



Neželjene nuspojave primjene nesteroidnih antireumatika i acetilsalicilne kiseline

Undesirable side-effect though application of non-steroidal antirheumatics and aspirin

Josip Čiček

Bjelovar General Hospital

Nesteroidni antireumatici najčešće se rabe kao analgetici, antiinflamatorici, antipiretici, a niske doze acetilsalicilne kiseline (ASK) se zbog antiagregacijskog učinka široko primjenjuju u sekundarnoj prevenciji koronarne i cerebrovaskularne bolesti. Ovi su lijekovi heterogena skupina koja uključuje nestereoidne protuupalne lijekove (nesteroidni antireumatici, NSAR), ASK i selektivne i neselektivne antagoniste ciklooksigenaze.

Zbog širokog indikacijskog područja NSAR su među najpropisivanijim lijekovima. Prema podacima iz SAD-a više od 70% osoba starijih od 65 godina uzima NSAR barem jednom tjedno, a polovina od tog broja bolesnika uzima najmanje 7 doza NSAR tjedno. Prema istraživanju potrošnje lijekova tijekom 2001. i 2002. godine u Zagrebu utvrđeno je da je za četiri najčešće propisivanih NSAR (diklofenak, piroksikam, ketoprofen, ibuprofen) ostvaren promet veći od 1,6 milijuna EUR-a, bez obuhvaćenih NSAR u slobodnoj prodaji.

Uz svoje blagotvorne učinke ovi lijekovi imaju vrlo česte nepoželjne gastrointestinalne (GI) nuspojave. Sve šira primjena ASK u primarnoj, a napose i u sekundarnoj prevenciji kardiovaskularnih bolesti, rezultira i potencijalnim nuspojavama. Valja naglasiti da se sve češće u bolesnika s reumatskim bolestima i osoba s koronarnom bolesti srca sve češće primjenjuju kombinacije NSAR koje značajno povećavaju rizik od GI komplikacija.

Ovim člankom se želi upozoriti na može bitne neželjene nuspojave prilikom liječenja NSAR i ASK te dati i neke praktične mjere prosudbe može bitnih rizika i moguće mjere sprječavanja nuspojava (preventivna primjena inhibitora protonske pumpe, primjena alternativnih antipiretika i analgetika - paracetamol, tramadol).

Kliničke manifestacije gastrointestinalnih nuspojava zbog primjene NSAR i ASK

Pet najvažnijih čimbenika za ozbiljne GI nuspojave povezane s primjenom NSAR i ASK, prema American College of Gastroenterology, su: prijašnja anamneza bolesti GI trakta (4-5x viši rizik), visoke doze NSAR (doze više od dvostrukih povisuju rizik 10x), primjena peroralnih antikoagulanasa (rizik viši 10-15x), primjena u visokorizičnih i bolesnika s komorbiditetima, te primjena ASK u obliku koji se otapa u crijevima (smanjenje endoskopski znakova oštećenja GI trakta, ali ne i klinički značajnog smanjenja krvarenja iz GI trakta koja su izazvana sistemskim, a ne lokalnim učincima lijekova).

Akutna ozljeda sluznice želuca nastaje već 15 do 30 minuta nakon jednokratne primjene ASK u dozi od 600

Non-steroidal antirheumatics are most often used as analgesics, anti-inflammatories, antipiretics, and low doses of aspirin due to anti-aggregation effects are widely administered in secondary prevention of coronary and cerebrovascular diseases. Such medications belonging to the heterogeneous group include non-steroidal anti-inflammatory medication (non-steroidal anti-rheumatics, NSAIDs), aspirin as well as selective and non-selective antagonists of cyclooxygenase.

Due to the wide indicative area, NSAIDs are amongst the most prescribed medications. Based on information obtained by the USA, more than 70% of persons older than 65 years of age take NSAIDs at least once a week, while a half of these patients take at least 7 doses of NSAIDs on a weekly basis. Based on research of consumption of medications during 2001 and 2002 in Zagreb, it has been determined that the four most frequently prescribed NSAIDs are (diclofenac, piroxicam, ketoprofen, ibuprofen) generating revenues exceeding 1.6 million EUR, not taking into account NSAIDs freely sold.

Along with their mild effects, this medication very often results in undesirable gastrointestinal (GI) side-effects. Ever wider administration of aspirin in primary, and especially in secondary prevention of cardiovascular diseases results in potential side-effects. It is important to emphasize that there is increasing administration a combination of NSAIDs in patients experiencing rheumatic illnesses and persons with coronary heart disease, which significantly increases the risk of GI complications.

