International Journal of Pharmaceutics 392 (2010) 29–34

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Taste-masked quinine pamoate tablets for treatment of children with uncomplicated *Plasmodium falciparum* malaria

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ARTICLE INFO

Article history:
Received 15 January 2010
Received in revised form 2 March 2010
Accepted 7 March 2010
Available online 15 March 2010

Keywords:
Malaria
Quinine
Taste
Tablets
Bioavailability
Efficacy
Paediatrics

ABSTRACT

Children with uncomplicated malaria are generally treated with oral medication, except those unable to take oral drugs. Even though quinine has shown to be effective in treatment of African children with uncomplicated malaria its high bitterness limited the paediatric use. This study aimed to develop taste-masked quinine tablets suitable for children and offering dosing flexibility to adjust the quinine dose in function of body weight.

Methods: Insoluble quinine pamoate was used to formulate fast-disintegrating tablets, using a specific tablet design (rectangular tablet which can be divided into 8 subunits) to allow dosing flexibility. The physical properties of tablets were evaluated in vitro, as well as the quinine bioavailability in healthy adults ($n = 18$) and the efficacy for treatment of children with uncomplicated *Plasmodium falciparum* malaria ($n = 56$) using a 7-day regimen of 8 mg quinine/kg.

Results: Quinine pamoate tablets complied with the pharmacopoeial requirements for mass uniformity, friability, content uniformity, breakability, disintegration and dissolution. The quinine pharmacokinetic parameters after single administration of a quinine pamoate tablet were similar to a commercially available quinine sulfate tablet. The fast decline in parasitemia (28.6%/24 h), the reduction rate of fever (all children were apyretic after 72 h) and the steady state quinine plasma concentration (5.7–15.8 μg/ml) proved the efficacy of the quinine pamoate tablets against *P. falciparum*.

Conclusion: Fast-dispersible and taste-masked quinine pamoate tablets improved dosing accuracy, allowed easy administration and resulted in a high efficacy during the treatment of children with uncomplicated malaria.

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1. Introduction

Malaria causes about 850 000 child deaths every year (UNICEF, WHO, and Rool Back Malaria' Programme, 2006) with the majority of malaria-related morbidity and mortality among children in Africa and Asia. In 2003, about 90% of all malaria deaths in the world occurred in sub-Saharan Africa and malaria is the cause of at least 20% of all deaths in children under 5 years of age (WHO/UNICEF, 2003). It has been estimated that in Africa every 20 s a child dies due to malaria (Bourée, 2006). The high rate of mortality is due to the fact that the majority of infections in Africa are caused by *Plasmodium falciparum*, the most dangerous of the four human malaria parasites.

The treatment of malaria involves different types of medicines in monotherapy or combination therapy. The artemisinin-based combinations, such as artesunate-amodiaquine (Adjuik et al., 2002) and artemether-lumefantrine (van Vugt et al., 2000), are currently the most advocated for treating African children with uncomplicated *P. falciparum* malaria. However, *P. falciparum* is also sensitive to quinine (Bjorkman, 1991; Bourée, 2006), and the available evidence reports that African strains of *P. falciparum* generally remain sensitive to quinine (Barennes et al., 1996; Henry et al., 2006; Pradines et al., 2006; Tinto et al., 2006; Quashie et al., 2007). Even though quinine resistance was first documented in 1910, *P. falciparum* sensitivity to quinine is still retained throughout the world (Deen et al., 2008), and more than half of the national malaria control programs in Africa still recommend monotherapy with oral quinine as second line treatment. In routine practice, the use of oral quinine

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0378-5173/$ – see front matter © 2010 Published by Elsevier B.V.
doi:10.1016/j.ijpharm.2010.03.023

as a first line treatment seems to be widespread (Reyburn et al., 2009). Currently, quinine is recommended by WHO as the first line treatment in combination with clindamycin and in monotherapy as second line for most countries, except those in Southeast Asia and the Amazon basin (Kremsner et al., 1994; Bar-Zeev and White, 2006).

