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Interakcije klopidogrela i inhibitora protonske pumpe

Interaction between clopidogrel and proton pump inhibitors

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SAŽETAK: *Krajem svibnja je Europska agencija za lijekove, a odmah zatim i Agencija za lijekove i medicinske proizvode Republike Hrvatske, objavila priopćenje o mogućoj interakciji klopidogrela i inhibitora protonske pumpe što u bolesnika koji istovremeno uzimaju ove lijekove može dovesti do povišenja rizika od infarkta miokarda, cerebralne tromboze te tromboze koronarnog stenta ili premosnice zbog smanjenog učinka klopidogrela.*

KLJUČNE RIJEČI: *Klopidogrel, inhibitori protonske pumpe, interakcije*

SUMMARY: *At the end of May, the European Medicines Agency, and soon afterwards, the Agency for Medicinal Products and Medical Devices of the Republic of Croatia, publicized a statement of a potential interaction between clopidogrel and proton-pump inhibitors which may, in patients who are simultaneously using these medicines, lead to an increased risk of myocardial infarction, cerebral thrombosis, coronary stent thrombosis or coronary artery bypass thrombosis.*

KEYWORDS: *Clopidogrel, proton pump inhibitors, interaction*

Krajem svibnja je Europska agencija za lijekove (EMEA), a odmah zatim i Agencija za lijekove i medicinske proizvode Republike Hrvatske (ALMP), objavila priopćenje o mogućoj interakciji klopidogrela i inhibitora protonske pumpe (IPP) što u bolesnika koji istovremeno uzimaju ove lijekove može dovesti do povišenja rizika od infarkta miokarda, cerebralne tromboze te tromboze koronarnog stenta ili premosnice zbog smanjenog učinka klopidogrela. Kako klopidogrel može uzrokovati poremećaje probavnog sustava (npr. dispepsiju, mučninu, gastritis, ulkus, gastrointestinalno krvarenje i sl.) često se primjenjuje s IPP. Prema podacima iz Velike Britanije oko pola milijuna bolesnika godišnje je na terapiji klopidogrelom, a polovici od njih istovremeno se propisuju i IPP. Mi točnih podataka o broju bolesnika koji uzimaju klopidogrel nemamo, ali se zna da je, prema zadnjim dostupnim podacima ALMP RH o potrošnji lijekova, za preparate s djelatnom tvari klopidogrel 2007. potrošeno 21.133.122 kuna. Ako znamo da je prosječna cijena kutije te godine iznosila 240 kn, a bolesniku godišnje treba 13 kutija lijekova, to znači da je te godine oko 7.000 bolesnika bilo na terapiji klopidogrelom. Kako je kod nas sve više bolesnika kojima se rade intervencijski kardiološki postupci, taj broj je sada sigurno značajno veći.

Temeljem navedenog priopćenja EMEA, ALMP je 8. lipnja 2009. godine dala preporuku zdravstvenim djelatnicima prema kojoj svim bolesnicima koji istovremeno uzimaju klopidogrel i IPP treba ponovno razmotriti potrebu za istovremenu primjenu ovih lijekova te da ih se propisuje samo ako je to neophodno. Također bi trebalo provjeriti da li bolesnici koji su na terapiji klopidogrelom samoinicijativno uzimaju IPP te ih savjetovati o mogućim interakcijama. Također ALMP će pozorno pratiti sva nova saznanja o ovoj problematici te će uskladiti Sažetak opisa svojstava lijeka i Uputu o lijeku sukladno prihvaćenom u Europskoj uniji gdje je Povjerenstvo za humane lijekove EMEA preporučilo uključivanje ovih saznanja u informacije o lijeku za sve lijekove s djelatnom tvari klopidogrel.

Slično priopćenje je objavila i Američka agencija za lijekove početkom ove godine.

