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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

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GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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Fax: +995(32) 253 70 58, e-mail: ninomikaber@geomednews.com; nikopir@geomednews.com

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CONTACT ADDRESS IN TBILISI

GMN Editorial Board
7 Asatiani Street, 4th Floor
Tbilisi, Georgia 0177

Phone: 995 (32) 254-24-91
995 (32) 253-70-58
Fax: 995 (32) 253-70-58

CONTACT ADDRESS IN NEW YORK

NINITEX INTERNATIONAL, INC.
3 PINE DRIVE SOUTH
ROSLYN, NY 11576 U.S.A.

Phone: +1 (917) 327-7732

WEBSITE
www.geomednews.com

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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ავტორთა საყურადღებოდ!

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1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

რონარულპაციენტებისთვის, მხოლოდ Apple, Mio და Garmin შეიძლება იყოს რეკომენდებული. ამასთანავე, შემდგომი გამოკვლევები აუცილებელია კლინიკურ და არაკლინიკურ გარემოში, სადაც უნდა გათვალისწინებულ იქნას სხვადასხვა სახის სპორტული აქტივობები.

COMBINED PHARMACOLOGICAL THERAPY INCLUDING SEVERAL ANTIARRHYTHMIC AGENTS FOR TREATMENT OF DIFFERENT DISORDERS OF CARDIAC RHYTHM

Kapustnick Yu., Lutsenko R., Sydorenko A.

Poltava State Medical University, Department of Experimental and Clinical Pharmacology, Clinical Immunology and Allergology, Ukraine

In widespread clinical practice, there is often a need for treatment of cardiac arrhythmias with simultaneous administration of antiarrhythmic agents of I or III classes in accordance with Vaughan Williams classification together with antiarrhythmic preparations of II or IV classes (β-blocker adrenergic drugs and calcium channel blocker agents). In severe and stable cardiac arrhythmias combined therapy on the bases of two antiarrhythmic agents, including preparations of I and III classes should be used [12,13,15].

However, at the same time it is necessary to understand well the goals, possible effects and dangers of such combined treatment. The main principle of any combined therapy lines in simultaneous action on different pathological mechanisms, which are the reason of development of cardiac arrhythmia. It allowes to reduce doses of antiarrhythmic agents [2,8].

Under antianginal and hypotensive therapy the combined tratment is often used even during beginning of the illness. However, antiarrhythmic therapy is performed according to other principle. Because only one antiarrhythmic preparation must be used for treatment of arrhythmias in most cases because all antiarrhythmic agents have fairly similar side effects that leads to exacerbation of their side effects that can be under combined therapy [2].

The requirement of combined therapy including the several antiarrhythmic agents for treatment of different disorders of cardiac rhythm arises in the following situations:

1. Monotherapy with administration of only one antiarrhythmic agent is effective. However, a therapeutic dose of the drug causes side effects that requires its correcting. In this case, the complete cancellation of the drug is possible with its replacement by other antiarrhythmic agent, which is effective and well-tolerated, Nevertheless, the possibility of such choice might not be available, because other drugs are not tolerated or ineffective [4,5].

For example, a patient with paroxysmal atrial fibrillation uses amiodarone in daily dose 400 mg with the most complete antiarrhythmic effect (compared to other agents). However, under administration of amiodarone in daily dose 400-600 mg and more in the sunny period of the year such side action as photosensitization can be development. This undesirable effect can be eliminated by reducing the daily dose of amiodarone to 200 mg. In this case amiodarone in the dose 200 mg during the morning must be administered for strengthening of antiarrhythmic effect together with one agent from antiarrhythmic preparation of IC subclass, which must be administered in half daily dose (allapinin 25-50 mg/day or ethacizin 75 mg/day).

2. The effect of antiarrhythmic agent is not complete, but it is impossible to in rease its dose to maximal, because can be development undesirable effects. Sometimes these side effects occur after administration of antiarrhythmic drug in moderate dose. For example, amiodarone was given in the daily dose 300 mg. This dose was sufficient to eliminate paroxysms of atrial fibrillation. In this case other antiarrhythmic agents are not effective. However, after administration of amiodarone in daily dose 300 mg night brady-depended supraventricular extrasystolic arrhythmia occurred. This disorder of cardiac rhythm is poorly tolerated by patient. Besides, supraventricular extrasystolic arrhythmia can be transform in atrial fibrillation. [6,8]. That is why for preventive maintenance of such undesirable effects of amiodarone should be administered the decreased dose of this preparation and additional administration of allapinin in the evening orally in single dose 12,5-25 mg (1/2-1 tablet).

3. Antiarrhythmic monotherapy is effective. However, after administration of one antiarrhythmic agent undesirable side effects are developed. That is why the cancellation of the first antiarrhythmic agent is required. For instance, antiarrhythmic agent of IA subclass quinidine was given orally in dose 200 mg trice a day. But marked sinus tachycardia due to its vagolytic influence developed due to administration of this preparation. Quinidine decreases tonicity of pneumogastric nerve due to cholinolytic action on pacemaker cells in atrioventricular node. For suppression of sinus tachycardia, it is required to cancel quinidine and administration of β-blocker agent or calcium channel blocker drug for example verapamil.

4. All possible antiarrhythmic agents as monotherapy are not effective. In this case the combination of the two ineffective drugs may be effective.

5. A patient has several types of cardiac rhythm disorders, each of which is sensitive to one antiarrhythmic agent only. For example, two variants of paroxysmal tachycardia occurred periodically: 1) verapamil-sensitive reciprocal sinus tachycardia; 2) paroxysmal atrial fibrillation. Bolus administration of 4 ml 0,25% solution (10 mg) of verapamil intravenously is required for suppression of first disorder of cardiac rhythm. Administra-

tion of 4-6 ml of 0,5% solution (20-30 mg) of allapinin administration of 4-6 ml of 0,5% solution (20-30 mg) of allapinin intravenously is used to interrupt of paroxysm of atrial fibrillation.

After renewal of the normal sinus rhythm verapamil and allapinin are used orally. Verapamil was administered in dose 40 mg twice a day (at 8 o'clock during in morning and at 15 o'clock in the afternoon). Allapinin was administered in dose 25 mg before sleeping at 22 o'clock. When combine antiarrhythmic therapy is used of the basic principles of administration of this therapy should be provided. They are as follows:

1. It is impossible to administer antiarrhythmic drugs of the same class at the same time.

2. The doses of the drugs, which are used in combination, are below the average therapeutic doses (about half of the usual daily dose).

