ORGANSKI NITRATI U AKUTNOM KORONARNOM SINDROMU

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SAŽETAK

U velikim kliničkim studijama pokazano je da rutinska primena nitroglicerina (iv ili oralno) u akutnom koronarnom sindromu (AKS) ne smanjuje značajno mortalitet. Međutim, nitrati i dalje imaju svoje mesto u terapiji posebnih grupa bolesnika sa AKS i uspešno se primenjuju za ublažavanje ishemije. Nitroglicerin se primenjuje za otklanjanje perzistentnog bola i kao vazodilatator u pacijenata sa akutnim infarktom miokarda (AIM) i slabošću levog srca. Ukoliko, međutim, pacijent nema rekurentni ishemijski bol ili kongestivnu srčanu slabost, nitrati se ne primenjuju rutinski u pacijenata sa AKS. Pacijenti sa velikim transmuralnim infarktom posebno prednjeg zida imaju najviše koristi od primene nitrata u svetlu smanjenja remodelovanja komora. U takvih pacijenata se primenjuju nitrati u obliku intravenske infuzije rutinski tokom 24 do 48 sati. Treba nastaviti davanje nitrata duže od 48 sati bolesnicima koji imaju rekurentnu ishemiju ili slabost srca.

Ključne reči: akutni koronarni sindrom, organski nitrati, mehanizmi kliničkih dejstava

UVOD

Pojam akutni koronarni sindrom (AKS) obuhvata 1. AKS sa elevacijom ST segmenta, odnosno akutni infarkt miokarda (AIM) sa ST elevacijom (STEMI) i visokim vrednostima troponina i 2. AKS bez elevacije ST segmenta, koji podrazumeva nestabilnu anginu pektoris (NAP) (troponin je negativan) i AIM bez ST elevacije (NSTEMI) (troponin je lako pozitivan). Sva ova tri vida AKS obično nastaju rupturom aterosklerotskog plaka u jednoj od koronarnih arterija. Rupturom ateroma oslobađaju se mnoge trombogene supstance u dovoljnoj količini tako da se formira tromb koji dovodi do ishemije. U lečenju sva tri vida AKS mogu učestvovati i organski nitrati (1,2,3)

Sublingvalno, gliceril trinitrat (nitroglicerin), se primenjuje bezbedno skoro svim bolesnicima sa AKS do tri puta u 5-minutnim intervalima. Nakon toga se više ne preporučuje sublingvalna primena. Ukoliko ne postoje ograničenja, terapiju nitroglicerinom bi trebalo nastaviti intravenskim (*iv*) putem u prvih 24 do 48 sati kod bolesnika sa AIM i srčanom insuficijencijom, velikim infarktom prednje lokalizacije ili perzistentnom ishemijom. Terapiju nitratima bi međutim, trebalo izbegavati u pacijenata sa niskim sistolnim arterijskim pritiskom (<90 mmHg), posebno uz prateću bradikardiju (ispod 50 otkucaja/min) ili sa sumnjom na infarkt desne komore. U velikim kliničkim studijama pokazano je da rutinska primena nitroglicerina (*iv* ili oralno) u STEMI i NAP/NSTEMI ne smanjuje značajno mortalitet. Međutim, nitrati i dalje imaju svoje mesto u terapiji posebnih grupa bolesnika sa AKS, zbog toga što smanjuju pritisak punjenja komora i srčani rad i poboljšavaju koronarni

protok posebno u ishemičnim zonama, doprinoseći na taj način poboljšanju kliničkog stanja bolesnika (1,2,3).

1. MEHANIZAM DEJSTVA ORGANSKIH NITRATA

Nitrati dovode do vazodilatacije bez obzira da li je očuvan endotel krvnog suda ili ne. Nakon prelaska u unutrašnjost glatkomišićne ćelije krvnog suda, nitroglicerin se transformiše do NO u mitohondrijama pod dejstvom aldehidne dehidrogenaze (reduktaze). NO aktivira gvanilat-ciklazu (GC), a ovaj enzim pretvara gvanozintrifosfat (GTP) u ciklični gvanozin monofosfat (cGMP). cGMP kao drugi glasnik u ćeliji onda aktivira fosfokinazu G (PKG). Važno ciljno mesto dejstva PKG je fosfataza lakih lanaca miozina. Ova fosfataza vrši defosforilaciju lakih lanaca miozina, što za posledicu ima smanjenje koncentracije intracelularnog kalcijuma [Ca^{+2}] i relaksaciju glatke muskulature krvnog suda. Farmakološki i biohemijski efekti nitratnih vazodilatatora su identični efektima endotelnog faktora relaksacije (EDRF), za koga se danas zna da je po strukturi NO. Mada mnoga istraživanja ukazuju da je glavni celularni mehanizam dejstva nitrata oslobađanje NO - formiranje cGMP- intracelularno smanjivanje jona kalcijuma [Ca^{+2}], eksperimentalni podaci ukazuju da možda ovo nije i jedini mehanizam dejstva. U *in vitro* uslovima je pokazano da nitroglicerin ostvaruje dilataciju arterija i putem otvaranja kalijumovih kanala, pod dejstvom NO-cGMP (4,5,6).

Kardiovaskularni efekti

Organski nitrati prouzrokuju vazodilataciju vena i arterija (uključujući i koronarne), ali predominantno deluju na vensku cirkulaciju. Venodilatacijom se smanjuje količina krvi koja dolazi u srce, odnosno prethodno opterećenje srca (preload), čime se smanjuje pritisak na kraju dijastole i potrošnja kiseonika. Arterijskom i arteriolarnom dilatacijom se smanjuje otpor koji srce mora da savlada da bi izbacilo krv u sistemsku cirkulaciju (naknadno opterećenje srca, afterload). Ovim se olakšava rad srca i smanjuje potrošnja kiseonika od strane miokarda (5,7).

