Stručni rad | Professional article

Valsartan i kombinacija njegovih fiksnih doza s hidroklorotiazidom za liječenje arterijske hipertenzije

Place of valsartan and its fixed-dose combination with hydrochlorothiazide in the treatment of hypertension

Polona Knavs Vrhunec, Breda Barbič-Žagar*, Mateja Grošelj
Krka, d. d., Novo mesto, Slovenija
Krka, d. d., Novo mesto, Slovenia

SAŽETAK: *Arterijska hipertenzija se povezuje s povećanim rizikom od koronarne bolesti srca, srčanog zatajivanja, moždanog udara, bolesti bubrega i recidivirajućim kardiovaskularnim epizodama. Snižavanje vrijednosti arterijskog tlaka dovodi do značajnog smanjenja rizika od kardiovaskularnog pobola i smrtnosti. Učinkovitost valsartana, vodećeg svjetskog antagonista angiotenzinskih receptora dobro je dokazana u različitih skupina pacijenata. Krkin valsartan i kombinacije njegovih fiksnih doza s hidroklorotiazidom (Valsacor®, Valsacombi®) su među prvim generičkim valsartanima koji svojom dostupnošću omogućuju moderno liječenje arterijske hipertenzije većem broju pacijenata.*

KLJUČNE RIJEČI: *valsartan, arterijska hipertenzija, arterijski tlak, antagonisti angiotenzinskih receptora.*

ABSTRACT: *Hypertension is associated with an increased risk of coronary heart disease, heart failure, stroke, renal disease and recurrent cardiovascular events. Lowering blood pressure results in significant decreases in the risk of cardiovascular morbidity and mortality. The efficacy of valsartan, the leading angiotensin receptor blocker in the world has been well demonstrated in various patient groups. Krka's valsartan and its fixed-dose combination with hydrochlorothiazide (Valsacor®, Valsacombi®) were among the first generic valsartans, which made modern treatment of hypertension accessible to a greater number of patients.*

KEYWORDS: *valsartan, hypertension, blood pressure, angiotensin receptor blocker.*

CITATION: *Kardio list. 2010;5(11):288-292.*

Iako arterijska hipertenzija (AH) predstavlja značajan zdravstveni problem diljem svijeta, još uvijek se slabo dijagnosticira i liječi. Dobrobit snižavanja vrijednosti arterijskog tlaka (AT) hipertenzivnih pacijenata na pobol i smrtnost dobro je utemeljena, a većini pojedinaca je potrebno više lijekova kako bi postigli kontrolu AT[1-3].

Antagonisti angiotenzinskih receptora (ARB) su visoko učinkoviti lijekovi za snižavanje povišenih vrijednosti AT. Imaju dokazan renoprotektivan učinak, smanjuju kardiovaskularni (KV) rizik, pružaju zaštitu organa te predstavljaju jednu od najbolje podnošenih vrsta antihipertenzivih lijekova[3].

Valsartan je nepeptidni ARB koji selekivno blokira vezanje angiotenzina II na receptore angiotenzina II tipa 1. Mnoge kliničke studije su dokazale učinkovitost, podnošljivost i sigurnost valsartana u snižavanju AT u različitih skupina pacijenata te u poboljšanju KV ishoda, kao i ishoda kronične bolesti bubrega[4].

Glavne prednosti primjene valsartana i kombinacije njegovih fiksnih doza s hidroklorotiazidom su sljedeće:

1. Brza uspostava kontrole vrijednosti arterijskog tlaka

Brzo sniženje AT može smanjiti kardiovaskularni rizik povezan s AH[5]. U kliničkim studijama srednje vrijeme postizanja ciljnog AT (<140/90 mmHg) je u usporedbi s placebom nastupilo značajno ranije s valsartanom i valstartanom/hidroklorotiazidom. Nije bilo razlika u sigurnosti i podnošljivosti između skupina pacijenata[6].

Hypertension is a major health problem worldwide, yet remains under-diagnosed and under-treated. The morbidity and mortality benefits of lowering blood pressure (BP) in hypertensive patients are well established, with most individuals requiring multiple drugs to achieve BP control[1-3].

Angiotensin receptor blockers (ARB) are highly effective at reducing BP; they exhibit renoprotective properties, reduce cardiovascular risk, provide organ protection, and are among the best tolerated classes of antihypertensives[3].