3. It is impossible to administer combined antiarrhythmic therapy including drugs with unidirectional action on heart rate, atrio-ventricular (AV) and intraventricular conductivity, duration of QT interval, myocardial contractility, as well as to administer antiarrhythmic drugs with a relatively high frequency of proarrhythmic action.

4. In the case of the administration of several antiarrhythmic agents, it is particularly important to understand those electrophysiological mechanisms that are intended to be affected using two antiarrhythmic preparations.

5. Antiarrhythmic preparations should be administered sequentially: the second drug is used only after the evaluation of safety and tolerability of the first antiarrhythmic preparation.

In rare cases administration of two antiarrhythmic agents of the I class is required for treatment of hazardous and refractor arrhythmias. However, the use of these preparations must be in different time and with caution [9,10].

Ideally the choice of antiarrhythmic agents is realized with taking in account electrophysiological properties of development of cardiac arrhythmias. The main electrophysiological mechanisms of arrhythmias development according to the concept of "Sicilian Gambit" [9,14] include five positions:

1. Pathological or accelerated normal automatism. It occurs due to the increase of nerve stimulation, hypokalemia, and decrease of resting potential in cells of the His-Purkinje system, myocardium of the atria and ventricles in combination with suppression of the function of the sinus node or suppression sino-atrial conduction. According to these mechanisms different paroxysmal tachycardias (supraventricular and ventricular), some types of extrasystolic arrhythmias (supraventricular and ventricular) develop [12]. It is necessary to extend phase 4 of the action potential, for suppression of pathological automatism, i.e. to cause block of slow calcium current into the cell (it can happen after the use of Ca antagonists or β-blocker agents), after hyperpolarization of the membrane due to activation of potassium current from the cell in phase 4 (it is typical for digoxin and adenosine). The increase of action potention duration, which is developed after block Na current into the cell during 0 phase (fast depolarization) is typical for antiarrhythmic agents of I class. Amiodarone and other preparations of III class cause retardation of K current from the cell in extra-cellular space during I and II phases of repolarization.

2. Trigger activity (early and late postdepolarization). It occurs as a result of elongation of action potention, repolarization slowing (especially in Purkinje fibers), or overload with Ca^{2+} ions due to sympatic stimulation. According to these mechanisms ventricular tachycardia of the type "pirouette" (torsade de pointes) and some types of extrasystoles (ventricular and supraventricular) develop. It is necessary to reduce the duration of action potention due to acceleration of repolarization for suppression of early postdepolarization. This process develops after activation of potassium current from the cell in extra-cellular space during 1 and 2 phases of action potention due to the action of β-blocker drugs and cholinolytic agents. The reducing of action potention is developed as a result of suppression of spontaneous depolarization in 4th phase of action potention, which is realized after block of calcium and sodium current [13]. These processes occur after using of calcium channel blocker drugs, magnesium preparations and antagonists of sodium current in cell (antiarrhythmic agents of I class according to Vaughan Williams classification). The decrease of action potention can be as a result suppressing of sympathetic stimulation due to administration of β-blocker agents.

It should be taken in account that the reduction of the intracellular Ca^{++} concentration is necessary for suppression of late postdepolarization. This process is realized due to block of calcium current into the cell during the 4th phase of action potention and the sodium current into the cell during the 0 phase (fast depolarization). Administration of Ca antagonists, β-blocker agent, I class antiarrhythmic drugs enhances the development of these processes.

3. Re-entry mechanism (micro-re-entry and macro-re-entry) occur due to differences in conductivity and refractivity of different links in the chain of development of pathogenesis of cardiac rhythm disorders. Reciprocal arrhythmias are most typical for paroxysmal supraventricular and ventricular tachyarrhythmias, atrial fibrillation, atrial flutter, some kinds of ventricular and supraventricular extrasystoles (premature beats). In order to suppress the re-entry mechanism with a large excitation period, it is necessary to primarily cause slowing of the conductivity in the structures with Na^{+} or Ca^{++} channels (to cause block of 0 phase of action potention). These effects are developed after the use antiarrhythmic preparations of I class or antagonists of calcium or β-blocker agents, respectively. For suppression of re-entry mechanism with or without a short excitation period it is required to increase refractory period due to blocking of sodium current into the cell and slowing down the repolarization process due to the blockage of potassium current from the cell in extracellular space. This blockage of sodium current occurs after administration of antiarrhythmic agents of I class. Preparations of III class (amiodarone and sotalol) cause blockage of potassium current fromc extra-cellular space in cell during repolarization phase I and phase II.

The majority of antiarrhythmic agents induce suppression of automatism of cells pacemakers of sinus and atrioventricular nodes. Besides, they cause the suppression or liquidation of re-entry mechanism and reciprocal activation due to changing of velocity of conductivity or as a result duration of refractory period increase. Due to these electrophysiological effects the majority of antiarrhythmic preparations have wide range of action.

Procainamide (novocainamide), quanidine, etmozine (moracisine), ethacizine, gilurytmal (ajmalin), disopyramide (rytmilen), allapinin, β-blocker agents and potassium preparations cause delay of velocity of conductivity in heart conductive system, whereas antiarrhythmic preparations of IB subclass: lidocaine (xylocaine, xycaine), trimecaine, mexiletine (mexitil, tametil), tocainide (tonocard), phenytoine (diphenin) cause acceleration of cardiac conductivity. In case of the use of antiarrhythmic agents in small daily doses they cannot change the velocity of heart conductivity. Antiarrhythmic agents of IA subclass (novocainamide, disopyramide, quanidine), IC subclass

– propafenone (ritmonorm, propanorm), allapinin, encainide, IBC subclass: etmozine, other antiarrhythmic preparations of I class e.g. ethacizine and gilurytmal and antiarrhythmic agents of III class: amiodarone (cordarone), sotalol (sotalex), bretylium tosilate (ornidum) directly and β-blocker agents non-directly cause elongation of refractory period, whereas antiarrhythmic preparations of IB subclass (lidocaine, trimecaine, mexiletine, tocainide, phenytoine) and potassium preparations cause directly shortening of this period.

