REVIEWS

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Spiramycin: The past and future of an antibiotic with pleiotropic effects in the therapy of community-acquired infections

O.I. Butranova[1], S.K. Zyryanov[1,2], A.A. Abramova[1]

[1] Peoples' Friendship University of Russia named after Patrice Lumumba, 6 Miklukho-Maklay Str., Moscow, Russia, 117198
[2] Municipal Clinical Hospital No. 24 of the Moscow City Health Department, 10 Pistsovaya Str., Moscow, Russia, 127015

E-mail: butranova-oi@rudn.ru

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The aim of the work was to search and analyze works on pharmacokinetic (PK) and pharmacodynamic (PD) parameters of spiramycin, allowing to evaluate the potential of this macrolide in the therapy of community-acquired infections.

Materials and methods. The abstract databases of PubMed, Google Scholar, EMBASE, the ResearchGate scientific information network and elibrary.ru were used to search for the materials. The following key queries were used in the work: "pharmacokinetics of spiramycin", "pharmacokinetic parameters of spiramycin", "pharmacodynamics of spiramycin", "mechanism of action of spiramycin", "targets for spiramycin", "pharmacodynamic effects of spiramycin". The search depth – 69 years (1955–2024), the total number of publications included in the literature review in the areas of "pharmacokinetics" and "pharmacodynamics" was 72. The total number of the sources used in the article amounted is 152.

Results. With the spread of the antibiotic resistance (AR) among the pathogens of both nosocomial and community-acquired infections, it is important for physician to search for strategies to preserve the possibility of using first-line antibacterial drugs (ABDs) in patients with infectious diseases. Spiramycin has been characterized by a minimal consumption by the population in the last decades, thus, it has a potential for the therapy of infectious diseases. The analysis of the PK spiramycin parameters indicates the ability to form effective concentrations in various tissues and organs, as well as a minimal risk of drug interactions that can alter the therapeutic response. The evaluation of its antibacterial activity *in vitro* and *in vivo* yields different results, indicating the ability of the drug to exhibit significantly greater efficacy *in vivo*. This paradox may be based on pleiotropic effects of spiramycin involving both host cells (immunomodulatory and anti-inflammatory effects, the ability to favorably affect the tissue regeneration, the antitumor activity, the inhibition of adipogenesis) and pathogen targets (the ability to reduce the virulence of *P. aerugenosa*, the antiviral effect, the reduction of the adhesion ability of cocci).

Conclusion. The PK and PD parameters and the properties of spiramycin along with the results of the published clinical studies evaluating its efficacy indicate that, despite its lower *in vitro* activity, the presence of additional pleiotropic effects may be the key to its superiority over the traditional macrolides in *in vivo* methods.

Keywords: spiramycin; macrolides; community-acquired respiratory tract infections; toxoplasmosis; pleiotropic effects

Abbreviations: ABDs – antibacterial drugs; AR – antibiotic resistance; CI – confidence interval; DNA – deoxyribonucleic acid; GIT – gastrointestinal tract; IL – interleukin; CFU – colony-forming unit; IUs – international units; MIC – minimum inhibitory concentration; AR – adverse reaction; RR – relative risk; OR – odds ratio; PAE – post-antibiotic effect; PMNs polymorphonuclear leukocytes; RNA – ribonucleic acid; PD – pharmacodynamics; PK – pharmacokinetic; aP2 – activating protein 2; AUC – area under the curve; C/EBPα – CCAAT/enhancer-binding protein alpha; clogp – logarithm of the octanol-water distribution coefficient; C_{max} – maximum concentration; CYP3A4 – cytochrome P450 3A4; ERK – extracellular signal-regulated kinase; ERM – erythromycin ribosomal methylase; GLUT4 – glucose transporter type 4; I(Kr) – K+-delayed rectification current; IC_{50} – half maximal inhibitory concentration; iNOS – inducible form of nitric oxide synthase; JNK – Jun N-terminal kinases; MAPK – mitogen-activated protein kinase; NF-κB – nuclear factor kB; Pgp – P-glycoprotein; PPARγ – peroxisome proliferator-activated receptor gamma; Ro5 – Lipinski's rule of five; SASP – senescence-associated secretory phenotype; SREBP1c – sterol regulatory element-binding protein;$T_{1/2}$ – half-life period.

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ОБЗОРЫ

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Спирамицин: прошлое и будущее антибиотика с плейотропными эффектами в терапии внебольничных инфекций

О.И. Бутранова[1], С.К. Зырянов[1,2], А.А. Абрамова[1]

[1] Федеральное государственное автономное образовательное учреждение высшего образования «Российский университет дружбы народов имени Патриса Лумумбы», 117198, Россия, г. Москва, ул. Миклухо-Маклая, д. 6

[2] Государственное бюджетное учреждение города Москвы «Городская клиническая больница № 24 Департамента здравоохранения города Москвы», 127015, Россия, г. Москва, ул. Писцовая, д. 10

E-mail: butranova-oi@rudn.ru

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Цель. Поиск и анализ работ, посвященных фармакокинетическим (ФК) и фармакодинамическим (ФД) параметрам спирамицина, позволяющим оценить потенциал данного макролида в терапии внебольничных инфекций.

Материалы и методы. Для поиска материалов были использованы реферативные базы данных: PubMed, Google Scholar, EMBASE, научно-информационная сеть ResearchGate и elibrary.ru. В работе использовали следующие ключевые запросы: «фармакокинетика спирамицина», «фармакокинетические параметры спирамицина», «pharmacokinetics of spiramycin», «pharmacokinetic parameters of spiramycin», «фармакодинамика спирамицина», «механизм действия спирамицина», «мишени для спирамицина», «фармакодинамические эффекты спирамицина», «pharmacodynamics of spiramycin», «mechanism of action of spiramycin», «targets for spiramycin», «pharmacodynamic effects of spiramycin». Глубина поиска – 69 лет (1955–2024 гг.), общее число публикаций, включённых в литературный обзор по направлениям «фармакокинетика» и «фармакодинамика», – 72. Общее число использованных в статье источников составило 152.

Результаты. В условиях распространения феномена антибиотикорезистентности (АБР) среди возбудителей как нозокомиальных, так и внебольничных инфекций, актуальным для врача является поиск стратегий, позволяющих сохранить возможность использования антибактериальных препаратов (АБП) первой линии в ведении пациентов с инфекционными заболеваниями. Спирамицин в последние десятилетия характеризовался минимальным уровнем потребления среди населения, в связи с чем имеет потенциал для терапии инфекционных заболеваний. Анализ ФК параметров спирамицина свидетельствует о способности формировать эффективные концентрации в различных тканях и органах, а также о минимальном риске лекарственных взаимодействий, способных изменять терапевтический ответ. Оценка его антибактериальной активности *in vitro* и *in vivo* даёт различные результаты, свидетельствующие о способности препарата проявлять значительно большую эффективность в условиях живого организма. В основе этого парадокса могут лежать плейотропные эффекты спирамицина, вовлекающие как клетки организма хозяина (иммуномодулирующее и противовоспалительное действие, способность благотворно воздействовать на процессы регенерации тканей, противоопухолевая активность, угнетение адипогенеза), так и мишени возбудителей (способность снижать вирулентность *P. aerugenosa*, противовирусное действие, снижение способности кокков к адгезии).

Заключение. ФК и ФД параметры и свойства спирамицина наряду с результатами опубликованных клинических исследований, оценивавших его эффективность, указывают на то, что, несмотря на меньшую активность *in vitro*, наличие дополнительных плейотропных эффектов может быть залогом его превосходства над традиционными макролидами в методах *in vivo*.

