Clinical researches

QTc INTERVAL DURATION CLASS AND DRUG THERAPY OF PATIENCE IN A FIRST YEAR AFTER PACEMAKER IMPLANTATION

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49 patients (28 female, 21 male) with implanted DDD/DDDR, VVI/VVIR and CRT pacemakers are investigated. Purpose frequency and dose rate of anticoagulants, antiplatelet agents, direct thrombin inhibitors, cardiac glycosides, amiodarone; ivabradine, diuretics, aldosterone antagonists, beta-adrenergic blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), statins were evaluated before, in acute postoperative period (3–5 days), 6 months and 1 year after pacemaker implantation. Patients were divided into classes 1 (normal QTc (320–440 ms)) – 24 (49 %) patients) and 2 (long QTc (> 440 msec)) – 25 (51 %) patients) of QTc interval duration. To process the data using standard statistical procedures using Microsoft Excel. It was more often prescriptions of new anticoagulants, beta-adrenergic blockers, ARBs, statins to patients in the first year after pacemaker implantation. QTc interval duration lengthening was associated with a greater purpose frequency and doses of amiodarone, diuretics, beta-adrenergic blockers, ACE inhibitors, ARBs and statins. Patients with implanted pacemaker need individualized drug therapy according to QTc interval duration, in particular, enhancing antiischemic, antihypertensive, antiarrhythmic therapy and therapy of chronic heart failure in patients with QTc interval duration lengthening.

KEY WORDS: pacemaker, drug therapy, QTc interval duration

КЛАС ТРИВАЛОСТІ ІНТЕРВАЛУ QTc ТА МЕДИКАМЕНТОЗНИЙ МЕНЕДЖМЕНТ ПАЦИЄНТІВ В ПЕРШИЙ РІК ПІСЛЯ ІМПЛАНТАЦІЇ ЕЛЕКТРОКАРДІОСТИМУЛЯТОРУ

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Обстежено 49 пацієнтів (28 жінок, 21 чоловік) з імплантованими електрокардіостимуляторами (ЕКС) в режимах DDD/DDDR, VVI/VVIR і CRT. Оцінювали до, в гострому післяопераційному періоді (3–5 добу), через півроку і 1 рік після імплантації ЕКС частоту призначення і коефіцієнт дози антикоагулянтів, антиагрегантів, прямих інгібіторів тромбіну, серцевих глікозидів, аміодарону; івабрадину, діуретиків, антагоністів альдостерону, блокаторів бета-блокатори, антагоністів кальцію, інгібіторів ангіотензіперетворюючого ферменту (АПФ), блокаторів рецепторів ангіотензину II (БРА), статинів. Пацієнти були розділені на класи 1 (нормального QTc (320–440 мс)) – 24 (49 %) пацієнтів) та 2 (подовженого QTc (> 440 мс)) – 25 (51 %) пацієнтів) тривалості інтервалу QTc. Для обробки даних використовувалися стандартні статистичні процедури за допомогою Microsoft Excel. Пацієнтам в перший рік після імплантації ЕКС більш часто призначаються нові антикоагулянти, блокатори бета-блокатори, БРА, статини. Подовження тривалості інтервалу QTc асоціювалося з більшими частотою призначення і дозами аміодарону, сечогінних препаратів, блокаторів бета-блокатори, інгібітори АПФ, БРА і статинів. Пацієнти з імплантованими ЕКС потребують індивідуалізованого медикаментозного менеджменту з урахуванням тривалості інтервалу QTc, зокрема, посилення антиішемічної, антигіпертензивної, антиаритмічної терапії і терапії хронічної серцевої недостатності (ХСН) у пацієнтів зі збільшенням тривалості інтервалу QTc.

КЛЮЧОВІ СЛОВА: електрокардіостимулятор, медикаментозний менеджмент, тривалість інтервалу QTc

КЛАСС ПРОДОЛЖИТЕЛЬНОСТИ ИНТЕРВАЛА QTc И МЕДИКАМЕНТОЗНЫЙ МЕНЕДЖМЕНТ ПАЦИЕНТОВ В ПЕРВЫЙ ГОД ПОСЛЕ ИМПЛАНТАЦИИ ЭЛЕКТРОКАРДИОСТИМУЛЯТОРА

