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EFFICACY AND SAFETY OF PROLONGED-RELEASE LAPPACONITINE HYDROBROMIDE IN PREMATURE ATRIAL CONTRACTIONS: PILOT OBSERVATIONAL STUDY

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Aim. To evaluate the efficacy and safety of the prolonged-release formulation of lappaconitine hydrobromide at the minimum dose of 25 mg twice daily in patients with premature atrial contractions (PACs) and no structural heart disease.

Methods. This retrospective open-label non-randomized observational study included 52 patients (20 men) aged 31-79 years with symptomatic PACs and/or paroxysmal atrial fibrillation requiring antiarrhythmic therapy. All patients underwent two Holter ECG recordings: before treatment initiation and after 2-3 weeks of therapy with prolonged-release lappaconitine hydrobromide 25 mg twice daily. All quantitative indices of atrial ectopic activity were normalized to 24 hours. Efficacy was assessed by changes in the number of single, paired, and grouped PACs, episodes of paroxysmal focal atrial tachycardia (AT), the ectopic burden index, and the distribution of responders. Safety was assessed by changes in heart rate, P-wave, QRS complex, PQ, QT and QTc intervals duration. Analysis of individual forms of atrial ectopic activity was performed only in patients in whom the corresponding types of arrhythmia were present at baseline and for whom complete data were available to assess their changes during therapy.

Results. Therapy was associated with a statistically significant reduction in all forms of atrial ectopic activity, including single PACs, paired PACs, grouped PACs, and episodes of paroxysmal focal AT (all $p<0.001$). In most patients, the reduction in arrhythmia frequency was ≥75%. A similar effect was observed in the subgroup with a high baseline PAC burden (>500 PACs per 24 hours). Heart rate decreased moderately; a statistically significant but clinically insignificant increase in the PQ interval was observed. No significant changes were found in P-wave duration, QRS duration, or QT and QTc intervals.

Conclusion. The prolonged-release formulation of lappaconitine hydrobromide at the minimum daily dose of 50 mg provides a statistically significant reduction in atrial ectopic activity in patients without structural heart disease and is characterized by a favorable safety profile when administered twice daily.

Key words: premature atrial contractions (beats); single premature atrial contractions; paired premature atrial contractions; grouped premature atrial contractions; paroxysmal atrial tachycardia; prolonged-release lappaconitine hydrobromide; Holter ECG monitoring; efficacy; safety

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Premature atrial contractions (PACs) are among the most common cardiac rhythm disorders detected by Holter ECG monitoring in both patients with cardiovascular disease and apparently healthy people [1-4]. For a long time, PACs were considered predominantly a benign ECG phenomenon without independent clinical significance. However, this view now appears overly simplistic. First, PACs may be accompanied by pronounced subjective symptoms: palpitations, a feeling of irregular heartbeats, internal discomfort, anxiety, reduced exercise tolerance, which can significantly impair patients' quality of life [5-8]. Therefore, symptomatic PACs in itself may be regarded as a rationale for prescribing antiarrhythmic therapy (AAT). Second, PACs play an important role in the pathogenesis of atrial fibrillation (AF). Classic electrophysiological studies have shown that AF paroxysms are initiated by atrial ectopic impulses arising predominantly from the pulmonary vein ostia [9]. Subsequent studies have demonstrated that a high PAC burden is associated with an increased risk of AF and is considered a marker of atrial electrical instability [10-14]. Moreover, a reduction in PAC frequency may reflect decreased activity of the arrhythmic trigger mechanism. Thus, reducing PAC frequency has not only symptomatic significance but may also potentially lower the likelihood of AF occurrence.