Ключевые слова: спирамицин; макролиды; внебольничные инфекции дыхательных путей; токсоплазмоз; плейотропные эффекты

Список сокращений: АБП — антибактериальные препараты; АБР — антибиотикорезистентность; ДИ — доверительный интервал; ДНК — дезоксирибонуклеиновая кислота; ЖКТ — желудочно-кишечный тракт; ИЛ — интерлейкин; КОЕ — колониеобразующие единицы; МЕ — международные единицы; МПК — минимальная подавляющая концентрация; НР — нежелательная реакция; ОР — отношение рисков; ОШ — отношение шансов; ПАЭ — постантибиотический эффект; ПМЯЛ — полиморфоядерные лейкоциты; РНК — рибонуклеиновая кислота; ФД — фармакодинамика; ФК — фармакокинетика; aP2 — активирующий белок; AUC — площадь под фармакокинетической кривой; C/EBPα — цитозин-цитозин-аденозин-аденозин-тимидин/альфа-белок, связывающий энхансер; clogp — логарифм коэффициента распределения октанол-вода; C_{max} — максимальная концентрация; CYP3A4 — цитохром P450 3A4; ERK — внеклеточная сигнальная регулируемая киназа; ERM —эритромицин-рибосомальная метилаза; GLUT4 — глюкозный транспортёр тип 4; I(Kr) — блокада калиевого тока задержанного выпрямления; IC_{50} — среднеингибирующая концентрация; iNOS — индуцируемая форма синтазы оксида азота; JNK — Jun N-концевые киназа; MAPK — митоген-активируемая протеинкиназа; NF-κB — ядерный фактор κB; Pgp — P-гликопротеин; PPARγ — рецептор, активируемый пероксисомным пролифератором гамма; Ro5 — правило пяти Липински; SASP — секреторный фенотип, связанный со старением; SREBP1c — белок, связывающий регуляторный элемент стерола-1; $T_{1/2}$ — период полувыведения.

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INTRODUCTION

In the history of the antibacterial drugs (ABDs) use, the 21st century represents a separate milestone, indicating that mankind has not won the victory over bacterial infections. The analysis of more than 100 years of this pharmacological group use (if we take 1910, when the first ABD, salvarsan [1], was first used as a starting point, signifies the fact that the more actively ABDs are used, the more intensively antibiotic resistance (ABR) mechanisms of bacteria develop. Modern clinical practice reveals dramatic trends in the spread of multidrug-resistant bacteria among infectious agents [2]. It is important to note that the problem of AR is currently relevant not only for pathogens of nosocomial infections, but also for those that cause community-acquired infections. Thus, the world practice demonstrates that about 40% of *Streptococcus pneumoniae (S. pneumoniae)* strains, the main causative agent of community-acquired pneumonia (as well as a frequent causative agent of bacteremia, meningitis, otitis media and sinusitis), are characterized by resistance to such ABDs of choice as beta-lactams and macrolides [3]. A national assessment of S. pneumoniae resistance to macrolides in the United States revealed greater values in outpatients (45.3% vs 37.8% in hospitalized patients). At the same time, the proportion of resistant isolates from the respiratory tract was 47.3%, and the proportion of the isolated ones from the blood was significantly lower — 29.6% [4]. In Europe, the resistance of *S. pneumoniae* to erythromycin is maximum in Bulgaria (58.5%), in Asian countries this phenomenon is almost absolute: in China and Japan the level is more than 94% [5–8]. There are published studies indicating that more than 99% of *S. pneumoniae* strains isolated in China (northern regions) have simultaneous resistance to macrolides, lincosamides and streptogramine [9]. According to the study by Mohammadi Gharibani K. et al. conducted in Iran, the resistance of pneumococci to both erythromycin and azithromycin exceeds 70% [10].

In the Russian Federation, the situation with *S. pneumoniae* resistance can be illustrated by the results of the multicenter epidemiological study "PeGAS 2014–2017". It was found out that 24.3% of the strains showed the resistance to erythromycin, 28.5% to clarithromycin, and 31% to azithromycin [11].

Another pathogen of community-acquired infections, *S. pyogenes,* is characterized by a relatively low level of resistance to macrolides (from 0 to 25%) in Europe and the USA, but extremely high in China (about 75 to 100%) [12]. According to the data obtained in the Russian Federation (2013–2018, 601 strains isolated in the infections of the respiratory tract and ENT-organs in 14 cities of the Russian Federation), *S. pyogenes* resistance to erythromycin was noted in 10.5%, to clarithromycin – in almost 12%, and to azithromycin – in 16.5% [13].

Mycoplasma pneumonia, a pathogen characterized by an intracellular localization and a natural lack of sensitivity to beta-lactam ABDs, is one of the common causative agents of community-acquired respiratory tract infections. Macrolides are the drugs of choice in the management of patients with mycoplasma infections, but the possibility of their effective use is also rapidly decreasing in recent years due to the active spread of resistant strains. Thus, according to a multicenter study conducted in China (11 clinics in Beijing, 822 children with community-acquired respiratory tract infections, including 341 ones with confirmed *M. pneumoniae* infection), 87.69% of the strains were resistant to macrolides (erythromycin, azithromycin, josamycin) [14]. In European countries, the prevalence of macrolide-resistant mycoplasmas is an order of magnitude lower, which follows from the results of a systematic review and meta-analysis of 22 studies; however, most of the studies included in the analysis were published in 2011–2015, which limits the value of this meta-analysis for understanding the current picture of *M. pneumonia* AR dynamics in the European region [15].

Toxoplasma gondii is another agent of widespread community-acquired infections in the human population. It is believed that this pathogen can infect up to one third of the human population (the prevalence is highest in developing countries, where it can reach 90%) [16–18]. Among the isolated strains, the level of resistance is maximally high to pyrimethamine and sulfadiazine, and the spread of resistance genes to macrolides and lincosamides is also noted [19].

Analyzing the spectrum of macrolides typically used for the therapy of outpatient infections, it can be noted that erythromycin, clarithromycin and azithromycin are among the most used ABDs of choice both in the world and in the Russian Federation [20–22]. The increasing proportion of resistant bacterial strains in the outpatient practice triggers a cascade of events that aggravates the ABR phenomenon in general. In particular, the inability to use first-line ABDs in the therapy of community-acquired infections forces the physician to prescribe a reserve drug, which in the long term contributes to a significant limitation of antibiotic therapy tools.

Spiramycin is a representative of 16-member macrolides, the use of which in clinical practice in recent decades has been minimal. It was originally discovered in 1952 in the products of *Streptomyces ambofaciens*, and now methods have been developed to intensify its production, in particular, under the action of 0.5% methyl-β-cyclodextrin [23]. In the form for the oral administration, it began to be used since 1955, and since 1987, parenteral spiramycin has become available [24]. The structure features of the macrolactone spiramycin ring, underlie its improved pharmacodynamic characteristics. Spiramycin molecules are able to penetrate deeper into the protein exit tunnel of ribosomes, blocking the maximum number of domains of the peptidyl transferase center for the assembly of pathogen proteins. This action contributes to the

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reduction of virulence of prokaryotes, as well as several clinical benefits, including the improved tolerability (e.g., less gastrointestinal adverse reactions — ARs) and lower risk of drug interactions [25, 26]. The lack of a history of a widespread use of this drug may suggest its success as an alternative to other macrolides characterized by a marked increase in ABR [27].

In order to understand the place and role of spiramycin in the management of patients with various infectious diseases, it is necessary to understand both the individual characteristics of the patient, the causative agent and the localization of the infection, as well as knowledge of the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of the drug. Regarding the latter, it should be noted that PK / PD indices of ABDs determine the choice and ways to optimize the dosing regimen, as they describe the quantitative relationship between PK and PD parameters. There are three main variants of PK / PD indices describing the ABDs efficacy [28, 29]:

– the ratio of the area under the concentration-time curve (AUC) from zero to 24 h (AUC_{0-24}) to the minimum inhibitory concentration (MIC) — f_{AUC} / MIC;

– the ratio of the maximum plasma concentration (C_{max}) to MIC — fC_{max} / MIC;

– the time at which the free plasma concentration exceeds the MIC — $\%f_T$ >MIC.

Although macrolides exhibit a bacteriostatic activity, under certain circumstances they also exhibit a bactericidal activity. Accordingly, macrolides differ from other ABDs classes in the following: they do not rely on a single PK / PD index, but on both ones — $\%f_T$ >MPK and f_{AUC} / MPK [30, 31]. Significant PD factors determining the efficacy of macrolides, are also a post-antibiotic effect (PAE) [32–34] and the effects unrelated to the antibacterial action (e.g., immunomodulation and anti-inflammatory effects) [27, 35–38].

THE AIM of the work was to analyze the published works on pharmacokinetic (PK) and pharmacodynamic (PD) parameters of spiramycin, making it possible to evaluate the potential of this macrolide in the therapy of community-acquired infections.

