Literature Review

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Auditory and vestibular changes associated with the use of mefloquine: an integrative review

Alterações auditivas e vestibulares associadas ao uso da mefloquina: uma revisão integrativa

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ABSTRACT

Objective: To describe through a literature review auditory and/or vestibular alterations associated with the short or long-term use of mefloquine. **Research strategy:** Integrative review performed on the following databases: Pubmed, Web of Science, Scielo, Lilacs, Scopus, Science Direct, Cochrane Library, Embase, Open Grey, DissOnline, OAlster. **Selection Criteria:** The articles selected included studies with participants that were 18 years old or over, who used mefloquine and who were submitted to an auditory evaluation and/or a questionnaire regarding auditory and vestibular function. Literature reviews, book chapters, and studies using mefloquine associated with other drugs were excluded. **Results:** 1,267 studies were identified in the databases used, 28 articles were selected for full reading, and out of these, twelve were included in the review according to the eligibility criteria. Four articles pointed out the presence of vestibular and auditory diseases, two indicated only auditory disorders, and six solely vestibular disorders. Regarding auditory manifestations, tinnitus and hearing loss (HL) were the most frequent symptoms. Vertigo/dizziness and imbalance matched to the vestibular changes were commonly observed. **Conclusion:** Auditory and vestibular manifestations were referred to in the short and long-term after treatment with the drug. The discontinuation of its use made it possible to reverse the manifestations; however, in some cases, the permanence of the disorders was reported. Audiological and vestibular follow-up during mefloquine use is considered important, given its toxicity profile and possible side manifestations of an auditory and vestibular nature.

Keywords: hearing; hearing loss; vestibular diseases; vertigo; mefloquine

RESUMO

Objetivo: descrever, por meio de revisão da literatura, alterações auditivas e/ou vestibulares relacionadas ao uso em curto ou em longo prazo da mefloquina. **Estratégia de pesquisa:** trata-se de uma revisão integrativa, realizada nas seguintes bases de dados: PubMed, Web of Science, SciELO, LILACS, Scopus, ScienceDirect, Cochrane Library, Embase, OpenGrey, DissOnline e OAlster. **Critérios de seleção:** foram incluídos estudos com participantes a partir de 18 anos de idade, que fizeram uso de mefloquina e que foram submetidos à avaliação auditiva e/ou questionário referente à função auditiva e vestibular. Foram excluídas revisões de literatura, capítulos de livros e estudos que utilizaram a mefloquina combinada a outros medicamentos. **Resultados:** foram identificados 1.267 estudos nas bases de dados utilizadas, sendo selecionados 28 artigos para leitura completa. Destes, 12 foram incluídos na revisão, de acordo com os critérios de elegibilidade. Quatro artigos apontaram a presença de alterações vestibulares e auditivas, 2 indicaram apenas alterações auditivas e 6 apenas desordens vestibulares. No que se refere às manifestações auditivas, zumbido e perda auditiva foram os sintomas mais frequentes. Vertigem/tontura e desequilíbrio corresponderam às alterações vestibulares comumente apresentadas. **Conclusão:** manifestações auditivas e vestibulares foram referidas em curto e longo prazo, após o tratamento com a droga. A descontinuação de seu uso possibilitou a reversão das manifestações, porém, em alguns casos, foi observada a permanência das afecções. Considera-se importante a realização de acompanhamento audiológico e vestibular durante a ingestão da mefloquina, visto o seu perfil de toxicidade e possíveis manifestações colaterais de caráter auditivo e vestibular.

Palavras-chave: audição; perda auditiva; doenças vestibulares; vertigem; mefloquina

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INTRODUCTION

Many cases of respiratory system related diseases started to appear in Wuhan (China) hospitals at the end of December 2019 and, in a month only, 9,692 cases of this disorder were confirmed. From analyses of samples of one of the patients' bronchoalveolar liquid, the respiratory infection was confirmed to have been caused by a new type of coronavirus. For this reason, the disease was named Covid-19, an abbreviation for *Coronavirus Disease 19,* or SARS-CoV-2, an abbreviation for *Severe Acute Respiratory Syndrome Coronavirus 2*[1,2].

