Loading, Pretreatment, and Interindividual Variability Issues With Clopidogrel Dosing

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Clopidogrel, a thienopyridine, decreases adenosine diphosphate (ADP)–induced platelet aggregation. Clopidogrel is an inactive prodrug that requires in vivo conversion in the liver by the cytochrome P450 (CYP) 3A4 enzyme system to an active metabolite that exerts its antiplatelet effect by noncompetitive inhibition of the platelet ADP receptor subtype P2Y12.1 The 75-mg once-daily dose was approved by the US Food and Drug Administration (FDA) in November 1997 after the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial2 showed superior reduction of adverse cardiovascular events with clopidogrel versus aspirin. The 75-mg once-daily dose had been used in CAPRIE because it produced inhibition of platelet aggregation equivalent to that produced by ticlopidine 250 mg administered twice daily. FDA approval for the 300-mg loading dose in patients with acute coronary syndromes was granted in February 2002 after the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial3 demonstrated a reduction of adverse cardiovascular events with dual antiplatelet therapy versus aspirin. Clopidogrel is not approved by the FDA for adjunctive antiplatelet therapy in percutaneous coronary intervention (PCI), although it has become the standard of care. It is curious that investigations into the optimal loading and maintenance doses of clopidogrel have been pursued only recently.

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In this issue of Circulation, Hochholzer et al4 performed optical platelet aggregometry and flow cytometry before and after a 600-mg oral dose of clopidogrel in 1001 potential PCI candidates undergoing cardiac catheterization. The findings are consistent with previous observations from small studies with regard to the 600-mg clopidogrel loading dose: Maximal inhibition of ADP-induced platelet aggregation was achieved 2 hours after ingestion,5 interindividual variability of platelet response was considerable,6 and there was no significant effect of concomitant statin therapy on platelet inhibition.7,8 Although no additional reduction in adverse cardiac events was noted by performing PCI >2 hours after clopidogrel ingestion, the 30-day event rate was extremely low (1.9%), and no data were furnished on biomarker-diagnosed periprocedural myocardial infarction (MI) or subacute stent thrombosis rates.

Loading Dose

Without a loading dose, clopidogrel 75 mg daily induces inhibition of ADP-induced platelet aggregation as early as 2 hours after the first dose but requires 3 to 7 days to achieve maximal inhibition of platelet aggregation.9 The 3- to 7-day delay can be shortened to <6 hours with a loading dose of 300 to 600 mg.3 Although Hochholzer et al4 claim that the 600-mg dose achieves maximal platelet inhibition at 2 hours in a large population of patients, we and others have data (unpublished) with frequent serial measurements in the same individuals that suggest that time to maximal platelet inhibition after 600 mg takes at least 4 hours and is similar to that seen with a 300-mg dose; however, the 600-mg dose does acutely increase the level of inhibition of platelet aggregation as compared with the 300-mg dose5,10 and may decrease the number of low responders.6 The ceiling effect for platelet inhibition with clopidogrel has yet to be defined, so it remains unclear whether even higher loading doses (900 mg) would increase acute platelet inhibition.

Both the 300-mg and the 600-mg loading dose accomplish maximal platelet inhibition in time to decrease subacute stent thrombosis rates. The potential advantage of using the higher loading dose would be maximal drug effect during the periprocedural period when pretreatment has not been given, a common occurrence with ad hoc PCI. Any potential clinical benefit could be measured by lower biomarker-defined periprocedural MI rates, as has been seen with periprocedural platelet inhibition with glycoprotein (GP) IIb/IIIa inhibitor agents. Available data have yet to demonstrate consistently that clopidogrel prevents periprocedural MI10–14 and are confounded by loading dose and whether clopidogrel was given several hours before or immediately after PCI. Although the clinical benefit for increasing the loading dose from 300 to 600 mg remains to be defined, there is no medical reason to favor the lower dose.

Pretreatment

The Clopidogrel for the Reduction of Events During Observation (CREDO) trial11 randomized PCI patients to placebo or a 300-mg loading dose 3 to 24 hours before PCI; all patients received 75 mg immediately after the procedure. Therefore, it was really a trial of loading dose versus no loading dose, not a trial comparing pretreatment with a loading dose versus a loading dose at the time of PCI.
Nevertheless, there were no significant differences in outcome at 30 days. A prespecified subgroup analysis did, however, show a trend toward benefit in the patients who received the study drug >6 hours before PCI. A subsequent post hoc analysis\textsuperscript{15} suggested that clopidogrel had to be ingested at least 15 hours before PCI to decrease 30-day clinical events. If maximal platelet inhibition is achieved 6 hours after a loading dose of 300 mg, then this suggests that any clinical advantage associated with clopidogrel pretreatment lags behind the pharmacological benefit of platelet inhibition, an observation that requires further study. Others have found no benefit with clopidogrel pretreatment in preventing periprocedural MI or clinical events\textsuperscript{12,13,16}; therefore, the present clinical enthusiasm for preloading is not yet evidence based.

