Stručni rad UDK / UDC 616.1-085.273=111 615.273 Professional paper

Nove spoznaje o istodobnoj primjeni klopidogrela i inhibitora protonske pumpe

New insights on concomitant use of clopidogrel and proton pump inhibitors

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SAŽETAK: *Antitrombocitni lijek klopidogrel predstavlja učinkovit medikament za liječenje aterotrombotske bolesti. To je prolijek koji se pretvara u aktivni oblik pomoću izoenzima citokrom P450. Stoga lijekovi koji su u interakciji s ovim enzimom mogu potencijalno utjecati na antitrombocitno djelovanje klopidogrela, uzrokujući povećan rizik od neželjenih srčanih ishoda. Zbog velike vjerojatnosti krvarenja kod bolesnika koji su na dvostrukoj antitrombocitnoj terapiji (klopidogrel i acetilsalicilna kiselina) često se propisuje istovremena profilaksa s lijekom iz skupine inhibitora protonske pumpe (IPP). Postoji bojazan da neki od lijekova iz skupine IPP mogu ometati sposobnost klopidogrela u inhibiciji agregacije trombocita i time povećati rizik od smrti i ponovne hospitalizacije zbog akutnog koronarnog sindroma. U ovom članku dajemo pregled postojećih podataka koji se odnose na interakciju IPP i klopidogrela. Postojeće studije ukazuju da omeprazol najvjerojatnije uzajamno djeluje na klopidogrel. Pantoprazol ima malu sklonost interakcije s klopidogrelom zbog svog metabolizma i identificiran je kao IPP koji se ne povezuje s gubitkom korisnih djelovanja klopidogrela. U slučajevima potrebe za IPP pri istodobnoj terapiji s klopidogrelom, pantoprazol predstavlja lijek izbora u skupini IPP.*

KLJUČNE RIJEČI: *antitrombocitni lijekovi, klopidogrel, pantoprazol, interakcija lijekova*

ABSTRACT: *The antiplatelet agent clopidogrel is effective in the treatment of atherotrombotic disease. It is a prodrug converted to its active form by cytochrome P450 isoenzymes. Hence, drugs that interfere with this enzyme could potentially influence clopidogrel's antiplatelet effect, leading to an increased risk of adverse cardiac outcomes. Due to the greater probability of bleeding in patients on dual antiplatelet therapy (clopidogrel and acetylsalicylic acid), concomitant prophylaxis with a proton pump inhibitor (PPI) is frequently prescribed. There are concerns that some PPIs may interfere with the ability of clopidogrel to inhibit platelet aggregation and thereby increase the risk of death and re-hospitalisation for acute coronary syndrome. This article reviews existing data relating to drug interaction between PPIs and clopidogrel. Existent studies show that omeprazole is the most likely to interact with clopidogrel. Pantoprazole has a small propensity for an interaction with clopidogrel based on its metabolism and was identified as a PPI not associated with a loss of the beneficial effects of clopidogrel. In cases when a PPI is needed as concomitant therapy with clopidogrel, pantoprazole becomes the PPI of choice.*

KEYWORDS: *antiplatelet therapy, clopidogrel, pantoprazole, drug interaction*

Klopidogrel predstavlja antitrombocitni lijek koji se koristi za smanjenje učestalosti kardiovaskularnih događaja nakon hospitalizacije zbog akutnog koronarnog sindroma (ACS) kod bolesnika koji se liječe medikamentno ili primjenom perkutane koronarne intervencije (PCI)[1]. Zbog povećane sklonosti krvarenju u bolesnika koji su na dvostrukoj antitrombocitnoj terapiji (klopidogrel i acetilsalicilna kiselina), često se propisuje antiulkusna profilaksa s inhibitorima protonske pumpe (IPP)[2]. Od nedavno pažnja se posvećuje istovremenoj upotrebi lijekova iz skupine IPP i klopidogrela, budući da kako se pretpostavlja, neki IPP djeluju na sposobnost klopidogrela u inhibiciji agregacije trombocita, povećavajući rizik od smrti i ponovne hospitalizacije zbog ACS[3].

