Use of digoxin in older patients

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Abstract
In the treatment of worsening of systolic heart failure important role maintains digoxin. In the management of older patients it is important to take into account age-related changes of pharmacokinetics and pharmacodynamics, decreased glomerular filtration rate, sex and concomitant diseases. Older individuals have lower tolerance of digitalis than younger. They have increased risk of digitalis toxicity. Digitalis Investigation Group clinical study has proven that in patients aged 65 years and older only small serum digoxin concentration (0.5–0.9 ng/mL) is related to reduce in all cause mortality. The recommended daily dose of digoxin for these patients is 0.125 mg per day. Digoxin could be administered to all patients with heavy heart failure and decreased systolic function together with ACE inhibitors, beta-blockers, spironolactone, diuretics. Thus, the role of digoxin in treatment of heart failure remains secondary.

Keywords:
older patients, digoxin toxicity, daily dose of digoxin

Treatment of chronic heart failure (HF) has rapidly progressed during last 20 years. Big randomized clinical studies have shown benefit of suppression of renin-angiotensin-aldosteron and sympathetic nervous systems. Heart resynchronization treatment was introduced. Optimization of medicamental treatment with angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers, beta-blockers, aldosteron antagonists reduced morbidity and mortality due to HF. Nevertheless, in many patients despite treatment HF is progressing. In the treatment of worsening of systolic HF important role maintains digoxin [1]. Digitalis glycosides which are among the most ancient medications in treatment for cardiovascular diseases have been firstly described by British doctor William Withering in 18th century [2, 3]. Cardiac glycosides have positive inotropic action, they improve contractile function, not increasing heart rate. In cellular level digoxin is suppressing enzyme sodium-potassium adenosine triphophatase, thus increasing intracellular level of calcium. Digoxin has potential of neurohormonal suppression [2–4]. The first big clinical trials RADIANCE (Randomized Assessment of Digoxin and Inhibitors of Angiotensin Converting Enzyme) and PROVED (Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin) performed in 1990 have proven big clinical benefit of digoxin use in treatment of worsening of HF [4, 5]. DIG (Digitalis Investigation Group) trial has shown that digoxin improves clinical symptoms and reduces hospitalization in patients with systolic HF treated with ACE inhibitors and diuretics. However, in patients treated with digoxin and in placebe group mortality was similar, there was no influence on cardiovascular mortality [6, 7].
Thus, the aim of digitalis therapy is to improve quality of life, decreasing the symptoms and signs of heart failure and to prevent hospitalization.

Heart failure is the most frequent cause of hospitalization among persons aged 65 years and above [2, 8]. Cardiac glycosides are widely used in older patients to treat congestive HF and supraventricular tachyarrhythmias such as atrial fibrillation [9].

In the management of older patients it is important to take into account age-related changes of pharmacokinetics and pharmacodynamics, decreased glomerular filtration rate, sex, and concomitant diseases [10]. Older individuals have lower tolerance of digitalis than younger and the risk of digitalis toxicity is increasing with age [2–4, 11]. Digitalis toxicity in 80% of cases is diagnosed in patients aged 65 years and above [4]. Mortality from acute digoxin intoxication in older age ranges from 8 to 58% [9]. In older age electrolyte imbalance and impaired renal function is met more often. Although serum creatinine level is normal, glomerular filtration rate can be decreased especially in patients with lower body mass [12]. The most frequent causes predisposing to intoxication with digoxin are loss of potassium due to diuretics or secondary hyperaldesteronism, older age, myocardial infarction or ischemia, hypothyrosis, hypercalcemia, renal failure. Older patients often have several diseases, they use many medications. Drugs increasing digoxin toxicity are chinidin, eritromycin, verapamil, diltiazem, captopril, anticholinergics, ibuprofen, amiodarone, clindamycin [3].

Digoxin toxicity can be displayed with various symptoms and signs: head ache, nausea, vomiting, diarrhea, changes in vision of colors, general malaise. More complex are arrhythmias caused by digoxin: sinus bradycardia, sinus pauses, atrioventricular blocks, ventricular tachyarrhythmias [3–5, 8, 9]. Risk for digitalis caused arrhythmias is increased by age, low potassium level, chronic obstructive pulmonary disease (COPD), amyloidosis, worsening of kidney disease [4]. Digoxin can cause pulmonary vasoconstriction in COPD patients. These patients due to hypoxia and acidosis make high risk group. Digoxin therapy should be avoided in treatment of right ventricular failure, caused by COPD [6].

