https://doi.org/10.33380/2305-2066-2022-11-1-140-147
UDC 615.03

Research article / Оригинальная статья

Pharmacokinetics Study of the Long-acting Antiarrhythmic Drug of Lappaconitine Hydrobromide (Allaforte®, JSC "Pharmcenter VILAR", Russia)

Olga A. Archakova[1]*, Natalia S. Bagaeva[1], Timofey N. Komarov[1,2], Anton V. Rogov[3], Dana S. Shchelgacheva[1], Alexandra V. Suvorova[1], Polina K. Karnakova[1,4], Polina A. Karpova[1,4], Igor E. Shohin[1,2]

[1] LLC "CPHA", 20/3, Nauchny proezd, Moscow, 117246, Russia
[2] National Research Nuclear University MEPhI (Moscow Engineering Physics Institute), 31, Kashirskoe highway, Moscow, 115409, Russia
[3] JSC "Pharmcenter VILAR", 7/29, Grina str., Moscow, 117216, Russia
[4] I. M. Sechenov First MSMU of the Ministry of Health of the Russian Federation (Sechenov University), 8/2, Trubetskaya str., Moscow, 119991, Russia

***Corresponding author:** Olga A. Archakova. **E-mail:** o.archakova@cpha.ru

ORCID: Olga A. Archakova – https://orcid.org/0000-0001-6621-1060; Natalia S. Bagaeva – https://orcid.org/0000-0001-7496-8186;
Timofey N. Komarov – https://orcid.org/0000-0001-8354-7877; Anton V. Rogov – https://orcid.org/0000-0001-8791-1971;
Dana S. Shchelgacheva – https://orcid.org/0000-0003-4894-7001; Alexandra V. Suvorova – https://orcid.org/0000-0003-2611-501X;
Polina K. Karnakova – https://orcid.org/0000-0002-7518-0777; Polina A. Karpova – https://orcid.org/0000-0001-6777-5976; Igor E. Shohin – https://orcid.org/0000-0002-1185-8630.

Received: 14.12.2021 **Revised:** 04.02.2022 **Published:** 25.02.2022

Abstract

Introduction. Allaforte® (JSC "Pharmcenter VILAR", Russia) is an antiarrhythmic long-acting drug. The dosage form of the drug Allaforte® provides a decrease in the frequency of taking the drug and also reduces the risk of side effects. It is relevant when taking antiarrhythmic drugs of the IC class. However, the pharmacokinetics of this drug has not been studied on humans. Therefore, it is important to fully study the pharmacokinetics to ensure the maximum efficacy and safety of arrhythmia therapy.

Aim. The aim is pharmacokinetics study of long-acting antiarrhythmic drug Allaforte® (JSC "Pharmcenter VILAR", Russia), 25 mg.

Materials and methods. Concentration of lappaconitine and its active metabolite N-desacetyllappaconitine in human plasma determinates by high performance liquid chromatography with tandem mass-spectrometry. Pharmacokinetic parameters calculated by R Project 3.5.1 software (package «bear», version 2.8.3-2), originally created by Hsin-ya Lee and Yung-jin Lee, Taiwan.

Results and discussion. Pharmacokinetic parameters of lappaconitine and N-desacetyllappaconitine were calculated. Averaged pharmacokinetic profiles (in linear and semi-log scale) of lappaconitine and N-desacetyllappaconitine after single administration under fasting were built. The means of the maximum concentrations (C_{max}) determined in the blood plasma of volunteers after single administration Allaforte® are 5.09 ± 4.07 ng/ml for lappaconitine and 11.66 ± 6.21 ng/ml for N-deacetyllappaconitine (Mean ± SD). The peak time of the maximum concentrations (T_{max}) is 4.43 ± 3.54 hours for lappaconitine and 4.04 ± 2.18 hours for N-deacetyllappaconitine. The means of the areas under the curve plasma concentration – time from 0 to 48 hours (AUC_{0-t}) and under the curve plasma concentration–time from zero to infinity ($AUC_{0-\infty}$) of Allaforte® is 42.96 ± 34.48 ng · h/ml and 71.24 ± 43.20 ng · h/ml for lappaconitine; 167.42 ± 114.41 ng · h/ml and 189.42 ± 115.20 ng · h/ml for N-deacetyllappaconitine. Allaforte® was eliminated from blood plasma with means of terminal half-life ($T_{1/2}$) 8.45 ± 5.10 hours for lappaconitine and 9.04 ± 2.57 hours for N-deacetyllappaconitine.

Conclusion. Pharmacokinetics study of long-acting antiarrhythmic drug Allaforte® (JSC "Pharmcenter VILAR", Russia) after single administration was researched. Results of the study allows to conduct an effective therapy of arrhythmia by study drug and minimize side effects.

Keywords: lappaconitine, N-desacetyllappaconitine, Allaforte®, plasma, pharmacokinetics, arrhythmya

Conflict of interest. The authors declare that they have no obvious and potential conflicts of interest related to the publication of this article.

