Organization guidelines,<sup>10</sup> frequencies of deterioration to severe malaria, fever clearance, and time to starting oral intake. The fever clearance time was defined as the time from the start of treatment to the first of two temperature readings below 37.5°C.

### Statistical analysis

The data were analysed on an intention to treat basis.  $\chi^2$  and Fisher's exact tests were used for categorical variables, Student's *t* test and analysis of variance (F test) for normally distributed continuous data, and Bartlett's test to verify the homogeneity of variances. If necessary, non-parametric Mann-Whitney and Kruskal Wallis's tests were used. The groups were compared using absolute differences, with 95% confidence intervals.

## Results

A total of 898 children and young people were randomly assigned to either rectal quinine or intramuscular quinine (see bmj.com). The treatment

groups were comparable at baseline (see bmj.com). The dropout rate was higher in the intramuscular quinine group after day 3.

Blood in stools was rare but was more common in the rectal group and resolved after withdrawal of rectal quinine (in 19 children by day 5 and in two children by day 14; table 1). Blood in stools was associated with anoscopic lesions in nine of 21 patients (43%). Few parasitological or bacteriological infestations potentially responsible for the presence of the blood were observed. Expulsion of mucoid stools—the most common side effect—correlated with painful anal contraction but not with bloody stools, diarrhoea, or abnormalities on anoscopy. Mucoid stools decreased rapidly with change to the oral route (see bmj.com). Early rectal expulsion of quinine occurred in 40 (8.8%) children, with no subsequent expulsion after administration of half dose quinine.

Anoscopic examination was carried out in 248 (55%) children given intramuscular quinine and in 259 (57%) given rectal quinine. Non-specific hyperaemia of the rectal mucosa was observed in both the intramuscular (n=1) and rectal (n=3) groups. Noticeable inflammation of the mucosa was observed in nine children in the rectal group. Six children with mild inflammations or single microulcerations recovered within two days and two children with moderate multiple microulcerations recovered within four and 11 days. One child who had severe ulceration of the rectum, normal results after an anal sphincter examination, and a cutaneous perianal abscess that required surgical treatment, recovered within one month.

Intramuscular injection was painful and caused local inflammation and a high rate of transitory impaired mobility (n=68, 15%). Inflammation at the injection site occurred rapidly (211/443, 47% and 95/44, 21% after the first and second injection), persisted (24%, 92/375 on day 7), and was associated with a higher fever recurrence rate (table 2).

Early treatment failure was higher in the rectal group (table 2). All children had negative blood slide results at day 5 except two children in each group who were aparasitaemic on days 7 and 14. Fever recurrence was higher with intramuscular quinine and related to inflammation of the gluteus. Other secondary efficacy outcomes (late clinical failure, late parasitological failure, fever clearance time, time to starting oral intake and rate

**Table 2** Therapeutic responses to intramuscular and rectal administration of quinine in children with malaria. Values are means (95% confidence intervals) unless stated otherwise

Variable	Rectal group (n=450)	Intramuscular group (n=448)
Quinine doses (mg/kg)	20.0 (18.1 to 22.0)	12.8 (11.2 to 14.3)
No of quinine administrations before switching to oral route	3.4 (2.1 to 4.8)	3.6 (2.3 to 5.0)
No (%) with early treatment failure on day 3*	26/417 (6)	13/413 (3)
Late clinical failure	1	0
Late parasitological failure	0	0
Fever clearance time (days)	1.8 (0.5 to 3.1)	1.7 (0.3 to 3.1)
Time to oral intake (days)	1.3 (0.2 to 2.3)	1.3 (0.5 to 2.0)
No (%) with fever recurrence on day 7†	18/395 (5)	37/375 (10)

\*Absolute difference 3.0% (95% confidence interval 0.2% to 5.9%), P=0.05.

†Intramuscular v rectal: absolute difference 5.3% (1.6% to 8.9%), P<0.005.

of deterioration to severe malaria) did not reach statistical significance between the groups (table 2). Clinical deterioration and mortality were similar between the intramuscular and rectal groups (9/448 v 4/450).

## Discussion

Quinine administered by the rectal route has an acceptable safety profile in the early management of moderately severe malaria in children who are unable to take oral treatment. Efficacy was lower, although still acceptable, than with intramuscular quinine at three days but achieved rates similar to intramuscular quinine from day 5 onwards.

The rectal route was painless. Its main drawback, mucoid stools, was not associated with diarrhoea and probably resulted from over-stimulation of the rectal mucosa.

Blood in stools and lesions detected on anoscopy were higher than expected from previous observations in Niger where enemas are infrequent,<sup>11</sup> and required discontinuation of rectal treatment. The past use of traditional enemas was highly correlated with a history of anal symptoms (see [bmj.com](http://bmj.com)) and may sensitise the rectal mucosa to the irritant effect of the solution. We would expect the frequency of blood in children's stools to be lower in most of Africa, where enemas are not routinely used. We observed one severe lesion, with complete recovery. In Niger, rectal quinine was officially adopted in 1994. One case of severe anal abscess with complete recovery and one severe complication from intramuscular injection were reported.<sup>12</sup>

The main disadvantage of rectal administration was expulsion. Early expulsion during the first hour after administration of quinine decreases blood concentrations of quinine by 50%, but immediate administration of half a dose restores an effective blood concentration-time profile.<sup>9</sup>

Pain (90%) and inflammation (79%) of the injection site were the main side effects of intramuscular quinine. Fear of injections can impair compliance with treatment. Fever associated with developing abscesses after intramuscular quinine may lead to a mistaken diagnosis of late treatment failure. Limb paralysis associated with intramuscular quinine is rare but devastating. In field conditions, transmission of bloodborne pathogens through intramuscular injection is high.<sup>2</sup>

In both treatment groups the frequency of clinical deterioration to severe malaria was similar, although the rectal group had a higher frequency of early treatment failures. Operational constraints and field conditions limited the follow-up to 14 days. Differences observed between the groups were moderate and a cost worth paying as deterioration to severe malaria was prevented in 446 of 450 (99%) patients given rectal quinine compared with 439 of 448 (98%) patients given intramuscular quinine ( $P = 0.2$ ).

