Ivabradin u liječenju zatajivanja srca

Ivabradine in Heart Failure Treatment

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SAŽETAK: Ivabradin je lijek za usporivanje srčane frekvencije, koji djeluje selektivnom i specifičnom inhibicijom I_f struje predvodnika srčanog ritma, koji regulira spontanu dijastoličku depolarizaciju u sinusnom čvoru i frekvenciju srca. Učinci na srce odnose se specifično na sinusni čvor, bez učinka na intraatrijska, atrioventrikulska ili intraventrikulska vremena provođenja, ni na kontraktilnost miokarda ili ventrikulsku repolarizaciju. Ivabradin je indiciran u liječenju bolesnika s kroničnim zatajivanjem srca NYHA klasifikacije II.-IV. sa sistoličkom disfunkcijom, u bolesnika u sinusnom ritmu u kojih je frekvencija ≥ 75/min, u kombinaciji sa standardnom terapijom, uključujući beta-blokator, ili kad je beta-blokator kontraindiciran ili slabo podnošljiv. U takvih bolesnika ivabradin poboljšava prognozu smanjenjem rizika od svih uzroka smrti, kardiovaskularne smrti i smrti zbog zatajivanja srca. Poboljšava svakodnevno život povećanjem podnošenja tjelesnog napora te sprječava progresiju bolesti smanjenjem volumena lijeve klijetke i poboljšanjem istisne frakcije.

SUMMARY: Ivabradine is the first specific heart rate-lowering agent that selectively and specifically inhibiting the pacemaker (I_f) current, which regulates spontaneous diastolic depolarization in the sinus node and the heart rate. It directly affects the sinus node, with no effect on the interatrial, atrioventricular, or intraventricular conduction times, myocardial contractility, or ventricular repolarization. Ivabradine is indicated for patients with chronic heart failure, New York Heart Association (NYHA) classification II to IV, with systolic dysfunction and in patients with sinus rhythm with heart rate ≥75/min, in combination with standard therapy that includes beta blockers, or when beta-blockers are contraindicated or poorly tolerated. Ivabradine improves the prognosis in such patients, reducing the risk of mortality from all causes and mortality from cardiovascular events and heart failure. It improves quality of life by increasing tolerance for physical exertion and prevents progression of the disease by reducing the volume of the left ventricle and improving the ejection fraction.

KLJUČNE RIJEČI: ivabradin, frekvencija srca, zatajivanje srca.

KEYWORDS: ivabradine, heart frequency, heart failure.

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Ivabradin je lijek za usporivanje frekvencija srca, koji djeluje selektivnom i specifičnom inhibicijom I_f struje predvodnika srčanog ritma, koji regulira spontanu dijastoličku depolarizaciju u sinusnom čvoru i frekvenciju srca. Učinci na srce odnose se specifično na sinusni čvor, bez učinka na intraatrijska, atrioventrikulska ili intraventrikulska vremena provođenja, ni na kontraktilnost miokarda ili ventrikulsku repolarizaciju.[1]

Glavno farmakodinamsko svojstvo ivabradina jest specifično usporivanje frekvencije srca koje ovisi o dozi. Analiza usporenja frekvencije srca dozama do 2 x 20 mg upućuje na postojanje tren-

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The main pharmacodynamical characteristic of ivabradine is the specific reduction in heart rate that depends on the dosage. Analysis of the reduction in heart rate using doses up to 2 x 20 mg indicates that there is a trend towards

da prema plato učinku, što se slaže sa smanjenim rizikom od teške bradikardije s manje od 40/min. Uz uobičajene preporučene doze, frekvencija srca u mirovanju i tijekom fizičkog napora se usporuje za oko 10/min. To dovodi do smanjenja radnog opterećenja srca i potrošnje kisika u miokardu. Ivabradin ne utječe na intrakardijalno provođenje, kontraktilnost (nema negativnoga inotropnog učinka) ili na ventrikulsku repolarizaciju. Tijekom elektrofizioloških kliničkih ispitivanja ivabradin nije imao učinka na atrioventrikulska ili na intraventrikulska vremena provođenja ili korigirane QT intervale, dok u bolesnika s disfunkcijom lijeve klijetke (LVEF; istisna frakcija lijeve klijetke od 30 do 45%) ivabradin nije imao nikakav negativan utjecaj na LVEF.[2]