Contribution of the authors. Timofey N. Komarov, Olga A. Archakova, Dana S. Shchelgacheva, Alexandra V. Suvorova, Polina K. Karnakova and Polina A. Karpova participated in the analytical phase of the study. Natalia S. Bagaeva carried out statistical processing of the obtained results. Anton V. Rogov and Igor E. Shohin carried out the organization of work in this direction. All the above authors participated in the discussion of the results in the format of scientific discussion.

For citation: Archakova O. A., Bagaeva N. S., Komarov T. N., Rogov A. V., Shchelgacheva D. S., Suvorova A. V., Karnakova P. K., Karpova P. A., Shohin I. E. Pharmacokinetics Study of the Long-acting Antiarrhythmic Drug of Lappaconitine Hydrobromide (Allaforte®, JSC "Pharmcenter VILAR", Russia). *Razrabotka i registratsiya lekarstvennykh sredstv = Drug development & registration.* 2022;11(1):140–147. (In Russ.) https://doi.org/10.33380/2305-2066-2022-11-1-140-147

Изучение фармакокинетики пролонгированного антиаритмического препарата лаппаконитина гидробромида (Аллафорте®, АО «Фармцентр ВИЛАР», Россия)

О. А. Арчакова[1]*, Н. С. Багаева[1], Т. Н. Комаров[1,2], А. В. Рогов[3], Д. С. Щелгачева[1], А. В. Суворова[1], П. К. Карнакова[1,4], П. А. Карпова[1,4], И. Е. Шохин[1,2]

[1] ООО «Центр Фармацевтической Аналитики» (ООО «ЦФА»), 117246, Россия, г. Москва, Научный пр., д. 20, стр. 3
[2] ФГАОУ ВО «Национальный исследовательский ядерный университет «МИФИ» (НИЯУ МИФИ), 115409, Россия, г. Москва, Каширское шоссе, д. 31
[3] АО «Фармцентр ВИЛАР», 117216, Россия, г. Москва, ул. Грина, д. 7, стр. 29
[4] ФГАОУ ВО Первый МГМУ им. И. М. Сеченова Минздрава России (Сеченовский университет), 119991, Россия, г. Москва, ул. Трубецкая, д. 8, стр. 2

***Контактное лицо:** Ольга А. Арчакова. **E-mail:** o.archakova@cpha.ru

ORCID: О. А. Арчакова – https://orcid.org/0000-0001-6621-1060; Н. С. Багаева – https://orcid.org/0000-0001-7496-8186;
Т. Н. Комаров – https://orcid.org/0000-0001-8354-7877; А. В. Рогов – https://orcid.org/0000-0001-8791-1971; Д. С. Щелгачева – https://orcid.org/0000-0003-4894-7001;
А. В. Суворова – https://orcid.org/0000-0003-2611-501X; П. К. Карнакова – https://orcid.org/0000-0002-7518-0777; П. А. Карпова – https://orcid.org/0000-0001-6777-5976;
И. Е. Шохин – https://orcid.org/0000-0002-1185-8630.

Статья поступила: 14.12.2021 **Статья принята в печать:** 04.02.2022 **Статья опубликована:** 25.02.2022

Резюме

Введение. Аллафорте® (АО «Фармцентр ВИЛАР») – отечественный антиаритмический лекарственный препарат, обладающий пролонгированным действием. По сравнению с аналогичными препаратами, зарегистрированными на территории Российской Федерации, лекарственная форма препарата Аллафорте® обеспечивает уменьшение кратности приема лекарственного препарата, а также снижает риск развития побочных эффектов, что является актуальным при приеме антиаритмических препаратов класса IC. Однако фармакокинетика данного препарата не была ранее изучена на людях, что привело к необходимости ее полноценного изучения для обеспечения максимальной эффективности и безопасности терапии аритмии.

Цель. Целью исследования является изучение фармакокинетики лекарственного препарата Аллафорте®, таблетки пролонгированного действия 25 мг (АО «Фармцентр ВИЛАР», Россия).

Материалы и методы. Концентрации лаппаконитина и его активного метаболита N-дезацетиллаппаконитина в плазме крови здоровых добровольцев определялись методом высокоэффективной жидкостной хроматографии с тандемным масс-спектрометрическим детектированием. Фармакокинетические параметры вычислены с помощью программного обеспечения R Project 3.5.1 (расширение «bear», версия 2.8.3-2), разработчики Hsin-ya Lee и Yung-jin Lee, Тайвань.

Результаты и обсуждение. Рассчитаны основные фармакокинетические параметры лаппаконитина и N-дезацетиллаппаконитина, а также построены усредненные фармакокинетические профили (в линейных и полулогарифмических координатах) лаппаконитина и его метаболита N-дезацетиллаппаконитина после однократного приема исследуемого препарата. Средние значения максимальных концентраций (C_{max}), определяемых в плазме крови добровольцев после приема исследуемого препарата Аллафорте®, составляют 5,09 ± 4,07 нг/мл для лаппаконитина и 11,66 ± 6,21 нг/мл для N-дезацетиллаппаконитина (Mean ± SD). Время достижения максимальных концентраций лаппаконитина и N-дезацетиллаппаконитина (T_{max}) составляет 4,43 ± 3,54 часа и 4,04 ± 2,18 часа соответственно. Средние значения площадей под кривой «концентрация – время» с момента приема лекарственного препарата до последней определяемой концентрации во временной точке *t* (AUC_{0-t}) и площади под кривой «концентрация – время» с момента приема лекарственного препарата до бесконечности ($AUC_{0-\infty}$) исследуемого препарата Аллафорте® составляют 42,96 ± 34,48 нг · ч/мл и 71,24 ± 43,20 нг · ч/мл соответственно (лаппаконитин); 167,42 ± 114,41 нг · ч/мл и 189,42 ± 115,20 нг · ч/мл, соответственно (N-дезацетиллаппаконитин). Исследуемый препарат элиминировался из плазмы крови со средним значениями периода полувыведения ($T_{1/2}$) 8,45 ± 5,10 часа для лаппаконитина и 9,04 ± 2,57 часа для N-дезацетиллаппаконитина.