Antiarrhythmic agents of first class and amiodarone are as rule effective preparations for treatment of major types of supraventricular and ventricular arrhythmias. β-blocker agents have less efficacy for treatment of paroxysmal supraventricular arrhythmias in comparison with antiarrhythmic preparations of I class and they are contraindicated for treatment of tachyarrhythmias in patients with pre-excitation syndromes (WPW syndrome – Wolf-Parkinson-White syndrome and CLC syndrome – Clerc-Levy-Critesco syndrome). β-blocker drugs have sufficient effectiveness for treatment of ventricular extrasystolic arrhythmia. Lidocaine, trimecaine, mexiletine, tocainide and phenytoine have basically effectiveness for treatment of ventricular disorders of cardiac rhythm and for therapy of toxic arrhythmias, which are caused by cardiac glycosides. Indications for treatment of antiarrhythmic agents of IV class – calcium channel blockers (verapamil, diltiazem) are supraventricular disorders of cardiac rhythm [4,6]. On the grounds of the abovementioned antiarrhythmic preparations must be divided into two such groups:

1. Antiarrhythmic agents, which cause decrease of automatism (phase 4 – spontaneous diastolic depolarization) and induce the delay of conductivity – antiarrhythmic agents of IA, IC, IBC subclasses and other antiarrhythmic preparations of I class – ethacizine and gilurytmal, preparations of II subclass (β-blocker agents), antiarrhythmic agents of III subclass (amiodarone, sotalol, bretylium tosilate), medicinal agents, containing potassium (kalium chloride, panangin, asparcam).

2. Antiarrhythmic agents, which cause decrease of automatism (phase 4 – spontaneous diastolic depolarization) and induce acceleration of conductivity or in minimal doses they do not change conductivity (antiarrhythmic agents of IB subclass: lidocaine, trimecaine, mexiletine, tocainide and phenytoine).

For because of preparations from first and second groups have such effect as decrease of automatism (phase 4 – spontaneous diastolic depolarization) all these agents are effective for therapy of ectopic tachyarrhythmias, which occur as a result of mechanism of the increased automatism [14].

Preparations of second group are useful also for treatment of cardiac arrhythmias, which are caused by mechanism of secondary entering wave of excitation (re-entry). Arrhythmias, which occur according to secondary entering of impulses, are happen as a result of functional blockade in one direction together with delay of conductivity in some microcells and macrocells structures of conductive system. This pathological changes in cardiac conductive system are reason of occurrence movement of impulses across cycle re-entry.

The velocity of cardiac conductivity and duration of refractory period are two main factors, which induce occurrence and supporting of ectopic disorders of cardiac rhythm, which were caused by conductivity of impulses across re-entry loop. Having such influence as elongation refractory period and the delay of conductivity, antiarrhythmic agents of first class in accordance with Vaughan Williams classification, β-blocker agents, antiarrhythmic preparations of III class (amiodarone, sotalol, bretylium tosilate), potassium preparations cause local blockade. As a result of action of these agents block in one direction transforms in block in two directions, whereas antiarrhythmic agents of IB subclass (lidocaine, trimecaine, mexiletine, tocainide and phenytoine) cause liquidation of block in one direction due to such effects as shortening of refractory period and acceleration of conductivity. Thus, after the use of preparations of two groups liquidation of cardiac arrhythmias, which occur according to mechanism secondary entering of excitation (re-entry) are interrupted.

The treatment of refractor ectopic tachyarrhythmias, which are caused by mechanism of the increased automatism or re-entry mechanism using combined antiarrhythmic therapy (administration of two or more antiarrhythmic agents) is in many cases more effective as compared to monotherapy (using only one antiarrhythmic agent). Chances for suppression of cardiac arrhythmia increase after administration of combined antiarrhythmic therapy [1,3].

In tachycardias, which are caused by mechanism re-entry, in case of absence of possibility for transformation of blockade in one direction in blockade in two directions using the antiarrhythmic preparations of first group can be their administration together with antiarrhythmic preparations of second group for strengthening of suppression blockade in one direction. Due to the administration of two antiarrhythmic agents with same electrophysiological properties can be increased antiarrhythmic effect. That is why combined therapy is more effective in comparison with monotherapy for suppression of cardiac arrhythmias.

Combined therapy including two antiarrhythmic drugs (preparation of I class and agent of II class) has greater opportunity for termination of arrhythmias, which are caused by re-entry mechanism. Antiarrhythmic preparations of these two groups have such effect as suppression of automatism. The administration of preparations of I class and II class together can cause stronger suppression of automatism even after the use of small doses of these two antiarrhythmic agents. In this case the positive effect is decrease the development of toxic complications risk.

Ideally every antiarrhythmic agent must cause suppression of disorder of cardiac rhythm. Besides, it must be without serious undesirable side effects. Therapeutic blood concentration of these preparations occurs after short period. But now it is very difficult to find such antiarrhythmic agent. Many antiarrhythmic preparations have slow absorption in gastrointestinal tract. Quick distraction of other antiarrhythmic drugs is the reason of their limitation for termination of paroxysmal tachyarrhythmias.

Undesirable side effects of antiarrhythmic agents can be associated with their big doses. It should be taken in account that in case of combined therapy the possibility of development of side effects of antiarrhythmic preparations decreases. The prevalence of the administration of combined therapy using several antiarrhythmic agents is the smaller possibility of side effect development in comparison with monotherapy of cardiac rhythm disorders, especially when using one antiarrhythmic preparation in big dose.

Before choosing antiarrhythmic preparations for combined therapy careful analysis of their electrophysiological properties must be done. Due to this it becomes possible to select the optimal combination of antiarrhythmic agents. In clinical practice the following combinations of antiarrhythmic agents can be used:

1. Disopyramide (rytmilen) and quinidine are preparation of choice among preparations of IA subclass for combined therapy including these agents and β-blocker adrenergic agents. Pro-

cainamide for prophylactic treatment of cardiac arrhythmias has small effectiveness. Disopyramide and quanidine cause delay of conductivity in cardiomyocites of atria, ventricles and in His-Purkinje system. These antiarrhythmic preparations slightly increase the duration of action potention due to suppression of such its phases as 0, 3-ed and 4-th phases. Including β-blocker drugs into complex therapy together with disopyramide or quanidine is justified due to the fact that β-blocker agents cannot enhance action of disopyramide or quinidine. This action is conditioned by synergic action of β-blocker agents with antiarrhythmic preparations in respect to 4-th phase of action potention [2, 7]. This enhanced suppression of disorders of cardiac rhythm may be beneficial for treatment of arrhythmias which are conditioned by trigger mechanism or they appear as a result of the increased automatism. Combined therapy including disopyramide or quanidine together with β-blocker agents can be useful for treatment of tachyarrhythmias, which are conditioned by re-entry mechanism in sinus and atrio-ventricular nodes.