This paper aims to warn of the possible undesirable side-effects when treating with NSAIDs and aspirin, and offers some practical measures in assessing possible risks and measures in preventing side-effects (preventive administration of proton pump inhibitors, and administration of alternative antipiretics and analgesics - paracetamol, tramadol).

Clinical Manifestations of Gastrointestinal Side-Effects Due to Administration of NSAIDs and aspirin

The five most important factors in serious GI side-effects related to the administration of NSAIDs and aspirin according to the American College of Gastroenterology are: past history of illness relating to the GI tract (4 to 5 times the risk), high doses of NSAIDs (more than double doses increase the risk by 10 times), administration of peroral anti-coagulants (risk increases 10 to 15 times), application in high-risk persons and patients with comorbidity, and administration of aspirin in a form that is soluble in the intestine (reduces endoscopic signs of damage in the GI tract, but not the clinically significant reduction of bleeding from



mg, a manifestira se petehijalnim krvarenjem. Višekratna primjena ASK tijekom 24 sata u dozi 650 mg 4x dnevno rezultira nastajanjem erozija želuca. Akutne površinske ozljede sluznice GI sustava značajno su rjeđe kod primjene neaspirinskih NSAR, nego uz primjenu ASK. Kronična primjena NSAR može uzrokovati ezofagitis i strikturu.

Neki NSAR uzrokuju akutne promjene u tankom crijevu, koje često rezultiraju nastankom kroničnih ulceracija. Toksičnost NSAR prema tankom crijevu može se manifestirati kao aktivna upala, kronični gubitak krvi, a ponekad i perforacija tankog crijeva. Oštećenja tankog crijeva češće su u NSAR koji se izlučuju putem žuči prelaze u enterohepatičku cirkulaciju kao što su derivati propionske kiseline (ibuprofen, ketoprofen, naproksen), derivati octene kiseline (diklofenak, indometacin). Moguće je da NSAR povećavaju propusnost debelog crijeva, uz dokaze da mogu biti povezani s upalnim promjenama kolona. Ovo je opažanje podkrepljeno epidemiološkim dokazima o povezanosti promjena NSAR s relapsima i novonastalim ulceroznim kolitisom.

Najčešća nuspojava dugotrajne primjene NSAR su ulkusi (oštećenja sluznice najmanje 5 mm u promjeru i u dubinu). Češće nastaju u želucu nego u dvanaesniku, a u pravilu 7 dana od početka kronične primjene ASK u najmanje 8% bolesnika. Kronična primjena ASK tijekom 3 mjeseca rezultira pojavom ulkusa u 25-30% bolesnika, a nakon 6 mjeseci u njih 45%. Prosječna učestalost ulkusa u kroničnih korisnika NSAR je od 15 - 30%. Napredovanju u nastanku ulkusa pogoduje što NSAR otežavaju cijeljenje već nastalih oštećenja sluznice, a analgetskim učinkom prikrivaju bol i maskiraju kliničku sliku. Stoga je zanimljivo opažanje da se većina ulkusa u kroničnih korisnika NSAR otkrije se slučajno prilikom endoskopije.

Dugotrajnu primjenu NSAR često prate mikroskopske promjene antruma želuca klasificirane kao C tip gastritisa. Ovaj tip gastritisa karakteriziraju epitelna, endotelna i muskularna hiperplazija. U ovom entitetu nisu potvrđene upalne promjene, pa izraz ne odražava njegovu pravu etiopatogenezu.

Topički akutni učinci nastaju direktnim oštećenjem GI sluznice već nakon nekoliko minuta (petehije, erozije). Sistemski učinci tijekom kronične primjene NSAR su sustavna supresija prostaglandina. To objašnjava pojave GI oštećenja koja se nalaze i u slučaju intravenske, intramuskularne i rektalne primjene.

Raščlambom brojnih studija prevencije GI komplikacija zbog primjene NSAR i ASK utvrđeno je:

1. Antagonisti H₂ receptora nisu učinkoviti u standardnim dozama u prevenciji ulkusne bolesti i ostalih GI komplikacija.

2. Visoke doze famotidina su učinkovite u primarnoj i sekundarnoj prevenciji NSAR inducirane ulkusne bolesti koja je endoskopski utvrđena.

3. Lanzoprazol i esomeprazol su prema Američkoj upravi za hranu i lijekove priznati kao lijekovi za prevenciju NSAR uzrokovanih ulkusa.

4. Primjena NSAR s manje toksičnim potencijalom na GI (specifični inhibitori COX) .

the GI tract which are caused by systematic and not local effects of medications).