Antianginalna i antiishemijska djelotvornost ivabradina

Antianginalna i antiishemijska djelotvornost ivabradina ispitivana je u pet dvostruko slijepih, randomiziranih studija (tri s obzirom na placebo, a po jedna s obzirom na atenolol i amlodipin). U tim je studijama sudjelovalo ukupno 4111 bolesnika s kroničnom stabilnom anginom pektoris, od kojih je 2617 liječeno ivabradinom. U roku od 3 do 4 tjedna liječenja pokazalo se da je ivabradin u dozi od 2 x 5 mg imao učinak na parametre testa fizičkog opterećenja. Djelotvornost je potvrđena i dozom od 2 x 7,5 mg. Dodatna je prednost pred dozom od 2 x 5 mg utvrđena u referentnoj studiji s obzirom na atenolol: ukupno trajanje fizičkog opterećenja pri najnižoj koncentraciji lijeka povećano je za oko 1 minutu nakon mjesec dana liječenja dozom od 2 x 5 mg te se i dalje popravljalo za gotovo 25 sekundi nakon dodatnoga tromjesečnog razdoblja s ubrzanom titracijom na 2 x 7,5 mg. U toj su studiji potvrđene antianginalne i antiishemijske prednosti ivabradina u bolesnika u dobi od 65 godina i starijih. Djelotvornost doza od 5 i 7,5 mg dvaput na dan na parametre testa fizičkog opterećenja bila je postojana tijekom ispitivanja (ukupno trajanje fizičkog opterećenja, vrijeme do ograničavanja angine, vrijeme do nastupa angine te vrijeme do depresije ST-segmenta od 1 mm) i povezana sa smanjenjem brzine napadaja angine od oko 70%. Režim doziranja ivabradina od dva puta na dan rezultirao je ujednačenom djelotvornosti tijekom 24 sata.[3]

U randomiziranom, placebom kontroliranom ispitivanju kod 889 bolesnika primjena ivabradina uz postojeću primjenu atenolola u dozi od 50 mg jednom na dan pokazala je dodatnu djelotvornost na sve parametre u testu opterećenja u najnižoj točki djelovanja lijeka (12 sati nakon primjene per os).[4] U randomiziranom, placebom kontroliranom ispitivanju kod 725 bolesnika pokazalo se da ivabradin nema dodatne djelotvornosti povrh aktivnosti amlodipina od 10 mg jednom na dan pri najnižoj koncentraciji lijeka (12 sati nakon primjene), dok je u vršnoj koncentraciji uočena dodatna djelotvornost (3 – 4 sata nakon primjene). U randomiziranom, placebom kontroliranom ispitivanju kod 1277 bolesnika primjena ivabradina uz postojeću primjenu amlodipina od 5 mg jednom na dan ili nifedipina od 30 mg jednom na dan pri najnižoj koncentraciji lijeka (12 sati nakon primjene ivabradina per os) pokazala je statistički značajnu dodatnu djelotvornost u odgovoru na liječenje (definirano kao smanjenje od najmanje 3 napadaja

a plateau effect, which is in line with the reduced risk of severe bradycardia with less than 40/min. At common recommended doses, heart frequency at rest and during physical exertion is reduced by about 10/min. This leads to a reduction of the cardiac workload and myocardial oxygen consumption. Ivabradine does not affect intracardiac conduction, contractility (there is no negative inotropic effect), or ventricular repolarization. During electrophysiological clinical testing, ivabradine had no effect on atrioventricular and intraventricular conduction times or on corrected QT intervals, and patients with dysfunction of the left ventricle (LVEF; left ventricular ejection fraction from 30% to 45%) showed no negative effect on LVEF when treated with ivabradine.[2]

Antianginal and anti-ischemic effectiveness of Ivabradine

The antianginal and anti-ischemic effectiveness of ivabradine was tested in five double-blind, randomized trials (three in comparison with placebo, and one each in comparison with atenolol and amlodipine). A total of 4111 patients with chronic stable angina pectoris took part in these trials, 2617 of whom were treated with ivabradine. Ivabradine was shown to have an effect on physical exertion test parameters within 3 to 4 weeks of treatment in doses of 2 x 5 mg. The effectiveness of 2 x 7.5 mg doses was shown as well. An additional advantage compared with the 2 x 5 mg dose was shown in a reference study that compared it with atenolol: the total duration of physical exertion at the lowest dosage increased by about 1 minute after a month of treatment with the 2 x 5 mg dose, and improved further by almost 25 seconds after an additional three-month treatment with faster titration to 2 x 7.5 mg. That study also showed the antianginal and anti-ischemic advantages of ivabradine in patients over 65 years of age. The efficacy of the doses of 5 mg and 7.5 mg b.i.d. in improving physical exertion test parameters was consistent throughout the study period (total duration of physical exertion, time to limiting angina, time to angina onset, and time to ST-segment depression of 1 mm) and correlated with an improvement in the time before the advent of angina pain by about 70%. The dosage of two ivabradine doses per day resulted in a consistent efficacy over 24 hours.[3]

