

The use of oral suspension and rationally prescribing alternatives may be supplemental to the implementation of clopidogrel new algorithm comprising *CYP2C19* pharmacogenetics and drug interactions

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Dear editor

We read with great interest the study by Saab et al,¹ which shows that all patients who received combination therapy of clopidogrel and cytochrome P540 2C19 (*CYP2C19*) substrates require clopidogrel dose adjustment if they are not *CYP2C19**1/*1 carriers and that therapeutic dose of 75 mg clopidogrel should be tailored in patients with different genotypes (eg, lowered to 6 mg or increased to 215 mg) for the sake of efficacy and safety. We especially appreciate the new clinical pharmacogenetic algorithm they developed to optimize clopidogrel-based treatment. However, we found two points worthy of discussion and would like to share our perspectives in the following paragraphs.

Use of oral suspension

The conventional maintenance dose of clopidogrel is 75 mg once daily orally. There are two dosage forms and strengths for Plavix[®] (clopidogrel bisulfate, Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, Bridgewater, NJ, USA), that is, 75 and 300 mg per tablet.² So, a practical breaking problem is encountered, that is, how can clopidogrel at a special dose (eg, 6 or 215 mg) be administered to patients? Generally, a small piece (a quarter of a pill) is the bottom line in subdividing (“breaking”) of an intact tablet because the tablet splitting process is annoying as well as being susceptible to inaccuracy of dosage.^{3,4} Extemporaneously compounded suspensions of clopidogrel (5 mg/mL) in a 1:1 mixture of Ora-Plus and Ora-Sweet were stable for at least 60 days when stored in amber plastic bottles at room temperature and under refrigeration.⁵ Also, a 5 mg/mL clopidogrel oral suspension stored under refrigeration and at room temperature maintains chiral stability as the active S-enantiomer.⁶ A study by Zafar et al⁷ shows that a 300 mg loading dose of clopidogrel given crushed via nasogastric tube provides faster absorption than an equal dose taken orally as whole tablets, but bioavailability was similar over the 24-hour period with both administration methods. Collectively, clopidogrel at a special dose (eg, 6 or 215 mg) may be administered in the form of oral extemporaneously compounded suspension. It is promising to develop a liquid pharmaceutical formulation of clopidogrel for the sake of convenience and dose accuracy.

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Rationally selecting alternatives

We observe that the kind of proton pump inhibitor (PPI) or P2Y₁₂ inhibitor determines the risk level of CYP2C19-mediated drug–drug interactions between classes of drugs. Clinicians should avoid prescribing omeprazole and esomeprazole for patients taking clopidogrel. The potential of proton pump inhibitors (PPIs) to attenuate the efficacy of clopidogrel could be minimized by use of pantoprazole, dexlansoprazole, or rabeprazole, rather than esomeprazole or omeprazole.⁸ Meanwhile, the P2Y₁₂ inhibitors have different pharmacokinetic characteristics. The conversion of clopidogrel to its active metabolite requires two sequential oxidative steps. The first step leads to the formation of 2-oxo-clopidogrel, followed by conversion to the active metabolite. CYP2C19 contributes substantially to both oxidative steps and CYP3A4 contributes substantially to the second oxidative step. Prasugrel is also a prodrug that is activated by a two-step metabolism initiated by plasma esterases and further catalyzed by a single CYP-dependent step that primarily involves CYP3A and CYP2B6, and only partially CYP2C9 and CYP2C19. Ticagrelor undergoes extensive CYP3A4-mediated metabolism to produce an active metabolite; both the parent drug and the active metabolite can reversibly inhibit the P2Y₁₂ receptor. PPIs use was associated with higher platelet reactivity with clopidogrel but not ticagrelor.⁹ There is no substantive evidence that PPIs attenuate the therapeutic effect of prasugrel or ticagrelor; therefore, prasugrel and ticagrelor may be alternatives that can escape the adverse drug–drug interactions induced by PPIs compared with clopidogrel.^{8–11}

We reported that incidence rate of CYP2C19 poor metabolizers in Chinese populations is far higher than that in Caucasians (25% versus 2%–5%) and it is very necessary to perform genotyping of *CYP2C19* prior to initiation of clopidogrel treatment in Chinese subjects.¹² The new clinical algorithm comprising *CYP2C19* pharmacogenetics and drug interactions developed by Saab et al is very practical and beneficial in optimizing clopidogrel treatment.¹ Their study along with our perspectives may bring a more detailed guide in personalized antiplatelet therapy.

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Disclosure

The authors report no conflicts of interest in this communication.

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