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# Terapijski profil valsartana

# Therapeutic profile of valsartan

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***SAŽETAK:*** *Valsartan ima dobar antihipertenzivni učinak u svih skupina pacijenata bez obzira na dob, spol i rasu. Učestalost nuspojava se ne razlikuje od placeba. Djelovanje lijeka putem AT1 receptora pokazuje nesavladivi antagonizam koji je povezan s dugotrajnim učinkom. Studije bioekvivalencije su potvrdile da je terapijski profil Krkinog valsartana (Valsacor®) jednak originatoru.*

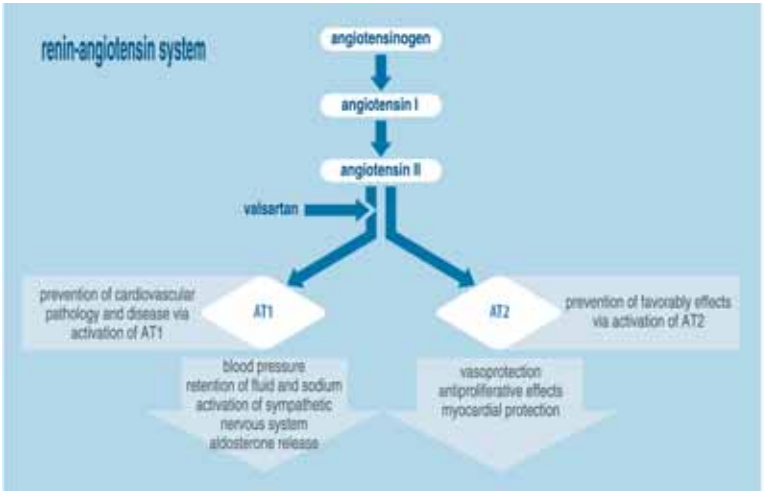
***KLJUČNE RIJEČI:*** *valsartan, arterijska hipertenzija, arterijski tlak.*

***ABSTRACT:*** *Valsartan has been found to have good antihypertensive effect in all patient populations, irrespective of age, sex, and race. It has a side-effect profile indistinguishable from that of placebo. Its action at the AT1 receptor displays insurmountable antagonism, which is associated with a long duration of action. Bioequivalence studies proved that therapeutic profile of Krka's valsartan (Valsacor®) is equivalent to originator.*

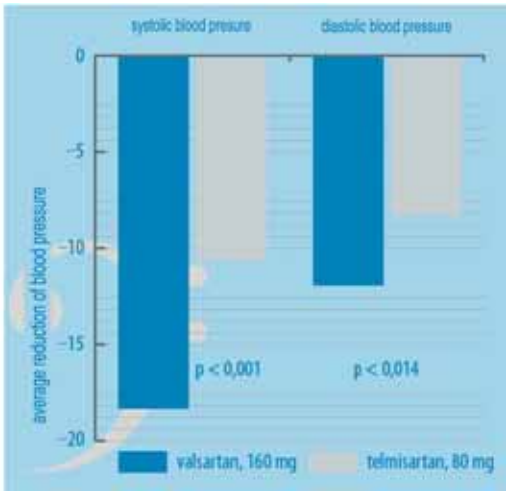
***KEYWORDS:*** *valsartan, hypertension, blood pressure.*

Valsartan predstavlja snažan i visoko selektivni blokator angiotenzin II receptora (ARB). Blokiranjem učinaka angiotenzina II nastalog u sustavu renin-angiotenzin na AT1 receptoru (**Slika 1**), valsartan kontrolira ponovnu apsorpciju natrija, sekreciju aldosterona, vazokonstrikciju i aktivaciju simpatičkog živčanog sustava, što sve može dovesti do povišenja arterijskog tlaka (AT). In vitro, valsartan pokazuje sklonost prema AT1 receptoru 20.000 puta više nego što ima sklonost prema AT2 receptoru. Nepostojanje djelovanja na AT2 receptoru predstavlja prednost, obzirom da taj receptor posreduje u inhibiciji rasta, apoptozi i vazodilataciji[1-4].

Valsartan is a powerful and highly selective angiotensin II receptor blocker (ARB). By blocking the binding of angiotensin II produced by the renin-angiotensin system at the AT1 receptor (**Picture 1**), valsartan controls sodium reabsorption, aldosterone release, vasoconstriction, and activation of the sympathetic nervous system, all of which can increase blood pressure (BP). In vitro, valsartan has an affinity for the AT1 receptor 20,000 times that of its affinity for the AT2 receptor. The lack of action at the AT2 receptor may be an advantage because this receptor appears to mediate growth inhibition, apoptosis and vasodilatation[1-4].




