

Editorial Focus

Clopidogrel and proton pump inhibitors: Gastric protection at expense of vascular benefit?

Victor Serebruany¹; Shinya Goto²

¹Johns Hopkins University (Neurology) Towson, Maryland, USA; ²Department of Medicine (Cardiology), Tokai University, Kanagawa, Japan

Clopidogrel as a monotherapy, or in combination with low-dose aspirin is presently the cornerstone antiplatelet agent for prevention of thrombotic events in patients with vascular occlusions including coronary, cerebral, and peripheral disease. Being the second after atorvastatin, the mostly prescribed medication, clopidogrel is commonly used with other pharmaceuticals such as proton pump inhibitors (PPI). Physicians prescribe PPI to treat heartburn and gastroesophageal reflux, stomach and intestinal ulcers, or conditions associated with excess stomach acidity. Importantly, PPIs are often prescribed for empiric therapy of a suspected diagnosis of one of the above conditions, without confirmation from invasive studies. This makes PPI use even more common and also makes it more likely to be prescribed for symptomatic relief rather than for therapeutic intent. One large registry suggests that general US practitioners prescribed at least one PPI in 5.6% of all outpatients during 2003 (1). Similar to clopidogrel, PPI are sharing the same metabolic pathway extensively metabolising in the liver (2). Furthermore, it is well known that all PPI might alter the degree of absorption of certain medications through modifying intragastric pH (3). As a consequence, PPI might affect numerous drug classes well beyond clopidogrel.

Since clopidogrel prescribing became very popular in the antiplatelet drug arena about a decade ago, the drug is under scope, and undergoing endless vicious attacks somewhat orchestrated by the newer drug developers, or supported by small self-promoting observational studies, in contrast with lack of aspirin response, which is real. The classical example of such controversy was a dispute whether or not clopidogrel interacts with atorvastatin due to the similar and competitive metabolism by hepatic CYP3A4 pathway. Although earlier reports raised this concern (4, 5), more comprehensive platelet studies (e.g. 6, 7), and clinical evidence yielded from clinical trials (8) and registries (9) did not confirm this "sensation".

Perhaps it would be worth noting that clinical use of clopidogrel was promoted without exact understanding the mechanism of its action. Indeed, the mechanism of antiplatelet effects of

clopidogrel was not known until P2Y₁₂ receptor was cloned in 2001 (10). The extent of receptor blockage in individual patients is still unknown. Similarly, the initial evidence on potential clopidogrel-PPI interactions appear unjustified. In fact, the data regarding higher rate of gastrointestinal bleeding after monotherapy with clopidogrel versus aspirin and esomeprazole combination in patients with previous ulcer bleeding are intriguing but controversial, and confusing (11). Although the study raised important concerns, it was difficult to agree with the comprehension of the data. In fact, what study really suggests is that esomeprazole is useful in preventing haemorrhagic ulcer recurrences. Moreover, considering reduced acidity of the gastric pH after esomeprazole, (12) aspirin may lack antiplatelet efficacy due to the insufficient absorption (13). Indeed, the study compared low-dose (80 mg) aspirin under gastric protection of esomeprazole versus more potent antiplatelet agent (clopidogrel) with no PPI on board. Not surprisingly, the bleeding rate was much higher (8.6%) in the clopidogrel group. Another limitation is that the primary study was done exclusively in Asians, who are known to exhibit less platelet activation, than other races (14), and in whom more delicate antiplatelet regimens may be preferred (15) especially in patients with the previous haemorrhagic episodes.

Despite the initial controversy, the issue of potential clopidogrel-PPIs interaction unquestionably has merit for better comprehension, and evaluating of benefit/risk ratio. A timely, elegant, well-designed, and convincing cross-sectional observational large study in 1,000 patients undergoing coronary intervention published by Sibbing et al. in this issue of *Thrombosis and Haemostasis* is an important contribution to the field (16). Since most data on potential interactions between clopidogrel and PPI have been reported for omeprazole, investigators expand their observations by adding pantoprazole, and esomeprazole to the study design. The main message of the index paper is that while omeprazole does diminishes antiplatelet potency of clopidogrel the two other PPI did not affect platelet inhibition in the clopidogrel treated patients. The finding that PPI differ in their

Correspondence to:
Dr. Serebruany
HeartDrug™ Research Laboratories
Johns Hopkins University, Osler Medical Building
7600 Osler Drive, Suite 307, Towson, MD 21204, USA
Tel.: +1 410 847 9490, Fax: +1 443 583 0205
E-mail: heartdrug@aol.com

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impact of antiplatelet agents represents the most important clinical validity of these data providing us with several therapeutic options.

