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Clopidogrel pathway

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Keywords

clopidogrel; CYP2C19; CYP2C19*2; 2-oxo-clopidogrel; PharmGKB; pharmacokinetics; platelet aggregation; thienopyridine

Clopidogrel, a thienopyridine derivative, binds specifically and irreversibly to the platelet P2RY12 purinergic receptor, inhibiting ADP-mediated platelet activation and aggregation [1,2].

After oral administration, clopidogrel is rapidly absorbed. Owing to its extensive metabolism, clopidogrel is not detected in human plasma. Clopidogrel is a prodrug that is absorbed in the intestine [3,4] and activated in the liver [5]. The conversion of clopidogrel to its active metabolite requires two sequential oxidative steps. As shown in Fig. 1, the first step leads to formation of 2-oxo-clopidogrel, followed by the conversion of 2-oxoclopidogrel to the active metabolite. CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5 are implicated as cytochrome P450 enzymes involved in the metabolism of clopidogrel. However, the relative importance of the individual enzymes and which part of the reaction they are involved in are controversial, as discussed in the literature. Savi *et al.* [1] showed that clopidogrel was converted into 2-oxo-clopidogrel by cytochrome P450 monooxygenase-dependent metabolism *in vitro* and that hydrolysis of 2-oxo-clopidogrel generates the active metabolite. Several publications indicate a major role for CYP3A4 [6,7]. Other in-vitro studies showed that CYP1A2, CYP2B6, and CYP2C19 were capable of forming the 2-oxo-clopidogrel form from clopidogrel in liver microsomes [8,9]. When 2-oxo-clopidogrel was used as a substrate, the enzymes CYP3A4, CYP2C9, CYP2C19, and CYP2B6 produced the active metabolite [8,9]. The study by Kazui *et al.* [9] concluded that CYP2C19 contributes substantially to both oxidative steps and that CYP3A4 contributes substantially to the second oxidative step.

In a competing metabolic reaction, about 85% of the drug is hydrolyzed to an inactive carboxylic acid derivative by esterases [3,10]. The active metabolite of clopidogrel contains a thiol group which binds to a free cysteine on the P2RY12 receptor and irreversibly blocks ADP binding and receptor activation (Fig. 1) [1]. Once this blockage has occurred, platelets are affected for their entire lifespan of approximately 7–10 days.

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Supplemental digital content for the drug clopidogrel (PA449053) and the clopidogrel pathway (PA154424674) is available at http://www.pharmgkb.org/do/serve?objId=PA449053&objCls=Drug and http://www.pharmgkb.org/do/serve?objId=PA154424674&objCls=Pathway.

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Drug–drug interactions of clopidogrel were reported with atorvastatin [11], the calcium-channel antagonist verapamil [12], and the proton-pump inhibitor omeprazole [13–15]. The clinical implications of these findings are still under investigation [16,17]. Several clinical studies did not support the finding that atorvastatin can interfere with the effect of clopidogrel [18–20].

Recent studies indicate that the pharmacodynamic response to clopidogrel is variable, with 20–40% of patients being classified as nonresponders, poor responders or resistant to clopidogrel because of low inhibition of ADP-induced platelet aggregation or activation [21]. Nongenetic factors influencing the clopidogrel response include age, diabetes, renal failure, and cardiac failure [22]. As described above, the prodrug clopidogrel requires activation in the liver. A growing number of studies investigated the effect of pharmacokinetic variables (intestinal absorption and metabolic activation) on response to clopidogrel. ABCB1 is involved in the intestinal absorption of clopidogrel. Two recent studies found an influence of the C3435T variant (rs1045642) in *ABCB1* on clopidogrel absorption in patients with cardiovascular diseases [23,24]. A genome-wide association study of ADP-stimulated platelet aggregation in response to clopidogrel found no association between this single-nucleotide polymorphism (SNP) and clopidogrel response [25].

CYP2C19 is one of the hepatic cytochrome P450 enzymes involved in the formation of clopidogrel's active metabolite. Genetic polymorphisms of *CYP2C19* are associated with impaired clopidogrel metabolism in healthy volunteers and in patients [21,24,26–30]. This poor metabolizer phenotype has also been associated with an increased risk of cardiovascular events. The *CYP2C19*2* genetic variant, 681 G > A (rs4244285), was identified as a major determinant of prognosis in young patients who received clopidogrel treatment after myocardial infarction [29]. Furthermore, patients carrying any two *CYP2C19* loss-of-function alleles [*2, *3 (rs4986893), *4 (rs28399504), or *5 (rs56337013)] had a higher rate of cardiovascular events than patients who did not have these alleles [24]. Similarly, another study showed that carriers of a reduced-function *CYP2C19* allele had significantly lower levels of clopidogrel's active metabolite, diminished platelet inhibition, and a higher rate of major adverse cardiovascular events [30]. A genome-wide association analysis identified 13 SNPs on chromosome 10q24 within the *CYP2C18-CYP2C19-CYP2C9-CYP2C8* cluster showing strong evidence for association with clopidogrel response in an Amish population. The SNP rs12777823 within this cluster was the most significantly associated variant. All 13 SNPs were in strong linkage disequilibrium with each other and also with the loss-of-function variant *CYP2C19*2*, which further findings showed accounted for most of all the association with diminished platelet response to clopidogrel. *CYP2C19*3* and **5* were not polymorphic in the Amish population. The extension and replication of these results in a population with high risk of cardiovascular disease showed an association of *CYP2C19*2* with poorer cardiovascular outcomes [25].

