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Fiksna kombinacija perindoprila i indapamida u liječenju arterijske hipertenzije

Fixed dose combination of perindopril and indapamide in the treatment of arterial hypertension

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SAŽETAK: Pridržavanje uputa za liječenje u posljednjih je nekoliko godina prepoznato kao jedan od glavnih čimbenika koji utječe na kontrolu arterijskog tlaka (AT) u hipertenzivnih bolesnika. Uporaba fiksnih kombinacija poboljšava suradljivost, što rezultira boljom kontrolom vrijednosti AT. Fiksna kombinacija perindoprila i indapamida zaslužuje posebnu pažnju zbog rezultata opsežnih istraživanja koja su pokazala prednost ne samo kod snižavanja vrijednosti AT, nego i kod kardiovaskularne prognoze. Nalazi kliničkih ispitivanja također su se potvrdili i u svakodnevnoj kliničkoj praksi. S vlastitom fiksnom kombinacijom perindoprila i indapamida Krka nudi mogućnost individualizirane terapije bilo za početak ili nastavak liječenja antihipertenzivima.

KLJUČNE RIJEČI: arterijska hipertenzija, kontrola arterijskog tlaka, fiksne kombinacije, perindopril, indapamid.

SUMMARY: Adherence of patients to therapy has in the past years been identified as one of the major factors influencing blood pressure (BP) control in treated population. The use of fixed dose combinations improves adherence, and consequentially increases the rate of BP control. The fixed dose combination of perindopril and indapamide deserves special attention because of the large-scale outcome trials which have shown its advantages beyond blood pressure lowering as well as improved cardiovascular prognosis. The results of the clinical trials have also been confirmed in daily clinical practice. With its fixed dose combination of perindopril and indapamide Krka offers the opportunity of individualized therapy either for start or for continuation of antihypertensive treatment.

KEYWORDS: arterial hypertension, blood pressure control, fixed dose combination, perindopril, indapamide.

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Nedovoljno kontrolirana vrijednost arterijskog tlaka (AT) predstavlja glavni čimbenik rizika za kardiovaskularne bolesti. Loša kontrola AT kod bolesnika s arterijskom hipertenzijom (AH) rezultira nezadovoljavajućim smanjenjem pojavnosti koronarne bolesti srca te porastom učestalosti kongestivnog zatajivanja srca i terminalnog zatajenja bubrega. Kontrola arterijskog tlaka (AT) tako ostaje jedno od najvažnijih pitanja u zbrinjavanju hipertenzije.[1]

Najvažniji čimbenik vezan uz pacijente koji rezultira neodgovarajućom kontrolom AT je nepridržavanje propisane antihipertenzivne terapije.[1,2] Studija iz Velike Britanije utvrdila da je oko 20% novodijagnosticiranih bolesnika s AH prekinulo terapiju unutar 6 mjeseci, a učestalost prekida je porasla na gotovo 30% unutar prve godine. Neke druge analize su pokazale još lošije rezultate. Trošak liječenja također može biti razlog slabog pridržavanja. Međutim, značajniji čimbenici su kompleksnost načina liječenja te podnošljivost lijekova. Promjene u terapiji, kao što su to dodatak novog lijeka, ukidanje

Inadequately controlled blood pressure is a major risk factor for cardiovascular disease. Poor blood pressure control rates result in disappointing reductions in prevalence of coronary artery disease, in high incidence of congestive heart failure and in even increasing incidence of end-stage renal failure among hypertensive patients. Blood pressure (BP) control thus remains one of the most important issues in the management of hypertension.[1]

The most important patient-related factor resulting in inadequate control of BP is non-adherence to the prescribed antihypertensive therapy.[1,2] A study in the UK has shown that approximately 20% of newly diagnosed hypertensive patients have discontinued therapy by 6 months and the discontinuation rate has increased to almost 30% by 1 year. Some other analyses showed even worse results. The cost of therapy may be a reason for poor adherence. However, the more decisive factors are too complex treatment regimens and drug tolerability. Changes in therapy, such as

ili zamjena lijeka također su povezani sa smanjenim pridržavanjem. Korisno je skrenuti pozornost bolesnicima na potrebu dugoročne primjene preporučenog liječenja.[2-4]

