Stručni rad / Professional article

Suvremeno liječenje arterijske hipertenzije fiksnom kombinacijom telmisartan-hidroklorotiazid

Contemporary treatment of hypertension by fixed-dose combination of telmisartan-hydrochlorothiazide

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SAŽETAK: Fiksna kombinacija telmisartana i hidroklorotiazida predstavlja još jednu suvremenu mogućnost učinkovitog liječenja arterijske hipertenzije. To je kombinacija antagonista receptora angiotenzina II, telmisartana i tijazidskog diuretika, hidroklorotiazida. Telmisartan smanjuje kardiovaskularni rizik ne samo smanjenjem vrijednosti arterijskog tlaka (AT), nego i smanjenjem drugih metaboličkih parametara koji imaju pozitivan učinak na srčanožilne bolesti, primjerice selektivna modulacija PPAR-γ. Hidroklorotiazid ima učinak na renalne tubularne mehanizme reapsorpcije elektrolita, izravno povećavajući ekskreciju natrija i klorida u približno jednakim količinama. Različite kombinacije telmisartana i hidroklorotiazida (40/12,5; 80/12,5 i 80/25 mg) se primjenjuju u liječenju arterijske hipertenzije odraslih osoba čiji AT nije dobro kontroliran uz primjenu samog telmisartana ili kod bolesnika koji su prethodno stabilizirani telmisartanom i hidroklorotiazidom davanim zasebno.

KLJUČNE RIJEČI: telmisartan, hidroklorotiazid, arterijska hipertenzija, arterijski tlak, kardiovaskularni rizik.

SUMMARY: Fixed-dose combination of telmisartan and hydrochlorothiazide is another contemporary option of effective treatment of hypertension. It is a combination of an angiotensin II receptor blocker, telmisartan and thiazide diuretic, hydrochlorothiazide. Telmisartan reduces cardiovascular risk not only by reducing blood pressure (BP), but also by reducing other metabolic parameters that have a positive effect on cardiovascular diseases, especially selective modulation of PPAR-γ. Hydrochlorothiazide has an effect on the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equal amounts. Different combinations of telmisartan and hydrochlorothiazide (40/12,5; 80/12,5 and 80/25 mg) are used in the treatment of hypertension in adults whose BP is not well controlled by using telmisartan alone or in patients who have been previously stabilized by telmisartan and hydrochlorothiazide administered separately.

KEYWORDS: telmisartan, hydrochlorothiazide, hypertension, blood pressure, cardiovascular risk.

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Fiksna kombinacija telmisartana i hidroklorotiazida predstavlja još jednu suvremenu mogućnost učinkovitog liječenja arterijske hipertenzije.[1] To je kombinacija antagonista receptora angiotenzina II, telmisartana i tijazidskog diuretika, hidroklorotiazida. Obje tvari pomažu u kontroli povišenog arterijskog tlaka (AT).

Telmisartan pripada skupini lijekova koji se nazivaju antagonisti receptora angiotenzina II. Angiotenzin II je tvar koja se proizvodi u organizmu, a dovodi do sužavanja krvnih žila i na taj način povišenja AT. Telmisartan blokira učinak angiotenzina II tako što opušta krvne žile i snižava AT. Hidroklortiazid pripada skupini lijekova koji se nazivaju tijazidski diuretici koji uzrokuju povećano izlučivanje urina, što također dovodi do snižavanja AT.

Kombinacija ovih sastojaka ima aditivni antihipertenzivni učinak koji snižava AT u većoj mjeri nego što to čini svaka

Fixed-dose combination of telmisartan and hydrochlorothiazide is another contemporary option of effective treatment of hypertension.[1] It is a combination of an angiotensin II receptor blocker, telmisartan and thiazide diuretic, hydrochlorothiazide. The both substances help to control high blood pressure (BP).

Telmisartan belongs to a group of angiotensin II receptor blockers. Angiotensin II is a substance produced in the body, leading to the narrowing of the blood vessels, thereby elevating BP. Telmisartan blocks the effect of angiotensin II so that it relaxes blood vessels and lowers BP. Hydrochlorothiazide belongs to a group of thiazide diuretics, which cause increased urine output, which also leads to lowering BP.