For being a novel virus with high reproduction capacity, the disease spread throughout many countries very fast, provoking a global emergency state, as declared by the World Health Organization (OMS)[3,4]. The pandemic outbreak and the fast search for specific antiviral strategies to combat the virus, in addition to tests of medication to treat and prevent the disease have become the focus of clinical tests and research. Therefore, the use of new drugs in patients infected by the SARS-CoV-2 has been carried out worldwide in an attempt to control the complications caused by the Covid-19[5-7].

One of the drugs that has been used in the treatment of SARS-CoV respiratory disease and as a potential medication against SARS-CoV-2 is the mefloquine compound (MQ)[8,9]. It is known as an antimalarial and antiparasitic drug, developed in 1970 and considered a quinine compound synthetic analogue that belongs to the 4-quinoline methane aromatic group. Both substances are considered traditionally active in the prophylaxis and treatment of human malaria caused by *Plasmodium Falciparum*, which is resistant to the chloroquine compound[10].

In a study developed in China, researchers reported that the MQ hydrochloride provoked complete inhibition of the cell culture cytopathic effects and suggested that the medication should be considered in the investigation of additional therapeutical strategies for the treatment of the Covid-19 infection[11].

Russia was the first country to test an MQ-based medication in the treatment of individuals infected by the novel coronavirus, introducing in March 2020 a treatment based on the substance for the efficient combat of SARS-CoV-2 in the human body and with a promising action in the disease prevention[12]. However, the compound has been associated to a variety of adverse side effects of neurological origin in patients submitted to the prophylactic use of the substance, who commonly report vertigo, sight impairment and idiosyncratic effects such as balance disorder, peripheral neuropathy, paresthesia, shaking chills and ataxia[13].

Although the MQ used as an antiviral drug has benefits, studies on antimalarial medication used against viral infections reported that its neurotoxicity has to be taken into consideration, due to the likelihood of severe adverse reactions[14,15].

Considering the MQ toxicity, alterations in the auditory function and/or vestibular disorders might be also caused by the use of this antimalarial medication.

Due to the diversity of drugs tested in the current Covid-19 pandemic and the need to know their adverse effects, either auditory or vestibular related to the use of such medication, this review is considered relevant.

OBJECTIVE

This integrative review aimed to describe functional auditory and/or vestibular alterations related to the MQ short or long-term use in young people, adults and the elderly.

RESEARCH STRATEGY

The review was guided by the following research question: "What's the effect of the MQ short and long-term use on the functional auditory and/or vestibular system in humans?"

The PICo strategy was used and defied as follows: Population (P): individuals that used MQ; Intervention (I): functional auditory and/or vestibular evaluation, along with self-report of auditory or vestibular complaints; Context (Co): functional auditory and/or vestibular alterations, along with self-report of auditory and/or vestibular complaints.

This study was carried out by surveying the main data bases available in May and June 2020, namely, PubMed, Web of Science, Scientific Electronic Library Online (SciELO), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Scopus, ScienceDirect, Cochrane Library and Embase, also including the following data bases for grey literature: OpenGrey, DissOnline and OAlster.

No restrictions of idiom or date of publication were applied. Aiming at reaching the highest number of articles possible, two search keys were used associated to the Boolean connectors AND and OR as follows: *mefloquine* AND *hearing* OR *hearing loss* OR *hearing diseases* OR *hearing disorders* OR *deafness; mefloquine* AND *vestibular diseases* OR *labyrinth diseases* OR *vertigo.* All the descriptors used in the Search Keys were obtained from the Medical Subject Headings (MeSH) system.

SELECTION CRITERIA

Two independent reviewers selected the papers, initially by reading the title and abstract and, finally, by the reading of the full text, according to pre-set inclusion and exclusion criteria. Discrepancies related to paper selection and data extraction were discussed by the reviewers at the end of each phase, aiming to reach a consensus and, in the absence of agreement, a third reviewer assisted the process.

There was no restriction to the design of the studies, however, the studies included had to present: (1) description of young, adult and older human patients that were 18 years old or over, who had used MQ and who had been submitted to any type of auditory evaluation and/or self-perception questionnaire related to the auditory and vestibular functions; (2) and/or hypotheses or evidence of physiopathology of the auditory impairment associated to the use of the medication under evaluation. The exclusion criteria adopted were: literature reviews; book chapters; studies reporting MQ use combined with other medication without separating the adverse effects of each drug; studies including individuals that already showed auditory and/or vestibular functional alterations before the use of the drug.