At the end of May, the European Medicines Agency (EMEA), and soon afterwards the Agency for Medicinal Products and Medical Devices of the Republic of Croatia (ALMP), publicized a statement of a potential interaction between clopidogrel and proton pump inhibitors (PPI) which may, in patients who are simultaneously using these medicines, lead to an increased risk of myocardial infarction, cerebral thrombosis, coronary stent thrombosis and coronary artery bypass thrombosis. Since clopidogrel may cause disorders of the digestive tract (e.g. adverse effects of dyspepsia, nausea, gastritis, ulcers, gastrointestinal bleeding etc.), it is commonly prescribed together with the PPI. According to data from the United Kingdom, around half a million of patients are annually receiving the clopidogrel therapy, while a half of them are simultaneously being prescribed PPI. We don't have accurate data about the number of patients taking clopidogrel, but we know that according to the last available data by ALMP of the Republic of Croatia on medicine consumption HRK 21,133,122 was spent for substances with clopidogrel as an active ingredient in 2007. With an average price of a box of medicine that year amounting to HRK 240, and with a patient needing 13 boxes of medicine annually, this means that during that year, 7000 patients were on the clopidogrel therapy. Since we have an increasing number of patients with cardiac intervention procedures, that number must certainly have risen by now.

According to the aforementioned EMEA statement, on the 8th June 2009 ALMP issued a recommendation to healthcare professionals according to which, the need for simultaneous use of clopidogrel and PPI in patient should be revised and they should be prescribed together only if required. Also, we should check if the patients on clopidogrel therapy are taking PPI by themselves and they should be advised about any potential interactions. In addition, the ALMP will diligently monitor all new discoveries about this issue and will adjust the Summary of the medicine properties description and Instructions for use in accordance with those accepted in European Union where the Committee for Medicinal Products for Human Use of the EMEA has recommended the inclusion of these discoveries into information of medicine for all the medicines with clopidogrel as an active ingredient.

Similar statement has been issued by the U.S. Food and Drug Administration at the beginning of this year.

Kako je klopidogrel predlijek, njegova aktivacija se odigrava u jetri postupnom oksidacijom putem citokroma P450. Uz više enzima koji u tome sudjeluju najvažniji je 2C19, koji može imati nukleitidni polimorfizam što dovodi do njegove smanjene, ali i pojačane učinkovitosti. Zbog toga u oko 30% osoba bijele rase klopidogrel ima slabiji antiagregacijski učinak, odnosno može izazvati više nuspojava (najčešće gastrointestinalnih i bolova u zglobovima), ali i njegov učinak može biti promijenjen djelovanjem drugih lijekova. Tako je prije nekoliko godina temeljem *in vitro* studija dosta pisano o mogućoj interakciji klopidogrela i atorvastatina te kalcijskih antagonista što je u kasnijim velikim kliničkim ispitivanjima opovrgnuto. Sada je u tijeku ARCTIC klinička studija u kojoj se ispituje da li primjena klopidogrela temeljena na ispitivanju genetskog polimorfizma nakon koronarne intervencije ima bolji klinički ishod od standardne primjene.

Najnovija zabrinutost za smanjeni učinak klopidogrela primjenjenog istodobno s IPP zasnovana je, uz ranije poznate podatke, na dvije nedavno objavljene opservacijske studije. U prvoj koja je publicirana u JAMA u ožujku ove godine ispitivana je primjena klopidogrela u 8.205 bolesnika s implantiranim koronarnim stentom od kojih je u 63,9% propisan i IPP pri izlasku iz bolnice. Bolesnici kojima je propisan IPP uz klopidogrel imali su 25% višu stopu smrtnosti ili rehospitalizacija zbog akutnoga koronarnog sindroma (ACS) u odnosu na one koji nisu uzimali klopidogrel uz IPP (29,8% : 20,8%) u praćenom periodu (1. listopada 2003. do 31. siječnja 2006.). Pri tome su bolesnici uz IPP imali više ponovljenih hospitalizacija zbog ACS (14,6% : 6,9%) i revaskularizacijskih postupaka (15,5% : 11,9%), ali zato ukupna smrtnost nije bila statistički značajno različita (19,9% : 16,6%). U skupini bolesnika s ugrađenim stentom koja je uzimala IPP, a bez klopidogrela, nije bilo povećane smrtnosti ili rehospitalizacije zbog ACS. Temeljem ovih rezultata autori su zaključili da istovremena primjena IPP i klopidogrela nakon koronarne intervencije s ugradnjom stenta smanjuje učinkovitost klopidogrela.

