



The Ototoxicity of Chloroquine and Hydroxychloroquine: A Systematic Review

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Abstract

Introduction Chloroquine and hydroxychloroquine are antimalarial drugs widely used in the treatment of rheumatic diseases. With the global pandemic caused by the new coronavirus, there was an increase in the prescription of these drugs, which led to a major concern regarding their ototoxic effects.

Objectives The objective of the present study was to assess existing scientific evidence about the toxic effects of chloroquine and hydroxychloroquine on the peripheral and/or central auditory system.

Data Synthesis A systematic literature review was performed by searching the PubMed (Medline), Scopus, Web of Science, LILACS, and SciELO electronic databases, in a search of articles that fulfilled the predefined inclusion and exclusion criteria. The review was conducted in three phases and, in all of them, analyses were performed by two independent researchers. Disagreements were discussed with a third researcher until a consensus was reached. A total of 437 articles were found and 8 were included in this review. Seven of the included studies reported hearing loss in their samples and presented a diagnostic hypothesis of ototoxicity induced by chloroquine or hydroxychloroquine. The most common type of hearing loss was sensorineural, with varying laterality and degrees of severity. The most frequently used audiological test was pure tone audiometry, and only two studies assessed brainstem evoked responses.

Conclusion The scientific evidence compiled in this research showed that chloroquine and hydroxychloroquine have an ototoxic effect in the peripheral auditory system. These drugs can cause cochlear damage, including changes in the stria vascularis and lesions in sensory hair cells.

Keywords

- chloroquine
- hydroxychloroquine
- ototoxicity
- hearing loss

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Introduction

Chloroquine (CQ) and hydroxychloroquine (HCQ) are anti-malarial agents that are widely used to treat rheumatic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), discoid lupus erythematosus (DLE), and Sjögren syndrome (SS).¹⁻⁸ The advent of the new coronavirus (SARS-CoV-2) pandemic spurred investigations into the efficacy and safety of these two drugs in combating this virus and led to an increase in their use.^{2,9,10} Due to the large-scale issue of prescriptions, a greater concern also arose regarding the ototoxic effects of the two drugs.

Both drugs are derived from quinoline^{1,3-5,11} but, although they have a similar composition, HCQ has fewer toxic properties than CQ.^{4,8,9} Regarding pharmacokinetics, CQ and HCQ are well absorbed orally, with good bioavailability, wide distribution, and prolonged elimination half-life (between 40–60 days).¹² They also share similar adverse side effects, such as epithelial lesions, rashes and skin hyperpigmentation, retinopathy, and other visual disorders.^{1-3,5,7,8,13} These are caused by strong melanin binding.¹² Usually, the toxicity of these drugs is monitored through periodic ophthalmological evaluations.^{1,4,8} However, questions regarding ototoxicity and possible hearing disorders have not been equally considered nor assessed.^{1,5,6,14}

There are reports on the possible changes that CQ^{1,5,13,15-20} and HCQ^{3,6,7,11,14,21,22} induce in the auditory system. However, the ototoxic action of these drugs is not fully understood and, although there are some hypotheses about the mechanisms behind their effects in the inner ear (IE),^{5,18,23,24} there is still no consensus on what happens. Despite the limited evidence regarding their ototoxicity, the World Health Organization²⁵ has identified antimalarial drugs as possible causes of hearing loss in adults, among other types of medication.

Given the inconsistencies in the information on this topic, this study aimed to analyze existing scientific evidence about the toxic effects of CQ and HCQ on the peripheral and/or central auditory system of those who take them.

Review of the Literature

This is a systematic review of the literature based on the following research questions: “Are there audiological changes in patients exposed to CQ and HCQ?”; “If so, which ones are the most common?”; “Is there any difference between the ototoxic properties of the two drugs?” These questions were structured using the Population, Intervention, Comparison, Outcome (PICO) framework :

- Population: subjects, without any age or gender restriction, who had used CQ and/or HCQ during their medical treatment;
- Intervention: taking CQ and/or HCQ during any medical treatment;
- Comparison: individuals who were not exposed to either drug;
- Outcome: normal hearing or hearing loss due to CQ or HCQ ototoxicity.

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)²⁶ recommendations to conduct this review and registered our research on the International Prospective Register of Systematic Reviews (PROSPERO) platform, under the registration number CRD42020182698.

