EXPERIMENTAL AND CLINICAL EVALUATION OF MEFLOQUINE EFFECTIVENESS AGAINST THE INFECTION CAUSED BY SARS-COV-2

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The efficacy of mefloquine has not been studied in the *in vivo* experiments and clinical trials involving COVID-19 patients. The study was aimed to assess the effects of mefloquine on the SARS-CoV-2 accumulation in the lungs of infected animals and to study the efficacy and safety of mefloquine compared to hydroxychloroquine in patients with COVID-19. During the experiment, a total of 96 Syrian hamsters were infected with SARS-CoV-2. Accumulation of the virus in lungs was compared in the groups of animals treated with mefloquine and ribavirin and in the control group. During the clinical trial, the mefloquine and hydroxychloroquine safety and efficacy in patients with mild and moderate COVID-19 (172 individuals) was assessed based on the symptom changes over time and the computed tomography results. The experiment showed that the SARS-CoV-2 accumulation in the lungs of Syrian hamsters 6 days after infection and mefloquine treatment was 2.2 ± 0.18 lg PFU/g, which was lower ($p < 0.05$) than in the control group (3.5 ± 0.21 lg PFU/g) and ribavirin group (5.2 ± 0.05 lg PFU/g). During the clinical trial, it was found that 50.0% of patients in the mefloquine group and 32.4% in the hydroxychloroquine group ($p < 0.05$) developed a mild disease, and the completely resolved respiratory failure was registered in 76.5% and 44.6%, respectively ($p < 0.001$). Adverse events were observed in 86.7 % and 77% of patients in the mefloquine and hydroxychloroquine groups, respectively ($p > 0.05$). Thus, during the experiment, mefloquine contributed to the faster virus titer reduction in the lungs. During the clinical trial, the mefloquine efficacy was non-inferiority or, based on a number of indicators, higher compared to hydroxychloroquine, with comparable safety.

Keywords: hydroxychloroquine, SARS-CoV-2, mefloquine, antiviral activity, COVID-19

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Compliance with ethical standards: animal experiments were approved by the Bioethics Commission of RMC “Home of Pharmacy» (protocol № 3.71/20 dated December 23, 2020); all the procedures involving animals were performed in accordance with the Directive N 2010/63/EC of the European Parliament and of the Council of the European Union "On the Protection of Animals Used for Scientific Purposes" of September 22, 2010. The animals' housing and care complied with GOST R 53434-2009 (Principles of Good Laboratory Practice) and the Guidelines for Laboratory Animals (2010). The clinical trial was approved by the Ethics Commitees of the clinical centers of Burnasyan Federal Medical Biophysical Center of FMBA, Federal Clinical Center for High Medical Technologies of FMBA, Center for Specialized Medical Assistance and Medical Technologies of FMBA, National Medical Research Center for Otorhinolaryngology of FMBA; the trial was carried out in accordance with the Russian Federation Government Decree № 441 of April 3, 2020; the informed consent was obtained from all patients.

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ОЦЕНКА ЭФФЕКТИВНОСТИ МЕФЛОХИНА В ОТНОШЕНИИ ИНФЕКЦИИ, ВЫЗВАННОЙ SARS-COV-2 В КЛИНИЧЕСКИХ И ЭКСПЕРИМЕНТАЛЬНЫХ УСЛОВИЯХ

