Klinische en farmacologische studies met artemether voor de behandeling van malaria
van Agtmael, M.A.

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Outline of this thesis
Traditional Chinese Medicine differs from Western Medicine not only in its interpretation of health and disease but also in the ways to diagnose and treat disease. The Western scientific world is unaware of most developments in traditional Chinese medicine because their study results are almost exclusively published in Chinese literature. Despite these differences, there is increasing interest in traditional medicines, especially those drugs who have shown therapeutic effect confirmed by clinical studies, for example in stroke therapy or in malaria therapy.

Artemether is a derivative of artemisinin or 'qinghaosu' which means derived from the herb qinghao or *Artemisia annua*, used in traditional Chinese Medicine for thousands of years for fevers and chills. In 1972 Chinese researchers isolated this compound from the leaves and flowers of this plant and when they found that it was very active after a review on artemisinin drugs in chapter 2, we validate a sophisticated technique (High Performance Liquid Chromatography Assay with Electrochemical Detection) developed in our laboratory to measure artemisinin derivatives and one major metabolite in plasma in chapter 3. It enables us to use quantitative determinations of artemisinin derivatives in plasma for pharmacokinetic studies. The results from these studies will provide insight into how the human body absorbs, distributes, metabolizes and eliminates these new compounds. These data are necessary to design the optimal dosing regimen with the highest efficacy, lowest toxicity and without recrudescence or reoccurrence of malaria after the treatment.

In chapter 4 we evaluate a different, more easy to handle, technique (Enzyme Linked Immuno Sorbent Assay), developed in our laboratory as well, to detect these compounds in urine after drug
against malaria parasites, the Western world became interested. Since then many clinical studies were done and now, more then 25 years later, a derivative of this Chinese medicine has recently been registered in Europe for the treatment of malaria. Increasing problems of resistance and side-effects of the existing antimalarial drugs make this new treatment more than welcome, having no documented resistance until now and little side-effects.

Many years with many empirical clinical studies have passed without the knowledge of what dose and duration of treatment with these artemisinin drugs were necessary to cure the patient with malaria. In this thesis we will discuss several studies with oral artemether to gain insight in what the human body does with this new drug, how it is metabolized in healthy subjects and in malaria patients, the ways to detect it in blood and urine, to analyze certain interactions with other compounds and to investigate the efficacy in travellers with malaria.

intake. In a further development towards a urine dipstick device this easy method could be applied in drug-compliance and drug-utilization studies. Because most of the artemisinin drugs are unfortunately available as 'over-the-counter'-drugs in many malaria endemic areas, this urine test could evaluate use (and misuse) of these drugs, e.g. before inclusion into a study.

Because artemisinin is hardly soluble in water or oil, derivatives were developed for intramuscular, rectal and intravenous administration and for better oral absorption. In chapter 5 we discuss differences between these derivatives in their behavior in the human body as well as their activity against malaria parasites.

Drug levels of artemether and the active metabolite dihydroartemisinin were monitored in Chinese malaria patients to get detailed information on the pharmacokinetics of this new drug. In a study, described in chapter 6, we evaluate the effect of multiple dosing on the pharmacokinetics, look at a possible influence of the Chinese ethnicity and
investigate if malaria as febrile disease state alters the pharmacokinetic behavior of artemether.

We present the results of a randomized clinical trial in chapter 7. In a multi-center trial, carried out in the Academic Medical Center in Amsterdam and in 7 French hospitals, the efficacy and safety is evaluated of an oral combination tablet containing artemether and lumefantrine. This new drug was compared with halofantrine in travellers returning from the tropics with malaria. Special attention in this study is paid to recrudescence, or the reoccurrence of malaria, a known problem for the artemisinin drugs. Side effects are carefully monitored especially neurotoxicity, which has been described in animal experiments with high dosages of artemether and arteether. Cardiotoxicity, monitored with frequent electrocardiograms, is evaluated because cardiac arrests have been described in patients taking halofantrine. These arrests were caused by 'torsades des pointes' related to drug-induced prolongation of the QTc-interval. An important consideration consider the question: "is artemether subject to 2D6 or 2C19 metabolism?" an important question to answer.