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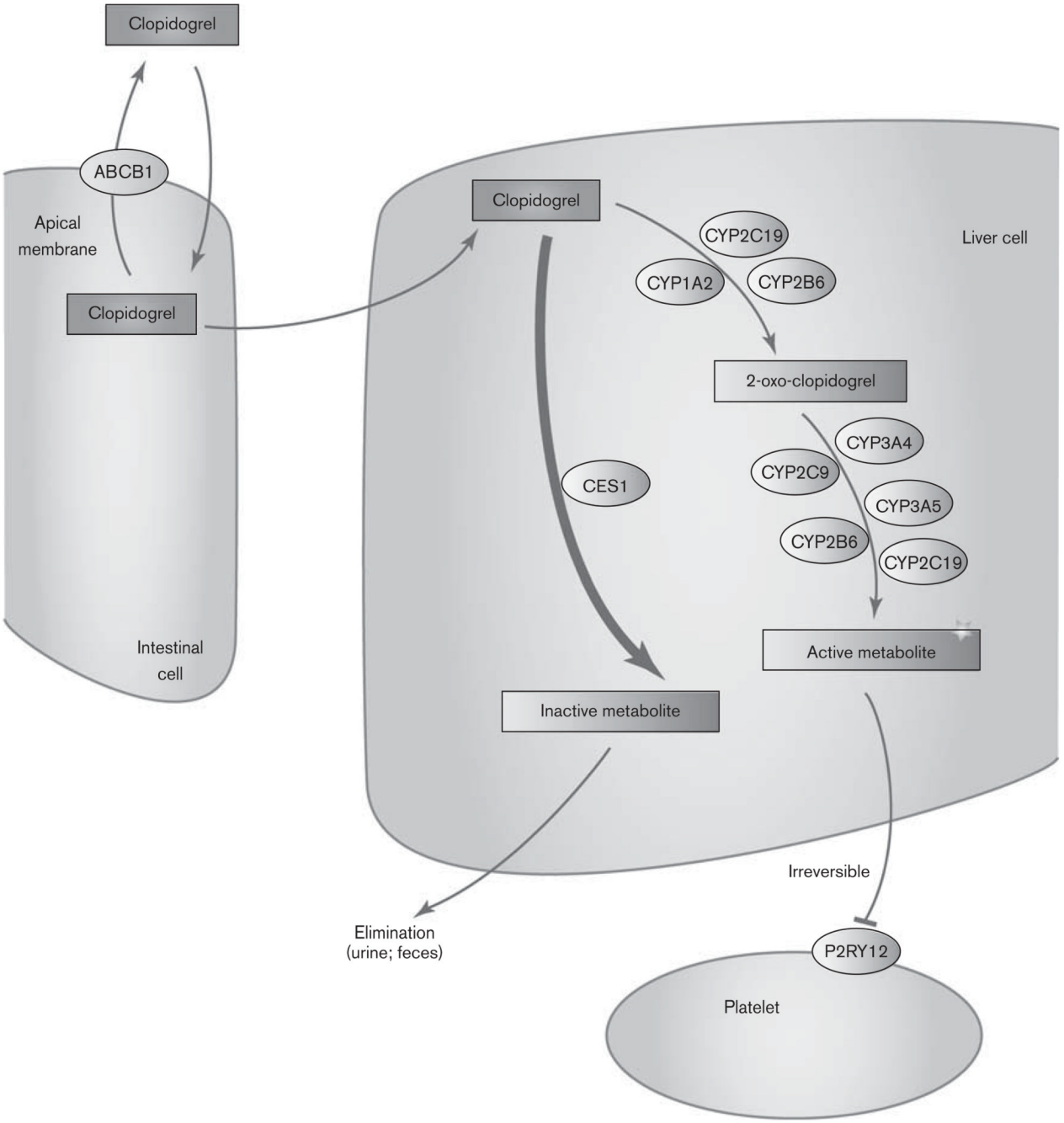

Fig. 1.
Representation of the candidate genes involved in the metabolism of clopidogrel and its primary mechanism of action.