Заключение. Проведено изучение фармакокинетики препарата Аллафорте®, таблетки пролонгированного действия 25 мг (АО «Фармцентр ВИЛАР») при однократном применении с участием здоровых добровольцев. Полученные данные позволяют обеспечить проведение эффективной терапии аритмии исследуемым препаратом, минимизировав вероятность возникновения побочных эффектов.

Ключевые слова: лаппаконитин, N-дезацетиллаппаконитин, Аллафорте®, плазма, фармакокинетика, аритмия

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. Т. Н. Комаров, О. А. Арчакова, Д. С. Щелгачева, А. В. Суворова, П. К. Карнакова и П. А. Карпова участвовали в проведении аналитического этапа исследования. Н. С. Багаева проводила статистическую обработку данных. А. В. Рогов и И. Е. Шохин отвечали за организационную часть исследования. Все вышеуказанные авторы участвовали в обсуждении полученных результатов в форме научной дискуссии.

Для цитирования: Арчакова О. А., Багаева Н. С., Комаров Т. Н., Рогов А. В., Щелгачева Д. С., Суворова А. В., Карнакова П. К., Карпова П. А., Шохин И. Е. Изучение фармакокинетики пролонгированного антиаритмического препарата лаппаконитина гидробромида (Аллафорте®, АО «Фармцентр ВИЛАР», Россия). *Разработка и регистрация лекарственных средств*. 2022;11(1):140–147. https://doi.org/10.33380/2305-2066-2022-11-1-140-147

INTRODUCTION

Treatment and prevention of arrhythmias is one of the essential problems of modern cardiology. In most cases, the cause of death is atrial fibrillation (AF) that develops more often as complications of ischemic heart disease and myocardial infarction [1]. Atrial fibrillation is found in over 33 million people worldwide, with new cases registered in over 5 million people. The incidence of atrial fibrillation is expected to double over the next 20 years which will amount to 120 000 to 215 000 new cases per year by the end of 2040 only in Europe [2, 3].

Despite surgical methods for treatment of arrhythmias actively implemented to medical practice, drug therapy remains in the first place [4]. However, during anti-arrhythmic therapy, severe cardiac and non-cardiac adverse effects are highly probable [2, 5, 6], the incidence of which is proportional to dose and duration of drug therapy. In most cases, this leads to discontinuation of treatment of arrhythmias [2]. Therefore, nowadays, the development of effective and safe drugs for treatment of cardiac arrhythmias is the challenge for public health [7].

In the Russian Federation, lappaconitine agents have been used for many years for treatment of supraventicular and ventricular arrhythmias [8], anti-arrhythmic efficacy of which achieves 90 % during the first three months of observations, and by the end of the first year, they allow preserving cardiac rhythm in 57 % of cases with a relatively good tolerability [9]. In accordance with the statistics, for the control of cardiac rhythm, lappaconitine agents are administered in the following cases:

- in 8.9 % of cases, as the 1st line drug in patients without an organic heart disease or with minimal structural changes;
- in 19.07 % of cases, as the 2nd line drug in patients without an organic heart disease or with minimal structural changes;
- in 1.8 % of cases, as the 1st line drug in treatment of paroxysmal and persistent atrial fibrillation in patients with an organic heart disease in the absence of a clinically significant chronic heart failure (CHF);
- in 4.0 % of cases, as the 2nd line drug in treatment of paroxysmal and persistent AF in patients with an organic heart disease in the absence of a clinically significant CHF;
- in 5.2 % of cases, after isolation of pulmonary vein ostia [10].

Despite their high efficacy, lappaconitine agents have some dosing limitations [8] due to their high toxicity [11] and risk of pro proarrythmogenic [9], and also non-cardiac adverse effects as dizziness, headache, coordination disorders and dyplopia [12–15]. All these adverse events are directly related to a drug dose becoming more prominent with its increase, which determines in some cases the impossibility of achieving a dose-dependent anti-arrhythmic drug effect [12].

Due to that, company JSC "Pharmcenter VILAR" registered a drug product based on lappaconitine hydrobromide Allaforte®, a prolonged form of which contributes to the decrease of risk of adverse events of lappaconitine hydrobromide and the decrease of dosing frequency [12, 16]. As raw materials for production of anti-arrhythmic drug Allaforte®, terrestrial part of the white wrestler (*Aconitum leucostomum Worosch*) and rhizomes and roots of the northern wrestler (*Aconitum septentrionale Koelle*) family of buttercaps (*Ranunculaceae*) [17–19] are used.