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Эффективность мефлохина в экспериментах *in vivo* и клинических исследованиях у пациентов с COVID-19 не установлена. Целью исследования было оценить влияние мефлохина на накопление SARS-CoV-2 в легких инфицированных животных и изучить эффективность и безопасность мефлохина в сравнении с гидроксихлорохином при лечении пациентов с COVID-19. В ходе эксперимента 96 сирийских хомяков инфицировали SARS-CoV-2. Оценивали накопление вируса в легких в группах животных, которым вводили мефлохин, препарат сравнения рибавирин и контроля. В ходе клинического исследования безопасность и эффективность мефлохина и гидроксихлорохина в лечении пациентов с COVID-19 с легким и средне-тяжелым течением заболевания (172 участника) оценивали по динамике симптомов и результатам компьютерной томографии. В результате эксперимента накопление SARS-CoV-2 в легких сирийских хомяков через 6 суток после заражения и лечения мефлохином составило 2,2 ± 0,18 lg БОЕ/г, что было ниже ($p < 0,05$), чем в группе контроля (3,5 ± 0,21 lg БОЕ/г) и в группе рибавирина (5,2 ± 0,05 lg БОЕ/г). В результате клинического исследования 50,0% пациентов в группе мефлохина и 32,4% в группе гидроксихлорохина ($p < 0,05$) достигли легкой степени тяжести заболевания, у 76,5% и 44,6% соответственно зарегистрировали полное разрешение дыхательной недостаточности ($p < 0,001$). Нежелательные явления наблюдались у 86,7 и у 77% пациентов в группах мефлохина и гидроксихлорохина соответственно ($p > 0,05$). Таким образом, мефлохин в эксперименте способствовал более быстрому снижению титра вируса в легких, а в ходе клинических исследований эффективность мефлохина была не хуже, а по некоторым показателям лучше, чем у гидроксихлорохина, при сравнимой безопасности.

Ключевые слова: гидроксихлорохин, SARS-CoV-2, мефлохин, противовирусная активность, COVID-19

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Соблюдение этических стандартов: экспериментальное исследование на лабораторных животных одобрено Комиссией по биоэтике АО НПО «Дом Фармации» (протокол № 3.71/20 от 23 декабря 2020 г.); все процедуры с животными проводили в соответствии с Директивой № 2010/63/ЕС Европейского парламента и Совета Европейского Союза «О защите животных, использующихся для научных целей» от 22.09.2010. Содержание и обслуживание животных осуществляли в соответствии с ГОСТ Р 53434-2009 (Принципы надлежащей лабораторной практики) и «Руководством по лабораторным животным» (2010). Клиническое исследование одобрено этическими комитетами клинических центров ФГБУ ГНЦ ФМБЦ им. А. И. Бурназяна ФМБА России, ФГБУ ФКЦ ВМТ ФМБА России, ФГБУ ФНКЦ СВМП МТ ФМБА России, ФГБУ НМИЦО ФМБА России; проведено в соответствии с Постановлением Правительства Российской Федерации от 03.04.2020 № 441; все пациенты подписали информированное согласие.

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Quinoline derivatives, hydroxychloroquine and chloroquine, are the antimalarials that have proven effective in treatment of infections, caused by coronaviruses [1]. The drugs have a similar chemical structure and pharmacological activity, however, hydroxychloroquine is less toxic [2]. It has been shown that EC_{50} of hydroxychloroquine against SARS-CoV-2 in vitro in case of adding the drug 1 h before infection is 4.51–12.96 μM, and the cytotoxic dose is 100 times higher [2]. In case of adding hydroxychloroquine to the culture medium 2 h after infection with SARS-CoV-2, EC_{50} is 0.72–6.14 μM [3]. The above mentioned concentrations can be achieved *in vivo* after receiving the 400 mg therapeutic dose of the drug, given that the drug levels in lungs are 6 times higher than plasma levels.

Mefloquine is one more antimalarial that have proven effective against SARS-CoV-2 *in vitro* [4, 5]. The activity of mefloquine against causative agents of a number of dangerous viral infections [6, 7], including coronaviruses [8–10], has been established. It has been shown that mefloquine inhibits cytopathic effects of the coronavirus in cell culture and prevents the virus from replication at a concentration not exceeding 10 μM (4 μg/L) [9]. Clarification of the dosing ranges has established that in vitro suppression of SARS-CoV-2 replication is achieved by adding mefloquine to the Vero C1008 cell culture at a concentration exceeding 1.25 μM (0.5 μg/mL). Furthermore, the concentration of mefloquine sufficient for SARS-CoV-2 elimination could be achieved 2–3 days after starting taking the drug at a dose equivalent to therapeutic dose [5, 10, 11].

