REVIEW ARTICLE

Is it safe to use a proton pump inhibitor with clopidogrel?

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KEY WORDS

clopidogrel, drug interaction, proton pump inhibitors

ABSTRACT

Recent studies have raised concern that a significant clinical interaction may exist between clopidogrel and proton pump inhibitors (PPIs). We conducted a general review of the literature to examine the evidence for this interaction. There are theoretical reasons why clopidogrel may interact with PPIs as they are both metabolized by similar isoenzymes of the cytochrome P450 system. Laboratory studies suggest PPIs may diminish clopidogrel's effect. Studies have observed higher platelet aggregation levels in those on PPIs. Currently available clinical studies examining this question are all observational and the measures of risks associated with the combination of clopidogrel and PPIs generally low. The evidence from clinical studies is thus inconclusive. Therefore, up to now most (available) expert consensuses recommend the continued use of PPIs in patients on dual platelet therapy who have appropriate indications. However, it is important to review the clinical need for either drug as it may be appropriate to either stop the clopidogrel or the PPI. As both drugs have very short half-lives, taking them with a large time gap between drugs (e.g., morning and night) may theoretically decrease the chance of interaction.

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Received: August 22, 2009.
Accepted: August 22, 2009.
Conflict of interest: Clara K. Chow is supported by a Public Health (Sidney Sax) Overseas Fellowship co-funded by the National Health and Medical Research Council and National Heart Foundation of Australia. Philip J. Devereaux is supported by a Canadian Institutes of Health Research New Investigator Award.
Pol Arch Med Wewn. 2009; 119 (9): 564-568

Introduction While antiplatelet therapy has clear efficacy in the reduction of cardiovascular events in patients with cardiovascular disease[1], it also has the well-known side effect of gastrointestinal (GI) bleeding. The incidence of upper gastrointestinal peptic ulcer bleeding in patients on low-dose aspirin is approximately 0.5% per year (relative risk compared to placebo 2.07, 95% CI 1.61–2.66).[2] The risk of upper gastrointestinal bleeding (UGIB) with clopidogrel 75 mg vs. aspirin 325 mg is lower (1.99% vs. 2.66%, $p<0.002$), and a small randomized control trial (n = 320) with few events (14 recurrent bleeding ulcer events) suggested that a strategy of using low-dose aspirin with a proton pomp inhibitor (PPI) is superior to clopidogrel.[3] In a case-control study of 1443 subjects with serious UGIB compared with 57,720 age and sex matched controls, the use of both aspirin and clopidogrel was associated with about 7-fold higher risk of UGIB (OR: 7.4; 95% CI 3.5–15) compared to the use of acetylsalicylic acid (ASA) alone.[4] So should these patients be put on PPIs?

PPIs and the treatment and prevention of bleeding upper gastrointestinal ulcers PPIs are effective in both the treatment and prevention of upper gastrointestinal ulcers. In recent systematic reviews of randomized control trial data, PPI treatment initiated after endoscopic diagnosis of peptic ulcer bleeding significantly reduced re-bleeding (OR: 0.49; 95% CI 0.37–0.65).[5] There was no evidence of an overall effect of PPI treatment on all-cause mortality (OR: 1.01; 95% CI 0.74–1.40).[5]

The risk of non-steroidal anti-inflammatory drug (NSAID)-induced endoscopic gastric and duodenal ulcers was also reduced by PPI (relative risk [RR]: 0.37; 95% CI 0.27–0.51 for gastric ulcers).[6] These trials, however, evaluated endoscopic ulcers and there is a paucity of randomized trial evidence of PPI therapy as prophylaxis for clinically important endpoints such as peptic ulcer complications.

Epidemiological evidence suggests that PPI therapy is protective in preventing peptic ulcer bleeding associated with NSAIDs, and more specifically with low-dose aspirin or clopidogrel.

