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Synthesis and structure of new modified derivatives based on the quinine molecule and their biological activity

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The relevance of the subject matter is conditioned by the constantly growing need to meet human needs in the field of medicine, in particular, the search, study, and further introduction of new types of medicines into practical use. The purpose of this study is to investigate the synthesis of modified quinine alkaloid derivatives, and their structure, to identify the properties and biological activity of antimalarial drugs based on quinine molecules, and to structure the general data of these substances. The leading approach is the analysis of the synthesis of quinine derivatives, their chemical and physical properties, and their ability to exert a medicinal effect. The abstracting method allows structuring alkaloid derivatives and establishing a general relationship between the structural configuration of molecules and their impact on human health in a number of related derivatives. The study identifies the main antimalarial drugs based on quinine molecules, including a comparative analysis of their effectiveness and overall biological activity.

Keywords: Quinine derivatives; antimalarial drug; chloroquine; hydroxychloroquine.

INTRODUCTION

In the 21st century, medicine is facing new and increasingly complex challenges. This is conditioned by the fact that the pathogens of certain diseases inevitably multiply and adapt to new conditions, and new, mutating types of studied viruses and microbes are spreading. This confronts a person with the problem of finding new medicines. Pharmaceutical chemistry regularly solves the issues of identifying modern and effective substances that can meet the needs of humanity. Back in 1820, the French chemists P. J. Pelletier and J. B. Caventou derived the active quinine substance from the bark of a specific cinchona tree, whose habitat was the New World[1]. Quinine belongs to the group of nitrogen-containing organic compounds of the natural origin of alkaloids[2], and has a bitter taste[3]. Quinine was used by the indigenous population of America as an antipyretic, but due to its study, the world learned the main antimalarial agent[4], which until recently was actively used in the pharmaceutical production of medicines. Quinine is also useful for some muscle diseases, especially for night leg cramps and congenital myotonia. Due to its direct effect on muscle membranes and sodium channels, quinine has long been used as a remedy for muscle diseases. But despite its effectiveness in the medical field, in particular in the fight against malaria pathogens plasmodia[5–7], quinine has several significant disadvantages. Their striking example is the side effects of quinine, such as vomiting, nausea, tinnitus, dizziness, and disorientation in space. If the body is predisposed, quinine can cause cardiovascular disorders, such as heart failure[8–11]. A dose of quinine of ten grammes can provoke a fatal outcome. Due to the frequent adverse effects of treatment of malaria with quinine, modified quinine-based derivatives have been developed, which are also antimalarial drugs, but have greater effectiveness and a lower probability of negative side effects.

After identifying the shortcomings of the first antimalarial agent, researchers began to synthesise and study new substances that can have an antimalarial effect. Currently, derivatives of substances based on quinine molecules, such as chloroquine, hydroxychloroquine, are gaining increasing popularity in use[12, 13]. Such drugs are the safest and most effective. Quinine sulphate and quinine-based esters, which are also derivatives of the progenitor of malaria drugs, are used less often. Despite this, all of these derivatives are currently used in various fields, having differences in biological activity and effects on the human body[14]. At the moment, the problem of finding new types of medicines is more urgent than ever. This is conditioned by the current epidemiological situation. The SARS-CoV-2 virus, formerly 2019-nCoV, is a single-stranded RNA virus belonging to the genus Betacoronavirus. It belongs to the subgenus Sarbecovirus. SARS-CoV-2 was first detected in December 2019, causing the dangerous infectious disease COVID-19[15]. Studies of this virus, its structure and methods of involvement occur every day, but science cannot yet provide an effective drug against a novel coronavirus infection. Nevertheless, several countries suggest a positive impact of antimalarial drugs in combination with antibiotics in the treatment of COVID-19[16]. The effects of chloroquine, hydroxychloroquine, and other antimalarial drugs have neither positive nor negative evidence[17–19], but, in the absence of scientifically proven active substances for the treatment of coronavirus infection, these drugs are practised on a daily basis.

The purpose of this study is to investigate the synthesis of modified quinine alkaloid derivatives, and their structure, to identify the properties and biological activity of antimalarial drugs based on quinine molecules, and to structure the general data of these substances.

