Stručni rad / Professional article

Suvremeno liječenje arterijske hipertenzije telmisartanom

Contemporary management of hypertension with telmisartan

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SAŽETAK: Telmisartan je dugodjelujući, snažan, vrlo selektivan antagonist AT1 receptora angiotenzina II. Omogućuje precizniju i potpuniju blokadu djelovanja angiotenzina II od ACE inhibitora. Telmisartan je već etabliran kao učinkovit antihipertenzivni lijek s jednokratnim doziranjem koji se primjenjuje kod različitih skupina hipertenzivnih bolesnika. Dobro je podnošljiv i učinkovit antihipertenziv koji nudi potpunu 24-satnu kontrolu arterijskog tlaka čak i u slučaju izostanka doze. Iako je učinkovitost blokatora angiotenzinskih receptora (ARB) potvrđena u različitih tipova bolesnika, telmisartan je trenutno jedini ARB s jasnim dokazima i indikacijom za uporabu za smanjenje rizika od kardiovaskularnih događaja.

KLJUČNE RIJEČI: telmisartan, arterijska hipertenzija, arterijski tlak, antagonisti angiotenzinskih receptora, kardiovaskularne bolesti.

SUMMARY: Telmisartan is long-acting, potent, highly selective angiotensin II subtype 1 (AT1) receptor antagonist. It provides a more specific and complete blockade of the actions of angiotensin II than ACE inhibitors. Telmisartan has already been established as an effective once-daily blood-pressure-lowering drug in different types of patients. It is a well-tolerated and effective antihypertensive therapy, which offers full 24 h control of blood pressure even in the event of a missed dose. Nevertheless that the efficacy of angiotensin receptor blockers (ARBs) in different type of patients were confirmed, telmisartan is currently the only ARB with clear evidence and indication for usage in cardiovascular event risk reduction.

KEYWORDS: telmisartan, hypertension, blood pressure, angiotensin receptor antagonist, cardiovascular disease.

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Renin-angiotenzin sustav ima važnu ulogu u reguliranju kardiovaskularne homeostaze. Angiotenzin II uzrokuje vazokonstrikciju, smanjuje izlučivanje natrija i vode stimuliranjem izlučivanja aldosterona i olakšava simpatičku aktivnost. Svi ovi učinci povećavaju arterijski tlak (AT).

Pojedini blokatori angiotenzinskih receptora (ARB) razlikuju se međusobno u topljivosti lipida, distribuciji, bioraspoloživosti, biotransformaciji, poluživotu plazme i eliminaciji. Svi ovi čimbenici pridonose razlikama u trajanju njihovog djelovanja te utječu na njihove fiziološke rezultate. Telmisartan ima i jedinstvena farmakološka svojstva.[1-3] Vrlo je lipofilan i ima brzu kinetiku propusnosti membrane, što olakšava distribuciju u tkiva. Telmisartan se gotovo u cijelosti razgrađuje u jetri, ne metabolizira se sustavom citokroma P450 i dobro se podnosi kada se koristi u kombinaciji s drugim često korištenim lijekovima. Nije potrebna nikakva prilagodba doze ovisno o spolu, dobi ili bubrežnoj insuficijenciji. Telmisartan se može uzeti neovisno o obroku.[3,4]

Nakon početne brze apsorpcije, telmisartan se polako se eliminira sa prosječnim krajnjim poluživotom eliminacije od približno 24 sata.[5] To je najdulji poluživot među svim ARB do-

The renin-angiotensin system plays an important role in the regulation of cardiovascular homeostasis. Angiotensin II causes vasoconstriction, decreases sodium and water excretion via stimulation of the secretion of aldosterone and facilitates sympathetic activity. All of these effects increase blood pressure.

Differences between angiotensin receptor blockers (ARBs) are responsible for variations in lipid solubility, distribution, bioavailability, biotransformation, plasma half-life and elimination. All of these factors contribute to differences in their duration of action and, therefore, affect their physiological effects. Telmisartan has s unique pharmacological properties.[1-3] It is highly lipophilic and has rapid membrane permeability kinetics. These properties facilitate easy distribution into tissue. Telmisartan is cleared almost entirely by the liver and it is not metabolized by the cytochrome P450 system and is therefore well tolerated when used in combination with other commonly used medications. No dosage adjustment based on gender, age or in case of renal insufficiency is required. Telmisartan can be taken with or without food.[3,4]