Efekti na koronarnu cirkulaciju. Nitroglicerin izaziva dilataciju epikardijalnih arterija sa stenozom. Stenoza često nastaje usled ekscentrične lezije, a nitroglicerin izaziva relaksaciju glatke muskulature zida koronarne arterije koji nije zahvaćen ateromatoznim plakom. Čak i malo proširenje suženog arterijskog lumena može da dovede do značajnog smanjenja otpora proticanju krvi kroz suženi region. Nitrati takođe mogu da smanje vazokonstrikciju izazvanu oštećenjem endotela.

Nitroglicerin dovodi do redistribucije koronarnog protoka od područja sa normalnom perfuzijom ka ishemičnoj zoni, posebno u subendokardu. Ova redistribucija krvi može biti posledica proširenja kolaterala i smanjenja pritiska ventrikula u dijastoli odnosno smanjenja kompresije subendokarda. Redistribucija koronarnog protoka ka subendokardu nije tipična za sve vazodilatatore (4,5,8).

Mada nitroglicerin povećava koncentraciju cGMP i u trombocitima, što bi moglo doprineti njegovom antiagregacionom efektu, ovaj efekat je blag i mogao bi biti poništen mogućom farmakokinetičkom interakcijom sa heparinom u kojoj bi antikoagulantni efakat

heparina bio smanjen. Klinički značaj antiagregacionog efekta nitrata je posebno nejasan u svetlu nedavnih kliničkih studija u kojima nije pokazana značajna redukcija mortaliteta pri rutinskoj primeni u AIM (9,10).

Na bazi svega, može se zaključiti da organski nitrati ispoljavaju antianginozno dejstvo sledećim mehanizmima:

- smanjenjem potrošnje kiseonika od strane srčanog mišića, zbog redukcije prethodnog i naknadnog opterećenja srca
- redistribucijom koronarnog protoka prema ishemijskim zonama preko dilatacije kolaterala
- smanjenjem koronarnog spazma (5,7).

2. FARMAKOKINETIKA I FARMACEUTSKI OBLICI ORGANSKIH NITRATA

Mada je prošlo više od 100 godina od prve primene organskih nitrata u lečenju angine pektoris, još uvek nisu usaglašeni stavovi povodom njihove biotransformacije. Glatko-mišićne

generički naziv	zaštićeni nazivi	oblik i jačina	doziranje
gliceril trinitrat	**Nirmin*, Nitrolingual**	*Rast. za inj.* 1 mg/1,6 ml* *Konc. za rast. za inf.* 5 mg/1,6 ml* *Subl. sprej* 0,4 mg/dozi	iv inj.: 1 mg tokom 3 min, po potrebi ponoviti (najviše 2 puta), u razmacima od 10 min; iv inf. (posle efekta postignutog iv inj.): 0,01-0,2 mg/min (početi sa 0,01-0,02 mg/min, a zatim na 5-10 min povećavati za 0,005-0,01 mg/min do željenog odgovora); sublingvalno: sprej doza, po potrebi (najviše 3 u razmaku od 3-5 min)
pentaeritritil tetranitrat	**Dilcoran 80, Lentonitrat* 50**	*Tabl. sa modif. oslob.* 80 mg *Kaps. sa prod. oslob.* 50 mg*	2 x 80 ili 50* mg pre jela (ujutro i u podne a najkasnije do 16 h)
izosorbid dinitrat	**Cornilat*, Difutrat, Isosorb retard**	*Tabl.* 20 mg* *Kaps. sa prod. oslob.* 20 mg	40 mg/dan u jednoj ili dve doze, po potrebi dozu povećati na 60-80 mg/dan podeljeno u dve doze
izosorbid mononitrat	**Monizol, Monosan, Isocard***	*Tabl.* 20 i 40 mg *Kaps. sa prod. oslob.* 60 mg*	2 x 10 mg za bolesnike koji ranije nisu lečeni organskim nitratima; 1-2 x 20-40 mg (prva doza ujutro a druga posle 8 h), maks. 120 mg/dan podeljeno u 2-3 doze * 1 x 60 mg, maks. 1 x 120 mg
iv – intravenski			

***Tabela 1**. Organski nitrati registrovani za tržište Srbije (Registar lekova, 2012)*

ćelije krvnih sudova preuzimaju nitroglicerin iz krvi i nitratna grupa se redukuje do NO uz pomoć aldehidne reduktaze u mitohondrijama. Nitroglicerin se takođe hidrolizuje u plazmi a brzo se metaboliše i u jetri pod dejstvom glutatjon reduktaze, do manje aktivnih metabolita, dinitrata i mononitrata. Terapijski efekat intravenski primenjenog nitroglicerina postiže se za 1-2 minuta, a traje 3-5 minuta, dok terapijski efekat sublingvalne tablete i spreja nastupa za 1-3 minuta, a traje 30-60 minuta. Nitroglicerin se u značajnoj meri resorbuje i kroz kožu. Primenjen kao transdermalni flaster ili lekovita mast nitroglicerin postiže terapijski efekat za 30-60 minuta, a dužina terapijskog efekta je 24 sata za transdermalni flaster, odnosno do 8 sati za mast. Postoje i dugodelujuće forme oralno primenjenih nitrata predviđene za svakodnevnu, hroničnu primenu, u stabilnoj angini pektoris: izosorbid mononitrat, izosorbid dinitrat i pentaeritritil tetranitrat (9). U Tabeli 1. su prikazani organski nitrati registrovani na našem tržištu (11).

3. KONTRAINDIKACIJE ZA PRIMENU NITRATA

Kontraindikacije za primenu nitrata su: primena inhibitora 5-fosfodiesteraze u prethodna 24 sata; hipotenzija i hipovolemija; preosetljivost na nitrate; hipertrofična kardiomiopatija; teška aortna stenoza; tamponada srca; konstriktivni perikarditis; mitralna stenoza; povreda glave; cerebralna hemoragija; i izrazita anemija. Kod sumnje na infarkt desne komore, takođe se nitrati ne primenjuju (9,11,12).

