

## Drug-induced bradycardia as a medical and social problem: data from the Cardiac Drug Overdoses Hospital Registry (STORM)

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**Aim.** To analyze hospitalizations due to drug-induced bradyarrhythmia (DIB) over a 5-year period (2014-2018), its clinical characteristics, causes and outcomes.

**Material and methods.** The analysis included all hospitalizations due to DIB at the Ryazan Regional Vascular Center in 2017 and 2018 and retrospectively in 2014.

**Results.** A total of 325 cases of DIB were included in the analysis (age 76,0 [68,0; 82,0] years; men — 26,1%). The proportion of DIB as a hospitalization cause in 2017 increased by 4,3 times compared to 2014 ( $p < 0,001$ ), in 2018 compared to 2014 — by 6,3 times ( $p < 0,001$ ) and compared to 2017 — by 46,2% ( $p = 0,001$ ). We recorded the following manifestations of DIB: bradycardia ( $< 40$  bpm — 51,4%), atrioventricular (31,7%) and sinoatrial (29,2%) block, syncope (36,0%), Frederick's syndrome (8,6%), pauses  $> 3$  s (5,9%). Management in intensive care was required in 42,2% of patients, temporary cardiac pacing — in 7,7%, permanent pacemaker — in 6,2%. Mortality rate was 6,2%. Before hospitalization, patients took beta-blockers (65,1%), antiarrhythmic agents (39,6%), cardiac glycosides (23,0%),  $I_1$ -imidazoline receptor agonist moxonidine (13,5%, its prescription rate increased 8,9 times over 5 years,  $p = 0,004$ ), nondihydropyridine calcium channel blockers (7,9%), and other drugs (15,4%). In 60,1% of patients,  $\geq 2$  drugs with bradycardic action were used, in 22,0% —  $\geq 3$ , in 8,1% —  $\geq 4$ , in 10,6% — with an excessive single/daily dose.

**Conclusion.** The medical and social significance of DIB have been demonstrated. DIB due to exceeding the recommended dose was associated with independent try of patients to manage the deterioration. In other cases, DIB was due to the summation/potentialization of several drugs' action, the comorbidities contributing to the development of bradyarrhythmia and/or changes in pharmacokinetic properties of drugs.

**Key words:** drug-induced bradycardia, bradyarrhythmia, adverse drug reaction, overdose.

**Relationships and Activities:** none.

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The term “bradyarrhythmias” (BA) unites a heterogeneous group of cardiac arrhythmias characterized by a delayed production of electrical impulses or a slowed ventricular rhythm associated with a conduction block [1]. The main etiological factors of BA are degeneration, ischemia, inflammation, trauma and etc. Pharmaceuticals, of course, may be also such a factor, but they do not occupy leading positions [2]. There are publications devoted to overdose of nondihydropyridine calcium channel blockers (CCB) [3, 4], beta-blockers (BB) [4] and cardiac glycosides [5, 6]. It should be noted that for the listed drugs, the bradycardic effect is a direct pharmacodynamic action, well studied and well known to physicians.

In recent years, the list of drugs with bradycardic effect has expanded significantly [2, 7]. Moreover, some drugs (for example, psychoactive drugs, muscle relaxants [2]) are prescribed even by non-cardiologists/therapists. We did not find any data for an increase in the relevance of drug-induced bradyarrhythmia (DIB) in the literature, but in our clinical practice we encountered a significant increase in hospitalizations due to DIB. The pilot study (18 months) confirmed this data and justified the need for further study of DIB [8].

Thus, the purpose of this work was to analyze hospitalizations due to DIB over a 5-year period (2014–2018), its clinical characteristics, causes and outcomes.

### Material and methods

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standard at the Ryazan Regional Vascular Center. The medical ethics committee approved this study.

The analysis included all hospitalizations with verified DIB in 2017 and 2018, as well as retrospectively in 2014. Inclusion criteria were age  $\geq 18$ , verified DIB, signed informed consent. Exclusion criterion was BA due to acute coronary syndrome and other severe diseases. No additional interventions in the diagnostics or treatment of patients were performed within the registry.