Klopidogrel predstavlja prolijek koji se u jetri pretvara u aktivni metabolit koji ihhibira aktivaciju trombocita. Ova konverzija je potpomognuta izoenzimima citokroma P450, uglavnom CYP2C19. Stoga nije neobično da ova aktivnost enzima utječe na antitrombocitno djelovanje klopidogrela[4]. Pojedini IPP mogu inhibirati put CYP2C19 i tako ometati pretvorbu klopidogrela u aktivan oblik lijeka, a moguća promjena farmakintetike klopidogrela može uzrokovati povećane učestalost neželjenih srčanih ishoda[5,6]. Pojedini li-

Clopidogrel is used as an antiplatelet agent for reducing the incidence of cardiovascular events following hospitalization after acute coronary syndromes (ACS) in patients treated either medically or with percutaneous coronary intervention (PCI)[1]. Due to the greater probability of bleeding in patients on dual antiplatelet therapy (clopidogrel and acetylsalicylic acid), concomitant gastrointestinal ulcer prophylaxis with proton pump inhibitors (PPIs) is frequently prescribed[2]. Recently, attention has been focused on concomitant use of PPIs and clopidogrel, as, presumably, some PPIs interfere with the ability of clopidogrel to inhibit platelet aggregation, thus increasing the risk of death and re-hospitalization for ACS[3].

Clopidogrel is a prodrug that is converted in the liver to an active metabolite which inhibits platelet activation. This conversion is mediated by the cytochrome P450 isoenzymes, mostly by CYP2C19. It is therefore not unusual that the activity of the enzyme influences the anti-platelet effect of clopidogrel[4]. Certain PPIs can inhibit the CYP2C19 pathway and may interfere with the conversion of clopidogrel to its active form, possibly by altering clopidogrel's pharmacokinetics and potentially leading to an increased probability of adverse cardiac outcomes[5,6]. PPIs differ in their ability to inhibit CYP2C19 and hence they vary in the de-

jekovi iz skupine IPP razlikuju se po svojoj mogućnosti inhibiranja CYP2C19 pa stoga imaju i različit stupanj smanjenja antitrombocitnog djelovanja klopidogrela[6]. Između svih IPP omeprazol ima najveću sklonost za CYP2C19, a pantoprazol ima najmanju sklonost za ovaj enzim[5]. Stoga se postavlja pitanje postoji li IPP koji ima prednost kod antiulkusne profilakse pri istodobnoj primjeni s klopidogrelom.

Postoji različiti farmakološki i klinički dokazi o interakciji IPP i klopidogrela. Do danas su objavljene dvije velike epidemiološke studije s potpunim rezultatima[1,5], dok je nekoliko analiza dostupno samo u sažetku čime se onemogućava dubinska analiza rezultata[7].

Gillard i sur.[8] sugerirali su negativno djelovanje IPP na klopidogrel. U njihovoj studiji 140 bolesnika koji su se podvrgli implantaciji stenta liječeni su sedam dana omeprazolom ili placebom te je ocijenjena trombocitna funkcija vazodilatorno-stimulirajućim fosfoproteinom (VASP). Sedmog dana prosječni indeks reaktivnosti trombocita (PRI) bio je 39,8% (SD 15,4) za placebo grupu i 51,4% (SD 16,4) za omeprazolsku grupu. U skupini liječenih omeprazolom postojao je veći broj ispitanika sa slabijim odgovorom na klopidogrel, što ukazuje da je omeprazol značajno smanjio antitrombocitno djelovanje klopidogrela[8].