The combination of these ingredients has an additive antihypertensive effect, which lowers BP to a greater extent than what every component does separately. Dosing once a day

od komponenti zasebno. Doziranje jedanput dnevno dovodi do učinkovitog i ujednačenog sniženja AT u rasponu terapijskih doza.

Telmisartan je dugotrajno oralno učinkovit i specifičan jaki antagonist receptora angiotenzina II (AT1) pri čemu ne pokazuje parcijalnu agonističku aktivnost na AT receptore. On ne pokazuje niti afinitet za druge receptore, uključujući AT2 i druge manje karakteristične AT receptore. Vrijednosti aldosterona u plazmi se smanjuju uzimanjem telmisartana. Telmisartan ne inhibira renin u ljudskoj plazmi niti blokira ionske kanale. Također on ne inhibira enzim koji pretvara angiotenzin (kininaza II), pa ne dolazi do degradiranja bradikinina i sukladno tome nema pojačavanja nuspojava posredovanih bradikininom. Učestalost suhog kašlja je znatno niža kod bolesnika liječenih telmisartanom nego kod onih kojima su davani inhibitori angiotenzin konvertirajućeg enzima, sukladno rezultatima kliničkih ispitivanja koja izravno uspoređuju ova dva antihipertenzivna liječenja.[2,3]

Doza od 80 mg telmisartana primjenjena u zdravih pojedinaca gotovo u potpunosti inhibira povišenje AT uzrokovano angiotenzinom II. Inhibitorski učinak se održava tijekom 24 sata i može se objektivizirati i do 48 sati. Nakon prve doze telmisartana, antihipertenzivna aktivnost postupno postaje vidljiva unutar 3 sata. Maksimalno smanjenje AT se općenito postiže za 4-8 tjedana nakon početka liječenja te se održava tijekom dugotrajnog liječenja. Antihipertenzivni učinak zadržava se neprekidno tijekom 24 sata nakon doziranja te uključuje posljednja 4 sata prije sljedeće doze, kao što je pokazano kontinuiranim mjerenjima AT.

Kod bolesnika s hipertenzijom telmisartan snižava sistolički i dijastolički AT bez utjecaja na srčanu frekvenciju. Antihipertenzivna djelotvornost telmisartana usporediva je s djelotvornošću antihipertenziva koji spadaju u druge skupine primjerice s amlodipinom (blokator kalcijskih kanala), atenololom (blokator beta-receptora), enalaprilom (ACE inhibitor) ili hidroklorotiazidom (tijazidski diuretik).[4] Nakon naglog prekida liječenja telmisartanom AT se postupno vraća na vrijednosti prije liječenja tijekom perioda od nekoliko dana, bez objektivizacije tzv. naglog povratnog fenomena visokog AT. U kliničkoj studiji ONTARGET dokazano je da je telmisartan jednako učinkovit kao i ramipril u smanjenju kardiovaskularnih događaja kod različitih skupina rizičnih krvožilnih bolesnika, uz bolju podnošljivost.[5]

Telmisartan smanjuje kardiovaskularni rizik ne samo smanjenjem vrijednosti AT, nego i smanjenjem drugih metaboličkih parametara koji imaju pozitivan učinak na srčanožilne bolesti, primjerice selektivnu modulaciju PPAR-γ. To podrazumijeva sposobnost aktivacije ovog intracelularnog receptora koji je glavni regulator metabolizma lipida i ugljikohidrata odnosno regulator diferencijacije masnih stanica što ga čini jedinstvenim unutar skupine ARB. Aktivatori PPAR-γ imaju antiinflamacijske, antioksidativne i antiproliferatorne učinke na vaskularne stanice. To uzrokuje boljitak učinka na metabolizam glukoze i lipida, što je posebice korisno kod bolesnika s arterijskom hipertenzijom i/ili metaboličkim sindromom odnosno u procesu smanjenja rizika od ateroskleroze.[6] Telmisartan je jedini ARB s indikacijom smanjenja rizika od krvožilnih događaja.