MATERIALS AND METHODS

To write this literature review, the search for materials included the following abstract databases: PubMed, Google Scholar, EMBASE, ResearchGate scientific information network and a scientific electronic library (elibrary.ru). Each author performed an independent search for publications to exclude the errors in two areas: “pharmacokinetics of spiramycin” and ‘pharmacodynamics of spiramycin’. The keywords for the first direction of search included “pharmacokinetics of spiramycin, pharmacokinetic parameters of spiramycin”; for the second – “pharmacodynamics of spiramycin, mechanism of action of spiramycin, targets for spiramycin, pharmacodynamic effects of spiramycin”. The keywords for the second search direction were as follows: “pharmacodynamics of spiramycin”, “mechanism of action of spiramycin”, “targets for spiramycin”, “pharmacodynamic effects of spiramycin”. The depth of the search was 69 years (publications in the specified abstract databases from 1955 to 2024), a total of 5 720 publications were found out after excluding duplicates, invalid papers, publications with no free access to the full text; the total number of papers included in this literature review on PK and PD was 72. The total number of sources in the article is 152.

RESULTS AND DISCUSSION

Pharmacokinetics of spiramycin

Spiramycin consists of a 16-membered lactone ring with 2 amino sugars and 1 neutral sugar. The clinical efficacy of spiramycin is believed to be limited by the mean values of a half-life ($T_{1/2}$) and an oral bioavailability [39]. With regard to the half-life, it should be noted that it is compensated to some extent by the presence of a number of additional PD spiramycin effects, besides an antibacterial effect, discussed below (e.g., PAE, anti-inflammatory and immunomodulatory effects). The bioavailability of spiramycin, erythromycin and azithromycin is about 40% when taken orally (Table 1). The bioavailability of drugs is influenced by a membrane permeability, solubility and dissolution rate of the drug, the latter two being the main factors. Spiramycin is evaluated as a substance with a low solubility and a slow dissolution rate in water; among the methods to increase its solubility there is synthesis in a micronized form [40]. However, current evidence suggests that the dissolution behavior of spiramycin is more complex than previously thought. Historically, low molecular weight drugs have been developed with the Rule of Five (Lipinski C.A. (Ro5) [41]). According to Ro5, the oral absorption of a drug is higher if its molecular weight is ≤500 Da, the number of hydrogen bond donors ≤5, acceptors ≤10 and the calculated lipophilicity (cLogP) ≤5. There are hypotheses suggesting that the molecules of drugs beyond Ro5 have a certain flexibility that allows them to hide polar fragments when passing through the cell membrane and reveal them again when entering the aqueous medium [42]. Such substances are called molecular chameleons [43–45], they show a satisfactory solubility, an ability to overcome cellular barriers and form satisfactory absorption rates as a result. Among macrolides, roxithromycin and spiramycin are labeled as “complete molecular chameleons” [43, 45]. The “chameleon” effect is important both from the point of view of the PK analysis (an absorption and bioavailability formation) and from the point of view of PD, because it makes possible the interaction of drug molecules with targets that are difficult to reach (e.g., planar ones without distinct stereochemical configurations).

Another factor affecting the bioavailability of macrolides is the saturation of the intestinal efflux when they are administered in high doses [46, 47]. Macrolides

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are substrates for a number of transporter proteins including, first of all, P-glycoprotein (Pgp), among them azithromycin, roxithromycin and erythromycin show quite pronounced properties of P-glycoprotein (Pgp) inhibitors. Despite a relatively low membrane permeability for macrolides in the apical-basolateral direction, they move much more actively in the reverse basolateral-apical direction. When transporter proteins (Pgp) saturate more molecules of azithromycin, roxithromycin and erythromycin with an increasing oral bioavailability [47], there may be an increased risk of toxic reactions of the above macrolides when used at high doses. Spiramycin is also a substrate of Pgp, but does not have inhibitor or inducer properties, therefore, the value of its bioavailability is stable, which provides a stable therapeutic response.

The dose of spiramycin is standardly calculated in international units (IUs), which is, due to the natural origin of the drug – 1 mg of spiramycin, corresponds to 3 000 IUs.

All macrolides, including spiramycin, have a high value of the volume of distribution. In blood, macrolides are predominantly bound to alpha-1-acid glycoprotein, most to a significant extent (Table 1), which may be accompanied by variations in the proportion of the pharmacologically active fraction due to drug interactions or changes in the concentration of plasma proteins. Alpha1-acid glycoprotein is one of the proteins of the acute phase, its concentration increases in inflammation, especially in septicemia, sepsis, complicated surgical interventions, malignant neoplasms. Severe infection is the main factor of a significant increase in the concentrations of this protein, which can lead to a decrease in a pharmacologically active fraction of those macrolides that have a significant degree of binding (see Table 1), and therefore, to a decrease in their therapeutic efficacy.

Spiramycin is characterized by a minimal binding to plasma proteins regardless of the dose taken. This distinguishes it from azithromycin, for which the binding value depends on the concentration: at a level equal to 0.02 μg/mL, it is 51%, and when increased by 100 times, it decreases to 7% [48, 49]. Considering that the pharmacologically active (unbound) fraction of spiramycin is 75%, it penetrates into organs and tissues in high concentrations, which suggests its continued effectiveness in conditions accompanied by severe disturbances in plasma protein concentration.

Due to the ability to form high concentrations in lysosomes, macrolides are characterized by an accumulation in the lung fluid and in phagocytes. In the studies on healthy volunteers it was shown that 3 h after a single oral administration of 3 g (9 000 000 IUs) of spiramycin, the concentration in serum reached 2.8 mg/L [50], after an intravenous administration of 500 mg (1 500 000 IUs) within one hour – 3.10 mg/L [51]. Comparing the maximum blood concentrations of macrolides, it can be noted that the value formed during the oral administration of spiramycin is superior to that of most macrolides (see Table 1). The studies have demonstrated that the plasma concentration achieved with spiramycin exceeds the MIC for most sensitive pathogens [52–55].

With regard to the distribution of spiramycin in other liquids and tissues, the following can be noted. The content of spiramycin in saliva is 1.3–4.8 times higher than in serum [56, 57]. Maximum high concentrations of spiramycin are formed in respiratory tract tissues: in the lung tissue – 30-45 mg/kg, in bronchial mucosa – 6.5–36 mg/kg, in bronchial secretion and sputum – from 1.5 to 7.3 mg/l, in sinus mucosa – from 8 to 13 mg/kg, in tonsil and adenoid tissues – from 15 to 29.5 mg/kg (a multiple dose regimen) [50]. It can be also noted that spiramycin is characterized by a slow release from the intracellular space [58].

An important feature of such macrolides as clarithromycin and erythromycin is a rather high potential for drug interactions. The explanation is their ability to inhibit the CYP3A4 isoenzyme [59, 60], as well as the formation of metabolites with properties of cytochrome inhibitors (anhydroerythromycin [61], 14(R)-hydroxyclarithromycin and N-desmethylclarithromycin [62]). The advantageous difference of spiramycin is its inability to undergo significant metabolic transformations and the absence of inhibitory or inducing effects on the enzymes involved in the biotransformation of xenobiotics. Due to this, the risk of drug interactions of spiramycin is minimal, which limits the factors contributing to therapeutic failures during its administration.

The excretion of all macrolides is carried out mainly with bile. Transporter proteins, including Pgp, are involved in the process. Macrolides are characterized by binding to different bile acids, which is most pronounced in the cases of azithromycin and clarithromycin, showing a maximum affinity to cholate and deoxycholate micelles [63].

From the clinical point of view, a decreased binding of macrolides to bile acids (observed in the representatives with a lower lipophilicity) leads to a decrease in their excretion rate and an increase in the half-life, respectively; the exposure time increases. On the contrary, the use of more lipophilic macrolides characterized by a better binding to bile acids is accompanied by their faster elimination from the organism [63, 64]. The parameters of lipophilicity of spiramycin allow to refer it to moderately lipophilic preparations, which are not characterized by an accelerated excretion from the organism. An additional factor in the stable excretion of spiramycin from the body is the absence of its inducing or inhibitory effect on Pgp, which favorably distinguishes it from a number of other macrolides (see Table 1) [65, 66].

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Pharmacodynamics

Macrolides are inhibitors of bacterial protein synthesis, interacting with 50S subunit of 70S ribosome. For the realization of the action, it is necessary to bind macrolide molecules to the regions of the peptide exit tunnel of the forming peptide from the bacterial ribosome (NPET), located near the peptidyltransferase center. The traditional hypothesis explaining the mechanism of the macrolides action is to stop the translation process by closing NPET [72]. The studies revealing the absence of a complete arrest of protein synthesis in some pathogens, the studies devoted to the structural features of macrolides, as well as the peculiarities of the bacterial genome and changes in the bacterial protein synthesis during a prolonged exposure to ABDs, allow the authors to speak about the second theory that illuminates the details of the mechanism of the macrocyclic ABDs action [73, 74]. It consists in the fact that macrolides can act as context-specific inhibitors of a peptide bond formation, and both the features of the ABDs molecule's structure and the features of the proteins synthesized by bacteria determine the boundaries and degree of the protein synthesis arrest [72, 74].