Based on the positive results obtained in experimental studies and clinical trials [12, 13], hydroxychloroquine was included in the treatment regimen for patients with COVID-19 in many countries of the world, including Russia [14]. Antiviral activity of mefloquine against SARS-CoV-2, revealed during the experiment, contributed to mefloquine inclusion in the guidelines for treatment of patients with COVID-19, issued by the Ministry of Health of the Russian Federation in 2020 [14].

Regardless of the fact, that mefloquine has been approved as a treatment for patients with COVID-19, to date, no *in vivo* experimental studies of mefloquine effects on the course of the disease, as well as clinical trials of mefloquine efficacy against the novel coronavirus infection, have been carried out. This has defined the relevance of the study.

The study was aimed to assess the effects of mefloquine on the SARS-CoV-2 accumulation in the lungs of infected animals and to study the efficacy and safety of mefloquine compared to hydroxychloroquine in patients with COVID-19.

METHODS

Experimental procedure

The study involved male Syrian hamsters with body weight of 50–70 g (RMC "Home of Pharmacy»; Russia). The animals were kept under standard housing conditions, with free access to water and 12 h/12 h day/night cycle. The drug was suspended in the 1% starch solution, and the animals received the oral gavage of 100 μL daily for six days according to the following scheme: days 1 and 2 — 8.8 mg/kg; days 3–6 — 3.3 mg/kg. The controls received the 1% starch solution according to the same scheme. Ribavirin (Dragon Hwa ChemPharm Co. Ltd; China), administered by the intramuscular route at a dose of 14.3 mg/kg once a day for six days, was used as a reference substance. Each group included 10 animals.

The virus used was variant B of SARS-nCoV (48th Central Research Institute, Federal State Budgetary Institution under the Ministry of Defense of the Russian Federation). The infecting preparation was prepared using the Vero C1008 cell culture; multiplicity of infection was 1 PFU (plague-forming unit) per cell. The viral activity in the reference culture was 7.4 lg PFU/mL, and the cytopathic effect (CPE) was 6.5 CPE50/mL. The animals were infected orally at a dose of 3×10^5 PFU and followed up for 7 days. Virus accumulation (lg PFU/g) in lungs was assessed in animals, receiving mefloquine, compared to the control animals and animals, receiving ribavirin, on days 1, 2, 4 and 6 after infection. In addition, inhibitory quotient and the decrease in the virus accumulation in lungs were calculated.

Clinical trial

The open-label randomized multicenter comparative study of the efficacy and safety of mefloquine and hydroxychloroquine off-label use in treatment of patients with novel coronavirus infection, caused by SARS-CoV-2, was carried out in accordance with paragraph 3 of the Decree of the Government of the Russian Federation № 441 of 03.04.2020 from April 7, 2020 to July 21, 2020.

Inclusion criteria: male and female patients over 18 years of age with mild or moderate novel coronavirus infection, confirmed by PCR test for identification of viral RNA; hospitalization of the patient; submitted informed consent to participation (a total of 172 individuals). The patients with moderate course of the disease accounted for over 95%. The recommended classification was used to define the disease severity [14].

Table 1. Results of assessing the infectious SARS-CoV-2 titre in the lungs of Syrian hamsters

Drug	Parameters	Day after infection			
		1	2	4	6
Control	Virus accumulation, lg PFU/g, M ± σ	6.0 ± 0.21	6.0 ± 0.38	6.3 ± 0.04	3.5 ± 0.21*
Mefloquine	Virus accumulation, lg PFU/g, M ± σ	6.8 ± 0.07	5.8 ± 0.07	6.2 ± 0.04	2.2 ± 0.18
	Decrease in virus accumulation, Δlg	no	0.28	0.03	1.34
	Inhibitory quotient, %	no	47.5	7.4	95.5
Ribavirin	Virus accumulation, lg PFU/g, M ± σ	6.2 ± 0.04	5.0 ± 0.06	6.4 ± 0.03	5.2 ± 0.05*
	Decrease in virus accumulation, Δlg	no	0,08	no	no
	Inhibitory quotient, %	no	17.1	no	no

Note: * — the differences from the mefloquine group are considered significant when $p < 0.05$.