Therapeutic digoxin levels usually vary; the lower limit ranges from 0.6–1.3 ng/mL, while the upper limit generally is agreed to be 2.6 ng/mL [3, 13]. Although assessment of serum digoxin level is not recommended as obligatory routine test, serum concentration associated with toxicity overlap between therapeutic and toxic ranges because of big number of factors potentiating digoxin toxicity.

DIG clinical study has proven that in patients aged 65 yrs and older only small serum digoxin concentration (0.5–0.9 ng/mL) is related to reduce in all-cause mortality. Older patients quite often have chronic atrial fibrillation and heart failure. In these patients serum digoxin concentration 0.5–0.8 ng/mL is optimal [13, 14]. The recommended daily dose of digoxin for these patients is 0.125 mg per day [2, 11]. The treatment should be started with the same dose. Even lower digoxin dose, 0.125 mg every second day, is recommended for the patients aged 75 and older, women, patients with renal failure, treated with big doses of diuretics, with repeated pulmonary oedemas [2]. Special attention should be payed to women. They have increased risk of digitalis toxicity. In older women digitalis toxicity is met more often than in men [13, 15, 16]. Big digoxin doses increase lethality of older females [15, 17]. Digoxin concentration 0.5–0.8 ng/mL is associated with decreased lethality in women as compared with placebo group, thus recommended serum digoxin concentration is below 1 ng/mL [13, 15].

To control heart rate in older patients with impaired mobility digoxin monotherapy can be sufficient [12, 18]. However, many older adults live rather active life, are engaged in sports. In physical activity digoxin alone can not ensure control of heart rate. In these cases, digoxin can be used together with beta-blockers or calcium channel blockers (verapamil, diltiazem) [12, 19]. Combination of digoxin with beta-blockers is more effective and safe in comparison with combination of digoxin with calcium channel blockers [12]. Digoxin nowadays is not a drug of choice to control heart rate in atrial fibrillation [7]. Digoxin in combination with carvedilol increases ejection fraction of left ventricle and decreases symptoms of heart failure more effectively than both medications separately.

Digoxin is decreasing morbidity but has no influence on survival. Digoxin could be administered to all patients with heavy heart failure and decreased systolic function together with ACE inhibitors, beta blockers, spironolactone, diuretics. Thus, the role of digoxin in treatment of heart failure remains secondary. In treatment of older patients it is important to set the optimal dose, considering age, gender, renal function, concomitant diseases and medications used.
Conclusions
1. Aging is associated with increased digitalis toxicity.
2. For older patients recommended digoxin daily dose is 0.125 mg and serum digoxin concentration of 1 ng/mL is sufficient.
3. For patients aged 75 years and older, women, having renal failure, treated with big doses of diuretics recommended dose of digoxin is 0.125 mg each other day.
4. To control heart rate in physically active patients combination of digoxin with beta-blockers is recommended.

References
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DIGOKSINO VAROJIMAS VYRESNIO AMŽIAUS PACIENTAMS

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Santrauka

Progresuojančio sistolinio širdies neoakankamumo gydyme svarbią vietą tebeturi digoksinas. Gydant vyresnio amžiaus pacientus, svarbu atsižvelgti į amžiaus įtakotą pakitusią vaisų farmakokinetiką ir farmakodinamiką, mažėjantį glomerulų filtracijos greitį, lytį ir gretutrines ligas. Vyresnio amžiaus pacientai blogiau toleruoja digitalio preparatus nei jaunesni, o toksinio poveikio rizika didėja su amžiumi. DIG (Digitalis Investigation Group) klinikiniame tyrime išanalizavus 65 metų ir vyresnių pacientų, nustatyta, kad tik esant mažai digoksino koncentracijai (0,5–0,9 ng/ml) mažėja bendras mirštamuos. Šiems pacientams rekomenduojama digoksino dozė yra 0,125 mg dienai. Digoksinas galėtų būti skiriamas visiems pacientams, sergantiesiomis sunkiu širdies nepakankamumu ir sumažėjusia sistoline funkcija kartu su AKFI, beta-adreno-blokatoriais, spironolaktonu, diuretikais. Digoksino vaidmuo, gydant širdies nepakankamumą, išlieka antrinis.

Raktažodžiai:
vyresnis amžius, digoksino toksiškumas, digoksino dozavimas