Apparently, clopidogrel is not the only medication affected by the concomitant use with PPI. A large cohort study evaluated the effects of antisecretory agents or nitrates in combination with aspirin, non-steroidal anti-inflammatory drugs (NSAID), clopidogrel, and anticoagulants on upper gastrointestinal bleeding risks. Importantly, only PPI therapy was associated with a marked, consistent risk reduction among patients receiving all types of agents. Moreover, protection was not apparent in patients taking anticoagulants (17). With regard to the PPI use on top of single antiplatelet agent, the data are very limited. It seems that both aspirin, and clopidogrel are not able to exert full antiplatelet activity when PPI are on board (18). Apparently, the highest bleeding risks are present in patients who already experienced even minor haemorrhagic episode (19). Among those receiving clopidogrel as a monotherapy, it seems that gastric bypass patients are at highest risk (up to 40%) of bleeding complications (20). When clopidogrel and aspirin are used in combination, the bleeding risks are obviously more common (1.5–3.5%) than reported in major randomised trials, especially in Asian patients (21). The occurrence of only upper gastrointestinal bleeding rate in real life for a median follow-up of 5.8 months was as high as 4.0% (22). Importantly, omeprazole remarkably decreases bleeding risks after dual antiplatelet therapy by significantly diminishing platelet inhibition assessed by VASP phosphorylation test (23). However, in contrast to the reported omeprazole-clopidogrel interaction, the intake of pantoprazole or esomeprazole was not associated with impaired response to clopidogrel (24) which is in full agreement with the discussed study that not all PPI are “born equal”.

The US Food and Drug Administration recently conducted a review of clinical data on long-term use of PPI (particularly omeprazole or esomeprazole) to determine the risk-benefit profile for this class of drugs. The concern was that patients receiving PPI exhibited higher rates of cardiac events including myocardial infarctions, heart failure, and sudden cardiac death. Presently, the data are not conclusive in this regard, particularly because of the types of patients enrolled, the way the trials were de-

signed, and imbalances in patient characteristics between treated and untreated patients (25). Perhaps most importantly, these types of review will continue when more data became available. Moreover, recent guidelines on reducing gastrointestinal risks after antiplatelet therapy and NSAID (26) are somewhat controversial as well. While the postulate that eradication of *Helicobacter pylori* in patients with gastric ulcers is reasonable and beneficial, the co-administration of antiplatelet agents and PPI in high-risk patients raise legitimate concerns of denying vascular benefit by extra gastric protection. Withdrawing both clopidogrel and PPI in patients with upper gastric bleeding may represent a better option; however, randomised evidence is lacking. Ironically, but during the preparation of this Editorial, the COGENT-1 phase 3 trial testing combination of 75 mg clopidogrel with 20 mg of omeprazole, known as CGT-2168, was abruptly discontinued due to the sponsor's bankruptcy.

As highlighted recently, the phenomenon of so-called ‘clopidogrel resistance’ (and for that matter, ‘aspirin resistance’) still attracts much attention (27–30), and we have not heard the last of the debate on whether concomitant drug therapies such as PPI would influence this.

In summary, the body of available evidence suggests that: (a) some PPI (omeprazole) diminish antiplatelet potency of clopidogrel, while other (pantoprazole, esomeprazole) have no effect; (b) the most reasonable mechanism responsible for such association, is preventing proper absorption of clopidogrel by dramatic reduction of gastric acidity caused by PPI; (c) competitive deficiencies of hepatic cytochrome CYP3A4 or CYP2C9 are unlikely to be responsible; (d) use of clopidogrel and PPI combination is difficult to justify since the gastrointestinal protection comes at the expense of reducing vascular benefit of clopidogrel; (e) monitoring of gastric pH, and plasma levels of active (thiol) clopidogrel metabolite or extent of P2Y₁₂ inhibition of circulating platelets will help to define the real nature of gastric or hepatic clopidogrel-PPI interplay, and determine its clinical significance. Presently, concomitant use of PPI with clopidogrel cannot be recommended until more randomised and mechanistic data became available. Mimicking protection by denying outcome benefit does not seem to be the right approach.

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