Do Statins Inhibit Clopidogrel's Antiplatelet Activity?

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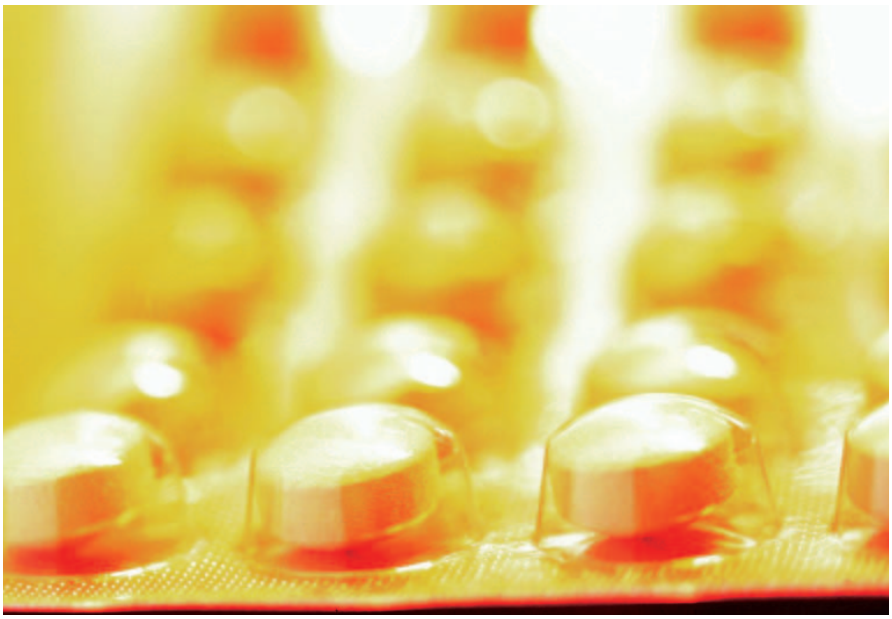
Pharmacy Times *is proud to publish this new column on drug interactions by the esteemed Drs. Horn and Hansten, professors of pharmacy at the University of Washington and authors of the pocket-sized drug interaction booklet* **The Top 100 Drug Interactions: A Guide to Patient Management** *and the loose-leaf reference* **Drug Interactions Analysis and Management**. *This column will appear monthly, and feedback is encouraged. For an electronic version, including references, see www.hanstenandhorn.com.*

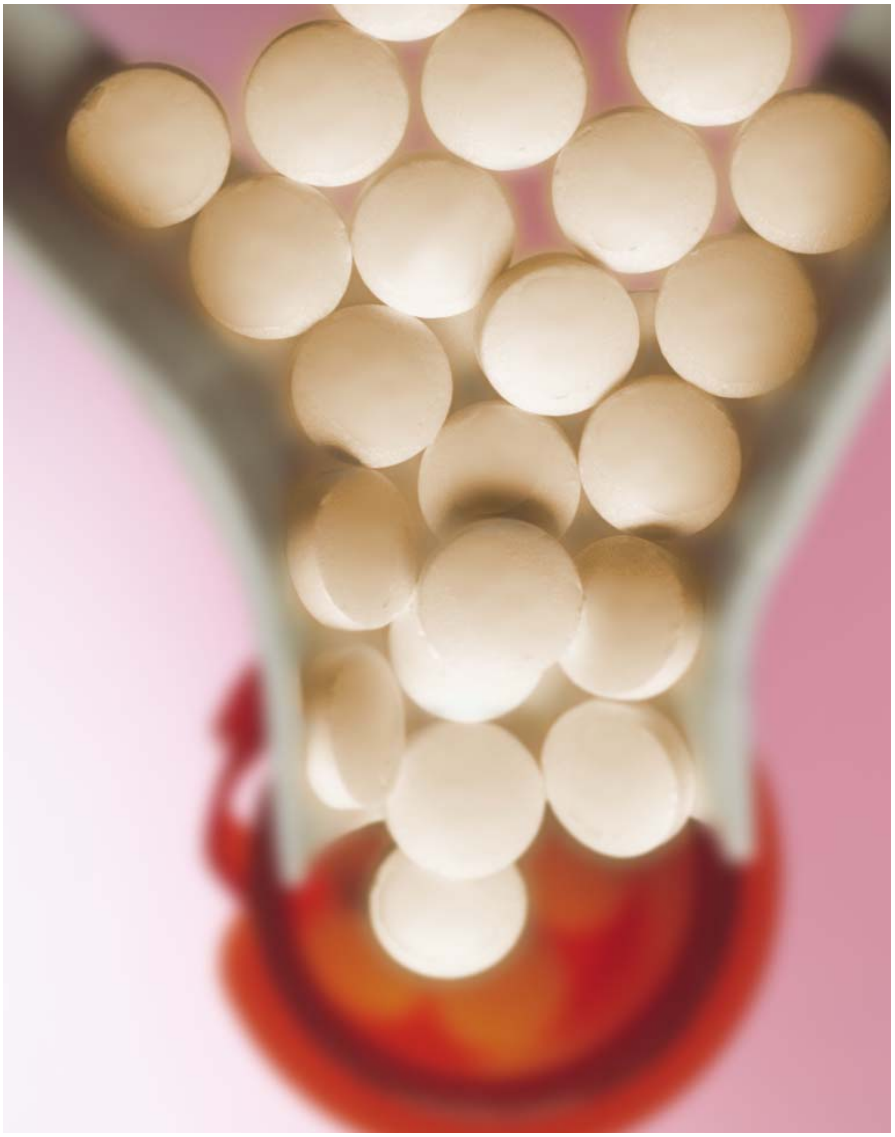
Recently a number of questions have arisen concerning potential interactions involving clopidogrel and statins. Clopidogrel is a prodrug that blocks platelet aggregation by binding to the platelet adenosine diphosphate (ADP) receptor. For clopidogrel to reduce platelet aggregation, it must first be metabolized to a thiol derivative. The conversion of clopidogrel to this active thiol metabolite appears to be catalyzed by cytochrome P450 3A4 (CYP3A4). Drugs that inhibit CYP3A4 activity could decrease the efficacy of clopidogrel by reducing its conversion to the active thiol metabolite.

