Stručni rad

Ramipril i fiksne kombinacije ramiprila s hidroklorotiazidom u liječenju pacijenata s arterijskom hipertenzijom

Professional article

Ramipril and ramipril fixed-dose combinations with hydrochlorothiazide in the treatment of hypertensive patients

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SAŽETAK: *Inhibitori enzima angiotenzin konvertaze (ACE inhibitori) predstavljaju najčešće propisivane antihipertenzive. Ramipril je jedan od najviše istraženih i najčešće korištenih ACE inhibitora diljem svijeta. Kombinacija ramiprila i hidroklorotiazida (HCTZ) ima dodatni učinak na sniženje vrijednosti arterijskog tlaka te omogućava bolji terapijski učinak kod niskih doza ramiprila i HCTZ uzrokujući pritom i manje nuspojava. Učinak, sigurnost i pozitivni učinci na ciljne organe Krkinog ramiprila (Ampril®) i njegovih fiksnih kombinacija (Ampril® HL i Ampril® HD) potvrđene su u 12 studija. Više od 8.500 hipertenzivnih bolesnika sa ili bez dodatnih kardiovaskularnih komplikacija (metabolički sindrom, koronarna bolest srca, dijabetes, bubrežni poremećaji ili zatajivanje srca nakon infarkta miokarda) bili su uključeni u studije.*

KLJUČNE RIJEČI: *arterijska hipertenzija, inhibitor enzima angiotenzin konvertaze, ramipril, fiksne kombinacije.*

SUMMARY: *The most commonly prescribed drugs for hypertensive patients are angiotensin-converting enzyme (ACE) inhibitors. Ramipril is one of the most studied and the most frequently used ACE inhibitors worldwide. The combination of ramipril and hydrochlorothiazide (HCTZ) has an additive effect on blood pressure (BP) reduction and enables a better therapeutic effect at lower doses of ramipril and HCTZ, consequently causing fewer adverse reactions. The efficacy, the safety and the positive effects on target organs of Krka's ramipril (Ampril®) and its fixed-dose combinations (Ampril®HL and Ampril® HD) were confirmed in 12 studies. More than 8,500 hypertensive patients with and without additional cardiovascular complications (metabolic syndrome, coronary heart disease, diabetes, renal disorders, heart failure after myocardial infarction) were included in the studies.*

KEYWORDS: *hypertension, angiotensin-converting enzyme inhibitor, ramipril, fixed-dose combinations.*

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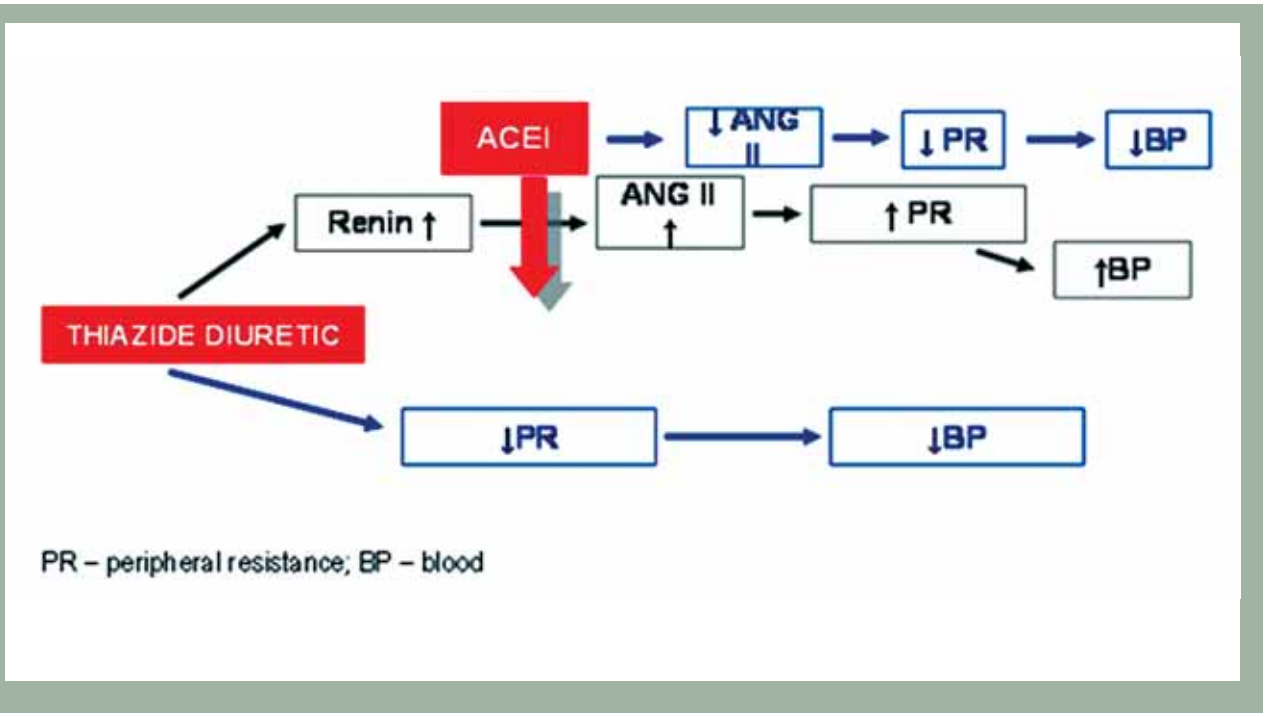
Ramipril je inhibitor enzima angiotenzin konvertaze (ACE inhibitor) koji smanjuje periferni vaskularni otpor izravnom inhibicijom ACE u cirkulacijskom sustavu i tkivima kako bi se spriječio pretvaranje angiotenzina I u njegov vazokonstrikcijski oblik angiotenzin II. Hidroklorotiazid (HCTZ) povećava renalno izlučivanje natrija i klorida i konačno može uzrokovati dugoročno smanjenje sistemske vaskularne rezistencije. Kombinacija ramiprila i HCTZ ima terapijski smisao zbog svojih različitih, ali opet komplementarnih i sinergijskih mehanizama djelovanja. Kombinacija ramiprila i HCTZ ima dodatan učinak na snižavanje vrijednosti arterijskog tlaka (AT) te omogućava bolji terapijski učinak kod niže doza ramiprila i HCTZ uzrokujući tako manje nuspojava. Antihipertenzivni učinak ove kombinacije traje do 24 sata[1-5].

