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Prolongation of the QT interval in patients with coronary heart disease as consequence of drug-drug interactions on metabolic rate

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ABSTRACT

Objective: Prolongation of the *QT* interval in patients with coronary heart disease (CAD) is a risk factor of polymorphic ventricular tachycardia (PVT) and as consequence, the sudden death. Drug-drug interactions (DDI) on metabolic rate involving cytochrome P-450 (CYP) is the one of the major cause of Long QT Syndrome (LQTS). The aim of the present study was to improve the safety of combined pharmacotherapy when using drugs that affect the *QT* interval.

Method and Results: Medication occurrence of potential dangerous combination of medicines that are affected on *QT* interval duration in patients with CAD are researched (outpatient medical records (patient history) analysis). Clinical relevance of DDI, which are associated with changes in CYP enzyme activity, categorized by *drugs.com Medication Guide*. Finding potential dangerous combination of medicines that are affected on *QT* interval duration were administered to patients with CAD in 3.6% cases in outpatient clinical practice. The most often prescribed combination of drugs is amiodarone and torasemide (13.3% evidence of all concomitant administration that are leading to *QT* prolongation). The potential mechanism of Amiodarone and Torasemide interaction on metabolic rate that are leading to *QT* prolongation are competitive substrates CYP 2C8 and a result of inhibited CYP 2C9 by amiodarone.

Conclusion: Ability to predict the prolongation of the *QT* interval caused by DDI on metabolic rate make possible to improve the safety concomitant administration to patients with CAD.

Keywords: coronary heart disease, safety of concomitant administration, *QT* interval, polymorphic ventricular tachycardia, sudden death, drug-drug interactions, metabolism

INTRODUCTION

In recent years, there is a close attention in clinical cardiology that is given to the problem of *QT* prolongation as a risk factor of life-threatening cardiac arrhythmias – polymorphic ventricular tachycardia (PVT). The basis of the Long *QT* Syndrome (LQTS) lies in asynchrony of different parts of ventricular myocardium repolarization, electrocardiographic indication of myocardial asynchrony is the prolongation of the *QT* interval, as well as the degree of its dispersion. Clinical aspects of the LQTS are proneness to arrhythmic syncope conditions and higher risk of developing fatal cardiac arrhythmias, mainly torsades de pointes (TdP) (1, 2).

The risk of sudden death in congenital LQTS without adequate treatment reaches 85%, while 20% of children die in their first year after first loss of consciousness and more than half of them during the first decade of their life (3). The acquired variant of the LQTS is more common in daily clinical practice, which is usually connected with drug use. The list of such drugs is constantly updated on the website of the The Arizona Center for Education and Research on Therapeutics (AZCERT) organization (http://crediblemeds.org) (4).

Cardiac arrhythmias may be caused by both cardiac drugs (antiarrhythmics) and other drugs (antihistamines, antidepressant medication, antipsychotics, neuroleptic drugs, beta-blockers, antimalarial drugs, serotonin reuptake inhibitors, certain vasodepressors, antimicrobial drugs) (4-8). Due to the adverse drug reaction (ADR), ever since the first

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sign of severe arrhythmias and cardiac arrest appeared, the registration of antihistamine drug Terfenadin (Teldane) was withdrawn in USA in 1998, and Astemizol in 1999. ADR data have been observed mainly in patients with compromised liver function and / or in simultaneous intake of ACE inhibitors (9). The Sertindol antipsychotic was withdrawn from the German market because of the risk of developing severe unwanted cardiovascular manifestations (dose-dependent prolongation of *QT*, sudden cardiac death), Janssen withdrew the Cisaprid prokinet from the market in April 2000, after the Food and Drug Administration registered more than 340 reports of cardiac arrhythmias, 80 cases of which were fatal.

