CHAPTER 1

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1.1. Introduction

Effective quinine monotherapy for malaria has been available for more than 350 years (1), well before the causative organisms of the disease were identified (2). After World War II, the golden age for antimalarial monotherapy was signalled by widespread use of fairly cheap and highly effective aminoquinolines, both as prophylactic and therapeutic agents (3). However, only 15 years after they were adopted, aminoquinoline monotherapies for Plasmodium falciparum malaria began to stop working simultaneously in south-east Asia and in Brazil (4), and resistance spread rapidly. Perhaps surprisingly, quinine has retained much of its efficacy, although it can no longer be used as monotherapy for uncomplicated malaria in south-east Asia (5). The development of folate antagonists, both as prophylactic and therapeutic agents, allowed only a short respite before true multidrug resistant malaria emerged.

The use of oral artemisinin-based monotherapies threatens the therapeutic life of Artemisinin based Combination Therapies (ACTs) by fostering the spread of resistance to artemisinins. By November 2010, 25 countries were still allowing the marketing of these products and 39 pharmaceutical companies were manufacturing them. Most of the countries that still allow the marketing of monotherapies are located in the African Region and most of the manufacturers are in India and China. The spread of resistance to antimalarial medicines over the past few decades has led to an intensification of efficacy monitoring to allow early detection of resistance. Despite the observed changes in parasite sensitivity to artemisinins, the clinical and parasitological efficacy of ACTs has not yet been compromised, even in the Greater Mekong sub-region. Nonetheless, both components of the drug combination are currently at risk and using an ACT with an ineffective partner medicine can increase the risk of development or spread of artemisinin resistance. A total of 11 countries and one area in the WHO African Region showed a reduction of more than 50% in either confirmed malaria cases or malaria admissions and deaths in recent years. A decrease of more than 50% in the number of confirmed cases of malaria between 2000 and 2009 was found in 32 of the 56 malaria-endemic countries outside Africa, while downward trends of 25%–50% were seen in

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8 other countries. Morocco and Turkmenistan were certified by the Director-General of WHO in 2009 as having eliminated malaria. In 2009, the European Region reported no cases of P. falciparum malaria for the first time. It is estimated that the number of cases of malaria rose from 233 million in 2000 to 244 million in 2005 but decreased to 225 million in 2009. The number of deaths due to malaria is estimated to have decreased from 0.985 million in 2000 to 0.781 million in 2009. Decreases in malaria burden have been observed in all WHO Regions, with the largest proportional decreases noted in the European Region, followed by the Region of Americas. The largest absolute decreases in deaths were observed in Africa. While progress in reducing the malaria burden has been remarkable, there was evidence of an increase in malaria cases in 3 countries in 2009 (Rwanda, Sao Tome and Principe, and Zambia). The reasons for the resurgences are not known with certainty. The increase in malaria cases highlight the fragility of malaria control and the need to maintain control programmes even if numbers of cases have been reduced substantially. The experiences in Rwanda and Zambia also indicate that monthly monitoring of disease surveillance data, both nationally and subnationally, is essential. Since many countries in sub-Saharan Africa had inadequate data to monitor disease trends, it is apparent that greater efforts need to be made to strengthen routine surveillance systems. Major epidemiological events could be occurring in additional countries without being detected and investigated (6).

Multi drug resistant parasites are the biggest therapeutic challenge to health care in most malaria-endemic areas. Resistance to chloroquine, the former first-line treatment, is also becoming apparent in *Plasmodium vivax*. (7-9). The consequences of antimalarial drug resistance are stark (10). When the cheapest affordable antimalarial does not work, an alternative regimen might simply be too expensive. When treatments do not cure patients, more serious morbidity results, even in initially uncomplicated cases of malaria. The problem of multiple drug resistance in *Plasmodium falciparum* malaria is increasing in the countries in South East Asia. Chloroquine resistance in *P. falciparum* was first reported from Assam, India in 1973, and it has spread gradually to other parts of India. Resistance to other antimalarial drugs such as sulfadoxine alone and with pyrimethamine is rare, but a few cases have been reported. Malaria outbreaks are yearly phenomena in different parts of country and are associated with high morbidity and mortality.
New antimalarial regimens, urgently needed because of the worldwide development of multidrug resistance, should aim to cure patients no longer responding to standard therapies. Such regimens should be incorporated into strategies aimed at controlling the spread of disease, such as insecticide spraying, use of impregnated bed nets, sustained chemoprophylaxis, and intermittent prophylactic treatment. Since none of these other measures is used routinely in most parts of Africa and because a vaccine is unlikely to emerge within the next decade, early and effective chemotherapy for malaria has a pivotal role in reducing morbidity and mortality (11).