4. NEŽELJENA DEJSTVA NITRATA

Neželjeni efekti nitrata uglavnom proističu iz njihovih farmakoloških dejstava. Najčešći neželjeni efekti su: pulsirajuća glavobolja, posturalna hipotenzija, tahikardija (ali se može javiti i paradoksalna bradikardija) i vrtoglavica; ređe se mogu javiti: muka, gađenje, povraćanje, crvenilo lica, osećaj paljenja na oralnoj sluznici (gliceril trinitrat, sublingvalno), gubitak svesti, prolazna hipoksemija, raš, lokalne reakcije na mestu primene kod transdermalnog flastera; vrlo retko: glaukom oštrog ugla. Methemoglobinemija se retko može javiti prilikom primene velikih doza nitrata, dok uobičajene doze nitrata mogu dovesti samo do malog povećanja methemoglobina koje uglavnom nije od kliničke važnosti (9,12).

Tolerancija na nitrate je naročito važna u pacijenata sa stabilnom anginom pektoris, koji su na hroničnoj terapiji dugodelujućim nitratima, dok nema takav značaj u pacijenata (sa NAP i AIM) koji su na kratkotrajnoj terapiji kratkodelujućim nitratima. Pod tolerancijom se podrazumeva gubitak ili smanjenje antianginoznog dejstva nitrata prilikom česte ili kontinuirane primene ovih lekova. Na intravenski dat gliceril trinitrat, tolerancija se obično razvija u pacijenata nakon produžene iv infuzije (5,12). Izgleda međutim, da je tolerancija na gliceril trinitrat nakon 48-časovne infuzije, ograničena na kapacitativne i rezistentne krvne sudove, ali ne i na velike sprovodne sudove, uključujući i epikardijalne koronarne arterije (13).

Mehanizam tolerancije na nitrate nije u potpunosti razjašnjen. Pretpostavlja se da postoji više mehanizama nastanka tolerancije na nitrate: 1. neurohumoralna aktivacija (povećanje kateholamina, angiotenzina II, vazopresina) i povećanje volumena cirkulišuće tečnosti

(putem povećanog oslobađanja aldosterona); 2. stvaranje slobodnih kiseoničkih radikala (superoksidnih anjona, $\bullet O_2^-$), koji onemogućavaju biotransformaciju nitrata do NO i 3. smanjenje odgovora ciljnih organa na NO. Podaci, međutim, ukazuju da povećana produkcija slobodnih kiseoničkih radikala, odnosno povećanje vaskularnog oksidativnog stresa, jeste centralni mehanizam nastanka tolerancije na nitrate. Gliceril trinitrat stimuliše stvaranje superoksidnih anjona, koji onda sa NO stvaraju peroksinitrit koji inhibira biotransformaciju gliceril trinitrata do NO. U mnogim studijama na životinjama je pokazano da slobodni kiseonički radikali koji se stvaraju pri produženom izlaganju krvnih sudova nitratima mogu da oštete endotel i inhibiraju endotelno-zavisnu vazodilataciju (12,14). Međutim, u eksperimentalnom modelu hiperholesterolemije velike doze nitrata štite endotel i smanjuju debljinu sloja intima-medija. Potrebno je sprovesti kliničke studije da bi se sudilo o kliničkom značaju ovih suprotstavljenih eksperimentalnih podataka (12,15).

Da bi se izbegla tolerancija na nitrate pribegava se takozvanom asimetričnom doziranju. Ovaj režim doziranja podrazumeva pauzu u primeni leka u trajanju od 10-12 sati (16). Međutim, tokom prekida primene dugodelujućih nitrata može da nastane ishemija, i tada se primenjuju kratkodelujući nitrati. Postoje podaci da primena blokatora angiotenzinskih receptora (kandesartan) može smanjiti toleranciju na nitrate (17). Ne zna se da li je potrebno praviti pauzu u doziranju kod svih pacijenata, imajući u vidu da mnogi pacijenti koji su na hroničnoj terapiji nitratima ne razvijaju klinički značajnu toleranciju.

5. INTERAKCIJE NITRATA SA DRUGIM LEKOVIMA

Alkohol i lekovi koji deluju hipotenzivno mogu da povećaju hipotenzivni potencijal nitrata.

Ukoliko se heparin i gliceril trinitrat daju istovremeno intravenskim putem, može doći do smanjenja efikasnosti heparina (18). Ako se, međutim, gliceril trinitrat primeni neposredno posle heparina, do interakcije ne dolazi (19).

Mada se trombolitici i nitrati često koriste u AIM, kombinovana primena alteplaze i gliceril trinitrata može smanjiti trombolizu, što se objašnjava povećanim metabolizmom alteplaze usled povećane prokrvljenosti jetre pod dejstvom gliceril trinitrata (20, 21).

Istovremena primena nitrata i inhibitora 5-fosfodiesteraze kao što su sildenafil (Viagra), tadalafil (Cialis) i vardenafil (Levitra), a koji se koriste kod erektilne disfunkcije, kontraindikovana je. Usled značajnog potenciranja hipotenzivnog efekta nitrata u prisustvu inhibitora 5-fosfodiesteraze dolazilo je i do smrtnih ishoda (22). Ukoliko pacijent koji je na nitratima želi da primeni sildenafil, treba da prekine primenu bar 24 sata pre primene sildenafila, i da u tom periodu koristi druge antianginozne lekove (npr. β blokatore) (5, 9).

6. KLINIČKA PRIMENA

U vreme kada još nije bila otkrivena reperfuziona terapija (tromboliza ili perkutana koronarna intervencija, PCI), meta analizom 10 randomizovanih kliničkih studija u kojima je intravenski primenjivan gliceril trinitrat ili nitroprusid tokom 24 sata od nastanka bola,

obuhvaćeno je oko 2.000 pacijenata sa AIM, i pokazano da nitrati smanjuju mortalitet za oko 35%. Najveće smanjenje smrtnosti zabeleženo je u prvoj nedelji terapije, ali korist od produžene terapije nakon tog ranog perioda nije jasno utvrđena (23).