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Обследованы 49 пациентов (28 женщин, 21 мужчина) с имплантированными ЭКС в режимах DDD/DDDR, VVI/VVIR и CRT. Оценивали до, в остром послеоперационном периоде (3-5 сутки), через полгода и 1 год после имплантации ЭКС частоту назначения и коэффициент дозы антикоагулянтов, антиагрегантов, прямых ингибиторов тромбина, сердечных гликозидов, амиодарона; ивабрадина, диуретиков, антагонистов альдостерона, блокаторов бета-адренорецепторов, антагонистов кальция, ингибиторов ангиотензипревращающего фермента (АПФ), блокаторов рецепторов ангиотензина II (БРА), статинов. Пациенты были разделены на классы 1 (нормального QTc (320–440 мс)) – 24 (49 %) пациентов и 2 (удлиненного QTc (> 440 мс)) – 25 (51 %) пациентов) продолжительности интервала QTc. Для обработки данных использовались стандартные статистические процедуры с помощью Microsoft Excel. Пациентам в первый год после имплантации ЭКС более часто назначаются новые антикоагулянты, блокаторы бета-адренорецепторов, БРА, статины. Удлинение продолжительности интервала QTc ассоциировалось с большими частотой назначения и дозами амиодарона, мочегонных препаратов, блокаторов бета-адренорецепторов, ингибиторов АПФ, БРА и статинов. Пациенты с имплантированными ЭКС нуждаются в индивидуализированном медикаментозном менеджменте с учетом продолжительности интервала QTc, в частности, усилении антиишемической, антигипертензивной, антиаритмической терапии и терапии хронической сердечной недостаточности (ХСН) у пациентов с увеличением продолжительности интервала QTc.

КЛЮЧЕВЫЕ СЛОВА: электрокардиостимулятор, медикаментозный менеджмент, продолжительность интервала QTc

INTRODUCTION

Cardiac pacing (CP) in different regimes is one of the leading therapies of bradyarrhythmias and chronic heart failure (CHF) [1]. Improving survival and quality of life of patients [1], it is almost always require the concomitant drug treatment as a pacemaker (PM) implantation previous diseases and conditions induced by the PM.

Currently, it is generally accepted the same approach drug therapy of patients with a spontaneous and stimulated rhythm [1–2], however, multi-center studies show that the use of different groups of drugs in patients with a permanent CP should have a number of features.

QTc interval duration lengthening is a poor prognostic indicator as for patients with spontaneous rhythm, as for patients with CP [3–4]. Despite this, especially drug therapy of patients with going of QTc interval duration beyond the normal physiological values after PM implantation has not yet been studied.

OBJECTIVE

The aim of the research is to evaluate drug therapy of patients in the first year after pacemaker implantation in QTc interval duration classes.

MATERIALS AND METHODS

49 patients aged 69 ± 10 (M ± sd) (28 – female, 21 – male) were examined in the department of ultrasound and instrumental diagnostics with miniinvasive interventions of GI «Zaycev V. T. Institute of General and Urgent Surgery of NAMS of Ukraine», 10 among them have an atrial fibrillation (AF). All patients were implanted pacemaker from 2008 to 2014, pacing is carried out in regimes: DDD (10 patients), DDDR (13 patients), VVI (7 patients), VVIR (11 patients), CRT (8 patients).

Patients aged less than 40 years, presence of concomitant stable angina IV functional class (FC), chronic heart failure (CHF) IV FC and/or stage III, the stimulation of the right ventricle (RV) and/or left ventricular (LV) less than 50 % were excluded from the study.

Chronic ischemic heart disease (IHD) was observed in 31 (63 %) patients, including 9 patients – myocardial infarction. Arterial hypertension was observed in 37 (76 %) patients, AF – in 10 (20 %) patients, CHF – in 35 (71 %) patients.

Drug therapy was represented by the following groups of drugs: B01A A anticoagulants (warfarin); B01A C antiplatelet therapy (aspirin, clopidogrel); B01A E direct thrombin inhibitors (dabigatran etexilate), and V01A F direct factor Xa inhibitors (rivaroxaban) (new anticoagulants); C01A cardiac glycosides (digoxin); C01B D01 amiodarone; C01E B17 ivabradine; C03 diuretics (furosemide, torasemide, hydrochlorothiazide); S03D A aldosterone antagonist (spironolactone); C07A beta-adrenergetic blockers (carvedilol, metoprolol, bisoprolol, nebivolol); C08C A calcium channel antagonists (dihydropyridine derivatives – amlodipine, nifedipine and fenilalkilamin derivatives – verapamil); C09A angiotensin converting enzyme (ACE) inhibitors (enalapril, lisinopril, ramipril); C09C angiotensin II receptor blockers (ARBs) (losartan, candesartan); C01A A hydroxymethylglutaryl inhibitors (HMG) coenzyme A (CoA) (statins) (atorvastatin, simvastatin).