Valsartan is a nonpeptide ARB that selectively blocks the binding of angiotensin II to the angiotensin II type 1 receptor. Many clinical studies have demonstrated the efficacy, tolerability and safety of valsartan in lowering BP in a variety of patient populations and in improving outcomes in cardiovascular disease and chronic kidney disease[4].

In general, the major benefits of treatment with valsartan and its fixed-dose combination with hydrochlorothiazide are:

1. Rapid blood pressure control

Prompt reduction of BP may reduce the cardiovascular risk associated with hypertension[5]. In clinical studies, the mean time to achieving BP goal (<140/90 mmHg) occurred significantly earlier with valsartan and valsartan/hydrochlorothiazide in comparison with placebo. There were no differences in safety or tolerability between patient groups[6].

2. 24-satna kontrola arterijskog tlaka

Učinkovitost valsartana i kombinacije valsartan/hidroklorotiazid je u cijelom nizu kliničkih studija procijenjena pomoću 24-satnog kontinuiranog mjerenja AT. Općenito, rezultati su za valsartan i valsartan/hidroklorotiazid pokazali dosljedno sniženje AT-a tijekom cijelog 24-satnog intervala doziranja, uz usporedivo dnevno i noćno sniženje. Kao što je prikazano (**slika 1, slika 2**), sniženje vrijednosti AT od početnih vrijednosti je održavano tijekom cijelog intervala doziranja, oponašajući normalne cikličke promjene AT[7-9].

2. 24-hour blood pressure control

The efficacy of valsartan and valsartan/hydrochlorothiazide has been evaluated, using 24-hour ambulatory BP monitoring, in a number of clinical studies. In general, results demonstrated consistent BP reduction throughout the 24-hour dosing interval for valsartan and valsartan/hydrochlorothiazide, with daytime and night-time reductions being of comparable magnitude. As shown (**Figure 1, Figure 2**), reductions in BP from baseline were maintained throughout the dosing interval, mimicking normal circadian variations in BP[7-9].

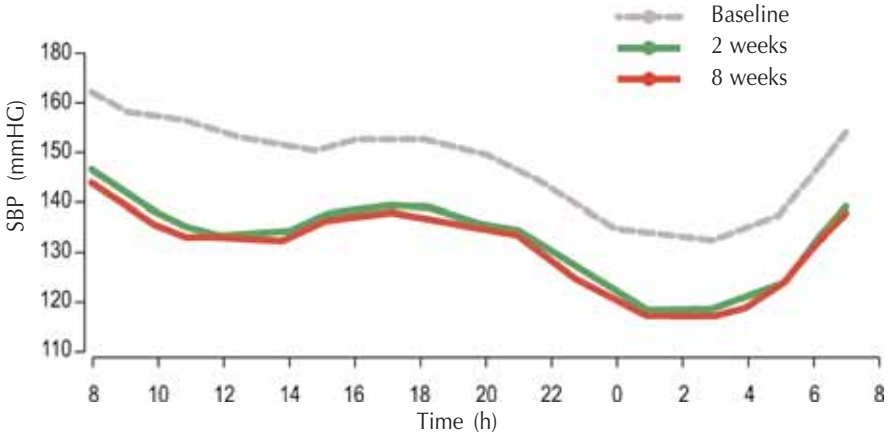

***Figure 1**. Systolic blood pressure reduction with valsartan and valsartan/hydrochlorothiayide.*

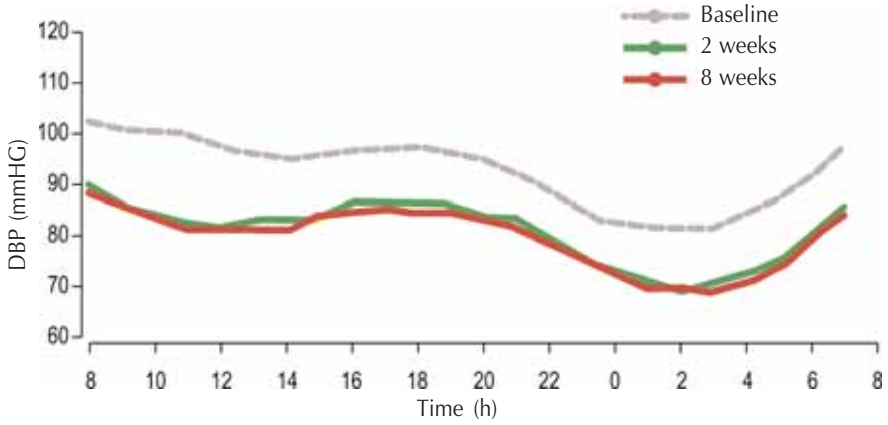

Figure 2. *Diastolic blood pressure reduction with valsartan and valsartan/hydrochlorothiayide.*