At the same time, assessing the efficacy of AAT and catheter ablation in AF is a complex task [15-18]. In clinical practice and research, various approaches are used, including subjective symptom assessment by the patient, standard ECG recording during an arrhythmia episode, periodic Holter monitoring, wearable event recorders, implantable loop recorders, etc. [19-24]. Each of these methods has certain limitations. Subjective symptoms do not always reflect the true arrhythmic burden, since a significant proportion of AF episodes are asymptomatic [25, 26]. Moreover, after treatment initiation or catheter ablation, the proportion of asymptomatic episodes may increase [25]. Standard ECG recording during an episode has high diagnostic accuracy but depends on the ability to capture the arrhythmia at the time of occurrence. Intermittent monitoring methods also cannot guarantee detection of rare and short AF episodes [19-24, 27, 28]. Therefore, assessment of treatment efficacy based solely on recording AF paroxysms may be incomplete. In this context, quantitative assessment of atrial ectopic activity (AEA) as an additional indicator of AAT efficacy is of interest. It should be emphasised that this is an addition rather than an alternative to the generally accepted criteria for AF treatment efficacy. The likelihood of AF paroxysm is determined not only by the presence of PAC triggers but also by the state of the atrial substrate, i.e., the extent of electrical and structural atrial remodelling [10-18]. Nevertheless, a reduction in PAC count may reflect decreased activity of a key arrhythmia mechanism.

For suppression of AEA in patients without structural heart disease, antiarrhythmic drugs of all four classes according to the E.M. Vaughan Williams classification (modified by B.N. Singh and D.C. Harrison) may be used [29, 30]. However, class IC drugs are considered the most effective: ethacizine, lappaconitine hydrobromide in its immediaterelease and prolongedrelease forms (Allapinin®, Allaforte®), propafenone (Ritmonorm®, Propanorm®, etc.), flecainide (Tambocor®, Fleicardil®, etc.). Despite a similar mechanism of action predominantly mediated by blockade of fast sodium channels, each of these drugs has a number of individual pharmacological features.

The efficacy and safety of most class IC drugs have been studied in considerable detail. This applies primarily to propafenone and also to flecainide, and to a lesser extent to ethacizine [31-47]. At the same time, the prolongedrelease formulation of lappaconitine hydrobromide (PRLH) appeared much later and remains substantially less studied: its efficacy and safety are reflected only in a limited number of publications [48-52]. Additional interest in studying this formulation is related to its pharmacokinetic properties. According to pharmacokinetic studies, the time to reach maximum concentration of PRLH is about 4.43±3.54 hours, and the elimination halflife is 8.45±5.10 hours [48]. These characteristics suggest the possibility of effective use with a twicedaily dosing regimen. Meanwhile, the official Instructions posted on the State Register of Medicines portal recommend administration of the prolongedrelease form three or even four times daily, which does not correspond to its pharmacokinetics and may be associated with an increased risk of adverse effects and proarrhythmic potential.

In view of the above, the aim of this study was to evaluate the efficacy and safety of PRLH at the minimum dose of 25 mg twice daily in patients with PACs and no structural heart disease.

MATERIAL AND METHODS

This retrospective openlabel nonrandomised observational study of the efficacy and safety of PRLH included 52 patients (20 men), mean age 63.1±9.1 years, left atrial diameter 40.0±4.4 mm, volume 74.0±19.2 mL, left ventricular ejection fraction 62.5±5.4%. In 46 patients, the main diagnosis was hypertension; in 1, autonomic nervous system dysfunction. In 5 patients, cardiac arrhythmias were idiopathic in nature in the absence of any underlying disease. The study was conducted in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki and was approved by the local ethics committee of the Multidisciplinary Medical Centre “Family Doctor” (AntMed LLC, Saint Petersburg, Russia).

Inclusion criteria were:

- presence of symptomatic PACs and/or paroxysmal AF requiring AAT;
- use of PRLH at a dose of 25 mg twice daily;
- availability of two Holter ECG recordings (before AAT prescription and after 23 weeks of treatment);
- absence of structural heart changes on echocardiography;
- absence of contraindications to PRLH.

Table 1.