MATERIALS AND METHODS

In the course of the study, the following methods were used: theoretical (analysis; synthesis; abstraction, deduction); empirical (study of the experience of existing studies, comparison), static (selective method); methods of graphic representation. The study was conducted based on existing experience, selecting the necessary

data, structuring the information received, analysing it, and synthesising subsequent conclusions. The study of the structure and synthesis of newly modified derivatives based on quinine molecules, and their biological activity, was carried out in five stages:

1. At the first stage, the initial quinine substance was considered; information was collected about its origin, and initially known properties, the first studies that led to the first-ever synthetic production of quinine in the laboratory. Descriptions of the class of alkaloids were given. The properties and structure of the initial quinine molecule were also revealed, its biological activity was analysed, and its ability to influence the physiology of a living organism with positive and negative consequences. The obtained data were structured using the deduction method as characteristic properties of a class of alkaloids, which include quinine and its derivatives.

2. At the second stage of the study, quinine derivatives were determined. The main feature of alkaloids was established – the alkaloid core. Four substances that are modified derivatives of the quinine molecule were selected by a selective method: quinine sulphate, quinine dihydrochloride, chloroquine, and hydroxychloroquine. Subsequently, an analysis of each derivative was performed. Their structures, methods of synthesis, properties and biological activities of these molecules, the effect on the body from the standpoint of medicines, and general chemical and physical properties were revealed.

3. At the third stage of the study, the similarities and differences of derivatives based on quinine molecules were established by the comparison method. By the method of abstraction, the properties important for medical use were revealed. Based on the results of a comparative analysis of some quinine derivatives selected by the sample, the best derivatives were identified from the standpoint of practical application in medicine with the best medicinal effect in comparison with their listed analogues.

4. At the fourth stage, the general medicinal properties of quinine derivatives and their role in pharmaceutical medicine today were synthesised. The results of the conducted studies on the effect of hydroxychloroquine on COVID-19 and the general potential of using hydroxychloroquine as an antiviral agent in coronaviruses are studied in detail.

5. At the fifth stage of the study of the structure and synthesis, and the biological activity of new modified derivatives based on the quinine molecule, all the properties of quinine derivatives, in particular hydroxychloroquine, were summed up. Comparing the properties and effect of the original quinine molecule and the same parameters of modern quinine-based derivatives, it was concluded that the discovery of new derivatives with better properties is effective.

RESULTS

Characteristics and properties of quinine

Quinine is a natural white crystalline alkaloid with antipyretic, antimalarial properties, analgesic and anti-inflammatory effects, and a bitter taste[20]. It is a stereoisomer of quinidine. The chemical formula of quinine is $C_{20}H_{24}N_2O_2$. The structural formula of quinine is shown in Figure 1.

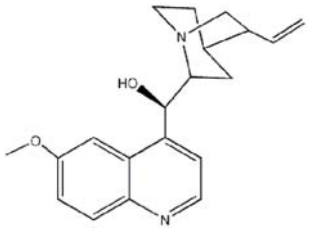


Figure 1. The structural formula of the quinine molecule

The name quinine comes from the original Quechua word of Native American origin, meaning the bark of the cinchona tree, "Quina" or "Quina-Quina", which roughly means "bark of the bark" or "sacred bark". Until 1820, the bark was first dried, ground to a fine powder, and then mixed with a liquid (usually wine) before use[21]. The widespread use of quinine as a preventive agent began around 1850, although Europeans have used it in an unextacted form since the beginning of the 17th century. For the first time, quinine was used to treat malaria in Rome in 1631. Cinchona trees remain the only natural source of quinine. Under the pressure of wartime, research was undertaken on its artificial production. The formal chemical synthesis was carried out in 1944 by American chemists R. Woodward and W. Doering[22], presented below (Figure 2). Since then, several effective complete syntheses of quinine have been designed, but none of them can compete from an economic standpoint with the isolation of an alkaloid from a natural source.