In a randomized placebo-controlled trial on 889 patients, treatment with ivabradine in conjunction with an existing atenolol treatment dosed at 50 mg once per day showed improvement in the exertion test across all parameters at the nadir effect of the medication (12 hours after oral ingestion).[4] A randomized placebo-controlled study on 725 patients showed that ivabradin has no additional effect over the effects of amlodipine 10 mg once per day at the nadir concentration (12 hours after administration of the drug), but at there was an additional effect at the highest concentration (3-4 hours after administration). In a randomized placebo-controlled trial on 1277 patients, the administration of ivabradine in conjunction with existing amlodipine therapy 5 mg once a day or nifedipine 30 mg once a day at the nadir concentration (12 hours after oral ingestion of ivabradine) showed a statistically significant added effect in treatment response (defined

angine na tjedan i/ili povećanje vremena do depresije ST-segmenta za 1 mm od najmanje 60 s za vrijeme testa opterećenja) tijekom 6 tjedana liječenja. Ivabradin nije pokazao dodatnu djelotvornost u sekundarnim ishodima parametara testa opterećenja pri najnižoj koncentraciji lijeka, dok je u vršnoj koncentraciji lijeka uočena dodatna djelotvornost (3 – 4 sata nakon primjene ivabradina).

U ispitivanjima djelotvornosti ivabradin se pokazao učinkovitim tijekom razdoblja liječenja u trajanju od 3 ili 4 mjeseca. Nije dokazano da tijekom liječenja nastaje farmakološka tolerancija, ni povratni fenomeni nakon naglog prekida liječenja. Antianginalni i antiishemijski učinci ivabradina bili su povezani s usporenjem frekvencije srca, koje je ovisilo o dozi te sa znatnim smanjenjem umnoška frekvencije i sistoličkoga tlaka u mirovanju i tijekom fizičkog napora. Učinci na arterijski tlak i periferni vaskularni otpor nisu bili klinički signifikantni.

U bolesnika liječenih ivabradinom najmanje godinu dana pokazalo se produljeno smanjenje frekvencije srca (n = 713). Nije zapažen utjecaj na vrijednosti glukoze u krvi ili metabolizam lipida. Antianginalna i antiishemijska djelotvornost ivabradina potvrđena je u dijabetičara (n = 457) sa sličnim sigurnosnim profilom kao u ostalih.

Ivabradin i koronarna bolest srca

Veliko ispitivanje BEAUTIFUL provedeno je kod 10 917 bolesnika s koronarnom bolesti srca (KBS) i disfunkcijom lijeve klijetke (LVEF < 40%) koji su bili liječeni uobičajenom terapijom, od kojih je 86,9% bolesnika primalo beta-blokatore. Glavni kriterij djelotvornosti bio je učinak na kardiovaskularni mortalitet, hospitalizacije zbog akutnog infarkta miokarda ili hospitalizacije zbog novonastalog ili pogoršanje postojećeg zatajivanja srca (ZS). Ispitivanje nije pokazalo razlike u primarnom ishodu između skupine s ivabradinom i one s placebom (relativan rizik ivabradin prema placebu 1,00, p = 0,945). U post-hoc analizi podskupine bolesnika sa simptomatskom anginom pri randomizaciji (n = 1507) sigurnost bolesnika nije bila ugrožena glede kardiovaskularne smrtnosti, hospitalizacije zbog akutnog infarkta miokarda ili ZS-a (ivabradin 12,0% prema placebu 15,5%, p = 0,005).[5]