Hidroklorotiazid je tijazidski diuretik. Tijazidi imaju učinak na renalne tubularne mehanizme reapsorpcije elektrolita, izravno povećavajući ekskreciju natrija i klorida u približno jednakim količinama. Diuretsko djelovanje hidroklorotiazida reducira volumen plazme, povećava aktivnost renina u plazmi, povećava sekreciju aldosterona s posljedičnim povećanjem gubitka kalija i bikarbonata urinom te smanjenjem kalija u

leads to an efficient and uniform BP reduction in the therapeutic dose range.

Telmisartan is a long-term orally efficient and specific potent antagonist of the angiotensin II receptor (AT1) where it does not show partial agonist activity on the AT receptors. It shows no affinity for other receptors, including AT2 and other less characterized AT receptors. Aldosterone levels in plasma are reduced by taking telmisartan. Telmisartan neither inhibits renin in human plasma nor does it block ion channels. Also it does not inhibit angiotensin converting enzyme (kininase II), so no degradation of bradykinin is caused, and accordingly there is no enhancement of side effects mediated by bradykinin. The incidence of dry cough was significantly lower in patients treated with telmisartan than in those who were administered angiotensin converting enzyme according to the results of clinical trials that directly compare these two antihypertensive treatment methods.[2,3]

Dose of 80 mg of telmisartan administered to healthy volunteers almost completely inhibit BP elevation caused by angiotensin II. The inhibitory effect is maintained during 24 hours and can be objectified up to 48 hours. After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction of BP is generally achieved in 4-8 weeks after the start of treatment and is maintained during long-term treatment. The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose, as shown by continuous measurements of BP.

Telmisartan reduces systolic and diastolic BP in patients with hypertension without affecting the heart rate. Antihypertensive efficacy of telmisartan is comparable to the efficacy of antihypertensive agents that belong to some other groups for instance with amlodipine (calcium channel blocker), atenolol (beta-receptor blocker), enalapril (ACE inhibitor) or hydrochlorothiazide (thiazide diuretic).[4] Following abrupt cessation of the treatment with telmisartan, BP gradually returns to the pre-treatment values over a period of several days, without the objectification of the so-called rapid return of the phenomenon of high BP. The clinical study ONTARGET demonstrated that telmisartan is as efficient as ramipril in reducing cardiovascular events in different groups of high-risk cardiovascular patients with better tolerability.[5]

Telmisartan reduces cardiovascular risk not only by reducing blood pressure (BP), but also by reducing other metabolic parameters that have a positive effect on cardiovascular diseases, especially selective modulation of PPAR-γ. This implies the ability of activation of this intracellular receptor which is a major regulator of lipid and carbohydrate metabolism, that is, the regulator of differentiation of fat cells which makes it unique within the ARB group. Activators of PPAR-γ have antiinflammatory, antioxidant and antiproliferative effects on vascular cells. This causes the benefit of effect on glucose and lipid metabolism, which is especially useful in patients with arterial hypertension and/or metabolic syndrome or in the process of reducing the risk of atherosclerosis.[6] Telmisartan is the only ARB with an indication of reducing the risk of cardiovascular events.

Hydrochlorothiazide is a thiazide diuretic. Hydrochlorothiazide drugs have an effect on the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equal amounts. Diuretic action of hydrochlorothiazide reduces plasma volume, increases the renin activity in plasma, increases aldosterone secretion with consequential increase in the loss of potassium and bicarbonate in urine and decrease in potassium in

serumu. Pretpostavlja se da putem blokade sustava renin-angiotenzin-aldosteron istodobna primjena telmisartana ima tendenciju poništavanja gubitka kalija povezanog s tijazidnim diureticima. Uz hidroklorotiazid početak diureze javlja se za oko 2 sata, a vršni učinak pojavljuje se nakon otprilike 4 sata, dok se djelovanje zadržava oko 6-12 sati. Epidemiološke studije pokazale su da dugotrajno liječenje hidroklorotiazidom reducira rizik od kardiovaskularne smrtnosti i morbiditeta.

serum. The presumption is that by the renin-angiotensin-aldosterone blocking, the concomitant use of telmisartan has a tendency to annul the potassium loss associated with the thiazide diuretics. With hydrochlorothiazide, the onset of diuresis occurs in about 2 hours, and the peak effect occurs after approximately 4 hours, while the action persists for approximately 6-12 hours. Epidemiological studies have shown that long-term treatment by hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