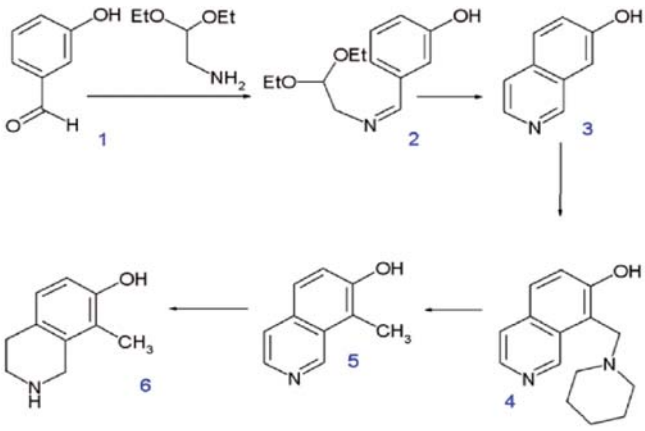


Figure 2. General synthesis of quinine according to Woodward-Doering

Quinine is a toxic substance for the malaria parasite plasmodium. It interferes with the parasite's ability to break down and digest hemoglobin, which results in its destruction[20]. Quinine, which is essentially an alkaloid, has several properties characteristic of this group of substances. Such properties include heterocyclicity, the presence of an alkaloid core, weak basicity properties, a pronounced bitter taste, and a pronounced effect on physiological processes, for example, depression or excitation of the nervous system (depending on the specific substance).

Features of the use of quinine sulfate

Quinine sulphate is known as an antimalarial drug indicated for the treatment of uncomplicated malaria caused by Plasmodium falciparum species. The substance

is crystals without colour and smell, it can be in the form of a powder. It has a bitter taste. In medicine, it is used in solid pill form. In addition, like quinine, it has some side effects: dizziness, vomiting, loss of orientation, nausea and others. In some cases, individual intolerance can provoke a fatal outcome.

Quinine sulphate is an alkaloid obtained from the bark of the cinchona tree and is the active ingredient of extracts of this plant, which were used to treat malaria until 1633. Quinine sulphate has proved to be an effective cure for malaria in those geographical regions where resistance to another quinine-derived drug, chloroquine, has been officially confirmed. Quinine sulphate is a sulphate salt form of quinine isolated from the quinidine alkaloid[23]. When heating such a salt, the isomerisation process will start, and quinine sulphate will pass into the form of quinotoxin, which is a dangerous toxic substance. Quinine has many mechanisms of action, including a decrease in oxygen consumption and carbohydrate metabolism; a violation of DNA replication and transcription through DNA intercalation; a decrease in the excitability of muscle fibres due to changes in the distribution of calcium. This agent inhibits the P-glycoprotein secreting drug pump, which is overexpressed in tumours with special drug resistance, and may increase the effectiveness of some antitumour agents. The structural formula of quinine sulphate is presented in Figure 3.

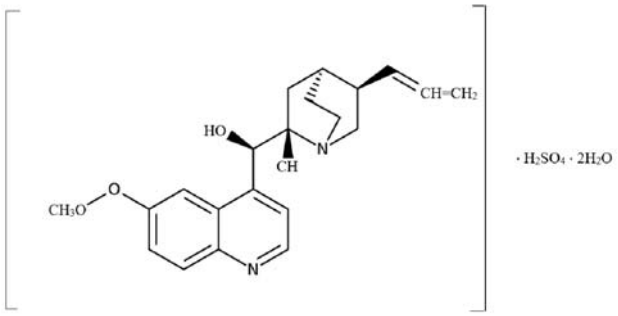


Figure 3. The structural formula of quinine sulphate

Quinine dihydrochloride is the only salt of the three quinine salts that is injected into the body in liquid form. For the treatment of tropical malaria, the solution is administered intravenously in several stages. The first stage: a dose at a concentration of 20 mg/kg in combination with a 5% glucose solution in a volume of 250 ml. Instead of glucose, it is possible to use a saline solution. It is administered by the drip method in small volumes for four hours. The second stage: a dose at a concentration of 10 ml/kg in combination with a 5% glucose solution in a volume of 250 ml. It is also allowed to replace glucose with a saline solution. The third stage: compliance with the interval between injections is at least eight hours three times a day. The fourth stage: when a stable state of the body is achieved, it is necessary to switch to the use of quinine and its antimalarial derivatives orally. This need is caused by the toxicity of all quinine compounds. With the injection method of administration of such antimalarial drugs, the risk of complications caused by side effects of drugs increases sharply. With prolonged intravenous use of quinine dihydrochloride, the body may react in the form of hemoglobinuria fever, hypoglycemia, and cardiac arrhythmia. The structural formula of quinine dihydrochloride is shown in Figure 4.