Quinidine is administered first of all for preventive maintenance of paroxysmal atrial fibrillation. The main purpose of adding for quinidine β-blocker agents is not only for strengthening of antiarrhythmic effect, but first of all for avoidances of sinus tachycardia. However, supraventricular premature beats can be terminated due to this combined therapy. But monotherapy using quinidine only is not efficient. In case of administration of this combined therapy the dose of quinidine is as ordinary one: 400-600 mg orally (like it was during monotherapy). wideness of QRS-complexes and elongation of QT-intervals does not occur after administration of quinidine in these doses. The dose of β-blocker agent is selected after taking in account the results of long-lasting monitoring of frequency of cardiac beats and duration of PQ intervals. As a result this therapy decrease of myocardium contractility can be clinically significant in patients with initial dysfunction of left ventricle.

Administration of β-blocker agents for example atenolol in dose 25-50 mg twice a day or propranolol in daily dose 10-40 mg 4 times a day together with disopyramide is possible to strengthen antiarrhythmic effect (especially in supraventricular disorders of cardiac rhythm) and to decrease proarrhythmic action (mostly in ventricular arrhythmias). The monitoring of number of beats per minutes (bpm), the duration of PQ intervals, and index of cardiac output – Δ S% must be realized during combined antiarrhythmic treatment using two preparations. Normal value of Δ S% must not be less than 55%, in cardiac insufficiency of I degree it must be from 45% to 55%, in cardiac failure II degree – from 35% to 45%, and in cardiac failure III degree – less than 35%. The dose of one from two antiarrhythmic preparations decreases in case of appearance of bradycardia, atrioventricular blockade and increase of congestive cardiac failure.

Antiarrhythmic agents of IB subclass cause delay of 0 phase of action potention. The administration of these preparations induces acceleration of process of repolarization, lead to the decrease of duration of action potention and QT interval. Such antiarrhythmic agents as β-adrenergic blocker preparations can increase action of antiarrhythmic agents of IB subclass due to additional delay of 4th phase of action potention in case of treatment of disorders of cardiac rhythm with trigger mechanism. The second reason of using of β-adrenergic blocker agents together with antiarrhythmic preparations of IB subclass as follows phenytoin (diphenylhydantoin, diphenin), mexiletin (mexitil), tocainide is the decrease of the risk of occurrence of sudden death in patient with potential lethal ventricular cardiac arrhythmias [11, 14]. It should be taken in account such property of β-adrenergic blocker agents as absence of effectiveness for therapy of arrhythmias, which are caused by non-trigger arrhythmias (especially for treatment of ventricular premature beats and ventricular paroxysmal tachycardia). For treatment of supraventricular arrhythmias preparations of IB subclass are not useful.

The results of therapy using diphenin and mexiletin are the insufficient effectiveness of the treatment of frequent and stable ventricular extrasystolic arrhythmia and paroxysmal ventricular tachycardia. Now the preparations of IB subclass are administered for preventive maintenance of hazardous potentially lethal ventricular arrhythmias in rare cases [11,12]. It is the best way to prevent these arrhythmias by using mexiletin.

Combined therapy including agents of IB subclass and β-adrenergic blocker agents has good tolerance and minimum side effects. The administration of these preparations does not have influence on widening of QRS complex. This combined therapy causes decrease of QT interval. In regard to frequency of cardiac beats and atrio-ventricular conductivity (duration of PQ interval) only β- adrenergic blocker agents have influence. That is why the decrease of dose preparations of IB subclass (diphenin and mexiletin) is not required. In case of administration of diphenin for suppression of arrhythmias, which are caused intoxication by cardiac glycosides, administration of β-blocker agents is contraindicated, because after administration of this combined therapy stable bradycardia can develop.

Antiarrhythmic preparations of IC subclass have effect mostly due to action on 0 phase action potention. It leads to suppression of conductivity across myocardium and Purkinje fibers. β-blocker agents can cause additional antiarrhythmic effect in trigger arrhythmias, which are conditioned by the increased automatism, for instance in extrasystolic arrhythmia and in reciprocal sinus and atrio-ventricular nodular paroxysmal tachycardia. Outof preparations of IC subclass allapinin is used in combination with β-blocker agents most frequently. This is conditioned by adrenergic action of allapinin. It causes increasing of myocardium contractility.

However, β-blocker agents cause not only suppression of sinus tachycardia, but they can cause decrease of out-cardiac side effects of allapinin. Due to the action of both preparations (allapinin and β-blocker agent) an elongation of duration PQ interval can appear. In this case the dose of allapinin must be decreased (to 25-50 mg (1-2 tab) per day). The reduction of the dose of β-blocker agents is not always possible, due to the fact that this can lead to a renewal of tachycardia.

One should remember, that the main role is played by allapinin in case of administration of this combined therapy, especially for treatment of atrial fibrillation and ventricular reciprocal disorders of cardiac rhythm. That is why the decreased dose of allapinin can lead to partial loss of its antiarrhythmic action. In this case one can try to select milder β-blocker agent (metoprolol, bisoprolol, betaxolol), in this case it is not required to decrease of allapinin dose.

The additional administration of β-blocker agents for treatment of patient, which were administered other preparation of IC subclass as fellows propafenone (ritmonorm), encainide, etmozine, ethacizine has the purpose to decrease arrhythmogenic effect of these agents [4]. The administration of β-blocker drugs is required also to decrease the risk of sudden death in patients with ventricular disorders of cardiac rhythm. The application of β-blocker agent together with preparation of IC subclass is required to strengthen antiarrhythmic action especially tachy-depended forms of cardiac arrhythmias [4,6,15]. Out of above-

mentioned antiarrhythmic agents only etmozine has in minimal influence on transverse conductivity. The combination of other preparations of IC subclass: propafenone (ritmonorm), encainide, ethacizine together with β-blocker agents can only be in case of monitoring of bpm and atrio-ventricular conductivity. It is required for prevention of stable bradycardia. In development of this stable bradycardia the decrease dose of β-blocker agent is required. The merit of β-blocker agents is the absence of influence on width of QRS complexes and duration of QT intervals.

2. Combination of antiarrhythmic agents of I class with calcium channel blocker agents (verapamil and dilthiazem) is used in more rare cases in comparison with combined therapy, which consist from preparations of I class together with β-blocker agents. It is caused by unavailability of anti-fibrillate activity in calcium channel blocker agents.

It should be taken in account that antiarrhythmic action of calcium antagonists can be useful only for suppression of trigger arrhythmias, which are connected with increased automatism and reciprocal tachycardias, having in their structures Ca-depended 0 phase of action potention. These structures are located in sinus and atrioventricular node.

