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Preliminary pharmaceutical development of antimalarial–antibiotic cotherapy as a pre-referral paediatric treatment of fever in malaria endemic areas

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ABSTRACT

Artemether (AM) plus azithromycin (AZ) rectal co-formulations were studied to provide pre-referral treatment for children with severe febrile illnesses in malaria-endemic areas. The target profile required that such product should be cheap, easy to administer by non-medically qualified persons, rapidly effective against both malaria and bacterial infections. Analytical and pharmacotechnical development, followed by *in vitro* and *in vivo* evaluation, were conducted for various AMAZ coformulations. Of the formulations tested, stability was highest for dry solid forms and bioavailability for hard gelatin capsules; AM release from AMAZ rectodispersible tablet was suboptimal due to a modification of its microcrystalline structure.

1. Introduction

According to recent WHO (world health organization) data (WHO, 2012a), 6.9 million of children under the age of five died in 2011. The risk of dying for a child is highest in the neonatal period, and about 16.5 times higher for children under five in sub-Saharan Africa compared to children in developed regions. WHO estimates that more than half of these early child deaths are caused by conditions that could be prevented or treated with existing simple, affordable interventions.

Pneumonia and malaria together cause the majority of deaths from infectious diseases, representing respectively 17% and 7% of deaths of children under five. Malaria deaths are caused by *Plasmodium falciparum*, and two-thirds of the pneumonia deaths are caused by *Streptococcus pneumoniae*; as a result these two organisms kill almost two million children each year in tropical countries (WHO, 2012a).

The difficulty in distinguishing severe malaria with acidotic breathing from pneumonia in children has been well documented (Bergman et al., 2004; Hoban et al., 2001; O'Dempsey et al., 1993, 1994). In general malaria is overdiagnosed and severe bacterial infections are underdiagnosed. Clinical and pathology studies point to the diagnostic uncertainty and considerable overlap between severe malaria and sepsis. In up to 20% of children dying with an in-hospital diagnosis of cerebral malaria, a different cause is found at autopsy (Taylor et al., 2004) and both conditions coexist in 15–20% of cases (Berkley et al., 2005).

Therefore correct diagnosis and treatment cannot be expected in villages and rural health centres where most cases occur. The integrated management of childhood illnesses guidelines, created in 1992 by UNICEF and WHO, recommend presumptive malaria

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treatment for all children with fever higher than 37.5 °C in malaria-endemic areas and that both antibiotics and antimalarial drugs are given to seriously ill febrile children as pre-referral treatment of malaria or bacterial sepsis.

To prevent death, treatment must be available near home, outside hospitals, and as close to the village or household as possible. Malaria and other febrile illnesses are frequently treated at home in malaria endemic areas (Dolecek et al., 2008; Greenwood et al., 2007). When oral treatment is no longer possible, and where injectable medications cannot be safely administered, rectal formulations can be administered by unqualified persons like parents or health volunteers. While rectal artesunate has been shown to be an effective pre-referral treatment for malaria (Gomes et al., 2009), were both malaria and pneumonia are prevalent, a combined antibiotic–antimalarial treatment is necessary. Treating malaria only might delay specific treatments of other febrile diseases with similar symptoms, such as sepsis and pneumonia (Whitty et al., 1999). Currently, systemic large spectrum antibiotics are available as oral or injectable formulations – of which none is suitable for pre-referral treatment in pneumonia and malaria endemic regions. A fixed-dose antimalarial–antibiotic coformulation would be highly desirable and practical and was thus investigated.

The minimal characteristics of the target product profile (TPP) were: (i) active principles: well-known, in-use; physico-chemical compatibility between active ingredients when co-formulated; (ii) formulation: uncomplicated, easy to scale-up, inexpensive to manufacture; well-known, inexpensive excipients; rapidly bio-available; (iii) product development: simple, rapid, inexpensive; (iv) stability: suited to tropical conditions; (v) price: low-cost (both cost-of-goods and final product); (vi) efficacy: rapidly acting antimalarial and broad-spectrum antibiotic (to include main bacterial species causing sepsis and pneumonia in neonates, infants, toddlers and children), with as little resistance existing as possible; (vi) safety: proven general safety profile of active ingredients. The preliminary, pre-clinical development of such formulation was described in this article.