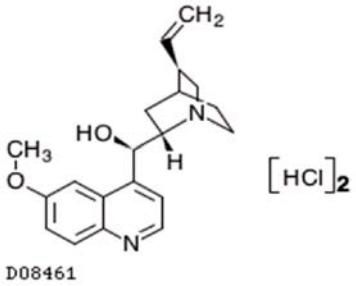


Figure 4. The structural formula of quinine dihydrochloride

Chloroquine and its advantages over other antimalarial drugs

Chloroquine is a 4-aminoquinoline with antimalarial, anti-inflammatory, and potential chemosensitising and radiosensitising effects. Although the mechanism is not completely understood, chloroquine has been shown to inhibit the parasitic enzyme heme polymerase, which converts toxic heme into non-toxic hemozoin, which leads to the accumulation of toxic heme inside the parasite. This agent can also interfere with the biosynthesis of nucleic acids. The potential chemosensitising and radiosensitising activity of chloroquine in cancer may be associated with its inhibition of autophagy, a cellular mechanism involving lysosomal degradation that minimises the production of reactive oxygen species associated with tumour reoxygenation and exposure to chemotherapeutic agents and radiation on the tumour. The structural formula of chloroquine is shown in Figure 5.

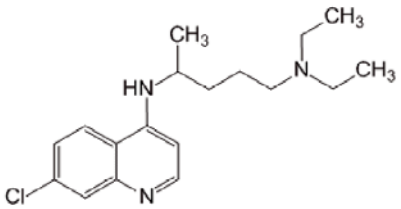


Figure 5. The structural formula of chloroquine

Chloroquine was first introduced in the 1940s and quickly became the drug of choice for the treatment of malaria. Chloroquine has several advantages over other antimalarial drugs: its low cost makes it accessible to everyone; its low toxicity meant that it was safe for children and pregnant women, the most vulnerable victims of malaria; and its high effectiveness meant that the treatment regimen was simple and easy to use.

The specificity of the structural formula of hydroxychloroquine

Hydroxychloroquine, like chloroquine, is also used to treat acute forms of malaria caused by such types of parasites as *Plasmodium vivax*, *Plasmodium malariae, Plasmodium ovale*[17], and sensitive forms of *Plasmodium falciparum*. It is also effective and safe, like chloroquine, and in the course of treatment is less likely to cause undesirable side effects. The structural formula of hydroxychloroquine is identical to the structure of chloroquine, except for the replacement of one hydrogen atom from the radical group with a hydroxyl group[24]. This formula is shown in Figure 6.

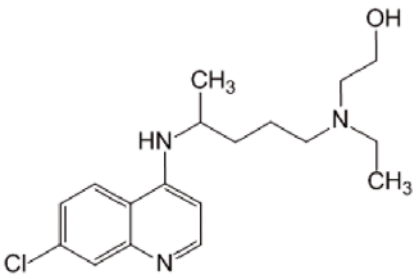


Figure 6. The structural formula of hydroxychloroquine

Hydroxychloroquine, designated in the systematic nomenclature as 7-chloro-4-[4-[ethyl (2-hydroxyethyl) amino]-1-methylbutylamino] quinoline (37.1.1.19), is obtained similarly to chloroquine. The interaction of 1-chloro-4-pentanone with 2-ethylaminoethanol gives the corresponding aminoketone (37.1.1.17), which undergoes reductive amination under certain conditions. As a result of this transformation, a substance with the formula 4- [ethyl (2-hydroxyethyl) amino] -1-methylbutylamine (37.1.1.18) is formed. Its further interaction with 4.7-dichloroquinoline (37.1.1.1) leads to the production of hydroxychloroquine. The scheme of the listed chemical transformations is shown in Figure 7.