Efficacy of prolonged release lappaconitine hydrobromide at a dose of 50 mg/day in the treatment of premature atrial contractions

	All patients				Patients with baseline PACs >500 per day			
	n	Before treatment	On therapy	p	n	Before treatment	On therapy	p
Single PACs	52	138 [58-3081]	18 [8-92]	<0.001	22	4430 [1623-10651]	424 [21-1625]	<0.001
Paired PACs	36	13 [3-64]	0 [0-7]	<0.001	20	38 [12-602]	5 [0-14]	<0.001
Grouped PACs	30	5 [1-26]	0 [0-3]	<0.001	19	5 [1-146]	0 [0-4]	<0.001
PAT	30	3 [1-15]	1 [0-2]	<0.001	21	2 [1-35]	1 [0-1]	0.005

Note: PACs - premature atrial contractions; PAT - paroxismal atrial tachycardia

Of the 52 patients included, paroxysmal AF was documented in 35, symptomatic PACs in 13, and another 4 had both AF and symptomatic PACs. In full accordance with realworld clinical practice, PAC "symptomaticity" was defined as a combination of patient complaints (feeling of "fading" or "irregularity" of heartbeats reducing quality of life) and a high PAC burden on baseline Holter monitoring. Of the 46 patients with hypertension, 42 received standard antihypertensive therapy (dihydropyridine calcium antagonists, ACE inhibitors, angiotensin II receptor blockers, thiazide diuretics), which was unchanged between the two Holter recordings. Among these, five received low doses of selective betablockers (bisoprolol or metoprolol succinate). In full accordance with the 2025 Clinical Guidelines "Atrial Fibrillation and Flutter", these were not discontinued when PRLH was initiated, and their dose was not changed. The remaining 10 patients received no other treatment besides antiarrhythmic therapy. Analysis of individual forms of AEA was performed only in patients in whom the corresponding types of arrhythmia were recorded at baseline and for whom complete data were available to assess their changes during therapy.

Since in realworld clinical practice the duration of Holter ECG monitoring ranged from 21 hours to 7 days, all quantitative indicators of AEA were recalculated (normalised) to 24 hours. The study did not include patients with AF or focal atrial tachycardia (AT) paroxysms lasting ≥1 hour in at least one of the two Holter recordings. If shorter paroxysms were present, this time was subtracted from the actual Holter duration before normalising the parameters to 24 hours. Table 1 presents a brief clinical characterisation of the patients.

Efficacy of AAT was assessed by changes in the number of single, paired, and grouped PACs and paroxysms of focal AT, normalised to 24 hours, as well as the ectopic burden index (number of PACs per 1000 heartbeats) and the proportion of responders (reduction in PACs and focal AT episodes by ≥50% and ≥75%, respectively) during therapy compared with baseline.

Safety of AAT was assessed by changes in heart rate (HR), Pwave duration, PQ interval, QRS duration, QT and QTc intervals during therapy compared with baseline.

Statistical processing was performed using standard descriptive and comparative statistics methods. Preliminary analysis of the distribution of quantitative variables demonstrated pronounced skewness; therefore, nonparametric statistical methods were used. Quantitative variables are presented as median and interquartile range - median [Q1-Q3], where Q1 corresponds to the 25th percentile and Q3 to the 75th percentile. Comparison of quantitative variables before treatment initiation and during treatment was performed using the Wilcoxon signedrank test. Analysis of AAT efficacy was conducted only in patients in whom the corresponding forms of AEA were recorded at baseline. Consequently, the number of patients included in the analysis for individual arrhythmia forms could differ. For additional assessment of treatment efficacy, for each patient the relative change in the number of corresponding AEA forms during treatment compared with baseline was calculated. Based on the magnitude of relative reduction, patients were categorised into three therapeutic response categories: reduction in arrhythmia frequency <50%, reduction by 5074%, and ≥75%. To exclude the possible influence of HR changes on the overall AEA burden, the total number of AEA per 1000 heartbeats was additionally analysed. In all cases, differences were considered statistically significant at $p<0.05$.