Inclusion and Exclusion Criteria

To select articles, we used the following inclusion criteria:

- a) Original articles published in scientific journals, with free access and no restrictions regarding the date of publication or design;
- b) Studies published in Portuguese, English, Spanish, or French;
- c) Research involving studies in humans;
- d) Articles in which hearing loss had been exclusively caused by the use of CQ or HCQ (in any of their forms), or by a combination of these drugs with other non-ototoxic medication;
- e) Studies presenting data concerning peripheral and/or central hearing assessments.

Studies with the following characteristics were excluded:

- a) Articles in which hearing loss could have occurred due to diseases or complications of underlying diseases in the population (i.e., diseases that may usually be treated with CQ or HCQ, but are reported in the literature as risks for hearing loss, such as SLE and RA), rather than an exclusive association with CQ or HCQ use;
- b) Studies assessing the hearing of infants with prenatal exposure to CQ or HCQ;
- c) Literature review articles;
- d) Letters to the editor and summaries for events, due to the low scientific evidence in these documents.

Search Strategy and Article Selection

Descriptors were selected using Health Sciences Descriptors (DeCs) and the Medical Subject Headings (MeSH) filters, as well as the Boolean operators “OR” and “AND” in search strategies. The electronic databases used for searching were PubMed (Medline), Scopus, Web of Science, LILACS, and SciELO.

The searches of the electronic databases were performed from May 1st to 11th, 2020, using the following strategy: (*chloroquine* OR *hydroxychloroquine*) AND (*hearing loss* OR *hearing impairment* OR *hypoacusis* OR *hypoacusis* OR *loss, hearing*). No search restriction filters were used. A new search was made between January 18th and March 7th, 2021.

In the first stage of the selection strategy, the titles and abstracts of the articles from the database search were read. The articles were chosen and selected for the next phase by two blind and independent researchers. In the second phase, the selected articles were read in full by the two researchers (following the same strategy in the previous step). Finally, a secondary search for more published research was done through a new selection of articles based on the references from all the selected studies. In the first two stages, a third researcher acted as a judge, analyzing, and comparing the

data collected by the two independent researchers. In all phases, disagreements over the selection of articles were discussed by all researchers until there was a consensus.

All articles were accessed in full through the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)/Ministério da Educação (MEC) portal of journals, using remote access via the federated academic community (café, in the Portuguese acronym). When access was not available through the portal, the studies were requested from other national and international university libraries, at no cost.

Data Extraction

To perform data extraction from the selected studies, a spreadsheet was prepared using the Microsoft Excel software (Microsoft Corp., Redmond, WA, USA). The following data were extracted:

- a) Basic information about the study (title, authors, year of publication, journal, language, country of origin, design, and objectives of the research);
- b) Data regarding the sample (size, average age, gender, pathology in the population, and inclusion and exclusion criteria);
- c) Data concerning the drugs of interest in this review (the drugs used and their dosages, forms of CQ and HCQ use, duration of treatment with these drugs, and adverse effects associated with their administration);
- d) Auditory symptoms and audiological testing (hearing loss and the duration of audiological complaints, audiological tests and descriptions of these tests, hypotheses regarding the cause of hearing loss);
- e) Strategies used in an attempt to reverse hearing loss;
- f) Results and conclusions (results of audiological testing, characteristics of hearing loss [type, degree, and laterality], results of attempts to reverse hearing loss, results of other tests and conclusions).

Data Analysis

The studies were analyzed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative guidelines²⁷ and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system.²⁸ The STROBE initiative is a checklist with 22 items that represent all the information that must be contained in an article. This checklist can be used to verify that all items are present in the title, summary, introduction, methodology, results, and discussion of observational studies. This initiative aims to offer a recommended guideline on the most appropriate way to report observational studies, to facilitate critical reading by editors, reviewers, and readers in general. The checklist, however, should not be used to measure the quality of the studies being analyzed.²⁷

The following strategy was used to complete the checklist and perform an analysis of each article: full compliance with the topic, so that all information regarding a specific item was present in the article; partial filling in of the topic, when the article contained some points required by the item, but not all; and non-compliance with the topic, which is the absence of any information required by that item.