Kada je počela da se primenjuje reperfuziona terapija, sprovedene su dve velike kliničke studije u vezi primene nitrata u AIM: GISSI-3 i ISIS-4. U GISSI-3 studiji, u kojoj je učestvovalo oko 20.000 pacijenata sa AIM, primena nitroglicerin u vidu infuzije tokom 24-časa nakon koje je usledila transdermalna primena nitroglicerina tokom 6 nedelja, odnosno 6 meseci, nije značajno uticala na stopu smrtnosti (24). Slično je bilo i u ISIS-4 studiji u kojoj je bilo uključeno oko 58.000 pacijenata sa AIM, oralna primena izosorbid mononitrata tokom 35 dana nije značajno uticala na smrtnost (25).

Međutim, nitrati i dalje imaju svoje mesto u posebnim grupama bolesnika sa AKS i uspešno se primenjuju za smanjenje ishemije. Kod malog, nekomplikovanog infarkta miokarda rutinska primena nitroglicerina (*iv*) nije opravdana. Neki od korisnih efekata nitrata mogu biti poništeni povećanjem srčane frekvence. Da bi se ovo izbeglo treba podesiti dozu nitrata i istovremeno primeniti β blokatore. Početna doza od 5 -10 μg/min treba da se poveća toliko da sniženje pritiska (sistolnog ili srednjeg) ne bude veće od 10% kod normotenzivnih, odnosno 10-15% kod hipertenzivnih. Ni u jednom slučaju ne sme sistolni pritisak da bude ispod 90 mmHg, a srčana frekvenca ne bi trebalo da se poveća za više od 20 otkucaja/min (4). Nepoželjno sniženje pritiska se javlja kod 10% bolesnika. U izvesnim slučajevima, usled razvoja tolerancije može se javiti potreba za povećanjem doze gliceril trinitrata kada se intravenska infuzija primenjuje duže od 24 sata.

7. UMESTO ZAKLJUČKA

Gliceril trinitrat (nitroglicerin) se primenjuje za otklanjanje perzistentnog bola i kao vazodilatator u pacijenata sa AIM i slabošću levog srca. Ukoliko, međutim, pacijent nema rekurentni ishemijski bol ili kongestivnu srčanu slabost, nitrati se ne primenjuju rutinski u pacijenata sa AKS. Pacijenti sa velikim transmuralnim infarktom posebno prednjeg zida imaju najviše koristi od primene nitrata u svetlu smanjenja remodelovanja komora. U takvih pacijenata se primenjuju nitrati u obliku intravenske infuzije rutinski tokom 24 do 48 sati. Treba nastaviti davanje nitrata duže od 48 sati bolesnicima koji imaju rekurentnu ishemiju ili slabost srca (4). Na oblike nitrata sa dugotrajnim dejstvom može se preći kada bolesnik uđe u stabilnu fazu nakon infarkta.

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LITERATURA

1. Vasiljević Z. Akutni koronarni sindrom. U: Kažić T, Ostojić M, urednici. Klinička kardiovaskularna farmakologija. 5. izdanje. Beograd: Integra; 2009, 263-321.
2. Antman EM, Braunwald E. ST-Elevation Myocardial Infarction: Pathology, Pathophysiology, and Clinical Features. In: Libby P, Bonow RO, Mann DL, Zipes DP, Braunwald

E, editors. Braunwald´s Heart Disease A Textbook of Cardiovascular medicine. 8th ed. Saunders Elsevier; 2008, 1207-32.
3. Cannon CP, Braunwald E. Unstable and Non-ST Elevation Myocardial Infarction. In: Libby P, Bonow RO, Mann DL, Zipes DP, Braunwald E, editors. Braunwald´s Heart Disease A Textbook of Cardiovascular medicine. 8th ed. Saunders Elsevier; 2008, 1319-51.
4. Antman EM. ST-Elevation Myocardial Infarction: Management. In: Libby P, Bonow RO, Mann DL, Zipes DP, Braunwald E, editors. Braunwald´s Heart Disease A Textbook of Cardiovascular medicine. 8th ed. Saunders Elsevier; 2008, 1233-1300.
5. Michel T, Hoffman BB. Treatment of Miocardial Ischemia and Hypertension. In: Brunton LL. ed. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. McGraw-Hill Medical, 2011: 1237-1273.
6. Gruhn N, Boesgaard S, Eiberg J, Bang L, Thiis J, Schroeder TV, Aldershvile J. Effects of large conductance Ca(2+)-activated K(+) channels on nitroglycerin-mediated vasorelaxation in humans. Eur J Pharmacol. 2002;446:145-50.
7. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. The Heart. In: Rang and Dale's Pharmacology 7th ed, Elsevier, Edinburgh, 2012: 372-384.
8. Bøttcher M, Madsen MM, Randsbaek F, Refsgaard J, Dørup I, Sørensen K, Nielsen TT. Effect of oral nitroglycerin and cold stress on myocardial perfusion in areas subtended by stenosed and nonstenosed coronary arteries. Am J Cardiol. 2002;89:1019-24.
9. Martindale: The Complete Drug Reference, The Pharmaceutical Press, 2011, Electronic version.
10. Münzel T, Mülsch A, Kleschyov A. Mechanisms underlying nitroglycerin-induced superoxide production in platelets: some insight, more questions. Circulation. 2002;106:170-2.
11. Ivanović Lj. ur., Registar lekova 2012. BB Soft, Beograd, 2012.
12. British National Formulary (BNF), Number 61. British Medical Association and Royal Pharmaceutical Society of Great Britain. London; 2011.
13. Morrow DA, Gersh Bj. Chronic coronary artery disease. U: Braunwald´s Heart Disease A Textbook of Cardiovascular medicine. 8th ed. Saunders Elsevier, 2008: 1353-1417.
14. Jeserich M, Münzel T, Pape L, Fischer C, Drexler H, Just H. Absence of vascular tolerance in conductance vessels after 48 hours of intravenous nitroglycerin in patients with coronary artery disease. J Am Coll Cardiol. 1995;26:50-6.
15. Gori T, Parker JD. Nitrate-induced toxicity and preconditioning: a rationale for reconsidering the use of these drugs. J Am Coll Cardiol. 2008;52:251-4.
16. Müller S, Laber U, Müllenheim J, Meyer W, Kojda G. Preserved endothelial function after long-term eccentric isosorbide mononitrate despite moderate nitrate tolerance. J Am Coll Cardiol. 2003;41:1994-2000.
17. Hirai N, Kawano H, Yasue H, Shimomura H, Miyamoto S, Soejima H, Kajiwara I, Sakamoto T, Yoshimura M, Nakamura H, Yodoi J, Ogawa H. Attenuation of nitrate tolerance and oxidative stress by an angiotensin II receptor blocker in patients with coronary spastic angina. Circulation. 2003;108:1446-50.