DATA ANALYSIS

The reviewers, independently, extracted the data from the papers selected in digital format, which included: paper title, author(s)' name(s), year of publication, country, study type and objective, sample size, age range of the group investigated, medication used, time of use of the medication, auditory alterations, vestibular alterations, main conclusions and level of evidence made available by the studies. To classify the papers included according to the level of scientific evidence, the new evidence-based medicine pyramid was used[16].

With the purpose of synthesizing the information found in the papers, the data extracted from the studies was compiled in a descriptive way in a previously elaborated table, which facilitated the identification and reformulation of the theme categorizations.

RESULTS

The initial search resulted in 1,267 studies, out of which 52 were selected after the reading of title and abstracts. After removing repeated studies, the full text of 28 papers was read following the selection phases described (Figure 1). Finally, 12 papers were selected after the exclusion of those that did not meet the methodology pre-set eligibility criteria. The reasons for exclusion were: literature review papers (5), auditory and/or vestibular alterations associated to the base diseases and not the medication being used (2), studies developed using animals (4), population investigated in a different age range than that defined for this review (2), use of another associated drug (3).

After analyzing all the studies included in the integrative review, the types of studies found were: 4 experimental studies, from which 2 were randomized clinical trials (level of evidence 2)[17,18] and 2 were non-randomized (level of evidence 3)[19,20], 4 observational studies (level of evidence 4)[21-24] and 4 case-studies (level of evidence 5)[25-28], according to the classification employed[16].

The studies included were developed between 1985 and 2017, in four different continents: Europe[19-22,25,27], America[17,24,26,28], Asia[23] and Oceania[18] (Chart 1).

The age of the participants of the studies ranged from 18 to 65 years old, and in three of the studies MQ was used to treat *falciparum* symptomatic malaria[17,25,27] and, in 9 studies, the use of the medication was prescribed to healthy individuals as a prophylactic treatment of the disease[18-24,26,28].

The MQ oral doses prescribed ranged from 100 to 6000 mg, varying in periods from 1 day to 6 months of treatment (Chart 2). Two papers reported the presence of auditory alterations only[25,26], 4 studies presented vestibular and auditory alterations[18,19,23,27] and the remaining 6 reported vestibular alterations only[17,20-22,24,28].

The auditory manifestations commonly reported after the use of MQ were tinnitus[18,23,25-27] and hearing loss (HL)[18,19,25,26]. Regarding vestibular disorders, vertigo and/or dizziness[15,18-24,27,28] were described, which could also be associated to unbalance[27,28].