U upravo objavljenim ESH/ESC smjernicama iz 2013. za zbrinjavanje arterijske hipertenzije[5] navodi se da bi liječnik trebao obratiti pozornost na nepovoljne učinke lijekova koji predstavljaju snažnu prepreku pridržavanju liječenja. Prednost započinjanja antihipertenzivnog liječenja kombiniranom terapijom predstavlja pametnu odluku zbog veće vjerojatnosti bržeg postizanja ciljne vrijednosti AT i manju vjerojatnost nepridržavanja uputa zbog mogućih promjena u liječenju. Pacijenti na kombinaciji antihipertenziva imaju manju učestalost odustajanja nego oni na monoterapiji. Daljnje prednosti čine fiziološke i farmakološke sinergije između različitih antihiperteziva koji mogu rezultirati većim smanjenjem vrijednosti AT i manjom učestalosti nuspojava, čime se osiguravaju veće koristi od pojedinačnog antihipertenziva. U smjernicama ESH/ESC iz 2013. prednost se pridaje uporabi fiksnih kombinacija dva antihipertenziva u jednoj tableti, jer se smanjenjem dnevnog broja tableta poboljšava pridržavanje preporuka za liječenje, a posljedično i kontrola vrijednosti AT.[5]

Meta-analiza je pokazala da je liječenje fiksnom kombinacijom rezultiralo 26% smanjenjem nepridržavanja u odnosu na kombinaciju pojedinačnih lijekova. Složenost liječenja može se smanjiti primjenom fiksne kombinacije koja uključuje komponente s 24-satnom učinkovitošću, čime se omogućuje davanje lijeka jednom dnevno.[2]

Pridržavanje preporuka o terapiji utječe i na ishode. Bolje pridržavanje nije povezano samo sa znatno boljom kontrolom AT, nego rezultira i značajno manjom potrebom za bolničkim liječenjem. Slabo pridržavanje uputa povezano je s povećanim rizikom od komplikacija. Analiza više od 15.000 pacijenata iz SAD ukazala je na 15% veću učestalost hospitalizacija u skupini pacijenta koji se ne pridržavaju terapije.[2] Druga analiza 137.000 bolesnika mlađih od 65 godina s dijabetesom, hipertenzijom, hiperkolesterolemijom i kongestivnim zatajivanjem srca je pokazala da su učestalost hospitalizacije i troškovi zdravstvene zaštite bili značajno niži u onih koji su se značajno pridržavali preporuka za liječenje. Kardiovaskularni događaji bili su gotovo dvostruko češći kod ispitanika koji se nisu pridržavali uputa za liječenje.[4]

Kombinacija ACE inhibitora i diuretika ostaje jedan od željenih izbora za početnu terapiju, kao i terapiju održavanja.[3,5] Od različitih fiksnih kombinacija, ona s perindoprilom i indapamidom zaslužuje posebnu pažnju zbog rezultata opsežnih istraživanja te potvrdom rezultata kliničkih ispitivanja u svakodnevnoj kliničkoj praksi.

Bogato kliničko iskustvo je stečeno s indapamidom. Ovaj dugodjelujući, tiazidima sličan diuretik snižava AT putem dva mehanizma: natriuretskim diuretskim učinkom i vazodilatacijskim učinkom. Indapamid korigira visoku reaktivnost noradrenalina i smanjuje periferni otpor. Vrlo je lipofilan i može se akumulirati u plazmatskoj membrani vaskularnih glatkih mišićnih stanica, smanjiti priljev transmembranskog kalcija i izazvati vazodilataciju. Indapamid se dobro podnosi, a suprotno tiazidskim diureticima, nema negativan utjecaj na glukozu i metabolizam lipida. Indapamid ne izaziva razvoj intolerancije glukoze i pojavu novonastalog dijabetesa, ne uzrokuje povećanje razina ukupnog kolesterola, LDL-kolesterola i triglicerida.[6-10]

Istraživanje PICASSO provedeno kombinacijom perindoprila i indapamida u svakodnevnoj kliničkoj praksi pokazalo je klinički značajna sniženja razina ukupnog kolesterola LDL-kolesterola, triglicerida, glukoze natašte i urične kiseline,

adding a new drug, dropping or switching drugs are also associated with decreased adherence. It is beneficial to keep patients taking the initially assigned treatment in the long-term.[2-4]

The recently issued 2013 ESH/ESC Guidelines for the management of arterial hypertension[5] state that physician should pay attention to adverse drug effects which are powerful hindrance to treatment adherence. The advantage of initiating antihypertensive treatment with combination therapy is a smart decision due to a greater probability of early achieving the target BP and a lower probability of discouraging patient adherence with many treatment changes. Patients receiving combination therapy have a lower drop-out rate than patients given monotherapy. Further advantages are the physiological and pharmacological synergies between different classes of agents that may result in a greater BP reduction and cause fewer side effects thus providing larger benefits than a single agent. The 2013 ESH/ESC Guidelines favour the use of fixed dose combinations of two antihypertensive in a single tablet, because reducing the number of tablets which have to be taken daily improves adherence, and consequentially increases the rate of BP control.[5]