Druga studija je prikazana na sastanku Američkog društva za kardiovaskularnu angiografiju i intervencije (SCAI) u svibnju ove godine u Las Vegasu. Prema tom opservacijskom ispitivanju (Clopidogrel Medco Outcomes Study) zasnovanom na jednogodišnjem praćenju 9.682 bolesnika s ugrađenim stentom koji nisu primali IPP te 6.828 bolesnika kojima je propisan jedan od IPP (omeprazol, esomeprazol, pantoprazol, lanzoprazol ili rabeprazol) rizik od velikog kardiovaskularnog događaja je bio za 51% viši u bolesnika koji su uzimali IPP (25,1% : 17,9%) pri čemu nije bilo statistički značajne razlike među praćenim IPP. Naravno, bolesnici koji su uzimali IPP su imali značajno manje GI krvarenja (oko 1,1%), a također kao u prethodnom ispitivanju bolesnici koji su uzimali IPP, a bez klopidogrela nisu imali povišen kardiovaskularni rizik. Mali broj bolesnika (472) u ovom ispitivanju koji su uzimali H2 antagoniste uz klopidogrel nisu imali statistički značajno viši broj kardiovaskularnih događaja u odnosu na one (9.390) koji ih nisu uzimali (20,3% : 17,8%). Autori također zaključuju da ispitivanje potvrđuje hipotezu da IPP smanjuju učinak klopidogrela te da ih se u bolesnika s koronarnim stentom smije istovremeno primjenjivati samo u jasnim indikacijama.

Since clopidogrel is a pro-drug, its activation takes place in the liver by gradual oxidation through P450 cytochrome. With many enzymes participating in this, the most important is the 2C19, which can have nucleotide polymorphismus leading to its not only decreased but also increased efficiency. This is the reason why in about 30% of Caucasians, clopidogrel has a weaker anti-aggregation effect, that is, it may lead to multiple side effects (most often gastrointestinal and joint pains), but its effects may also be changed by interaction with other medications. A few years ago on the basis of *in vitro* studies, a lot was written about a potential interaction of clopidogrel and atorvastatin as well as calcium antagonists which was later denied by large clinical trials. Currently, an ARCTIC clinical study is underway testing if the use of clopidogrel based on the gene polymorphism tests shows a better clinical outcome after coronary intervention compared with the standard application.

The latest concern about the decreased efficiency of clopidogrel applied along with PPI is based, alongside with earlier known data, on two recently published observational studies. The first study published in JAMA in March this year has tested the use of clopidogrel in 8,205 patients with coronary stent implant out of whom 63.9% have been also prescribed PPI upon release from hospital. Patients with PPI prescribed alongside with clopidogrel showed a 25% higher rate of mortality and rehospitalization owing to an acute coronary syndrome (ACS) compared with those not taking clopidogrel with PPI (29.8% : 20.8%) during the follow-up period (from 1st October 2003 to 31st January 2006). The patients using PPI showed more rehospitalizations because of ACS (14.6% : 6.9%) and revascularization procedures (15.5% : 11.9%), but there was no considerable statistical difference in mortality (19.9% : 16.6%). In the group of patients with stent implants who were taking PPI without clopidogrel there was no increase in mortality or rehospitalization because of ACS. On the basis of these results the authors concluded that simultaneous use of PPI and clopidogrel after coronary intervention with stent implant reduces the efficiency of clopidogrel.