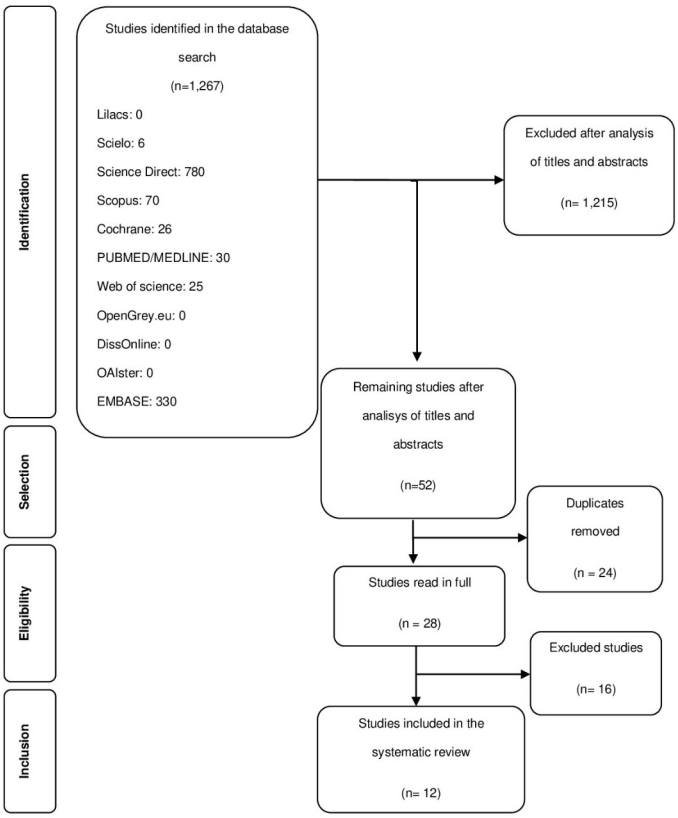

Figure 1. Paper selection flow diagram
Key: n = number of studies

Chart 1. Description of the studies included in the integrative literature review

Author, year	Title	Location	Objective	Type of study	Age range	Sample
De Souza et al.[17] (1985)	An open, randomized, phase III clinical trial of mefloquine and of quinine plus sulfadoxine-pyrimethamine in the treatment of symptomatic falciparum malaria in Brazil.	Brazil	To compare safety, efficacy and side effects of MQ to quinine plus sulfadoxine-pyrimethamine, in a 3-day period in the treatment of falciparum malaria.	Randomized clinical trial	18 to 55 years old	100
Hessén-Söderman[19] (1995)	Mefloquine prophylaxis and hearing, postural control, and vestibular functions.	Sweden	To investigate whether MQ affects hearing, vestibular function nand the postural control in volunteers during prophylaxis.	Non-randomized intervention study	29 to 50 years old	10
Davis et al.[18] (1996)	Neurological, cardiovascular and metabolic effects of mefloquine in healthy volunteers: a double blind, placebo-controlled trial.	Australia	To evaluate the side effects of MQ use in conventional prophylactic use in healthy volunteers.	Randomized clinical trial	Mean age 24 years	106
Van Riemsdijk et al.[21] (1997)	Neuro-psychiatric effects of antimalarials.	The Netherlands	To analyze the neuropsychiatric effects of antimalarial drugs.	Cohort	38 to 42 years old	394
Fusetti et al.[25] (1999)	Mefloquine and ototoxicity: A report of 3 cases	Italy	To report cases of patients using MQ to treat malaria.	Case study	Young and adult patients	3
Kollaritsch et al.[22] (2000)	Mefloquine concentration profiles during prophylactic dose regimens.	Austria	To relate MQ doses and side effects with the patients' gender.	Control case	Mean age 29.2 years	12
Rendi-Wagner et al.[20] (2002)	Unexpected frequency, duration and spectrum of adverse events after therapeutic dose of mefloquine in healthy adults.	Austria	To provide a reliable evaluation of adverse reactions associated to an MQ antimalarial therapeutical regimen.	Non-randomized clinical trial	22 to 37 years old	22
Yasutaka et al.[23] (2006)	Chemoprophylaxis according to the guidelines on malaria prevention for Japanese overseas travelers.	Japan	To evaluate the suitability of the malaria prophylaxis recommendation.	Control case	Mean age 34.8 years	52
Wise and Toovey[26] (2007)	Reversible hearing loss in temporal association with chemoprophylactic mefloquine use.	Canada	To discuss the possible etiology of the HL relation with MQ prescription.	Case study	67 years old	1
Nevin[13] (2012)	Limbic encephalopathy and central vestibulopathy caused by mefloquine: A case report.	England	To analyze the case of a patient with central vestibulopathy.	Case study	24 years old	1
Livezey et al.[28] (2016)	Prolonged neuropsychiatric symptoms in a military service member exposed to mefloquine.	USA	To describe the clinical background of a 32-year-old man that developed neuropsychiatric symptoms after the prophylactic use of MQ.	Case study	32 years old	1
Nevin and Leoutsakos[24] (2017)	Identification of a Syndrome Class of Neuropsychiatric Adverse Reactions to Mefloquine from Latent Class Modeling of FDA Adverse Event	EUA	To identify a new Neuropsychiatric syndrome class associated to the MQ use.	Sectional study	18 to 65 years old	933

Key: MQ = Mefloquine; HL = Hearing loss; USA = the United States of America

DISCUSSION

MQ is widely known for its antimalarial activity, in both the disease treatment and the prophylactic use. All studies included in this review reported its use via oral. The individuals participating in the research were mostly young adults and adults[17-25,27,28], and one study was developed with older people[26].