A case-control study of 2777 patients with UGIB and 5532 controls demonstrated that use of PPIs is associated with decreased risk of bleeding, OR: 0.32 (95% CI 0.22–0.51) in low-dose aspirin users and OR: 0.19 (05% CI 0.07–0.49) in clopidogrel users.[7] It is therefore on the basis of observational data that the use of PPIs with antiplatelet therapy has been recommended by some groups as an effective strategy to prevent UGIB[8], and recent studies indicate from 1 in 3 to 1 in 5 patients discharged on antiplatelet therapy following acute coronary syndrome (ACS) are prescribed a PPI[7,8].

Despite the potential benefits of the combination of clopidogrel and a PPI to prevent UGIB, several papers have raised concerns about a potential pharmacological interaction between PPIs and clopidogrel. Specifically, PPIs may attenuate clopidogrel's antiplatelet response which may then attenuate its cardioprotective effects.

PPIs and clopidogrel – how do they work?

Clopidogrel action Clopidogrel is a thienopyridine and inhibits platelet activation induced by adenosine diphosphate (ADP). To achieve its antiplatelet aggregation properties clopidogrel must be converted to its active metabolite. Cytochrome P450, in the liver, mediates clopidogrel's transformation to its active metabolite. The active metabolite then binds to the platelet P2Y12 ADP receptor blocking platelet activation via the IIb/IIIa complex. ADP activation results in dephosphorylation of intraplatelet vasodilator-stimulated phosphoprotein (VASP).[9] Thus measures of VASP can provide a metric for platelet reactivity. The higher the platelet reactivity index (PRI) the more frequently thrombosis occurs. Therefore, clopidogrel users should have lower measures of VASP compared to patients not taking clopidogrel.

Clopidogrel resistance The CYP2C19 isoenzyme of the cytochrome P-450 cascade seems to be one of the main determinants of the response to clopidogrel.[10] Studies have demonstrated that in patients on clopidogrel, those with polymorphisms causing loss of function of CYP2C19 retain more platelet aggregation compared with those without these polymorphisms.[11,12] Clopidogrel resistance is associated with poorer outcomes.[11,13] In one study of 797 patients undergoing percutaneous coronary intervention (PCI), patients with residual platelet aggregation (defined as platelet aggregation >14%) at pre-discharge had a 3-fold increase (95% CI 1.4–6.8, p = 0.004) in the 1-year incidence of death and myocardial infarction (MI).[11]

PPI metabolism PPIs are also metabolized by the cytochrome P450 system with the main isoenzymes involved being CYP2C19 and CYP3A4. CYP2C19 is responsible for 80% of omeprazole clearance.[14,15] Therefore, in theory, the use of PPIs in combination with clopidogrel could decrease the conversion of clopidogrel to its active metabolite through competitive inhibition of CYP2C19, and thereby decrease clopidogrel's therapeutic effect. Another explanation for why PPIs may alter the effects of clopidogrel is that PPIs change intragastric pH and may hence alter the absorption of clopidogrel. PPIs and their active metabolites both have short half-lives (<1 hour) and their long-lasting therapeutic effect occurs because they irreversibly inhibit the proton pump so that further acid secretion can only occur when the pump cells are replaced, which takes 12–24 h.

What is the evidence that use of PPIs decreases the efficacy of clopidogrel? Mechanistic studies suggest that PPIs may diminish clopidogrel's effect. In a study of 105 subjects on clopidogrel and monitored with VASP assays, PPI users had significantly higher PRI values (indicating higher levels of platelet aggregation).[16]

The same research group followed up this observation with a small randomized trial of 124 patients undergoing coronary artery stent implantation and usual dual antiplatelet therapy (aspirin 75 mg/day and clopidogrel loading dose 75 mg/day). The study assessed platelet reactivity using platelet phosphorylated-VASP on days 1 and 7. Platelet reactivity was 39.8% (standard deviation [SD] 15.4) in placebo patients and 51.4% (SD 16.4) in omeprazole patients, p <0.0001 on day 7, suggesting that omeprazole attenuated the antiplatelet effect of clopidogrel.[17] The impact of this attenuation on clinical outcomes was unclear and was therefore evaluated in database studies.