The available oral quinine drugs are presented as tablets of quinine hydrochloride, quinine dihydrochloride, quinine sulfate and quinine bisulfate, which are intensely bitter. Since children with uncomplicated malaria are generally treated with oral medication (except those who are vomiting or otherwise unable to take oral drugs) (Deen et al., 2008), such bitterness has limited the paediatric use of quinine, negatively affecting the compliance or requiring a compulsory supervision of caregivers. The treatment will be stopped before completion when children receive unpalatable oral quinine. Consequently, the available quinine salts are less recommended for ambulatory paediatric patients. The compliance cannot be improved by shortening the duration of treatment, because different studies have shown that the efficacy of quinine on uncomplicated *P. falciparum* malaria is obtained only if given on 7 consecutive days to cover 3 or 4 blood life cycles of the malaria parasite (White, 1997; Pukrittayakamee et al., 2003; Bourée, 2006).

Taste masking of the available quinine formulations by coating has shown to positively affect compliance in adults (Jansen et al., 1997; Douroumis, 2007). However, coating is less applicable to paediatric dosage forms since liquid preparations are the most suitable for paediatrics. In addition, the lack of appropriate paediatric formulations obliges caregivers to break the available quinine tablets for adults, and such practice also destroys the taste mask coating.

Moreover, quinine has revealed difficulties when administered via alternative routes: risk of limb paralysis following intramuscular injection (White and Krishna, 1989), poor availability when rectally administered with the eventual loss of medicine by expelling from the rectum (Pussard et al., 2004), and limited availability of appropriate equipment and trained staff required for perfusion of quinine at basic health centers in low and middle-income countries. Therefore, oral administration of quinine should be preferred on condition that the problem of bad taste is overcome.

In this perspective, a poorly soluble quinine salt (i.e. quinine pamoate) has been designed for efficient taste masking during the treatment of children (Vervaet and Remon, 2009). The objective of this study was to develop a solid paediatric quinine pamoate containing dosage form suitable for treatment of uncomplicated *P. falciparum* malaria in children. In addition, the bioavailability (in healthy adults) and clinical efficacy (in children with uncomplicated *P. falciparum*) was assessed.

2. Materials and methods

2.1. Materials

Quinine hydrochloride dihydrate and disodium pamoate salt (used for in situ precipitation of quinine pamoate) were obtained from Sigma–Aldrich (Germany). The following excipients were used to prepare quinine pamoate tablets: microcrystalline cellulose (Avicel® PH102, FMC, Ireland), sodium starch glycolate (Explotab®, JRS Pharma, Rosenberg, Germany), magnesium stearate (Fagron, Belgium) and colloidal silicium dioxide (Aerosil®) (Alpha Pharma, Belgium). Tablets containing 300 mg quinine sulfate (Batch SB 06-11016, Pharmakina, Bukavu, RD Congo) were donated by the University Hospital of Butare (Rwanda). Hydrochloric acid (VWR, Leuven, Belgium), acetonitrile (Biosolve, Valkensewaard, Holland) and ammonium acetate (UCB Pharma, Leuven, Belgium) were used as analytical reagents.

Table 1
Composition of the quinine pamoate tablet.

Ingredients	Amount per tablet
Quinine pamoate	300 mg
Microcrystalline cellulose (Avicel PH 102)	650 mg
Sodium starch glycolate (Explotab®)	40 mg
Colloidal silicium dioxide (Aerosil®)	5 mg
Magnesium stearate	5 mg

2.2. Preparation of quinine pamoate

Quinine pamoate (QP) was prepared via in situ precipitation by mixing 100 ml of an aqueous 4% (w/v) quinine hydrochloride dihydrate solution with 100 ml of an aqueous 2.4% (w/v) disodium pamoate salt solution. The precipitate was isolated by filtration, oven-dried at 50 °C for 24 h and sized through a 250 μm sieve.

2.3. Characterization of quinine pamoate powder

The residual moisture content was determined by weight loss using an infrared dryer at 105 °C (LP16, Mettler, Greifensee, Switzerland). The compressibility index (Carr's index) and the Hausner ratio were calculated based on the bulk (determined via the volume occupied by 100 g powder) and tapped density (determined via the volume occupied by 100 g powder after 1000 taps). Particle size distribution was analyzed via laser diffraction using the Mastersizer-S (Malvern, UK).