After the initial rapid absorption telmisartan is slowly eliminated, with a mean terminal elimination half-life of approximately 24 hours.[5] This is the longest half-life of any of the

stupnim za liječenje arterijske hipertenzije.[3] Korist od dugotrajnog djelovanja telmisartana je očit nakon propuštene doze. Ranojutarnje povišenje vrijednosti AT i 24-satni srednji AT je povezan s oštećenjem ciljnog organa i kardiovaskularnim događajima. Antihipertenzivi bi trebali održavati kontrolu AT, osobito u posljednjih 6 sati intervala doziranja ili ako je doziranje propušteno. Zbog duljeg poluživota, telmisartan pruža neprekidnu i kontinuiranu kontrolu vrijednosti AT. Djelovanje telmisartana preneseno iz prethodne doze nastavlja se i nakon 24-satnog intervala doziranja. Štoviše, telmisartan pruža 48-satnu zaštitu od gubitka kontrole AT usprkos propuštene doze, pruža dodatnu sigurnost za bolesnike koji povremeno moguće zaborave uzeti svoj lijek.[6]

Djelotvornost telmisartana je analizirana je u mnogim kliničkim ispitivanjima u širokom spektru hipertenzivnih bolesnika.[7] Telmisartan do 160 mg jednom dnevno je konstantno smanjivao sistolički arterijski tlak (SAT)u ležećem položaju i dijastolički arterijski tlak (DAT) ($p \geq 0,05$) u većoj mjeri od placeba u najnižoj razini ili tijekom 24-satnog intervala doziranja. Doze iznad 80 mg jednom dnevno nisu rezultirale daljnjim smanjenjem AT u bolesnika s blagom do umjerenom hipertenzijom. Osim placebom kontroliranih ispitivanja, telmisartan je uspoređen s ACE inhibitorima, sartanima, beta-blokatorima i blokatorima kalcijevih kanala. U tim studijama većina bolesnika je liječena od blage do umjerene hipertenzije. Rezultati kliničkih ispitivanja pokazuju da telmisartan obično smanjuje AT nakon prve doze, a postoji postupno povećanje antihipertenzivnog učinka za do 12 tjedana tijekom nastavka liječenja, s najvećim smanjenjem AT koji se dogodi tijekom prva 4 tjedna.[7]

Kao i svi lijekovi iz skupine ARB, telmisartan nema utjecaja na metabolizam bradikinina.[8] Komparativnim kliničkim ispitivanjima s ACE inhibitorima, primjerice s lizinoprilom, pokazalo se usporedivo smanjenje AT. Iako se obje terapije općenito dobro podnose, značajno manji broj liječenih telmisartanom je imao kašalj povezan s lijekovima, u odnosu na lizinopril (3% u odnosu na 7%, $p = 0,018$).[9]

Utjecaj promjene terapije kod bolesnika koji su ranije imali suhi kašalj na ACE inhibitor enalapril u telmisartanu je također pokazao smanjen rizik od kašlja.[10]

Telmisartan je uspoređen s ramiprilom u širokom presjeku bolesnika s povećanim kardiovaskularnim rizikom. U kliničkoj studiji ONTARGET dokazano je da je telmisartan jednako učinkovit kao i ramipril u smanjenju kardiovaskularnih događaja kod različitih skupina rizičnih kardiovaskularnih bolesnika, ali se bolje podnosi.[11]

Telmisartan smanjuje kardiovaskularni rizik ne samo smanjenjem vrijednosti AT, nego i smanjenjem drugih metaboličkih parametara koji imaju blagotvoran učinak na kardiovaskularnu bolest.[12] U terapijskim dozama telmisartan također ima PPAR (peroksisom proliferator aktiviranog receptora) — sposobnost djelovanja, a što se ne može vidjeti s drugim ARB.[3,13] To uzrokuje povoljne učinke na metabolizam glukoze i lipida, a koji bi mogli biti korisni u bolesnika s hipertenzijom i metaboličkim poremećajima.[3,14] Telmisartan je dosad jedini ARB s kliničkim dokazima i indikacijom smanjenja rizika od kardiovaskularnih događaja.[2,15]

U rujnu 2013. Krka se pohvalila svojim ARB portfeljem u Hrvatskoj s novim sartanom, telmisartanom pod nazivom Tolura® u dozama od 40 mg i 80 mg koji pruža fleksibilno i učinkovito liječenje hipertenzije među hrvatskim bolesnicima. Tolura® je indiciran za liječenje hipertenzije i kardiovaskularnu prevenciju — smanjenje kardiovaskularnog pobola u bolesnika s izraženom aterotrombotskom kardiovaskularnom bolešću (anamneza koronarne bolesti srca ili bolesti

ARB available for the treatment of hypertension.[3] The benefit of the long duration of action of telmisartan is apparent after a missed dose. Early morning blood pressure (BP) surge and 24h-mean BP is linked to target-organ damage and cardiovascular events. Antihypertensive agents should sustain BP control, particularly in the last 6 h of the dosing interval or if dosing is missed. Due to its longer half-life, telmisartan provides consistent and sustained control of blood pressure.The activity of telmisartan is carried over from the previous dose and activity persists beyond the 24 h dosing interval. Moreover, telmisartan provides 48 h protection against loss of BP control following a missed dose, providing extra reassurance for patients who might occasionally forget to take their medication.[6]