Dose coefficient for each group of drugs has been calculated as the average value among the ratios of each drug dose group versus middle therapeutically for this drug, taken as 1.0. It corresponds to the group of anticoagulants warfarin 5 mg; antiplatelet agents – 75 mg of aspirin and 75 mg clopidogrel; 75 mg of dabigatran etexilate and 5 mg rivaroxaban; in the group of cardiac glycosides – 0.00025 mg digoxin; 200 mg amiodarone; 10 mg ivabradine; in the group of diuretics – 40 mg furosemide, 5 mg torasemide, 12.5 mg hydrochlorothiazide, 2.5 mg indapamide; in the group of aldosterone antagonists – 50 mg spironolactone; in the group of beta-adrenergic blockers – 5 mg bisoprolol, 100 mg metoprolol, 12,5 mg carvedilol, 5 mg nebivolol, 5 mg betaxolol, 50 mg atenolol; in the group of calcium channel antagonists – amlodipine 10 mg, nifedipine 90 mg, verapamil 80 mg; in the group of ACE inhibitors – 10 mg enalapril, 10 mg of lisinopril, 5 mg ramipril, 10 mg fosinopril; group ARBs – 50 mg losartan, 8 mg candesartan; in the group of statins – 20 mg atorvastatin, 20 mg simvastatin, 10 mg rosuvastatin.

To measure the duration of the QT interval and heart rate of the patients before and after pacemaker implantation (3–5 days after surgery) were recorded on a computer ECG electrocardiograph «Cardiolab +» (HAI-Medica). The stimulated QTc interval duration was measured after the removal of the stimulus artifact in three consecutive complexes of the Q wave to the beginning of the descending segment of the return of the T wave in leads to the contour II, V5, and V6 with choosing of a maximum value. The corrected QT interval duration (QTc) of the patients with spontaneous rhythm and pacing was calculated by the Bazett formula: $QTc = QT/(RR \wedge 0,5)$. For patients with AF, QTc was calculated using the formula of Fermingem study for patients with atrial fibrillation: $QTc = QT + 0,154 \times (1000 - RR)$ [5], the measurement accuracy – 0.5 ms.

The patients with pacemakers were divided into 3 classes of stimulated QTc interval duration: class 1 – normal (in the physiological range of values) – 320–439 ms, class 2 – (qualified) an elongated QTc – > 440 ms, and class 3 (qualified) shortened the QTc – < 320 ms [6].

In class 1 of QTc interval duration 24 (49 %) patients were included, mean age 66 ± 10 years (men – 13, women – 11) and in class 2 – 25 (51 %) patients, mean age 69 ± 9 years (males – 8, female – 17). In the class 3 is not a single patient was registered. Frequency of prescribing groups and dose rate of each of the groups of drugs in relation to the middle therapeutically dose were evaluated before, in the acute postoperative period, after 6 months and 1 year after PM implantation in QTc interval duration classes.

The data were processed after formation the Microsoft Excel and Statistica base. For statistical evaluation of the results, the parametric criteria (mean – M, standard deviation – sd) and nonparametric ones (absolute (n, number) and relative (percentage of (p, %) and the mean percentage error (sP), the criterion χ2) units) were used. The probability of differences between groups was determined using a non-parametric U – Mann-Whitney test. The expected result is determined by levels of reliability p < 0.01 and p < 0.05.

RESULTS AND DISCUSSION

Before PM implantation it was the most commonly prescribed in the order of ACE inhibitors, antiplatelet agents, statins, beta-adrenergetic blockers, diuretics; and less likely: amiodarone, cardiac glycosides, calcium

channel blockers, aldosterone antagonists, new anticoagulants. In acute postoperative period after PM implantation frequency of appointment of beta-adrenergic blockers was increased, in the rest of drugs the frequency was not significantly changed. By 6 months, and 1 year frequency of appointments of anticoagulants, new anticoagulants, beta-adrenergic blockers, ARBs, statins were consistently increased; of digoxin - decreased; of other groups of drugs – there were no significant changes.

Frequency of appointments and dose ratio groups of drugs in patients in first year after PM implantation in QTc interval duration classes are shown in table.