The quinine content in quinine pamoate was determined via HPLC, after dissolution of quinine pamoate powder in 0.1 N HCl. The HPLC system consisted of a solvent pump (L-7110, Hitachi, Tokyo, Japan) set at a flow rate of 0.8 ml/min, a fluorescence detector (L-7480, Hitachi, Tokyo, Japan) set at 325 and 375 nm as excitation and emission wavelength, respectively, a C18 reversed phase column (Lichrospher 100 RP 18 (5 μm), Merck Darmstadt, Germany) and an automatic integration system (L-7000, Hitachi, Tokyo, Japan). The mobile phase consisted of a filtered and degassed mixture of 0.1 M ammonium acetate, acetonitrile and methanol 40/15/45). The pH was adjusted to pH 3.0 using perchloric acid.

2.4. Preparation of quinine pamoate tablets

Fast-disintegrating quinine pamoate tablets (Table 1) suitable for paediatric application were formulated using a specific tablet design, having a rectangular shape (22.4 mm long, 11.2 mm wide), with multiple score lines on both sides (dept 0.89 mm, angle 100°) to allow easy breaking into 8 subunits (Kayitare et al., 2009). Each tablet contained 300 mg quinine pamoate, equivalent to 160 mg of quinine base (i.e. the dose necessary for treatment of a 20 kg child (WHO/FCH/CAH/00.1, 2000).

The powders were mixed for 20 min using a tumbling mixer (Turbula, Switzerland) and compressed at 12 kN using a single punch tablet press (Korsch EK0, Berlin, Germany) (Kayitare et al., 2009).

2.5. In vitro tablet evaluation

Mass uniformity ($n = 3$), friability ($n = 3$) and disintegration time (in water, $n = 3$) of the tablets were assessed according to European Pharmacopoeia (EP6) methods (European Pharmacopoeia, 2009). In addition, the disintegration time of subunits of the tablets was evaluated by recording the time required for disintegration of a half, quarter and 1/8 tablet in a small amount of water (4 ml) on a spoon (Kayitare et al., 2009). The breakability of the tablets was assessed by determining the weight uniformity of the tablet subunits after manual breaking of the tablets in 1/2, 1/4, 3/4 and 1/8 (Kayitare et al., 2009).

The quinine content uniformity was assessed in entire tablets ($n = 10$) and in the smallest subunit (1/8 tablet, $n = 16$). Individual samples were dissolved in 100 ml 0.1 N HCl. After filtration through a 0.2 μm cellulose acetate filter (Sartorius, Goettingen, Germany), the quinine content was determined via HPLC analysis as previously described. Quinine release from the tablets was tested in 900 ml 0.1 N HCl using the EP6 paddle method (VK 7010, Varian, Belgium) at 50 rpm and 37 °C. An aliquot (5 ml) was withdrawn at specific time intervals (5, 10, 15, 20, 25, 30, 45 and 60 min) and the quinine concentration was spectrophotometrically determined at 248 nm. Quinine pamoate tablets and commercially available quinine sulfate tablets (Quinine Sulfate 300 mg, Pharmakina, Bukavu, R.D.Congo) were analyzed. The release profile from both type of tablets was compared using the f_2 similarity factor given by Moore and Flanner (FDA Guidance for Industry, 1997).

2.6. Bioavailability of quinine after single dose administration to healthy adults

Quinine bioavailability was determined in healthy adult volunteers after single oral administration of 240 mg quinine, via quinine pamoate (1.5 tablet per volunteer) or quinine sulfate tablets (1 tablet per volunteer). This study had an open randomised 2-period cross-over design. The washout period between each medication intake was two weeks. The study protocol was elaborated according to the Guidance on Good Clinical Practice (ICH E6 (R1), 2002I) and approved by the Ghent University Hospital Ethics Committee and by the Rwandan National Ethics Committee. The study was realized at the Teaching Hospital of Butare (CHUB, Rwanda).

18 volunteers (8 females and 10 males), aged between 20 and 35 years (26.7 ± 8.1 years) and weighing from 52 to 73 kg (62.6 ± 6.9 kg) participated in the bioavailability study.