In fact, there are two indications for administration of combined therapy, which includes antiarrhythmic agents of I class (mostly preparations of subclasses A and C) and calcium channel blocker drug (verapamil and dilthiazem): 1) pharmacological correction of sinus tachycardia, which is developed after using quinidine, disopyramide, allapinin if administration of β-blocker agents is contraindicated, because after the use of these preparations significant bronchial constriction can develop especially in patients with bronchial asthma or chronic obstructive pulmonary disease; 2) for treatment of two cardiac rhythm disorders: first are supraventricular, in more rare cases ventricular arrhythmias (paroxysmal tachycardia, which has high sensitivity for verapamil/dilthiazem and second arrhythmias, which are not treated or can be treated only in rare cases using verapamil as follows reciprocal ventricular arrhythmias, paroxysmal atrial fibrillation and atrial flutter.

The optimal combination is the administration of calcium antagonists and such preparation of I class as disopyramide, quinidine, allapinin. In such combination there is the smallest possibility of atrioventricular blockade development due to action of both group of preparations, which cause elongation of PQ interval duration. These preparations cause decrease of contractility of left ventricle especially in condition of its initial dysfunction. The administration of β-blocker preparations together with verapamil or dilthiazem is impossible. Combined therapy including propafenone and verapamil is not rational. It is conditioned by similar chemical structure of propafenone and non-selective β-blocker agent propranolol. Due to this similarity propafenone has properties of β-blocker agent. In addition, propafenone causes potentiating of the effect of verapamil in regard to such enzymes as liver cytochroms.

3. The combined administration of antiarrhythmic agents of III class (amiodarone, d,l-sotalol) together with β-blocker drugs cause suppression of such phases of action potention as first phase of repolarization (early repolarization), second phase of repolarization (plateau phase), third phase of repolarization (late repolarization). It leads to expressive elongation of action potention. The effect of agents of III class is increases due to this action not only in regard to atrioventricular nodal tachycardia and sinus reciprocal tachycardia, but in respect to re-entry-tachycardia of other origin, including atrial fibrillation and ventricular tachycardia.

No less important result of interaction between preparations of II and III classes is the decrease of the development risk of arrhythmias with trigger mechanism (including bidirectional spindle-shaped ventricular (torsade de pointes) tachycardia). This risk is increased in case of therapy with help of one preparations, which causes blockade of potassium channels during second and third phases of action potention due to elongation of process of repolarization. The administration of β-blocker drugs can cause partial decrease of this elongation due to suppression of Na^{+} and Ca^{++} current in cell from extra-cellular space. System cyclic adenosine monophosphate has prominent position for realization of this effect.

It has been believed for the long time, that combination of antiarrhythmic agents of III class with β-blocker agents is not expedient due to threat of bradycardia development and atrioventricular blockades. Indeed, this threat is present, because preparations of both groups cause suppression of transverse conductivity and to some extent the decrease in contractility of left ventricle in case of its initial dysfunction. These effects have bigger expressiveness after administration of antiarrhythmic preparations of III class (amiodarone and sotalol). [13,15]. These preparations have properties of β-blocker agents. However, in real clinical conditions the increase of congestive cardiac insufficiency can happen during treatment, including preparation of III class and β-blocker agent in rare cases only. It should be taken in account that amiodarone blocks calcium channels in lesser degree.

At the same time, it was proved in clinical trials, that using of β-blocker agents in combine with antiarrhythmic agents of III class causes significant decrease of occurrence frequency of proarrhythmic complications and the risk of sudden death in patient with hazardous potential lethal cardiac arrhythmias. The combined administration of amiodarone or sotalol together with β-blocker agents has no influence on duration of QT intervals and the width of QRS complexes [12]. That is why the monitoring of bpm and duration of QT intervals and the width of QRS complexes is required in order to prevent fatal disorders of cardiac rhythm. The higher initial frequency of cardiac beats is, the better is efficiency of combined therapy, including preparation of III class (especially amiodarone) + β-blocker agent. That is why in patients with malignant ventricular extrasystolic arrhythmia with premature beats of high gradations according to Lown-Wolf classification and fatal ventricular tachycardia additional administration of β-blocker agents together with the small doses of amiodarone is required to increase anti-fibrillate activity. The combined therapy amiodarone together with β-blocker agent should be administered for treatment of these hazardous arrhythmias. Amiodarone is administered in supporting daily dose 200-400 mg (1-2 tablets) and β-blocker agent to maximum tolerated dose, which is estimated accordant to the frequency of cardiac beats. It must be 55-70 bpm in rest condition. Therapy using β-blocker preparations is canceled in case of frequency of cardiac beats, which is equal to 50 bpm or less.

D, l-Sotalol has properties of antiarrhythmic agents of II and III classes. Its β-blocker effect is three times less than in propranolol. This effect occurs even after administration of sotalol in small doses. That is why the use of this preparation in combine with β-blocker agent is impossible. Amiodarone can be administered together with β-blocker agents in condition of bpm monitoring in constant form of atrial fibrillation and in sinus tachycardia, which is concomitant with frequent and stable extrasystolic arrhythmia, having prognostic significance. Besides, combined therapy including amiodarone and β-blocker agent is

used for treatment of cardiac tachyarrhythmias in case of absence of effect after the use of the therapy using only one antiarrhythmic agent.

4. The expediency of administration of antiarrhythmic agents of III class together with calcium antagonists is highly doubtful. After theoretical analysis it the conclusion was made about similarly action of β-blocker agents and calcium antagonists. Preparations of both groups have positive effect on treatment of arrhythmias with trigger genesis, which appeared sometimes after using of antiarrhythmic preparations of III class e.g. amiodarone and sotalol. This proarrhythmic effect after their administration is conditioned by retardation of current of potassium ions from cell in extra-cellular space during 1-st and 2-d phases of repolarization. There is experimental data for the ability of verapamil to raise threshold of ventricular fibrillation. However, according to clinical investigations there are no results, which would prove the decrease of the risk of development of proarrhythmias after administration of combined therapy, including preparations of III and IV classes.

This therapy is required only in two situations: 1) the presence of cardiac arrhythmia, which is very sensitive to verapamil or dilthiazem and in absence of effect after treatment using amiodarone; 2) the administration of calcium channel blocker agents does not have sufficient effect for preventive maintenance of ventricular arrhythmias and some atrial arrhythmias (atrial fibrillation and atrial flutter) [3,4].

In combined therapy the daily dose of amiodarone must not be more than 200-300 mg and the daily dose of verapamil not more than 120-240 mg. The monitoring of frequency of cardiac beats and duration of QT interval must be required during this combined therapy. It should be taken in account that verapamil and dilthiazem have no influence on width of QRS complexes and duration of QT intervals.