Signals and symptoms of auditory and vestibular alterations were reported such as tinnitus, HL, vertigo/dizziness and unbalance in individuals that used MQ for prophylaxis and/or malaria treatment. The auditory symptoms might appear

Chart 2. Characteristics related to the condition of medication use and main conclusions

Author/year	Condition	Dose	Time of use	Auditory alterations	Balance alterations	Main conclusions
De Souza et al.[17] (1985)	Falciparum malaria	A 100 mg MQ single dose via oral	42 days	_	16% participants presented dizziness	Dizziness was considered a light and transitory side effect, not requiring specific treatment. Thus, MQ was considered highly efficient, safe and well tolerated during the falciparum malaria treatment in adult Brazilian men. The advantages of this medication that can be taken in a single via oral dose to treat multi-resistant falciparum malaria are, therefore, obvious.
Hessén-Söderman[19] (1995)	Prophylaxis	250 mg MQ via oral once a week	6 weeks	A patient presented alteration, which was not specified.	A patient presented non-specific, light and constant dizziness.	Results showed that MQ was well tolerated and no general effect of the drug was noticed in the postural system.
Davis et al.[18] (1996)	Prophylaxis	1 pill a week: 250 mg MQ or 250 mg placebo	4 weeks	Tinnitus present in under 10% of the individuals and significant absence of HL at 6 KHz	Dizziness present in under 10% of the individuals	Despite evidence of the quinine acute auditory toxicity in healthy individuals, no HL provoked by the MQ use was observed.
Van Riemsdijk et al.[21] (1997)	Prophylasis	--	3 months	_	Vertigo, dizziness, inpaired sight and ataxia	Unfavorable reactions to the MQ use were observed. Great part of the drug users presented insomnia, dizziness, sickness, diarrhea, anxiety, depression, palpitation and vertigo. The results pointed out that despite being a drug that presents several side effects, MQ can still be considered a useful medication for the malaria treatment.
Fusetti et al.[25] (1999)	Falciparum Malaria	_	_	Tinnitus and high frequency sensorineural HL.	_	One patient presented HL partial remission after MQ discontinuation. No patient reported tinnitus improvement. Routine audiological evlauation during the MQ prophylactic use is suggested to monitor possible auditory deficit.
Kollaritsch et al.[22] (2000)	Prophylaxis	Six 250 mg MQ doses	28 days	_	Vertigo	Adverse reactions were more frequent in women. Headaches, insomnia and vertigo were the most common side effects. MQ lower tolerability in women might be due to the higher concentration of drugs in that group, indicating the need for a proper adjustment of the MQ dose in women.
Rendi-Wagner et al.[20] (2002)	Prophylaxis	1250 mg MQ in five 250mg pills, starting with three pills and six hours later the other two.	21 days	_	Vertigo present in 96% of the individuals, which was severe in 73%	Vertigo was described as dizziness associated to fast movements, causing problems of coordination, severe sickness and vomiting, starting within 24 hours and reaching a peak on the first day. These findings represent the first investigation with therapeutical doses, allowing the identification of adverse reactions associated to MQ, regardless of any malaria symptoms.
Mizuno et al.[23] (2006)	Prophylaxis	_	2 weeks	Tinnitues	Dizziness	The importance of knowing the toxicity profile and adverse effects of the MQ prolongued use is pointed out.
Wise and Toovey[26] (2007)	Prophylaxis	Three 250mg MQ doses (one dose a week)	21 dias	Tinnitus and sensorineural HL at 90 dB in 1 kHz and at 70 dB in 4 kHz	_	The case might provide a lesson regarding counterindication to the MQ use, and it seems wise to avoid the drug use in individuals with hearing impairment.
Nevin[13] (2012)	Falciparum Malaria	Three MQ doses	15 days	Tinnitus	Vertigo and unbalance	MQ caused balance alterations.

Key: MQ = Mefloquine; HL = Auditory loss.

Chart 2. Continued...