RESULTS

Data on the efficacy of PRLH in the entire cohort are presented in Table 1. Analysis of AAT efficacy based on Holter monitoring was performed in all patients in whom the corresponding forms of AEA were recorded at baseline. During treatment, a marked reduction in the frequency of all analysed AEA forms was observed. Single PACs were recorded at baseline in all 52 patients; their reduction during therapy was statistically significant ($p<0.001$) and accompanied by a substantial narrowing of the interquar-

Table 2.

Relative change in atrial arrhythmia frequency during treatment compared with baseline

	n	Reduction <50%	Reduction 50-74%	Reduction ≥75%
All patients				
Single PACs	52	15 (28.8) 95% CI 18.3-42.3	6 (11.5) 95% CI 5.4-23.0	31 (59.6) 95% CI 46.1-71.8
Paired PACs	36	6 (16.7) 95% CI 7.9-31.9	5 (13.9) 95% CI 6.1-28.7	25 (69.4) 95% CI 53.1-82.0
Grouped PACs	30	6 (20.0) 95% CI 9.5-37.3	0 (0.0) 95% CI 0.0-11.4	24 (80.0) 95% CI 62.7-90.5
PAT	30	9 (30.0) 95% CI 16.7-47.9	4 (13.3) 95% CI 5.3-29.7	17 (56.7) 95% CI 39.2-72.6
PACs/1000 beats	17	3 (17.6) 95% CI 6.2-41.0	2 (11.8) 95% CI 3.3-34.3	12 (70.6) 95% CI 46.9-86.7
Patients with baseline PACs >500 per day				
Single PACs	22	5 (22.7) 95% CI 10.1-43.4	2 (9.1) 95% CI 2.5-27.8	15 (68.2) 95% CI 47.3-83.6
Paired PACs	18	3 (16.7) 95% CI 5.8-39.2	3 (16.7) 95% CI 5.8-39.2	12 (66.7) 95% CI 43.7-83.7
Grouped PACs	15	3 (20.0) 95% CI 7.0-45.2	0 (0.0) 95% CI 0.0-20.4	12 (80.0) 95% CI 54.8-93.0
PAT	17	5 (29.4) 95% CI 13.3-53.1	2 (11.8) 95% CI 3.3-34.3	10 (58.8) 95% CI 36.0-78.4
PACs/1000 beats	10	2 (20.0) 95% CI 5.7-51.0	2 (20.0) 95% CI 5.7-51.0	6 (60.0) 95% CI 31.3-83.2

Note: n - number of patients; data are n (%); the slightly lower numbers for paired/grouped PACs and paroxysmal AT compared with Table 1 are due to inclusion only of patients with complete data to calculate relative changes.

tile range. Paired PACs were detected at baseline Holter in 36 patients, and grouped PACs in 30; during treatment, a marked reduction in the frequency of these arrhythmia types was observed, with high statistical significance. Among all forms of AEA, the most clinically significant was paroxysmal focal AT, detected in 30 patients; the reduction in its episodes was also statistically significant. Thus, PRLH administration was accompanied by a significant and highly significant decrease in the frequency of all analysed forms of AEA. The most pronounced changes were observed for more complex forms - paired and grouped PACs, whose median values during therapy decreased to zero.

Since the magnitude of the antiarrhythmic effect could be related to the baseline PAC frequency, an additional analysis of AAT efficacy was performed in patients with a higher AEA burden. For this purpose, a subgroup of patients with >500 single PACs per day on baseline Holter was identified from the overall cohort. This approach allowed exclusion of cases with minimal PAC counts and more objective assessment of AAT efficacy at clinically meaningful arrhythmia burden. Data on PRLH efficacy in these patients are shown in Table 1.

As follows from the table, this subgroup included 22 patients. Of these, paired PACs were found in 20, grouped PACs in 19, and paroxysmal AT in 21. Although the baseline PAC count in these patients exceeded the overall cohort value by more than 30fold, the therapeutic effect remained equally pronounced and significant. Thus, even in patients with high baseline AEA burden, AAT was accompanied by a multiple reduction in arrhythmia frequency: the median number of single PACs decreased more than 10fold, paired PACs more than 8fold, and the median grouped PAC value decreased almost to zero.

