Effects of *CYP2C19* Genetic Polymorphisms on the Pharmacokinetic and Pharmacodynamic Properties of Clopidogrel and Its Active Metabolite in Healthy Chinese Subjects

Bai-Li Song, MS[1,2]; Meng Wan, MS[2]; Dan Tang, MS[1]; Chao Sun, MS[1,2]; Yu-Bing Zhu, MS[2]; Nyame Linda, MS[1,2]; Hong-Wei Fan, PhD[2]; and Jian-Jun Zou, PhD[2]

[1]*School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Jiangsu, China; and the* [2]*Department of Clinical Pharmacology, Nanjing First Hospital, Nanjing Medical University, Jiangsu, China*

ABSTRACT

Purpose: Some studies in the white population have shown that carriers of at least 1 loss-of-function allele in the gene that encodes the cytochrome P-450 2C19 isozyme (*CYP2C19*) have lower levels of the clopidogrel active metabolite (CAM) and a reduced antiplatelet effect of clopidogrel. However, data are limited regarding the association between *CYP2C19* genetic variants and exposure to CAM and on the pharmacodynamic properties of CAM in the Chinese population. Data from the white population cannot be extrapolated to the Chinese population because of the marked interethnic differences in *CYP2C19* variants. This study was aimed to investigate the influence of *CYP2C19* genetic polymorphisms on the pharmacokinetic properties of CAM and the antiplatelet effect of clopidogrel in healthy Chinese volunteers, and to provide evidence for the role of a *CYP2C19* genotyping test in predicting the antiplatelet effect of clopidogrel in the Chinese population.

Methods: Twenty healthy subjects received a single 300-mg dose of clopidogrel and were assigned to 1 of 3 groups according to *CYP2C19* genotype: *CYP2C19* *1/*1 (normal metabolizers [NM]; n = 8), *CYP2C19* *1/*2 or *3 (intermediate metabolizers [IM]; n = 10) and *CYP2C19* *2/*2 or *3 and *3/*3 (poor metabolizers [PM]; n = 2). Blood samples were collected at baseline and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after administration. The plasma concentrations of clopidogrel and CAM were analyzed by LC-MS/MS, and adenosine diphosphate–induced platelet aggregation was measured by light-transmittance aggregometry.

Findings: There were no significant differences in C_{max} and AUC_{0-t} of clopidogrel prodrug in the NM group compared with the IM and PM groups. The mean CAM C_{max} value was significantly higher in the NM group than in IM and PM groups (45.39 [12.57] vs 29.15 [7.92] ng/mL [$P = 0.003$] and 19.55 [2.19] ng/mL [$P = 0.004$], respectively). The mean CAM AUC_{0-t} value was significantly higher in the NM group than in the IM and PM groups (61.05 [21.63] vs 37.67 [11.01] ng · h/mL [$P = 0.007$] and 27.08 [2.72] ng · h/mL [$P = 0.016$]). The NM group exhibited a significantly higher percentage of inhibition of platelet aggregation than did the IM or PM group ($P = 0.001$). The correlations between the pharmacokinetic properties (C_{max}, AUC_{0-t}) of CAM and the pharmacodynamic data (maximal and inhibition of platelet aggregation) were significant (both, Pearson $r > 0.5$ and $P < 0.01$).

Implication: In these healthy Chinese subjects, carriers of *CYP2C19* loss-of-function allele(s) had significantly reduced exposure of CAM and decreased levels of inhibition of platelet aggregation with clopidogrel; these genotypes therefore might be a determinant for the formation of CAM and its antiplatelet effects. Study identifier: ChiCTR-OCH-14004382. (*Clin Ther*. 2018;■:1–9)

Accepted for publication June 5, 2018.
https://doi.org/10.1016/j.clinthera.2018.06.001
0149-2918/$ - see front matter

Key words: active metabolite, clopidogrel, *CYP2C19*, pharmacodynamics, pharmacokinetics, polymorphisms.

