Are we making efficient use of clopidogrel?

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This editorial refers to "Limited early antiplatelet effect of 300 mg clopidogrel in patients with aspirin therapy undergoing percutaneous coronary interventions" by Lepantalo et al. on page 476.

Blood platelets play a major role in the occurrence of thrombotic complications after percutaneous coronary interventions (PCI). Introduction of the thienopyridine drug ticlopidine as an adjunctive antiplatelet therapy has considerably improved the outcome of patients who undergo PCI. Thienopyridines act via blockade of one (P2Y12) of the three adenosine 5′-diphosphate (ADP) receptors, reducing ADP-induced platelet activation and aggregation. Concerns about the side effects of ticlopidine, especially severe neutropenia and thrombotic thrombocytopenic purpura, were a major reason for the rapid replacement of this drug with clopidogrel. Another important limitation of ticlopidine is its delayed onset of action, with maximum inhibition of ADP-induced platelet aggregation achieved only several days after administration. Rapid inhibition of platelet aggregation is crucial for the prevention of post-interventional ischaemic complications, as demonstrated by the use of glycoprotein IIb/IIIa inhibitors during coronary artery stenting.

Clopidogrel, a newer thienopyridine derivative, has advantages over ticlopidine such as its better safety profile and quicker onset of action. Clopidogrel is not active in vitro and its hepatic biotransformation by cytochrome P450 (CYP) 3A4 produces as yet ill-defined active metabolite(s) with antiaggregatory effects. Depending on the dose used, the maximal effect of clopidogrel is achieved within a few hours (>300 mg) to several days (75 mg). The inhibition of aggregation lasts 8–10 days, which corresponds to platelet life span. Apart from the dose-dependence of the onset of the full action of clopidogrel, its efficacy is affected by a relevant interindividual variability in platelet response. Therefore, investigations on optimal dosing and timing of the administration of clopidogrel and factors underlying interindividual variability, as well as ways to overcome it, are of paramount importance in the current era of an explosive increase of the number of PCIs performed, especially after the tremendous success demonstrated with drug-eluting stents.

In this issue of the Journal, Lepantalo and colleagues report on the effects of 300 mg clopidogrel given as a loading dose to patients scheduled to undergo PCI. On the basis of platelet function assessed in blood samples collected approximately 2.5 hours after oral administration of 300 mg clopidogrel, they found an insufficient inhibition of ADP-induced aggregation in 40% of patients. Although the definition of sufficient clopidogrel efficacy has not yet been standardised, the present study sounds the alarm that the use of this loading protocol (300 mg clopidogrel given about 2.5 h before the procedure) leaves a considerable proportion of the patients undergoing PCI without the necessary protection against thrombotic complications. This is, in fact, an elegant confirmation of the clinical observation that patients loaded with 300 mg clopidogrel less than 6 h before PCI are at a greater risk for post-procedural ischaemic complications than those loaded with the same dose more than 6 h before the procedure. Another interesting finding of the present study is that insulin resistance seems to attenuate platelet response to clopidogrel. In other words, patients' characteristics may help to identify subsets in which traditional clopidogrel loading regimens may not ensure the desired level of protection and other alternatives should be sought. Thus, Lepantalo and colleagues tell us that we are still not making efficient use of the therapeutic potential of clopidogrel by continuing to apply the classical loading regimen of this drug. In addition, the results of the present study indicate that we have still a long way to go before completely understanding the...
mechanisms of interindividual variability in clopidogrel efficacy and developing optimal methods for reducing this variability.

The major causes of interindividual variability in clopidogrel efficacy should be sought in differences in the intestinal absorption of the drug, its hepatic biotransformation, and platelet response to clopidogrel. **Clopidogrel absorption:** Although clopidogrel bioavailability after oral ingestion is relatively independent from age and food ingested, the plasma pharmacokinetic parameters of clopidogrel (unmodified), such as peak plasma concentration and time to peak plasma concentration, are characterised by considerable interindividual differences. There is, however, a good correlation between the ingested dose of clopidogrel and peak plasma concentration of the drug. The combination of the latter finding with the finding of a strong correlation between peak plasma concentration and degree of platelet inhibition that we have observed in volunteers may convey an important message for medical practice: increasing the dose of clopidogrel may overcome patient characteristics tending to reduce clopidogrel efficacy. In fact, ingestion of a high dose of 600 mg clopidogrel has led within 2 h to a nearly maximal antiplatelet effect (defined as the degree of platelet inhibition achieved by chronic therapy with 75 mg clopidogrel). **Hepatic biotransformation:** Clopidogrel undergoes CYP3A4-dependent metabolism before exhibiting its antiaggregatory effect. Intensive work has focused on the identification of the active metabolite(s) responsible for the antiplatelet actions of the drug. Plasma concentration of the identified active metabolite follows the plasma concentration of clopidogrel itself and correlates strongly with the degree of platelet inhibition obtained with the drug. However, it would be illusory to expect that determinations of plasma concentration of the active metabolite would be part of the daily routine. The low inherent activity of the CYP3A4 enzyme or interference by statins that use this enzymatic pathway have been reported to attenuate the antiaggregatory effects of traditional loading doses of clopidogrel. On the contrary, these statins did not inhibit the effect of a high, 600-mg loading dose of clopidogrel. **Platelet response:** The factors that may affect platelet response to clopidogrel are of multiple origins. Recently, P2Y12 gene variations have been associated with enhanced ADP-induced platelet aggregation in untreated, healthy subjects. It is still not known whether these gene variations also interfere with clopidogrel efficacy. Lepantalo and colleagues identified insulin resistance as a factor that attenuates platelet response to 300 mg clopidogrel. The complex, as yet poorly understood, interplay of factors that affect platelet response to clopidogrel is commonly summarised in the concept of clopidogrel nonresponders. A relevant number of patients seem to behave as nonresponders after the usual loading dose of 300 mg clopidogrel. This number diminishes during chronic clopidogrel therapy or after administration of a higher, 600-mg loading dose of clopidogrel. **Can we make more efficient use of clopidogrel?** There is agreement in the interventional cardiology community that a rapid and effective pharmacological inhibition of platelet aggregation is of primary importance for ensuring a low-rate of ischaemic complications after PCI. Lepantalo and colleagues showed in the present manuscript that the usual 300-mg loading dose of clopidogrel cannot achieve this goal in a great number of patients. Increasing evidence demonstrates that a higher, 600-mg loading dose of clopidogrel provides a more effective and rapid platelet inhibition and reduces the number of non- or poor responders. Pretreatment strategies based on this clopidogrel dose have been found to be safe for patients. More importantly, a high loading dose has been shown to obviate the need for glycoprotein IIb/IIIa inhibitors in low-to-moderate risk patients undergoing PCI. Other drug preparations (e.g., intravenous clopidogrel) may be even more effective and helpful in these settings. Point-of-care tests that allow a simple and quick assessment of the individual response to the given dose of clopidogrel may help to identify the patients who need clopidogrel dose adjustments or even other antiplatelet therapy options before starting a PCI procedure. Therefore, much work is still required to better define how we can make more efficient use of this drug.

**References**