The inability to take oral treatment represents the first step towards severe malaria in children.<sup>1</sup> Effective management requires the ability to initiate prompt treatment with a potent antimalarial drug. The availability of safe and effective drug administration is a major limiting factor in field conditions.

Quinine vials are available in many remote areas of Africa, but injectable disposables are not. The rectal

## What is already known on this topic

Intramuscular quinine is the treatment of choice for severe *Plasmodium falciparum* malaria in the field

High mortality in children with severe malaria is related to a lack of early treatment of potentially evolving cases

Intramuscular injections of quinine are painful, may transmit infectious diseases, and may lead to impaired mobility

## What this study adds

Rectal quinine has an acceptable safety profile

Rectal quinine could be used to treat moderately severe malaria in the field when qualified staff and equipment are not available

administration of a quinine solution formulated for parenteral injection represents a pragmatic approach allowing availability and immediate treatment anywhere.

We thank the staff of Hamdallaye Health Centre, the Centre Muraz Epidemiological Unit, and the Malaria Unit (RT Guiguemde), the National Hospital Sanou Souro Medecine, Surgery and Pediatric (B Nacro) ward in Burkina Faso, the Bicêtre Hospital Pharmacological Unit (France), and the statistical staff of MRC (France); RT Guiguemde and M Sawadogo for helpful advice; A Sawadogo and F Rasoananadrasana for examination for parasites; J Achan, P Newton, L Srour, and M Strobel for revising the document. We also thank the French Ministry of Foreign Affairs for technical assistance.

Contributors: See [bmj.com](http://bmj.com).

Funding: Impact Malaria, Sanofi-Synthelabo (Gentilly France).

Competing interests: None declared.

Ethical approval: Centre Muraz ethical committee and Ministry of Health of Burkina Faso.

- 1 World Health Organization. Severe falciparum malaria. *Trans R Soc Trop Med Hyg* 2000;94(suppl 1)(3rd ed):1-90.
- 2 Simonsen L, Kane A, Lloyd J, Zaffran M, Kane M. Unsafe injections in the developing world and transmission of bloodborne pathogens: a review. *Bull WHO* 1999;77:789-800.
- 3 Van Hoogdale EJ, De Boer AG, Breimer DD. Pharmacokinetics of rectal drug administration. Part I. General considerations and clinical applications of centrally acting drugs. *Clin Pharmacokinet* 1991;21:11-26.
- 4 Barennes H, Kahiatani F, Pussard E, Clavier F, Meynard D, Njifountawouo S, et al. Intrarectal Quinimax for the treatment of *Plasmodium falciparum* malaria in children in Niger: efficacy and pharmacokinetics. *Trans R Soc Trop Med Hyg* 1995;89:418-21.
- 5 Barennes H, Pussard E, Mahaman SA, Clavier F, Kahiatani F, Granic G, et al. Efficacy and pharmacokinetics of a new intrarectal quinine formulation in children with *Plasmodium falciparum* malaria. *Br J Clin Pharmacol* 1996;41:389-95.
- 6 Barennes H, Munjakazi JM, Verdier F, Clavier F, Pussard E. An open randomized clinical study of intrarectal versus infused Quinimax for the treatment of childhood cerebral malaria in Niger. *Trans R Soc Trop Med Hyg* 1998;92:437-40.
- 7 Barennes H, Daouda K, Pussard E, Munjakazi JM, Fernan M, Sherouat H, et al. Administration intrarectale de la quinine: un traitement précoce du paludisme grave de l'enfant? *Cahiers Santé* 2001;11:145-53.
- 8 Del Nero L, Lamizana L, Nebie I, Sare S, Bougouma L, Pietra V. In vivo sensitivity of *Plasmodium falciparum* to halofantrine hydrochloride in Burkina Faso. *Am J Trop Med Hyg* 1994;50:102-6.
- 9 Pussard E, Straczek C, Kaboré I, Bicaba B, Balima-Koussoubé T, Bourrée P, et al. Dose-dependent resorption of quinine after intrarectal administration to children with moderate falciparum malaria. *Antimicrob Agents Chemother* 2004;48(11):4422-6.
- 10 World Health Organization. *Monitoring antimalarial drug resistance. Report of a WHO consultation*. Geneva: WHO, 2001.
- 11 Barennes H, Mahaman S, Munjakazi JM, Khenine A. Tolérance de la quinine en solution intrarectale chez l'enfant africain. *Med Trop* 1999;59:383-7.
- 12 Harouna Y, Gamatié Y, Gamatié S, Mounkaila H, Boureima M. A propos de deux complications chirurgicales graves de l'usage de la quinine intramusculaire et intrarectale. *Bull Soc Pathol Exot* 2000;93:328-30.

(Accepted 23 February 2006)