The situation is exacerbated by chronic patients with comorbidity, who were observed for a long time as an outpatient, receive drug combination therapy for years, due to the presence of several diseases or lack of efficacy of the monotherapy (10, 11). The drug-drug interaction (DDI) is possible in such combination therapy. Potentially dangerous combination of drugs is a serious clinical problem. There is evidence that between 17% and 23% of drug combinations prescribed by physicians are potentially dangerous. The danger of such combination can be enhanced in the presence of DDI on metabolic rate. The main mechanisms of DDI are associated with their pharmacokinetic or pharmacodynamics change (12-16). According to modern ideas, the most significant changes are pharmacokinetic changes in the interaction of drugs on metabolic rate involving cytochrome P-450 (17-21).

Combinations of drugs with a probable and conditional risk of prolonging the *QT* interval between themselves, as well as a combination of these drugs with drugs that can affect the activity of the cytochrome P450 isoenzymes that metabolize them, require special care from the doctor.

In this regard, it is important to identify the most frequently used drugs in the outpatient clinic practice that are affected on *QTc* interval duration, combinations of drugs with a probable and conditional risk of prolonging the *QT* interval, and the effect of these drugs on the activity of the cytochrome P450 isoenzymes that metabolize them (22,23).

MATERIALS AND METHODS

935 patient history were researched in outpatient clinic of the Moscow Health Department with a case of *QT* prolongation caused by drug-induced LQTS: 620 men and 315 women aged 50-75 years, the average age was 59,2±8,3.

The analysis revealed that the *QT* prolongation was observed in 86 (9.2%) of 935 patients (54 men and 32 women, the average age is 57 ± 7.2 years), from whom a group of 34 (3, 6%) patients with coronary heart disease (CAD) with suspicion of prolongation of the *QT* interval was selected due to pharmacotherapy.

The clinical profile of patients with CAD included in the study is presented in **Table 1**. All patients with CAD had exertional angina of varying degrees of severity: FC I exertional angina was diagnosed in 12 (13.9%) patients, FK II in 67 (77.9%), FK III in 7 (8.1%) patients. 9 (10.4%) patients with CAD had arterial hypertension (AH) of the I degree, 36 (41.9%) patients had AH of the II degree, 41 (47.7%) patients had AH of the III degree. The course of CAD in 53 patients was complicated by the development of congestive heart failure (CHF): FC I CHF in 15 (17.4%), FC II CHF in 38 (44.2%) patients. Myocardial infarction and acute disorders of cerebral circulation had a history of 12% and 2% of patients, respectively; cardiac arrhythmias were recorded in approximately one third of patients in the work sample: ventricular premature beats (VPB) in 15 (17.4%) patients, permanent atrial fibrillation (AF) in 11 (12.8%) patients, paroxysmal AF in 16 (18,6%) patients.

The *QT* prolongation ranged from 355 to 506 ms; the corrected *QT* prolongation (*QT* (*c*)) - from 461 to 656 ms.

According to the analysis of patient history with CAD, the following information was collected:

1. Clinical and pharmacological anamnesis (patient complaints, medical history, pharmacological anamnesis);
2. Underlying disease and comorbidity;
3. The use of drugs including their total number;
4. Drugs and drug combinations that have an impact on the *QT* interval;
5. Drugs and drug combinations that have an impact on the *QT* interval on metabolic rate of cytochrome P450;
6. ECG finding (cardiac rate, *PQ*, *QT* and corrected *QT* (*QT*(*c*)) prolongation);
7. Daily monitoring of ECG finding;
8. Blood chemistry values, including electrolyte metabolism, blood glucose level and thyroid hormones.

DDI were researched and categorized by *drugs.com*: the possible clinical relevance of DDI on their metabolic rate was assessed, as well as possible adverse events in simultaneous admission. The drugs data that extend the *QT* interval was analyzed by *crediblemeds.org*

To calculate the statistical criteria, the computer program Primer of Biostatistics of 4.03 version was used.