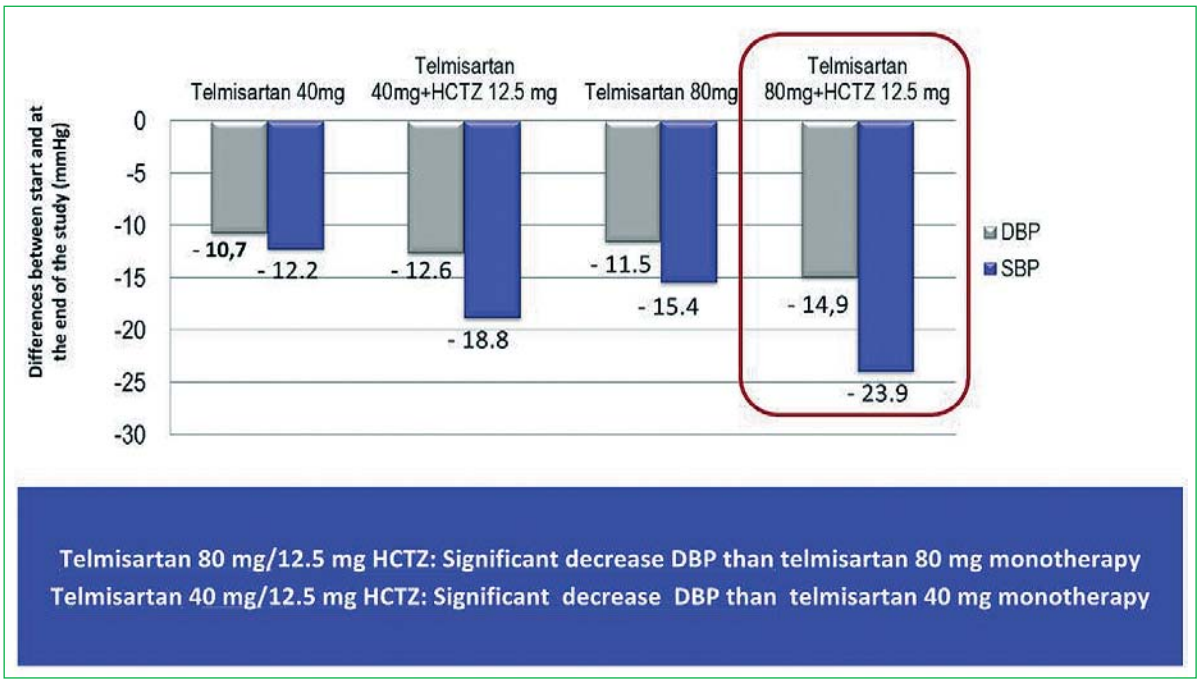

Figure 1. *Combination of telmisartan/hydrochlorothiazide gives the better antihypertensive effect than monotherapy.*

Kombinacija telmisartana i hidroklorotiazida (40/12,5; 80/12,5 i 80/25mg) se primjenjuje u liječenju esencijalne hipertenzije) kod odraslih osoba čiji AT nije dobro kontroliran uz primjenu samog telmisartana ili kod bolesnika koji su prethodno stabilizirani telmisartanom i hidroklorotiazidom davanim zasebno.[7]

Nakon intravenske i peroralne primjene 14C označenog telmisartana većina primijenjene doze (>97 %) eliminira se fecesom putem bilijarne ekskrecije. Samo su minorne količine pronađene u urinu. Ukupni plazmatski klirens telmisartana nakon peroralne primjene je >1.500 ml/min. Poluvrijeme eliminacije je >20 sati. Hidroklorotiazid se izlučuje gotovo u potpunosti u nepromijenjenom obliku putem urina. Oko 60% oralne doze se eliminira unutar 48 sati. Renalni klirens je oko 250-300 ml/min. Poluvrijeme eliminacije hidroklorotiazida je 10-15 sati. Koncentracije telmisartana u plazmi su općenito 2-3 puta veće kod žena nego kod muškaraca. Međutim, u kliničkim ispitivanjima nisu pronađena značajna povećanja u odgovoru AT ili incidenciji ortostatske hipotenzije kod žena.[8] Nije potrebno prilagođavanje doze. Postojao je trend prema većim koncetracijama hidroklorotiazida u plazmi kod žena nego kod muškaraca što se ne smatra klinički značajnim.