Interindividual Variability

It is now widely appreciated that there is marked interindividual variability in platelet inhibition after clopidogrel ingestion.\textsuperscript{6,17–19} Patients showing little platelet inhibition after clopidogrel have been labeled “hyporesponders,” “low responders,” “nonresponders,” and “resistant.” The incidence depends on whether one uses relative\textsuperscript{17} or absolute\textsuperscript{18} differences in platelet aggregation before and after clopidogrel and whether one uses arbitrary cut points\textsuperscript{17,18} or 2 standard deviations from the mean\textsuperscript{19} to define low responders. Importantly, increasing the clopidogrel loading dose to 600 mg does not decrease the phenomenon of interindividual variability.\textsuperscript{4,6}

Although there have been no prospective studies demonstrating that the degree of platelet inhibition is directly related to clinical outcomes, several reports have shown an association between less platelet inhibition and more adverse clinical events after PCI with aspirin,\textsuperscript{20} clopidogrel,\textsuperscript{21} or GP IIb/IIIa inhibitor\textsuperscript{22} therapy. Because the pharmacological mechanism of clopidogrel in patients undergoing PCI is to inhibit platelet aggregation, it would appear that many low responders are receiving suboptimal platelet inhibition as compared with patients with excellent responses to clopidogrel or patients receiving GP IIb/IIIa inhibitor therapy. The fact that approximately one third of patients being treated with clopidogrel for PCI are receiving suboptimal platelet inhibition may be the most important message from the study by Hochholzer et al.\textsuperscript{4,18}

Clopidogrel–Atorvastatin Interaction

The principle of competitive inhibition in drug–drug interactions has been overlooked by retrospective reports that claim no clinical significance for the clopidogrel–atorvastatin interaction we described previously.\textsuperscript{1} Atorvastatin and clopidogrel are competitive substrates for the CYP 3A4 enzyme system. The degree of competitive inhibition depends on their relative affinities for the binding site and their relative concentrations. Clopidogrel doses of 75 to 300 mg are inhibited by atorvastatin in a dose-dependent manner.\textsuperscript{1} Conversely, clopidogrel doses of 600 mg may overcome this inhibition.\textsuperscript{4,7,8} Whereas it is reassuring that higher loading doses of clopidogrel may acutely negate this drug–drug interaction, it again should be noted that there are no consistent clinical data suggesting that clopidogrel prevents death or MI during hospitalization for either acute coronary syndromes or PCI.\textsuperscript{3,10–14,16} The clinical benefit seen with clopidogrel in both the CURE\textsuperscript{3} and CREDO\textsuperscript{11} trials was noted during the chronic maintenance dosing of clopidogrel 75 mg daily, a dose that can be inhibited by atorvastatin. Because 50% of atorvastatin prescriptions are for 10 mg and 30% are for 20 mg, the clinical significance of a mild drug–drug interaction would require large numbers of patients to detect; however, the interest in initiating atorvastatin therapy at 80 mg in these patients may well make this interaction clinically important by significantly inhibiting the conversion of clopidogrel to its active metabolite. The rofecoxib (Vioxx; Merck and Co.) controversy should make the clinician more skeptical about accepting unfounded reassurances that a drug can be widely prescribed when there are pharmacological mechanisms that suggest the drug may have limitations.

Another misconception is that all statins or all lipophilic statins (atorvastatin, simvastatin, lovastatin) interfere with clopidogrel activation. Atorvastatin is unique among the statins for its long half-life (14 hours versus 2 hours), which could make it the only statin constantly competing with clopidogrel for the CYP 3A4 binding site. Importantly, statins probably have different binding affinities for CYP 3A4. In addition, dose equivalents are different among the statins, with 10 mg atorvastatin, 20 mg simvastatin, 40 mg lovastatin, and 40 mg pravastatin having similar low-density lipoprotein–lowering effects.\textsuperscript{23}

CYP 3A4

The interindividual variability of the antiplatelet effect of clopidogrel is probably more often the result of drug–drug interactions involving CYP 3A4, the enzyme system that metabolizes half of the drugs prescribed, and environmental and genetic influences on CYP 3A4 activity levels and platelet receptor function.\textsuperscript{24} Platelet number and receptor density also are important variables. For instance, there is a 40-fold difference in CYP 3A4 expression between individuals. We have demonstrated that platelet inhibition by clopidogrel can be decreased by CYP 3A4 inhibitors (erythromycin, troleandomycin) and competitive substrates (atorvastatin, cyclosporin).\textsuperscript{1} Conversely, we have shown that CYP 3A4 inducers (rifampin, St. John’s wort) increase platelet inhibition by clopidogrel and convert nonresponders to responders.\textsuperscript{24,25} The problem with fixed clopidogrel dosing, of course, is that high responders may be at increased risk for bleeding and low responders may be at increased risk for thrombosis. Individual measurement of CYP 3A4 activity levels, receptor polymorphisms, or platelet aggregation responses might allow individual clopidogrel dosing that would maximize its efficacy and safety. The development of new thienopyridines, however, may simplify platelet ADP P2Y\textsubscript{12} receptor–inhibitory therapy. Prasugrel (CS-747) has twice the platelet-inhibitory activity of clopidogrel and much less interindividual variability, and it avoids the low-responder phenomenon because of unique metabolic characteristics that prevent CYP 3A4 from slowing down the conversion of the prodrug to its active metabolite.\textsuperscript{26} The efficacy of superior platelet inhibition with this agent in decreasing adverse cardiovascular events will be tested in the TRITON TIMI-38 trial that will...
compare prasugrel and clopidogrel in 13 000 patients with acute coronary syndromes and planned PCI.

**Conclusion**

Dual antiplatelet therapy with aspirin and clopidogrel reduces platelet-mediated adverse cardiovascular events in patients undergoing PCI. Nevertheless, both drugs are limited by interindividual variable responses and drug–drug interactions, and a significant number of patients are poor responders or nonresponders. It is important to note that despite the widespread acceptance that higher loading doses of clopidogrel or pretreatment with clopidogrel further decreases complication rates, there are no clinical trial data to support these perceptions. Clopidogrel only decreases ADP-induced platelet aggregation by 50%. The true potential of thienopyridines to reduce PCI periprocedural complication rates will require the development of third-generation agents with improved pharmacological profiles.

**Disclosures**

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