Veliko ispitivanje ishoda, SIGNIFY, provedeno je kod 19 102 bolesnika s KBS-om bez kliničkih znakova ZS-a (LVEF < 40%), uz optimalnu osnovnu terapiju. Primijenjena je terapijska shema viša u odnosu prema odobrenom doziranju (početna doza lijeka 2 x 7,5 mg dva puta, odnosno 2 x 5 mg uz dob ≥ 75 godina; titracija doze sve do 2 x 10 mg). Glavni kriterij djelotvornosti bio je zbroj kardiovaskularne smrtnosti ili nefatalnog infarkta miokarda. Ispitivanje nije pokazalo razliku u stopi primarnoga zajedničkog ishoda (PZI) u ivabradinskoj skupini u usporedbi s placebom (relativni rizik ivabradin prema placebu 1,08, p = 0,197). Bradikardija je zabilježena u 17,9% bolesnika koji su uzimali ivabradin (2,1% u placebo skupini). Verapamil, diltiazem ili snažni inhibitori CYP3A4 primijenjeni su u 7,1% bolesnika tijekom ispitivanja. Mali, ali statistički značajan porast u PZI zabilježen je u prethodno definiranoj podskupini bolesnika s početno utvrđenom anginom pektoris CCS klase II ili više (n = 12 049) (godišnje stope 3,4% prema 2,9%, relativni rizik ivabradin

as a reduction of at least 3 angina attacks and/or increased period to 1 mm ST-segment depression by at least 60 s during an exertion tests) over a 6 week treatment period. Ivabradine showed no added effect in secondary outcomes of exertion test parameters at the nadir concentration, whereas an effect was found at the highest concentration of the medication (3-4 hours after administration).

In efficacy studies, ivabradine was shown to be effective during a treatment period of 3 or 4 months. Development of pharmacological tolerance was not noted during the treatment, and neither were rebound phenomena after sudden cessation of treatment. The antianginal and anti-ischemic of ivabradine corresponded to reduced heart rate, which was dependent on the dose and a significant decrease of the product of frequency ¥ systolic pressure at rest and during exertion. Effects on the arterial pressure and peripheral vascular resistance were not clinically significant.

Patients treated with ivabradine for at least a year showed extended heart rate reduction (n = 713). There was no effect on glucose values in the blood of lipid metabolism. The antianginal and anti-ischemic efficacy of ivabradine was also shown in diabetics (n = 457) with a similar safety profile as with other patients.

Ivabradine and coronary heart disease

The large BEAUTIFUL trial was performed on 10 917 patients with coronary heart disease (CHD) and left ventricle dysfunction (LVEF <40%) treated with the standard treatment, of which 86.9% received beta-blockers as well. The main criterion of efficacy was the effect on cardiovascular mortality, hospitalization for acute myocardial infarction, or hospitalization for newly-appeared or deteriorating heart failure (HF). The study showed no difference in primary outcomes between the ivabradine and placebo groups (relative risk ivabradine *vs.* placebo 1.00, p = 0.945). In post hoc analysis of the subgroup of patients with symptomatic angina at randomization (p = 0.945), the safety of patients was not compromised regarding cardiovascular mortality, hospitalization for acute myocardial infarction, or HF (ivabradine 12.0% compared with placebo 15.5%, p = 0.005).[5]

SIGNIFY, a large outcome trial, included 19 102 patients with CHD with no clinical signs of HF (LVEF < 40%) with optimal basic treatment. The applied therapeutic scheme was higher than the approved dosage (starting dose 2 x 7.5 mg twice a day or 2 x 5 mg for age ≥ 75; titration to 2 x 10 mg). The main primary composite outcomes (PCO) of was the sum of cardiovascular mortality or non-fatal myocardial infarction. The trial found no difference in PCO between the ivabradine and control groups (relative risk ivabradine vs. placebo 1.08; p = 0.197). Bradycardia was noted in 17.9% of the patients on ivabradine (2.1% in the control group). Verapamil, diltiazem, or strong CYP3A4 inhibitors were administered to 7.1% of the patients during the trial. A small but significant increase in PCO was found in a previously defined subgroup with initially diagnosed angina pectoris CCS class II or higher (n = 12 049) (annual rates 3.4% compared with 2.9%, relative risk ivabradine vs. placebo 1.18; p = 0.018), but not in the subgroup of the

din prema placebu 1,18, p = 0,018), ali ne u podskupini cjelokupne populacije bolesnika s anginom pektoris CCS klase ≥ I (n = 14 286) (relativni rizik ivabradin prema placebu 1,11; p = 0,110). Veća doza lijeka od odobrene primijenjena u ispitivanju nije u potpunosti objasnila ovakve rezultate.[6]

Ivabradin i zatajivanje srca

Zatajivanje srca jedan je od najvećih javnozdravstvenih problema u razvijenim zemljama i zemljama u razvoju, unatoč napretku u suvremenom farmakološkom zbrinjavanju i kontroli čimbenika rizika. U liječenju kroničnog ZS-a, velikog problema suvremene medicine, postoji potreba za razvojem novih terapijskih pristupa pa je svaki novi medikamentni utjecaj u nepovoljni patofiziološki tijek ove bolesti vrijedan pažnje kardiologa.