Author/year	Condition	Dose	Time of use	Auditory alterations	Balance alterations	Main conclusions
Livezey et al.[28] (2016)	Prophylaxis	250 mg a week	6 months	_	Dizziness, unbalance and vertigo	The study reports the potential appearance of neuropsychiatric side effects induced by MQ, varying from central vestibulopathy to significant behavioral alterations, also presenting sleep disorders.
Nevin and Leoutsakos[24] (2017)	Prophylaxis	_	_	_	Vertigo and dizziness	The appearance of neurological symptoms such as dizziness, vertigo and paresthesia might help to improve the findings of MQ case studies on the drug severe adverse reactions. Whenever these symptoms appear, the drug use should be discontinued.

Key: MQ = Mefloquine; HL = Auditory loss.

immediately or in the short term, for example on the first day after having taken the drug, considered as the drug concentration peak[19,20,26], a week after the start of the treatment[18] or even at the end of it[17,25].

Among the studies included, five reported audiometry examination in the participants[18,19,25-27] and three carried out otoneurologic evaluation[19,27,28]. The vestibular system assessment was mainly carried out via spontaneous nystagmus vestibular examination and after head movement[19], rotational chair testing[27,28], videonystagmography, optokinetic and motor control tests[27] and evaluation of the vestibulocochlear reflex[28].

As for side effects to the MQ use classified by sex, women presented a significantly higher general score[20,22] when compared to men, showing lower MQ tolerability among women.

Regarding vestibular symptom remission, they tend to disappear after the discontinuation of the medication, with complete elimination of symptoms after six weeks[19,20]. In some cases, no remission was observed, and persistence of multiple vertigo episodes and falls caused by dizziness even four years after the end of the treatment were reported[28], as well as the need for referral to vestibular rehabilitation with suspected lesion of the oculomotor and vestibular nuclei[27].

In auditory alterations, both the possibility of symptom remission[19,25,26] and unchanged auditory condition were reported, even after the interruption of the drug use[25,27].

Despite the adverse side effects found, there is relative safety in the prophylactic use of MQ in healthy people[18], considering the drug tolerance in some of the individuals studied, since the auditory and vestibular manifestations found were not significant[19]. However, despite the fact that some of the studies did not find auditory toxicity evidence associated to MQ, a study pointed out that possible low degree (<5 dB) auditory alterations could not be identified according to the test phase used[18].

In individuals being treated for malaria, MQ prescribed in a single 1,000 mg oral dose was considered highly efficient and safe[17], considering the low percentage of adverse effects observed. However, it seems relevant to emphasize that despite such conclusions, all studies identified auditory and/or vestibular manifestations in the participants and that the sample size (relatively small) was also considered by the authors.

On the other hand, some studies pointed out the risks related to this medication and observed that MQ adverse effects might occur, even in patients without counterindications to the drug use, along with manifestations such as dizziness and/or vertigo that might occur after having taken a single 250mg pill[27]. They also call attention to the fact that MQ is known for its neurotoxicity, and that ototoxicity is an adverse effect of this substance. For this reason, its use should be avoided, whenever possible, in individuals that already suffer from HL[26].

The MQ treatment should be discontinued when symptoms such as dizziness and/or vertigo appear, allowing the reversion of such manifestations[24]. A routine auditory evaluation, before and after the prophylactic use of antimalarial medication, can also be considered, aiming at observing and investigating more closely possible auditory deficit[25].

Although some studies did not confirm ototoxicity caused by MQ, some authors[20] mentioned that, in patients with malaria, which is considered a potentially fatal disease that requires treatment, the reversible reaction to medication might be considered relatively acceptable in controlled hospital environments. This might be one of the reasons why some studies consider good tolerability of the drug by humans.

In addition, malaria patients' bed rest in hospital might mask their reaction to the medication, such as vertigo and/or dizziness. Thus, side effect rates potentially associated to the MQ use might have been underestimated in the past[20].

Due to the scarcity of studies on the MQ efficacy and toxicity, medical support to prescribe the drug to healthy individuals, or to treat malaria[20] is very important, and considering the risks of side effects associated to its use is necessary[23].

Considering the variability of the appearance of ototoxic effects, the time of manifestation of such alterations, and the limitations regarding the MQ toxicity knowledge found in the studies surveyed and its use in test in the Covid-19 pandemic, further studies are needed to broaden the knowledge of the impact of this drug use, both on the auditory and vestibular systems.