Siller-Matula i sur.[9] objavili su studiju u kojoj su ocjenjivali da li je ovo negativno djelovanje zapravo djelovanje klase. Proučavali su djelovanje pantoprazola i esomeprazola na trombocitnu reaktivnost klopidogrela pri analizi VASP. Utvrdili su da nema razlike u PRI kod bolesnika na pantoprazolu (n = 152, PRI = 50%) ili esomeprazolu (n = 74, PRI = 54%) u odnosu na bolesnike bez IPP (n = 74, PRI = 49%; P = 0.382). Za razliku od rezultata studije od Gillarda[8], kojom se dokazalo da omeprazol mijenja inhibiciju trombocita uzrokovanu klopidogrelom, utvrđeno je da se trombocitna inhibicija ne mijenja ako se koristi pantoprazol ili esomeprazol.

Klinički značaj interakcije IPP i klopidogrela istraživao je Juurlink[5] u studiji od 13.636 bolesnika koji primaju klopidogrel nakon akutnog infarkta miokarda. U primarnoj analizi upotreba IPP se povezuje s povišenim rizikom od ponovnog infarkta (OR 1.2; CI: 1.03 — 1.57). Nije bilo moguće otkriti povišeni rizik od ponovnog infarkta među bolesnicima koji uzimaju pantoprazol. Istovremena terapija s IPP osim pantoprazola povezivala se s gubitkom korisnih djelovanja klopidogrela[5].

U retrospektivnoj studiji Ho i suradnika[1] 8205 bolesnika s ACS koji su uzimali klopidogrel po otpustu iz bolnice, uporaba klopidogrela uz IPP povezivala se s rizikom od smrti ili ponovne hospitalizacije za ACS (OR 1.25; 95% CI 1.11-1.41) u usporedbi s upotrebom klopidogrela bez IPP-a. Kod ocjene pojedinačnih lijekova iz skupine IPP, stalno povezivanje s povišenim rizikom otkriveno je kod omeprazola (OR 1.24; 95% CI 1.08-1.41) i rabeprazola (OR 2.83; 95% CI 1.96-4.09)[1].

Potrebne su studije za dobivanje dodatnih podatka radi boljeg razumijevanja i karakteriziranja utjecaja IPP na klopidogrel. Međutim, postojeća istraživanja ukazuju da određeni IPP mogu negativno djelovati na antitrombocitno djelovanje klopidogrela, iako ovo djelovanje ne mora biti djelovanje klase. Smanjenje antitrombocitne aktivnosti je uglavnom vidljivo pri istodobnoj uporabi omeprazola. Ostali IPP, kao što rabeprazol i lanzoprazol također mogu utgree to which they reduce the antiplatelet activity of clopidogrel[6]. Among the PPIs, omeprazole has the greatest affinity for CYP2C19 and pantoprazole has the lowest affinity for this enzyme[5]. Thus, a question arises if there is a preferred PPI that should be used for gastrointestinal (GI) ulcer prophylaxis in combination with clopidogrel.

There exists various pharmacological and clinical evidence of interaction between PPIs and clopidogrel. To date, two large epidemiologic studies have been published with full results [1, 5], while several analyses are available only in abstract form, which limits in-depth analysis of the findings[7].

Gillard et al.[8] suggested a negative impact of PPIs on clopidogrel. In their study, 140 patients undergoing coronary stent replacement received omeprazole or placebo for seven days and platelet function assessment by vasodilator-stimulated phosphoprotein (VASP) was performed. On day 7, the mean PRI (platelet reactivity index) was 39.8% (SD 15.4) for the placebo group and 51.4% (SD 16.4) for the omeprazole group. There was a higher number of poor clopidogrel responders in the omeprazole group, indicating that omeprazole significantly decreased the antiplatelet effect of clopidogrel[8].

Siller-Matula et al.[9] published a study in which they assessed whether this negative effect is a class effect. They studied the pantoprazole and esomeprazole effects on clopidogrel platelet reactivity with the VASP assay. They established that there was no difference in the PRI in patients on pantoprazole (n = 152, PRI = 50%) or esomeprazole (n = 74, PRI = 54%) compared with patients without a PPI (n = 74, PRI = 49%; P = 0.382). In contrast to the study results by Gillard et al.[8], showing that omeprazole alters platelet inhibition by clopidogrel, they found out that platelet inhibition was not altered when pantoprazole or esomeprazole were used.