The purpose of the GRADE system is to classify the quality of the evidence and the strength of the recommendations, taking into account the study design, the quality, consistency, and objectivity of the results, and the probability of bias. According to the GRADE system, the levels of evidence are^{28,29}:

- High (A): Consistent evidence from randomized clinical trials with no significant limitations or exceptionally strong evidence from observational studies. Further research is unlikely to change the reliability of the effect estimate.
- Moderate (B): Evidence from randomized controlled trials with important limitations (such as inconsistent, indirect, or inaccurate results and flaws in the methodology) or very strong evidence from observational studies. Additional research is likely to have an important impact on the reliability of the effect estimate and may change it.
- Low (C): Evidence of at least one critical result from observational studies, case series, or randomized clinical trials, with serious flaws or indirect evidence. Additional research is very likely to have a major impact on the reliability of the effect estimate and is likely to change it.
- Very low (D): Any effect estimate is very uncertain.

Results

Of the 437 articles found, only 8 studies were selected for the review. The results of each stage of the study selection process, as well as the complete search strategy, can be seen in ►Fig. 1.

Regarding the GRADE system,²⁸ all studies were observational and classified in category C, with a low level of evidence. ►Table 1 shows the analysis of the articles, based on the STROBE initiative's checklist.²⁷

Seven studies reported hearing loss in their patient populations and presented a diagnostic hypothesis of CQ or HCQ-induced ototoxicity.^{3,5,6,13,17-19} One of the articles did not show conclusive evidence about hearing loss, since no significant hearing impairment was revealed in the group as a whole. Only 2 of the 11 participants showed changes in their results.¹⁵ Four studies classified the hearing losses as sensorineural,^{3,5,6,18} while three other publications did not include this information.^{13,17,19} The degree of hearing loss varied from mild to profound,^{3,5,17-19} and there was also diverse laterality.^{3,13,18}

In six studies, CQ was administered,^{5,13,15,17-19} whereas, in two other reports, HCQ was prescribed.^{3,6} There was some variation in treatment doses among samples, mainly related to the age groups of the participants. In all eight studies, the patients underwent pure tone audiometry,^{3,5,6,13,15,17-19} while three studies also performed acoustic immittance testing.^{3,13,17} Only two investigations used brainstem evoked response audiometry (BERA).^{3,5}

►Table 2 shows the data concerning the characteristics of the selected studies and exposure to CQ and HCQ. ►Table 3 presents information about auditory symptoms and

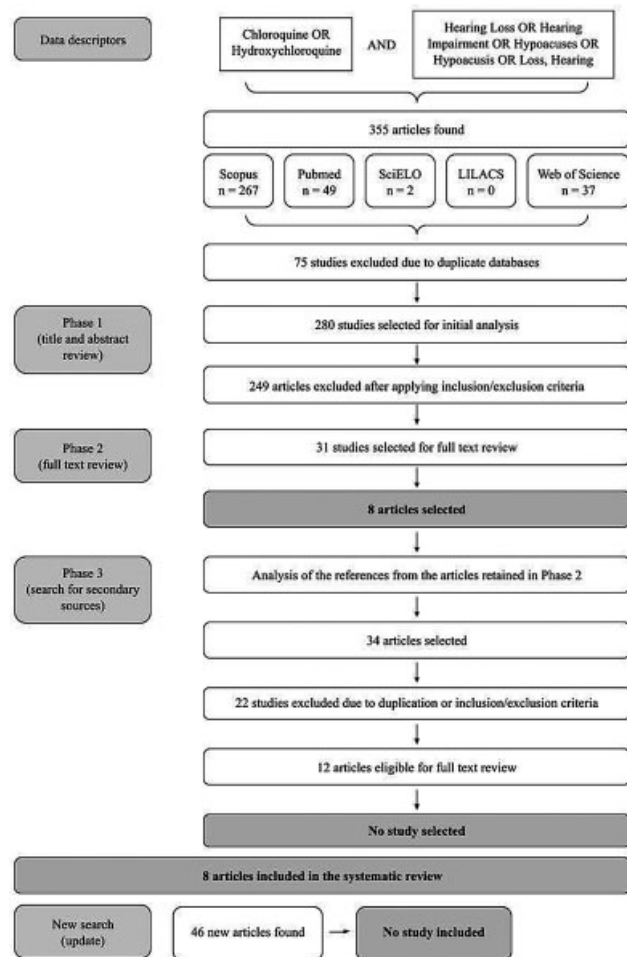


Fig. 1 Fluxogram.

methods of audiological testing and diagnoses. ► **Table 4** shows comparative data about exposure to the drugs, audiological outcomes, and reversibility of hearing loss.