The structure of macrolide molecules largely determines the type of an antibacterial action, whether it will be bacteriostatic or bactericidal [72, 75]. Macrolides with a bacteriostatic action only and macrolides also capable of a bactericidal effect differ from each other, first of all, by such parameters as the kinetics of binding and dissociation from the ribosome, not just the affinity degree [76]. Representatives with a bactericidal action demonstrate a pronounced slowdown in the rate of dissociation from the ribosome, which is associated with the presence of an elongated side chain in their molecules. The longer the macrolide is bound to the ribosome, the longer the translation of the pathogen protein stops; as a result, the factors critical for the resumption of a gene expression may be completely depleted in the bacterial cell, and the cell dies [76]. If the macrolide molecule dissociates rapidly from the ribosome, a predominantly bacteriostatic action is manifested. Spiramycin, binding three domains of the peptidyl-transferase center on the prokaryote ribosome, provides a prolonged translation arrest, which determines its bactericidal effect [25, 26].

Comparative estimation of bactericidal effect of different macrolides (erythromycin, azithromycin, clarithromycin, dirithromycin, roxithromycin and spiramycin) against 10 strains of pneumococci with different levels of susceptibility to penicillin was carried out in the work by Fuursted K., et al. As a result, a bactericidal effect (a decrease in the number of colony-forming units (CFUs) per milliliter ≥3 log10 after 4 h of the exposure to a concentration 10 times higher than the MIC) was established for all drugs except azithromycin. A comparative analysis of the severity of this effect found out that spiramycin and clarithromycin had significantly higher bacterial killing rates after 1 h of the exposure compared with azithromycin, dirithromycin, and erythromycin. Among all macrolides, spiramycin showed the most pronounced bactericidal effect comparable to penicillin G after 4 hours of the exposure, while azithromycin showed a minimal bactericidal activity. The development rate of the bactericidal macrolides effect did not depend on the sensitivity of the pathogen to penicillin [32].

The structural spiramycin features (the presence of a disaccharide consisting of a mycaminose and a micarose in the C5 carbon atom position) ensure a pronounced binding to the peptidyl transferase center in the NPET region. From the molecular point of view, the features of the macrocyclic spiramycin ring allow it to penetrate deeper into the protein exit tunnel and form stronger bonds when interacting with the ribosome, which may indicate its increased activity against resistant bacterial strains and its ability to counteract the AR formation in general [25, 26]. This fact favorably distinguishes spiramycin from 14-membered macrolides, the use of which can trigger AR genes in relation not only to macrolides, but also to lincosamides and streptogramins (e.g., *ERM*) [26, 77]. This thesis is supported by the fact that 16-member macrolides show a clinically significant activity against erythromycin-resistant *Staphylococcus aureus* strains [26].

Spiramycin is characterized by both bacteriostatic and bactericidal actions. The latter is characteristic when ABDs are used in a dosage form containing 3 000 000 IUs in one tablet. This form is represented by the preparation "Doramytsin VM".

Analyzing the antibacterial activity of spiramycin, it is necessary to dwell on its ability to produce a PAE. Having a high affinity for tissues, spiramycin is slowly released from cells and provides both a direct antibacterial action and an indirect one, through the realization of PAE [78, 79]. In the studies of *Staphylococcus aureus* strains, the spiramycin PAE was found to be more pronounced and prolonged compared to erythromycin [78]. The PAE spiramycin value against mutant *E. coli* strains (ΔacrAB strains with the presence of an efflux pump) was found to be 1.7±0.26 h, which was higher than that obtained for erythromycin (0.2±0.1 h) and azithromycin (1.3±0.28) [80]. With respect to *Streptococcus pneumonia,* the mean duration of PAE was significantly higher for macrolides. The maximum value was found for spiramycin (3.88 h), smaller values were found for clarithromycin (3.60 h), erythromycin (3.50 h), roxithromycin (3.13 h) and azithromycin (2.83 h) [32].

The spectrum of the antimicrobial macrolides activity includes predominantly Gram-positive pathogens and only some Gram-negative ones. Spiramycin has demonstrated a high activity against *Staphylococcus*

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aureus [30, 71], coagulase-negative staphylococci [30], β-hemolytic streptococci [30], pneumococci [80, 81], *Haemophilus influenzae* [30, 71], some pathogenic *Neisseria* species [30, 71, 82], *Bordetella* [30, 82], *Corynebacterium* [30], *E. Coli* [83], *Rickettsia* [30], *Legionella* [30, 71], *Chlamydia* [30, 82, 84], *Mycoplasma* [30, 71, 82, 84], *Toxoplasma (Toxoplasma gondii)* [82, 84, 85], some *Cryptosporidium* species [84] and *Moraxella* [71].

Among Gram-negative microorganisms sensitive to spiramycin, the main ones are intracellular pathogens. All the more interesting are the results of the studies that investigated the spiramycin effect on the pathogens included in the group of the microorganisms especially dangerous for humans, ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp.*). Calcagnile M. et al. (2022) demonstrated the results of a spiramycin action on the blue bacillus, *Pseudomonas aeruginosa,* which has a natural resistance to this ABDs as well as to any other macrolides. The authors found a decrease in the virulent properties of this pathogen, in particular, a decrease in the formation of pyocyanin, pyoverdine and rhamnolipids [86]. The studies in this direction were further developed by the authors; in their later work, they confirmed the ability of spiramycin to suppress the expression of virulence determinants in *P. aeruginosa*: in its presence, the production of pyoverdine and pyocyanin was significantly reduced, the concentrations causing the reduction were 15.6 and 7.8 μg/mL, respectively. Spiramycin also found important effects concerning the inhibition of a biofilm formation (almost twofold at spiramycin concentrations of 30 μg/mL or more), the reduction of a bacterial swarming motility and a rhamnolipid production. The treatment of *P. aeruginosa* with spiramycin (at concentrations ranging from 60 to 180 μg/ml) resulted in the sensitization of the bacterial cell to the damaging effect of hydrogen peroxide. The results were obtained both *in vitro* and *in vivo*; the latter revealed a decrease in the mortality rate by approximately 50% when spiramycin was administered against the background of the *P. aeruginosa* infection (the model with *Galleria mellonella*), as well as the presence of an immunomodulatory activity of this macrolide [87].

When analyzing the spiramycin PD, it is necessary to recall such a concept as the “spiramycin paradox” used for the first time in 1988 [88]. The paradox consisted in the fact that the antibacterial effect of this ABD was inferior to that of erythromycin *in vitro*, but superior in *in vivo* studies. The explanation is the complex mechanism of the spiramycin action, which includes both a direct antibacterial action on bacterial cells (and, as it was found, on some other pathogens) and the effect on host cells, the study of which allowed to reveal pleiotropic effects of the macrolide in question.

Additional pharmacodynamic effects of spiramycin

Antiviral activity

Macrolides are a group of drugs that have discovered the ability not only to antibacterial, but also to antiviral actions [89]. This feature is based on the “chameleon” effect of the macrolides discussed above. It is macrocyclic chameleon compounds that exhibit a unique ability to interact with hard-to-reach targets, which are characteristic of viruses [43–45].

Among macrolides, the antiviral activity has been reported in a number of representatives, including spiramycin. The early studies revealed the effect of clarithromycin against H1N1 influenza virus, but a comparative study of different macrolides (josamycin, spiramycin, erythromycin, clarithromycin) conducted in 2014 demonstrated that it had the lowest activity measured *in vivo* and assessed by the survival rate of laboratory animals and their weight dynamics after the infection with a lethal dose of H1N1. The 16-member macrolides josamycin and spiramycin were recognized as the most effective [90].

The use of macrolides has shown definite prospects in the treatment of enteroviral vesicular stomatitis (the causative agents are enterovirus A71 (EV-A71) and coxsackie virus A16 (CV-A16)). Zeng S. et. al. (2019) showed the comparative study results of the effects of 8 macrolides (erythromycin, clarithromycin, dirithromycin, roxithromycin, azithromycin, midecamycin, jozamycin and spiramycin) on EV-A71 and CV-A16 *in vitro*, finding the presence of anti-enteroviral activity in spiramycin and azithromycin. Spiramycin most significantly reduced EV-A71 RNA and protein levels by likely disrupting a viral RNA replication. The average inhibitory concentration (IC_{50}) of spiramycin against EV-A71 and CV-A16 was 15 and 75 μM, respectively. The values for azithromycin were 26 and 50 μM, respectively. The authors noted that the inhibition of the viral replication by spiramycin and azithromycin was not accompanied by cytotoxic reactions, and both drugs showed an anti-enteroviral activity, more pronounced against EV-A71 and less for CV-A16. With respect to EV-A71, spiramycin proved to be a stronger replication inhibitor than azithromycin [91].