Subjects fasted for at least 8 h before entering the test facility and no food or fluid intake was allowed until 2 h after medication intake. The quinine tablets were administered with 200 ml of water. The subjects were observed for 4 h after drug administration and remained in the testing facility for 24 h after receiving the dose.

Venous blood samples (6 ml) were taken 0.5 h before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 h after drug administration. Blood samples were collected in heparinized tubes and centrifuged for 10 min at 1500 × *g* within 2 h after collection. Separated plasma was transferred in plastic tubes and stored at −20 °C until assayed.

Quinine plasma concentrations were determined using a validated reverse phase HPLC method. Before analysis the plasma samples were extracted using the liquid–liquid extraction method described by Salako and Sowunmi (1992): 500 μl internal standard solution (5 μg/ml propranolol) and 500 μl 2 N sodium hydroxide were added to 500 μl plasma sample and vortex-mixed for 1 min. 3 ml diethylether was added to this mixture. After intense mixing and centrifugation (5 min at 2500 × *g*) the upper layer was transferred to another tube and evaporated to dryness under nitrogen stream. The residue was reconstituted in 500 μl mobile phase and 20 μl was injected into the chromatograph. The mobile phase was composed of a mixture of 0.1 M ammonium acetate, acetonitrile and methanol (40/15/45; v/v/v), pH was adjusted to 3.0 using perchloric acid.

The pharmacokinetic parameters (C_{max}, t_{max} and $AUC_{0-24\,h}$) after administration of both tablet formulations were statistically compared using a *t*-test.

2.7. Efficacy and steady state pharmacokinetics after administration of quinine pamoate tablets to children with uncomplicated malaria

The therapeutic efficacy of taste-masked quinine pamoate tablets was evaluated based on the assessment of clinical and parasitological outcomes (White, 1997) of a 7-day treatment, and on the reappearance of parasites in blood after 7 and 14 days.

The study was conducted according to the WHO guidelines on antimalarial drug efficacy assessment. Therefore, the study was a simple, one-arm and prospective evaluation of the clinical and parasitological response during treatment of uncomplicated malaria (WHO/HTM/RBM/2003.50, 2003).

As a minimum of 50 participants is recommended by WHO for the evaluation of antimalarial treatment (in case of a test drug with an expected failure less than 15%) (WHO/HTM/RBM/2003.50, 2003), 56 children were included in this study. The study was held at the District Hospital of Kabutare in Rwanda where in 2007 a parasite prevalence rate of 2.4% was reported in children under 5 years of age (WHO, 2008).

The inclusion criteria were those defined in the WHO guidelines on antimalarial drug efficacy assessment. Patients were selected on the basis of the following criteria: aged between 6 and 59 months, slide-confirmed infection with *P. falciparum* only (i.e. no mixed infections), initial parasite density between 2000 and 200 000 parasites/μl, absence of general danger signs (inability to drink or breastfeed; vomiting; recent history of convulsions; lethargy or unconsciousness; inability to sit or stand up), absence of signs of severe and complicated falciparum malaria, armpit temperature above 37.5 °C (WHO/HTM/RBM/2003.50, 2003).

The exclusion criteria also included: history or allergy to quinine, use of halofantrine or quinine within the previous two weeks, presence of febrile conditions caused by diseases other than malaria, presence of mixed infection, severe anaemia, and abnormal function of kidney, liver and heart as confirmed by the laboratory tests.

All children received oral quinine (8 mg quinine base/kg body weight every 8 h) for a 7-day regimen. To control the exact drug dosing time (every 8 h) and to allow regular clinical assessments during the initial part of the study, the patients were hospitalized (in rooms separate from the paediatric ward) for 4 days at the beginning of treatment, whereas the final 3 treatment days were completed at home with pre-packed individual doses. The required quinine dose per child was calculated based on the body weight, and the quinine pamoate tablets were accurately broken using the score lines to adjust the quinine dose. The tablet (or subunits thereof in function of the required dose) were dispersed in a small amount of water on a spoon and administered as a liquid to the children by nurses at the hospital and by parents at home. The patient was observed for at least 30 min after drug administration to ascertain retention of the drug. If the patient vomited within the first 30 min post administration, the treatment was repeated with the same dose.