2. Material and methods

2.1. Material

Artesunate (AS), AM, AZ and dihydroartemisinin (DHA) were purchased from Knoll BASF Pharma (Liestal, Switzerland), Sanofi (France), Pfizer (USA) and Sigma–Aldrich (Saint-Quentin Fallavier, France), respectively. Excipients were of pharmaceutical grade. Sodium laurylsulfate (SLS), colloïdal silica (Aerosil 300), sodium croscarmellose, polyvinylpyrrolidone (PVP), talc and magnesium stearate were pourchased from Cooper (France). Different grades of PEG (polyethylenglycol) were purchased form Fagron (France). Microcrystaline cellulose (Avicel PH302) was purchased from FMC Biopolymer (Ireland). Betain and Lutrol were purchased form VWR (france) and BASF (Germany) respectively. Analytical solvents, acetonitrile and methanol were isocratic HPLC grade, purchased from Prolabo VWR (Leuden, Belgium). KH_2PO_4 and Na_2HPO_4, $12H_2O$ were from Merck (Darmstadt, Germany).

2.2. HPLC analysis and method optimization

2.2.1. HPLC conditions

The liquid chromatography system consisted of a Spectra System P4000 pump, a UV 6000LP detector with a cell path length of 50 mm, an AS 3000 autosampler and a SN 4000 system controller from TSP (Courtaboeuf, France). Column was Luna C8 (2) 100 A EC 5 μm, 150 × 4.6 mm (Phenomenex, France) thermostated with 560-CIL (Cluzeau Info Labo, Saint Foy la Grande, France). The flow rate was 1 mL min^{-1}. The sample injection volume was 5 μL.

For method optimization, several mobile phases and detection wavelenghts were screened (Tables 1 and 2).

Table 1
Comparison of pH mobile phases composed by 80% of CH_3OH and 20% of phosphate buffer (30 mM).

${}^{w}_{w}$pHof buffer	${}^{s}_{w}$pHmobile phase[a]	k_{AZ}	k_{AM}	Asymmetry of AZ peak	$Rs_{AM/AZ}$
8.4	10.3	4.48	3.15	1.13	2.27
8.0	10.2	4.34	3.12	1.11	2.76
7.5	10.0	4.21	3.14	1.12	2.49
7.0	9.4	4.01	3.19	1.10	1.67

[a] Measurement performed at room temperature (i.e. 22 °C, air conditioned).

2.2.2. Solubility study of AM and AZ in presence of lutrol

In a dissolution tester three bowls were filled with 1 L of phosphate buffer 15 mM pH 8 to simulate rectal pH conditions. Accurately weighed amounts of approximately 400 and 300 mg of AZ and AM were respectively added to each vessel. Lutrol was added to two of the three vessels at 2% and 5% of tablet mass (1.4 g). Samples were taken at time zero and at time points of 1 h, 2 h and 4 h. Homogeneity of solutions was tested by sampling each time point twice.

Determination of active pharmaceutical ingredient (API) content was obtained by calibration curves of AM and AZ at five different concentration levels (10%, 40%, 70%, 100% and 120%) in presence or absence of lutrol at 5%. Stock solution for each concentration level of AZ and AM were prepared by dissolving an accurately weighed amount of each drug and/or excipient in 50 mL of mobile phase then filtrated in a 0.45 μm filter. One milliliter of the filtrated solution of each concentration level was diluted with phosphate buffer pH 8 up to 20 mL. A 100% standard solution contained 400 and 300 mg L^{-1} of AZ and AM, respectively. These values were based on the theoretical tablet drug content. All calibration curves were proven to be linear. Furthermore, no difference was observed in presence or in absence of lutrol at 5%.

2.3. Formulations tested

2.3.1. Compatibility study between AZ and AM

Compatibility study between both APIs, namely AZ and AM, was performed. Binary physical mixture of precisely weighted APIs was mixed using Turbula (France) at 67 rpm for 10 min. The mixture was divided into three parts, T0, ambient condition and accelerated (40 °C) condition. Samples were taken up till 3 months and analyzed using HPLC method as described.

AM and AZ compatibility was further evaluated using differential scanning calorimetry (DSC). DSC analysis was performed using Mettler Toledo TA controller and DSC30, (Switzerland) with STAR^e software. DSC method consisted in a heating rate of 5 °C min^{-1} in the range of 30–180 °C. Samples of 6–8 mg were precisely weighted in aluminium pans, sealed and

Table 2
S/N ratio of compounds at various wavelengths.

Compound	Wavelength (nm)		
	210	212	215
	S/N		
DHA 500 mg L^{-1}	72	92	100
AM 350 mg L^{-1}	28	31	30
AZ 500 mg L^{-1}	220	201	172

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