Effect on human cells and tissues

The ability of spiramycin to have not only an antibacterial effect, but also to affect the host cells, causing a comprehensive improvement in their function, has been shown in a number of studies involving patients with infections of various etiologies. In particular, this applies to such a typical indication for spiramycin as toxoplasmosis, where this ABD contributes to the improvement of tissues of the internal organs. The

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phenomenon may be based on the improvement of tissue regeneration rates in the presence of spiramycin, which has been shown for liver, spleen and brain cells [92]. Regular spiramycin passes through the blood-brain barrier poorly, but its modified form based on chitosan nanoparticles provides an effective crossing of histohematic barriers with the formation of sufficient concentrations in the brain tissue [93]. The nanoparticles loaded with spiramycin have shown a maximum efficacy in the treatment of acute toxoplasmosis, including those with a central nervous system damage [94]. Clinical data indicate a marked reduction in the number of brain cysts (by 88.7%) and an improvement of the brain tissue in patients with chronic toxoplasmosis [95]. A complex improvement of the organs and tissues state was also observed with the use of a combination of probiotics *(Lactobacilli acidophilus)* and spiramycin in the patients with toxoplasmosis against the background of diabetes mellitus [96].

Potential of spiramycin in the therapy of obesity

The ability to inhibit adipogenesis and reduce the severity of obesity caused by a high-fat diet, has been demonstrated for spiramycin. A spiramycin-induced suppression of a preadipocyte differentiation against the background of the attenuation of an intracellular lipid accumulation underlies a weight loss. Spiramycin has been shown to inhibit the expression of key adipocyte regulators (PPARγ, C/EBPα and SREBP1c) and their target genes (FAS, aP2 and GLUT4), as well as to activate the phosphorylation of an adenosine monophosphate-activated protein kinase, AMPK, in 3T3-L1 cells during their early differentiation. In *in vivo* models, spiramycin led to a significant weight loss by reducing the adipose tissue mass and also contributed to minimizing a lipid accumulation in hepatocytes. In the liver, a decrease in the severity of steatohepatosis was found against the background of a spiramycin administration [97]. The ability of spiramycin to counteract adipogenesis distinguishes it from other macrolides, for which (primarily azithromycin), on the contrary, the studies have revealed a certain relationship with the development of obesity. It was found out that both in the USA and in Europe, macrolide uses at the population level had a positive association with a subsequent childhood obesity that persisted regardless of the period between the ABDs use and the formation of overweight [98]. Another large-scale study analyzed the relationship between the consumption of the most common macrolides and the development of obesity in adults, revealing the ability of this group of ABDs to induce processes leading to the weight gain [99].

Anti-inflammatory and immunomodulatory effects of spiramycin

Macrolides have quite pronounced immunomodulatory properties that have the potential to correct an immune dysregulation even in critical patients, but they do not inhibit endogenous antimicrobial defense mechanisms [100]. The anti-inflammatory potential of macrolides has been demonstrated in modeling septic processes and tissue damages of various localizations caused by the infectious process [101].

The anti-inflammatory and immunomodulatory actions of spiramycin are based on their effect on several cell types, primarily macrophages. The results of a study evaluating the anti-inflammatory potential of a topical application of spiramycin in humans (an application to the skin) have been published. They found the ability of this ABD to reduce the secretion of interleukins, ILs (IL-6 and IL-1β) by macrophages, reduce the NO synthesis by affecting the expression of the inducible form of nitric oxide synthase (iNOS) by inhibiting the nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways [102]. In general, an effective attenuation of the macrophage activation in the presence of spiramycin and its significant potential for use as a topical anti-inflammatory agent have been observed [102].

Another study of the topical spiramycin effect (applied to the nasal mucosa) showed its actions on fibroblasts. The structure analysis of the cells exposed to the ABDs revealed the absence of damage to the cytoskeleton and nuclei, and a preservation of the spindle shape. Spiramycin increased a viability of fibroblasts and had no damaging effect on them at a short-term application for 24 and 48 h, but decreased a viability at doses of 50 and 100 μM at a long-term application for 72 h. As a result, the authors recommended using spiramycin in the form for a topical application during septorhinoplasty procedures [57].

It was shown that macrolides can change the differentiation and maturation of mononuclear phagocytes, endothelial and epithelial cells and fibroblasts [103]. Thus, the inhibition of the activation of inflammatory phenotype M1 macrophages and the enhancement of the formation of phenotype M2 macrophages, contributing to the arrest of inflammatory processes and a subsequent healing, were found out [104].

Macrolides also act as inhibitors of the adhesion molecules expression on neutrophils and endothelial cells. This effect leads to the inability of leukocytes to adhere to the endothelium at the very beginning of the diapedesis process (the transition of cells from blood to tissues through the vascular wall, which is typical for

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an inflammation) [105]. Macrolides have demonstrated the ability to induce phagocytosis and enhance the formation of certain lines of macrophages, and both in relation to macrophages and neutrophils ABDs of this group, have demonstrated the ability to inhibit the so-called "oxidative burst" [100].

The results of the spiramycin treatment of *Staphylococcus aureus* and various species of streptococci *(S. pyogenes, S. mutans, S. sanguis,* and *S. faecalis)* with a subsequent evaluation of the degree of their adhesion to buccal cells and the efficiency of phagocytosis by polymorphonuclear leukocytes are of interest. A pretreatment of cocci with a serial twofold spiramycin dilutions (1/2 to 1/1024 MPC) resulted in an increase in the diameter of bacterial cells and a decrease in their adhesion to buccal cells. The exposure of streptococci to spiramycin led to an increase in the phagocytic ability of polymorphonuclear leukocytes, and the effect was observed both when using the therapeutic concentration (2 mg/L) and when using 1/4 MIC [53].

Another aspect of a macrolides action is their effect on the mucus secretion in the respiratory tract. The basis is the inhibition of a cytokine induction of a mucin 5AC (MUC5AC) gene expression [106, 107].

In addition to their anti-inflammatory and immunomodulatory actions, macrolides have important effects such as slowing down the aging process. Aging cells can produce and secrete pro-inflammatory cytokines, they are called "senescence-associated secretory phenotype (SASP)". SASP is a major factor in the chronic inflammation and tissue damage [108] and has a close relationship with inflammasomes.

There have been published works demonstrating the senolytic activity (an ability to inhibit aging processes in the body) of a number of macrolides manifested in the form of death of lung fibroblasts damaged by aging processes, against the background of the effect absence on healthy normal fibroblasts [109]. The specific effect of spiramycin on a number of proinflammatory cytokines and cell signaling pathways allowed the authors to identify it as a drug with a potential of the antitumor action. This potential was found, in particular, in experiments with a MCF-7 cell line, representing a human breast cancer cell line with estrogen, progesterone and glucocorticoid receptors [110]. The mechanism underlying the beneficial effects included the ability to bind topoisomerase II and inhibit a complex formation between this enzyme and DNA. Antiproliferative properties of spiramycin were manifested against the background of its rather low concentration (IC_{50}=0.67±0.43 μM), very close to the concentration of the standard antitumor drug from the ABDs group, doxorubicin. A comparison of the antitumor potential of spiramycin, roxithromycin, clarithromycin and azithromycin performed on the MCF-7 cell line revealed the unambiguous superiority of spiramycin [110].

The combined PD effects of spiramycin, complementary to its antibacterial action, are summarized in Figure 1.

Clinical efficacy of spiramycin

A high intracellular concentration of spiramycin, formed in cells of various organs and tissues, along with its antimicrobial spectrum, underlie the possibility of a fairly wide use of this ABD in the therapy of community-acquired infections.

One of the most topical issues of a spiramycin application is its use in patients with community-acquired bacterial infections of the upper and lower respiratory tract. Clinical studies indicate the effectiveness of this macrolide in patients with pharyngitis and tonsillitis, which is due, in particular, to its high concentrations in tonsil and pharyngeal tissues, and a high content in saliva [56]. An efficacy comparison of spiramycin (3 000 000 IU (1 g) 2 twice a day, *n*=49) and amoxicillin (500 mg capsules 3 times a day, *n*=50) in the therapy of patients with acute community-acquired upper respiratory tract infections revealed comparable results (success of antibiotic therapy in 89% in the spiramycin group and 83.3% in the amoxicillin group) [111].