Table 1: *Clinical profile of patients with CAD included in the study*

Indicators			Number of patients, abs (%) (n=86)
Average age, years			57±7.2
Male / female, abs (%)			54 (62.8)/32 (37.2)
Exertional angina	I FC		12 (13.9)
	II FC		67 (77.9)
	III FC		7 (8.1)
Arterial hypertension, abs (%)	I degree		9 (10.4)
	II degree		36 (41.9)
	III degree		41 (47.7)
Congestive heart failure, abs (%)	I FC		15 (17.4)
	II FC		38 (44.2)
	III FC		0 (0%)
Myocardial infarction with a history			10 (11.6)
ADCC with a history			2 (2.3)
Cardiac arrhythmias	VPB		15 (17.4)
	Permanent AF		11 (12.8)
	Paroxysmal AF		16 (18.6)
Surgical treatment	Electric cardiac pacemaker (ECP)		8 (9.3)
	Coronary stenting		2 (2.3)
	Coronary artery bypass graft (CABG)		2 (2.3%)
QT prolongation, ms		Min	355
		Max	506
Corrected *QT* (*QT(s)*) prolongation, ms		Min	461
		Max	656

Table 2: *The number of polypharmacy units to one patient with CAD (patient history analysis)*

Indicators	The number of polypharmacy units								
	Less than 5	5	6	7	8	9	10	11	12
Patients with *QT* prolongation (n=86)									
n	42	16	8	10	4	2	2	0	2
%[1]	48.8	18.5	9.3	11.6	4.6	2.3	2.3	0	2.3
%[2]	4.5	1.7	0.8	1.07	0.4	0.2	0.2	0	0.2
All patients (n=935)									
n	347	235	159	91	34	18	21	15	15
%[2]	37.1	25.1	17	9.7	3.6	1.9	2.24	1.6	1.6

Note: *n* is the number of patients; %[1] of the number of patients with long *QT* interval, %[2] of the total number of patients

RESULTS

The number of polypharmacy units to patients with CAD per patient. Analysis of the number of polypharmacy in patients with CAD showed that 51% of patients take 5 or more medicines: 5 drugs – 16 (18.5%), 6 drugs – 8 (9.3%); 7 drugs – 10 (11.6%); 8 drugs – 4 (4.6%); 9 drugs – 2 (2.3%); 10 drugs – 2 (2.3%); 12 drugs – 2 (2.3%) patients (**Table 2**).

The results of the analysis of drug therapy according to records in patient history showed that 63% of CAD patients took more than 5 drugs simultaneously, which may indicate a drug polypharmacy. The average number of drug use units in the entire group of patients was 5.2 ± 2.4, among patients with polypharmacy – 6.4 drugs ± 2.4. The average number of drug use units in the group of patients with *QT* prolongation was 5.1 ± 2.2, among patients with polypharmacy was 6.6 drugs ± 2.8. None of the patients who took 5 or more drugs, was consulted by a doctor – a clinical pharmacologist.

Drugs prolonging the *QT* interval and their combinations, which are most often prescribed to patients with CAD in outpatient practice. A prolonged *QT* interval was detected in 86 (9.20%) patients with CAD while resting ECG, and 34 (3.64%) of them received drugs that can prolong the *QT* interval *(https://crediblemeds.org*). A more detailed analysis of drug therapy in outpatients with stable CAD revealed 188 drug combinations in which drugs, that prolong the *QT* interval, were used (**Figure 1**).

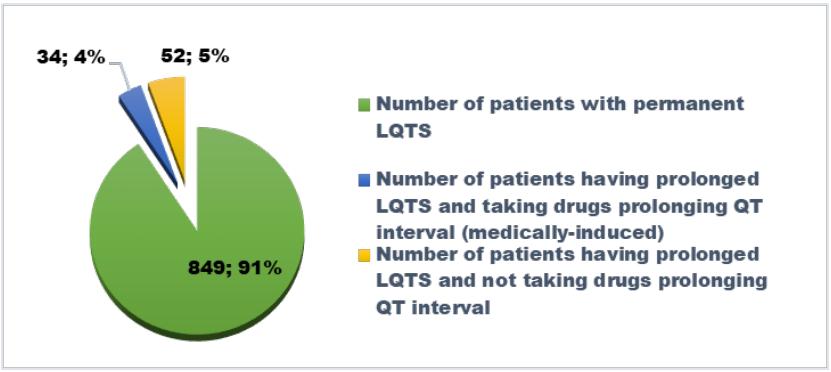

Figure 1: *Characteristics of patients according to the QT prolongation*

According to The Arizona Center for Education and Research on Therapeutics *(https://crediblemeds.org/)*, the drugs, affecting the *QT* interval, include amiodarone, sotalol, ivabradine, torasemide, furosemide, hydrochlorothiazide, indapamide.