18. Habbab MA, Haft JI. Heparin resistance induced by intravenous nitroglycerin. A word of caution when both drugs are used concomitantly. Arch Intern Med. 1987;147:857-60.
19. Bode V, Welzel D, Franz G, Polensky U. Absence of drug interaction between heparin and nitroglycerin. Randomized placebo-controlled crossover study. Arch Intern Med. 1990; 150:2117-9.
20. Nicolini FA, Ferrini D, Ottani F, Galvani M, Ronchi A, Behrens PH, Rusticali F, Mehta JL. Concurrent nitroglycerin therapy impairs tissue-type plasminogen activator-induced thrombolysis in patients with acute myocardial infarction. Am J Cardiol. 1994 Oct 1;74(7):662-6.
21. Romeo F, Rosano GM, Martuscelli E, De Luca F, Bianco C, Colistra C, Comito M, Cardona N, Miceli F, Rosano V, et al. Concurrent nitroglycerin administration reduces the efficacy of recombinant tissue-type plasminogen activator in patients with acute anterior wall myocardial infarction. Am Heart J. 1995 Oct;130(4):692-7.
22. Cheitlin MD, Hutter AM Jr, Brindis RG, Ganz P, Kaul S, Russell RO Jr, Zusman RM. Use of sildenafil (Viagra) in patients with cardiovascular disease. Technology and Practice Executive Committee. Circulation. 1999;99:168-77.
23. Yusuf S, Collins R, MacMahon S, Peto R. Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials. Lancet. 1988;1(8594):1088-92.
24. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet. 1994;343(8906):1115-22.
25. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Lancet. 1995; 345(8951):669-85.

ORGANIC NITRATES IN ACUTE CORONARY SYNDROME

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ABSTRACT

Large randomized trails have shown that routinely applied nitrates (iv or orally), in acute coronary syndrome (ACS) do not reduce significantly mortality. Nevertheless, nitrates still have a place in therapy of certain patients with ACS and they are effective in alleviating ischaemia. Nitroglycerin is indicated for the relief of persistent pain and as vasodilator in patients with acute myocardial infarction associated with left ventricular failure. However, in the absence of recurrent angina or congestive heart failure, we do not routinely prescribe them for patients with ACS. Patients with large transmural infarction particularly of the anterior wall, have the most to gain from nitrates in the light of reduction of ventricular remodeling. In such patients nitrates are given as intravenous infusion routinely for 24 to 48 hours. Nitrates should not prescribed beyond the first 48 hours, unless angina or ventricular failure is present.

Key words: acute coronary syndrome, organic nitrates, mechanisms of clinical effects

INTRODUCTION

Acute coronary syndrome (ACS) include 1. acute coronary syndrome with ST-elevation or acute myocardial infarction (AMI) with ST-elevation (STEMI) and high level of troponin, and 2. acute coronary syndrome without ST-elevation which involves unstable angina pectoris (UAP) (with negative troponin) and acute myocardial infarction (AMI) without ST-elevation (NSTEMI) (with slightly increased troponin). All of these presentations of ACS are usually caused by rupture of an atherosclerotic plaque in one of the coronary arteries. When plaque disruption occurs, a sufficient quantity of thrombogenic substances is exposed and subsequent thrombosis happens and leads to ischaemia. Treatment of all the types of ACS could involve organic nitrates.

Glyceryl trinitrate or nitroglycerin applied sublingually can be given safely to almost all patients with ACS, up to three doses at about 5-min intervals. After that sublingual application is not recommended. If there are no limitations, nitroglycerin should be continued intravenously (iv) during 24 to 48 hours in patients with AMI associated with left ventricular failure, large transmural infarctions especially of the anterior wall, or persisting ischaemia. Therapy with nitrates should be avoided in patients who present with low systolic arterial pressure (<90 mmHg), especially if accompanied by bradycardia (below 50 beats/min) or in whom there is clinical suspicion of right ventricular infarction. Large randomized trails have shown that routinely applied nitrates (iv or orally), in STEMI and UAP/NSTEMI do not reduce significantly mortality. Nevertheless, nitrates have the role in some special groups

of patients with ACS, because they reduce the ventricular filling pressure and cardiac work and improve the coronary blood flow, especially in ischemic zones, making improvement in clinical features.

1. MECHANISM OF ACTION OF ORGANIC NITRATES

Nitrates have the ability to cause vasodilatation, regardless of whether the endothelium is intact. After entering the vascular smooth muscle, nitroglycerin is converted to bioactive NO through the action of mitochondrial aldehyde dehydrogenase (reductase). NO activates soluble guanylyl cyclase (GC), which transforms guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). The second messenger cGMP activates phosphokinase G (PKG). Important target of this kinase is the myosin light-chain phosphatase. This phosphatase leads to dephosphorylation of the myosin light chain and thereby to reduction of cytoplasmatic calcium [Ca^{+2}] and promote smooth muscle vasorelaxation. Pharmacological and biochemical effects of nitrate vasodilators are identical as that of endothelium-derived relaxing factor (EDRF), which chemical structure is known to be a NO. Although many evidences support the release of NO – production of cGMP – reduction of cytoplasmatic calcium as a major cellular mechanism of action of nitrates, experimental data raised evidences that maybe it is not the only mechanism. In particular, the arterial vasodilatory effects of nitroglycerin in vitro is mediated at least in part by potassium channel-opening, which is activated by NO-cGMP (4,5,6).