In patients with lower respiratory tract infections, the efficacy of spiramycin is demonstrated by the results of an open multicenter study (Brazil and Colombia, *n*=125, patients with a radiologically confirmed pneumonia, acute bronchitis or exacerbation of chronic bronchitis). Clarithromycin was administered at a dose of 500 mg every 12 h and spiramycin at a dose of 3 000 000 IUs (1 g) every 12 h in the courses of 5–10 days. The clinical efficacy scores of the drugs did not show significant differences, nor did the safety scores (*p*=0.768 and 0.236, respectively) [112]. Another open randomized multicenter study (*n*=55, patients with pneumonia and/or bronchitis) demonstrated a similar comparable efficacy of spiramycin and clarithromycin. the antibiotic therapy success was observed in 96.15% of patients in the spiramycin group and 96.43% in the clarithromycin group. Side effects were slightly less frequent in the spiramycin group (7.69 vs. 10.71% for clarithromycin) [113].

The use of spiramycin (1 500 000 IUs 3 times a day) in 30 patients (adults aged 16–65 years) with community-acquired pneumonia revealed a high clinical efficacy – approximately half of the patients showed positive clinical dynamics on the 3rd day after starting ABDs. At the end of the course of the antibiotic therapy the clinical efficacy was 90.0%. ARs were observed in 20.0% [114]. A 100% efficacy of spiramycin in patients

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with pneumonia was demonstrated in another domestic study (*n*=30, a moderately severe course, a mean age 35±12 years) [115].

A high efficacy of spiramycin was also found in the outpatient practice (dose 3 000 000 IUs, the duration of treatment – up to 14 days, *n*=21). The treatment efficacy was 95.2%, and no side effects were registered [116]. A comparison of the efficacy of oral spiramycin and ampicillin in the management of children with infectious-inflammatory diseases of the respiratory tract, tonsils and middle ear revealed a number of advantages of macrolide. The study found pronounced positive dynamics: a rapid reduction of fever, a sore throat on swallowing and some symptoms of intoxication [117].

The above studies were predominantly published in the twentieth century, attracting an increased interest in the contemporary data that could illustrate the activity of spiramycin against the strains of streptococci circulating today. In 2024, the Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy (Russia) performed an *in vitro* activity testing of the spiramycin substance from the manufacturer World Medicine, Turkey (350 strains of *S. pneumonia* and *S. pyogenes* from patients with community-acquired respiratory tract infections from sixteen cities in the Russian Federation). The results demonstrated the sensitivity of 70.5% of *S. pneumonia* and 94.7% of *S. pyogenes* strains to spiramycin. Among the streptococci resistant to 14- and/or 15-member macrolides (erythromycin, clarithromycin, roxithromycin, azithromycin), 25–36% of *S. pneumonia* strains and 69.6-97.3% of *S. pyogenes* isolates showed the sensitivity to spiramycin[1].

The oral cavity is a close anatomical region in relation to the upper respiratory tract. A high content of spiramycin in saliva, gums and bones makes it a promising drug for use in dental practice, which has been confirmed by a number of studies [118–120].

Helicobacter pylori, a major etiologic factor in the peptic ulcer disease, is a pathogen with rapidly increasing ARs. The macrolide traditionally used in *H. pylori* eradication is clarithromycin, and the resistance growth of the pathogen against this ABD is dramatic [121–123]. Spiramycin has no history of use as a traditional component of eradication regimens despite the fact that several papers were published in the 1990s indicating its efficacy in *H. pylori* eradication comparable to tetracycline [124], oxytetracycline [125], and amoxicillin [126]. A modern evaluation of the efficacy and safety of spiramycin when used as a part of the triple therapy of the first-line *H. pylori* eradication was performed in the study including 122 patients with a confirmed *H. pylori* infection and no history of the eradication therapy (70 people — a study group, received pantoprazole 40 mg twice a day, spiramycin 1 500 000 IUs and metronidazole 250 mg – 3 times a day for 10 days; 52 people – a control group, received pantoprazole, clarithromycin and amoxicillin for 14 days). A month after the therapy completion, the status of *H. pylori* was evaluated. In the study group, the eradication was noted in 74.3%, in the control group – in 86.58%. No significant differences between the groups were found (*p*=0.097). Side effects were observed in 54.5% in the study group and in 45.5% in the control one (nausea, abdominal pain and diarrhea), there were no statistically significant differences between the groups (*p*=0.266). The authors concluded that the comparable efficacy of macrolides against the background of a satisfactory safety profile suggests the potential of spiramycin in the eradication of *H. pylori* in conditions of the increasing resistance to clarithromycin [127].

A high activity of spiramycin against intracellular pathogens includes chlamydia. The risk of chlamydiosis in the world and in the Russian Federation population shows increasing trends [128]. The published studies indicate the effectiveness of spiramycin in respiratory tract infections caused by *Chlamydia pneumonia* [129], genital infections caused by *C. trachomatis* [130]. An interesting publication describes the use of spiramycin in a 30-year-old patient with acute pleuro-myocarditis developed against the background of the community-acquired pneumonia caused by *C. psittaci* (as a result of a professional contact with birds). The patient received intravenously 1 g of amoxicillin and 1 500 000 IUs of spiramycin 3 times a day in combination with 0.5 mg of colchicine 4 times a day and 1 g of acetylsalicylic acid 3 times a day. Positive dynamics was noted starting from the third day of the ABDs administration (the absence of fever and chest pain), laboratory tests revealed a normalization of blood leukocyte and lymphocyte counts, as well as a reduction of C-reactive protein to 23 mg/L on the fifth day. Amoxicillin was discontinued, the patient continued taking spiramycin for 14 days, no side effects were reported, a further follow-up for 3months revealed normal ECG values, and no cardiac abnormalities were detected for 2 years [131].

For the diseases listed above, the use of spiramycin is not currently widespread and most published studies date back to the twentieth century. The situation is different for an infectious disease such as toxoplasmosis. Spiramycin is the main drug of choice for the treatment of toxoplasmosis in various categories of patients [132–135], including pregnant women [136, 137]. It has no teratogenic potential and is safe for use in the first trimester of pregnancy, which distinguishes it from pyrimethamine and sulfadiazine, which should not be used until the second trimester of pregnancy because of significant adverse effects on the fetus [134].

[1] The in vitro activity of macrolides against S. pneumoniae and S. pyogenes was studied // Pharmaceutical Bulletin. Available from: https://pharmvestnik.ru/ content/news/Izuchena-in-vitro-aktivnost-makrolidov-v-otnoshenii-S-pneumoniae-i-S-pyogenes.html. Russian

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Table 1 – Comparative pharmacokinetic parameters of macrolides

Macrolide	Bioavailability, %	C_{max}, mg/L proteins	Volume of distribution Binding to plasma proteins	Binding to plasma proteins	$T_{1/2}$	Clearance	Metabolism	Excretion	Effect on transporter proteins	Source
Erythromycin	18–45%	1,5±0,6	2,34±1,76 l/kg	80–90%	2,4–3,1 h	Healthy individuals: In the presence of cirrhosis: Increased 3–fold or more	Substrate CYP3A4 inhibitor	95% in bile and 5% in urine	Pgp inhibitor	[59–61, 65, 66]
Roxithromycin	50–60%	2,3±0,39	0,43–0,44 l/kg	96%	12 h	Reduced in the elderly	Virtually unmetabolized Weak CYP3A4 inhibitor	53% by feces; 10% in urine	Pgp inhibitor	[67,68]
Clarithromycin	50%	2,1±0,7	3–4 l/kg	70%	3–4 h	29,2–58,1 l/h	Substrate for CYP3A4 CYP3A4 inhibitor	70–80% in bile; 20–30% in urine	Weak Pgp inhibitor	[59, 60, 63, 65]
Azithromycin	37%	0,43±0,2	31,1 l/kg	51% – at a concentration of 0.02 µg/mL in plasma; 7% – at a concentration of 2 µg/mL in plasma	68 h	Healthy individuals: 630 ml/min.	Minimal metabolism No effect on cytochromes	94% – in bile; 6% – in urine	No significant effect on Pgp	[47–49, 63, 65, 66, 69]
Josamycin	51%	1.64+0.67 mg/mL (intravenously); 0.05 to 0.71 mg/mL (orally)	300 L	15%	1–2 h	4,71 l/kg/h	Substrate for a number of cytochromes in liver. Probable inhibitor of a number of CYP450 isoenzymes.	75–80% – in bile; 15–20% – in urine	No significant effect on Pgp	[68, 70]
Spiramycin	30–39%	2,8 mg/mL (orally) 3,1 mg/mL (intravenously);	300 L (about 5 l/kg)	10–25%	On average: 6,2–7,7 h Intravenous: young adults (18 to 32 years of age): 4.5 to 6.2 hours; the elderly (73 to 85 years of age): 9.8 to 13.5 hours. Orally: 5.5 to 8.0 hours	1.42 l/min (renal clearance – 144 ml/min, extrarenal clearance – 887 ml/min	Minimal metabolism. No effect on cytochromes	More than 80% – in bile; up to 14% in urine	No significant effect on Pgp	[51, 71]

Note: C_{max} — maximum concentration; $T_{1/2}$ — half-life time period.