Discussion

The present review aimed to investigate and analyze existing evidence in the literature about the toxic effects of CQ and HCQ on the peripheral and/or central auditory system of its users. The data in the study selection showed that there is scientific evidence that these drugs can cause changes in the auditory system, such as hearing loss, mostly of the sensorineural type and with varying degrees.^{3,5,6,13,17–19}

In the sample of selected articles, there was a wide variety among participants regarding age and gender. Most studies included children^{3,5,17–19} and non-elderly adults,^{6,13,15,17,19} but there was one article that also included elderly patients.¹⁷ As for gender, two articles reported on female-only samples^{3,18} and three populations only included males,^{5,13,15} while three other patient samples were mixed.^{6,17,19} However, since four articles studied patients diagnosed with malaria,^{5,13,18,19} there was not much variability concerning the diseases of the participants in the selected studies. The other articles presented pathologies

Table 1 Article analysis based on the STROBE initiative checklist

Item	Total n (%)	Partial n (%)	No n (%)
Title and abstract	1 (12.5%)	7 (87.5%)	0 (0%)
Background/Rationale	8 (100%)	0 (0%)	0 (0%)
Objectives	2 (25%)	6 (75%)	0 (0%)
Study design	7 (87.5%)	1 (12.5%)	0 (0%)
Setting	6 (75%)	2 (25%)	0 (0%)
Variables	4 (50%)	4 (50%)	0 (0%)
Data sources/Measurement	2 (25%)	4 (50%)	2 (25%)
Descriptive data	0 (0%)	8 (100%)	0 (0%)
Main results	4 (50%)	0 (0%)	4 (50%)
Limitations	1 (12.5%)	2 (25%)	5 (62.5%)
Interpretation	4 (50%)	3 (37.5%)	1 (12.5%)
Generalisability	5 (62.5%)	1 (12.5%)	2 (25%)

such as idiopathic pulmonary hemosiderosis,³ connective tissue disease, and subacute cutaneous lupus erythematosus.⁶ Chloroquine and HCQ are not well-known for treating the first two of these three diseases. In one of the articles,¹⁵ the participants were healthy (i.e., not affected by underlying diseases) and, in another study,¹⁷ the underlying condition was not mentioned. In all studies whose populations had malaria, CQ was prescribed to the patients.^{5,13,18,19} However, no evidence was found to prove that HCQ is less effective than CQ in combating this disease.

As for the use of CQ and HCQ in research, it is known that both drugs show similar efficiency under diverse clinical conditions.³⁰ Hydroxychloroquine is presented as less toxic than CQ,^{4,8,9} and was considered a safer option in 1955.³⁰ However, HCQ was only used in two of the studies included in this review.^{3,6} In the other six articles, CQ was chosen for treatment^{5,13,15,17–19} and four of these studies were performed in developing countries, such as Nigeria^{17–19} and India.¹³ It is believed that this choice may be partly related to the antimalarial efficacy of CQ against erythrocyte invasion by *Plasmodium falciparum* parasites, as well as the cost and availability of this prescribed drug in these countries.

In two studies, other therapeutic methods were prescribed (medicated or not) in conjunction with CQ and HCQ. Coutinho and Duarte³ reported that the patient was prescribed the simultaneous use of HCQ and prednisolone. No associations were found between prednisolone and hearing loss. On the contrary, this drug was used to treat some cases of hearing loss.^{7,11} On the other hand, in the research of Kokong et al.,¹⁷ they divided a sample of 156 patients into groups according to the medications that were administered, but only analyzed the data from a group of 22 participants who underwent CQ monotherapy.

Concerning the doses of CQ and HCQ prescribed in the research, the diversity among studies seems to be more

Table 2 Characteristics of the study selection and exposure to chloroquine and hydroxychloroquine

