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Short communication

Effect of CAR polymorphism on the pharmacokinetics of artemisinin in healthy Chinese subjects☆

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ABSTRACT

Repeated pretreatment with the antimalarial drug artemisinin (QHS) could lead to reduced exposure to the parent drug, which is mainly mediated by auto-induction of CYP2B6 activity. CYP2B6 is most sensitive to the inductive effect of constitutive androstane receptor (CAR), which can be activated by QHS. CYP2B6 polymorphism has no influence on pharmacokinetics of QHS derivatives. This study aimed to investigate the effect of CAR (C540T) polymorphism on the auto-induction metabolism-mediated pharmacokinetics of QHS. Healthy Chinese subjects (six in each group with the genotypes of CAR 540C/C, 540C/T and 540T/T; all carrying the CYP2B6*1*1 genotype) received a recommended two-day oral doses of QHS-piperaquine (PQ) to assess the pharmacokinetics of QHS and its metabolite deoxyartemisinin (DQHS). The exposures to QHS and DQHS were significantly lower ($p < 0.05$) in subjects homozygous for the CAR 540T/T genotype than those with the 540C/C genotype after the repeated dose. QHS did not show different induction clearance in subjects homozygous for the 540C/C genotype (1.3-fold), compared with those carrying the heterozygous 540C/T (2.1-fold) or homozygous 540T/T (1.7-fold) genotype. In conclusion, the CAR (C540T) genotype contributed to the interindividual variability of QHS pharmacokinetics, and the dose regimen for QHS deserves further evaluation especially in specific populations.

1. Introduction

Artemisinin (QHS)-based combination therapy (ACT) is the recommended treatment for uncomplicated *Plasmodium falciparum* malaria by WHO. Artequick is a recently marketed and relatively inexpensive ACT, which contains QHS instead of its derivatives (dihydroartemisinin, artemether or artesunate) plus piperaquine (PQ). QHS has not been used to a great extent in ACT because of its low bioavailability and time-dependent pharmacokinetics, which have been confirmed in healthy volunteers and infected patients as a several-fold decrease in plasma concentration of QHS with a corresponding increase in oral clearance after repeated oral administrations for several days [1–3]. The auto-induction metabolism has been suggested for this time-dependency [4,5].

The elimination of QHS is mediated primarily by CYP2B6, with a probably secondary contribution of CYP3A and CYP2A6 [6,7]. QHS appears to induce several enzymes including CYP2B6 [3,5]. CYP2B6 is most sensitive to the inductive effect of constitutive androstane receptor (CAR), which can be activated by QHS [8,9]. The human genes coding for CYP2B6 and CAR are highly polymorphic [10,11], which could probably lead to interindividual variability in QHS pharmacokinetics, auto-induction metabolism and response to treatment. No effect of CYP2B6*6 on the pharmacokinetics of QHS derivatives (dihydroartemisinin, artemether and artesunate) was found in Cambodia and Tanzania patients; [12] however, the effect of CAR polymorphism on the pharmacokinetics of QHS drugs remains unknown.

This study was designed to investigate the effect of CAR (rs2307424; C540T) polymorphism on the time-dependent pharmacokinetics of QHS in healthy Chinese subjects. The results were expected to explain the interindividual variability in QHS pharmacokinetics and to provide recommendations for dosage adjustment of QHS.

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2. Materials and methods

2.1. Clinical study

The present study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Shandong University (Jinan, China) and the Institutional Review Board of Qilu Hospital (Shandong University, China), which was registered with Trial-201301021. Subjects were genotyped for CAR (C540T) and CYP2B6 by PCR-RFLP (Table S1). Eighteen non-smoking male subjects with specific CAR genotypes (six in each group with 540C/C, 540C/T and 540T/T; all carrying the CYP2B6*1*1 genotype) were enrolled in the clinical trial after signing written informed consent. Before and after the experiment, their health was assessed by physical examination and clinical biochemistry analysis.

Each subject was treated with QHS-PQ tablets (Artequick; Artepharm Co. Ltd., Guangzhou, China) according to the manufacturer's recommendation (125 mg of QHS plus 750 mg of PQ each day for two consecutive days). Venous blood samples were taken before and after each dose of QHS-PQ.

2.2. Assay

An LC-MS method was applied for quantification of QHS and its metabolite DQHS on a Thermo Electron LTQ-Orbitrap XL hybrid mass spectrometer (ThermoFinnigan, Bremen, Germany). The sample preparation, chromatographic and mass spectrometric conditions were shown in a previous report [3].

2.3. Pharmacokinetic analysis

The peak plasma concentration (C_{max}) and the time to C_{max} (T_{max}) were obtained from experimental observations. The area under the plasma concentration-time curve (AUC_{0-t}) was calculated using the linear trapezoidal rule to approximately the last point. Oral clearance (CL/F) of QHS was calculated as dose/AUC_{0-t}. The exposures to QHS and its metabolite DQHS were evaluated by AUC/dose, and the induction clearance of QHS was assessed by changes of QHS CL/F after two-day oral doses.