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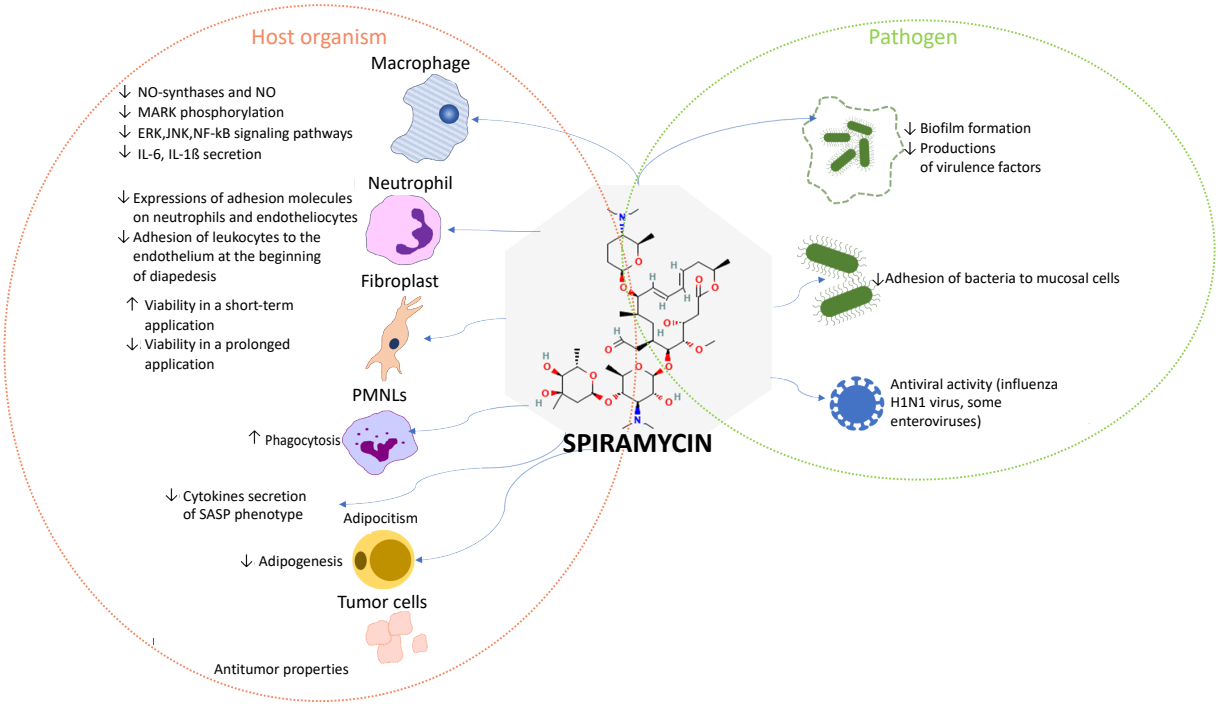

Figure 1 – Pharmacodynamic effects underlying the pleiotropic action of spiramycin
Note: MARK – mitogen-activated protein kinase; ERK – extracellular signal-regulated kinase; JNK – Jun N-terminal kinase; NF-κB – nuclear factor κB; IL – interleukin; PMNL – polymorphonuclear leukocytes.

According to a 2015 year meta-analysis, spiramycin was recognized as a drug with a high efficacy against the infections caused by *T. gondii.* The pooled negative conversion rate values (a positive test before the treatment, a negative test after it) for spiramycin, azithromycin and trimethoprim-sulfamethoxazole were 83.4% (95% confidence interval (CI): 72.1 to 90.8%); 82.5% (95% CI: 75.9 to 87.6%) and 85.5% (95% CI: 71.3 to 93.3%). The analysis of the incidence of a vertical mother-to-child transmission after a course of spiramycin in pregnant women with a primary infection included 11 publications (*n*=3596) and found a minimum value of 9.9% (95% CI: 5.9 to 16.2%). The evaluation of a spiramycin efficacy in toxoplasmosis encephalitis was based on the data from 14 publications (*n*=727), with a pooled cure rate of 49.4% (95% CI: 37.9 to 60.9%) [138].

In 2021, another meta-analysis was published to evaluate the efficacy of spiramycin in pregnant women followed by pyrimethamine-sulfonamide-folic acid or without it, compared with the absence of treatment. The evaluation was based on the incidence of a mother-to-child transmission of *T. gondii* and the incidence / severity of the sequelae in children. The meta-analysis pooled 33 studies (32 cohort and 1 cross-sectional study, number of mothers was *n*=15 406, newborns was *n*=15250). The incidence of the vertical transmission was significantly lower in the patients receiving the spiramycin monotherapy, 17.6% (95% CI: 9.9 to 26.8%) compared with the group of the therapy absence, 50.7% (95% CI: 31.2 to 70%; *p* <0.001), indicating an unequivocal efficacy of spiramycin [139]. A high efficacy in curing pregnant patients from toxoplasmosis and preventing a vertical transmission was found for the combination of spiramycin with co-trimoxazole (the data from a retrospective study including 120 pregnant women and 123 newborns, the period from 1992 to 2011) [140].

The data analysis of 685 pregnant patients with toxoplasmosis treated with spiramycin in Germany (spiramycin is the standard of care in the country's clinical guidelines) confirmed the efficacy of its use (from the diagnosis time until the 16th week of pregnancy, followed by pyrimethamine, sulfadiazine, and folinic acid for at least 4 weeks) in combination with a standardized follow-up program to reducea transplacental transmission and the disease burden in the newborn [141].

According to the Russian draft clinical guidelines on diagnosis, treatment and prevention of congenital toxoplasmosis, macrolides belong to the second-line etiotropic therapy of newborns, among which spiramycin is the drug of choice (the first line – pyrimethamine+sulfadimezine for 4–6 weeks).[2]

[2] Clinical recommendations [project] for the diagnosis, treatment and prevention of congenital toxoplasmosis. Available from: https://www.raspm.ru/files/toksoplazmoz.pdf. Russian

The dosing regimen of spiramycin in pregnant women with toxoplasmosis according to the clinical guidelines 2023, Germany, is as follows [135]: Up to 14+6 weeks of gestation – spiramycin (3.0 g or 9 000 000 IU/day); from 15+0 weeks of gestation – for at least 4 weeks the combination of pyrimethamine (50 mg on day 1 and 25 mg from day 2)+sulfadiazine (50 mg/kg/day; 3 g/day for a body weight up to 80 kg; 4 g/day for a body weight of 80 kg or more)+folinic acid (10–15 mg/day, a folic acid intake should be discontinued).

If sulfadiazine intolerance/inability: 15+0 weeks gestation: Spiramycin (3.0 g or 9 IUs/day)+co-trimoxazole (2×960 mg/day)+folinic acid (10–15 mg/day, a folic acid intake should be discontinued) or co-trimoxazole (2×960 mg/day)+folinic acid (10–15 mg/day, folic acid should be discontinued) or pyrimethamine (50 mg/day)+ clindamycin (3×600 mg/day)+folinic acid (10 to 15 mg/day, folic acid should be discontinued).

Summarizing the reviewed results of a spiramycin clinical use, it can be noted that its use at a dose of 3 000 000 IUs twice/day provides an effect superior or comparable to that of other 14- or 15-member macrolides and aminopenicillins. Comparing the dosing regimen of spiramycin given in the studies with that of the second 16-member macrolide, josamycin (1–2 g/day, divided into 2 or 3 doses), a similar result based on the data of PK and PD characteristics analysis of the drugs, can be assumed.

