Digoksin u terapiji zatajivanja srca, zastario ili još uvijek koristan?

Digoxin for heart failure, obsolete or still useful?

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Digoksin je pozitivni inotropni agens, jedini podoban za kroničnu peroralnu primjenu u bolesnika sa sistoličkim zatajivanjem srca (HFrEF < 45-50%) sa ili bez fibrilacije atrija. Značajna su i neurohumoralna svojstva suzbijajući prekomjernu aktivnost simpatičkog i renin-aldosteronskog sustava. Brojna ispitivanja potvrđuju da ostvaruje izuzetne hemodinamske učinke povećavajući ejekcijsku frakciju lijeve klijetke (LVEF), kardijalni indeks smanjujući plućni kapilarni tlak. Usporava rad srca i neutralno utiče na arterijski tlak. Stoga za razliku od beta-blokatora i ACE-i/ARB-a može se sigurno primijeniti kod bolesnika s nižim vrijednostima arterijskog tlaka. Digoksin je povezan i s poboljšanjem bubrežne funkcije, procijenjeno porastom glomerularne filtracije za 20%. Stoga se za razliku od inhibitora renin-angiotenzin-aldosteronskog sustava, može primijeniti u bolesnika s graničnom funkcijom bubrega bez rizika od daljnjeg oštećenja bubrega.

Digoksin je bio lijek prvog izbora dugi niz godina, sve dok istraživanje DIG skupine 1997. godine nije dokazalo da lijek ne smanjuje smrtnost kod bolesnika u stupnju III./IV. prema NYHA s vrijednostima LVEF ≤40% ili u onih u II. stupnju prema NYHA klasifikaciji s LVEF≤ 30% neovisno o prisutnosti fibrilacije atrija, iako doprinosi smanjenju simptoma i učestalosti bolničkog liječenja.[1] DIG studiji se može zamjeriti da u terapiji zatajivanja srca u to vrijeme nisu korišteni beta-blokatori i antagonisti aldosterona, a propisivane su relativno visoke doze digoksina koje danas nisu uobičajene. Samo posljednjih desetak godina primjena digoksina u liječenju HFrEF pala je za dvije trećine. Prema navodima američkog registra GWTH-HF na 250.000 bolesnika sa HFrEF učestalost primjene digoksina preporučenoj kod otpusta smanjena je sa 33,1% 2005. na 10,7% bolesnika tijekom 2014. godine.[2,3]

Aktualne Europske (razina preporuka IIb) i Američke smjernice (razina preporuka IIa) preporučuju digoksin kod bolesnike s HFrEF koji imaju stalne simptome unatoč optimalnoj terapiji, a u cilju smanjenja učestalosti hospitalizacije. Prilikom primjene digoksina preporučuju se male doze ekvivalentne serumskoj koncentraciji < 0,9 ng/ml.

U studijama sa stabilnom HFrEF kada je prekinuta terapija digoksinom uslijedilo je pogoršanje simptoma, smanjila se tolerancija opterećenja i registriran je pad LVEF. U izrazito teških slučajeva HFrEF uvođenjem digoksina uspjelo se ukloniti mehaničku cirkulatornu potporu i intravenske inotropne lijekove.

Posljednjih dvadesetak godina uvelike se promijenila terapija zatajivanja srca. Pored moderne terapije uključujući i mehaničku potporu, transplantaciju srca nedostaje interes industrije za digoksin te je malo vjerojatno da će drugo kliničko ispitivanje veličine DIG biti sponzorirano. Treba poći i od činjenice da je digoksin vrlo jeftin lijek.

Kliničar se suočava s dilemom oslanjanja na kvalitetu podataka koji proizlaze iz kliničkih ispitivanja provedenih prije više od dva desetljeća i prije nego što je moderna terapija zatajivanja srca bila dostupna ili na

Digoxin is a positive inotropic agent, the only one suitable for chronic oral administration in patients with systolic heart failure (HFrEF < 45-50%) with or without atrial fibrillation. Significant neurohumoral properties are also significant by suppressing the excessive activity of the sympathetic and renin-aldosterone system. Numerous studies confirm that it gives exceptional hemodynamic effects by increasing the left ventricular ejection fraction (LVEF), the cardiac index by reducing pulmonary capillary pressure. It slows down the heart function and neutralizes blood pressure. Therefore, unlike beta-blockers and ACEs/ARBs, it can safely be used in patients with lower blood pressure values. Digoxin is also associated with the improvement of the renal function, estimated by 20% increase in glomerular filtration. Therefore, unlike the renin-angiotensin-aldosterone system inhibitor, it can be used in patients with limiting renal function without the risk of further renal impairment.

Digoxin has been the first choice drug for many years until the 1997 DIG trial proved that the drug does not reduce mortality in patients in III/IV stage according to NYHA with the values of LVEF ≤40% or those in the II stage according to the NYHA classification with LVEF≤ 30% regardless of the presence of atrial fibrillation, although it contributes to the reduction of the symptoms and frequency of inpatient treatment.[1] DIG study may not be criticized for not using beta-blockers and aldosterone antagonists in the heart failure therapy at that time and relatively high digoxin doses were prescribed, which are not common today. Only in the last decade, the use of digoxin in the treatment of HFrEF has decreased by two-thirds. According to the US GWTH-HF register of 250,000 patients with HFrEF, the frequency of use of digoxin recommended at the time of release was reduced from 33.1% in 2005 to 10.7% patients in 2014.[2,3]

Current European (IIb recommendation level) and US guidelines (IIa recommendation level) recommend digoxin in patients with HFrEF who have permanent symptoms despite optimal therapy in order to reduce the incidence of hospitalization. When using digoxin, small doses equivalent to serum concentrations <0.9 ng/ml are recommended.

In studies with stable HFrEF, the discontinuation of the digoxin therapy was followed by worsening of symptoms, where the physical stress tolerance was reduced and LVEF fall was recorded. In extremely severe cases of HFrEF, the introduction of digoxin managed to remove the mechanical circulatory support and intravenous inotropic drugs.

For the last twenty years, the heart failure treatment has changed considerably. Owing to modern therapy including the mechanical support and the heart transplantation, the industry shows no interest in digoxin and is very likely that some other DIG volume clinical trial will be sponsored. We should also emphasize the fact that digoxin is a very cheap drug.

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dokaze iz uglavnom opservacijskih studija. Digoksin vjerojatno još uvijek ima opravdanje u bolesnika s teškom uznapredovalom sistoličkom disfunkcijom koji nisu u stanju tolerirati visoke doze lijekova zbog graničnih vrijednosti arterijskog tlaka, bubrežne funkcije. Lijek također treba koristiti s ciljem smanjenja ponovljenih hospitalizacija, a današnji bolesnik sa sistoličkim zatajivanjem srca je u prosjeku 10 godina stariji nego u DIG ispitivanju i dnevna doza od 0,10 može biti odgovarajuća za veći broj bolesnika.

A clinician faces the dilemma of whether he should rely on the data quality resulting from clinical trials conducted more than two decades ago and before modern heart failure therapy was available or on the evidence from mostly observational studies. Digoxin is probably still justified in patients with severely advanced systolic dysfunction who are unable to tolerate high doses of drugs due to limit values of blood pressure, renal function. The drug should also be used to reduce recurrent hospitalization, and the today's patient with systolic heart failure is on the average 10 years older than the one in the DIG trial and a daily dose of 0.10 may be adequate for a larger number of patients.

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