Ramipril, najčešće propisivan ACE inhibitor u svijetu, također ima osnovne mehanizme kojima sprječava kardiovaskularne (KV) epizode te smanjuje rizik od moždanog udara, KV smrti i infarkta miokarda neovisno o sniženju AT. To pokazuje da bi visokorizične bolesnike trebalo liječiti visokim dozama ramiprila uz ostale preventivne mjere bez obzira na njihov početni AT[3,6,7]. Zaštitni učinci ramiprila na vaskularnu stijenku bi se mogli objasniti smanjenim oksidativnim stresom i smanjenim proliferacijskim i upalnim reakcijama rezultirajući pozitivnim učinkom na sprječavanje progresije aterosklerotskih plakova. Protuupalni odgovor na ACE inhibiciju može dovesti do stabilizacije plaka. Ovi uzročni koncepti su podržani rezultati-

Ramipril is an angiotensin-converting enzyme (ACE) inhibitor which reduces peripheral vascular resistance by directly inhibiting ACE in the circulatory system and tissues in order to prevent the conversion of angiotensin I to its vasoconstrictor form angiotensin II. Hydrochlorothiazide (HCTZ) increases the renal excretion of sodium and chloride and may ultimately produce a long-term decrease in systemic vascular resistance. The combination of ramipril and HCTZ makes therapeutic sense due to their different but complementary and synergistic mechanisms of action. The combination of ramipril and HCTZ has an additive effect on blood pressure (BP) reduction and enables a better therapeutic effect at lower doses of ramipril and HCTZ, consequently causing fewer adverse reactions. The antihypertensive effect of the combination lasts for up to 24 hours[1-5].

Ramipril is the most frequently prescribed ACE inhibitor in the world and also has the underlying mechanisms by which it prevents cardiovascular (CV) events and decreases the risk for stroke, CV death and myocardial infarction independently of the reduction in BP. This shows that high-risk patients should be treated with high doses of ramipril in addition to other preventive measures irrespective of their initial BP[3,6,7].The protective effects of ramipril on the vascular wall could be explained by decreased oxidative stress and decreased proliferative and inflammatory responses, resulting in a beneficial effect against the progression of atherosclerotic plaques. The anti-inflammatory response of ACE inhibition may lead to plaque stabilisation.