Thus, AAT efficacy was maintained regardless of baseline AEA. However, analysis of median values does not allow assessment of individual response variability. Therefore, to detail the treatment efficacy, an additional analysis was performed: the distribution of individual responses to treatment. For each patient, the relative change in each AEA variant during AAT compared with baseline was calculated. Depending on the magnitude of effect, patients were categorised into three groups: reduction in arrhythmia frequency <50%, 5074%, and ≥75%. The results for the entire cohort are presented in Table 2.

As shown, a marked therapeutic effect was observed in most patients. A ≥75% reduction in single PACs was observed in 31 of 52 patients (59.6%), while a reduction of <50% occurred in only 15 patients (28.8%). Even more pronounced effects were observed for more complex AEA forms. A ≥75% reduction in paired PACs was seen in 25 of 36 patients (69.4%). For grouped PACs, the proportion with marked effect was 80.0% (24 of 30). A similar pattern was observed for AT episodes: a ≥75% reduction occurred in 17 of 30 patients (56.7%), while a reduction <50% was seen in 9 patients (30.0%). Additionally, to exclude possible influence of HR changes on overall AEA burden, comparison of total AEA per 1000 heartbeats at baseline and during AAT was performed. As can be seen, a marked antiarrhythmic effect was observed in the majority of patients (70.6%). A similar analysis was conducted in the subgroup with baseline high PAC burden (>500 single PACs per day) (Table 2).

As shown, in this subgroup the distribution of response to AAT was comparable to the overall cohort. A marked reduction in single PACs (≥75%) was observed in 68.2% of cases. For paired PACs, the proportion with such an effect was 66.7%. The most pronounced effect was for grouped PACs, where a ≥75% reduction was noted in 12 of 15 patients (80.0%). A similar trend was observed for AT, where a marked response was seen in 10 of 17 patients (58.8%). In the analysis of total PACs per 1000 heartbeats, the most significant reduction was observed in 6 of 10 patients (60.0%). Thus, a marked AAT effect was found both in the overall cohort and in patients with high AEA burden, independent of baseline counts.

For a more illustrative demonstration of the therapeutic response structure, the results are also presented graphically in Fig. 1. The figure shows the distribution of patients by response category for different AEA forms.

The graphical representation clearly demonstrates that patients with marked reduction in AEA frequency (≥75%) predominate in all analysed groups, whereas the proportion of patients with no clinically significant effect (<50%) is substantially smaller. Thus, the results indicate a