In 1991 Bailey et al found by serendepity that grapefruit juice could increase the bioavailability of many drugs like felodipine, cyclosporin, saquinavir, terfenadin, lovastatin, midazolam and others. The poor bioavailability of artemether and the decline in druglevels after multiple dose regimens are the main reasons to test the effect of grapefruit juice on the pharmacokinetics of artemether as well. Furthermore it will teach us something about the routes of metabolism of artemether. This grapefruit juice-drug-interaction is thought to be caused by a still not clearly identified compound, possibly naringin or bergamottin, present only in grapefruit juice, and not in other juices. This compound can selectively block the activity of the enzyme CYP 3A4 present in small intestinal epithelium, particularly in the apical region of the mature enterocytes at the tip of the microvillus. This enzyme is important in the first pass metabolism of many drugs. We test the influence of fresh frozen
for this extensive cardiac monitoring was that lumefantrine has similarities in chemical structure with halofantrine, both being aminoalcohols.

In the last part of this thesis we carry out 4 studies in healthy volunteers. In the first study in chapter 8 we evaluate the effect of inhibition of the enzymes CYP 2D6 and CYP 2C19 successively on the metabolism of artemether. These 2 isoenzymes belong to the cytochrome P-450 family and are important in the hepatic biotransformation of many drugs. For these two enzymes genetic polymorphism is described, meaning that the activity of these enzymes play a role in interindividual and interethnic differences in drug metabolism. Thus 7% of the Caucasian population have an inactive CYP 2D6 and are so called ‘poor metabolizers’ for the drug oxidized by this enzyme, whereas only 1% of Oriental people have an inactive 2D6. For CYP 2C19 3% of Caucasians and 22% of Orientals represent a ‘poor metabolizer’ phenotype. Because artemether is and will be used among many different races, we double concentrated grapefruit juice on the pharmacokinetics of artemether after oral intake in Dutch healthy subjects and hereafter examined the effect of local, fresh grapefruit juice on artemether kinetics in Vietnamese healthy subjects and malaria patients in South-Vietnam. The results are discussed in chapter 9.

In this study we simultaneously collect saliva samples for detection of artemether and its metabolite, using the same assay described in chapter 3. The objective of measuring drug concentrations in saliva was to evaluate a non-invasive mode of sampling which could be valuable in (large) pharmacokinetic studies in the field.

Because asymptomatic prolongation of the QTc-interval has been described in clinical studies with artemether, we also look in chapter 9 at concentration-dependent cardiographic changes after artemether administration in healthy subjects. With this study we try to answer the question whether these effects on the electrocardiogram found in patients are related to the drug or to the malaria.
In chapter 10 we evaluate the effect of grapefruit juice on the time-dependent decline in artemether plasma levels in healthy subjects. A high rate of recrudescence is reported in monotherapy with artemisinin derivatives. Factors contributing to this reduced efficacy are the short half-life of these compounds and possibly the remarkable time-dependent decrease in bioavailability during a 5 days treatment regimen which is probably caused by autoinduction. In this study we evaluate this time-dependent decline in bioavailability in a multiple dose study in healthy subjects and study the antagonizing effect of grapefruit juice on this decline in plasma levels over time. A glass of grapefruit juice added to a drug regimen with artemether would be a very simple and cost-effective way to increase drug levels and possibly increase the efficacy of artemether in the treatment of malaria.

Finally in chapter 11 I give a summary of the thesis in English and Dutch including a Dutch review article in which the WHO guidelines for implementation of the artemisinin drugs for the treatment of malaria are elaborated. The summary closes with a general discussion on the results from this thesis and my ideas on the studies that could be done in continuation of our results for the questions that have remained unanswered.