Among drugs with a proven risk of developing torsades de pointes (TdP), amiodarone and sotalol were most commonly used (7 and 5 prescription, respectively). Amiodarone was most often used in combination with torasemide – 7 prescriptions (3.7%), bisoprolol – 4 prescriptions (2.1%), metoprolol – 3 prescription (1.6%), and 2 prescriptions (1.06%) with warfarin, atorvastatin, rosuvastatin, perindopril, enalapril, amlodipine, aspirin, and metformin.

Sotalol was most often used in combination with hydrochlorothiazide – 5 prescriptions (2.6%), and 2 prescriptions (1.06 %) with aspirin, omeprazole, enalapril, mexicor.

Prescription of medicine, belonging to the category of drugs with a possible risk of developing torsades de pointes, were not recorded in the patients examined by us.

The drugs, which are associated with a conditional risk of developing torsades de pointes, were prescribed to 34 patients. The frequency of their use was as follows: 9 prescriptions of torasemide (26.4%), 12 prescriptions of hydrochlorothiazide (35.2%), 9 prescriptions of indapamide (26.4%), 2 prescriptions of ivabradine (5.8%), 2 prescriptions of furosemide (5.8%).

Among combinations of drugs with a conditional risk of torsades de pointes, combinations with other drugs prolonging the *QT* interval were found: torasemide and amiodarone (7 prescriptions – 3.7%), torasemide and ivabradine (2 prescriptions – 0.98%), hydrochlorothiazide and 5 prescriptions of sotalol - 2.6%), hydrochlorothiazide and indapamide (1 prescription – 0.98%).

Categorization of identified DDI, prolonging the *QT* interval on metabolic rate. In the analysis of medicine prescriptions, 34 cases (3.6%) of drug combinations were identified that could affect the *QT* prolongation. Some of the drug combinations are categorized by *the Drugs.com Medication Guide*. The result of DDI, each of which contributes to the prolongation of the *QT* interval on metabolic rate, is an increased risk of ADR caused by the effect of the *QT* interval prolongation.

According to the website, "MINOR" (non-significant) interactions are the combinations with minimal clinical significance: drugs that have a minimal risk of developing ADR or ineffective treatment: a combination of Torasemide and Clopidogrel, which was prescribed to patients in our sample in 4 cases, which was 11,8% of the total number of drug combinations that prolong the *QT* interval.

The category "MODERATE" (significant) includes potential DDI of medium significance. Such combinations often require more thorough clinical, laboratory and instrumental monitoring of efficacy and safety of treatment: combinations of Indapamide and Bisoprolol; Amiodarone and Bisoprolol; Amiodarone and Atorvastatin; Amiodarone and Rosuvastatin; Torasemide and Omeprazole; Ivabradine and Bisoprolol, which were prescribed to patients in 16 cases, which in total amounted to about 47% of the total number of drug prescriptions prolonging the *QT* interval.

The category "MAJOR" (potentially dangerous) includes DDI, in which the risk of their use exceeds the benefit to the patient. That is why in most cases it is necessary to avoid the prescription of such drugs combinations or to apply these combinations of drugs in minimal doses. Potentially dangerous combinations include combinations of Amiodarone and Torasemide; Amiodarone and Warfarin, which were prescribed 9 times, which in total was 26.5% of the total number drug prescriptions prolonging the *QT* interval.