Godine 2010. objavljeni su rezultati istraživanja SHIFT (*Systolic Heart failure treatment with the IF inhibitor ivabradine Trial*), koje je ispitalo učinak dodatka ivabradina u bolesnika sa ZS-om, prethodno liječenih prema smjernicama. Studija je potvrdila da dodatno usporivanje frekvencije srca ivabradinom može pojačati prednosti neurohormonalne blokade u kroničnom ZS-u. Na rezultate ovog istraživanja reagirala su i svjetska kardiološka društva, i to prilagođivanjem postojećih nacionalnih smjernica ili objavljivanjem konsenzusa, koji čvrsto definiraju mjesto ivabradina u liječenju bolesnika sa ZS-om.[7-8]

Studija SHIFT, veliko multicentrično, međunarodno, randomizirano, dvostruko slijepo, placebom kontrolirano ispitivanje ishoda, provedeno je kod 6505 odraslih bolesnika sa stabilnim kroničnim ZS-om (trajanje ≥ 4 tjedna), NYHA stupnja II. – IV., sa smanjenom istisnom frakcijom lijeve klijetke (LVEF ≤ 35%) i frekvencijom srca u mirovanju ≥ 70/min.[9]

Bolesnici su liječeni standardnim terapijskim pristupom, uključujući beta-blokatore (89%), inhibitore ACE i/ili antagoniste angiotenzina II (91%), diuretike (83%) i antagoniste aldosterona (60%). U skupini bolesnika liječenih ivabradinom 67% bolesnika liječeno je dozom 2 x 7,5 mg. Medijan razdoblja praćenja bio je 22,9 mjeseci. Liječenje ivabradinom bilo je povezano s prosječnim smanjenjem frekvencije srca od 15/min s početnih 80/min. Razlika u frekvenciji srca između skupina liječenih ivabradinom i placebom bila je 10,8/min nakon 28 dana; 9,1/min nakon 12 mjeseci i 8,3/min nakon 24 mjeseca. Ovo je ispitivanje pokazalo klinički i statistički značajno smanjenje relativnog rizika od 18% za PZI (kardiovaskularna smrtnost i hospitalizacija zbog pogoršanja ZS-a), što je postalo očito unutar prva tri mjeseca od početka liječenja. Smanjenje apsolutnog rizika iznosilo je 4,2%. Rezultati vezani za PZI većim su dijelom posljedica ishoda ZS-a, ishoda hospitalizacija zbog pogoršanja ZS-a (smanjenje apsolutnog rizika za 4,7%) i smrti zbog ZS-a (smanjenje apsolutnog rizika za 1,1%).[9-11]

Smanjenje PZI zabilježeno je konzistentno bez obzira na spol, NYHA stupanj, etiologiju ZS-a te prisutnost dijabetesa ili arterijske hipertenzije. U podskupini bolesnika s frekvencijom srca ≥ 75/min (n = 4150) zabilježeno je izraženije smanjenje PZI od 24%, kao i za ostale sekundarne ishode, uključujući ukupnu smrtnost i smrt zbog kardiovaskularnih uzroka. U

total patient population with angina pectoris CCS class ≥I (n = 14 286) (relative risk ivabradine vs. placebo 1.11; p = 0.110). Higher doses than approved that were used in the study did not fully account for these results.[6]

Ivabradine and heart failure

Heart failure is one of the greatest public health issues in developed and developing countries, despite the advancements in modern pharmacological treatment and risk factor control. There is a constant need for the development of new therapeutic approaches in the treatment of chronic HF, so any newly discovered medication effect on the course of this disease is worth noting.

In 2010, the results of the SHIFT (Systolic Heart failure treatment with the IF inhibitor ivabradine Trial) trial were published, which looked at the effect of adding ivabradine treatment to patients with HF, previously treated according to existing guidelines. The trial showed that the additional reduction in heart rate from ivabradine can amplify the positive effects of neurohormonal blockade in chronic HF.[7-8]

The SHIFT trial was a large multicentric, international, randomized, double blind, placebo-controlled outcome trial performed on 6505 adult patients with stable chronic HF (duration ≥4 weeks) of NYHA classes II to IV, with reduced ejection fraction of the left ventricle (LVEF ≤ 35%) and resting heart rate ≥70/min.[9]