U dvostruko-slijepom kontroliranom kliničkom ispitivanju (djelotvornost ocjenjivana na n = 687 bolesnika) kod osoba koje nisu reagirale na kombinaciju 80 mg / 12,5 mg, pokazao se inkrementalni učinak snižavanja AT kombinacije 80

Different combinations of telmisartan and hydrochlorothiazide (40/12.5; 80/12.5 and 80/25 mg) are used in the treatment of essential hypertension) in adults whose BP is not well controlled by using telmisartan alone or in patients who have been previously stabilized by telmisartan and hydrochlorothiazide administered separately.[7]

After intravenous or oral administration of 14C labeled telmisartan most of the administered dose (>97%) is eliminated by the faeces by biliary excretion. Only minor amounts were found in urine. Total plasma clearance of telmisartan after oral administration is >1,500 ml/min. Elimination half-life is >20 hours. Hydrochlorothiazide is excreted almost entirely in unchanged form in the urine. About 60% of the oral dose is eliminated within 48 hours. Renal clearance is about 250-300 ml/min. Elimination half-life of hydrochlorothiazide is 10-15 hours. The concentrations of telmisartan in plasma are generally 2-3 times higher in women than in men. However, clinical studies have not found significant increases in response to BP or the incidence of orthostatic hypotension in women.[8] No dosage adjustment is necessary. There was a trend toward higher concentrations of hydrochlorothiazide in plasma in women than in men, which is not considered clinically significant.

Double-blind controlled clinical trial (efficacy was evaluated on n = 687 patients) in persons who have not responded to the 80/12.5 mg combination, showed the incremental effect of lowering BP by 80/25 mg combination compared to con-

mg / 25 mg u odnosu na stalno liječenje s kombinacijom 80 mg / 12,5 mg, u vrijednosti 2,7/1,6 mmHg (SKT/DKT) (razlika u prilagođenim prosječnim promjenama u odnosu na početnu vrijednost). U ispitivanju praćenja, s kombinacijom 80 mg / 25 mg, AT se nastavio snižavati (što je rezultiralo ukupnim smanjenjem od 11,5/9,9 mmHg (SKT/DKT).[9]

Telmisartan i kombinacija telmisartan/hidroklorotiazid imaju niski potencijal za interakcije s drugim lijekovima. Telmisartran se ne metabolizira putem citokromskog P 450 sustava, dok se hidroklorotiazid poglavito ne metabolizira i gotovo u potpunosti se izlučuje putem bubrega u obliku nepromijenjene tvari.[8]

U konačnici možemo kazati da na hrvatsko tržište u portfelju Krke dolazi još jedna dobra nova vijest, spomenuta kombinacija telmisartana i hidroklorotiazida, pod nazivom Tolucombi® i to u tri doze u rasponu od 40/12,5 mg, preko 80/12,5 mg do 80/25 mg od kojih se može očekivati učinkovito liječenje arterijske hipertenzije.

tinuous treatment with 80/12.5 mg combination, evaluated at 2.7/1.6 mmHg (SBP/DBP) (difference in adjusted mean changes compared to the baseline). BP continued to be lowered in follow-up by the 80/25 mg combination (which resulted in a total reduction of 11.5/9.9 mmHg (SBP/DBP).[9]

Telmisartan and the telmisartan/hydrochlorothiazide combination have a low potential for interactions with other drugs. Telmisartran is not metabolized via cytochrome P 450 system, while hydrochlorothiazide is particularly not metabolized and is almost completely excreted by the kidneys in the form of an unchanged substance.[8]

In the end we can say that there is another good news that comes to the Croatian market, namely, the above mentioned telmisartan and hydrochlorothiazide combination, called Tolucombi® in three doses in the range of 40/12.5 mg, via 80/12.5 mg to 80/25 mg which can be expected to efficiently treat hypertension.

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