3. Učinkovitost u posebnih populacija pacijenata

a. Pacijenti starije životne dobi

U nekoliko studija procjenjena je učinkovitost i sigurnost valsartana u monoterapiji i u kombinaciji s hidroklorotiazidom u pacijenata starije životne dobi. Sniženje vrijednosti sistoličkog i dijastoličkog AT bila su klinički i statistički značajna, a promjene sistoličkog AT su općenito bile više kod starijih nego kod mlađih ispitanika[10-12].

b. Pacijenti s dijabetesom

Nekoliko kliničkih studija je procijenilo učinkovitost valsartana i valsartana/hidroklorotiazida u pacijenata s dijabetesom, mikroalbuminurijom i proteinurijom. Valsartan se pokazao učinkovitim i sigurnim za ove ispitanike[13].

c. Pretili pacijenti

Valsartan bi mogao imati prednosti za pretile pacijente budući da se pokazalo da značajno snižava vrijednost lep-

3. Efficacy in special populations

a. Elderly patients

Several studies have evaluated the efficacy and safety of valsartan in monotherapy and in combination with hydrochlorothiazide in elderly patients. Reductions in systolic and diastolic BP were clinically and statistically significant, with systolic BP changes generally being higher in elderly patients than in younger subjects[10-12].

b. Patients with diabetes

Several clinical studies have evaluated the effect of valsartan and valsartan/hydrochlorothiazide in patients with diabetes, microalbuminuria and proteinuria. Valsartan has been shown to be efficacious and safe in this population[13].

c. Obese patients

Valsartan may offer advantages in obese patients because it has been shown to lower significantly the plasma

tina u plazmi (10% od osnovne vrijednosti), vrijednost rezistina (14-18% od osnovne vrijednosti) te homeostatskog modela procjene inzulinske rezistencije (12-20% od osnove vrijednosti)[14].

4. Dodatni učinci pored kontrole vrijednosti arterijskog tlaka

a. Kardiovaskularni ishodi

U cijelom nizu velikih kliničkih istraživanja ustanovljena je vrijednost valsartana u smanjenju KV pobola i smrtnosti kod visokorizičnih pacijenata. Studije Val-HeFT i VALIANT su pokazale da je KV dobrobit valsartana usporediva s inhibitorima angiotenzin konvertirajućeg enzima (ACE), uz bolju podnošljivost. U studiji VALUE je terapija valsartanom i amlodipinom rezultirala sličnim stopama zajedničkih KV ishoda (10,6% i 10,4%, za svaku)[15-17].

b. Cerebrovaskularni ishodi

Velike studije su dokazale da valsartan snižava rizik od moždanog udara u stupnju sličnom onom koji se postiže ACE inhibitorima ili amlodipinom[18].

c. Ishodi kod bolesti bubrega

Poboljšanja ishoda pomoću valsartana kod kronične bolesti bubrega uključuju statistički i klinički značajno sniženje mikroalbuminurije kod pacijenata s dijabetesom tipa 2; čini se da su učinci neovisni o njegovoj sposobnosti snižavanja vrijednosti AT. Valsartan je također učinkovit u snižavanju izlučivanja proteina u urinu kod pacijenata s nedijabetičkom bubrežnom insuficijencijom[13].

d. Metabolički ishodi

Valsartan je u kratkoročnim kliničkim studijama poboljšao ili stabilizirao cijeli niz znakova metaboličke funkcije kod određenih skupina pacijenata ili je bio metabolički neutralan u usporedbi s ostalim antihipertenzivima[19].

leptin level (10% from baseline), the resistin level (14-18% from baseline), and the homeostasis model assessment of insulin resistance (12-20% from baseline)[14].

