Drug Interactions With Good Old Clopidogrel

Case Closed*

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Dual antiplatelet therapy with aspirin and the platelet P2Y12 receptor antagonist clopidogrel has become the cornerstone of the treatment of patients undergoing coronary stenting and of those with acute coronary syndromes (ACS) with or without stent implantation (1). Consequently, many patients remain on dual antiplatelet therapy consisting of aspirin and clopidogrel.

The only important side effect of dual antiplatelet therapy is increased bleeding compared with aspirin alone. This has been established in the large trials with clopidogrel in ACS (2,3) and after ACS (4), as well as in atrial fibrillation (5). In the latter, dual antiplatelet therapy has shown to be as hazardous as oral anticoagulation (6). The novel platelet P2Y12 receptor antagonists prasugrel and ticagrelor are more effective than clopidogrel in patients, but show increased major bleeding including cerebral hemorrhage compared with clopidogrel (7,8).

Figure 1. Concomitant Drug Therapy in the Major Clopidogrel Trials

Percentage of patients on statins (blue) or calcium channel blockers (red) in the 9 major clopidogrel trials over time. 2nd = secondary; ACS = acute coronary syndromes; NA = not available; PCI = percutaneous coronary intervention.

The other problem with clopidogrel is its cumbersome metabolism to its active metabolite, which is not only due to its genetic polymorphisms but also to inhibition of its effect by concomitant medications metabolized by the same pathways by which clopidogrel is converted to its active metabolite. As to the latter effects, the isoenzymes CYP3A4 (statins and calcium channel blockers) and CYP2C19 (omeprazole and esomeprazole) are the major players (9). Statins and calcium blockers are very often used in coronary patients receiving clopidogrel, and proton pump inhibitors are advised in many cases because of the bleeding risks associated with clopidogrel. Numerous pharmacodynamic studies have confirmed the interaction of these agents with the in vitro antiplatelet effects of clopidogrel in coronary disease patients as well as in healthy volunteers. However, the clinical consequences with regard to proton pump inhibitors have never been substantiated. In the only placebo-controlled trial of omeprazole in patients undergoing percutaneous coronary intervention (PCI) treated with clopidogrel, there was no harm with regard to ischemic endpoints. However, the gastrointestinal protection by omeprazole was significant (10). With regard to the pharmacodynamic statin-clopidogrel interaction, clinical data are contradictory in registry cohort studies (11,12) and reassuring in the major clinical placebo-controlled clopidogrel trials CREDO (Clopidogrel for reduction of Events During Observation) (13) and CHARISMA (Clopidogrel for High Atherothrombotic Risk, Ischemic Stabilization, Management and Avoidance) (14). Finally, for calcium channel blockers, there are only limited pharmacodynamic data on their interaction with clopidogrel (15,16), and large-scale clinical observations on this topic are lacking.

In this issue of JACC: Cardiovascular Interventions, the results of a retrospective analysis of the clopidogrel patients from the well-known TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) trial evaluating novel antiplatelet therapy in patients with ACS undergoing early PCI (17) are reported. This is by far the largest cohort of ACS patients treated with clopidogrel undergoing PCI, in which interactions between the drugs mentioned have been studied. Therefore, it is an important contribution to the clopidogrel interaction issues. The bottom line is that the clinical impact of clopidogrel interactions with commonly prescribed drugs...
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in interventional cardiology is simply nonexistent. This is reassuring, especially for the concomitant use of statins, which, unlike calcium blockers, are used more and more in combination with clopidogrel (Fig. 1).

Why should we be making a fuss about an old agent that will be replaced by the newer P2Y12 receptor blockers prasugrel and ticagrelor? No important drug interactions have been reported with the new agents. There are no known polymorphisms reducing their antiplatelet activity. Prasugrel is metabolized in almost all patients, and ticagrelor is not a prodrug. Both agents induce faster and stronger clinical antiplatelet activity than clopidogrel. Yet their uptake in cardiology practice is slow worldwide because of cost, fear of bleeding, dyspnea (ticagrelor), and limited applicability (prasugrel). Furthermore, they are not tested in elective PCI with stenting, for which clopidogrel is still the standard of care.

Clopidogrel is an effective, inexpensive, and well-known agent for patients undergoing elective stenting and in many patients with ACS with and without coronary intervention. Despite its limited antiplatelet activity in subgroups of patients, there are no important clinical drug interactions, and, therefore, it is a drug that is here to stay.

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Key Words: acute coronary syndromes • calcium-channel blocker • clopidogrel • statin.