During pre-authorization studies of drug Allaforte®, the pharmacokinetics was not investigated in humans which could result in dosing errors, adverse reactions. Therefore, the post-authorization study of Allaforte® on healthy volunteers has been carried out to ensure maximal efficacy and safety of anti-arrhythmic therapy.

MATERIALS AND METHODS

The clinical and analytical stages of the pharmacokinetic study of Allaforte®, prolonged action tablets 25 mg (JSC "Pharmcenter VILAR", Russia), as well as, statistical data processing were carried out within the comparative pharmacokinetic study of Allaforte®, prolonged action tablets 25 mg (JSC "Pharmcenter VILAR", Russia), and the analogous drug product of the national manufacturer.

Clinical stage of the study

Male and female healthy volunteers aged 18 to 45 years inclusive took part in the study.

Volunteers had the cubital heparinized catheter installed for 12 hours. After the catheter installation, 5–10 minutes prior to the dosing, blood was withdrawn at baseline (0). Being supervised by specialists, volunteers took the study product once in dose 25 mg (1 tablet in the morning in fasted condition with 200 ml of drinking water (still). Blood was further sampled for the pharmacokinetic study in 15 minutes, 30 minutes, 45 minutes, 1 h; 80 min; 1,5; 2; 2,5; 3; 4; 5; 7, 8; 12; 24 and 48 hours after administration of the study product.

Then blood samples taken were centrifuged, and plasma was subsequently withdrawn to separate labeled tubes containing K2EDTA as an anticoagulant. All plasma samples were frozen, kept and shipped to the analytical laboratory at temperature not above –20 °C.

Analytical stage of the study

Concentrations of lappaconitine and its active metabolite N-deacetyllappaconitine in plasma of healthy volunteers were determined with the method of high performance liquid chromatography and tandem mass-spectrometry (HPLC/MS/MS) using the electrospray as an ionization source. As an internal standard, trimebutine was used. Lappaconitine, N-deacetyllappaconitine and internal standard trimebutine were identified in the regime of multiple reaction monitoring. As a mobile phase, 0.1 % formic acid solution in water with the addition of 0.08 % ammonium (by volume) and 0.1 % formic acid solution in methanol with the addition of 0.08 %

ammonium were used. The analysis was made in the gradient elution mode using chromatographic column YMCPack Pro C18, 100 ± 2.0 mm, 3 μm. Analytical ranges were 0.50–50.00 ng/ml for lappaconitine and 0.50–100.00 ng/ml for N-deacetyllappaconitine [20].

Statistical data processing

Pharmacokinetic profiles of changes in plasma concentrations of lappaconitine and its metabolite N-deacetyllappaconitine in humans over the time recorded following the administration of Allaforte®, were characterized with maximum drug concentration (C_{max}) and time to maximum concentration (T_{max}) under the "time-concentration" curve after the dosing up to the last measurable concentration at time point *t* (AUC_{0-t}) calculated with the linear logarithmic trapezoidal rule, area under the "concentration-time" curve since the dosing to infinity ($AUC_{0-\infty}$). In addition, the following pharmacokinetic parameters were determined: half-life ($T_{1/2}$), elimination rate constant (K_{el}) assessed by the slope of the regression line calculated with the least square method, natural logarithmic concentration in relation to the time of the last measurable concentration values (at least three) above the lower limit of the quantification.

Pharmacokinetic parameters were calculated with software R Project 3.5.1 (extension "bear", version 2.8.32), developers Hsinya Lee and Yungjin Lee, Taiwan. The distribution of pharmacokinetic parameters was described with the main measures of central tendency (mean arithmetic, mean geometric, median) and measure of data dispersion (standard deviation).

RESULTS AND DISCUSSION

Pharmacokinetic parameters of lappaconitine. The mean value of maximum concentrations (C_{max}) determined in plasma of volunteers after the administration of study product Allaforte® is 5.09 ± 4.07 ng/ml (Mean ± SD). Time to reach maximum concentration of lappaconitine (T_{max}) is 4.43 ± 3.54 hours. Mean values of the area under the "concentration-time" curve since the drug dosing up to the last measurable concentration at time point *t* (AUC_{0-t}) and area under the "concentration-time" after the dosing of study product Allaforte® to infinity ($AUC_{0-\infty}$) are 42.96 ± 34.48 ng · h/ml and 71.24 ± 43.20 ng · h/ml, respectively. The study product was eliminated from plasma with the mean half-life value ($T_{1/2}$) 8.45 ± 5.10 hours (table 1).

Pharmacokinetic parameters of N-deacetyllappaconitine. Mean values of maximum concentrations (C_{max}) determined in plasma of volunteers following administration of study product Allaforte®, is 11.66 ± 6.21 ng/ml (Mean ± SD). Time to maximum concentration of N-deacetyllappaconitine (T_{max}) is 4.04 ± 2.18 hours. Mean values under the "concentration-time" curve since the drug dosing up to the last measurable concentration at time point *t* (AUC_{0-t}) and area under the "concentration-time" curve since the drug dosing up to infinity ($AUC_{0-\infty}$) of study product Allaforte® are 167.42 ± 114.41 ng · h/ml and 189.42 ± 115.20 ng · h/ml, respectively. The study product was eliminated from plasma with the mean half-life value ($T_{1/2}$) 9.04 ± 2.57 hours (table 1).

