Atherothrombotic events and clopidogrel therapy

In their study of the risk of atherothrombotic events associated with cytochrome P450 3A5 polymorphism in patients taking clopidogrel, Jung-Won Suh and colleagues observed failures in clopidogrel therapy in patients with the non-expressor genotype for the 3A5 isoenzyme of the cytochrome P450 3A system (*3 allele).[1] Because clopidogrel is a prodrug, it is reasonable to hypothesize that its effectiveness will be reduced when metabolism into its active form is reduced. Unfortunately, the lack of any concentration data (of either the parent compound or its metabolite) precludes confirmation of this hypothesis. Without pharmacokinetic data for clopidogrel, the failures in clopidogrel therapy observed by Suh and colleagues cannot be linked to a change in clopidogrel metabolism or in the activity of the cytochrome P450 3A system.

A future examination of these significant observations should include concentration data to confirm a change in clopidogrel pharmacokinetics and establish a pharmacokinetic–pharmacodynamic model. A pharmacogenomically diverse population should also be studied to determine the impact of the cytochrome P450 3A5 non-expressor genotype (*3 allele) on clopidogrel pharmacokinetics and pharmacodynamics. Once a pharmacokinetic–pharmacodynamic model has been established for clopidogrel, clinicians may be able to determine with a single blood draw whether patients require additional antiplatelet therapy.

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We read with interest the recent study in which Jung-Won Suh and associates showed an increased risk of atherothrombotic events 1–6 months after implantation of coronary bare-metal stents in a subset of patients with the non-expressor genotype for the 3A5 isoenzyme of the cytochrome P450 3A system.[1] It is important to note that these atherothrombotic events occurred only after the cessation of clopidogrel administration.

Extensive clinical trial data show that combined therapy with thienopyridines and ASA is beneficial in patients undergoing implantation of bare-metal stents and is also effective after implantation of drug-eluting stents.[2] However, there is increasing concern over "hyper" or rebound effects on platelet aggregation following acute cessation of thienopyridine administration in a subpopulation of patients taking clopidogrel.[2] The mechanism for this rebound effect has not yet been identified. A recent study by Angiolillo and colleagues showed that withdrawal of clopidogrel therapy is associated with increased levels of platelet and inflammatory biomarkers in patients with diabetes.[3]

We interpret the study by Suh and colleagues as confirming that there is an increased risk of late atherothrombotic events when thienopyridine therapy is withdrawn prematurely, with the additional finding that cytochrome P450 3A5 polymorphism may be a risk factor or biomarker for the rebound effect after clopidogrel withdrawal. The continued administration of ASA does not always prevent such a rebound effect.[4] Other factors must also be taken into consideration when assessing the risk of an adverse atherothrombotic event after cessation of clopidogrel administration, such as ASA resistance. In particular, the way in which ASA resistance affects the pharmaceutical management of patients prescribed combined ASA plus clopidogrel therapy must be considered.[4,5]

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