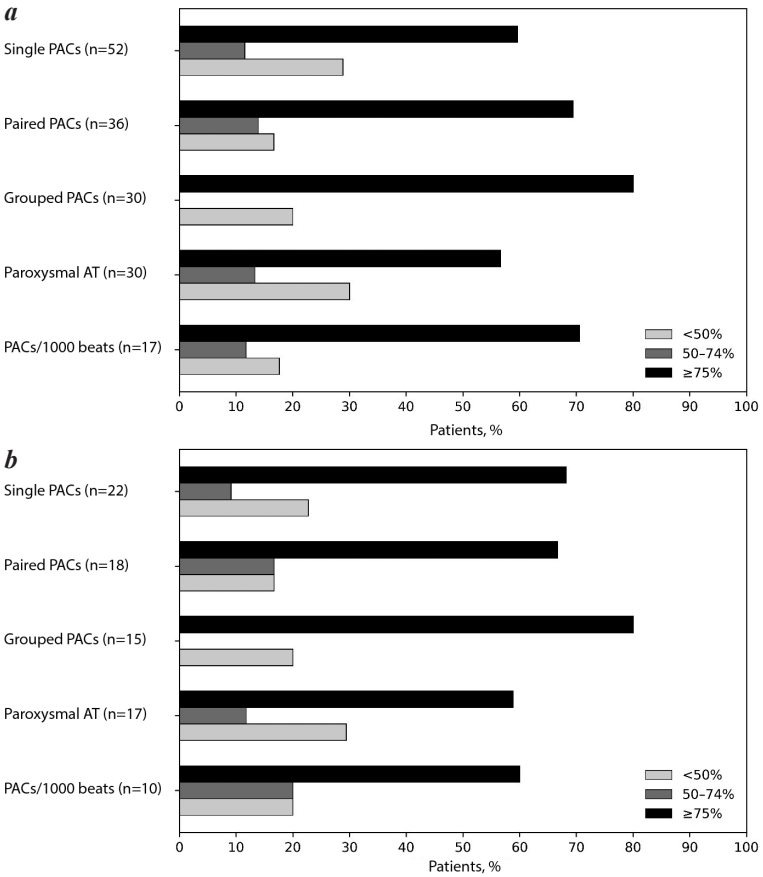

Fig. 1. Distribution of patients by categories of antiarrhythmic effect for various forms of atrial ectopic activity: a - entire cohort; b - patients with high arrhythmia burden.

marked reduction in various forms of AEA during AAT. A significant reduction was observed both in the overall cohort and in the highburden subgroup. Individual response analysis also showed that the majority of patients experienced a marked reduction, with the proportion of marked responders (≥75%) prevailing in all groups. These results testify to the high efficacy of therapy for various PAC and AT forms.

Alongside the efficacy assessment, treatment safety was evaluated, i.e., the effect of therapy on key ECG parameters. The analysis included baseline and ontreatment assessment of HR, Pwave duration, QRS duration, PQ interval, and QT and QTc (Bazett) intervals from Holter data. Results are presented in Table 3. Quantitative data are shown as median and interquartile range [Q1Q3]. The Wilcoxon test was used for statistical significance.

As can be seen, median HR on therapy was slightly reduced compared with baseline: from 72 [6879] to 69 [6275] bpm. The difference was statistically significant (p=0.001). Pwave duration did not change substantially: 100 [100103] ms before and 100 [100110] ms on therapy. The PQ interval slightly increased during AAT (p=0.017), but its median values remained within physiological ranges. QRS duration did not change: 90 [9090] ms before and 90 [9095] ms on therapy (p=0.080). QT interval remained stable and showed no changes: 410 [400420] ms and 410 [405420] ms, respectively (p=0.072). A similar picture was observed for QTc, with median values of 430 [425440] ms at baseline and 430 [430445] ms on therapy (p=0.492). Notably, the electrical systole characteristics could not change substantially, since class IC drugs are known not to affect them. Thus, ECG parameter analysis revealed no clinically significant effect of therapy on major conduction and repolarisation parameters.

Summarising the above, the study demonstrated a marked reduction in various AEA forms during AAT. The efficacy of PRLH with twicedaily administration at the minimum dose was observed both in the overall cohort and in the highburden group. At the same time, ECG assessment showed no clinically significant changes in major conduction and repolarisation parameters, indicating a satisfactory safety profile.

DISCUSSION

The study results showed that PRLH at the minimum dose of 25 mg twice daily is associated with a significant reduction in AEA. During therapy, a statistically significant decrease in the number of single, paired, and grouped PACs, as well as paroxysms of focal AT, was observed. An identical result was obtained in the group of patients with a high baseline PAC burden. The clinical significance of these findings is determined by the fact that PACs may cause pronounced symptoms and significant deterioration in quality of life [58]. Reducing PAC frequency in such cases is an independent therapeutic goal. This study shows that PRLH effectively suppresses not only single PACs but also more complex forms of AEA. Furthermore, PACs are regarded as one of the beststudied triggers of AF [9]. Current concepts of AF pathogenesis are based on the interaction of trigger factors and the arrhythmogenic substrate [1014]. PACs, especially those arising from the myocardial sleeves at the pulmonary vein ostia, can initiate AF paroxysms, whereas arrhythmia persistence is determined by the severity of structural and electrical atrial remodelling. From this perspective, a reduction in PAC frequency during AAT may be considered a reflection of decreased trigger activity.

