Concomitant Use of Proton Pump Inhibitors and Clopidogrel Is Not Associated with Adverse Outcomes after Ischemic Stroke in Chinese Population

Xingyang Yi, MD,* Qiang Zhou, MD,† Chun Wang, MSc,* Jing Lin, MD,† Wen Cheng, MSc,* and Lifen Chi, MD†

Background and Purpose: Conflicting data exist as to whether proton pump inhibitors (PPIs) diminish the efficacy of clopidogrel. We, therefore, assessed the effect of concomitant PPI use in ischemic stroke (IS) patients receiving clopidogrel. *Methods:* We consecutively enrolled 535 IS patients receiving clopidogrel, 166 of whom were concomitantly taking PPIs. Platelet aggregation was measured before and after 7-10 days of treatment with clopidogrel. Single nucleotide polymorphisms of *CYP3A4*, *CYP3A5*, *CYP2C19*2*, and *CYP2C19*3* were examined. The primary outcome was a composite of recurrent ischemic stroke (RIS), myocardial infarction (MI), and vascular death occurring during the 6-month follow-up. The secondary outcome was the modified Rankin Scale score at the end of follow-up. *Results:* The primary outcome occurred in 45 patients and the frequency did not differ in patients with or without PPI treatment. The percentage inhibition of platelet aggregation and the frequency of clopidogrel resistance were similar between patients treated with or without PPIs after clopidogrel treatment. However, for patients carrying a reduced-function *CYP2C19*2* (AG/AA genotype) or *CYP3A5* (GG/AG genotype), the inhibition of platelet aggregation was significantly lower in patients treated with PPIs. Cox regression analysis showed that diabetes mellitus, clopidogrel resistance, *CYP2C19*2* AG/AA genotype, and patients carrying two loss-of-function variant alleles were independent risk factors for the primary outcome, but not the use of PPIs. *Conclusions:* The concomitant use of PPIs and clopidogrel in patients with IS may not be associated with an increased risk of RIS, MI, or vascular death. Further well-designed randomized controlled studies are necessary to confirm our current results. **Key Words:** Clopidogrel—proton pump inhibitor—cytochrome P-450 enzymes—single nucleotide polymorphism—ischemic stroke—outcome.

From the *Department of Neurology, People's Hospital of Deyang City, Deyang, Sichuan, China; and †Department of Neurology, Third Affiliated Hospital of Wenzhou Medical College, Wenzhou, Zhejiang, China.

Received May 26, 2016; revision received July 27, 2016; accepted August 1, 2016.

Grant support: This study was supported in part by a grant from the Scientific Research Foundation of Sichuan Provincial Health Department (#140025) and the Deyang City Science and Technology Research Foundation (#2014SZ035).

Clinical Trial Registration-URL: http://www.chictr.org/. UniqueIdentifier: ChiCTR-OCH-14004724.

Address correspondence to Xingyang Yi, MD, Department of Neurology, People's Hospital of Deyang City, 173, North Taishan Road, Deyang, Sichuan 618000, China. E-mail: yixingyang64@126.com.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.08.001

Introduction

Platelet aggregation plays an important role in the pathogenesis of ischemic stroke (IS).[1] Antiplatelet drugs such as aspirin and clopidogrel are widely prescribed for secondary stroke prevention in patients after IS or transient ischemic attack.[2-5] Clopidogrel is a prodrug that requires biotransformation into an active metabolite by cytochrome P-450 (CYP) enzymes which can irreversibly inhibit the platelet P2Y12 ADP receptor.[6,7] CYP enzymes, including CYP2C9, CYP2C19, and CYP3A4/5, are involved in the metabolism of clopidogrel.[8]