5. The combined therapy including antiarrhythmic agents of I and III classes has the strongest effect. This can be explained by the following: the delay all phases of action potention occurs, that result into significant enlargement of its duration and refractory period of myocardium. It is clear that such a powerful effect is required first of all for treatment of re-entry arrhythmias with or without short excitability period. In these arrhythmias possibility for suppression of tachycardia is absent due to the action in respect to impulse conductivity across myocardium. However, prominent increase of duration of action potention after combined using of antiarrhythmic preparations of I and III classes leads to the increased risk of life-threatening trigger arrhythmias development such as ventricular paroxysmal tachycardia without pulse and bidirectional spindle-shaped ventricular tachycardia (torsade de pointes). That is why constant monitoring of cardiac beat frequency and alterations of ECG must be obvious. The choice of this therapy is only realized in hospital conditions.

Especially high risk of development of cardiac blockade appears in case of combined administration of antiarrhythmic agents of IA subclass preparations (in particular quinidine) and III class. It is caused by the fact that subclass IA induces strengthening of blockade of potassium channels during third phase of action potention. Each of these preparations is always administered in half dose (or less) in comparison with an ordinary daily dose. No less important result of this interaction is: 1) the decrease of cardiac beats frequency. Especially it refers to the patients with sick sinus syndrome and atrioventricular blockade. In order to prevent disorder of cardiac conductivity it is better to use of amiodarone together with such preparations of IA subclass as allapinin or disopyramide; 2) the elongation of PQ interval. To the lesser extent it is characteristic for combination of preparations of III class in ordinal doses and propafenone. In case of the use of this combination of antiarrhythmic agents it may occur the widening of QRS complexes due to the delay of intraventricular conductivity. It occurs relatively rare in allapinin or propafenone therapy together with small doses of amiodarone or sotalol; 3) the elongation of QT-interval is associated with proarrhytmic effect of antiarrtythmic agents. In this respect, the most dangerous combined treatment includes one of the I class preparations (encainide, flecainide, etmozine, ethacizine) together with agents of III class (amiodarone or sotalol).

At administration of β-blocker agents together with sotalol may lead to the development of additional β-blocker action, because sotalol has properties of antiarrhythmic agents of second and third classes (even in case of using of small doses of sotalol).

It should be taken into account that amiodarone has property of β-blocker agent. Besides, it is to some extent calcium channel blocker agent. The combination of amiodarone with preparations IB subclass (lidocaine, mexiletine, diphenin) is relatively beneficial, since the use of this combined therapy is conditioned by minimal possibility of development cardiac undesirable effects, including arrhythmogenic action and occurs of stable bradycardia, in comparison with preparations IA and IC subclasses. Mexiletine and diphenin have sufficient effect for treatment of ventricular extrasystolic arrhythmia and ventricular tachycardia that have both trigger and non-trigger origin.

On the one hand, the administration of diphenin or mexiletine in addition to class III drugs can lead to weakening of the antiarrhythmic effect of amiodarone or sotalol due to the counterdirectional action in respect to phase 2. That is why the velocity of repolarization is decreased after administration of agents of III class. But, on the other hand, the risk of triggering ventricular arrhythmias, which is provoked by class III drugs is reduced by the same mechanism due to administration of β-blocker agents. It should be emphasized that the administration of a combination of preparations of IA/C subclass + III class is possible only in patients without severe organic heart damage.

In real clinical practice, the following combination of antiarrhythmic agents can be useful: allapinin 50 mg (in dose 25 mg in the daytime and at the night or 12.5 mg 4 times a day) + d, l-sotalol 80 mg (40 mg in the morning and in the evening); d, l-sotalol in the same regimen together with disopyramide (100 mg 2 times a day or 50 mg 4 times a day); d, l-sotalol in the same regimen with gilurytmal (50 mg 3 times a day). These combinations are most favorable due to the multidirectional action of drugs on heart rate and are very effective. Moreover, the use of allapinin and disopyramide in half doses can significantly improve their tolerance. The administration of amiodarone or sotalol in half doses possesses decrease of development of their undesirable effects.

After the use of abovementioned combinations of antiarrhytmic agents proarrhythmias, significant prolongation of QT interval, and widening of QRS complex are rare, with the main side effect being moderate, in most cases prolongation of PQ interval. Besides, the following can be used:

1. Amiodarone 200-300 mg (in the morning) + allapinin 12.5-25 mg or gilurythmal 50 mg trice a day or disopyramide 50-100 mg in the evening and / or at night. It should be taken in account that administration of disopyramide especially advisable in the presence of nocturnal brady-dependent arrhythmias that cannot be eliminated by increasing of amiodarone dose. The best choice of using of disopyramide in combine with amiodarone should be made in case of treatment of frequent and stable extrasystolic

ventricular arrhythmias of vagal genesis. After administration of amiodarone together with allapinin or disopyramide the most common side effect is lengthening of QT interval.

2. Amiodarone 200-300 mg (2-3 doses) + ethacizin 50-75 mg (2-3 doses) or etmozine (moracisin) 100-150 mg (2-3 doses) or propafenone 300-450 mg (2-3 times a day) or flecainide 100 mg (in 1-2 doses). During this therapy constant control of following must take place: the duration of PQ interval and QT interval. Besides, the degree of intraventricular blockade (width of QRS complex) must be asseses.

3. Sotalol 80 mg per day (must be divided into two equal doses) together with the same drugs (along with other side effects, the incidences of development of bradycardia can occur more often).

4. Amiodarone 200-300 mg per day or d, l-sotalol 80 mg per day (must be divided into two equal doses) together with diphenin 1/2 tablets 3 times a day (one tablet contains in dose 0,1 mg or 0,117 mg) or with mexiletine 100-150 mg (for 2-3 administrations). Combined therapy using III class preparations (amiodarone or sotalol) together with antiarrhythmic agents of IB subclass (diphenin or mexiletine) is quite safe from the point of view of development of cardiac side effects. This therapy can enhance the antiarrhythmic action of class III drugs in relation to ventricular rhythm disturbances. One should bear in mind that amiodarone increases the plasma concentration of disopyramide, flecainide and diphenin. The combination of amiodarone or sotalol with flecainide is, apparently, one of the most unsafe.

The authors of this article have developed a new method of combined therapy of paroxysmal supraventricular tachyarrhythmias in patients with ischemic heart disease, including the using of allapinin and cardiac glycosides. The author's certificate of invention was obtained for this method.