ma studije SECURE u kojoj je napredovanje ateroskleroze značajno usporeno ramipirilom u odnosu na placebo. Važno je da je učinak doze od 10 mg, kako se koristilo u studiji HOPE, bilo bolje nego učinak doze od 2,5 mg. Ovime se naglašava potreba za povećanjem doze ramiprila kako bi se u potpunosti iskoristio njegov preventivni potencijal[3]. Nadalje, primjenom ramiprila od 5 mg dva puta dnevno bolesnicima s klinički dokazanim zatajivanjem srca (ZS) nakon akutnog infarkta miokarda (AIM) značajno se smanjila ukupna smrtnost. Na temelju rezultata ramipril se može koristiti kod bolesnika sa ZS nakon AIM[8,9]. Istraženo je nekoliko važnih mehanizama djelovanja ramiprila u višim dozama u HOPE istraživanju i podstudijama: smanjeno napredovanje ateroskleroze, poboljšanje vaskularne funkcije, izravan utjecaj na prevenciju hipertrofije miokarda, sniženje razine glukoze i mogućnost sprječavanja dijabetesa[10]. Ramipril također značajno snižava rizik glavnih KV i mikrovaskularnih (dijabetička nefropatija i zakazivanje bubrega) epizoda kod osoba s dijabetesom[11].

Učinkovitost i sigurnost liječenja Krkinim ramiprilom (Ampril®) i/ili kombinacijom ramiprila i HCTZ(Ampril® HL i Ampril® HD) potvrđene su u postautorizacijskoj studiji sigurnosti i učinkovitosti koja je uključivala 943 hipertenzivna bolesnika. Tri mjeseca liječenja donijela su dobrobit sniženja vrijednosti sistoličkog i dijastoličkog AT za 15,5% odnosno 13%. Tijekom tromjesečnog razdoblja liječenje se dobro podnosilo i više od 87% bolesnika je postiglo ciljni AT bez nuspojava[4].

Učinkovitost i sigurnost Krkinog ramiprila i njegove kombinacije fiksnih doza potvrđeni su u 12 studija:

• Jedna tableta ramiprila dnevno osigurava 24-satnu kontrolu AT te dobru podnošljivost i prihvatljivost[12]

• Nakon tromjesečne terapije ramiprilom kod bolesnika nakon AIM došlo je do značajnog sniženja razine CRP i LDL te porasta razine HDL; nakon jednogodišnje terapije pozitivni učinci su bili još značajniji[13,14]

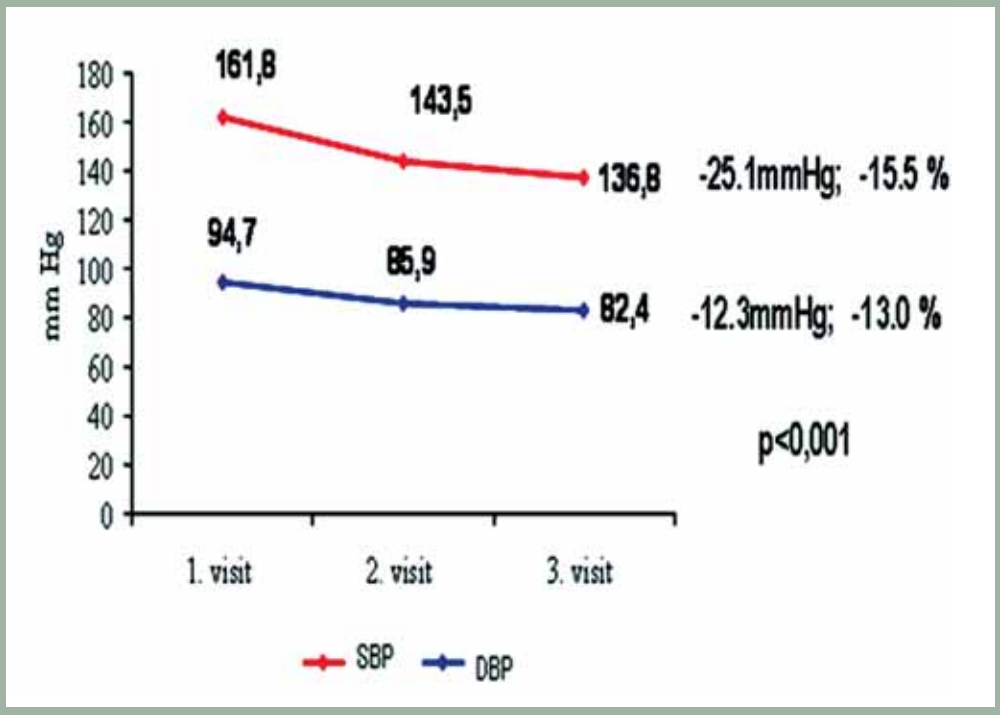
These causal concepts were supported by the SECURE study in which progression of atherosclerosis was significantly reduced by ramipril compared with placebo. Importantly, the effect of the 10 mg dose, as used in the HOPE study, was better than the effect of the 2.5 mg dose. This underlines the need for titrating ramipril to a higher dose to exploit its full preventive potential[3]. Furthermore, administering ramipril 5 mg twice daily to patients with clinical evidence of heart failure (HF) after acute myocardial infarction (AMI) significantly reduced the risk of all-cause mortality. Based on results ramipril can be used in patients with HF following AMI[8,9]. Several important mechanisms of action of ramipril in higher dosages were explored within the HOPE trial and its substudies: decrease in atherosclerosis progression, improvement in vascular function, direct impact in preventing myocardial hypertrophy, and reduction in glucose levels and potential to prevent diabetes[10]. Ramipril also significantly lowers the risk of major CV and microvascular (diabetic nephropathy and renal failure) events in patients with diabetes[11].

