In vitro and in vivo studies of artemisinin endoperoxides

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In vitro and in vivo studies of artemisinin endoperoxides

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ABSTRACT
Artemisinin and its semi-synthetic derivatives (eg. Artemether/ARM, artesunate/ARS, dihydroartemisinin/DHA) play an important role in combating malaria, and treatments containing an artemisinin derivative (artemisinin-based combination therapies, ACTs) are today the standard treatment worldwide for Plasmodium falciparum malaria. In addition to their antimalarial effect, artemisinin endoperoxides have been demonstrated to exert cytotoxic effects, making them interesting candidates for oncologic indications.

This thesis specifically aimed to (1) investigate in vitro effects of artemisinin endoperoxides on human liver Cytochrome P450 (CYP) enzyme activity, and to (2) study the pharmacokinetics of ARS and DHA in plasma and saliva during long-term oral ARS treatment in patients with breast cancer. In vitro experimental assays using recombinant and microsomal CYP enzymes were conducted to assess potential inhibitory effects of artemisinin, ARM, ARS and DHA (Papers I and II). Results were extrapolated to evaluate the risk of drug-drug interactions (DDIs) in vivo. An LC-MS/MS method was optimized and validated for the quantification of ARS and DHA in human plasma and saliva (Paper III). Drug concentration-time profile data was analyzed by non-compartmental analysis (Paper IV) and population pharmacokinetic modelling (Paper V) to characterize the pharmacokinetic properties of the two compounds in patients with breast cancer, and to evaluate the relationship between salivary and plasma DHA concentrations.

In conclusion, artemisinin endoperoxides exerts inhibitory effects on the activity of CYP enzymes in vitro, which could result in clinically significant DDIs. This could be a concern in both malaria and cancer therapies, which often include concomitant administration of multiple drugs. Also, for the first time, the presented bioanalytical method offers the possibility to quantify ARS and DHA in saliva. Therefore, based on both plasma and saliva data, the pharmacokinetics of the two compounds have been characterized during long-term oral ARS treatment in patients with breast cancer. Prior knowledge regarding the pharmacokinetics of these antimalarial drugs is based on single dose or short-term (up to 7 days) regimens in healthy volunteers or in malaria patients, making the results presented here significant.

Keywords: artemisinin, artesunate, breast cancer, Cytochrome P450, dihydroartemisinin, inhibition, LC-MS/MS, pharmacokinetics, plasma, saliva

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