Acute injury of the mucous membrane of the stomach occur even 15 to 30 minutes after single administration of aspirin in doses starting from 600 mg, and manifest as petechial hemorrhage. Multiple administration of aspirin during 24 hours in doses of 650 mg 4 times a day results in the occurrence of erosions of the stomach. Acute superficial injuries of the mucous membrane in the GI system are more seldom with the administration of non-aspirin NSAIDs, than when administering aspirin. A chronic administration of NSAIDs may cause esofagitis and strictures.

Some NSAIDs cause acute changes in the small bowel which often results in the occurrence of chronic ulcers. Toxicity of NSAIDs relating to the small bowel may occur as active inflammation, chronic loss of blood, and sometimes perforation of the small bowel. Damage to the small bowel is more often caused by NSAIDs which are secreted through gall bladder and passes into enterohepatic circulation such as are propionic acid derivatives (ibuprofen, ketoprofen, naproxen), acetic acid derivatives (diclofenac, indometacin). It is possible that NSAIDs may increase the permeability of the colon, along with evidence that they may be related to inflammatory changes in the colon. This observation is supported by epidemiological evidence of the relation of NSAID changes with relapses and newly occurring ulcerous colitis.

The most often side-effects of long-term administration of NSAIDs are ulcers (damage to the mucous membrane at least 5mm in diameter and in depth). They occur more often in the stomach rather than in the duodenum, and as a rule 7 days since the start of chronic administration of aspirin in at least 8% of patients. Chronic administration of aspirin during 3 months results in side-effects of the ulcer in 25-30% of patients, and following six months in 45% of cases. The average occurrence of ulcers in chronic users of NSAID ranges from 15-30%. Progression in the occurrence of ulcer contributes to NSAIDs making healing more difficult of the damages to the mucous membrane that have already occurred, and through analgesic effect they ease pains while hiding the real clinical manifestations. Therefore, it is interesting to note that the majority of ulcers in chronic users of NSAIDs are discovered accidentally during endoscopy.

Long-term administration of NSAIDs is often followed by microscopic changes in the antrum of the stomach classified as C type gastritis. This type of gastritis is characterised by epithelial, endothelium and muscular hyperplasia. This entity does not confirm inflammatory changes, hence the appearance does not reflect the true etiopathogenesis.

Topical acute effects occur through direct damage to the GI mucous membrane after only a few minutes (petechia, erosions). Systematic effects during chronic administration of NSAIDs are systematic suppression of prostaglandins. This explains the occurrence of GI damage that appears and in the event of intravenous, intramuscular and rectal administration.

Division of the numerous studies in prevention of GI complications due to administration of NSAIDs and aspirin has determined the following:



5. Mnogo su češće GI komplikacije NSAR u bolesnika s pozitivnom *Helicobacter pylori* infekcijom. Stoga bi, shodno tome, osobito kod kardiovaskularnih bolesnika, bilo uputno provesti trojnu ili četvornu terapiju prije primjene NSAR.

6. Temeljem dostupnih, kontroliranih randomiziranih kliničkih studija je zaključeno da bi povećani rizik od kardiovaskularnih događaja mogao biti "class effect" svih NSAR (osim paracetamola i ASK) te se od proizvođača zahtijevaju promjene upute u smislu upozorenja na navedene ozbiljne nuspojave, kao i isticanje kontraindikacije za primjenu neposredno nakon aortokoronarnog premoštenja. Obveza je proizvođača NSAR da na pakiranju naročito selektivnih COX-2 inhibitora naznače kako uz istodobne kardiovaskularne bolesti ili čimbenike kardiovaskularnog rizika uzimanje ovih lijekova može potaknuti nastanak kardiovaskularnih komplikacija.

7. Kako su nepovoljni kardiovaskularni učinci ovisni o dnevnoj dozi NSAR savjetuje se njihova primjena u najnižim djelotvornim dozama.

