Effect of multiple doses of omeprazole on the pharmacokinetics, pharmacodynamics, and safety of a single dose of rivaroxaban.


Abstract

ABSTRACT: Many patients with acute coronary syndrome receive chronic dual antiplatelet therapy (acetylsalicylic acid and clopidogrel) for secondary event prophylaxis, and new oral anticoagulants are being investigated as adjunctive therapy in this indication. Gastrointestinal side effects such as bleeding are commonly associated with antiplatelet use; accordingly, many patients receive proton pump inhibitors (PPIs) to mitigate this. PPIs can reduce the antiplatelet activity of clopidogrel through cytochrome P450 2C19 inhibition, and pantoprazole reduces the bioavailability of dabigatran, a direct thrombin inhibitor that acts via cytochrome P450 2C19-independent mechanisms. These observations support the investigation of potential pharmacokinetic and pharmacodynamic interactions between PPIs and anticoagulants. We evaluated the influence of administering once-daily omeprazole 40 mg for 5 days on the pharmacokinetics and pharmacodynamics of a single 20-mg dose of the oral direct factor Xa inhibitor, rivaroxaban, in a randomized, open-label, 2-way, crossover, drug-drug interaction study in healthy subjects. No clinically meaningful interactions were observed; geometric mean ratios were 101%, 101%, and 93.5% for rivaroxaban area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration (AUClast), or until infinity (AUC∞), and maximum plasma concentration (Cmax), respectively. Prothrombin time increased similarly in both treatment groups, with maximal values observed approximately 4 hours post rivaroxaban administration. A single 20-mg rivaroxaban dose appears well tolerated when administered alone or after 5 days of once-daily omeprazole 40 mg administration.

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Omeprazole, but not pantoprazole, reduces the antiplatelet effect of clopidogrel: a randomized clinical crossover trial in patients after myocardial infarction evaluating the clopidogrel-PPIs drug interaction.

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Source

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Abstract

BACKGROUND:

Proton pump inhibitors (PPIs) are usually prescribed to patients undergoing dual antiplatelet therapy to decrease the risk of gastrointestinal bleeding. Recent studies have raised concerns that PPIs could reduce clopidogrel's efficacy by competitive inhibition of cytochrome P450 2C19 isoenzyme. All PPIs are metabolized by cytochrome P450 2C19, although to varying degrees, and according to in-vitro studies, pantoprazole is the weakest inhibitor of this isoenzyme. We hypothesized that this drug interaction might not be a class effect.

METHODS:

One month after an acute myocardial infarction 34 consecutive patients undergoing dual antiplatelet therapy were prospectively analyzed. Platelet function was measured (VerifyNow system), in each patient, in three consecutive clinical scenarios: (i) first, after a 1-month washout period, without any PPI, (ii) after a 4-week period taking omeprazole 40 mg, and (iii) after another 1-month washout period, followed by 4-weeks taking pantoprazole 40 mg. In this crossover trial, patients were first randomized to receive either omeprazole or pantoprazole.

RESULTS:

We observed a significant reduction in clopidogrel's effect when patients were initiated with omeprazole; the mean P2Y12 reaction units (PRU) increased from 202±52 to 235±58 with omeprazole (P<0.001). With pantoprazole, clopidogrel efficacy was
preserved (PRU 215±54, P=0.16). Without any PPI, 26% of patients were 'nonresponders' to clopidogrel (PRU >240) but when patients started omeprazole, this proportion increased to 45 versus 23% with pantoprazole.

CONCLUSION:

In this randomized crossover study analyzing patients after acute myocardial infarction, omeprazole coadministration showed a significant pharmacodynamic interaction with clopidogrel, whereas pantoprazole did not. These data suggest that the clopidogrel-PPIs drug interaction may not be a class effect.

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