A Canadian database linkage study evaluated patients who filled out a prescription for clopidogrel within 3 days of discharge following an acute MI and were readmitted with another MI (734 cases) compared to age and sex matched controls (n = 2057). Exposure to PPIs was established using prescription records. Patients taking both PPIs and clopidogrel had more comorbidities (higher rates of renal failure, heart failure and diabetes with complications). After adjusting for comorbidities, current use of PPIs in patients taking clopidogrel was associated with an increased risk of death/readmission for MI (OR: 1.27; 95% CI 1.03–1.57).[18]

Another study (i.e., a Veterans Affairs Hospital cohort study) of 8205 patients who had suffered ACS and were taking clopidogrel after discharge demonstrated similar findings to the Canadian study. Nearly ⅔ of patients were prescribed PPIs at discharge or during follow-up and this group was compared with those who were not taking PPIs. Patients taking PPIs were older and had more comorbidities (previous MI, heart failure, renal failure, chronic obstructive pulmonary disease, cancer). In multivariable analyses, use of clopidogrel plus PPI was associated with an increased risk of death or rehospitalization for ACS compared with use of clopidogrel without PPI (adjusted OR: 1.25; 95% CI 1.11–1.41). A similarly increased risk has also been observed in a 3rd

recent report from a medical and pharmaceutical database in the United States.[19]

A study from the National Medco Integrated Database file in the United States reviewed clinical outcomes in patients who had a stent and were at least 80% compliant with clopidogrel. The 1 year incidence of major adverse cardiovascular (CV) events was higher in those who took clopidogrel with PPIs (n = 4521) compared to those on clopidogrel alone (n = 9862), OR: 1.79, 95% CI 1.62–1.97.[20]

In contrast to the above findings a subanalysis of the data from the CREDO trial (trial that evaluated different clopidogrel dosing regimens for PCI) found that although overall PPI use was independently associated with increased endpoints at 1 year (HR: 1.5; 95% CI 1.1–2.1, p = 0.012), clopidogrel reduced adverse events at 1 year to an approximately similar degree whether or not patients were on a PPI.[21] These findings suggest that patients taking PPIs may be "sicker" for other reasons, which explains higher event rates in patients on PPIs who are taking clopidogrel. Moreover, risk factors for bleeding overlap with risk factors for major CV events and this also supports the possibility that patients at higher risk of a major CV event are more likely to take a PPI. This raises the possibility that the associations demonstrated in many of the observational studies may reflect residual confounding as opposed to a true association between PPI use and increased CV events in patients who simultaneously take clopidogrel. The full reports of this and the Medco study have not yet been published.

Further clinical studies are clearly needed. The COGENT-1 trail (Clopidogrel and the Optimization of Gastrointestinal Events; NCT00557921) randomizing patients with coronary artery disease to ASA plus clopidogrel in combination with omeprazole 20 mg or placebo could have provided further insights but this trial has been discontinued due to sponsor bankruptcy.[8,22]

If there is an association between clopidogrel and a PPI, another issue to consider is whether there is a class effect or an effect associated with specific PPIs. While most PPIs are mainly metabolized by the cytochrome P450 system, principally by the isoenzymes CYP2C19 and CYP3A4, pantoprazole has less affinity for these isoenzymes and is metabolized by a sulphotransferase outside the CYP system.[14,23] In a cross-sectional observational study of 1000 consecutive patients on clopidogrel, ADP-induced platelet aggregation was measured with multiple electrode platelet aggregometry. Platelet aggregation was significantly higher in patients with omeprazole treatment compared to patients without PPI treatment, p = 0.001. Platelet aggregation was, however, similar in patients on pantoprazole or esomeprazole compared with patients without PPI treatment.[24] In the Canadian study discussed above, results were stratified and pantoprazole use was associated with no increase in risk of death/MI (OR: 1.02; 95% CI 0.70–1.47) while other PPIs were associated with an increased risk of death/MI (OR: 1.40; 95% CI 1.10–1.77). However a more appropriate analysis is to evaluate whether patients taking pantoprazole were statistically significantly different in outcomes from those taking other PPIs.[25] When this analysis is conducted there is no significant difference between PPIs. Furthermore, other observational studies did not observe pantoprazole to have any different outcome compared with other PPIs.[19,20] There is therefore little data to support that one PPI is any "safer" than another when it comes to possible interactions with clopidogrel.

