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.

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).