CONCLUSION

The data gathered in this review allowed the knowledge of evidence on the auditory and vestibular alterations associated to the prophylactic use of mefloquine in the treatment of malaria in human patients, HL and tinnitus were reported along with vestibular manifestations such as dizziness/vertigo and unbalance. The symptoms tended to appear in the short and long term after treatment with this medication. The discontinuation of its use

enabled the reversion of the symptoms, however, in some cases, the permanence of alterations was observed.

The knowledge of these adverse effects for the auditory and vestibular systems as a result of the mefloquine use might help the choice of the substance, considering its toxicity profile and possible side effects. For this reason, being alert to possible risks inherent in the drug use before treatment along with auditory and vestibular monitoring during its use are necessary.

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REFERENCES

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9. http://dx.doi.org/10.1001/jama.2020.1585. PMid:32031570.

2. Kannan S, Shaik Syed Ali P, Sheeza A, Hemalatha K. COVID-19 (Novel Coronavirus 2019) - recent trends. Eur Rev Med Pharmacol Sci. 2020;24(4):2006-11. http://dx.doi.org/10.26355/eurrev_202002_20378. PMid:32141569.

3. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020;27(2):taaa021. http://dx.doi.org/10.1093/jtm/taaa021.

4. WHO: World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 51 [Internet]. 2020 [cited 2020 May 1]. Available from: https://www.who.int/docs/defaultsource/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10

5. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. Int J Antimicrob Agents. 2020;105955(5):105955. http://dx.doi.org/10.1016/j.ijantimicag.2020.105955. PMid:32234468.

6. Ahn DG, Shin HJ, Kim MH, Lee S, Kim HS, Myoung J, et al. Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19). J Microbiol Biotechnol. 2020;30(3):313-24. http://dx.doi.org/10.4014/jmb.2003.03011. PMid:32238757.

7. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, Epidemiology, Pathogenesis, and Control of COVID19. Viruses. 2020;12(4):372. http://dx.doi.org/10.3390/v12040372. PMid:32230900.

8. Dyall J, Coleman CM, Hart BJ, Venkataraman T, Holbrook MR, Kindrachuk J, et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. Antimicrob Agents Chemother. 2014;58(8):4885-93. http://dx.doi.org/10.1128/AAC.03036-14. PMid:24841273.

9. Serafin MB, Bottega A, Foletto VS, da Rosa TF, Hörner A, Hörner R. Drug repositioning is an alternative for the treatment of coronavirus COVID-19. Int J Antimicrob Agents. 2020;55(6):105969. http://dx.doi.org/10.1016/j.ijantimicag.2020.105969. PMid:32278811.

10. Nevin RL. Idiosyncratic quinoline central nervous system toxicity: historical insights into the chronic neurological sequelae of mefloquine. Int J Parasitol Drugs Drug Resist. 2014;4(2):118-25. http://dx.doi.org/10.1016/j.ijpddr.2014.03.002. PMid:25057461.

11. Fan HH, Wang LQ, Liu WL, An XP, Liu ZD, He XQ, et al. Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-novel coronavirus-related coronavirus model. Chin Med J (Engl). 2020;133(9):1051-6. http://dx.doi.org/10.1097/CM9.0000000000000797. PMid:32149769.

12. FMBA: Federal Biomedical Agency. Russia's [Internet]. Presented a drug for the treatment of coronavirus infection. 2020 [cited 2020 Jun 15]. Available from: http://fmbaros.ru/press-tsentr/novosti/detail/?ELEMENT_ID=38052&sphrase_id=15694

13. Nevin RL. Investigating channel blockers for the treatment of multiple sclerosis: considerations with mefloquine and carbenoxolone. J Neuroim. 2012;243(1-2):106-7. http://dx.doi.org/10.1016/j.jneuroim.2011.12.016.

14. D'Alessandro S, Scaccabarozzi D, Signorini L, Perego F, Ilboudo DP, Ferrante P, et al. The use of antimalarial drugs against viral infection. Microorganisms. 2020;8(1):85-111. http://dx.doi.org/10.3390/microorganisms8010085. PMid:31936284.