Assessment of clinical and hemodynamic parameters of patients with CAD who received potentially dangerous combinations of drugs that affect the *QT* prolongation. The clinical and hemodynamic parameters were

Table 3: *Dynamics of the QT prolongation in patients with CAD who received potentially dangerous combinations of drugs that affect the QT prolongation (according to ECG values)*

***QT* interval parameters**	**Baseline (n=29)**	**Amidarone (n=22)**	**Torasemide (n= 15)**	**Amidarone + torasemide (n= 18)**
QT, ms	356.6±29.5	398.6±28.7	0.380± 27.5	478±31.9**
QTc, ms	381±41.3	409.0±31.6 *	385±31.7	482.0±36.7 *
DQT, ms	44.7 ±8.7	60.4±13.7 *	43.9±8.6	68.1±16.9 **

Note: *- compared to the baseline at p<0.05; **- compared to the baseline at p<0.001

Table 4: *Dynamic metrics of the QT prolongation in patients with CAD who received potentially dangerous combinations of drugs that affect the QT prolongation (according to the daily monitoring of ECG)*

QT interval parameters	**Baseline (n=29)**	**Amidarone (n=22)**	**Torasemide (n= 15)**	**Amidarone + Torasemide (n= 18)**
QT, мс	379.8±28.6	416.1±35.7 *	390.5±26.1	456±37.1 *
QTc, мс	384.0±33.5	422.3±31.7 *	418.2±24.5	461.2±31.6 *
DQT, мс	41.9 ±8.2	61.2±13.6 **	43.2±7.9	67.3±18.9 **

Note: *- compared to the baseline at p<0.05; **- compared to the baseline at p<0.001

analyzed only in 18 from 30 patients with CAD, who received a potentially dangerous combination of drugs (amiodarone and torasemide), in which the medical records contained the results of resting ECG and daily monitoring of ECG. It was revealed that before taking amiodarone and torasemide, the main ECG parameters were initially within the normal range: *QT* – 356.6 + 29.5 ms, *QTc* – 381 + 41.3 ms, D*QT* – 44.7 +8.7 ms (**Table 3**).

The duration of resting ECG interval's values in association with torasemide were comparable with the baseline: *QT* – 0.380 + 27.5ms (p> 0.05), *QTc* – 385 + 31.7ms (p> 0.05), D*QT* – 43.9 + 8.6 ms (p> 0.05). Amiodarone led to an unreliable prolongation of the *QT* intervals to 398.6 + 28.7 ms (p> 0.05) compared to the source data, a significant *QTc* prolongation to 409.0 + 31.6 ms (p <0.05), D*QT* up to 60.4 + 13.7 ms (p <0.001). An increase in the frequency of the above normative values of the *QT* and *QTc* intervals was noted. Analysis of dynamic ECG showed that in patients with CAD in association with amidarone and torasemide combination, there was a significant increase in the prolongation of *QTc* – 478 + 31.9ms (p <0.05), *QTc* – 482.0 + 36.7 (p <0.05), D*QT* – 68.1 + 16.9 ms (p <0.001).

The ECG analysis results show that there was a significant increase in the prolongation of *QT*, *QTc* and *QT* dispersion in patients with CAD, however the values do not go beyond the recommended criteria for drug-induced *QT* prolongation.

The analysis of the main values of daily monitoring of dynamic ECG showed that, in association with taking a combination of amiodarone and torasemide, there was a significant increase in the *QT* prolongation – 456 + 37.1 ms (p <0.05), *QTc* – 461.2 + 31.6 ms (p < 0.05), D*QT* – 67.3 + 18.9 ms (p <0.001) (**Table 4**).

A high correlation was noted when comparing two measurement methods – the resting ECG at and Holter monitoring (daily monitoring of ECG), especially in the V5-lead (r = 0.868-0.968). The *QT* prolongation in V1-lead with Holter monitoring was less by 2-16 ms than on the standard ECG, and in the V5 lead it exceeded the standard ECG values by 6-17 ms.

The analysis of fatal cardiac arrhythmias showed that in association with amiodarone and a combination of amiodarone and torasemide, there was a significant decrease in the total number of premature ventricular contraction (Δ%-57,7 and Δ%-57,7 respectively), isolated PVCs rate (Δ%-57,6 and Δ%-54,2 respectively), paired PVCs (Δ%-54,2 and Δ%-31,5 respectively), torsade de pointes (Δ% -45,6 and Δ% -32,5 respectively) and atrial fibrillation (AF) (Δ%-74,9 and Δ%-26,6 respectively), however with the addition of torasemide to therapy, this dynamics was less pronounced (**Table 5**).