Another study was presented on the meeting of the American Society for Cardiovascular Angiography and Interventions (SCAI) in May this year in Las Vegas. According to this one year follow-up observational study (Clopidogrel Medco Outcomes Study), 9,682 patients with stent implants who did not receive PPI and 6,828 patients who were prescribed one of PPIs (omeprazole, esomeprazole, pantoprazole, lansoprazole or rabeprazole), the risk of a major cardiovascular event was 51% higher in patients taking PPI (25.1% : 17.9%), whereas there was no significant difference between monitored PPIs. Of course, patients had taken PPI had significantly less GI hemorrhage (about 1.1%) and also as in the previous study patients who had taken PPI without clopidogrel did not show increased cardiovascular risk. A small number of patients (472) in this study who were taking H2 antagonists with clopidogrel had statistically no greater number of cardiovascular events compared to those (9,390) who were not taking them (20.3% : 17.8%). The authors also concluded that the study confirmed the hypothesis that PPI reduces the effects of clopidogrel and that it may be simultaneously administered to patients with coronary stent only when this is clearly indicated.

Despite the results of the aforementioned studies, many authorities in this field think it to be too early to reach a conclusion about is an interaction between clopidogrel

Usprkos rezultatima navedenih studija dosta autoriteta u ovom području smatra da je još prerano za zaključak da postoji interakcija između klopidogrela i IPP. Točno je da ispitivanja pokazuju da bolesnici koji uzimaju klopidogrel uz IPP imaju lošiji ishod od onih koji ga uzimaju samog, no tome može biti više objašnjenja: IPP mogu utjecati na nastajanje aktivnih metabolita klopidogrela, oni izravno mogu biti štetni neovisno o klopidogrelu te radi se o opservacijskim ispitivanjima gdje na krajni ishod mogu utjecati činitelji koji se ne mogu kontrolirati dizajnom studije (npr. bolesnici koji uzimaju klopidogrel i IPP su puno stariji i imaju više komorbiditeta od onih koji uzimaju samo klopidogrel, ne uzima se u obzir samomedikacija te uzimanje drugih lijekova kojih ovi bolesnici više troše, također bolesnici koji uzimaju IPP često ne uzimaju istovremeno acetilsalicilnu kiselinu zbog gastrointestinalnih nuspojava što smanjuje učinkovitost klopidogrela itd.).

Rezultati naknadne analize randomiziranih kliničkih pokusa, u kojima interakcija klopidogrela i IPP nije bio primarni cilj ispitivanja, ali dizajn kliničkih studija daje puno bolje izbalansirane skupine bolesnika s manje nuzčinitelja koji mogu utjecati na rezultate, ne potvrđuju interakcije klopidogrela i IPP. Tako naknadne analize CREDO studije (primjena klopidogrela nakon koronarne intervencije) i TRITON studije (usporedba klopidogrela i prasugrela nakon PCI u ACS) ne pokazuju povećani broj incidenata uz istovremenu primjenu klopidogrela i IPP, ali pokazuju da su bolesnici koji su uzimali IPP tijekom studija bili stariji, imali više komorbiditeta te uzimali više lijekova istovremeno. Nije bilo razlike u ishodu onih koji su uzimali IPP i blokatore H2 receptora, ali su ti bolesnici u odnosu na one koji nisu uzimali antulkusne lijekove bili stariji i bolesniji.

Također je još otvoreno pitanje da li postoji razlika između IPP u komedikaciji s klopidogrelom. Nedavno publicirana *in vitro* studija, a i jedna kanadska klinička studija, ukazuju da pantoprazol u odnosu na omeprazol ima povoljniji farmakokinetski profil kada se primjenjuje s klopidogrelom.

