Stručni rad / Professional article

Prednosti perindoprila kao monoterapije i kombinacije s indapamidom u odnosu na ostale ACE inhibitore u kardiovaskularnih bolesnika

Advantages of perindopril as monotherapy and combinations with indapamide compared to other ACE inhibitors in cardiovascular patients

Mario Pehar*
Klinička bolnica Dubrava, Zagreb, Hrvatska
Clinical Hospital Dubrava, Zagreb, Croatia

SAŽETAK: Inhibitori angiotenzin konvertirajućeg enzima (ACE-inhibitori) imaju ključnu ulogu u liječnju bolesnika duž čitavog kardiovaskularnog kontinuuma, od nekomplicirane arterijske hipertenzije do razvijene koronarne bolesti i bolesti srčanog mišića. Temeljem provedenih randomiziranih kliničkih studija može se zaključiti da uz temeljni antihipertenzivni učinak imaju značajni kardio i vazoprotektivni učinak. Bitno je napomenuti da se unutar klase ACE inhibitora, perindopril upravo ističe svojim značajnim učincima na poboljšanje funkcije endotela, zapravo inhbirajući patofiziološki proces od samoga početka. Logična je kombinacija perindoprila s diuretikom — indapamidom s obzirom da je njihov kombinirani učinak aditivan, odnosno rezultira optimalnom kontrolom renin angiotenzin-aldosteron sustava i snažnom antihipertenzivnom reakcijom. Perindopril i ramipril su jasno pokazali redukciju kardiovaskularnog rizika u randomiziranim kliničkim pokusima u skupini bolesnika sa stabilnom anginom pektoris, dočim kvinapril i trandolapril nisu imali navedeni učinak. Od svih kardiovaskularnih lijekova, ACE inhibitori imaju navišu razinu dokaza u smislu prevencije kardiovaskularnih događanja tijekom čitavog spektra kardiovaskularnih bolesti. Krkin perindopril, odnosno fiksna kombinacija perindoprila s indapamidom dostupna je u različitim dozama i pakiranjima što ga čini optimalnim izborom na tržištu.

KLJUČNE RIJEČI: arterijska hipertenzija, inhibitori angiotenzin konvertirajućeg enzima, perindopril, indapamid.

SUMMARY: Angiotensin-converting enzyme (ACE) inhibitors play a key role in the treatment of patients along the entire cardiovascular continuum from uncomplicated hypertension to developed coronary artery disease and myocardial disease. Based on the conducted randomized clinical trials, we can conclude that they have a significant cardiac and vasoprotective effect in addition to the basic antihypertensive effect. It is important to note that within the class of ACE inhibitors, perindopril is characterized by its very significant effects on improvement of endothelial function, thereby inhibiting pathophysiological process from the outset. The combination of perindopril with the diuretic — indapamide is logical given that their combined effect is additive, that is, it results in an optimal control of the renin angiotensin-aldosterone system and strong antihypertensive reaction. Perindopril and ramipril have clearly demonstrated the reduction of cardiovascular risk in randomized clinical trials in the group of patients with stable angina pectoris, whereas quinapril and trandolapril did not show the above effect. Of all cardiovascular drugs, ACE inhibitors have the highest level of evidence in terms of prevention of cardiovascular events during the entire spectrum of cardiovascular diseases. Krka's perindopril, or a fixed combination of perindopril with indapamide is available in different dosages and packaging, making it the optimal choice on the market.

KEWYORDS: hypertension, angiotensin-converting enzyme inhibitors, perindopril, indapamide.

CITATION: Kardio list. 2012;7(1-2):53-55.

Inhibitori angiotenzin konvertirajućeg enzima (ACE-inhibitori) imaju ključnu ulogu u liječnju bolesnika duž čitavog kardiovaskularnog kontinuma, od nekomplicirane arterijske hipertenzije (AH) do razvijene koronarne bolesti srca i bolesti srčanog mišića. Upravo najučinkovitija strategija u prevenciji i liječenju kardiovaskularnog morbiditeta je inhibicija renin angiotenzin-aldosteron (RAAS) sustava temeljena

Angiotensin-converting enzyme (ACE) inhibitors play a key role in treatment of patients along the entire cardiovascular continuum from uncomplicated hypertension to developed coronary artery disease and myocardial disease. The most effective strategy in prevention and treatment of cardiovascular morbidity is the inhibition of the renin angiotensin-aldosterone (RAAS) system based on the use

na primjeni ACE-inhibitora. Sukladno medicini baziranoj na dokazima ACE-inhibitori se učinkovito primjenjuju kao terapija AH, infarkta miokarda i srčanog popuštanja, a pokazuju koristan aditivni učinak i u liječenju dijabetesa, fibrilacije atrija i periferne arterosklerotske bolesti.