A recent report concerning a small number of patients noted a reduction in clopidogrel's antiplatelet activity when it was administered with drugs known to inhibit CYP3A4 activity.[1] Clopidogrel administered alone reduced ADP-induced platelet aggregation to 42% to 45% of control values. When erythromycin or troleandomycin (both CYP3A4 inhibitors) were administered prior to clopidogrel, clopidogrel reduced platelet aggregation to only 55% to 78% of control. This demonstrates a lessening of clopidogrel's antiplatelet activity following the CYP3A4 inhibitors. Similarly, the authors noted that when atorvastatin was coadministered with clopidogrel, mean platelet aggregation was 77%, compared with 34% when clopidogrel was administered alone.



It is not known what degree of inhibition of platelet aggregation is necessary for clopidogrel to prevent thrombus formation. The reduction in clopidogrel's activity during atorvastatin administration was suggested to be due to competitive inhibition between clopidogrel and atorvastatin for CYP3A4 enzymes. Pretreatment with pravastatin, a drug that is not metabolized by CYP3A4, did not result in a significant change in clopidogrel's effects on platelet aggregation.

Although atorvastatin is not usually considered an inhibitor of CYP3A4, both atorvastatin and clopidogrel are substrates for the enzyme. It is possible for 2 substrates of the same metabolizing enzyme to compete for catalytic sites on the enzyme and for 1 of the substrates to access the sites while excluding the other substrate. The enzyme would then metabolize the excluded drug more slowly. This is referred to as competitive inhibition. If clopidogrel is not metabolized as fast as usual, less thiol metabolite would be formed and loss of platelet inhibition may occur. In vitro studies have shown that equimolar concentrations (50 micromolar) of atorvastatin lactone (a metabolite of atorvastatin) and clopidogrel result in inhibition of clopidogrel metabolism.[2] This likely represents competitive inhibition between the 2 CYP3A4 substrates. The concentration



of atorvastatin used in this in vitro study, however, was much higher than the concentration of atorvastatin found in vivo following conventional doses. Further study is needed to conclusively establish competitive inhibition of CYP3A4 as the mechanism of the purported interaction between clopidogrel and atorvastatin. Other potential mechanisms might include atorvastatin inhibition of clopidogrel absorption by active transporters.

Because clopidogrel and statins are likely to be coadministered to patients with cardiovascular disease, it is important to determine if a clinically significant interaction occurs. No attempt was made in the study cited above to determine the effect of atorvastatin on the ability of clopidogrel to reduce thrombus formation.[1] Analysis of data from large clinical trials of clopidogrel, however, found no reduction in clopidogrel's antiplatelet effects in patients concurrently taking statins, including atorvastatin.[3,4] The same authors found that statins did not alter the effect of clopidogrel on platelet function in patients undergoing coronary artery stenting procedures.[4] Nifedipine, also a substrate of CYP3A4, was found to have no effect on clopidogrel's inhibition of ADP-induced platelet aggregation when administered to patients with atherosclerosis.[5]

It is important to consider that clopidogrel is usually administered with aspirin to prevent thrombus formation. If atorvastatin, or any other statin, does reduce the effect of clopidogrel on ADP-induced platelet aggregation, the antiplatelet effects of aspirin will still be present. Furthermore, it has been noted that statins produce an antithrombotic effect of their own.[6,7] Thus, the potential for atorvastatin to reduce the efficacy of clopidogrel and significantly increase the risk of thrombus formation in the typical patient would seem to be slight. Patients not taking aspirin (ie, patients who are aspirin allergic) may represent a greater risk for antiplatelet failure during coadministration of clopidogrel and CYP3A4 inhibitors such as erythromycin, clarithromycin, ketoconazole, itraconazole, and many of the antiviral drugs.

Based on the data currently available, the reported interaction between clopidogrel and atorvastatin raises several interesting questions, particularly regarding its mechanism and the appropriate methods to test for the interaction. Because some patients receiving clopidogrel or aspirin do not achieve marked platelet inhibition, it may be reasonable to use platelet aggregometry to measure drug effect in patients at high risk for thrombus formation, particularly if they are concurrently receiving known inhibitors of CYP3A4. PT

For a list of references, send a stamped, self-addressed envelope to: References Department, Attn. D. Ryan, Pharmacy Times, 241 Forsgate Drive, Jamesburg, NJ 08831; or send an e-mail request to: dryan@mwc.com.