15. Ramos-Martín V, González-Martínez C, Mackenzie I, Schmutzhard J, Pace C, Lalloo DG, et al. Neuroauditory toxicity of artemisinin combination therapies: have safety concerns been addressed? Am J Trop Med Hyg. 2014;91(1):62-73. http://dx.doi.org/10.4269/ajtmh.13-0702. PMid:24865683.

16. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. Evid Based Med. 2016;21(4):125-7. PMid:27339128.

17. de Souza JM, Sheth UK, de Oliveira RM, Roulet H, de Souza SD. An open, randomized, phase III clinical trial of mefloquine and of quinine plus sulfadoxine-pyrimethamine in the treatment of symptomatic falciparum malaria in Brazil. Bull World Health Organ. 1985;63(3):603-9. PMid:3899397.

18. Davis TM, Dembo LG, Kaye-Eddie SA, Hewitt BJ, Hislop RG, Batty KT. Neurological, cardiovascular and metabolic effects of mefloquine in healthy volunteers: a double-blind, placebo-controlled trial. Br J Clin Pharmacol. 1996;42(4):415-21. http://dx.doi.org/10.1111/j.1365-2125.1996.tb00003.x. PMid:8904612.

19. Hessén-Söderman AC, Bergenius J, Palme IB, Bergqvist Y, Hellgren U. Mefloquine prophylaxis and hearing, postural control, and vestibular functions. J Trav Medic. 1995;2(2):66-9. http://dx.doi.org/10.1111/j.1708-8305.1995.tb00629.x.

20. Rendi-Wagner P, Noedl H, Wernsdorfer WH, Wiedermann G, Mikolasek A, Kollaritsch H. Unexpected frequency, duration and spectrum of adverse events after therapeutic dose of mefloquine in healthy adults. Acta Trop. 2002;81(2):167-73. http://dx.doi.org/10.1016/S0001-706X(01)00210-8. PMid:11801224.

21. Van Riemsdijk MM, van der Klauw MM, van Heest JAC, Reedeker FR, Ligthelm RJ, Herings RMC, et al. Neuro-psychiatric effects of antimalarials. Eur J Clin Pharmacol. 1997;52(1):1-6. http://dx.doi.org/10.1007/s002280050240. PMid:9143859.

22. Kollaritsch H, Karbwang J, Wiedermann G, Mikolasek A, Na-Bangchang K, Wernsdorfer W H. Mefloquine concentration profiles during prophylactic dose regimens. Wien Klin Wochenschr. 2000;112(10):441-7. PMID: 10890135.

23. Mizuno Y, Kudo K, Kano S. Chemoprophylaxis according to the guidelines on malaria prevention for Japanese overseas travelers. Southeast Asian J Trop Med Public Health. 2006;37(Suppl 3):11-4. PMid:17547042.

24. Nevin RL, Leoutsakos J-M. Identification of a syndrome class of neuropsychiatric adverse reactions to mefloquine from latent class modeling of FDA adverse event reporting system data. Drugs R D. 2017;17(1):199-210. http://dx.doi.org/10.1007/s40268-016-0167-3. PMid:28063022.

25. Fusetti M, Eibenstein A, Corridore V, Hueck S, Chiti-Batelli S. Mefloquine and ototoxicity: a report of 3 cases. La Clinica Terapeutica. 1999 Sep-Oct;150(5):379-82.

26. Wise M, Toovey S. Reversible hearing loss in temporal association with chemoprophylactic mefloquine use. Travel Med Infect Dis. 2007;5(6):385-8. http://dx.doi.org/10.1016/j.tmaid.2007.08.006. PMid:17983978.

27. Nevin RL. Limbic encephalopathy and central vestibulopathy caused by mefloquine: a case report. Travel Medicine and Infectious Disease. 2012 Apr;10(3):144-51. http://dx.doi.org/10.1016/j.tmaid.2012.03.006.

28. Livezey J, Oliver T, Cantilena L. Prolonged neuropsychiatric symptoms in a military service member exposed to mefloquine. Drug Safety - Case Reports. 2016 Jun;3(1):1-6. http://dx.doi.org/10.1007/s40800-016-0030-z.