A meta-analysis showed that fixed-dose combination therapy resulted in a 26% decrease in non-adherence compared with free-drug component regimens. Complexity of treatment regimen can be reduced with fixed-dose combination that includes components with 24-hour efficacy, allowing for once-daily administration.[2]

Adherence to therapy predicts the outcomes. Better adherence is not associated only with a significantly better BP control, but also results in significantly lower hospitalization rates. Poor adherence on the other hand is associated with an increased risk of complications. An analysis of more than 15,000 patients in the US showed a 15% higher rate of hospitalization in the group of non-adherent patients.[2] Another analysis of 137,000 patients under the age of 65 with diabetes, hypertension, hypercholesterolemia, and congestive heart failure, hospitalization rates and health care costs were significantly lower for patients with high adherence. Cardiovascular events were almost twice as frequent in non-adherent study participants.[4]

The combination of ACE inhibitor and diuretic remains one of the preferred choices for initial as well as maintenance therapy.[3,5] Of various fixed dose combinations the one of perindopril and indapamide deserves special attention because of the large-scale outcome trials which have been performed with it and because the findings of the clinical trials have also been confirmed in daily clinical practice.

Wide clinical experience has been accumulated with indapamide. This long-acting thiazide-like diuretic lowers BP through two mechanisms: the natriuretic diuretic effect and the vasorelaxant activity. Indapamide corrects the high noradrenaline reactivity and reduces peripheral resistance. It is highly lipophilic and may accumulate in the plasma membrane of vascular smooth muscle cells, reduce transmembrane calcium influx and cause vasodilation. Indapamide is well tolerated and, contrary to the thiazide diuretics, has no adverse impact on glucose and lipid metabolism. Indapamide does not induce development of glucose intolerance and new-onset of diabetes and neither does it cause increase in total cholesterol, LDL-cholesterol and triglyceride levels.[6-10]

The PICASSO trial conducted with combination of perindopril and indapamide in daily clinical practice has shown clinically significant reductions in the levels of total cholesterol

dok su razine HDL-kolesterola, natrija i kalija ostale nepromijenjene.[10] Blagotvorne promjene metaboličkih parametara su prvenstveno pripisane zamjeni lijekova s nepovoljnim metaboličkim profilima, poput HCTZ i beta-blokatora.[10] Zbog metaboličke neutralnosti, indapamid je prikladan i kod bolesnika s dijabetesom tipa 2 te starijih osoba.[7]

Kombinacija perindoprila i indapamida učinkovito snižava AT i ima dodatno povoljne učinke: poboljšava disfunkciju endotela (poput poboljšanja protoka zbog dilatacije) što rezultira povoljnijom kardiovaskularnom prognozom; smanjuje krutost velikih arterija (prikazano smanjenom brzinom pulsnog vala i sniženim centralnim arterijskim tlakom u istraživanju REASON); smanjuje hipertrofiju lijeve klijetke (prikazano regresijom indeksa mase lijeve klijetke u istraživanju PICXEL i REASON), a smanjuje izlučivanje albumina urinom. Time se odgađa progresija i onemogućava pojava dijabetičke nefropatije.[7]

Rezultati velikog istraživanja kombinacije perindoprila i indapamida su ukazali na povoljne učinke i poboljšane kardiovaskularne ishode u bolesnika s AH, uključujući starije osobe i bolesnike s visokim kardiovaskularnim rizikom. Istraživanje PROGRESS je ukazalo na značajno smanjenje rizika od moždanog udara za 28% aktivnim liječenjem kombinacijom perindoprila i indapamida ili samo perindoprilom, dok je rizik fatalnog ili nefatalnog moždanog udara znatno smanjen za 43% kombinacijom perindoprila i indapamida. U istraživanju ADVANCE, fiksnom kombinacijom perindoprila i indapamida smanjen je relativni rizik od kardiovaskularne smrtnosti za 18%. Njome je također smanjen rizik od nefatalnog infarkta miokarda, nefatalnog moždanog udara i novonastale ili pogoršanja nefropatije. U dodatnoj analizi, fiksnom kombinacijom smanjen je rizik razvoja mikro- i makroalbuminurije za 21%, odnosno 31%. Ovom kombinacijom je istovremeno postignuta zaštita bubrega i kardiovaskularnog sustava. Liječenje su dobro podnosili 73% odnosno 74% sudionika koji su bili podvrgnuti aktivnom liječenju odnosno placebu, odnosbo pridržavanje terapije se nastavilo nakon prosječnog razdoblja od 4,3 godine praćenja.[9] U istraživanju HYVET, kombinacijom perindoprila i indapamida smanjena je učestalost fatalnog i nefatalnog moždanog udara za 30% te kardiovaskularnog mortaliteta za 23%, pri čemu je učestalost zatajivanja srca smanjena za 64%.[7]