Side effects

Macrolides have a very high level of safety and are generally well tolerated by patients of various ages. Nevertheless, a real clinical practice has revealed a number of ARs characteristic of this group, the spectrum of which depends on the specific macrolide. A Cochrane review including 183 studies and nearly a quarter of a million patients treated with macrolides (*n*=252 886) [142] found the highest risk gastrointestinal tract (GIT) ARs (odds ratio, OR=2.16 [95% CI: 1.56 to 3.00]). Among ARs on the GI side, an abdominal pain (OR=1.66 [95% CI: 1.22 to 2.26]), diarrhea (OR=1.70 [95% CI: 1.34 to 2.16]), and nausea (OR=1.61 [95% CI: 1.37 to 1.90]) were leading. In most cases, mac rolide-induced diarrhea is not a consequence of impaired gut microflora, but is associated with an activation of motilin receptors. It was found that 14-membered macrolides erythromycin and oleandomycin have a pronounced affinity for them, comparable, in fact, with motilin itself, and exhibit the properties of their agonists, which leads to a pronounced stimulatory effect on the intestinal motility [143]. This distinguishes them from 16-membered macrolides, which do not cause such a reaction due to their structural features, which do not allow them to bind to this type of receptors. Thus, a connection between the structure and function of macrolide ABDs and their GIT side effects can be noted [64, 144].

Taste disturbances are another typical side effect of macrolides, compared to placebo, with an OR of 4.95 (95% CI: 1.64 to 14.93) [142]. The data are based on the results of the most common representatives of the group (azithromycin, erythromycin, clarithromycin, roxithromycin).

Hearing impairment is a rare AR occurring in some patients taking macrolides. According to the Cochrane review, hearing loss was slightly more common in patients taking the most common ABDs in this group (OR=1.30; 95% CI: 1.00 to 1.70) compared to placebo [142]. The association between macrolides and hearing impairment is also supported by the results of a systematic review and meta-analysis from 2024 (13 studies included, 1 142 021 patients, 267 546 of whom received macrolides, 875 089 were controls), which demonstrated a pooled OR of 1.25 (95% CI: 1.07 to 1.47) [145]. A similar OR of hearing impairment, 1.25 (95% CI: 1.07 to 1.46), was also found in the results of the analysis carried out as a part of the population-based Rotterdam Study (started in Rotterdam, the Netherlands, in 1989, a cross-sectional analysis – 4 286 patients, a longitudinal analysis – 636) [146].

Negative effects of macrolides on the heart have been a matter of debate for a long time. The Cochrane review found no evidence of a significant increase in the risk of cardiac pathology associated with macrolides (OR=0.87; 95% CI: 0.54 to 1.40) compared to placebo [142]. A meta-analysis of 80 studies involving almost 40 million patients demonstrates different results. Compared to the group of patients who had not taken macrolides, those who had used them had a significant risk of ventricular arrhythmia or a sudden cardiac death: for azithromycin the hazard ratio, OR, was – 1.53 (95% CI: 1.19 to 1.97), for clarithromycin – 1.52 (95% CI: 1.07 to 2.16). The authors [147] also found an association between an azithromycin intake and a higher risk of a cardiovascular death (OR=1.63; 95% CI: 1.17 to 2.27) and an increased risk of myocardial infarction (OR=1.08; 95% CI: 1.02 to 1.15).

It is assumed that the basis of macrolides cardiotoxicity is the ability of some of them to prolong the QT interval and cause ventricular tachycardia of a pirouette type (Torsades de pointes, TdP). This fact is associated with the third phase prolongation of the action potential, a disruption of depolarization and repolarization processes. In turn, these processes are a consequence of blocking special potassium channels

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in the membrane of cardiomyocytes (blockade of a potassium current of a delayed rectification – I(Kg)) [148]. It is known that the severity of I(Kr) blockade under the action of macrolides is presented as follows: clarithromycin≈roxythromycin>erythromycin [147, 149]. The level of evidence regarding the risk of TdP for clarithromycin and erythromycin is B, for roxithromycin it is C [148]. Similar mechanisms of cardiotoxicity have also fluoroquinolones, the ABDs group, the representatives of which are often used as an alternative to macrolides.

Azithromycin has long been considered one of the safest macrolides, but a population-based analysis found a significant association between its use and an increased risk of death from a cardiovascular disease [147]. An increase not only in the risk of myocardial infarction, but also in ventricular arrhythmias and a sudden cardiac death was noted. The cardiotoxicity of azithromycin is based on slightly different mechanisms that distinguish it from clarithromycin, roxithromycin, erythromycin and fluoroquinolones. High concentrations of this macrolide have been found to cause an increased heart rate and acute shortening of the QT interval. At the subcellular level, a change in the activity of lysosomes was observed; it was accompanied by an excessive formation of autophagosomes, leading to the formation of vacuoles, damage to sarcomeres, and cardiomyocyte death [150].

In the studies reviewed above that evaluated the profile of the ARs characteristic of macrolide ABDs, the most common drugs were azithromycin, clarithromycin, roxithromycin, and erythromycin. There are no meta-analyses on spiramycin, which is due to its rare use in modern practice. Nevertheless, in the light of a potential influence on the cardiovascular system, the results of a spiramycin long-term use in a patient with acute myocarditis, indicating its safety and absence of cardiotoxic properties, are interesting [131]. The data on the wide use of spiramycin in pregnant women, which revealed no cases of cardiac disorders in newborns, are also indicative [151]. In general, the evidence analysis of a spiramycin safety use in humans indicates its favorable profile, the absence of influence on the GI motility, hepatotoxicity and cardiotoxicity [152].

CONCLUSION

Macrolide ABDs have lost their leading position in recent years and are now alternative drugs in the treatment of community-acquired infections. It is interesting to note that for this group, an *in vitro* efficacy is not always identical to an *in vivo* efficacy. A vivid illustration of this thesis is spiramycin; its MIC against many pathogens is quite high, but, nevertheless, due to additional pleiotropic effects, the results of its clinical use may exceed those of many traditional macrolides. These effects include, first of all, anti-inflammatory and immunomodulatory ones, which allow spiramycin to effectively eliminate the symptoms of infectious diseases against the background of the improvement of tissues condition of various organs damaged as a result of the disease. The properties of spiramycin considered in the present literature review explain its greater effectiveness in *in vivo* studies compared to those conducted *in vitro* and make it possible to consider this ABD an effective tool for the antibiotic therapy of community-acquired infections. If josamycin cannot be used, a 16-membered macrolide such as spiramycin may be an alternative when choosing an ABD.[3]

[3] The specialist reported on the successful import substitution of the Japanese antibiotic. Bulletin of Pharmacy. Available from: https://pharmvestnik.ru/content/news/Specialist-zayavil-ob-uspeshnom-importozameshenii-yaponskogo-antibiotika.html. Russian).The appearance of a new drug “Doramycin VM” 3 000 000 IU on the Russian pharmaceutical market makes it possible to add to the arsenal of doctors a macrolide with pleiotropic favorable effects and a low ABR level, which favorably distinguishes it from the traditional representatives of this group.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS’ CONTRIBUTION

Olga I. Butranova – search and analysis of literature sources, systematization of information, writing and editing the text of the manuscript; Sergey K. Zyryanov – search and analysis of literature sources, editing the text of the manuscript; Anna A. Abramova – search and analysis of literature sources, writing and editing the text of the manuscript. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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AUTHORS

Olga I. Butranova – Candidate of Sciences (Medicine), Associated Professor of the Department of General and Clinical Pharmacology of the Medical Institute of Peoples' Friendship University of Russia named after Patrice Lumumba. ORCID ID: 0000-0001-7729-2169. E-mail: butranova-oi@rudn.ru;

Sergey K. Zyryanov – Doctor of Sciences (Medicine), professor, the Head of the Department of General and Clinical Pharmacology of the Medical Institute of Peoples' Friendship University of Russia named after Patrice Lumumba; deputy Chief Medical Officer of Municipal Clinical Hospital No. 24 of the Moscow City Health Department. ORCID ID: 0000-0002-6348-6867. E-mail: zyryanov_sk@rudn.university.

Anna A. Abramova – postgraduate student of the Department of General and Clinical Pharmacology of the Medical Institute of Peoples' Friendship University of Russia named after Patrice Lumumba. ORCID ID: 0009-0003-5739-4610. E-mail: abramova-aa@rudn.ru