The efficacy of this combined therapy for suppression of supraventricular paroxysmal tachyarrhythmias was analyzed compared to treatment with allapinin alone.

Paroxysmal atrial fibrillation and paroxysmal supraventricular tachyarrhythmia's can be treated with administration of several preparations. In accordance with such new method it was used of combination of two preparations with antiarrhythmic action (allapinin + cardiac glycosides). This method can be used to treat paroxysmal supraventricular arrhythmias in patients with significant heart failure disease.

Allapinin is the alkaloid of bromhydrate lappaconitine. This alkaloid was extracted from the perennial plant. It can be extracted from the wild plant of the aconite, which belongs to the group of buttercup plants. It is produced in tablets at 50 mg and in solution for intravenous or intramuscular administration: 0,5% solution in ampoules at 2 ml. Allapinin occupies the special place among antiarrhythmic agents of the 1st class according to Vaughan-Williams classification. It differs from agents of IA and IB subclass. Being different from quinidine, procainamide, gilurytmal and others agents of the 1st class of antiarrhythmic drugs allapinin in effective antiarrhythmic doses has small influence on the width of ventricular QRS complex, P-Q interval and Q-T interval. Allapinin in doses, which provide significant antiarrhythmic effect, unlike the other antiarrhythmic drugs, does not lead to reduction of the system arterial pressure and to negative inotropic action in myocardium fibers.

In accordance with the new method of treatment of paroxysmal supraventricular tachyarrhythmias a cardiac glycoside – digoxin (lanoxin) in dose 0,25 mg or strophantin in dose 0,25 mg is administered intravenously. Then in 20-30 minutes after administration of cardiac glycoside allapinin is used intravenously in dose 30-40 mg

In case of suppression of paroxysmal tachyarrhythmia prophylactic treatment must be used of abovementioned preparations. Allapinin is administered orally in the daily dose 75 mg (25 mg 3 times daily). In combination with allapinin digoxin is used orally in the dose 0,25 mg (1 tab) 1-2 times daily. In case of positive result of therapy, the daily dose of allapinin can be reduced to 50 mg (1 tablet 2 times a day) and digoxin to the minimum effective one, which is 0,25 mg (1 tablet) once a day.

The criterion of such positive result of therapy is occurrence of the periods without paroxysms of tachyarrhythmia, which are greater than 1,5-2 periods. Such periods occurred earlier between paroxysms of tachyarrhythmia. Thus, this therapy provides prophylactic effect in respect to occurrence of tachyarrhythmia attack.

The significant advantage of this method is the possibility of using it for the patients with severe heart failure. Unlike the majority of other antiarrhythmic drugs of synthetic origin allapinin does not have any negative inotropic action in effective antiarrhythmic doses. For the patients with cardiac failure the use of cardiac glycoside leads to improving of metabolism in myocardial cells. Such improvement of myocardium metabolism contributes to the elimination of paroxysmal tachyarrhythmias.

The most expressive effect of combined therapy is observed in case of administration of digoxin (lanoxin) in dose 0,25 mg or strophantin in dose 0,25 mg intravenously and the use of allapinin in single dose 30-40 mg intravenously in 20-30 minutes after administration of cardiac glycoside. Such combination of these agents is conditioned by their pharmacodynamics. The beginning of antiarrhythmic effect of allapinin occurs only in 10-15 minutes after its intravenous administration. The maximal effect of allapinin is achieved in 20-40 minutes after using this drug. This property of allapinin is conditioned the time of intravenous administration of cardiac glycoside. Antiarrhythmic effect of digoxin and strophantin occurs significantly sooner than after using of allapinin.

This combined therapy was realized with 37 patients having ischemic heart disease and supraventricular paroxysmal tachyarrhythmias. They were included in the main group of patients [8]. To control the effectiveness of the combined therapy the monotherapy – only using intravenous administration of allapinin in single dose 40-50 mg was realized with 38 patients having ischemic heart disease and supraventricular paroxysmal tachyarrhythmias.

The therapy results in the main and in the control group of patients are submitted in the Table.

Table. The therapy results in the main and in the control group of patients

Form of paroxysmal tachyarrhythmia	Number of patients in main group	Positive result of therapy	Number of patients in control group	Positive result of therapy
Paroxysmal supraventricular tachyarrhythmia	16	12	15	8
Paroxysmal form of atrial fibrillation	14	11	15	7
Paroxysmal form of atrial flutter	7	5	8	3

The use of cardiac glycoside increases the antiarrhythmic effect of allapinin. This combined treatment is more efficient in comparison with the monotherapy with the help of only one preparation (allapinin). Such combined using of these two medicines contributes to shortening of the time, which is needed for suppression of tachyarrhythmia paroxysm. After renewal of the normal sinus rhythm the supporting treatment (oral administration of allapinin and cardiac glycosides) must be administered in the earliest possible period. [8,14].

It is forbidden to use such combinations of antiarrhythmic agents: β-adrenergic blocker agent + verapamil; β-adrenergic blocker agent + dilthizem; propafenone + verapamil; propafenone + dilthizem, propafenone + β-adrenergic blocker agents. The administration of latter combination is impossible because propafenone has similar chemical structure with non-selective β-blocker agent propranolol. After using of such combined therapy possibility of development of medicinal (toxic) disfunction of sinus node increases.

Conclusions.

1. During combined antiarrhythmic therapy monitoring of ECG the must take place, including such its indices as frequency of cardiac beats, duration of PQ and QT intervals, and width of QRS complexes.

2. It is impossible to administer antiarrhythmic drugs of the same class at the same time.

3. It is impossible to administer combined antiarrhythmic therapy in case of using drugs with unidirectional action on heart rate, atrio-ventricular (AV) and intraventricular conductivity, duration of QT interval and myocardial contractility.

4. The doses of drugs used in combined therapy are below in comparison with average therapeutic doses (about half of the usual daily dose).

5. Antiarrhythmic agents should be administered sequentially: the second drug is used only after the evaluation safety and tolerability of the first antiarrhythmic preparation.

6. In order to prevent hazardous potentially lethal arrhythmias, having trigger or re-entry mechanisms, most efficient are combinations including preparations of II class together with III class and simultaneous using of antiarrhythmic agents of I and III classes.

7. The new method of combined therapy of paroxysmal supraventricular tachyarrhythmias, including the using of allapinin and cardiac glycosides has bigger effecientcy in comparison with administration allapinin one only.