Nakon svega navedenog pitanje štetnosti istovremenog uzimanja klopidogrela i IPP i dalje ostaje otvoreno. Premda je kliničko ispitivanje COGENT-1 koje je bilo dizajnirano u cilju rješenja ovog pitanja prekinuto zbog financijskih problema sponzora, nadamo se da će njegovom razjašnjenu pomoći dvije kliničke studije koje će biti prezentirane na sljedećem Europskom kardiološkom kongresu u Barceloni krajem ovog mjeseca (OASIS 7/CURRENT i PLATO) te naknadna analiza podatka CAPRIE studije koja je u tijeku.

Što raditi svakodnevno kada se suočimo s bolesnikom koji mora primati klopidogrel, a ima indikaciju za IPP. Mislimo da se je razumno držati preporuke ALMP iz Pisma liječnicima od 9. lipnja ove godine, ali i zaključaka SCAI iz svibnja koji kažu, da do rješenja ovog pitanja koje zahtjeva još puno istraživanja, kod bolesnika koji primaju klopidogrela, a imaju ulkusne tegobe, treba pokušati primjeniti druge antiulkusne lijekove ako je to moguće (H2-antagoniste, antacide), dok primjenu IPP treba maksimalno ograničiti.

Možda će rješenje ovog problema biti i uporaba prasugrela za koga do sada nisu poznate interakcije s IPP.

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and PPI. It is correct that studies show that patients taking clopidogrel alongside with PPI have a worse outcome than those who are taking it only, but there can be several explanations for it: PPIs can influence the formation of active metabolites of clopidogrel, they may directly be harmful irrespective of clopidogrel and these are observational studies whereas a final outcome may be influenced by factors which can not be controlled by the study design (e.g. patients taking clopidogrel and PPI are much older and have greater comorbidities than those taking clopidogrel only, while self-medication and taking other medicines used by these patients in greater amount was not considered, also patients using PPI often don't take aspirin because of gastrointestinal side effects which reduces the efficiency of clopidogrel etc.).

The results of subsequent randomized clinical trials, whereas the interaction of clopidogrel and PPI was not the primary goal, however the design of clinical studies gives more balanced groups of patients with fewer side effects which may influence the results, did not confirm the interaction between clopidogrel and PPI. Similarly, the subsequent CREDO studies (the use of clopidogrel after coronary intervention) and TRITON studies (the comparison of clopidogrel and prasugrel after PCI in ACS) don't show an increased number of incidents with simultaneous use of clopidogrel and PPI, but they show that patients taking PPI during these studies were older, had more comorbidities and took several medicines at the same time. There was no difference in the outcome in those taking PPI and H2 receptor blockers, but those patients were older and sicker compared to those who didn't take antiulcer medications.

Besides there is a still open issue if there is a difference between PPI in co-medication with clopidogrel. Recently published *in vitro* study and also one similar Canadian study show that pantoprazole compared to omeprazole has a more favorable pharmacokinetic profile when used with clopidogrel.

To conclude the issue concerning harmfulness of simultaneous use of clopidogrel and PPI still remains open. Although the clinical trial COGENT-1 designed with the aim to resolve the issue has been stopped as a consequence of sponsor's financial problems, we hope that the two clinical studies that will be presented at the next European Society of Cardiology Congress in Barcelona by the end of this month (OASIS 7/CURRENT and PLATO) and the subsequent analysis of the ongoing CAPRIE study will help the resolution and clarification of this issue.

What should we do on a daily basis when we face a patient who must receive clopidogrel and has an indication for PPI. We find it reasonable to follow not only the recommendation of ALMP stated in the Letter to physicians dated June 9 this year, but also the conclusions of SCAI of May stating that the solution to this problem requires much more research, with patients taking clopidogrel, and having ulcer problems, if possible we should try to use other antiulcer medicines (H2 antagonists, antacids), while the use of PPI should be limited to the greatest possible extent.

The solution to this problem may be the use of prasugrel which has been proved to show no interactions with PPI.

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