The efficacy and safety of the treatment with Krka's ramipril (Ampril®) and/or the combination of ramipril and HCTZ (Ampril® HL and Ampril® HD) were confirmed in the post-authorisation safety and efficacy study that included 943 hypertensive patients. Three months of treatment resulted in a reduction of both systolic and diastolic BP by 15.5% and 13%, respectively. Throughout the 3-month period the treatment was very well tolerated and more than 87% of the patients reached the target BP without experiencing any adverse reactions[4].

The efficacy and safety of Krka's ramipril and its fixed-dose combinations were confirmed in 12 studies:

• One ramipril tablet per day provided 24-h BP control and ensured good tolerability and patient compliance[12]

• After 3 months of therapy with ramipril in patients after AMI, there was a significant reduction of CRP and LDL



• Terapijom ramiprilom poboljšava endotelnu funkciju i elastičnost krvnih žila kod hipertenzivnih dijabetičara[15]

• Naglašen nefroprotektivan učinak i poboljšana zaštita srca je uočena kombiniranom terapijom ramiprilom i amlodipinom[16]

• Ramipril titriran do doze 10 mg pokazao je najbolje rezultate u poboljšanju bubrežne funkcije — smanjene razine proteinurije i mikroalbuminurije kod hipertenzivnih bolesnika s koronarnom bolesti srca (KBS)[17]

• Kod hipertenzivnih bolesnika s metaboličkim sindromom (MS) ramipril je poboljšao endotelnu, dijastoličku i atrijsku funkciju uz smanjenje hipertrofije lijeve klijetke[18]

• Ramipril u kombinaciji s amlodipinom predstavlja učinkovitu antihipertenzivnu kombinaciju kod pacijenata s prvim i drugim stupnjem arterijske hipertenzije i MS u postmenopauzi. Kombinacijom se također postiže pozitivan metabolički učinak i ima vazozaštitno djelovanje[19]

• Terapija ramiprilom se povezuje sa smanjenjem indeksa mase lijeve klijetke. Vezano uz antihipertenzivni i učinak na zaštitu organa, ramipril također pokazuje i antiaritmijski učinak[20]

• Dodatak ramiprila standardnoj terapiji pacijenta s arterijskom hipertenzijom i KBS rezultira mogućnošću antiishemijskih učinaka, poboljšava funkcijsko stanja endotela i smanjuje učestalost ventrikularnih ekstrasistola i supraventrikularnih aritmija[21].

U studije je bilo uključeno više od 8.500 hipertenzivnih bolesnika s i bez dodatnih KV komplikacija (MS, KBS, dijabetes, bubrežni poremećaji i srčano zatajivanje nakon infarkta miokarda).

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levels and an increase of HDL levels; after 1 year of therapy, positive effects were even more significant1[3,14]

• Therapy with ramipril improved endothelial function and elasticity of blood vessels in hypertensive diabetic patients[15]

• A marked nephroprotective effect and improved protection of the heart were observed during combined therapy with ramipril and amlodipine[16]

• Ramipril titrated up to 10 mg brought best results in the improvement of renal function — reduced levels of proteinuria and microalbuminuria in hypertensive patients with coronary heart disease (CHD)[17]

• In hypertensive patients with metabolic syndrome (MS), ramipril improved endothelial, diastolic and atrial function plus reduced left ventricular hypertrophy[18]

• Ramipril is in combination with amlodipine an effective antihypertensive drug in patients with first or second degree of arterial hypertension and MS in the post-menopausal period. The combination also produces a positive metabolic effect and has vasoprotective activity[19]

• Therapy with ramipril has been associated with a decrease of left ventricular mass index. Related to its antihypertensive and organ-protective properties, ramipril also demonstrated anti-arrhythmic effects[20]

• Addition of ramipril to standard therapy in patients with hypertension and CHD results in potentiation of antiischemic effects, promotes improvement of the functional state of the endothelium, and decreases ventricular ectopic beats and supraventricular arrhythmias[21]

More than 8,500 hypertensive patients with and without additional CV complications, such as MS, CHD, diabetes, renal disorders, or HF after myocardial infarction, were included in the studies.

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