Table 2. Comparative evaluation of mefloquine and hydroxychloroquine efficacy based on primary efficacy endpoints

Indicator	Number of patients having reached the point, *n* (%)		Average time for achieving the endpoint (SD), days	
	Mefloquine	Hydroxychloroquine	Mefloquine	Hydroxychloroquine
Developing mild disease	49/98* (50.0%)	24/74 (32.4%)	11,3 (6.08)	10.0 (10.34)
Resolved respiratory failure	75/98# (76.5 %)	33/74 (44.6 %)	6.5 (6.40)	4.4 (5.68)

Note: * — significant differences from the comparison group, $p < 0.05$; # — significant differences from the comparison group, $p < 0.001$.

Exclusion criteria: severe and critical COVID-19; neurological and mental disorders; history of mental disorder; seizures or low seizure threshold, epilepsy; cardiomyopathy, retinopathy; pregnancy and lactation; liver failure or exacerbation of chronic liver disease; active cancer; severe uncontrolled cardiovascular disease; other disorders and conditions that prevented the patients from the study participation.

The average age of the patients was 52.5 years, the ratio of men to women was 45/55. The patients were randomized and divided into two groups: the patients of group 1 (98 individuals) were prescribed mefloquine. and the patients of group 2 (74 individuals) were prescribed hydroxychloroquine. The drug were prescribed in accordance with the schemes, recommended by the Ministry of Health of Russian Federation [14].

The average duration of the disease prior to screening (M ± SD) was 8.4 ± 5.35 days in the mefloquine group, and 7.9 ± 4.66 in the hydroxychloroquine group. The main symptoms of the disease were as follows: body temperature exceeding 38.5 °C, nonproductive cough, fatique and chest congestion. According to computed tomography (CT), the lung involvement matched CT-2–CT-3 grade.

Both groups received the drugs for 7 days. The clinical status of the patient was registered 11 days after starting taking the drug. In case of clinical recovery, the patient was discharged from the hospital. In case of the need for longer hospital stay, the follow-up was continued.

The following indicators of clinical improvement were used as the primary efficacy endpoints: development of mild coronavirus infection, resolved respiratory failure.

Secondary efficacy endpoints: patient's condition improvement based on CT; achieved CT grade 1 or lower; resolved pneumonia; achieved grade 1 respiratory failure; being provided oxygen support.

The frequency of adverse events (AEs) and serious adverse events (SAEs) was analyzed, and the conditions, which served as basis for the studied drug withdrawal, were registered in order to assess the drug safety.

Statistical analysis was performed using the SAS version 9.3 software package (SAS Institute Inc.; USA). Comparative analysis of parametric data was carried out using the two-way ANOVA for parametric indicators, as well as the comparison of the results using the contingency table approach (chi-square test or Fisher's exact test). The data were tested for normality with the Shapiro–Wilk test. The groups were compared using the Student's *t*-test (for normal distribution) or the Mann–Whitney *U* test. The differences between groups were considered significant when $p < 0.05$.

RESULTS

Experimental assessment of mefloquine effects on the virus accumilation in lung tissue of Syrian hamsters infected with SARS-CoV-2

The results of assessing the infectious SARS-CoV-2 titre in the lung tissue of Syrian hamsters are presented in Table 1. In addition, the decrease in the virus accumulation and the inhibitory quotient are provided for the mefloquine and ribavirin groups, calculated in relation to the controls.