***Picture 1.*** *Valsartan action mechanism.*




***Picture 2.*** *Comparison of efficiency of valsartan and telmisartan (according to the literature reference 14).*

Valsartan je učinkovit antihipertenziv. Brojna klinička ispitivanja su dokazala statistički i klinički značajan antihipertenzivni učinak koji se dugoročno dobro održava i povezan je s kontrolom vrijednosti AT tijekom 24 sata uz primjenu jedne dnevne doze. Tipične nuspojave antihipertenziva, poput glavobolje, vrtoglavice i umora, nisu bile češće kod primjene valsartana u odnosu na placebo[5-7].

Dokazano je da valsartan sprječava kardiovaskularni pobol i smrtnost te da ima dodatne prednosti osim sniženja vrijednosti AT. Različita klinička ispitivanja, koja su

Valsartan is an effective antihypertensive agent. Numerous clinical trials have shown statistically and clinically significant antihypertensive effects that is well maintained in the long term and is associated with BP control over 24 hours after once daily dosing. Typical adverse events reported with antihypertensive drugs such as headache, dizziness, and fatigue were no more frequent with valsartan than with placebo[5-7].

Additionally valsartan has been also proved to prevent cardiovascular morbidity and mortality and to have addi-

uključila više od 50.000 pacijenata, dokazala su prednosti valsartana u sprječavanju srčanog popuštanja, nakon infarkta miokarda, kod visokorizičnih pacijenata, nefroprotektivni učinak lijeka, kao i sprječavanje razvoja tipa 2 dijabetesa kod bolesnika sa poremećenom tolerancijom glukoze[8-10].

U otvorenoj i prospektivnoj studiji istraživan je učinak valsartana na seksualnu funkciju muškaraca s arterijskom hipertenzijom (AH). Valsartanom su postignuta značajna poboljšanja u svim područjima seksualne funkcije identificirana Međunarodnim indeksom erektilne funkcije[11].

Učinkovitost valsartana je istražena u odnosu na ostale skupine antihipertenziva, primjerice ACE inhibitore, blokatore kalcijskih kanala (BKK), diuretike, beta-blokatore i druge predstavnike lijekova iz skupine ARB u nizu randomiziranih studija koje su obično uključivale liječenje u trajanju 8 do 12 tjedana. Valsartan je bio barem jednako učinkovit kao slični lijekovi, uz bitno veći učinak.

ACE inhibitori i ARB predstavljaju dvije klase lijekova koje djeluju izravno na renin-angiotenzin-aldosteron sustav (RAAS). Obje skupine lijekova imaju značajan učinak na sniženje vrijednosti sistoličkog i dijastoličkog AT kod populacije ispitanika s AH, ali se njihovo podnošenje i nuspojave bitno razlikuju. Iritirajući suhi kašalj koji se opaža kod 15% bolesnika dugotrajno liječenih ACE inhibitorima ne karakterizira primjenu valsartana[5-7]. Stoga se pacijentima s kašljem nakon ACE inhibitora može preporučiti liječenje valsartanom.

U odnosu na amlodipin, lijek iz skupine BKK, učinak valsartana na vrijednosti AT je bio sličan ili viši, uz manje nuspojava. U odnosu na BKK, valsartan nije uzrokoao periferne edeme i imao je nižu učestalost drugih nuspojava[5,6,12].

Valsartan snižava AT jednako učinkovito kao i beta-blokator atenolol u slučajevima teškog stupnja esencijalne hipertenzije. Bolesnici su bili liječeni primjenom 160 mg valsartana ili 100 mg atenolola tijekom razdoblja od 6 tjedana. Učinak dva liječenja oba lijeka bio je komparabilan (sniženje vrijednosti AT za 30 i 20 mmHg za vrijednosti sistoličkog i dijastoličkog AT kod valsartanske grupe, odnosno 25,5 i 20,4 mmHg za sistolički i dijastolički AT u onih na atenololu). U pacijenata liječenih atenololom registrirano je statistički značajno sniženje frekvencije srca u sjedećem položaju u odnosu na grupu liječenu valsartanom. U skupini pacijenata liječenih valsartanom bilo je manje potrebe za dodatnom antihipertenzivnom terapijom u odnosu na atenolol[13].

U usporednoj studiji kod neliječenih pacijenata s blagim do umjerenim stupnjem AH primjenom valsartana u dozi od 160 mg i telmisartana 80 mg, bolesnike se nasumično raspoređivalo na uzimanje spomenutih lijekova ujutro. Na početku i nakon 3 mjeseca liječenja učinjeno je kontinuirano 24-satno mjerenje AT. Sniženje prosječnih vrijednosti AT tijekom 24 sata (**Slika 2**) bilo je znatno izdašnije u skupini pacijenata na valsartanu (18,6/12,1 mmHg) nego u onih na telmisartanu (10,8/8,4 mmHg)[14].