According to Holter monitoring data in patients with CAD who received treatment with amiodarone before the addition of torasemide, there were higher values of *T*-wave alternans (TWA) relative to baseline values (60±12 μV and 51±14 μV respectively (p>0.05)).

In clinical medicine the TWA has recently been given a significant role in predicting the cardiovascular death. Several retrospective and prospective clinical study analysis showed that the value of TWA cut-off point above 65 microvolts (μV) is associated with the risk of high mortality in the adult population, according to Holter monitoring data. The values of TWA in patients with cardiovascular pathology and cardiac arrest were 72 ± 20 μV versus 52 ± 15 μV in patients without life-threatening conditions. Detection of TWA in Holter monitoring above 65 μV in adults is recommended to reflect in the conclusion as a manifestation of signs of electrical instability of a myocardium (24).

Table 5: *Dynamic metrics of the average daily heart rate and ectopic activity in patients with CAD, who received potentially dangerous combinations of drugs that affect the QT prolongation (according to the daily monitoring of ECG)*

Indicators	Baseline (n=29)	Amiodarone (n=22)		Amiodarone + torasemide (n=18)	
	M±SD	M±SD	Δ %	M±SD	Δ %
Average heart rate/ day, beats per min.	77.6±7.1	64.3±8.5	- 17.3	67.4±5.9	-13.1
Lg of PVC (total number)	2.318±0.5	0.98±0.7** p<0.01	- 57.7	1.006±0.5** p<0.01	- 57.7
Lg of isolated PVC	2.398±0.6	1.016±0.4** p<0.01	- 57.6	1.096±0.9** p<0.01	-54.2
Lg of paired PVC	1.021±0.4	0.468±0.3** p<0.01	-54.2	0.699±0.2	-31.5
Lg of TdP episodes	0.489±0.4	0.266±0.5** p<0.01	-45.6	0.330±0.6* p<0.05	-32.5
Lg of AF episodes	0.601±0.5	0.151±0.5** p<0.01	-74.9	0.441±0.4* p<0.05	-26.6

Note: Lg – log 10; *p* – significance of differences between groups; * - p<0.05; ** - p<0.01

It is known that amiodarone is an agent of choice for the treatment of fatal cardiac arrhythmias, paroxysmal AF, however chronic administration of drug requires dynamic ECG monitoring of *QT* prolongation, which is not always performed in outpatient settings, as our study showed.

Decrease in the dynamics of reducing the frequency of paired PVCs in patients with CAD, who received the combination of Amiodarone and Torasemide, episodes of VT and AF in the course of increase of TWA against the background of long-term amiodarone and torasemide therapy, may indicate the signs of electrical instability of the myocardium. Timely diagnosis of *QT* prolongation and its dispersion (including in Daily monitoring of ECG) allows to isolate a group of patients with CAD with an increased risk of cardiac arrhythmias, syncopal conditions and sudden death (25).

CONCLUSION

In outpatient clinic, patients with coronary heart disease CAD were administered drugs ignoring prognosis for DDI, which are associated with changes in cytochrome P-450 (CYP) enzyme activity. 13.3% evidence of all concomitant administration with patients who have *QT* prolongation were prescribed a dangerous combination of Amiodarone and Torasemide.

The potential mechanism of interaction Amiodarone and Torasemide on metabolic rate that are leading to *QT* prolongation are competitive substrates CYP 2C8 and a result of inhibited CYP 2C9 by amiodarone.

Ability to predict the prolongation of the *QT* interval caused by DDI on metabolic rate in combination therapy, using drugs with possible and conditional risk of *QT* prolongation, assessment of the corrected *QT* prolongation from the first days of drug therapy, the active detection of individual and family history of syncopal conditions and initially prolonged *QT* interval, recognition of the patient's predictors of *QT* prolongation make possible to improve the safety concomitant administration using drugs with possible and conditional risk of *QT* prolongation.

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