Istraživanjem PRIMUS je potvrđena dobrobit perindoprila i indapamida u svakodnevnoj kliničkoj praksi. Ovom kombinacijom učinkovito su smanjene vrijednosti AT i pulsnog tlaka kod različitih bolesnika: novo dijagnosticiranih, starijih, onih s izoliranom sistoličkom AH, onih s dodatnim, kao i višestrukim kardiovaskularnim čimbenicima rizika, pridruženim kardiovaskularnim stanjima ili oštećenjem ciljnih organa i/ili dijabetesom tipa 2. Ukupno 98% ispitanika je odgovorilo na liječenje, a zabilježeno je tek nekoliko neželjenih događaja. Nisu zabilježene klinički značajne promjene laboratorijskih varijabli. Podnošljivost liječenja bila je ocjenjena kao dobra ili vrlo dobra kod 90% ispitanika.[8]

U Hrvatskoj Krka nudi cjelokupni asortiman perindoprila, uključujući kombinaciju perindoprila s indapamidom. Co-Perineva® je dostupna u tri terapijske doze (2mg/0,625mg; 4 mg/1,25 mg i 8 mg/2,5 mg) i nudi mogućnost individualizirane terapije bilo za početak ili nastavak liječenja antihipertenzivima.

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LDL-cholesterol, triglycerides, fasting glucose, and uric acid, while the levels of HDL-cholesterol, sodium, and potassium remained unchanged.[10] Beneficial changes in metabolic parameters were primarily attributed to replacement of drugs with unfavourable metabolic profiles, such as HCTZ and beta-blockers.[10] Due to metabolic neutrality indapamide is appropriate also in patients with type 2 diabetes and in elderly.[7]

The combination of perindopril and indapamide effectively lowers BP and has further favourable effects: it improves endothelial dysfunction (as shown by the improved flow-mediated dilation) which results in more favourable cardiovascular prognosis; it reduces large artery stiffness (as shown by decreased pulse wave velocity and reduced central blood pressure in the REASON trial); it reduces left ventricular hypertrophy (as shown by regression of the left ventricular mass index in the trials PICXEL and REASON) and decreases urinary albumin excretion. It delays progression of and reverses diabetic nephropathy.[7]

Large outcome trials with combination of perindopril and indapamide have shown the favourable properties and the improved cardiovascular outcomes in hypertensive patients, including the elderly and the high cardiovascular risk patients. The PROGRESS trial showed a highly significant stroke risk reduction of 28% by the active treatment with perindopril indapamide combination or perindopril alone, whereas the risk of fatal and non-fatal stroke was markedly decreased by 43% with combination of perindopril and indapamide. In the ADVANCE trial, the fixed dose combination of perindopril and indapamide reduced the relative risk of cardiovascular mortality by 18%. It also decreased the risk of non-fatal myocardial infarction, non-fatal stroke and new or worsening nephropathy. In a sub-analysis the fixed dose combination decreased the risk of developing micro- and macroalbuminuria by 21% and 31%, respectively. With this combination, simultaneous protection of the kidney and the cardiovascular system has been achieved. The treatment was well tolerated, with 73% and 74% of participants who received active treatment and placebo, respectively, still adherent to therapy after an average of 4.3 years of follow-up.[9] In the HYVET trial, the combination of perindopril and indapamide reduced the fatal or non-fatal stroke rate by 30% and the cardiovascular mortality by 23% whereas the rate of heart failure was reduced by 64%.[7]

The PRIMUS trial confirmed beneficial action of perindopril and indapamide in daily clinical practice, where this combination effectively reduced the BP rates and pulse pressure in various patients: newly diagnosed patients, the elderly, patients with isolated systolic hypertension, patients with additional, also multiple cardiovascular risk factors, associated cardiovascular conditions or target organ damage and/or type 2 diabetes. 98% of patients responded to treatment, and few adverse events were recorded. No clinically relevant changes in laboratory values were noted. Physicians rated treatment tolerability as good or very good in 90% of patients.[8]

In Croatia, Krka offers the entire perindopril portfolio including the combination of perindopril and indapamide. Co-Perineva® is available in three therapeutic dosages (2 mg / 0.625 mg; 4 mg / 1.25 mg and 8 mg / 2.5 mg) and offers the opportunity of individualized therapy either for start or for continuation of antihypertensive treatment.

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