Patients were treated using a standard therapeutic approach that included beta-blockers (89%), ACE inhibitors and/or angiotensin II inhibitors (91%), diuretics (83%), and aldosterone antagonists (60%). In the group of patients treated with ivabradine, 67% were treated with a 2 x 7.5 mg dose. The median follow-up period was 22.9 months. Ivabradine treatment was associated with an average reduction in heart rate of 15/min from the initial 80/min. The difference in heart rate between the ivabradine and placebo groups was 10.8/min after 28 days; 9.1/min after 12 months, and 8.3/min after 24 months. This study showed a clinically and statistically significant reduction in relative risk of 18% for PCO (cardiovascular mortality and hospitalization for deteriorating HF), which became clear within the first three months of the treatment. The reduction in absolute risk was 4.2%. Results related to PCO were mostly a consequence of HF outcomes, outcomes of hospitalization for deteriorating HF (4.7% reduction in absolute risk), and death due to HF (reduction in absolute risk of 1.1%).[9-11]

The reduction in PCO was consistent regardless of gender, NYHA class, HF etiology, or the presence of diabetes or arterial hypertension. In the subgroup of patients with a heart rate ≥75/min (n = 4150) a more significant reduction in PCO of 24% was noted, as well as of other secondary outcomes, including total mortality and mortality from cardiovascular causes. The safety profile of ivabradine in this subgroup was the same as in the other groups.

A significant effect on PCO was noted in the whole group of patients taking beta-blockers. In the subgroup of patients with heart rate ≥75/min that received the recommended target dose of beta-blockers, there was no significant improvement in PCO or other secondary outcomes. A significant improve-

ovoj podskupini bolesnika sigurnosni profil ivabradina jednak je profilu ostalih.

Značajan učinak na PZI zabilježen je u cjelokupnoj skupini bolesnika koji primaju terapiju beta-blokatorima. U podskupini bolesnika sa frekvencijom srca ≥ 75/min koji primaju preporučenu ciljnu dozu beta-blokatora nije zabilježena značajna korist za PZI ni za ostale sekundarne ishode. Zabilježeno je znatno poboljšanje NYHA stupnja kod posljednje zabilježene vrijednosti, 887 (28%) bolesnika liječenih ivabradinom postiglo je poboljšanje, za razliku od 776 (24%) bolesnika u placebo skupini (p = 0,001).

SHIFT studija upozorila je na činjenicu da se dodatkom ivabradina, koji usporuje frekvenciju srca inhibiranjem depolarizacije sinusnoga čvora, poboljšavaju ishodi u bolesniika sa ZS-om zbog sistoličke disfunkcije lijeve klijetke sa sinusnim ritmom i uz frekvenciju ≥ 70/min. Pozitivan ishod studije potvrđuje smanjenje broja hospitalizacija zbog ZS-a, a *post-hoc* analiza upozorila je na moguću dobrobit na preživljenje bolesnika i s frekvencijom srca u mirovanju ≥ 75/min.[9,12,13]

U sklopu studije SHIFT 275 bolesnika koji su dobivali ivabradin 2 x 7,5 mg bili su uključeni u ehokardiografsku podstudiju. Zabilježeno je smanjenje frekvencije srca, ali i povišenje udarnog volumena, što je rezultiralo održavanjem minutnog volumena.[14]

U drugoj ehokardiografskoj podstudiji kod 411 bolesnika i pri praćenju tijekom 8 mjeseci u skupini s ivabradinom zabilježeno je statistički značajno smanjenje volumena lijeve klijetke na kraju dijastole za 5,5 mL/m^2 prema skupini na placebu te dobrobit mjerena istisnom frakcijom od 2,7%. Smanjenje frekvencije srca u bolesnika sa ZS-om i sistoličkom disfunkcijom imalo je pozitivan učinak na remodeliranje lijeve klijetke. Smanjenje volumena lijeve klijetke i poboljšanje istisne frakcije upućuje i na poboljšanje prognoze bolesti.[15]

U studiji CARVIVA, prospektivnoj, randomiziranoj, otvorenoj, slijepoj studiji u kojoj su bolesnici dobivali optimalnu dozu ACE inhibitora, dodatak ivabradina ili uzimanje u kombinaciji s karvedilolom rezultiralo je znatnim poboljšanjem podnošenja tjelesnog opterećenja u odnosu prema bolesnicima koji su dobivali samo beta-blokator (27% prema 15%).[16]

Procjena ivabradina u smjernicama NICE preporučuje ga kao dodatak za bolesnike s frekvencijom srca u mirovanju ≥ 75/min, koji su već na standardnoj terapiji, uključujući i prikladan beta-blokator na maksimalno podnošljivoj dozi.[17]

