Atorvastatin and the Ability of Clopidogrel to Inhibit Platelet Aggregation

To the Editor:

Lau et al.1 recently reported that coadministration of CYP3A4-metabolized statins (atorvastatin, simvastatin, and lovastatin) but not pravastatin (fluvastatin and rosuvastatin) inhibited the “antiplatelet activity of clopidogrel in a dose-dependent manner,” using an in vitro point-of-care MICROs cell counter (ABX Diagnostics) and the Plateletworks test platform (Helena Laboratories).

Platelet activity is measured by the combination of the following three tests: (a) platelet aggregation by adenosine diphosphate (ADP) or collagen-induced whole blood (or platelet-rich plasma) platelet aggregometry, (b) platelet adhesion by ex-vivo perfusion (Badimon) chamber,2 and (c) platelet activation by flow-cytometry measurement of the surface membrane expression of CD62p (p-selectin, GMP140) in the whole blood.3,5 All three tests are needed to test platelet function.

Clopidogrel, an ADP receptor antagonist, selectively and irreversibly inhibits ADP-induced platelet activation and aggregation, thereby preventing atherothrombosis.

In their interesting and provocative article, Lau et al.1 found that atorvastatin, and not pravastatin, blunted the in vitro antiaggregation effect of clopidogrel in patients after stent deployment. However, the authors measured only the platelet antiaggregation pathway and left the other two pathways (platelet adhesion and platelet activation) unexplored. Blocking only one pathway does not necessarily predict stent restenosis (and/or in-stent thrombosis) and/or a worse clinical outcome. I suggest, therefore, that the authors assess the impact of clopidogrel alone and its administration with atorvastatin or pravastatin on platelet adhesion and activation before concluding that CYP3A4-metabolized statins, and not pravastatin, inhibit the “antiplatelet activity of clopidogrel.”

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Response

We reported that atorvastatin, but not pravastatin, inhibited the “antiplatelet activity of clopidogrel in a dose-dependent manner.”1 We offered no data on simvastatin, lovastatin, fluvastatin, or rosuvastatin, nor did we offer any data on how the atorvastatin-clopidogrel drug-drug interaction might influence clinical outcomes. These subjects require additional evaluation.

We agree with Dr Shechter that testing platelet adhesion and activation would offer a more complete evaluation of platelet function. However, the main observation of our paper was that clopidogrel, a prodrug, is metabolically activated by the cytochrome P450 (CYP) 3A4 and that atorvastatin inhibits this activation. It is the low concentration of the active clopidogrel metabolite that results in an attenuated response to clopidogrel when coadministered with atorvastatin, not a direct competition between the drugs for the adenosine diphosphate (ADP) platelet receptor. Additional data on the pharmacology of this observation have been obtained with in vitro studies using microscopes containing human cytochromes P450.2

We and others are performing additional platelet aggregation and flow cytometry studies on the interaction of clopidogrel with other CYP 3A4 substrates. Others are developing new thiopyridines with higher bioavailability and better binding characteristics to CYP3A4 and to the P2Y12 ADP platelet receptor.

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Circulation. 2003;107:e210
doi: 10.1161/01.CIR.0000076180.03211.BD
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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