Authors, year	Country	Study design	Sample size	Age/age range	Underlying disease in the population	Medication	Route of administration	Doses	Treatment duration
Kokong et al., 2014 ¹⁷	Nigeria	Retrospective cross-sectional study	156	5 to 85 years (32.1 ± 30.7 average)	Not mentioned	Chloroquine (22)▲	Parenteral (intra-muscular injection), described for 1 case	Not mentioned	Not mentioned
Coutinho and Duarte, 2002 ³	Portugal	Case study	1	7 years	Idiopathic pulmonary hemosiderosis	Hydroxychloroquine*	Not mentioned	200mg/day	2 years
Johansen and Gran, 1998 ⁶	Norway	Case study	2●	44 years	Connective tissue disease and sub-acute cutaneous lupus erythematosus	Hydroxychloroquine	Not mentioned	400mg/day (1990–1993; 1994–1996), 200mg/day (1993–1994)	3 years and 9 months
Hadi et al., 1996 ⁵	United States of America	Case study	1	2.5 years	Malaria	Chloroquine	Parenteral (intra-muscular injection)	65mg of CQ (0.5-mg/kg body weight)	1 day
Obiako, 1985 ¹⁹	Nigeria	Observational study	50	3 children younger than 10 years N.B.: there was no mention of other ages, minor or adult.	Malaria N.B.: no other diseases were mentioned	Chloroquine	Parenteral (intra-muscular injection)	200mg/day N.B.: no other doses were mentioned	1, 3, and 4 days N.B.: no other periods were mentioned
Gustafsson et al., 1983 ¹⁵	Uruguay	Case series	11	20 to 36 years	None (healthy subjects)	Chloroquine	Parenteral (intravenous route) and oral (solution and tablet)	3 doses of 300mg CQ base, each.	3 days (with an interval of 56 days between doses)
Mukherjee, 1979 ¹⁸	Nigeria	Case study	1	6 years	Malaria	Chloroquine	Parenteral (intra-muscular injection)	5 ml/day (50mg of active compound per ml)	7 days
Dwivedi and Mehra, 1978 ¹³	India	Case study	1	52 years	Malaria	Chloroquine	Oral (tablet)	4 tablets (0.25 g each)	1.5 hours

± (standard deviation), ▲ (the rest of the sample used medicinal herbs and other medications such as gentamicin, chloramphenicol, unknown agents, quinine, oxytocin, streptomycin, furosemide, aspirin, ibuprofen, antineoplastic drugs, sulfadoxine/pyrimethamine, and sodium thiopental)* (used in association with prednisolone), mg (milligram), mg/day (milligram per day), mg/kg (milligram per kilogram), g (gram), ml (milliliter), ml/day (milliliter per day) CQ (chloroquine), ● (sample of 2 participants but only 1 will be presented in the Figure since the other patient had systemic lupus erythematosus).

Table 3 Data regarding inner ear symptoms, and hearing assessment methods and diagnoses

Authors	Inner ear symptoms (duration of presenting complaint)	Adverse side effects of medication, besides hearing impairment	Audiological testing	Results
Kokong et al. ¹⁷	Yes (not mentioned)	Tinnitus, vertigo	<ul style="list-style-type: none"> Pure tone audiometry Tympanometry 	<ul style="list-style-type: none"> Pure tone audiometry: Patients with a history of CQ use were assessed and, in the sample of 44 ears, 9 presented normal responses while the remaining ears demonstrated some degree of hearing loss: 6 mild, 7 moderate, 7 severe, and 15 profound.
Coutinho and Duarte ³	Yes (3 weeks)	Fullness in AD	<ul style="list-style-type: none"> Otoscopy Pure tone audiometry (AC: 125 - 8000 Hz) (BC: 250 - 4000 Hz) Speech audiometry Acoustic immittance testing BERA (click-evoked) 	<ul style="list-style-type: none"> Otoscopy: Normal. Pure tone audiometry: Normal hearing in the AS and mild to severe sensorineural hearing loss in the AD. Speech audiometry: Excellent speech recognition in the AS (100%) and diminished recognition in the AD (50%). Acoustic immittance testing: No signs of middle ear impairment (using tympanometry) and no acoustic reflexes in the AD. BERA: In the AS, easily identifiable, strong, and normal waves, with normal absolute and interpeak latencies. In the AD, absent identifiable or replicable waves at 90 dB HL.
Johansen and Gran ⁶	Yes (1 month)	Not mentioned	Pure tone audiometry	Pure tone audiometry (in June 1994 and 1996): Sensorineural hearing loss.
Hadi et al. ⁵	Yes (8 days)	Unsteadiness while walking	<ul style="list-style-type: none"> BERA Pure tone audiometry (AC: 250–8,000 Hz) (BC: 500–4,000 Hz) 	<ul style="list-style-type: none"> BERA: 10 days after injection: Bilaterally absent responses. 9 months after: An ambiguous hearing threshold at 80 dB in the AS, and absent responses in the AD. At 4 years: A hearing threshold between 70–75 dB in the AS and absent responses in the AD.
Nrako ¹⁹	Yes (1 or 2 days after the last injection [no other periods are mentioned])	Vertigo, tinnitus, ataxia	Pure tone audiometry	Pure tone audiometry: 10 patients presented absolute deafness; 25 demonstrated severe hearing loss, more than 80 dB at all frequencies; 15 exhibited moderate hearing loss, between 25–30 dB at speech frequencies and more than 40 dB at the higher frequencies. About 8 patients presented recruitment.
Gustafsson et al. ¹⁵	No	Dizziness	<ul style="list-style-type: none"> Pure tone audiometry (125–8,000 Hz) High-frequency audiometry (8,000–14,000 Hz) 	<ul style="list-style-type: none"> Pure tone audiometry: No unusual results were recorded in the audiogram. High-frequency audiometry: The results did not reflect any significant damage to hearing or balance in the entire group.
Mukherjee ¹⁸	Yes (10 days)	Unsteadiness while standing	Pure tone audiometry (AC: 128–8,192 Hz) (BC: 256–4,096 Hz)	<ul style="list-style-type: none"> Pure tone audiometry: The first audiometry (the assessment occurred one week after the last CQ injection): Severe sensorineural hearing loss in AU. After 10 days of treatment: Considerable improvement in hearing.