The clinical assessments were made on days 1, 2, 3, 4, 7 and 14 (WHO/HTM/RBM/2003.50, 2003). As patients were discharged from hospital after clinical assessment on day 4, the patients were asked to return to hospital on days 7 and 14 for control assessments. The data of a subject were only evaluated if the entire study was completed (i.e. including the control tests at days 7 and 14).

Since parasites of *P. falciparum* are sequestered in the microcirculation (White et al., 1992), parasitological recovery from malaria was assessed by the clearance of parasites from peripheral blood smears (White, 1997). The percentage of parasitaemia during treatment was calculated on days 1, 2, 3, 7 and 14 based on the parasite burden before the first quinine dose (i.e. 100% parasitaemia). The time required for the complete parasite clearance was also recorded.

The body temperature was measured every 8 h, just before dose administration. Fever clearance time (FCT) was defined as the time required for the body temperature to fall below 37.5 °C and remain below this value at least 48 h.

Table 2
Pharmacokinetic parameters (mean ± SD, $n = 18$) after oral administration of 240 mg quinine via quinine pamoate and quinine sulfate tablets to healthy volunteers.

	Quinine pamoate tablets	Quinine sulfate tablets
C_{max} (μg/ml)	1.8 ± 0.2	1.7 ± 0.3
T_{max} (h)	2.4 ± 0.3	2.6 ± 0.5
$T_{1/2}$ (h)	10 ± 0.9	10.2 ± 1.1
$AUC_{0-24\,h}$ (μg h/ml)	19.4 ± 3.1	20.5 ± 2.5

On the 4th treatment day the steady state quinine plasma concentrations were determined over the 8 h interval between the 10th and 11th dose administration. Blood samples were taken every hour, but as per child only a single blood sample was taken the children were randomly divided into 8 groups (7 children/group). EMLA patches were used for local anesthesia and venous blood samples (3 ml) were collected in heparinized plastic tubes. The samples were analyzed as previously described for the bioavailability study in healthy adults.

3. Results and discussion

3.1. Physical characteristics of quinine pamoate powder

The residual moisture content of the powder was 4.2% (SD = 0.2), and its compressibility index of 23 and Hausner ratio of 1.2 indicated that the powder has a fair flowability (Schussele and Bauer-Brandl, 2003), which was favorable for direct compression (Gibson, 2001).

The mean particle size of the quinine pamoate powder was 14.3 μm, with a d_{10} and d_{50} of 0.7 and 53.1 μm, respectively. HPLC showed that 100 mg quinine pamoate powder contained 52.6 ± 1.1 mg quinine.

3.2. Development of solid oral paediatric quinine pamoate formulations

Tablets formulated with the quinine pamoate powder resulted in high quality tablets which complied with the EP 6 requirements for friability (0.7 ± 0.2%), mass uniformity (1002.8 ± 1.5, 501.6 ± 3.9, 250.5 ± 4.5 and 125.2 ± 5.1 mg for the entire, half, quarter and 1/8 tablet, respectively), content uniformity (161.1 ± 3.1 and 18.8 ± 0.9 mg for the entire and 1/8 tablet, respectively), breakability (4.1% CV, weight loss (0.5% in case of 1/8 tablet), disintegration time (<15, 18, 20 and 15 s for the entire, half, quarter and 1/8 tablet, respectively) and dissolution (>90% of quinine pamoate within 10 min). The dissolution profiles of the quinine pamoate tablets and the commercially available quinine sulfate tablets were not significantly different ($f_2 > 50$).

3.3. Bioavailability of quinine after single dose oral administration to healthy adults

The quinine bioavailability after oral administration of the newly designed quinine pamoate tablets was determined in adult volunteers (in comparison to a commercially available quinine formulation) prior to the assessment of the efficacy of the quinine pamoate tablets in children.

Table 2 presents the pharmacokinetic parameters, and Fig. 1 the average plasma concentration–time profile, after oral administration of 240 mg quinine via quinine pamoate and quinine sulfate tablets.