Table 1. Summary data of pharmacokinetic parameters of lappaconitine and N-desacetyllappaconitine after a single administration under fasting of Allaforte®

Pharmacokinetic parameter	Lappaconitine	N-desacetyllappaconitine
C_{max}, ng/ml		
Number of volunteers	28	28
Mean	5.09	11.66
Geometric Mean	4.06	10.29
Median	3.60	9.88
SD	4.07	6.21
AUC_{0-t}, ng · h/ml		
Number of volunteers	28	28
Mean	42.96	167.42
Geometric Mean	33.18	138.59
Median	26.64	133.28
SD	34.48	114.41
$AUC_{0-\infty}$, ng · h/ml		
Number of volunteers	22	26
Mean	71.24	189.42

Pharmacokinetic parameter	Lappaconitine	N-desacetyllappaconitine
Geometric Mean	58.42	158.35
Median	57.98	154.35
SD	43.20	125.20
T_{max}, h		
Number of volunteers	28	28
Mean	4.43	4.04
Geometric Mean	3.37	3.62
Median	2.75	4.00
SD	3.54	2.18
K_{el}, h^{-1}		
Number of volunteers	22	26
Mean	0.114	0.083
Geometric Mean	0.097	0.080
Median	0.085	0.079
SD	0.066	0.024
$T_{1/2}$, h		
Number of volunteers	22	26
Mean	8.45	9.04
Geometric Mean	7.17	8.70
Median	8.30	8.77
SD	5.10	2.57

Note. AUC – area under the pharmacokinetic curve; SD – standard deviation.

The averaged pharmacokinetic profiles (in linear and semi-logarithmic coordinates) of lappaconitine and its metabolite N-deacetyllappaconitine after administration of the study product are given in figures 1 and 2.

In figures 1 and 2, we see that product Allaforte® allegedly has a two-phase elimination kinetics of lappaconitine and N-deacetyllappaconitine, however, it can be related to a high variability of values T_{max} of lappaconitine [coefficient of variation (CV) = 79.84 %] and N-deacetyllappaconitine (CV = 53.94 %), as well as, a large dispersion of individual values (0.75 hours to 12 hours for lappaconitine; 1.5 hours to 12 hours for N-deacetyllappaconitine).

It can be also stated that there are no significant differences in T_{max} of lappaconitine and T_{max} of N-deacetyllappaconitine following administration of Allaforte® (Wilcoxon test, $p > 0.05$). It may lead to the increase of the therapeutic effect when maximum concentrations of lappaconitine and N-deacetyllappaconitine are reached in plasma of patients.

The area under the pharmacokinetic curve of N-deacetyllappaconitine is higher in 3.9 times than the one of lappaconitine which allows assuming a low probability of adverse events as N-deacetyllappaconitine has a low toxicity compared to lappaconitine [21].

As well, Allaforte®, compared to analogous drugs registered in the Russian Federation, has a longer time to maximum blood concentration (4.43 ± 3.54 hours) and half-life of lappaconitine (8.45 ± 5.10 hours). For comparison, T_{max} and $T_{1/2}$ of lappaconitine contained in Allapinin® are 1.5 hours and 1.17–2.4 hours, respectively [21]. Correspondingly, the administration of Allaforte® may reduce the dosing frequency.

The results of the pharmacokinetic study should be compared with pharmacodynamic studies, which will allow correcting the dosing regime for Allaforte® [22]. However, the half life values of lappaconitine from the data obtained varied from 2.71 to 22.74 hours (CV = 60.39 %), therefore an individual approach to the selection of dosing regime should be provided, and when possible to perform a therapeutic drug monitoring during Allaforte® administration to provide an effective and safe therapy of arrhythmias [23–26].

CONCLUSION

The pharmacokinetic study of Allaforte®, prolonged action tablets 25 mg (JSC "Pharmcenter VILAR") after a single dosing in healthy volunteers was carried out. Based on the concentrations of lappaconitine and its active metabolite N-deacetyllappaconitine obtained during the analytical stage of the study, the main pharmacokinetic parameters were calculated, and the averaged pharma-