Angiotenzin konvertirajući enzim ključan je u pretvorbi angiotenzina I u angiotenzin II koji sa svojim vazokonstriktornim efektom uzrokuje povišenje vrijednosti arterijskog tlaka (AT) uz stimulaciju lučenja aldosterona s posljedičnom retencijom natrija i vode. S obzirom na navedeno ACE-inhibitori snižavaju AT, zaustavljaju hipertrofiju lijeve klijetke, no smanjuju i rizik nastanka hipertenzivne nefropatije te ključno, smanjuju ukupni kardiovaskularni mortalitet.

Temeljem provedenih randomiziranih kliničkih studija može se zaključiti da uz temeljni antihipertenzivni učinak imaju značajni kardio i vazoprotektivni učinak. ACE je enzim primarno lokaliziran u tkivima te se samo 10% ukupnog enzima nalazi slobodno u plazmi. Svojstva i učinci ACE inhibitora su često pripisani efektu skupine, no bitno je naglasiti da nisu svi ACE inhibitori isti. Razlikuju se u osnovnim farmakološkim svojstvima, farmakokinetici, intermedijalnom metabolizmu i aktivaciji lijeka, duljini djelovanja, kao i T/P indeksu ("trough/peak plasma concentration"), odnosno distribuciji u perifernim tkivima.

Bitno je napomenuti da se unutar klase ACE inhibitora, perindopril upravo ističe sa svojim značajnim učincima na poboljšanje funkcije endotela, zapravo inhbirajući patofiziološki proces od samoga početka. Konkretno, perindopril je prolijek koji zahtjeva aktivaciju metaboličkom modifikacijom u jetri na način da nastaje perindoprilat, koji je izrazito potentan, lipofilan ACE inhibitor s visokim afinitetom za tkivni ACE uz svojstvo dugog djelovanja. Perindoprilat reducira plazmatske koncentracije angiotenzina II, što dovodi do povišene aktivnosti renina i smanjene sekrecije aldosterona (**Tablica 1**).

of ACE-inhibitors. According to evidence-based medicine, ACE-inhibitors are effectively applied as a therapy of hypertension, myocardial infarction and heart failure, also showing a beneficial additive effect in the treatment of diabetes, atrial fibrillation and peripheral atherosclerotic disease.

ACE is essential in the conversion of angiotensin I into angiotensin II, which with its vasoconstrictor effect causes elevated values of blood pressure (BP) thereby stimulating aldosterone secretion with consequential sodium and water retention. Since the above ACE-inhibitors lower BP, they reduce the left ventricular hypertrophy, but they also reduce the risk of occurrence of hypertensive nephropathy and what is essential, they reduce total cardiovascular mortality.

Based on the conducted randomized clinical trials, we can conclude that they have a significant cardiac and vasoprotective effect in addition to the basic antihypertensive effect. ACE is an enzyme that is primarily localized in the tissues, and only 10% of the total enzymes are free in plasma. Properties and effects of ACE inhibitors are often attributed to the class effect, but it is important to emphasize that not all ACE inhibitors are the same. They differ in the basic pharmacological properties, pharmacokinetics, intermedial metabolism and drug activation, length of action, as well as T/P index (trough/peak plasma concentration), or distribution in peripheral tissues.

It is important to note that within the class of ACE inhibitors, perindopril is characterized by its very significant effects on improvement of endothelial function, thereby inhibiting pathophysiological process from the outset. Specifically, perindopril is a pro-drug that requires activation by metabolic modification in the liver in the manner that perindoprilat occurs, which is a highly potent, lipophilic ACE inhibitor with a high affinity for tissue ACE with the characteristic of long-lasting effect. Perindoprilat reduces plasma concentrations of angiotensin II, which results in elevated renin activities and reduced secretion of aldosterone (**Table 1**).

Table 1.
Some pharmacokinetics of the perindopril.

Fast onset of effect
24h blood pressure control
Once-a-day dosing interval
Better compliance
Bioavailability from 65% to 70%

Logična je kombinacija perindoprila s diuretikom — indapamidom s obzirom da je njihov kombinirani učinak aditivan. Diuretik primarno uzrokuje depleciju volumena koja stimulira aktivaciju RAAS sustava te shodno tome povećava sintezu angiotenzina II. Konačni efekt povišene koncentracije angiotenzina II zapravo poništava antihipertenzivni učinak diuretika. Upravo istovremena primjena ACE-inhibitora s diuretikom rezultira optimalnom kontrolom RAAS sustava i snažnom antihipertenzivnom reakcijom.