The efficacy of telmisartan has been evaluated in many clinical trials in broad spectrum of hypertensive patients.[7] Telmisartan up to 160 mg once daily consistently reduced supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) ($p \geq 0.05$) to greater extent than placebo at trough or throughout the 24-hour dosage interval. Dosages above 80 mg once daily did not result in further BP reduction in patients with mild to moderate hypertension In addition to placebo controlled trials, telmisartan has been examined with the ACE inhibitors, the ARBs, the beta-blockers and the calcium channel blockers. In these studies, most patients were treated for mild-to-moderate hypertension. The results of clinical studies show that telmisartan typically reduces BP after the first dose, and there is a gradual increase in its antihypertensive effect for up to 12 weeks during continued treatment, with most of the BP reduction occurring during the first 4 weeks.[7]

Like all ARBs telmisartan has no effect on bradykinin metabolism.[8] Comparative clinical trials with ACE inhibitors, for instance lisinopril showed comparable reduction of BP. Although both treatments were generally well tolerated, significantly fewer patients receiving telmisartan experienced treatment-related cough compared with lisinopril (3% vs. 7%; $p=0.018$).[9]

The impact of switching patients who had previously experienced dry cough with the ACE inhibitor enalapril to telmisartan, also showed reduced risk of cough.[10]

Telmisartan has been compared with ramipril in a broad cross-section of patients at increased cardiovascular risk. In the ONTARGET clinical study it was demonstrated that telmisartan is as effective as ramipril in reducing cardiovascular events in a wide cross-section of at-risk cardiovascular patients, but it was better tolerated.[11]

Telmisartan reduces CV risk not only by reducing the BP, but also by reducing other metabolic parameters which has beneficial effect on CV disease.[12] At the therapeutic doses telmisartan also exerts PPAR (peroxisome proliferator-activated receptor) — activating ability, which cannot be seen with other ARBs.[3,13] This causes favourable effects on glucose and lipid metabolism, which could be benefitial in patients with hypertension and metabolic disturbances.[3,14] Telmisartan is so far the only ARB with clinical evidence and indication of cardiovascular event risk reduction.[2,15]

In September 2013 Krka has complimented its ARBs portfolio in Croatia with a new sartan, telmisartan named Tolura® in dosages of 40 mg and 80mg, providing flexible and effective treatment of hypertension among the Croatian patients. Tolura® is indicated for the treatment of hypertension and cardiovascular prevention — reduction of cardiovascular morbidity in patients with manifest atherothrombotic cardiovascular disease (history of coronary heart disease or pe-

perifernih arterija) ili dijabetesa mellitusa tipa 2 s dokumentiranim oštećenjem ciljnih organa.

ripheral arterial disease) or type 2 diabetes mellitus with documented target organ damage.

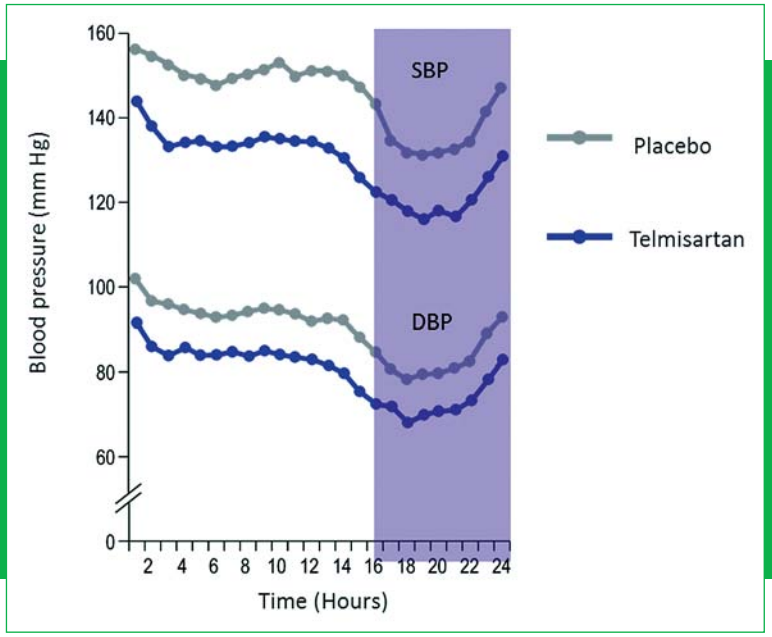

Figure 1.
Mean hourly systolic (SBP) and diastolic (DBP) ambulatory blood pressure after 12 weeks of treatment with telmisartan. Adapted from Lacourciere Y, Lenis J, Orchard J, et al. Blood Pressure. 1998;3:295-302.

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