2.4. Data analysis

The two-tailed *t*-test was used for paired comparison of the pharmacokinetic parameters (AUC/dose and C_{max}) between the single dose and multiple doses after logarithmic transformation. The mean changes in pharmacokinetic parameters among different genotype groups were compared using one way ANOVA followed by Tukey Post-Hoc test, which were performed with SPSS (version 19.0, SPSS Inc., Chicago, IL, USA). The comparison of T_{max} for the different treatment groups was performed using the Wilcoxon signed-rank test.

3. Results

3.1. Pharmacokinetics of QHS and its metabolite DQHS

QHS was rapidly eliminated after an oral administration of QHS-PQ (Fig. S1), with a high mean CL/F of 11.4 L/h/kg. The time-dependent pharmacokinetics existed for QHS in 13 out of 18 subjects (Fig. S2), and the second oral dose of QHS-PQ resulted in a 47.1% (95% CI, 40.4–53.7%) decrease in AUC_{0-t}, compared with the first dose. The corresponding CL/F value significantly increased 2.0-fold (95% CI, 1.7–2.2) in 13 subjects.

The AUC/dose of the metabolite DQHS decreased significantly ($p < 0.01$) by 35.2% (95%CI, 26.4–44.0%) in 16 out of 18 subjects, after multiple oral doses of QHS (Fig. S2).

3.2. The effect of CAR genotype on the exposure of QHS and DQHS

After the second dose, QHS displayed significantly ($p < 0.05$) lower AUC/dose in subjects with the homozygous 540T/T genotype (0.05 h kg/L) or the 540C/T genotype ((0.06 h kg/L), compared with those carrying the 540C/C genotype (0.13 h kg/L) (Fig. 1 and Table 1). No significant ($p > 0.05$) difference in C_{max} was observed for QHS in subjects with the 540T allele.

Significantly lower AUC/dose was observed for DQHS in subjects carrying the homozygous 540T/T genotype (0.03 h kg/L) compared with the 540C/C genotype (0.09 h kg/L) after the second dose (Fig. 1 and Table 1).

3.3. The effect of CAR genotype on the induction of QHS clearance

Repeated doses did not result in different induction clearance of QHS in subjects carrying the 540C/T (2.1-fold) or 540T/T genotype (1.7-fold), compared with 540C/C genotype (1.3-fold) (Table 1).

4. Discussion

Several published studies have evaluated the pharmacokinetics of the parent drug QHS in healthy adults and patients including children, after oral administration of QHS either as monotherapy or ACT [1–3,13]. These findings suggest that PQ should not influence the pharmacokinetic characteristics of QHS when co-administered in the proposed fixed oral combination [13]. The change of QHS exposure and clearance was supposed to be the contribution of QHS in the present study. The extent of the increase in QHS CL/*F* has been reported to be 5–7-fold after five days' oral treatment with 500 mg of QHS. There was also evidence of a more rapid auto-induction of QHS metabolism (the AUC of QHS decreased to 0.27) in infected children after the second dose [14]. In the present study, two-day oral administration of the recommended dose of QHS resulted in a decrease of AUC/dose in most subjects, with the corresponding increased oral clearance of QHS (2.0-fold). Out of expectation, the metabolite DQHS also showed reduced concentration level in 16 out of 18 subjects, which was probably caused by the further induction metabolism and/or more rapid subsequence clearance of DQHS via phase I/II biotransformation.

Induction of CYP2B6, involved in the metabolism of QHS, was the underlying mechanism of the time-dependent pharmacokinetics of QHS [4,5]. CYP2B6 is most sensitive to regulation by CAR, and QHS was an agonist of CAR1/3 [8,9]. No polymorphic influence of CYP2B6*6 was detected for QHS derivatives (dihydroartemisinin, artemether and artesunate) in Cambodia and Tanzania patients [12]. In the present study, the pharmacogenetic effect of CAR on the pharmacokinetics of QHS was investigated, and healthy subjects with specific CAR genotype and CYP2B6*1*1 were selected to avoid the potential influence of CYP2B6*6 or diseases.

The present findings showed that subjects carrying at least one variant allele of CAR (540C/T or 540T/T) tended to have lower exposure (AUC/dose) to QHS and its metabolite DQHS after the repeated oral dose. Patients in Africa and Southeast Asia were found to have CAR (C540T) genes mutated with a relatively high frequency (18–40%), suggesting that a non-negligible number of patients might be at risk of reduced exposure of QHS. An association of CAR genotype (C540T) with plasma concentrations has been found for other drugs, such as Efavirenz [15].

CYP3A played a minor role in the auto-induction metabolism of QHS [5]. The between-subject variability in CYP3A4 activity may be