On day 2 after the infection, the decrease in the viral load was observed in animals, which received mefloquine and ribavirin. However, there were no significant differences from the control group. On day 4 after the infection, the increased viral load was observed in all groups. On day 6, the virus titre in the mefloquine group was significantly lower ($p < 0.05$) compared to both controls and ribavirin group. The decrease in SARS-CoV-2 accumulation compared to controls was 1.34 lg, and the inhibitory quotient was 95.5%.

Comparative evaluation of mefloquine and hydroxychloroquine efficacy in patients with novel coronavirus infection

The results of the primary efficacy endpoint analysis are presented in Table 2.

The proportion of patients having developed the mild disease was significantly higher ($p = 0.021$) in the mefloquine group compared to the hydroxychloroquine group. Regardless of the fact that this endpoint was reached faster after receiving hydroxychloroquine, there were no significant differences between groups ($p > 0.05$).

The proportion of patients with completely resolved respiratory failure (RF) was higher ($p < 0.001$) in the mefloquine group compared to the hydroxychloroquine group. Regardless of the fact that RF resolved faster after receiving hydroxychloroquine, there were no significant differences between groups according to this indicator.

Table 3. Comparative evaluation of mefloquine and hydroxychloroquine efficacy based on secondary efficacy endpoints

Indicator	Number of patients having reached the point, *n* (%)		Average time for achieving the endpoint (SD), days	
	Mefloquine	Hydroxychloroquine	Mefloquine	Hydroxychloroquine
Improvement based on CT	50 (51.0%)	32 (43.2%)	9.4 (4.48)	9.0 (4.56)
Score CT-1 or lower	54 (55.1%)	36 (48.6%)	2.5 (5.62)	1.1 (4.24)
Resolved pneumonia	15 (15.3%)	9 (12.2%)	7.3 (8.37)	4.4 (5.15)
Achieved grade 1 respiratory failure	77 (78.6%)	54 (73.0%)	1.5 (3.26)	1.0 (3.02)
O_2 support provided	30 (30.6%)	18 (24.3%)	3.8 (1.93)	4.1 (3.42)

Table 4. Adverse events registered during the study

Indicator	Number of subjects, *n* (%)		Number of events, *n*		*p*-value (Fisher's exact test)
	Mefloquine	Hydroxychloroquine	Mefloquine	Hydroxychloroquine	
Laboratory and instrumental assessment data					
Any AE	54 (55.1%)	29 (39.2%)	54	29	0.046
Elevated transaminase levels	48 (49.0%)	29 (39,2%)	48	29	0.218
Decreased O2 saturation	5 (5.1%)	0 (0.0%)	5	0	0.071
Vascular dysfunction					
Any AE	37 (37.8%)	24 (32.4%)	37	24	0.521
Blood pressure fluctuations	37 (37.8%)	24 (32.4%)	37	24	0.521
Nervous system disorders					
Any AE	30 (30.6%)	23 (31.1%)	34	28	0.99
Headache	17 (17.4%)	19 (25.7%)	17	19	0.192
Vertigo	17 (17.4%)	9 (12.2%)	17	9	0.396
Gastrointestinal disorders					
Any AE	20 (20.4%)	18 (24.3%)	25	19	0.581
Diarrhea	9 (9.2%)	14 (18.9%)	9	14	0.073
Nausea	11 (11.2%)	4 (5.4%)	11	4	0.275
Vomiting	4 (4.1%)	0 (0.0%)	4	0	0.135
Abdominal pain	1 (1%)	1 (1.4%)	1	1	0.99

The results of the primary efficacy endpoint analysis, obtained during the clinical trial, are presented in Table 3.

Analysis of secondary efficacy endpoints revealed no significant differences in any of the studied parameters between the groups of patients, who received mefloquine and hydroxychloroquine.