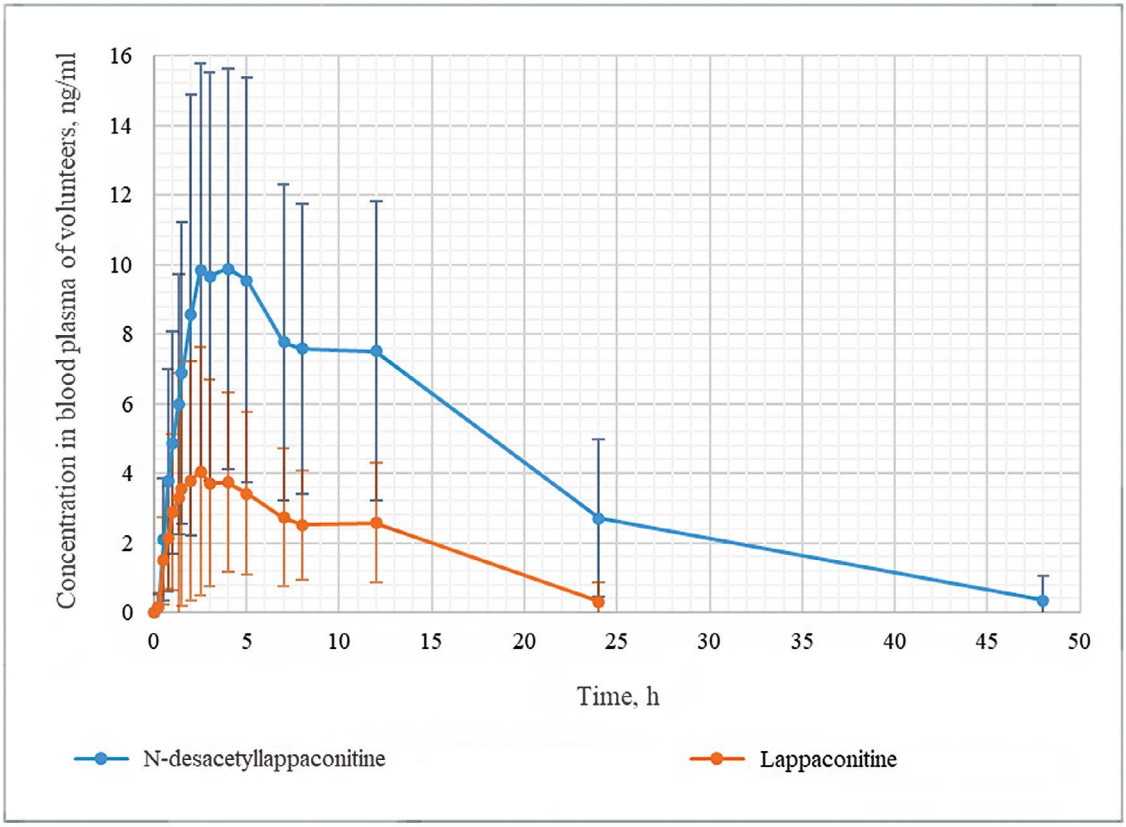

Figure 1. Average pharmacokinetic profiles (in linear scale with standard deviations) of lappaconitine and N-desacetyllappaconitine after single administration under fasting of Allaforte®, 25 mg

cokinetic profiles were plotted (in linear and semi-logarithmic coordinates) of the study substances following the single administration of prolonged product Allaforte®. The data obtained allow providing effective therapy of arrhythmias with the study product, minimizing the probability of adverse effects.

REFERENCES

1. Rybakova T. A., Stolyarova V. V., Nazarkina M. G., Leschankina N. Yu. Analysis of the Results of a Five-Year Patients Follow-up In Paroxysmal Atrial Fibrillation Treated with Antiarrhythmics. *Rossiyskiy kardiologicheskiy zhurnal = Russian Journal of Cardiology*. 2018;7:67–72. (In Russ.) DOI: 10.15829/1560-4071-2018-7-67-72.
2. Gagloeva D. A., Mironov N. Yu., Lajovich L. Yu., Mironova N. A., Golitsyn S. P. Atrial Fibrillation and Chronic Heart Failure: Interrelationship and Approaches to Treatment. *Kardiologicheskiy vestnik = Russian Cardiology Bulletin*. 2021;16(2):5–14. (In Russ.) DOI: 10.17116/Cardiobulletin2021160215.
3. Shkolnikova M. A., Jdanov D. A., Ildarova R. A., Shcherbakova N. V., Polyakova E. B., Mikhaylov E. N., Shalnova S. A., Shkolnikov V. M. Atrial Fibrillation Among Russian Men and Women Aged 55 Years and Older: Prevalence, Mortality, and Associations with Biomarkers in a Population-Based Study. *Journal of Geriatric Cardiology: JGC*. 2020;17(2):74–84.
4. Valiev N. V., Azizova M. A., Otaeva Sh. A., Sadikov A. Z., Sagdullaev Sh. Sh. Standardization of the Drug Substance Axaritmin. *Farmatsevticheskiy vestnik Uzbekistana*. 2017;1:56–60. (In Russ.)
5. Kanorskiy S. G. Modern Drug Therapy for Atrial Fibrillation: The Choice of Strategy, Antiarrhythmic Drugs and Treatment Regimens. *Lechashchiy Vrach*. 2012;7:66–70. (In Russ.)
6. Vatutin N. T., Taradin G. G., Gasendich E. S., El'-Khatib M. A., Reutova N. O. On The Safety Issues of The Use of Antiarrhythmic Drugs. *Universitetskaya klinika*. 2018;3(28):68–77. (In Russ.)
7. Mironov N. Y., Yuricheva Y. A., Vlodzyanovskiy V. V., Sokolov S. F., Dzaurova K. M., Golitsyn S. P., Shubik Y. V., Berman M. V., Medvedev M. M., Rivin A. E., Parkhomchuk D. S., Barybin A. E., Balandin D. A., Batalov R. E., Terekhov D. S., Evstifeev I. V., Kildeev I. R., Pyataeva O. V., Zenin S. A. Safety and Effectiveness of Pharmacologic Conversion of Atrial Fibrillation and Flutter: Results of Multicenter Trial. Part I: Study Rationale, Design and Assessment of Effectiveness. *Ratsional'naya Farmakoterapiya v Kardiologii*. 2021;17(2):193–199. (In Russ.) DOI: 10.20996/1819-6446-2021-03-05.
8. Mrochek A. G., Gubar' E. N. Allapinine Effectiveness in Patients with Coronary Heart Disease and Cardiac Arrhythmias. *Rossiyskiy kardiologicheskiy zhurnal*. 2010;5(85):116–121. (In Russ.)
9. Potapova K. V., Nosov V. P., Koroleva L. Yu., Amineva N. V. Modern Aspects to the Management of Atrial Flutter. *Kardiologiya i Serdechno-Sosudistaya Khirurgiya*. 2020;13(2):127–133. DOI: 10.17116/kardio202013021127.