4. Effects beyond blood pressure control

a. Cardiovascular outcomes

A number of large outcome clinical studies have established the value of valsartan in reducing cardiovascular morbidity and mortality in high risk patients. The studies Val-HeFT and VALIANT have demonstrated that valsartan is comparable with angiotensin-converting enzyme (ACE) inhibitors in terms of cardioprotective benefits, however, better tolerated. In the VALUE study, valsartan and amlodipine-based therapy resulted in similar rates of the composite cardiovascular endpoint (10.6% and 10.4%, respectively)[15-17].

b. Cerebrovascular outcomes

Large-scale studies have shown that valsartan reduces the risk of stroke to a degree similar to that observed with ACE inhibitors or amlodipine[18].

c. Renal outcomes

Improvements in chronic kidney disease outcomes reported with valsartan include statistically and clinically meaningful reductions in microalbuminuria in patients with type 2 diabetes; effects appear to be independent of its BP lowering capability. Valsartan is also effective in lowering urinary protein excretion in patients with nondiabetic renal insufficiency[13].

d. Metabolic outcomes

In short-term clinical studies, valsartan has improved or stabilised a number of indices of metabolic function in certain groups of patients or was metabolically neutral compared with other antihypertensive agents[19].

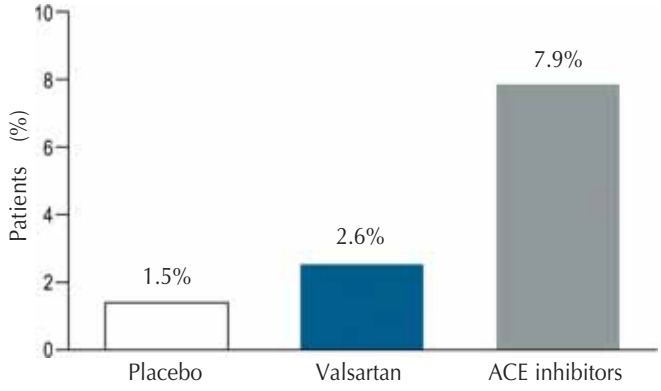

Figure 3. *Frequency of cough.*

5. Sigurnost i podnošljivost

Profil podnošljivosti valsartana je neovisan od dozi i trajanju liječenja te dosljedan bez obzira na dob, spol i etničku pripadnost pri dozama do 320 mg/dnevno. Učestalost i težina nuspojavaa kod valsartana/hidroklorotiazida je slična onima kod pacijenata na monoterapiji valsartanom ili onih na placebu. Osnovna prednost ARB nad ACE inhibitorima se odnosi na smanjenu učestalost kašlja (**slika 3**) i angioedema[13].

5. Safety and tolerability

The tolerability profile of valsartan is independent of dose and duration of treatment, and is consistent regardless of age, sex and ethnic group at dosages up to 320 mg/day. The frequency and severity of adverse events with valsartan/hydrochlorothiazide are similar to those of patients on valsartan monotherapy or receiving placebo. The main advantage of ARB over ACE inhibitors relates to the reduced incidence of cough (**Figure 3**) and angioedema[13].

U nizu kliničkih studija je dokazano da valsartan i kombinacije njegovih fiksnih doza s hidroklorotiazidom smanjuju incidenciju KV i cerebrovaskularnih epizoda kod pacijenata sa srčanim zatajivanjem, disfunkcijom lijeve klijetke nakon infarkta miokarda, dijabetesa i kronične bolesti bubrega te kod drugih skupina pacijenata koje imaju rizik KV epizoda. Krkin valsartan i kombinacija njegovih fiksnih doza s hidroklorotiazidom (Valsacor®, Valsacombi®) su stoga vrijedne terapije za područje kardiorenalne medicine.

Valsartan and its fixed-dose combination with hydrochlorothiazide have been proven in a number of clinical studies to reduce the incidence of cardiovascular and cerebrovascular events in patients with heart failure, left ventricular dysfunction following myocardial infarction, diabetes and chronic kidney disease, and in other groups at risk for cardiovascular events. Krka's valsartan and its fixed-dose combination with hydrochlorothiazide (Valsacor®, Valsacombi®), are thus valuable therapies in the field of cardiorenal medicine.

Received: 22nd Sep 2010

*Address for correspondence: Krka d.d., Dunajska 65, SLO-1000 Ljubljana, Slovenija; Phone: +386-1-4571-339;

E-mail: breda.zagar@krka.biz

Literature

1. Wellington K, Faulds DM. Valsartan/hydrochlorothiazide A review of its pharmacology, therapeutic efficacy and place in the management of hypertension. Drugs. 2002;62(13):1983-2005.