When assessing safety, a total of 165 adverse events (AEs) were registered in 85 patients (86.73%) of the mefloquine group and 112 AEs were registered in 57 patients (77.03%) of the hydroxychloroquine group (no significant differences between groups, $p = 0.108$). The total number of serious adverse events (SAEs) was 5 in four patients (86.7%) of the mefloquine group and 1 in one patient (1.35%) of the hydroxychloroquine group. Characteristics of the adverse events are presented in Table 4.

Other AEs, including mental disorders (associated with the main risk of mefloquine treatment), were observed in a few cases. Moreover, such AEs as delirium and acute psychosis were registered in only one patient after mefloquine administration.

Mild AEs were registered in the majority of the patients enrolled: 81 (82.7%) patients (160 events) after mefloquine administration and 56 (75.7%) patients (111 events) after hydroxychloroquine administration ($p = 0.339$). Moderate AEs were registered in one (1.02%) patient (1 event — acute psychosis) after mefloquine administration and in 0 (0.0%) patients after hydroxychloroquine administration ($p = 0.99$). Severe AEs were registered in four (4.08%) patients (5 events) after mefloquine administration and in one (1.35%) patient (1 event) after hydroxychloroquine administration ($p = 0.392$):

– mefloquine group: reduced oxygen saturation level in four patients (4.08%), and delirium in one (1.02%) patient;

– comparison group: acute coronary syndrome in one patient (1.35%).

The development of delirium required drug treatment (administration of antipsychotic medication), in other cases SAEs resolved after the drug withdrawal.

Association of AE with the studied drug was regarded as "possible" in one case and as "probable" in one case after mefloquine administration. The associations for other AEs were questionable or have not been established both for mefloquine and hydroxychloroquine.

DISCUSSION

When performing systematic review of the studies related to the use of hydroxychloroquine in patients with novel coronavirus infection, it was concluded that the drug reduces the rate of disease progression and accelerates the regression of clinical symptoms [15], however, the drug has no effect on the SARS-CoV-2 PCR negative conversion [16], hospital stay length, mortality and the need for mechanical ventilation [17]. Meta-analysis of clinical trials has shown that the use of hydroxychloroquine is associated with excess mortality in patients with COVID-19 [18]. However, this type of effect could be due to the fact that the drug dose used for treatment of the novel coronavirus infection often exceeds the safe dose [19].

Our study has showed that the efficacy of mefloquine prescribed to patients with novel coronavirus infection, which was assessed based on the reduction of symptom severity and dynamic changes of computed tomography imaging, was non-inferiorityl or, based on a number of indicators, higher compared to hydroxychloroquine. Mefloquine and hydroxychloroquine used in patients with novel coronavirus infection had comparable safety.

Currently, antimalarial medications have been excluded from the guidelines for treatment of COVID-19 patients due to unproven efficacy and the risk of side effects. However, the study results indicate that the effects of mefloquine on SARS-CoV2 in the *in vivo* experiments could be achieved by administration of the drug doses, 3–10 times lower compared to the single dose recommended for humans developing COVID-19 based on the interspecific transfer results [20]. Therefore, it can be assumed that confirmation of the lower-dose mefloquine antiviral activity would make it possible to reconsider the perspectives on using mefloquine in patients with COVID-19 and other viral infections.

CONCLUSIONS

1. In case of the course mefloquine administration at a dose of 75–150 mg in Syrian hamsters infected with SARS-CoV-2 at a dose of 5×10^5 PFU, the significantly decreased accumulation of the virus in lung tissue was observed compared to the control animals, receiving no treatment, and the group, receiving ribavirin. 2. When prescribed to patients with mild or moderate COVID-19, confirmed by PCR test for identification of viral RNA, the efficacy of mefloquine was non-inferiority or, based on a number of indicators, significantly higher compared to hydroxychloroquine. 3. Safety assessment results show the comparable safety profiles of mefloquine and hydroxychloroquine when used for treatment of patients with COVID-19 (mild and moderate course). Moreover, all registered adverse events are specified in the instruction leaflet for medical use of the medicinal product.

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