Zaključno, ivabradin je indiciran za simptomatsko liječenje kronične stabilne angine pektoris u odraslih bolesnika s KBS-om s normalnim sinusnim ritmom i s frekvencijom srca ≥ 70/min. Ivabradin je indiciran u odraslih bolesnika koji ne podnose beta-blokatore ili je njihova primjena kontraindicirana ili pak u kombinaciji s beta-blokatorima u bolesnika koji nisu adekvatno kontrolirani optimalnom dozom.[14]

Ivabradin je indiciran i u kroničnom ZS-u stupnja II. do IV. prema NYHA klasifikaciji sa sistoličkom disfunkcijom, u bolesnika u sinusnom ritmu s frekvencijom srca ≥ 75/min u kombinaciji sa standardnom terapijom, uključujući terapiju beta-blokatorom ili kada je primjena beta-blokatora kontraindicirana ili se ne podnosi. Liječenje treba započeti u bolesnika sa stabilnim ZS-om. Preporučuje se da ordinirajući liječnik

ment in NYHA class was found in the last recorded value; 887 (28%) patients treated with ivabradine achieved improvement, in comparison with 776 (24%) of patients in the placebo group (p = 0.001).

The SHIFT trial brought to attention the fact that adding ivabradine, which reduces heart rate by inhibiting the depolarization of the sinus node, improves outcomes in patients with HF caused by systolic dysfunction of the left ventricle with sinus rhythm and a heart rate ≥70/min. The positive outcome of the trial also indicated a positive effect on survival of patients with a resting heart rate ≥75/min.[9,12,13]

As part of the SHIFT trial, 275 patients receiving ivabradine 2 x 7.5 mg were included in an echocardiographic substudy. A reduction in heart rate was found, but also an increase in cardiac output (stroke volume), resulting in a stable minute volume.[14]

A second echocardiographic substudy on 411 patients found, over a 8 month follow-up, a statistically significant reduction in left ventricular end-diastolic volume of 5.5 mL/m^2 in comparison with the control group, and benefit as measured by the ejection fraction of 2.7%. A reduction in heart rate in patients with HF and systolic dysfunction had a positive effect on left ventricle remodeling. The reduction in left ventricular volume and an improvement in the ejection fraction indicate an improvement in the disease prognosis as well.[15]

The CARVIVA trial, a prospective, randomized, open, blinded study in which the patients received an optimal dose of ACE inhibitors and ivabradine or a combined treatment with carvedilol showed a significant improvement in tolerance for physical exertion in comparison with patients who received only beta blockers (27% vs. 15%).[16]

NICE guidelines recommend ivabradine as an additional medication for patients with resting heart rates ≥75/min who are already taking standard beta-blockers at a maximal tolerated dose.[17]

Finally, ivabradine is indicated for symptomatic treatment of chronic stable angina pectoris in adult patients with CHD with a normal sinus rhythm and a heart rate ≥70/min. Ivabradine is indicated in adult patients who do not tolerate beta-blockers or when their use is contraindicated, and in combination with beta-blockers in patients who were not adequately controlled by the optimal dose.[14]

Ivabradine is also indicated in chronic HF of classes II to IV according to the NYHA classification with systolic dysfunction in patients in sinus rhythm with a heart rate ≥75/min, in combination with standard treatment, including beta-blockers or when beta-blockers are contraindicated and poorly tolerated. Treatment should be started in patients with stable HF. It is recommended that the physician has experience in treating chronic HF. The usual starting ivabradine dose is 2 x 5 mg. After two weeks of treatment, the dose can be increased to 2 x 7.5 mg if the resting heart rate is constantly above 60/min, or reduced to 2 x 2.5 mg if the heart rate is constantly lower than 50/min or if symptoms associated with bradycardia present themselves, such as light headedness, fatigue, or hypotension. If the heart rate is between 50 and 60/min, the 2 x 5 mg dose should be maintained. If the resting heart rate falls below 50/min, the dose should be titrated to a lower level