The clinical significance of the interaction between PPIs and clopidogrel was investigated by Juurlink[5] in a case-control study of 13,636 patients receiving clopidogrel after acute myocardial infarction. In the primary analysis, the use of PPIs was found to be associated with an increased risk of reinfarction (odds ratio (OR): 1.2, confidence interval (CI): 1.03 — 1.57). There was no detectable increase in the risk of reinfarction among patients taking pantoprazole. Concomitant therapy with PPIs other than pantoprazole was associated with a loss of the beneficial effects of clopidogrel[5].

In a retrospective cohort study by Ho et al.[1] of 8,205 patients with ACS taking clopidogrel after discharge from the hospital, the use of clopidogrel plus PPI was associated with an increased risk of death or re-hospitalization for ACS (adjusted OR: 1.25; 95% CI: 1.11-1.41) compared with the use of clopidogrel without a PPI. When evaluating individual PPI agents, a consistent association with an increased risk was found with omeprazole (OR: 1.24; 95% CI: 1.08-1.41) and rabeprazole (OR: 2.83; 95% CI: 1.96-4.09)[1].

Studies to obtain additional information to better understand and characterize the effect of PPIs on clopidogrel have to be done. However, the available research suggests that certain PPIs may have a negative effect on clopidogrel antiplatelet activity although this effect may not be a class effect. A decrease of antiplatelet activity is seen primarily

jecati na klopidogrel, dok su pantoprazol i esomeprazol očito neutralni[7]. Među lijekovima iz skupine IPP, pantoprazol predstavlja najslabiji inhibitor CYPC219 te je malo vjerojatno da će postojati interakcija s klopidogrelom. Kao zaključak, postojeći podaci pokazuju da bi se u situacijama u kojima se indiciraju i klopidogrel i IPP, trebalo primjenjivati pantoprazol budući da će tada interakcija s klopidogrelom biti najmanje učestala[6,7].

Krka ima u svom portfelju klopidogrel (Zyllt®) i tri IPP: omeprazol (Ultop®), lansoprazol (Lanzul®) i pantoprazol (Nolpaza®). Krkin klopidogrel se na međunarodnom tržištu nalazi već četiri godine. To je vodeći generički klopidogrel u srednjoj, istočnoj i jugoistočnoj Europi. Njegova učinkovitost i sigurnost su dokazani u studijama o postautorizacijskoj sigurnosti i učinkovitosti te u vlastitim kliničkim studijama[10]. Krkin pantoprazol je bio među prvim generičkim pantoprazolima koji su proizvedeni u Europi i odobren je u 26 država. Njegova jedinstvena formula je predana za zaštitu patenta i godišnje se proizvode više od 200 milijuna tableta[11].

Received: 22nd Jul 2009

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with the concomitant use of omeprazole. Other PPIs, such as rabeprazole and lansoprazole, may also influence clopidogrel, while pantoprazole and esomeprazole appear to be neutral[7]. Among all PPIs, pantoprazole is the weakest inhibitor of CYPC219, making an interaction with clopidogrel very unlikely. In conclusion, the existing data show that in situations in which both clopidogrel and a PPI are indicated, pantoprazole should be used, since it is the PPI least likely to interact with clopidogrel[7].

Krka has in its portfolio clopidogrel (Zyllt®) and three PPIs: omeprazole (Ultop®), lansoprazole (Lanzul®) and pantoprazole (Nolpaza®). Krka's clopidogrel has been present on the international market for four years. It is the leading generic clopidogrel in Central, Eastern and Southeastern Europe. Its efficacy and safety have been proven in post-authorisation safety and efficacy studies and own clinical studies[10]. Krka's pantoprazole was among the first generic pantoprazoles produced in Europe and it is approved in 26 countries. Its unique formulation is filed for patent protection and more than 200 millions tablets are produced per year[11].

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