Lumefantrine (a racemic fluorine derivative originally called Bemflumetol) was synthesized in the 1970s by the Academy of Military Medical Sciences, Beijing and registered in China for use as an antimalarial drug in 1987. Lumefantrine is commercially available in combination with artemether as Coartem®/Riamet® for the treatment of Plasmodium falciparum malaria. Denis et.al & Ezzet et.al reported the pharmacokinetic parameters of lumefantrine while white et al reported the pharmacokinetics parameter in healthy and infected volunteers (12-14). Piperaquine (PQP), a bisquinoline antimalarial drug related to chloroquine (CQ) and other 4-aminoquinolines, was first synthesized in France and China in the 1960s. As a consequence of its higher potency and tolerability compared with those of CQ, PQP superseded CQ as the antimalarial regimen recommended by the Chinese Malaria Control Programme in 1978. Afterwards, 200 tons of piperaquine phosphate, the equivalent of 140 million adult treatment doses, were produced and distributed in China. The administration of PQP to more than 20 000 people in six Chinese provinces was associated with a decrease in malaria incidence (15). However, the campaigns of mass drug administration and the extensive use of PQP for both treatment and prophylaxis led to the emergence of Plasmodium falciparum PQP-resistant strains; thus, the use of piperaquine as monotherapy was progressively abandoned in the late 1980s. In the 1990s, piperaquine was reconsidered by Chinese scientists as one of the potential partner components of the so-called artemisinin-based combination therapies (ACTs).

Recently, preclinical pharmacokinetic studies have been reported for artemether and piperaquine (16-17). Further, despite the wide spread clinical use of lumefantrine, there is no study reporting the detailed preclinical pharmacokinetics. Hence there is a need to understand
the preclinical pharmacokinetics of lumefantrine in order to evaluate its candidature as potential partner drug for combination therapy.

Further, the need of hour is to explore drug combinations in order to combat multiple drug-resistant strains of malaria parasite. The world health organization has endorsed Artemisinin based Combination Therapies (ACTs) as first line treatment in malaria. The available marketed antimalarial combinations combine the rapid schizontocidal activity of an artemisinin derivative (artesunate, artemether or dihydroartemisinin) with a longer half-life partner drugs viz. mefloquine, lumefantrine, halofantrine and piperaquine. The major problems associated with currently available semisynthetic artemisinin derivatives are low oral bioavailability, time dependent pharmacokinetics (major cause of recrudescence), toxicity and high cost (due to poor yield of the artemisinin extraction process) etc.

In order to overcome these problems, there is a need to replace the semisynthetic artemisinin derivatives in the marketed antimalarial combinations with promising synthetic endoperoxide-based antimalarials (for instance, CDRI candidate antimalarials viz. 97-78 and 99-411) which are effective, cheap and have improved water solubility, thereby improving bioavailability. This may result in arriving at better antimalarial combinations.

Development of newer anti-malarial combinations necessitates having the knowledge of preclinical pharmacokinetic compatibility which is essential for clinical development of any new product. In order to explore newer anti-malarial combinations, it becomes the need of hour to study the pharmacokinetics of partner drugs alone as well as in combinations to make informed decisions regarding the selection of pharmacokinetically suitable combinations to combat the multi drug resistant malaria.
1.2. References

6. World malaria Report 2010
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