Proton pump inhibitors (PPIs) are often prescribed in combination with clopidogrel to help reduce the risk of gastrointestinal bleeding, a strategy that is endorsed by existing consensus guidelines.[9] However, several studies have raised the concern that PPIs, especially omeprazole, might diminish the antiplatelet effect[10,11] and the clinical effectiveness[12,13] of clopidogrel, possibly through inhibition of the hepatic CYP isoenzymes, and therefore the conversion of clopidogrel into its active metabolite. A number of other observational studies, however, did not show an interaction between clopidogrel and PPIs.[14,15] Given the conflicting data regarding a possible interaction between clopidogrel and PPIs, the optimal care of patients who require concomitant therapy with clopidogrel and PPIs remains uncertain.[16,17] In addition, genetic polymorphisms of CYP isoenzymes have been identified which could affect the response to clopidogrel and increase the likelihood of drug interactions mediated by CYP. Loss-of-function polymorphisms in the gene encoding for CYP2C19 and CYP3A5 are associated with the lower level of the active metabolite of clopidogrel, diminished platelet inhibition during clopidogrel treatment, and an increased risk of cardiovascular events.[18-20] However, there were few studies investigated whether polymorphism of CYP genes affect the pharmacodynamic effect or clinical efficacy of clopidogrel in IS patients who use concomitant therapy with clopidogrel and PPIs.

Few studies have specifically explored the potential drug–drug interaction between PPIs and clopidogrel in IS patients in Chinese population. In contrast to coronary artery disease, dual antiplatelet therapy is not generally recommended for long-term secondary stroke prevention.[4,21] Consequently, PPI-mediated attenuation of clopidogrel's effect may assume particular importance in patients receiving clopidogrel as the sole antiplatelet agent after stroke. In this study, we assessed whether the concomitant use of PPIs with clopidogrel was associated with diminished antiplatelet activity of clopidogrel and increased risk of adverse outcomes in IS patients in Chinese population. We also examined whether reduced-function CYP alleles were associated with a lower inhibition of platelet aggregation and a higher risk of adverse outcomes in IS patients who use concomitant therapy with clopidogrel and PPIs.

Patients and Methods

Study Design

This was a prospective, observational, cohort study. Patients who fulfilled the inclusion criteria but not the exclusion criteria (see below) were consecutively enrolled into this study. Demographic information as well as information regarding vascular risk factors, including body mass index, body weight, current smoker, diabetes mellitus, and hypertension, were collected. Fasting blood samples were collected to analyze blood glucose, total plasma cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and platelet aggregation.

All patients received standard secondary prevention therapies based on the guideline recommendation[2]: 75 mg clopidogrel once daily (Sanofi Co. Ltd., Beijing, China), or clopidogrel (75 mg, once daily) plus aspirin (200 mg, once daily, Bayer Healthcare Co. Ltd., Beijing, China) for 2 weeks in patients with minor stroke whose National Institutes of Health Stroke Scale (NIHSS) score was ≤3 or symptomatic carotid or intracranial artery stenosis, followed by clopidogrel (75 mg, once daily) for at least 6 months. Concomitant use of PPIs was defined as administration of PPIs that started on admission to at least 2 weeks. Patients who used PPIs from the middle of the follow-up period were excluded. The decision to co-treat with PPI was at the discretion of the treating physician in the present study. According to this, all enrolled patients were classified into PPI treatment group and without PPI treatment group.

All patients were followed up and drug therapy compliance was monitored via telephone or an outpatient clinic every month for 6 months. Scheduled follow-up telephone calls were made to support proper compliance, answer any queries, record complaints of any side effects, and evaluate the degree of disability by modified Rankin Scale (mRS) score.

This study protocol was reviewed and approved by the Ethics Committees of the People's Hospital of Deyang City and the Third Affiliated Hospital of Wenzhou Medical College. Informed written consent was obtained from each patient or a family member before enrollment in this study. The study was registered at http://www.chictr.org/ with the unique identifier of ChiCTR-OCH-14004724.

Study Population

We consecutively enrolled 535 patients who had suffered their first IS, were admitted into the two participating hospitals within 72 hours of their index stroke onset, and were treated with clopidogrel (this medication only or combined with aspirin) between June 2014 and June 2015. The inclusion criteria were the following: (1) age ≥40 years old; (2) diagnosis of IS based on both clinical findings and the results of a neurologic examination using