Should patients taking aspirin and clopidogrel be prescribed PPIs? The 2008 ACCF/ACG/AHA Expert consensus document[8] recommends use of PPIs for the prevention of gastrointestinal bleeding in patients on dual antiplatelet therapy, referring to evidence that combining a PPI with clopidogrel appears to result in less GI bleeding[7] and indicating that evidence of a clinical effect of a drug interaction is lacking.

Both clopidogrel and PPIs are widely prescribed by physicians. PPIs are often prescribed for symptomatic relief or for primary prevention and not just for treatment of a confirmed peptic ulcer or secondary prevention in patients with known peptic ulcer disease as were the indications examined in clinical trials. The high use of these drugs increases the imperative to better understand whether this interaction is harmful. The current evidence raises concerns; however, the evidence is limited and it is reasonable to conclude (as the Food and Drug Administration have done) that currently no change is needed in prescribing until more data are gathered. However, it is important to review the clinical need for either drug as it may be appropriate to either stop the clopidogrel or the PPI. If both drugs are clinically indicated and the clinician or patient is concerned about possible interaction, then it may be appropriate to give one drug in the morning and the other in the evening as both compounds have very short half-lives and this should in theory prevent interaction.

REFERENCES

1 Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001; 345: 494-502.

2 Laine L. Review article: gastrointestinal bleeding with low-dose aspirin - what's the risk? Aliment Pharmacol Ther. 2006; 24: 897-908.

3 Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med. 2005; 352: 238-244.

4 Hallas J, Dall M, Andries A, et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. BMJ. 2006; 333: 726.

5 Leontiadis GI, Sreedharan A, Dorward S, et al. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. Health Technol Assess. 2007; 11: iii-iv, 1-164.

6 Rostom A, Wells G, Tugwell P, et al. The prevention of chronic NSAID induced upper gastrointestinal toxicity: a Cochrane collaboration meta-analysis of randomized controlled trials. J Rheumatol. 2000; 27: 2203-2214.

7 Lanas A, Garcia-Rodriguez LA, Arroyo MT, et al. Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. Am J Gastroenterol. 2007; 102: 507-515.

8 Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Circulation. 2008; 118: 1894-1909.

9 Barragan P, Bouvier JL, Roquebert PO, et al. Resistance to thienopyridines: clinical detection of coronary stent thrombosis by monitoring of vasodilator-stimulated phosphoprotein phosphorylation. Catheter Cardiovasc Interv. 2003; 59: 295-302.

10 Hulot JS, Bura A, Villard E, et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood. 2006; 108: 2244-2247.

11 Trenk D, Hochholzer W, Fromm MF, et al. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. J Am Coll Cardiol. 2008; 51: 1925-1934.

12 Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 Genetic Polymorphisms and the Response to Prasugrel. Relationship to Pharmacokinetic, Pharmacodynamic, and Clinical Outcomes. Circulation. 2009; 119: 2553-2560.

13 Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation. 2004; 109: 3171-3175.

14 Chong E, Ensom MH. Pharmacogenetics of the proton pump inhibitors: a systematic review. Pharmacotherapy. 2003; 23: 460-471.

15 Ishizaki T, Horai Y. : cytochrome P450 and the metabolism of proton pump inhibitors--emphasis on rabeprazole. Aliment Pharmacol Ther. 1999; 13 Suppl 3: 27-36.

16 Gilard M, Arnaud B, Le Gal G, et al. Influence of omeprazol on the antiplatelet action of clopidogrel associated to aspirin. J Thromb Haemost. 2006; 4: 2508-2509.