Statistical processing was performed using the software packages Excel 2010 (Microsoft Corporation, USA) and Statistica 10.0 (Stat Soft Inc., USA). The Shapiro-Wilk test was used to determine the normality of distribution. The prevalence of a trait/event is presented as absolute and relative values (n and %). Nonnormally distributed quantitative variables are presented as median and interquartile range: Me [Q1; Q3]. To compare the relative qualitative traits in two independent groups, we used the Pearson's chi-squared test or Fisher's exact test in the case of the lowest expected value  $< 5$ . Quantitative characteristics

was compared using the Mann-Whitney test. Differences were considered significant at  $p < 0,05$ .

### Results

In total, 325 clinical cases of DIB were included in the analysis, which amounted to 1,0% of all hospitalizations to the cardiology departments. Most of them were persons of older age groups (76,0 [68,0; 82,0] years;  $\geq 65$  — 83,7%,  $\geq 75$  — 57,9%). The proportion of men was 26,1%.

At the same time, only 13,5% of the analyzed cases was in 2014. In 2017, the absolute number of hospitalizations for DIB increased by 2,6 times compared to 2014, in 2018 — by 3,8 times compared to 2014 and by 46,5% compared to 2017. This was accompanied by an increase in the proportion of DIB among the hospitalization causes: in 2017 compared to 2014 by 4,3 times ( $p < 0,001$ ), in 2018 compared to 2014 by 6,3 times ( $p < 0,001$ ) and compared to 2017 by 46,2% ( $p = 0,001$ ). There were severe clinical manifestations, a significant number of patients requiring intensive care, artificial pacing and a significant level of hospital mortality (11,4% in 2014). A decrease in the glomerular filtration rate (GFR)  $< 45$  ml/min\*1,73 m<sup>2</sup> was recorded in more than half (57,0%) of patients,  $< 30$  ml/min\*1,73 m<sup>2</sup> — in every third case (31,7%),  $< 15$  ml/min\*1,73 m<sup>2</sup> — in every tenth case (10,4%, Table 1).

At the next stage of the study, the analysis of drug therapy before hospitalization was carried out. All drugs with the same international nonproprietary name were regarded as one and the same medicinal product. First of all, attention is drawn to the high frequency of taking (60,1%) several drugs with bradycardic effect at once. Moreover, 22,0% of patients took  $\geq 3$  of these drugs at once. There were even patients (8,1%), which took  $\geq 4$  drugs with bradycardic effect. The relative frequency of therapy with several drugs with bradycardic effect among DIB cases did not change significantly over a 5-year period (except for an increase in the frequency of four-drug therapy in 2017–2018), but the absolute number of such cases increased (Table 2).

Among the groups of drugs with bradycardic effect taken by the patient before hospitalization, the following were most often recorded:

- BB (65,1%, no significant change in prescription rate),
- antiarrhythmic agents (39,6%, no change in prescription rate),
- cardiac glycosides (23,0%, no change in prescription rate),
- I<sub>1</sub>-imidazoline receptor agonist moxonidine (13,5%, prescription rate increased 8,9 times over 5 years,  $p = 0,004$ ; in 2018, moxonidine was registered in every fifth case of hospitalization with DIB),