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SUMMARY

COMBINED PHARMACOLOGICAL THERAPY INCLUDING SEVERAL ANTIARRHYTHMIC AGENTS FOR TREATMENT OF DIFFERENT DISORDERS OF CARDIAC RHYTHM

Kapustnick Yu., Lutsenko R., Sydorenko A.

Poltava State Medical University, Department of Experimental and Clinical Pharmacology, Clinical Immunology and Allergology, Ukraine

Combined therapy using several antiarrhythmic agents can be useful for treatment of different disorders of cardiac rhythm, including their hazardous and stable forms. It is especially required in case of insufficient efficacy after using one antiarrhythmic agent. As a combined therapy one can use the administration of several preparations e.g. 1) preparations of IA subclass

and β-blocker adrenergic agents; 2) antiarrhythmic agents of I class and calcium channel blocker agents (verapamil and dilthiazem); 3) III class (amiodarone or sotalol) together with β-blocker drugs; 4) antiarrhythmic agents of III class and calcium antagonists; 5) antiarrhythmic agents of I and III classes.

The latter combination has especially strong effect for treatment of arrhythmias caused by re-entry mechanism with or without a short excitability period. Antiarrhythmic agents of II class (β-blocker drugs) and III classes (amiodarone or sotalol) cause reduction of development risk of arrhythmias with trigger mechanism, including bidirectional spindle-shaped ventricular (torsade de pointes) tachycardia. Thus, combinations including preparations of II class together with III class and simultaneous using of antiarrhythmic agents of I and III classes should be administered to prevent hazardous potentially lethal arrhythmias.

The authors of this article have developed a new method of combined therapy of paroxysmal supraventricular tachyarrhythmias in patients with ischemic heart disease, including the use of allapinin and cardiac glycosides. The author's certificate of invention was obtained for this method. The efficacy of this combined therapy for suppression of supraventricular paroxysmal tachyarrhythmias was analyzed compared to treatment with allapinin alone. It was proved that combined therapy has bigger effectiveness in comparison with therapy with help allapinin only.

It is forbidden to use of such combinations of antiarrhythmic agents: β-adrenergic blocker agent + verapamil; β-adrenergic blocker agent + dilthizem; propafenone + verapamil; propafenone + dilthizem; propafenone + β-adrenergic blocker agent. After administration of such combined therapy, it is possible the occurrence medicinal (toxic) disfunction of sinus node. The administration of propafenone together with β-adrenergic blocker agent is impossible because propafenone has properties of β-blocker preparation. It is connected with similar chemical structure of propafenone and nonselective β-blocker agent propranolol.

Keywords: cardiac arrhythmias, antiarrhythmic agents, combined antiarrhythmic therapy, hazardous potentially lethal arrhythmias, re-entry mechanism, trigger mechanism.

РЕЗЮМЕ

КОМБИНИРОВАННАЯ ФАРМАКОТЕРАПИЯ, ВКЛЮЧАЮЩАЯ НЕСКОЛЬКО АНТИАРИТМИЧЕСКИХ ПРЕПАРАТОВ, ДЛЯ ЛЕЧЕНИЯ РАЗЛИЧНЫХ НАРУШЕНИЙ СЕРДЕЧНОГО РИТМА

Капустник Ю.А., Луценко Р. В., Сидоренко А.Г.

Полтавский государственный медицинский университет, кафедра экспериментальной и клинической фармакологии с клинической иммунологией и аллергологией, Украина

Авторами статьи разработан новый метод комбинированной терапии пароксизмальных суправентрикулярных тахиаритмий у больных ишемической болезнью сердца, включающий применение аллапинина и сердечных гликозидов. На этот метод получен сертификат на изобретение. Эффективность этой комбинированной терапии для ликвидации пароксизмальных суправентрикулярных тахиаритмий проанализирована в сравнении с терапией одним аллапинином. Доказано, что комбинированная терапия имеет большую эффективность, чем терапия только аллапинином.

Противопоказанием являются следующие комбинации антиаритмических препаратов: β-адреноблокаторы + верапамил; β-адреноблокаторы + дилтиазем; пропафенон + верапамил; пропафенон + дилтиазем. После применения комбинированной терапии возможно появление лекарственной (токсической) дисфункции синусового узла. Применение пропафенона совместно с β-адреноблокаторами недопустимо, так как связано с подобной химической структурой пропафенона и неселективного β-адреноблокатора пропранолола.

რეზიუმე

რამდენიმე ანტიარითმიული პრეპარატის შემცველი კომბინირებული ფარმაკოთერაპია გულის რიტმის სხვადასხვა დარღვევის მკურნალობისათვის

ი.კაპუსტნიკი, რ.ლუცენკო, ა.სიდორენკო

პოლტავას სახელმწიფო სამედიცინო უნივერსიტეტი, ექსპერიმენტული და კლინიკური ფარმაკოლოგიის კათედრა კლინიკური იმუნოლოგიით და ალერგოლოგიით, უკრაინა

ავტორების მიერ შემუშავებულია პაროქსიზმული სუპრავენტრიკულური ტაქიარითმიების კომბინირებული თერაპიის ახალი მეთოდი გულის იშემიური დაავადებით პაციენტებისათვის, რომელიც მოიცავს ალაპინინის და საგულე გლიკოზიდების გამოყენებას. ამ მეთოდზე მიღებულია გამოგონების სერთიფიკატი. აღნიშნული კომბინირებული თერაპიის ეფექტურობა პაროქსიზმული სუპრავენტრიკულური ტაქიარითმიების ლიკვიდაციისათვის გაანალიზებულია მხოლოდ ალაპინინით თერაპიასთან შედარებით. დამტკიცებულია, რომ კომბინირებულ თერაპიას აქვს მეტი ეფექტურობა, ვიდრე თერაპიას მხოლოდ ალაპინინით.

წინააღმდეგჩვენებას წარმოადგენს ანტიარითმიული პრეპარატების შემდეგი კომბინაციები: β-ადრენობლოკატორები + ვერაპამილი; β-ადრენობლოკატორები + დილთიაზემი; პროპაფენონი + ვერაპამილი; პროპაფენონი + დილთიაზემი. კომბინირებული თერაპიის გამოყენების შემდეგ შესაძლებელია განვითარდეს სინუსის კვანძის წამლისმიერი (ტოქსიკური) დისფუნქცია. პროპაფენონის გამოყენება β-ადრენობლოკატორებთან ერთად დაუშვებელია, რაც დაკავშირებულია პროპაფენონის და არასელექციური β-ადრენობლოკატორის, პროპრანოლოლის მსგავს ქიმიურ სტრუქტურასთან.