2. Smith D. Comparison of angiotensin II type 1 receptor antagonists in the treatment of essential hypertension. Drugs. 2008;68(9):1207-25.

3. Nash DT, McNamara MS. Valsartan combination therapy in the management of hypertension —- patient perspectives and clinical utility. Integrated Blood Pressure Control. 2009;2:39-54.

4. Black HR, Bailey J, Zappe D, Samuel R. Valsartan: more than a decade of experience. Drugs. 2009;69(17):2393-414.

5. Poulter NR, Wedel H, Dahl˜f B, Sever PS, Beevers DG, Caulfield M, et al. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). Lancet. 2005;366:907-13.

6. Jamerson KA, Zappe DH, Collins L, et al. The time to blood pressure (BP) control by initiating antihypertensive therapy with a higher dose of valsartan (160 mg) or valsartan/hydrochlorothiazide compared to low-dose valsartan (80 mg) in the treatment of hypertension: the VELOCITY study. J Clin Hypertens. 2007;9(5 Suppl A): A166.

7. Hermida RC, Calvo C, Ayala DE, Dominguez MJ, Covelo M, Fernandez JR, et al. Administration time-dependent effects of valsartan on ambulatory blood pressure in hypertensive subjects. Hypertension. 2003;42:283-90.

8. Neutel J, Weber M, Pool J, Smith D, Fitzsimmons S, Chiang Ytm et al. Valsartan, a new angiotensin II antagonist: antihypertensive effects over 24 hours. Clin Ther. 1997;19:447-58.

9. Ruilope LM, Heintz D, Brandao AA, Stolt P, Kandra A, Santonastaso M, et al. 24-hour ambulatory blood-pressure effects of valsartan and hydrochlorothiazide combinations compared with amlodipine in hypertensive patients at increased cardiovascular risk: a VAST sub-study. Blood Press Monit. 2005;10:85-91.

10. Mallion JM, Carretta R, Trenkwalder P, Martinez JF, Tykarsky A, Teitelbaum I, et al. Valsartan/hydrochlorothiazide is effective in hypertensive patients inadequately controlled by valsartan monotherapy. Blood Press Suppl. 2003;1:36-43.

11. Malacco E, Vari N, Capuano V, Spagnuolo V, Borgnino C, Palatini P; Val-Syst study. A randomized, double-blind, active-controlled, parallel-group comparison of valsartan and amlodipine in the treatment of isolated systolic hypertension in elderly patients: the Val-Syst study. Clin Ther. 2003;25: 2765-80.

12. Neutel JM, Bedigian MP. Efficacy of valsartan in patients aged ≥65 years with systolic hypertension. Clin Ther. 2000;22:961-9.

13. Hollenberg NK, Parving HH, Viberti G, Remuzzo G, Ritter S, Zelenkofske S, et al. Albuminuria response to very high-dose valsartan in type 2 diabetes mellitus. J Hypertens. 2007;25:1921-6.

14. Fogari R, Derosa G, Zoppi A, Rinaldi A, Lazzari P, Fogari E, et al. Comparison of the effects of valsartan and felodipine on plasma leptin and insulin sensitivity in hypertensive obese patients. Hypertens Res. 2005;28:209-14.

15. Maggioni AP, Latini R, Carson PE, Singh SN, Barlera S, Glazer R et al. Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J. 2005;149:548-57.

16. Pfeffer MA, McMurray JJV, Velazquez EJ, Rouleau JL, Kober L, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both; the Valsartan in Acute Myocardial Infarction Trial Investigators. N Engl J Med. 2003;349:1893-906.

17. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004;363:2022-31.

18. Sampson UK, Pfeffer MA, McMurray JJV, Lokhnygina Y, White HD, Solomon SD. Predictors of stroke in high-risk patients after acute myocardial infarction: insights from the VALIANT trial. Eur Heart J. 2007;28: 685-91.

19. Kjeldsen SE, Julius S, Mancia G, McInnes GT, Hua T, Weber MA, et al. Effects of valsartan compared to amlodipine on preventing type 2 diabetes in high-risk hypertensive patients: the VALUE trial. J Hypertens. 2006;24:1405-12.