ima iskustva u vođenju liječenja kroničnog ZS-a. Uobičajena preporučena početna doza ivabradina jest 2 x 5 mg. Doza se nakon dva tjedna liječenja može povećati na 2 x 7,5 mg ako je frekvencija srca u mirovanju stalno viša od 60/min ili smanjiti na 2 x 2,5 mg ako je frekvencija srca stalno niža od 50/min ili nastupe simptomi koji su povezani s bradikardijom, poput omaglice, umora ili hipotenzije. Ako je frekvencija srca između 50 i 60/min, potrebno je održavati dozu od 2 x 5 mg. Nastavi li se, tijekom liječenja, srčana frekvencija usporivati 50/min u mirovanju, ili u bolesnika nastupe simptomi koji su povezani s bradikardijom, doza se mora titrirati na sljedeću nižu u bolesnika koji primaju 2 x 7,5 mg ili 2 x 5. Ako je frekvencija srca stalno viša od 60/min u mirovanju, doza se može titrirati na višu u bolesnika koji uzimaju 2 x 2,5 mg ili 2 x 5 mg. Liječenje se mora prekinuti ako je frekvencija srca sporija od 50/min ili simptomi bradikardije ustraju.[9]

Pri farmakološkoj konverziji fibrilacije atrija u sinusni ritam, u bolesnika koji se liječe ivabradinom nije zabilježena opasnost od razvoja (prekomjerne) bradikardije. No, s obzirom na to da nema dovoljno podataka, elektivna DC kardioverzija može se učiniti 24 sata nakon posljednje doze ivabradina.

U ispitivanju SHIFT nešto veći broj bolesnika liječenih ivabradinom doživio je epizode povišenoga arterijskog tlaka (7,1%) u usporedbi s placebom (6,1%). Takve su se epizode najčešće pojavile ubrzo nakon promjene liječenja arterijske hipertenzije, bile su prolazne i nisu utjecale na terapijski učinak ivabradina. Ako se mijenja liječenje arterijske hipertenzije u bolesnika s kroničnim ZS-om liječenih ivabradinom, potrebno je pratiti vrijednosti tlaka u odgovarajućim intervalima.[18]

Zaključak

U zaključku možemo reći da je ivabradin indiciran u liječenju bolesnika s kroničnim ZS-om stupnja II. – IV. prema NYHA klasifikaciji, sa sistoličkom disfunkcijom, u bolesnika u sinusnom ritmu u kojih je frekvencija ≥ 75/min, u kombinaciji sa standardnom terapijom, uključujući beta-blokator, ili kad je beta-blokator kontraindiciran ili slabo podnošljiv. U takvih bolesnika ivabradin poboljšava prognozu smanjenjem rizika od svih uzroka smrti, kardiovaskularne smrti i smrti zbog ZS-a. Poboljšava svakodnevno život povećanjem podnošenja tjelesnog napora, sprječava progresiju bolesti smanjenjem volumena lijeve klijetke i poboljšanjem istisne frakcije.

Ivabradin se dobro podnosi, zabilježen je minimalan rizik od bradikardije i nije bilo rizika od hipotenzije. Lijek se lagano titrira i može se kombinirati s velikim brojem drugih kardiovaskularnih lijekova.[19,20]

in patients that are taking doses of 2 x 7.5 mg or 2 x 5 mg. If the resting heart rate is constantly above 60/min, the dose can be titrated to a higher level in patients taking 2 x 2.5 mg and 2 x 5 mg doses. Treatment must be discontinued if the heart rate falls below 50/min or if bradycardic symptoms persist.[9]

In pharmacological conversion of atrial fibrillation to sinus rhythm, patients treated with ivabradine showed no danger of developing (significant) bradycardia. However, since the data on this issue are not sufficient, elective direct-current cardioversion can be performed 24 hours after administering the last dose of ivabradine.

In the SHIFT trial, a somewhat larger number of patients treated with ivabradine experienced episodes of elevated arterial pressure (7.1%) compared with the control group (6.1%). These episodes most commonly occurred after a change in the treatment for arterial hypertension, were transitory, and did not influence the therapeutic effect of ivabradine. When introducing changes in treatment for arterial hypertension in patients with chronic HF treated with ivabradine, it is necessary to monitor arterial pressure at appropriate intervals.[18]

Conclusion

We can conclude that ivabradine is indicated in patients with chronic HF classes II to IV according to the NYHA classification with systolic dysfunction, in patients in sinus rhythm with a frequency ≥75/min, in combination with standard therapy including beta-blockers, or when beta-blockers are contraindicated or poorly tolerated. In such patients, ivabradine improves the prognosis by reducing mortality from all causes, cardiovascular death, and death due to HF. It improves quality of life by increasing tolerance for physical exertion and prevents disease progression by reducing the volume of the left ventricles and improving the ejection fraction.

Ivabradine is well tolerated, with minimal risk of bradycardia and no risk of hypotension. It is easy to titrate and can be combined with a large number of other cardiovascular medication.[19,20]

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