INTRODUCTION

Dual antiplatelet therapy with clopidogrel and aspirin is a mainstay treatment in patients with acute coronary syndrome.[1] Although newer and more potent P2Y12 inhibitors such as prasugrel and ticagrelor are more effective than clopidogrel, most physicians still use clopidogrel as the first choice of therapy because clopidogrel causes less bleeding and is more cost-effective.[2,3] Clopidogrel is a prodrug that is transformed into the clopidogrel active metabolite (CAM) via the cytochrome P-450 (CYP) system. CYP2C19 may be the crucial isozyme for the metabolic bioactivation of clopidogrel.[4]

In a previous study, we found that carriage of the loss-of-function (LOF) *CYP2C19* genetic variants *2 and *3 was significantly associated with attenuated platelet response to clopidogrel and an increased risk for cardiocerebral vascular incident in Chinese patients,[5,6] and similar results were found in white[7–10] and other Asian[11–14] populations. However, the correlation between *CYP2C19* genotypes and the pharmacokinetic (PK) properties of CAM has not been reported in the literature.[7–14] Several publications have described genetic polymorphisms of *CYP2C19* in relation to the PK properties of CAM in white,[15–18] Chinese,[19,20] Korean,[21,22] and Japanese[23–25] populations. However, there are great interindividual variabilities in the PK properties of CAM even between East Asian populations.[19–25] Moreover, it is well-known that there are marked interethnic differences in the frequencies of the *CYP2C19* *2 and *3 alleles, with the prevalences of *CYP2C19* LOF variants being much higher in the Asian population.[26,27] Therefore, data from white and Asian populations cannot be extrapolated to the Chinese population, and hence it is meaningful to study the effects of *CYP2C19* polymorphisms on the PK properties of CAM and the antiplatelet effects of clopidogrel in the Chinese population. The aim of the present study was to investigate the impact of *CYP2C19* polymorphisms on the PK properties of CAM and its antiplatelet effect, and to estimate the correlations between the PK and pharmacodynamic (PD) properties of clopidogrel and CAM in the Chinese population. To achieve these aims, healthy Chinese subjects were recruited to provide evidence for the crucial role of not only *CYP2C19* polymorphisms in the metabolism of clopidogrel, but also of a *CYP2C19* genotyping test in predicting the antiplatelet effect of clopidogrel.

MATERIALS AND METHODS

Subjects

The study protocol was approved by the ethics committee at Nanjing Hospital, Nanjing Medical University (Nanjing, China), and was conducted in accordance with the principles of the Declaration of Helsinki. Healthy male subjects with different *CYP2C19* genotypes were recruited in order to exclude other possible factors (diseases, comedications, diet, smoking, clopidogrel compliance, age, and body mass index) that could affect the metabolism of clopidogrel. All of the subjects provided written informed consent before participating in the study. Healthy male subjects were eligible based on the following criteria: age 18 to 40 years and body mass index between 19 and 24 kg/m^2. Additional inclusion criteria were nonsmoking status and normal findings on clinical history (no volunteers could have a history or evidence of a renal, gastrointestinal, hepatic, or hematologic abnormality; or any acute or chronic disease; or an allergy to any drugs), chest radiography, ECG, and laboratory tests (hematology, blood biochemistry, hepatic function, and urinalysis). Subjects were required to have negative test results for HIV as well as hepatitis B and C. The exclusion criteria were: (1) having taken any medications within 2 weeks before enrollment; (2) having donated blood or participated in another study within the 3 months before the study; and (3) having an allergy to any drug. The baseline characteristics of the healthy subjects, by *CYP2C19* *2 or *3 genotype, are presented in **Table I**.

Study Design

In this open-label, single-dose study, each participant was given a single oral loading dose of 300 mg of clopidogrel.* All participants were included in the PK and PD analyses. Blood samples for PK analyses (5 mL each) were drawn into collection tubes containing 3.8% sodium citrate at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after administration. Due to the limited stability of CAM in human whole blood, 25 μL