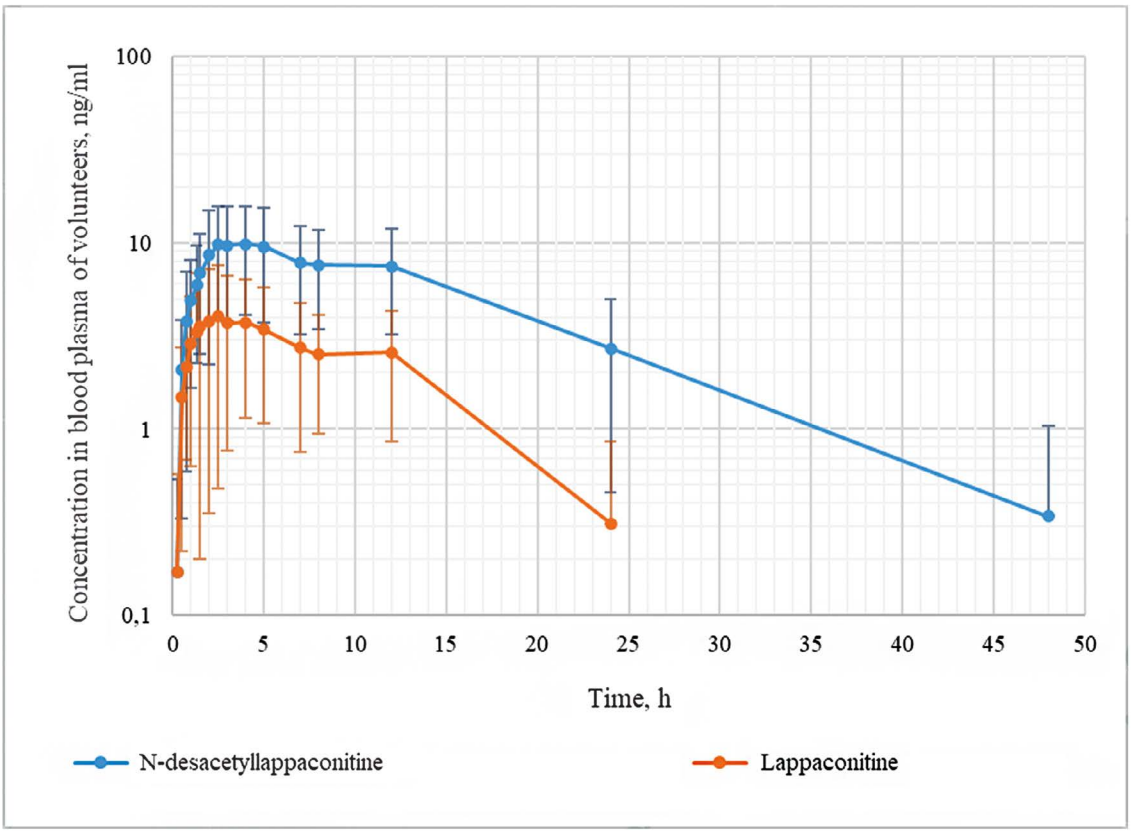

Figure 2. Average pharmacokinetic profiles (in semi-log scale with standard deviations) of lappaconitine and N-desacetyllappaconitine after single administration under fasting of Allaforte®, 25 mg