Table

Frequency of appointments and dose ratio groups of drugs in patients in first year after PM implantation in QTc interval duration classes

Pharmacological drugs		QTc interval duration class							
		Class 1				Class 2			
		Before PM implantation	Acute postoperative period	After 6 months CP	After 6 months CP	Before PM implantation	Acute postoperative period	After 6 months CP	After 6 months CP
B01A A Anticoagulants	Percentage of patients (% ± p)	6 ± 6*	14 ± 9	14 ± 9	20 ± 10	10 ± 7*	18 ± 8	26 ± 9	29 ± 9
	Dose ratio (M ± sd)	1	1	1,1 ± 0,3	1,2 ± 0,4	1	1,5 ± 0,5	1,3 ± 0,7	1,5 ± 0,5
B01A C Antiplatelets	Percentage of patients (% ± p)	38 ± 9	37 ± 13	50 ± 13	56 ± 14	35 ± 11	37 ± 9	45 ± 11	67 ± 16*
	Dose ratio (M ± sd)	1	1	1 ± 0,06	1	1 ± 0,5	1	1	1 ± 0,2
C01A Cardiac glycosides	Percentage of patients (% ± p)	12 ± 10	9 ± 6	7 ± 7	12 ± 10	31 ± 9*,**	23 ± 9	9 ± 6	21 ± 7*,**
	Dose ratio (M ± sd)	1	1	1	1	1	1	1	1
C01B D01 Amiodarone	Percentage of patients (% ± p)	13 ± 11	14 ± 9	21 ± 11	18 ± 9	13 ± 10	18 ± 8	27 ± 9**	32 ± 11**
	Dose ratio (M ± sd)	1 ± 0,4	0,75 ± 0,25	1,2 ± 1,3**	1 ± 0,4	1,2 ± 0,5	1,75 ± 0,4*,**	1 ± 0,3	1,9 ± 0,5*,**
C01E B17 Ivabradin	Percentage of patients (% ± p)	-	-	-	-	-	7 ± 7	7 ± 7	7 ± 7
	Dose ratio (M ± sd)	-	-	-	-	-	1	1	1
C03 Diuretics	Percentage of patients (% ± p)	13 ± 10	14 ± 9	29 ± 12**	26 ± 11**	21 ± 10	23 ± 9	36 ± 10**	39 ± 11*,**
	Dose ratio (M ± sd)	1 ± 0,3	0,75 ± 0,25	1,5 ± 0,75	1,1 ± 0,6	1,2 ± 0,5	1,8 ± 1*	1,9 ± 1	2,1 ± 1*
C03D A Aldosteron antagonists	Percentage of patients (% ± p)	10 ± 5	9 ± 6	16 ± 6*	12 ± 4	8 ± 5	7 ± 7	18 ± 8*	31 ± 13*,**
	Dose ratio (M ± sd)	1 ± 0,4	0,8 ± 0,4	1,2 ± 0,5	1 ± 0,4	0,8 ± 0,3	0,75 ± 0,25	1,3 ± 0,4**	1,6 ± 0,5**

Continuation of the table

C07A Beta-adrenergetic blockers	Percentage of patients (% ± p)	12 ± 7	57 ± 13**	64 ± 13**	69 ± 14**	19 ± 11	45 ± 11	73 ± 10**	82 ± 11**
	Dose ratio (M ± sd)	0,7 ± 0,3	0,9 ± 0,3	1,1 ± 0,4	0,9 ± 0,3	0,8 ± 0,3	0,9 ± 0,3	1,1 ± 0,6	1,5 ± 0,8
C08C A Dihidropiridin calcium channel antagonists	Percentage of patients (% ± p)	11 ± 7	9 ± 6	21 ± 11*,**	17 ± 9*,**	8 ± 5	5 ± 4	9 ± 7	12 ± 6
	Dose ratio (M ± sd)	0,8 ± 0,2	0,5	0,7 ± 0,2	0,5	1 ± 0,3	1,25 ± 0,3	0,8 ± 0,3	1,1 ± 0,3
C08D A01 Fenilalkilamin calcium channel antagonists	Percentage of patients (% ± p)	-	8 ± 6	17 ± 10*,**	14 ± 8	-	5 ± 4	9 ± 7	11 ± 9
	Dose ratio (M ± sd)	-	1,1 ± 0,1	1	1	-	1	1,1 ± 0,7	1,2 ± 0,7
C09A ACE ingibitors	Percentage of patients (% ± p)	39 ± 12	36 ± 13	43 ± 13	40 ± 11	31 ± 8	27 ± 9	45 ± 10**	62 ± 9**
	Dose ratio (M ± sd)	1,2 ± 0,2	1	0,7 ± 0,3	0,8 ± 0,3	1,1 ± 0,4	1 ± 0,3	1,6 ± 0,4**	1,2 ± 0,3
C09C ARBs	Percentage of patients (% ± p)	9 ± 6	9 ± 6	14 ± 9	26 ± 14**	4 ± 5	14 ± 7**	18 ± 8**	21 ± 10**
	Dose ratio (M ± sd)	1	1	1	1,2 ± 0,4	1 ± 0,2	1,3 ± 0,4	1	1,3 ± 0,4
C01A A Statins	Percentage of patients (% ± p)	20 ± 10	21 ± 11	36 ± 13**	30 ± 11**	20 ± 11	18 ± 8	36 ± 10**	49 ± 14*,**
	Dose ratio (M ± sd)	0,6 ± 0,2	0,8 ± 0,2	0,8 ± 0,2	0,6 ± 0,2	0,7 ± 0,2	0,9 ± 0,2	0,9 ± 0,2	1,3 ± 0,3*,**