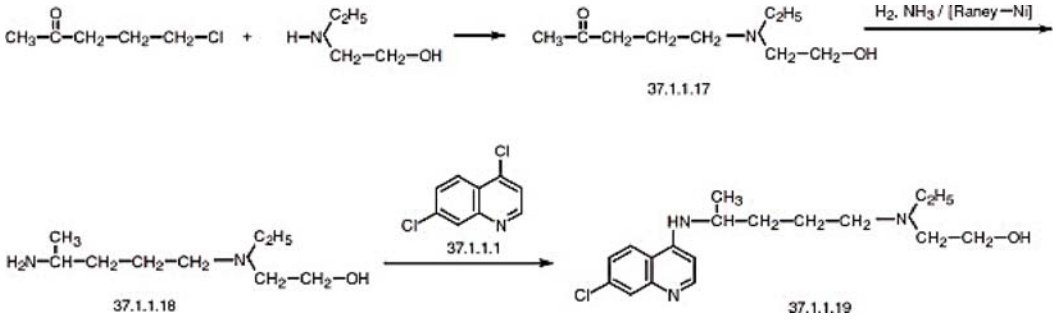


Figure 7. Scheme of production (synthesis) of hydroxychloroquine

DISCUSSION

As a result of the analysis of the collected data, the structural properties of the following modified derivatives based on quinine molecules were revealed: quinine sulphate, quinine dihydrochloride, hydroxychloroquine, chloroquine, and the starting substance of quinine itself. Based on all of the above, using the comparison method, it is possible to judge the relative effectiveness of the listed substances. The fundamental characteristics that affect the overall relative effectiveness of quinine sulphate, quinine dihydrochloride, hydroxychloroquine, and chloroquine are the following parameters: treatment methods, what types of plasmodium are used, the presence and strength of side effects[13]. Quinine sulphate is toxic to Plasmodium falciparum species, spread by Anopheles mosquitos, which are widespread on all continents, except Antarctica. Malaria caused by these parasites is called tropical and is known as the most dangerous form of malaria, leading to the largest percentage of deaths among those who become ill of all types of malarial diseases. Quinine sulphate, also known as sulphurous quinine, belongs to the pharmacological group of antimicrobial and antiparasitic drugs, drugs for the treatment of protozoal infections, and antimalarial drugs.

From the standpoint of the quality of treatment, quinine sulphate gives the following results: it is prescribed orally for both adults (in a daily dosage of 1.0 to 1.0 g) and children (in smaller dosages, depending on the age of the child, but not more than 1 g per day). The course of treatment is from five to seven days. With more severe forms of the disease, injections into the subcutaneous fat are possible on the first day of the disease and after 68 hours. In an extremely neglected form of malaria, intravenous injections are used, but with such methods of treatment, there is a high risk of tissue necrosis. Side effects of treatment with quinine sulphate are manifested in the same way as when using pure quinine: dizziness, tinnitus, and loss of orientation. Less often – urticaria, uterine bleeding, hemoglobinuric fever. Quinine dihydrochloride, unlike quinine sulphate and pure quinine, is used not only as an antimalarial agent. Today, this substance is used in obstetrics and oncology, is used in cardiology, and has the necessary properties as an antipyretic for pneumonia[11]. There is a well-known practice of using quinine dihydrochloride as a medicine for whooping cough, as well as neuralgia.

Because quinine and all its derivatives have the possibility of severe side effects and high toxicity, in many practices, treatment with these drugs is adjusted manually by an individual attending physician, depending on the patient's condition and physiology[3]. Nevertheless, the use of quinine dihydrochloride is in demand in many countries today. Chloroquine belongs to the group of other synthetic antibacterial agents and the group of antidepressants. Chloroquine is used to treat malaria caused by *Plasmodium vivax* Plasmodium and *Plasmodium malariae*. In addition to the prevention and treatment of malaria, it is used as a medicine for extra-intestinal amoebiasis, chronic and subacute forms of lupus erythematosus and rheumatoid arthritis. Side effects are similar to the effects of quinine treatment, but add the likelihood of allergic reactions (dermatitis, photosensitisation), myocardial damage, leukopenia[8]. Chloroquine is much more widespread on the drug market than quinine and quinine sulphate, so the instructions for this substance recommend regular oculist examinations and monitoring of the cellular composition of the blood during treatment. Hydroxychloroquine is used as a medicinal antimalarial agent against *Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae*, including sensitive strains of *Plasmodium falciparum*. These drugs have a larger range of antimalarial prescriptions, which makes them a more universal drug. The drug also has an anti-inflammatory

and immunosuppressive effect in chronic discoid or systemic lupus erythematosus, acute and chronic rheumatoid arthritis[25]. Side effects of treatment can provoke headache, tinnitus, convulsions, affective lability, anorexia, nervousness, psychosis, blurred vision, abdominal pain, nausea, vomiting, diarrhoea, arrhythmia, itching, rash. There is a large list of contraindications.