No significant difference (t-test, $p \geq 0.28$) was detected between the pharmacokinetic parameters. In other studies similar pharmacokinetic values after oral administration of quinine were found when the administered quinine dose was taken into account

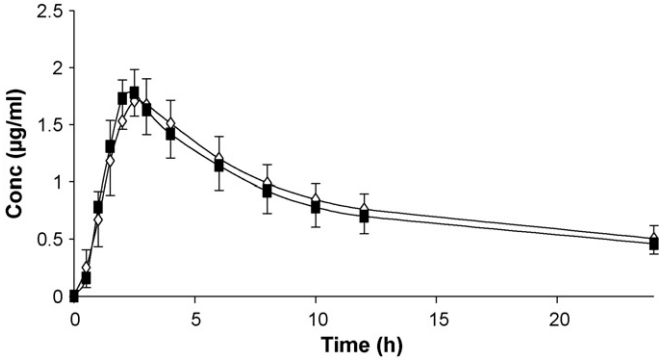

Fig. 1. Quinine plasma concentration vs. time profiles after oral administration of 240 mg quinine via quinine pamoate (■) and quinine sulfate (◊) tablets to healthy volunteers.

(Rimchala et al., 1996; Sowunmi, 1996; Kayumba et al., 2008; Soyinka et al., 2009).

3.4. Efficacy of quinine pamoate tablets in the treatment of children suffering from uncomplicated P. falciparum malaria

56 children (27 male and 29 female) with confirmed *P. falciparum* malaria and the following characteristics (mean ± standard deviation, range) were included in the study: age 28.5 ± 16.1 months (6–59 months), body weight 11.4 ± 2.9 kg (range, 6–20 kg), parasitaemia: 19 435 parasites/μl (2180–160 000 parasites/μl).

As the specific tablet design (with 8 subunits) allowed to dose with 20 mg dose intervals (corresponding to 2.5 kg of body weight), the doses administered to the children varied between 7.3 and 9.0 mg/kg (average = 8.1 mg/kg).

Since the tablets were fast disintegrating, dispersion of the tablet (or subunits thereof) in a limited volume of water (on a spoon) was suitable to administer the quinine dose to children, although some children (3 years and more) swallowed the formulation as a solid without dispersing it in water. The absence of bitterness of quinine allowed easy administration as all children were cooperative, no patients refused or spilled the drug. This was promising for compliance when the medication was continued at home during the 3 final treatment days. Indeed, all parents reported completion of treatment for all patients enrolled in the study.

Our findings showed that the parasitaemia decreased rapidly after administration of quinine pamoate tablets: 28.6 (±16.8), 4.8 (±4.1) and 0.4% after 24, 48 and 72 h, respectively. In terms of the average burden of *P. falciparum*, parasitaemia was 19 435, 5559, 914 and 96 parasites/μl of peripheral blood taken before and 24, 48 and 72 h after quinine administration, respectively. After 72 h, parasitaemia was not detected in 75% of the patients, and 100% tested negative at the 7th day of treatment, without recrudescence at day 14.

Our results were comparable to those obtained in a previous study assessing the efficacy of quinine given orally for 7 days to children with uncomplicated malaria in Cameroun, when a dose of 8.3 mg of quinine base/kg was given every 8 h. The parasitaemia was undetectable from the third day in all children ($n = 30$), no rebound was observed at days 7 and 14 (Le Jouan et al., 2005). Comparable results have also been reported by Barennes et al. (1996) after treating falciparum malaria in children using 12.8 mg quinine gluconate/kg administered via the intrarectal, intramuscular or intravenous route: parasitaemia after 48 h was 7.4 ± 16%, 4.1 ± 4.2% and 2.2 ± 3.8%, respectively; all children were aparasitemic on day 7 (Barennes et al., 1996).