Received: 25th February 2008
E-mail: josip.cicek2@sk.htnet.hr

Literature

1. Čiček J, Trumbetaš T, Povh G, Lukić M. Nesteroidni antireumatici. Izlaganje na 8. stručnom sastanku Hrvatskog gastroenterološkog društva: Komplikacije i rizici u gastroenterologiji. Bjelovar 16. i 17. studenoga 2007.
2. Fabijanić D, Kordum D, Banić M, Fabijanić A. Nesteroidni protuupalni lijekovi i ozbiljne gastrointestinalne nuspojave. Liječn Vjesn 2007;129:205-13.
3. Talley NJ, Evans JM, Fleming KC et al. Nosteroidal antiinflammatory drugs and dyspepsia in the elderly. Dig Dis Sci 1995;40:1345-50.
4. Singh G, Tradafilopoulos G. Epidemiology of NSAID-induced GI complications. J Rheumatol 1999;26:18-24.
5. Vukušić I, Štimac D, Čulig J. Cost-efficiency of nonsteroidal anti-inflammatory drug prescribing in Zagreb, Croatia. Coll Antropol 2005; 29:143-7.
6. O'Laughlin JC, Hoftiezer J W, Ivey KJ. Effect of aspirin on the human stomach in normals: endoscopic comparison of damage produced one hour, 24 hours, and 2 weeks after administration. Scand J Gastroenterol 1981;16:211-4.

9. Hrvatski simpozij o aritmijama i elektrostimulaciji srca Zagreb, 14. 3. 2008.

Radna skupina za aritmije i elektrostimulaciju srca Hrvatskog kardiološkog društva organizira 9. Hrvatski simpozij o aritmijama i elektrostimulaciji srca u hotelu Westin u Zagrebu 14. ožujka 2008. godine. Program simpozija preuzmite s <http://www.kardio.hr/>.

Cleveland Clinic in Zagreb, 14. 3. 2008.

Cleveland Clinic, Cleveland, Ohio, SAD i Klinička bolnica Dubrava Zagreb održat će 14. ožujka 2008. godine simpozij posvećen kardiovaskularnoj medicini "Cleveland Clinic in Zagreb" u hotelu Westin. Program simpozija preuzmite s <http://www.kbd.hr/kardkir/simpozijCC.htm>.

16th Annual Meeting of the Alpe Adria Association of Cardiology, Portorož, Slovenija, 5. do 7. 6. 2008.

Godišnji sastanak Alpe Adria Association of Cardiology za 2008. godinu održat će se u Portorožu, Slovenija, od 5. do 7. lipnja 2008. godine.

1. Antagonists of the H2 receptor are not effective in standard doses when preventing ulcer illnesses and other GI complications.

2. High doses of famotidin are effective in primary and secondary prevention of NSAIDs induced ulcer illnesses which are confirmed through endoscopy.

3. Lansoprazol and esomeprazol are based on the American Food and Drug Administration as medication for the prevention of NSAID caused ulcers.

4. Administration of NSAIDs with less toxic potential on GI (specific inhibitors COX).

5. More frequent are GI complications of NSAR in patients with positive *Helicobacter pylori* infections. Therefore, based on such conclusions, especially with cardiovascular patients, it would be wise to implement triple and quadruple therapy prior to administering NSAIDs.

6. Based on available, controlled and randomized clinical studies, it has been concluded that the increased risk of cardiovascular events could be "class effect" of all NSAIDs (except for paracetamol and aspirin) and the manufacturers are required to change instructions in terms of caution to the stated serious side-effects, as well as emphasizing the contraindications for administration directly following aortic-coronary bypasses. It is the responsibility of the manufacturers of NSAIDs to designate on the packaging of particularly selective COX-2 inhibitors for those suffering from cardiovascular illnesses or cardiovascular risk factors and taking such medication may cause cardiovascular complications.

7. Since undesirable cardiovascular effects depend on a daily dose of NSAID, it is advised that their administration occurs in the lowest effective doses.

9th Croatian Symposium on Arrhythmias and Cardiac Pacing, Zagreb, 14th March 2008

The Working Group on Arrhythmias and Cardiac Pacing of the Croatian Cardiac Society is organizing the 9th Croatian Symposium on Arrhythmias and Cardiac Pacing in the Westin hotel in Zagreb, on 14th March 2008. The program of the Symposium is to be downloaded from <http://www.kardio.hr/>

Cleveland Clinic in Zagreb, 14th March 2008

Cleveland Clinic, Cleveland, Ohio, SAD and Zagreb Dubrava Clinic Hospital will on 14th March 2008 organize the symposium dedicated to cardiovascular medicine "Cleveland Clinic in Zagreb" in the Westin hotel. The symposium program is to be downloaded from <http://www.kbd.hr/kardkir/simpozijCC.htm>

16th Annual Meeting of the Alpe Adria Association of Cardiology, Portorož, Slovenia, from 5th to 7th June 2008

The annual meeting of Alpe Adria Association of Cardiology for the year 2008 will be held in Portorož, Slovenia, from 5th to 7th June 2008. All details may be downloaded from <http://aac2008.sicardio.org>