Table 3 (Continued)

Authors	Inner ear symptoms (duration of presenting complaint)	Adverse side effects of medication, besides hearing impairment	Audiological testing	Results
Dwivedi and Mehra ¹³	Yes (1.5 hours after taking the pills)	Tinnitus, vertigo, vomiting	<ul style="list-style-type: none"> Otoscopy Pure tone audiometry (AC: 250–2,000 Hz) Acoustic immittance testing 	<p>After 2 more weeks: Recovery of "socially acceptable" hearing +.</p> <ul style="list-style-type: none"> Otoscopy: Clean external auditory canals and normal tympanic membranes. Pure tone audiometry: In the AS, no threshold responses were recorded within audiometric limits; in the AD, there were only responses to the 500, 750, and 2,000 Hz frequencies, at the loudest volume. Acoustic immittance testing: a normal tympanogram and very slow acoustic stapedial reflexes in AU, at 500 Hz and only at 125 dB.

Abbreviations: CQ, chloroquine; AD, right ear; AS, left ear; AU, both ears; AC, air conduction; BC, bone conduction; Hz, frequency in Hertz units; BERA, brainstem evoked response audiometry); dB, decibels; p, p-value.
 + (there is no definition or explanation in the article regarding the expression "hearing at a socially acceptable level")

related to the age of patients rather than their diseases. Two of the lowest doses found in the study selection were prescribed for children.^{5,18} In the four articles that addressed patients with malaria,^{5,13,18,19} each one described a different dosage. Treatment duration also varied, depending on how chronic the disease was. Individuals with malaria^{5,13,18,19} were all treated for less than 10 days. In two other studies,^{3,6} during which idiopathic pulmonary hemosiderosis, connective tissue disease, and subacute cutaneous lupus erythematosus were treated, the duration was much longer (more than 2 years).

During the selection of articles for this review, we excluded all articles in which hearing loss in the population could have occurred due to the complications of a disease, or the progression of an underlying condition.

Regarding the conditions of the patients that composed the samples of the selected studies (e.g., malaria, idiopathic pulmonary hemosiderosis, subacute cutaneous lupus erythematosus, and connective tissue disease), none of the compiled reports demonstrated evidence confirming the impact of any of these pathologies on the peripheral and/or central auditory system. As such, it was possible to proceed with our investigation of the ototoxic properties of medication and the effects of exposure.