17 Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol. 2008; 51: 256-260.

18 Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ. 2009; 180: 713-718.

19 Pezalla E, Day D, Pulliadath I. Initial assessment of clinical impact of a drug interaction between clopidogrel and proton pump inhibitors. J Am Coll Cardiol. 2008; 52: 1038-1039.

20 Aubert RE, Epstein RS, Teagarden JR, et al. Abstract 3998: Proton Pump Inhibitors Effect on Clopidogrel Effectiveness: The Clopidogrel Medco Outcomes Study. Circulation. 2008; 118: S_815.

21 Dunn SP, Macaulay TE, Brennan DM, et al. Abstract 3999: Baseline Proton Pump Inhibitor Use is Associated with Increased Cardiovascular Events With and Without the Use of Clopidogrel in the CREDO Trial. Circulation. 2008; 118: S_815.

22 Serebruany V, Goto S. Clopidogrel and proton pump inhibitors: Gastric protection at expense of vascular benefit? Thromb Haemost. 2009; 101: 607-609.

23 Li XQ, Andersson TB, Ahlstrom M, et al. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. Drug Metab Dispos. 2004; 32: 821-827.

24 Sibbing D, Morath T, Stegherr J, et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. Thromb Haemost. 2009; 101: 714-719.

25 Moayyedi P, Sadowski DC. Proton pump inhibitors and clopidogrel - hazardous drug interaction or hazardous interpretation of data? Can J Gastroenterol. 2009; 23: 251-252.

ARTYKUŁ POGLĄDOWY

Czy stosowanie inhibitorów pompy protonowej z klopidogrelem jest bezpieczne?

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SŁOWA KLUCZOWE

inhibitory pompy protonowej, interakcje leków, klopidogrel

STRESZCZENIE

Ostatnio wyrażano obawy o możliwość istnienia znaczącej klinicznie interakcji między klopidogrelem i inhibitorami pompy protonowej (IPP). Przeprowadziliśmy ogólny przegląd piśmiennictwa, aby ocenić dowody na te interakcję. Istnieją przesłanki teoretyczne uzasadniające możliwość interakcji klopidogrelu z IPP, ponieważ oba są metabolizowane przez podobne izoenzymy układu cytochromu P450. Badania laboratoryjne sugerują, że IPP mogą zmniejszać efekt klopidogrelu. Zaobserwowano w nich większy poziom agregacji płytek u pacjentów przyjmujących IPP. Obecnie dostępne badania kliniczne na ten temat były obserwacyjne; ryzyko związane z kojarzeniem klopidogrelu z IPP opisano jako niskie. Dowody z badań klinicznych nie są więc przekonujące. Dlatego dotychczas w większości dostępnych stanowisk uzgodnionych przez ekspertów zaleca się kontynuowanie stosowania IPP u pacjentów otrzymujących dwulekową terapię przeciwpłytkową, którzy mają odpowiednie wskazania do IPP. Ważne jednak, aby zweryfikować kliniczne wskazania do stosowania obu leków, ponieważ może się okazać właściwe odstawienie klopidogrelu albo IPP. Ponieważ oba leki mają bardzo krótkie okresy półtrwania, teoretycznie ich przyjmowanie w dużych odstępach czasu (np. rano i wieczorem) może zmniejszyć ryzyko interakcji.

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Praca wpłynęła: 22.08.2009.
Przyjęta do druku: 22.08.2009.
Zgłoszono sprzeczność interesów: Clara K. Chow otrzymuje stypendium Public Health (Sidney Sax) Overseas Fellowship współfinansowane przez National Health and Medical Research Council i National Heart Foundation of Australia. Philip J. Devereaux otrzymuje wsparcie finansowe w ramach Canadian Institutes of Health Research New Investigator Award.
Pol Arch Med Wewn. 2009; 119 (9): 564-568
Tłumaczył lek. Łukasz Strzeszyński