Table 3.

Safety of prolonged release lappaconitine hydrobromide at a dose of 50 mg/day in the treatment of atrial arrhythmias

	Before treatment	On therapy	p
HR, bpm	72 [68-79]	69 [62-75]	0.001
P, ms	100 [100-103]	100 [100-110]	0.416
PQ, ms	180 [160-200]	180 [160-220]	0.017
QRS, ms	90 [90-90]	90 [90-95]	0.080
QT, ms	410 [400-420]	410 [405-420]	0.072
QTc, ms	430 [425-440]	430 [430-445]	0.492

At the same time, PAC dynamics cannot be regarded as an independent efficacy criterion for AF treatment. Even pronounced suppression of AEA does not exclude the possibility of AF paroxysms, since their occurrence is determined not only by the trigger but also by the atrial substrate condition [1018]. Therefore, quantitative PAC assessment should be considered an additional efficacy indicator. This approach seems particularly useful given the limitations of traditional methods for assessing AF treatment efficacy [1528]. A significant proportion of arrhythmia episodes are asymptomatic, and intermittent monitoring methods cannot always detect rare or short paroxysms. Under these conditions, analysis of AEA dynamics may serve as an additional characteristic of the antiarrhythmic effect. Of particular note is the fact that marked PAC reduction was also observed in patients with high baseline AEA. It is in such patients that PACs are more often associated with clinical symptoms and may be closely linked to AF risk.

The dosing regimen deserves separate discussion. This study evaluated the efficacy of PRLH at the minimum dose of 25 mg twice daily. The results are of practical interest because they demonstrate the possibility of achieving a marked antiarrhythmic effect at a relatively low dose. Moreover, a twicedaily regimen for the prolongedrelease form appears pharmacokinetically justified [4852]. An important aspect is also therapy safety. This study did not reveal clinically significant changes in major ECG conduction and repolarisation parameters. Despite a statistically significant decrease in HR and a slight increase in the PQ interval, the median values remained within physiological ranges. QRS duration, QT, and QTc intervals did not change substantially. For class IC drugs, such data are particularly important, since their use requires careful assessment of conduction effects [29, 30].

Study limitations

The study was conducted in a retrospective, openlabel, nonrandomised, observational format without a control group, and the number of patients in individual subgroups was small. Moreover, the study did not aim to directly assess the effect of therapy on AF recurrence rate. Also, no standardised quantitative symptom assessment

using validated questionnaires was performed, which does not allow evaluation of the clinical effect of therapy, since the aim was to assess AEA dynamics by Holter monitoring rather than clinical efficacy.

An important limitation is the absence of data on adverse drug effects generally characteristic of class IC drugs, since most patients were included retrospectively and their medical records contained no information on adverse effects. The results obtained require confirmation in controlled studies.

CONCLUSION

The use of PRLH is associated with a significant reduction in the frequency of various PAC forms as assessed by Holter ECG monitoring. During therapy, a statistically significant decrease in the number of single, paired, and grouped PACs, as well as AT episodes, was observed. Individual response analysis showed that most patients experienced a marked therapeutic effect with substantial reduction in arrhythmia frequency. These results were maintained in the subgroup of patients with high baseline PAC burden. At the same time, therapy was not accompanied by clinically significant changes in key ECG parameters, including QRS duration and QT/QTc intervals. The data indicate high efficacy and a favourable safety profile of PRLH in the treatment of frequent and/or symptomatic PACs.

In the studied cohort of patients without structural heart pathology, PRLH demonstrated significant efficacy in AEA, with high antiarrhythmic activity achieved with a minimum dose of 25 mg twice daily. PRLH is characterised by a favourable safety profile, with only minor effects on HR and atrioventricular conduction.

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