Cardiovascular effects

The vasodilator effects of nitrates are evident in systemic (including coronary) arteries and veins, but they appear to be predominant in the venous circulation. This venodilatation decreases venous return, and ventricular preload and end-diastolic pressures and oxygen requirements. Arterial and arteriolar dilatations decrease resistance, and consequently reduce central (aortic) pressure and cardiac afterload. The action of nitrates facilitates heart work and decreases myocardial oxygen consumption (5,7).

Effects on the coronary circulation. Nitroglycerin causes dilatation of epicardial stenosis. These stenoses often due to eccentric lesions, and nitroglycerin causes relaxation of the smooth muscle in the wall of the coronary artery that is not encompassed by plaque. Even a small increase in a narrowed arterial lumen can produce a significant reduction in resistance to blood flow across obstructed regions. Nitrates may also decrease the vasoconstriction caused by endothelial dysfunction.

Nitroglycerin causes redistribution of blood flow from normally perfused to ischaemic areas, particularly in the subendocardium. This redistribution may be mediated in part by an increase in collateral blood flow and in part by lowering of ventricular diastolic pressure, thereby reducing subendocardial compression. Such redistribution of blood flow to subendocardium is not typical of all vasodilators (4,5,8).

Although nitroglycerin also increases cGMP in pletelets, which may contribute to its antiplatelet effect, this effect appears to be modest, and may be confounded by the potential

of nitrates to interact with heparin, reducing its anticoagulant effect. Clinical significance of this nitrate antipletelet activity is particularly unclear, in sight of recent clinical studies which established no survival benefit when nitrates are routinely used in AMI (9,10).

In summary, the antianginal action of nitrates involves:

- reduced cardiac oxygen consumption, because of reduced cardiac preload and afterload
- redistribution of coronary flow towards ischaemic areas via collaterals
- relief of coronary spasm (5,7).

2. PHARMACOKINETICS AND PHARMACEUTICAL ASPECTS OF ORGANIC NITRATES

Although more than 100 years passed until the first use of organic nitrates in treatment of angina pectoris, but still there is no agreement about their biotrasformation. Nitroglycerin is taken up by smooth muscle cells of blood vessels and the nitrate group is cleaved to NO

generic name	brand name	dosage form	dosage
Glyceryl Trinitrate	**Nirmin*, Nitrolingual**	*Sol. for inj.* 1 mg/1.6 ml* *Conc. for sol. for inf.* 5 mg/1.6 ml* *Subl. spray* 0.4 mg/dose	iv inj.: 1 mg during 3 min, repeated as required (max. 2 times), at 10 min intervals; iv inf. (after effect achieved by iv inj.): 0.01-0.2 mg/min (starting with 0.01-0.02 mg/min, and then increased in steps of 0.005-0.01 mg/min at intervals of 5-10 min, to appropriate response); subligually: spray dose, as needed (max. 3 doses at intervals of 3-5 min)
Pentaerythritol Tetranitrate	**Dilcoran 80, Lentonitrat* 50**	*Tabl. modif. release.* 80 mg *Caps. sustained release* 50 mg*	2 x 80 or 50* mg before meals (in the morning and then in the noon, no later than 16 h)
Isosorbide Dinitrate	**Cornilat*, Difutrat, Isosorb retard**	*Tabl.* 20 mg* *Caps. sustained release* 20 mg	40 mg daily in one or two doses, increased if necessary to 60-80 mg daily divided in two doses
Isosorbide Mononitrate	**Monizol, Monosan, Isocard***	*Tabl.* 20 and 40 mg *Caps. sustained release* 60 mg*	2 x 10 mg for patients not previously treated with nitrates; 1-2 x 20-40 mg (first dose in the morning and the second one 8 hours after), max. 120 mg daily divided in two or three doses * 1 x 60 mg, max. 1 x 120 mg daily
iv – intravenous			

Table 1*. Nitrates registered in the Serbian market (Drug Register, 2012)*

by mitochondrial aldehyde dehydrogenase (reductase). Glyceryl trinitrate also undergoes hydrolysis in plasma and is rapidly metabolized in the liver by glutathione reductase to less active metabolites, dinitrates and mononitrates. Therapeutic effect of nitroglycerin is apparent within 1-2 minutes after intravenous doses, and duration of action is 3-5 minutes, while therapeutic effects of nitroglycerin after sublingual tablets or sublingual spray administration are apparent within 1-3 minutes, and duration of action is 30-60 minutes. Nitroglycerin is also well absorbed through the skin. Therapeutic effect is apparent within 30-60 minutes of applying the transdermal patch or an ointment, while therapeutic effects last 24 hours after transdermal patch and up 8 hours after ointment. There are also nitrates for long-term management of stable angina pectoris in oral doses: isosorbide mononitrate, isosorbide dinitrate and pentaerithrityl tetranitrate. Nitrates registered in Serbia are shown in Table 1.

3. CONTRA-INDICATIONS OF ORGANIC NITRATES

Contra-indications for nitrates are: phosphodiesterase type-5 inhibitors during last 24 hours; hypotensive conditions and hypovolaemia; hypersensitivity to nitrates; hypertrophic cardiomyopathy; severe aortic stenosis; cardiac tamponade; constrictive pericarditis; mitral stenosis; head trauma; cerebral haemorrhage; and marked anaemia. When there is a suspicion of right ventricle infarction, nitrates are also contra-indicated (9,11,12).