Table 1

**Clinical and demographic characteristics of patients hospitalized with drug-induced bradycardia in 2014-2018**

Parameter	Year of follow-up			Total	P <sub>1-2</sub>	P <sub>1-3</sub>	P <sub>2-3</sub>
	2014	2017	2018				
	1	2	3				
n	44	114	167	325	-	-	-
Proportion of all hospitalizations to therapy departments, %	0,3	1,3	1,9	1,0	<0,001	<0,001	0,001
Age, years, Me [Q1; Q3]	73,5 [67,0; 82,0]	77,0 [70,0; 81,0]	77,0 [68,0; 82,0]	76,0 [68,0; 82,0]	1,000	1,000	1,000
Proportion of men, % of n	22,7	27,2	30,5	26,1	0,566	0,309	0,545
<b>Clinical manifestations</b>							
Bradycardia <40 bpm, % of n	47,7	53,5	50,9	51,4	0,514	0,708	0,667
SA block, % v	45,5	29,0	25,2	29,2	0,049	0,009	0,480
Frederick's syndrome, % of n	2,3	14,0	6,6	8,6	0,042	0,307	0,038
Heart pause >3 sec, % of n	4,6	3,5	7,8	5,9	0,760	0,457	0,140
Syncope, Adams-Stokes syndrome, % of n	31,8	36,8	36,5	36,0	0,554	0,562	0,957
First-degree AV block, % of n	9,1	7,0	10,2	8,9	0,659	0,830	0,361
Second-degree AV block, % of n	6,8	10,5	9,0	9,2	0,476	0,030	0,666
Third-degree AV block, % of n	4,6	16,7	14,4	13,6	0,044	0,078	0,567
<b>Renal filtration function</b>							
Known initial creatinine level, n1 (% of n)	43 (97,7)	111 (97,4)	155 (92,8)	309 (95,1)	0,898	0,228	0,095
GFR <60 ml/min*1,73 m <sup>2</sup> , % of n1	83,7	82,0	73,0	77,7	0,799	0,146	0,084
GFR <45 ml/min*1,73 m <sup>2</sup> , % of n1	65,1	56,8	54,8	57,0	0,344	0,228	0,756
GFR <30 ml/min*1,73 m <sup>2</sup> , % of n1	32,6	31,5	31,6	31,7	0,902	0,906	0,989
GFR <15 ml/min*1,73 m <sup>2</sup> , % of n1	9,30	9,9	11,0	10,4	0,909	0,754	0,782
<b>Treatment and outcome</b>							
Hospitalization by EMS, % of n	84,1	92,0	96,4	93,5	<0,001	<0,001	0,189
Management in intensive care unit, % of n	50,0	42,1	40,1	42,2	0,371	0,238	0,740
Temporary pacing, % of n	6,8	5,3	9,6	7,7	0,705	0,569	0,186
Permanent pacing, % of n	2,3	3,5	9,0	6,2	0,691	0,135	0,073
Death, % of n	11,4	7,0	4,2	6,2	0,373	0,068	0,301

**Abbreviations:** SA — sinoatrial, AV — atrioventricular, GFR — glomerular filtration rate, EMS — emergency medical service.

– nondihydropyridine CCB (7,9%, prescription rate decreased from 19,5% to 4,9%, p=0,002),  
 – other drugs with bradycardic effect (15,4%, prescription rate in 2018 increased by 2,1 times compared to 2017, p=0,021).

Of the 325 analyzed cases, the dose of drugs taken before hospitalization was known in 227 patients (69,8%), which made it possible in these cases to

analyze the adequacy of treatment regimen. Excess of the recommended single and/or daily dose was observed only in every tenth (10,6%) case.

### Discussion

The results obtained demonstrated the high medical and social significance of DIB: an increase over the analyzed 5-year period in the absolute