Chloroquine and hydroxychloroquine have similar pharmacokinetics. Both drugs are absorbed quickly and in an effective large volume from the intestine, the peak concentrations of both drugs in the blood serum are reached within no more than two hours[19]. From the standpoint of interaction with proteins, chloroquine shows a higher result in comparison with hydroxychloroquine: the binding to plasma proteins of chloroquine is approximately 55%, while hydroxychloroquine has from 30% to 40% of the same indicator, while the variability of binding of specific enantiomer proteins is taken into account. Both drugs have very large volumes of distribution; 116–285 kilograms per litre for chloroquine and 596–614 kilograms per litre for hydroxychloroquine. Chloroquine has a higher detectability index compared to hydroxychloroquine: the concentration of chloroquine can reach volumes five hundred times higher than the volumes of hydroxychloroquine in the liver, spleen, kidneys, lungs and leukocytes. The main pathway of chloroquine metabolism is deethylation with the formation of desethyl chloroquine. Hydroxychloroquine, in turn, undergoes N-dealkylation from the tertiary amine together with oxidative deamination from the primary amines. As a result of these processes, the probability of liver diseases as a result of treatment with these drugs is significantly reduced. Almost 50% of chloroquine and 25% of hydroxychloroquine are excreted unchanged in the urine, and the metabolites are also excreted by the kidneys. The final half-life of chloroquine varies from 12 to 60 days, and the half-life of hydroxychloroquine varies from 32 to 50 days. These indicators were observed in people who do not suffer from diseases that increase the risk of negative side effects.

In 2019, an epidemic of a new coronavirus infection that causes the disease COVID-19 began. Subsequently, the situation turned into a pandemic caused by a new strain of coronavirus, which is called the SARS-CoV-2 severe acute respiratory syndrome coronavirus. Previously, this disease was called “novel coronavirus 2019” or “2019-nCoV”[26]. The name SARS-CoV-2 was chosen because the virus is genetically related to the coronavirus that caused the SARS outbreak in 2003. Despite many similar aspects, viruses are fundamentally different from each other both in terms of the mechanism and in terms of the approach to treatment. The spread of SARS-CoV-2 began in Wuhan, a Chinese province, by the end of December 2019. As of February 17, 2020, the COVID-19 pandemic has spread around the world and infected more than 109,217,366 million people worldwide. The approximate number of deaths from the infection is more than 2,413,912 people. In 2020, active development of COVID-19 treatment methods began. In search of potential pharmacological agents that can reduce the percentage of infection, that is, work for preventive purposes, as well as treat patients with existing COVID-19, scientists have proposed introducing antimalarial drugs such as chloroquine and hydroxychloroquine into the treatment regimen. The reason for choosing this scheme in the first months of the pandemic was its practical application for the treatment of SARS-CoV-1, and experiments conducted in China, which showed that these agents can inhibit the replication of the virus. Despite the previous successful experience of implementing such a treatment regimen and experiments, opinions about the practical effectiveness of the use of chloroquine and hydroxychloroquine were divided into positive and negative. The latter was caused by the sharp side effects of these antimalarial drugs.

Coronaviruses have a spherical shape with an average diameter of 80–120 nanometres and have many club-shaped spikes of glycoproteins protruding from the surface of the viral envelope. The viral particle contains five main structural proteins, which are glycoprotein spikes, a shell protein, a matrix protein and a nucleocapsid protein. Glycoprotein spikes are necessary for the virus to attach to various receptors of the host cell, depending on the receptor-binding domain. When attached to the host cell receptor, the glycoprotein enhances the cleavage of the envelope protein. Studies have shown that antimalarial drugs, namely chloroquine and hydroxychloroquine, can affect the binding of gangliosides on the body cell and sialic acid, which prevents the virus from fixing to the host cell receptor and, as a result, prevents the virus from spreading in the body[27]. Studies of the effect of these drugs on SARS-CoV-2 have contradictory results. Researchers from France[16] conducted a study with a sample of 36 patients who were diagnosed with SARS-CoV-2. Sixteen patients underwent the usual symptomatic treatment, preventing the development of bacterial complications with antibiotics, and twenty others were prescribed an experimental course that included 200 mg of hydroxychloroquine three times a day (orally), as well as six patients – 500 mg of azithromycin (to prevent pneumonia) on the first day, and then 250 mg for four days. Figure 8 shows the data on the effect of hydroxychloroquine in patients with a positive test for SARS-CoV-2.