As for monitoring ototoxicity, according to the American Academy of Audiology,³¹ assessment is more clearly defined when it comes to testing the peripheral hearing function. However, there is still a need for a standard protocol for clinical practice. The tests that have been used most recently are conventional pure tone audiometry, high-frequency audiometry, and otoacoustic emissions.³¹ However, only using conventional audiometry makes it impossible to detect ototoxic changes early. For this reason, high-frequency audiometry and otoacoustic emissions are more suitable tests since they allow professionals to identify significant auditory changes earlier than with pure tone audiometry.³¹

Ideally, an audiological assessment should be performed before any pharmacological prescription is issued. The main responsibility in monitoring for toxicity lies in the comparison of audiological tests. This makes it possible to detect any changes in results. The battery of tests should include pure tone audiometry, high-frequency audiometry, tympanometry, speech audiometry, and otoacoustic emissions.³¹

Bernard¹ investigated the early detection of ototoxic changes by researching patients exposed to CQ. Using pure tone audiometry, the researcher noted that, although the auditory thresholds of the population remained unchanged, there were abnormal BERA results for 13 patients. The absolute latencies of waves III and V increased, while the latency of wave I remained stable. The I–III and I–V interpeak latencies also increased, but changes in the III–V interpeak latency were not as significant. The study demonstrated that the first signs of ototoxicity can be detected through BERA testing. In the selected studies in this review, these questions were not addressed, suggesting that further and more precise research is needed to support hypotheses about the neural injury that may be caused by these two drugs.

Table 4 Comparative data regarding exposure to the drugs, audiological outcomes, and hearing loss reversibility

Authors	Medication (dose)	Treatment period	Hearing impairment	Strategies used to reverse hearing impairment	Reversed hearing impairment
Kokong et al. ¹⁷	Chloroquine▲ (not mentioned)	Not mentioned	Yes	Administration of Pyritinol to most of the patients	Not mentioned
Coutinho and Duarte ³	Hydroxychloroquine* (200 mg/day)	2 years	Yes	None (treatment was not interrupted)	Not mentioned
Johansen and Gran ⁶	Hydroxychloroquine (400 mg/day; 200 mg/day)	3 years and 9 months	Yes	Interruption of treatment in March 1996	No
Hadi et al. ⁵	Chloroquine (65 mg)	1 day	Yes	Administration of steroids and plasma expanders	No
Nrako ¹⁹	Chloroquine (only mentioned for one case)	1, 3, and 4 days N.B.: No other periods were mentioned	Yes	Not mentioned	Not mentioned
Gustafsson et al. ¹⁵	Chloroquine (300 mg)	3 days	No	—	—
Mukherjee ¹⁸	Chloroquine (5 ml/day)	7 days	Yes	Administration of Prednisolone (two 5 mg tablets every 8 hours for 10 days, followed by a reduced dose of 1 tablet every 8 hours) and 1 Rovigon tablet every 8 hours	Yes (partial hearing recovery)
Dwivedi and Mehra ¹³	Chloroquine (1 g)	1.5 hours	Yes	Not mentioned	No

▲ (the rest of the sample used medicinal herbs and other medications such as gentamicin, chloramphenicol, unknown agents, quinine, oxytocin, streptomycin, furosemide, aspirin, ibuprofen, antineoplastic drugs, sulfadoxine/pyrimethamine, and sodium thiopental), * (used in conjunction with prednisolone), mg (milligram), mg/day (milligram per day), g (gram), ml (milliliter), ml/day (milliliter per day)

The audiological evaluation and tests presented in the articles included: pure tone audiometry,^{3,5,6,13,15,17-19} high frequency audiometry,¹⁵ speech audiometry,³ acoustic immittance testing^{3,13,17} and BERA.^{3,5} Half of the articles in this review used only behavioral hearing tests,^{6,15,18,19} while the other half used both behavioral and objective tests.^{3,5,13,17} Only two studies used electrophysiological tests.^{3,5} Pure tone audiometry was the most frequently performed assessment and was often the only examination that the patient underwent.^{6,18,19} High-frequency audiometry and speech audiometry were the least used exams. Coutinho and Duarte³ presented the most complete battery of audiological testing, per the recommendations of the American Academy of Audiology³¹ for monitoring ototoxicity.

Regarding audiological results, seven studies reported hearing loss among the participants in their samples.^{3,5,6,13,17-19} Sensorineural hearing loss was prevalent in all studies that described the type of hearing loss.^{3,5,6,18} This fact may be associated with cochlear damage these two drugs cause since, in cases of hearing losses induced by ototoxicity, the damage is usually exclusively cochlear.³¹ The degree of hearing loss also varied considerably between reports. Besides this, the researchers did not identify the classifications they used to describe the patients' hearing loss. This makes it even more difficult to understand the real effect of CQ and HCQ in the IE. Only three articles described the laterality of the hearing loss^{3,13,18} after using pure tone audiometry. In two of them,^{13,18} the losses occurred in both ears, and, in another article,³ the impairment was one-sided.