4. ADVERSE EFFECTS OF ORGANIC NITRATES

The main adverse effects of nitrates are a direct consequence of their pharmacological actions. The most common adverse effects are: throbbing headache, postural hypotension, tachycardia (paradoxical bradycardia has also been observed), and dizziness; less commonly adverse effects are: nausea, vomiting, flushing, localized burning sensation (nitroglycerin, sublingual tablets), syncope, temporary hypoxaemia, rash, application site reactions with transdermal patches; very rarely: angle-closure glaucoma. Methemoglobinemia is a rare complication of very large doses of nitrates, commonly used doses of nitrates cause small elevations of methemoglobin levels that are probably not of clinical significance (9,12).

Tolerance to organic nitrates is particularly important in patients, with stable angina pectoris, who are on chronic therapy with long-lasting nitrates, as opposed to those receiving short-acting courses of nitrates (with UAP and AMI). Tolerance is the loss or attenuation of the antianginal effects of nitrates particularly if frequent or continuous dosing is used. Tolerance to intravenous nitroglicerin develops often in patients after prolonged iv infusion (5,12). Nitrate tolerance appears to be limited to the capacitance and resistance vessels and has not been noted in the large conductance vesels, including the epicardial coronary arteries, despite continuous administration of glyceryl trinitrate for 48 hours (13).

The mechanisms of nitrate tolerance are incompletely understood. Multiple mechanisms have been proposed to account for nitrate tolerance including: 1. neurohumoral activation (via increasing concentration of catecholamines, angiotensin II, vasopressin) including

volume expansion (via increasing of aldosteron); 2. generation of free radicals which impaired biotransformation of nitrates to NO; and 3. decreased end-organ responsiveness to NO. Evidence has supported the hypothesis that increased generation of vascular superoxide anion associated with vascular oxidative stress is central to the process. Glyceryl trinitrate stimulates production of superoxide anions which with NO form peroxynitrite that inhibits biotraformation of glyceryl trinitrate to NO. Multiple animal experiments have demonstrated that extended exposure to nitrates can impair endothelial-dependent vasodilatation through the generation of free radical species (12,14). However, in an animal model of hypercholesterolemia, large doses of a nitrate had endothelial protective effects and attenuated the increase in intima-media thickness. Long-term studies in humans are necessary to determine the clinical relevance of these findings (12,15).

The method most commonly used to avoid the development of nitrate tolerance is so called asymmetrical dosage. In this regimen of dosage, nitrate-free interval of 10-12 hours has been proposed (16). However, rebound myocardial ischaemia may occur during nitrate-free interval for oral long-lasting preparations, and may require the use of short-acting nitrate preparations. There are data that angiotensin receptor blockers (candesartan) may attenuate nitrate tolerance (17). Whether a nitrate–free interval is necessary for all patients is unknown as many patients using continuous nitrates do not show clinical tolerance.

5. INTERACTION WITH OTHER MEDICINAL PRODUCTS

The hypotensive effects of nitrates may be enhanced by alcohol, and by drugs with hypotensive actions.

Glyceryl trinitrate has been reported to reduce the activity of heparin when both drugs are given simultaneously by the intravenous route (18). However, no interaction is reported when glyceryl trinitrate is given immediately after heparin (19).

Although thrombolytics and nitrates are both frequently used in AMI it seems that the combination of alteplase and glyceryl trinitrate may impairs thrombolysis, which may be due to increased hepatic metabolism of alteplase as a result of glyceryl trinitrate effect of increasing hepatic blood flow (20, 21).

The concurrent use of nitrates and phosphodiesterase type-5 inhibitors such as sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra) which are used for erectile dysfunction is contra-indicated. Deaths due to significant potentiation of the vasodilator actions of nitrate by phosphodiesterase type-5 inhibitors, have been reported (22). A patient who receives nitrate should stop it at least approximately 24 hours prior to sildenafil, and other anti-anginal therapy should be used during this time period (such as β blockers).

6. CLINICAL USE OF NITRATES

An overview of studies carried out before reperfusion (thrombolysis or percutaneous coronary intervention, PCI) a meta analysis of 10 randomized trails of administration of intravenous glyceryl trinitrate or nitroprusside within 24 hours of the onset of pain,

collectively enrolled about 2.000 patients with AMI, showed a reduction in mortality of 35% associated with nitrate therapy. The greatest reduction in mortality occurred during the first week, with a non-significant further reduction after this early period (23).

In the reperfusion era, two megatrails of nitrate therapy in AMI have been conducted: GISSI-3 and ISIS-4. In GISSI-3 study, about 20.000 patients with AMI, given intravenously glyceryl trinitrate for the first 24 hours followed by transdermal glyceryl trinitrate during 6 weeks and 6 months, there was no effect of nitrate on mortality rate (24). Similarly, in ISIS-4, included about 58.000 patients with AMI, oral isosorbide mononitrate had no effect on 35-day mortality (25).

However, nitrates still have a place in therapy of certain patients with ACS and they are effective in alleviating ischaemia. The routine iv application of nitroglycerine is not warranted in cases of relatively mild myocardial infarction without ensuing complications. Some of the useful effects of nitrates can be abolished with increase in heart rate. To avoid this, the dosage of the administered nitrates should be adjusted and β blockers should be introduced. The starting dose of 5 -10 μg/min should be increased so that the decrease of pressure (systolic or mean arterial pressure) is not greater than 10% in normotensive and 10-15% in hypertensive patients. In either case, the systolic blood pressure must not be allowed to fall below 90 mmHg, and neither should the heart rate be allowed to increase by 20 beats/min (4). An unfavourable drop in blood pressure is observed in 10% of patients. In certain cases, as a result of the development of tolerance, the dosage of nitroglycerine has to be increased if an iv infusion is applied for more than 24 h.

7. INSTEAD OF THE CONCLUSION

Glyceryl trinitrate (nitroglycerine) is indicated for the relief of persistent pain and as vasodilator in patients with AMI associated with left ventricular failure. However, in the absence of recurrent angina or congestive heart failure, we do not routinely prescribe them for patients with ACS. Patients with large transmural infarction particularly of the anterior wall, have the most to gain from nitrates in the light of reduction of ventricular remodeling. In such patients nitrates are given as intravenous infusion routinely for 24 to 48 hours. Nitrates should not be prescribed beyond the first 48 hours, unless angina or ventricular failure is present (4). Long acting nitrates can be administered when the patient enters a stable phase post myocardial infarction.