Table 2

## Drug therapy before hospitalization

Parameter	Year of follow-up			Total	p <sub>1-2</sub>	p <sub>1-3</sub>	p <sub>2-3</sub>
	2014	2017	2018				
	1	2	3				
n	44	114	167	325	-	-	-
Drugs with bradycardic effect							
BB, % of n	68,3	69,0	61,6	65,1	0,931	0,426	0,203
Antiarrhythmic agents, % of n	43,9	43,4	36,0	39,6	0,952	0,349	0,215
Cardiac glycosides, % of n	17,1	25,6	22,6	23,0	0,266	0,945	0,551
I <sub>1</sub> -imidazoline receptor agonist, % of n	2,4	6,2	21,3	13,5	0,353	0,004	<0,001
Nondihydropyridine CCB, % of n	19,5	8,0	4,9	7,9	0,043	0,002	0,293
Other drugs with bradycardic effect, % of n	19,5	8,9	18,9	15,4	0,069	0,929	0,021
Number of drugs taken							
≥2, % of n	73,2	55,8	59,8	60,1	0,051	0,113	0,507
≥3, % of n	24,4	18,6	23,8	22,0	0,427	0,935	0,302
≥4, % of n	7,3	4,4	9,8	8,1	0,475	0,630	0,010
Analysis of treatment regimen							
Dose is known, n <sub>1</sub> (% of n)	21 (47,7)	79 (69,3)	127 (76,0)	227 (69,8)	0,012	<0,001	0,209
Proportion of cases exceeding the recommended dose, % of n <sub>1</sub>	14,3	12,7	9,4	10,6	0,844	0,496	0,468

**Abbreviations:** BB — beta-blockers, CCB — calcium channel blockers.

number of hospitalizations, an increase in the proportion of DIB in the hospitalization structure and the high level of in-hospital mortality. Such a pronounced changes, in our opinion, cannot be explained by any changes in the health care organization. We believe that the prevalence of DIB may be even higher, and the prognosis even more unfavorable, since the register did not include prehospital deaths. At the same time, postmortem verification of the relationship between a death and inadequate treatment regimen in routine clinical practice seems to be difficult. Most likely, such lethal cases are registered under the guise of other, more often chronic, diseases [9, 10].

The majority of patients hospitalized for DIB were elderly and senile persons. On the one hand, this corresponds to the age structure of cardiovascular morbidity [11-13]. On the other hand, such patients have a high risk of DIB due to pharmacokinetic changes of drugs, multimorbidity, polypharmacy, and drug interactions associated with it. Also, a risk factor for inadequate treatment regimen is the cognitive impairment at this age. There is experience

in limiting the use of bradycardic drugs in elderly and senile age (STOPP criteria, Beers List, etc.) [14].

It also relevant to draw the attention to DIB problem due to the inclusion of a combination of BB with nondihydropyridine CCB in the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes [15] without specifying clear criteria for monitoring the safety and restrictions in elderly and senile people.

Drug overdose as a cause of DIB was quite expected. DIB due to exceeding the recommended dose was associated with independent try of patients to manage the deterioration (hypertensive crisis, episode of angina and/or atrial fibrillation). At the same time, patients increased the dose of the drug due to non-achievement of the expected effect, not taking into account the bradycardic effect. It should be emphasized that the proportion of moxonidine prescription in patients with DIB increased significantly over the observed period (2014-2018). At the same time, some patients used moxonidine as a chronic therapy, others — for treatment of hypertensive crisis, and others — in combination.

The high prevalence of clinical manifestations of bradycardic drug overdose without exceeding the therapeutic dose was quite unexpected for the researchers. The main reason (54,1%) of this is the summation/potentialization of several drugs' action. The second reason, in our opinion, should be considered the development/progression of cardiac disease, which itself contributes to BA [2]. In such cases, previously optimal doses of drugs with bradycardic effect become excessive. In this group, permanent pacing with an implantable pacemaker was required in 9,4% of cases. Timely identification of indications for permanent pacing would allow avoiding DIB and, if necessary, safely continuing therapy with bradycardic drugs.

Finally, a significant role, in our opinion, was played by a decrease in the renal filtration function.

The influence of other reasons (multimorbidity, drug interactions), which could lead to a change in the pharmacokinetics of the drug, cannot be ruled out.

### **Conclusion**

The medical and social significance of DIB have been demonstrated. It has been demonstrated that DIB due to exceeding the recommended dose occurs only in every tenth case and is associated, most often, with independent try of patients to manage the deterioration. The majority of analyzed DIB cases were associated not with a violation of treatment regimen, but with the lack of a comprehensive assessment of therapy safety in general.

**Relationships and Activities:** none.

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