The fever clearance was monitored by taking the armpit temperature every 8 h. A body temperature above 37.5 °C was considered

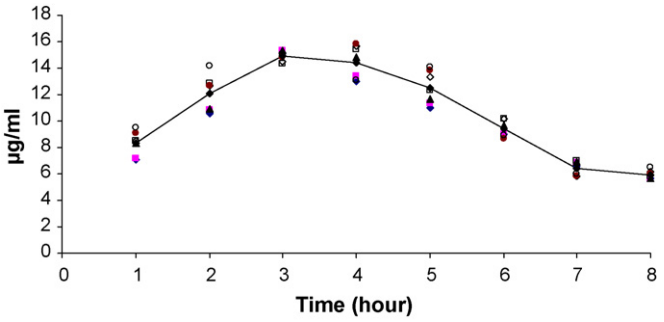

Fig. 2. Steady state quinine plasma concentrations ($n = 7$) in function of time after repeated administration of quinine (8 mg/kg body weight). A quinine dose was administered at $t = 0$ h.

as fever and an antipyretic (paracetamol syrup) was administered to prevent febrile convulsions (Lell et al., 2001). The first day of treatment was characterized by fever in the majority of patients, 8 h after start of treatment the average axial temperature was 37.6 (±0.5) °C, compared to 37.1 (±0.5) °C. and 36.9 °C on the 2nd and 3rd day, respectively. The average delay before apyrexia was 39.3 ± 22.6 h, which was comparable with 34.7 ± 22.6 h reported by (Sailler et al., 2001).

The reduction rate of fever episodes was correlated with the reduction of parasitaemia and other symptoms of malaria like vomiting (not more observed after the 2nd treatment day). The percentage of children without an episode of fever increased with the duration of treatment and is in accordance with other studies where quinine was used to treat uncomplicated *P. falciparum* malaria in children (at 72 h all children were apyretic) (Pussard et al., 2004; Le Jouan et al., 2005).

The average plasma concentration of quinine was 10.4 ± 3.4 μg/ml with a minimum of 5.7 μg/ml and a maximum of 15.8 μg/ml (Fig. 2). The maximum concentration was obtained 3 h after administration. Oral administration of quinine sulfate formulated in pellets resulted in comparable plasma concentrations. However, the specific design of the quinine pamoate tablets offers technological advantages as the entire dose range for children up to 20 kg is covered with a single dosage form, whereas body weight adapted dosing by means of the pellets required that the pellets were packed into capsules of different sizes (Kayumba et al., 2008). Following treatment of children with 8 mg/kg quinine three times a day for 7 days similar plasma concentrations were also reported by different authors (Pussard et al., 2004; Le Jouan et al., 2005).

Since the quinine concentration in plasma and red blood cells must remain within therapeutic ranges to inhibit parasite replication throughout the course of treatment and to eradicate the infection (White et al., 1983; Pukrittayakamee et al., 2003), our results were compared to other literature reports. White et al demonstrated that quininemia obtained with 25 mg quinine/kg/day ranged between 8 and 20 μg/ml, claiming that these concentrations were required to obtain therapeutic efficacy (White, 1996). However, other studies showed good therapeutic outcomes with quinine plasma concentrations ranging between 5 and 18 μg/ml. Sailler et al. showed that a dose of 8 mg quinine base/kg/12 h resulted in a quininemia between 5 and 10 μg/ml, providing a high rate of early therapeutic success against uncomplicated African malaria (Sailler et al., 2001). Based on these studies it is evident that the steady state quinine plasma concentrations observed in this study resulted in complete parasite clearance as the 7-day treatment period covered 4 life cycles of *P. falciparum* parasites (Kofoed et al., 1997; White, 1997).

In our study, all children were cured after completion of the treatment; and no serious side effects were recorded. The two cases of children withdrawn from the study were not considered as early treatment failure because the parasitaemia was reduced within 48 h, but due to persistent vomiting, a parenteral therapy was necessary (WHO/HTM/RBM/2003.50, 2003).

4. Conclusions

Based on the taste-masking, fast-disintegration, flexible drug dosing, high bioavailability and therapeutic efficacy, the quinine pamoate tablets developed in this study are high efficient for treatment of *P. falciparum* malaria in children.

Acknowledgments

We thank the authorities and staff of the Teaching Hospital of Butare, especially Dr. A. Musemakweri and Dr. G. Ganza for their involvement in the quinine bioavailability study. We are grateful to the authorities and staff of the paediatric wards of the District Hospital of Kabutare, and the Health Centers of CUSP, Mbazi, Matyazo, Rango, Rubona and Rusatira for their help during the efficacy study. Our acknowledgements are also addressed to TRAC Plus/Malaria Unit-Rwanda for their financial support.

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