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REFERENCES

1. Vasiljević Z. Akutni koronarni sindrom. U: Kažić T, Ostojić M, urednici. Klinička kardiovaskularna farmakologija. 5. izdanje. Beograd: Integra; 2009, 263-321.
2. Antman EM, Braunwald E. ST-Elevation Myocardial Infarction: Pathology, Pathophysiology, and Clinical Features. In: Libby P, Bonow RO, Mann DL, Zipes DP, Braunwald

E, editors. Braunwald´s Heart Disease A Textbook of Cardiovascular medicine. 8th ed. Saunders Elsevier; 2008, 1207-32.
3. Cannon CP, Braunwald E. Unstable and Non-ST Elevation Myocardial Infarction. In: Libby P, Bonow RO, Mann DL, Zipes DP, Braunwald E, editors. Braunwald´s Heart Disease A Textbook of Cardiovascular medicine. 8th ed. Saunders Elsevier; 2008, 1319-51.
4. Antman EM. ST-Elevation Myocardial Infarction: Management. In: Libby P, Bonow RO, Mann DL, Zipes DP, Braunwald E, editors. Braunwald´s Heart Disease A Textbook of Cardiovascular medicine. 8th ed. Saunders Elsevier; 2008, 1233-1300.
5. Michel T, Hoffman BB. Treatment of Miocardial Ischemia and Hypertension. In: Brunton LL. ed. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. McGraw-Hill Medical, 2011: 1237-1273.
6. Gruhn N, Boesgaard S, Eiberg J, Bang L, Thiis J, Schroeder TV, Aldershvile J. Effects of large conductance Ca(2+)-activated K(+) channels on nitroglycerin-mediated vasorelaxation in humans. Eur J Pharmacol. 2002;446:145-50.
7. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. The Heart. In: Rang and Dale's Pharmacology 7th ed, Elsevier, Edinburgh, 2012: 372-384.
8. Bøttcher M, Madsen MM, Randsbaek F, Refsgaard J, Dørup I, Sørensen K, Nielsen TT. Effect of oral nitroglycerin and cold stress on myocardial perfusion in areas subtended by stenosed and nonstenosed coronary arteries. Am J Cardiol. 2002;89:1019-24.
9. Martindale: The Complete Drug Reference, The Pharmaceutical Press, 2011, Electronic version.
10. Münzel T, Mülsch A, Kleschyov A. Mechanisms underlying nitroglycerin-induced superoxide production in platelets: some insight, more questions. Circulation. 2002;106:170-2.
11. Ivanović Lj. ur., Registar lekova 2012. BB Soft, Beograd, 2012.
12. British National Formulary (BNF), Number 61. British Medical Association and Royal Pharmaceutical Society of Great Britain. London; 2011.
13. Morrow DA, Gersh Bj. Chronic coronary artery disease. U: Braunwald´s Heart Disease A Textbook of Cardiovascular medicine. 8th ed. Saunders Elsevier, 2008: 1353-1417.
14. Jeserich M, Münzel T, Pape L, Fischer C, Drexler H, Just H. Absence of vascular tolerance in conductance vessels after 48 hours of intravenous nitroglycerin in patients with coronary artery disease. J Am Coll Cardiol. 1995;26:50-6.
15. Gori T, Parker JD. Nitrate-induced toxicity and preconditioning: a rationale for reconsidering the use of these drugs. J Am Coll Cardiol. 2008;52:251-4.
16. Müller S, Laber U, Müllenheim J, Meyer W, Kojda G. Preserved endothelial function after long-term eccentric isosorbide mononitrate despite moderate nitrate tolerance. J Am Coll Cardiol. 2003;41:1994-2000.
17. Hirai N, Kawano H, Yasue H, Shimomura H, Miyamoto S, Soejima H, Kajiwara I, Sakamoto T, Yoshimura M, Nakamura H, Yodoi J, Ogawa H. Attenuation of nitrate tolerance and oxidative stress by an angiotensin II receptor blocker in patients with coronary spastic angina. Circulation. 2003;108:1446-50.

18. Habbab MA, Haft JI. Heparin resistance induced by intravenous nitroglycerin. A word of caution when both drugs are used concomitantly. Arch Intern Med. 1987;147:857-60.
19. Bode V, Welzel D, Franz G, Polensky U. Absence of drug interaction between heparin and nitroglycerin. Randomized placebo-controlled crossover study. Arch Intern Med. 1990; 150:2117-9.
20. Nicolini FA, Ferrini D, Ottani F, Galvani M, Ronchi A, Behrens PH, Rusticali F, Mehta JL. Concurrent nitroglycerin therapy impairs tissue-type plasminogen activator-induced thrombolysis in patients with acute myocardial infarction. Am J Cardiol. 1994 Oct 1;74(7):662-6.
21. Romeo F, Rosano GM, Martuscelli E, De Luca F, Bianco C, Colistra C, Comito M, Cardona N, Miceli F, Rosano V, et al. Concurrent nitroglycerin administration reduces the efficacy of recombinant tissue-type plasminogen activator in patients with acute anterior wall myocardial infarction. Am Heart J. 1995 Oct;130(4):692-7.
22. Cheitlin MD, Hutter AM Jr, Brindis RG, Ganz P, Kaul S, Russell RO Jr, Zusman RM. Use of sildenafil (Viagra) in patients with cardiovascular disease. Technology and Practice Executive Committee. Circulation. 1999;99:168-77.
23. Yusuf S, Collins R, MacMahon S, Peto R. Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials. Lancet. 1988;1(8594):1088-92.
24. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet. 1994;343(8906):1115-22.
25. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Lancet. 1995; 345(8951):669-85.