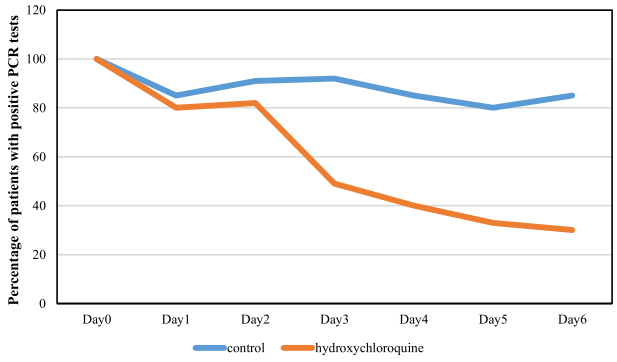


Figure 8. The effect of hydroxychloroquine in patients with a positive test for SARS CoV-2

As can be seen from the graph[28], on the third day of treatment with COVID-19 hydroxychloroquine, the percentage of patients with positive tests drops sharply, which may indicate the successful effect of the drug on the spread of the virus. On the fourth day, the number of cases decreased by another 10%, and by the end of

the experiment, the incidence rate decreased to 30%. From this experiment, it follows that antimalarial drugs really work as antiviral drugs in the case of coronavirus infection. However, many researchers are opposed to such a treatment regimen for COVID-19, and even make claims that antimalarial drugs not only do not have an effective effect, but are also harmful to the body[29]. The World Health Organisation (2021) does not recommend hydroxychloroquine for the treatment of COVID-19[30]. This recommendation is based on 30 studies involving more than 10.000 patients with this disease. As a result of the study, it was recorded that hydroxychloroquine did not reduce mortality, the need, or the duration of artificial lung ventilation. Taking hydroxychloroquine for the treatment of COVID-19 can increase the risk of heart rhythm problems, blood and lymph diseases, kidney damage, liver problems, and cause kidney failure[30].

Currently, the practical treatment of COVID-19 with antimalarial drugs is no longer relevant. More and more studies show that the positive dynamics of treatment with such a scheme are less than negative ones, and there are also high risks of worsening the condition of patients with coronavirus due to the side effects of hydroxychloroquine. However, scientists still agree that hydroxychloroquine is the best drug developed against malaria and lupus erythematosus, since other drugs are equal or superior in effectiveness to hydroxychloroquine and have not yet been synthesised. This is conditioned by the special structure of its molecule, the properties of the alkaloid core, the studied synthesis and the established system for its production. Studying in the field of modified derivatives based on the quinine molecule, such as hydroxychloroquine, can lead to the discovery of new, more practical drugs.

CONCLUSIONS

As a result of studying the structure and synthesis of modified derivatives based on quinine molecules, several common properties were revealed that combine these derivatives into a class of antimalarial drugs. The mechanisms of influence on the body of such substances as quinine sulphate, quinine dihydrochloride, chloroquine, and hydroxychloroquine were identified. Their biological activity has been established, medicinal properties and mechanisms of action, side effects of treatment, and situations requiring the use of specific drugs have been identified. The effectiveness of the use of hydroxychloroquine for the treatment of COVID-19 was investigated, the mechanism of infection with the SARS-CoV-2 virus was studied, and the effect of derivatives based on the quinine molecule on this virus was considered based on the research conducted in laboratories of various countries. Considering all of the above, it can be concluded that the most practical drug to use from many alkaloid derivatives based on a quinine molecule with a pronounced alkaloid core inherent in this class is hydroxychloroquine. Hydroxychloroquine is medically indicated for such diseases (malaria, lupus erythematosus), which have a limited number of studied and effective drugs for treatment. This makes hydroxychloroquine a particularly indispensable drug.

This study is of practical relevance to students of medicine, biology and biochemistry. The material of the study involves further pharmacological, biological, chemical and medical research on these substances, as well as studies on the effectiveness of antimalarials as antiviral agents. These studies would help in the search for the latest modified derivatives based on the quinine molecule, which would combine the best properties of their predecessors, but without such negative properties as sharp side effects that worsen the condition of patients.

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