Za razliku od često upotrebljavanih diuretika tiazidske skupina koji imaju negativne metaboličke učinke primarno po-

The combination of perindopril with a diuretic — indapamide is logical, given that their combined effect is additive. Diuretic primary causes volume depletion, which stimulates the activation of RAAS system, consequently increasing the synthesis of angiotensin II. The ultimate effect of elevated concentration of angiotensin II actually reverses antihypertensive effect of diuretics. That concomitant application of ACE-inhibitor with a diuretic results in an optimal control of the RAAS system and strong anti-hypertensive response.

Unlike the frequently used thiazide diuretics that have negative metabolic effects primarily increasing the risk of occur-

većavajući rizik nastanka dijabetesa i hiperlipidemije, indapamid je diuretik s načelno neutralnim metaboličkim učinkom, što ga čini izrazito prihvatljivim u skupini bolesnika s dijabetesom i metaboličkim sindromom. Bitno je naglasiti da se farmakokinetski profili perindoprila i indapamida ne modificiraju kada se primjenjuju u fiksnoj kombinaciji te pokazuju kontinuiran učinak kroz 24h sata. Upravo indeks T/P (*through-to-peak*) mjeri postotak ukupnog sniženja AT tijekom maksimalnog učinka u odnosu na učinak koji lijek postiže nakon 24h. Konkretno, T/P indeks od 50% znači da lijek 24h nakon primjene ostvaruje 50% učinka kojeg ostvaruje tijekom maksimalne, vršne koncentracije lijeka u plazmi. Zaključno, što je viši T/P to je učinak lijeka konstantan, a što je osobito bitno zbog redukcije ukupnog kardiovaskularnog rizika tijekom jutarnjih sati kada je incidencija neželjenih kardiovaskularnih događanja visoka.

Od svih kardiovaskularnih lijekova, ACE inhibitori imaju navišu razinu dokaza u smislu prevencije kardiovaskularnih događanja tijekom čitavog spektra kardiovaskularnih bolesti. Bitno je naglasti da nisu svi ACE inhibitori isti u smislu farmakološke učinkovitosti i tolerancije. Perindopril i ramipril su jasno pokazali redukciju kardiovaskularnog rizika u randomiziranim kliničkim pokusima u skupini bolesnika sa stabilnom anginom pektoris, dočim kvinapril i trandolapril nisu imali navedeni učinak. Dokazi za perindopril se temelje na studijama ASCOT-BPLA (*Blood Pressure Lowering Arm*), ADVANCE I PROGRESS što ga jasno izdvaja kao lijek izbora u skupini kardiovaskularnih bolesnika.

Received: 21st Dec 2011

*Address for correspondence: Klinička bolnica Dubrava, Avenija Gojka Šuška 6, HR-10000 Zagreb, Croatia.

Phone: +385-1-2902-444

E-mail: jakovpehar@hotmail.com

rence of diabetes and hyperlipidemia, indapamide is a diuretic with principally neutral metabolic effect, which makes it highly acceptable for a group of patients with diabetes and metabolic syndrome. It is important to note that the pharmacokinetic profiles of perindopril and indapamide are not modified when applied in a fixed combination, and show a continuous effect throughout a 24 hours' period. It is the index T/P (*through-to-peak*) that measures the rate of the total reduction in BP during the maximal effect compared to the effect achieved by the drug after 24 hours. Specifically, 50% T/P index means that the drug accomplishes 50% of its effect achieved by it during the maximum, peak drug concentration in plasma 24 hours after its administration. To conclude, the higher T/P results in more constant effect of the drug, which is, however, especially important due to the reduction of total cardiovascular risk during the morning hours when the incidence of adverse cardiovascular events is high.

Of all cardiovascular drugs, ACE inhibitors have the highest level of evidence in terms of prevention of cardiovascular events during the entire spectrum of cardiovascular diseases. It needs to be mentioned that not all ACE inhibitors are the same in terms of pharmacological efficacy and tolerance. Perindopril and ramipril have clearly demonstrated the reduction of cardiovascular risk in randomized clinical trials in the group of patients with stable angina pectoris, whereas quinapril and trandolapril did not have the above effect. The perindopril is based on the trials ASCOT-BPLA (*Blood Pressure Lowering Arm*), ADVANCE and PROGRESS which certainly makes it distinguished as a drug of choice in the group of cardiovascular patients.

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