Valsartan predstavlja suvremeni antihipertenzivni lijek iz grupe ARB kojeg karakterizira odlična podnošljivost. To je najpropisivaniji lijek iz skupine ARB diljem svijeta. Lijek je indiciran za liječenje AH i srčanog popuštanja (NYHA klasa II-IV) kod bolesnika koji ne podnose ACE inhibitore. Također je indiciran za poboljšanje preživljenja nakon infarkta miokarda kod klinički stabilnih bolesnika sa simptomima ili radiološkim nalazom popuštanja lijeve klijetke

tional benefits beyond BP lowering. Different clinical trials, involving more than 50.000 patients, have demonstrated cardioprotective benefit of valsartan in heart failure (HF), after myocardial infarction (MI), in high risk patients, renal protection and prevention of development of type 2 diabetes in patients with impaired glucose tolerance[8-10].

In open and prospective study it was investigated the effect of valsartan on sexual function in hypertensive males. Valsartan was associated with significant improvements in all domains of sexual function identified by the International Index of Erectile Function[11].

Efficacy of valsartan has been extensively investigated in comparison with other antihypertensive agents, such as angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs), diuretics, beta blockers and other ARBs in a series of randomized, parallel group studies with duration of treatment usually between 8 and 12 weeks. Valsartan is at least as effective as comparator drugs and response rates are usually higher.

There are two classes of drugs that act directly on renin-angiotensin-aldosterone system (RAAS), the ACE inhibitors and the ARBs. Both classes of drugs produce a comparable reduction in systolic and diastolic BP in hypertensive populations; however, tolerability and adverse reactions differ between these classes. The irritating cough seen in 15% of patients treated with ACE inhibitors, in the long term does not seem to occur with valsartan[5-7]. Patients having cough after an ACE inhibitor could be therefore proposed to valsartan treatment.

In comparison with CCB amlodipine, the BP efficacy of valsartan was similar to or greater than that of amlodipine, with fewer side-effects. Unlike CCB valsartan does not cause peripheral oedema. The lower rate of adverse events was significantly in favor of valsartan[5,6,12].

Valsartan lowers BP as effectively as beta-blocker atenolol, as shown in a study with severe essential hypertension. Patients received 160 mg valsartan or 100 mg atenolol for 6 weeks. Efficacy was comparable between the two treatments (reduction of 30 and 20 mm Hg for systolic and diastolic BP, respectively at valsartan group and 25.5 and 20.4 mm Hg for systolic and diastolic BP, respectively at atenolol group). Atenolol group had a statistically significant reduction in the sitting heart rate when compared to the valsartan group. There was less need for additional antihypertensive therapy at patients receiving valsartan compared with those receiving atenolol[13].

In comparative study with valsartan 160 mg and telmisartan 80 mg in untreated patients with mild to moderate hypertension, patients were randomly assigned to valsartan 160 mg or telmisartan 80 mg each morning. Ambulatory BP was measured at baseline and after 3 months of treatment. The BP reduction was significantly greater over 24 hours (**Picture 2**) with valsartan (18.6/12.1 mmHg) than with telmisartan (10.8/8.4 mmHg)[14].

Valsartan is a modern antihypertensive drug from the group of ARB. It is a representative of the most prescribed ARB worldwide with an excellent tolerability profile. Valsartan is indicated for the treatment of hypertension and heart failure (NYHA class II-IV) in patients intolerant to ACE inhibitors. It is also indicated to improve survival following MI in clinically stable patients with signs, symptoms or radiological evidence of left ventricular failure

i/ili sistoličke disfunkcije lijeve klijetke. Tablete valsartana kojeg proizvodi Krka (Valsacor®) su bioekvivalentne originatoru što dokazuju studije bioekvivalencije koje su provedene sukladno međunarodnim standardima (EMEA, FDA). Valsacor® je razvijen koristeći inovacijski pristup sa farmaceutskom formulacijom zaštićenog patenta. Lijek je već registriran u 19 europskih država. Druga prednost Krkinog valsartana je predstavljaju filmom obložene tablete koje se mogu razdijeliti u jednake polovice, što je dokazano prilikom ispitivanja na lomljenje[16].

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and/or left ventricular systolic dysfunction. Krka's valsartan tablets (Valsacor®) are bioequivalent to the originators, as proven by the bioequivalence studies performed according to the international standards (EMEA, FDA). Valsacor® was developed by using an innovative approach with patent-protected pharmaceutical formulation. The drug has been already registered in 19 European countries. Additional benefit of Krka's valsartan is that tablets are film-coated and can be divided into equal halves, which was proven with the breakability tests[16].

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