10. Shubik Yu. V., Medvedev M. M., Mikhaylov E. N., Gasymova N. Z., Gilyarov M. Yu. Management of Atrial Fibrillation in Russia: Real Clinical Practice and Current Clinical Guidelines. *Vestnik aritmologii = Journal of Arrhythmology*. 2021;28(2):55–63. (In Russ.) DOI: 10.35336/VA-2021-2-55-63.
11. Cheremnykh K. P., Savel'ev V. A., Shkurko O. P., Shults E. E. Synthesis of Hybrid Molecules Containing Pyrimidine and Diterpene Alkaloid Lappaconitine Fragments. *Chemistry of Heterocyclic Compounds*. 2018;54(12):1131–1138. DOI: 10.1007/s10593-019-02404-w.
12. Sokolov S. F., Belyaeva M. M., Bakalov S. A., Golitsyn S. P. Lappaconitine Hydrobromide and Its Sustained-Release Form in Case of Ventricular Premature Beats in Patients without Organic Heart Disease: Efficiency and Safety. *Kardiologiya: Novosti. Mneniya. Obuchenie = Cardiology: News, Opinions, Training*. 2018;2(17):29–37. (In Russ.)
13. Sanoev Z. I., Khamroev T. T., Djaxangirov F. N., Sadikov A. Z., Sagdullaev S. S. Antiarrhythmic Activity of N-Deacety lappaconitine when Administered Orally. *Annals of the Romanian Society for Cell Biology*. 2021;25(2):2339–2346.
14. Doshchitsin V. L., Syrov A. V., Pavlova T. V. The Use of Antiarrhythmic Drugs: Guidelines and Actual Clinical Practice. *Consilium Medicum*. 2019;21(10):86–94. (In Russ.)
15. Sturov N. V., Syrov A. V., Kobylyanu G. N., Prokofieva E. B., Berisha A., Freire Da Silva T., Kotidis I., Belikov I. I. Rational Pharmacotherapy of Some Cardiac Arrhythmias in Outpatients. *Trudnyj Pacient*. 2018;16(12):6–10. (In Russ.)
16. Kanorskiy S. G., Kovalenko Yu. S. State of the Art Pharmacological Therapy for Atrial Fibrillation. *Rossiyskiy kardiologicheskiy zhurnal = Russian Journal of Cardiology*. 2017;7(147):171–177. (In Russ.) DOI: 10.15829/1560-4071-2017-7-171-177.
17. Nie J., Wang F., Ji T., Zhao J., Zhao F. Assessment of *in vitro* Cardiotoxicity of Extract Fractions and Diterpene Alkaloids from *Aconitum Leucostomum Worosch*: A Short Communication. *Journal of pharmaceutical and biomedical analysis*. 2017;137:84–89. DOI: 10.1016/j.jpba.2017.01.003.
18. Zhigunova S. N., Ibatullina Z. A., Mikhaylenko O. I., Fedorov N. I. Stock of *Aconitum Septentrionale* (*Ranunculaceae*) Underground Parts in the Pine-Birch Forests and Fellings of the Southern Urals. *Rastitel'nye resursy*. 2017;53(3):357–371. (In Russ.)
19. Samorodov V. V. *Sredstvo dlya lecheniya aritmii serdtsa* [Drug Preparation for the Treating Cardiac Arrhythmia]. Patent RUS № 2513580 C1. 20.04.2014. Available at: https://www.elibrary.ru/download/elibrary_37445337_55047738.pdf Accessed: 20.01.2022. (In Russ.)
20. Archakova O. A., Komarov T. N., Rogov A. V., Shchelgacheva D. S., Aleshina A. V., Bagaeva N. S., Shohin I. E. Determination of Lappaconitin, Diterpene Alkaloide Obtained from Plants *Aconitum leucostomum*, and its Active Metabolite N-desacetyllappaconitin in Human Plasma and Blood. *Razrabotka i registratsiya lekarstvennykh sredstv = Drug development & registration*. 2021;10(3):105–113. (In Russ.) DOI: 10.33380/2305-2066-2021-10-3-105-113.

21. Sokolov S. F. Results of Clinical Studies of Allapinin and Up-To-Date Approaches to Treatment of Patients with Cardiac Arrhythmias. *Vestnik aritmologii*. 2011;64:60–70. (In Russ.)
22. Grover A., Benet L. Z. Intermittent Drug Dosing Intervals Guided by the Operational Multiple Dosing Half Lives for Predictable Plasma Accumulation and Fluctuation. *Journal of Pharmacokinetics and Pharmacodynamics*. 2011;38(3):369–383. DOI: 10.1007/s10928-011-9198-0.
23. Sokolov A. V., Tishchenkova I. F., Belousov Yu. B. Optimization of Pharmacotherapy Based on Therapeutic Drug Monitoring. *Lechebnoe Delo*. 2004;3:34–39. (In Russ.)
24. Doki K., Shirayama Y., Sekiguchi Y., Aonuma K., Kohda Y., Homma M. Optimal Sampling Time and Clinical Implication of the SCN5A Promoter Haplotype in Propafenone Therapeutic Drug Monitoring. *European Journal of Clinical Pharmacology*. 2018;74(10):1273–1279. DOI: 10.1007/s00228-018-2541-2.
25. Gui Y., Lu Y., Li S., Zhang M., Duan X., Liu C. C., Jia J., Liu G. Direct Analysis in Real Time-mass Spectrometry for Rapid Quantification of Five Anti-arrhythmic Drugs in Human Serum: Application to Therapeutic Drug Monitoring. *Scientific Reports*. 2020;10(1)1–10. DOI: 10.1038/s41598-020-72490-w.
26. Rahman M., Couchman L., Povstyan V., Bainbridge V., Kipper K., El-Nahhas T., Johnston A., Holt D. Rapid Quantitation of Flecainide in Human Plasma for Therapeutic Drug Monitoring Using Liquid Chromatography and Time-of-Flight Mass Spectrometry. *Therapeutic Drug Monitoring*. 2019;41(3):391–395. DOI: 10.1097/FTD.0000000000000586.