Note: M-average value; sd - standard deviation; *p < 0.05 – between values in classes; **p < 0.05 – between values before, in the acute postoperative period, 6 months and 1 year CP.

Frequency of appointment of anticoagulants, new anticoagulants and antiplatelet agents before and during acute postoperative period after PM implantation did not differ in QTc interval duration classes 1 and 2. By 6 months and 1 year, and it has increased in both classes without significant change drugs doses.

Frequency of digoxin prescription at baseline was greater in QTc interval duration class 2, successively decreasing to 6-month observation period in both classes. By the year it has increased in the class 2 and even more diminished in class 1. The dose of digoxin remained middle therapeutically at all stages of monitoring.

Destination frequency of amiodarone did not differ before and after PM implantation in classes 1 and 2. The dose increase in class 2 to 6 months and a year of observation.

Frequency of appointment and dose ratio of diuretics before PM implantation did not differ in QTc interval duration classes, at 6 months and 1 year consistently increased in both classes 1 and 2. Destination frequency and dose ratio of aldosterone antagonists has also increased to a year, but only in QTc interval duration class 2.

Initially, the same frequency of beta-adrenergic blockers destination, with PM implantation at observation stages consistently increased in both QTc interval duration classes, to a greater degree in the class 2. The dose of beta-adrenergic blockers increased 6 months after PM implantation only in QTc interval duration class 2.

Frequency of appointment of ACE inhibitors and ARBs did not differ before PM implantation in QTc interval duration classes. With implantation to 6 months it has increased

in the class 2 with increasing of ACE inhibitors doses.

Destination frequency of statins before and during acute postoperative period after PM implantation did not differ, however, increased after 6 months in both QTc interval duration classes. Increasing the dose of statins was observed only in the class 2 1 year after PM implantation.

Frequencies of destination and dose ratio of ivabradine, dihydropyridine and fenilalkilamin calcium channel antagonists were the same before and on the stages of follow-up after PM implantation in studied QTc interval duration classes.

We have shown an increase of appointment frequency of anticoagulants, new anticoagulants, beta-adrenergic blockers, ARBs in patients in the first year after PM implantation, that's corresponds to [7–8].

Lack of communication of frequency of appointment increasing for new antiplatelet agents and anticoagulants with QTc interval duration lengthening, shown by us, is consistent with [9] for patients with spontaneous rhythm.

Described in our study the relationship QTc interval duration lengthening and greater frequency of amiodarone destination corresponds to the data [10], diuretics – [11], selective blocker of beta-adrenergic receptors - [12–13] for patients with a spontaneous rhythm without CP. This relationship may be due to the fact of repolarization process violation with the QTc interval duration lengthening is one of the manifestations of myocardial dyssynchrony and, as a consequence, a greater risk of heart failure, and arrhythmias developing [14].

A larger increase in amiodarone, diuretics, and statins dose in patients with QTc interval duration lengthening had shown us, corresponds to the data [10] for patients without a PM. Relation of dose ratio of different groups cardiovascular drugs with QTc interval duration class in patients 1 year after PM implantation has not previously been studied.

CONCLUSIONS

1. Patients in first year after PM implantation more often were prescribed new anticoagulants, beta-adrenergetic blockers, ARBs, statins.

2. QTc interval duration lengthening is associated with a greater frequency of appointments and doses of amiodarone, diuretics, beta-adrenergic blockers, ACE inhibitors, ARBs and statins in patients in first year after PM implantation.

3. Patients with implanted PM need individualized drug management according to QTc interval duration, in particular, enhancing antiischemic, antihypertensive, antiarrhythmic therapy and therapy of CHF in patients with a QTc interval duration lengthening.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate to examine the connection of QTc interval duration changes with the appointment frequency and dose ratio of cardiovascular drugs in period more than a year after PM implantation.

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