In the two studies that performed BERA testing,^{3,5} there was no response in the right ear. However, waves were present for the left ear (with normal absolute and interpeak latencies in one study,³ and altered electrophysiological thresholds in the other⁵). There is no known scientific evidence to justify or clarify the worse performances of the right ear in audiological tests, but such results have already been published by Cunha et al.³² based on research performed on Wistar rats exposed to toxic agents. The rats presented worse distortion product otoacoustic emissions (DPOAEs) results in the right ear.

The BERA results from the two articles mentioned above^{3,5} reinforce the hypothesis that CQ and HCQ end up exerting a damaging influence on the IE, and probably sensory hair cells. The BERA findings of both studies showed that, although there were changes, they corroborated the pure tone audiometry results that had already shown characteristics reflecting cochlear impairment. When electrophysiological thresholds increase, the absolute and interpeak latencies of waves I, III, and V stay within normal range, and the interaural time difference is less than 0.3 milliseconds, so it is likely that the impairment was originated in the cochlea.³³

The selected literature did not reveal any standard audiometric configuration or an audiological profile for cases of hearing impairment induced by CQ or HCQ. However, some articles^{3,34} define the hearing loss caused by quinine (a drug with a similar molecular structure and antimalarial action).¹⁸ Quinine-induced hearing impairment is generally

of the sensorineural type, with mild-to-moderate, bilateral, and symmetrical losses. Quinine ototoxicity produces a hearing loss curve that is, in most cases, flat, or evident only at high frequencies.^{3,34}

Concerning the reversibility of hearing loss, only one article¹⁸ describes an improvement in hearing, although the recovery was not complete. In three studies,^{5,6,13} hearing loss was permanent and, in another three,^{3,17,19} this information was not included. The lesions caused by the action of ototoxic drugs are, for the most part, irreversible and can lead to the progressive damage of cochlea hair cells and changes in the stria vascularis. These changes alter the composition of endolymph.³⁵ Interrupting treatment can lead to the suspension of adverse transformations in the endolymph, which can give reversible characteristics to any lesions that may be present.³⁵ Failure to recover healthy hearing thresholds, even after discontinuing treatment, may be related to the loss of OHCs or IHCs. In the case of the article that reported an improvement in hearing,¹⁸ while the study did not mention if any prescribed medication had been suspended, the authors did describe the use of corticosteroids to attempt to reverse hearing loss. According to Mukherjee,¹⁸ corticosteroids may have controlled inflammatory reactions in the arteries or the hypersensitive reaction of the cochlear arteries to the CQ, allowing normal blood supply to be restored and cochlear responses to improve. These changes resulted in the partial recovery of hearing thresholds.

Regarding the origin of the ototoxicity of these drugs, there are some hypotheses about the etiology of CQ ototoxicity. All of them, in some way, relate to findings of the drug's affinity with melanocytes. According to Savin,³⁶ the presence of melanocytes in the IE has been extensively studied over the years. These cells are present in the spiral ligament, stria vascularis (in greater quantity), modiolus, bony spiral lamina, and planum semilunatum. These structures are richly vascularized, and melanocytes tend to adhere directly to the walls of the vessels or regions closest to them. Lindquist and Ullberg²⁴ were the first researchers to establish a relationship between the changes caused by CQ in the IE and the affinity of the drug for melanin. In their study, large concentrations of the drug were found in the IEs of the fetuses of pigmented rats in their final stages of development. This correlation was reinforced when Dencker and Lindquist²³ observed an intense accumulation of CQ in the stria vascularis, modiolus, plana semilunata, saccule and utricle walls, and semicircular ducts of pigmented rats. However, these animals presented no drug accumulation in the endolymph, perilymph, sensory cells, or nerves.

Some authors^{5,18} believe that the auditory alterations could be caused by cochlear artery spasms, due to the sensitivity of these vessels to CQ. These contractions would, consequently, interfere with the oxygen supply to the sensory hair cells and stria vascularis. Hadi et al.⁵ assume that this ischemia can lead to varied lesions in the cochlear hair cells, a reduction in the number of neurons, loss of support cells, and atrophy of the stria vascularis. Furthermore, Dencker and Lindquist²³ suggest that the process could be

somewhat more indirect. The stria vascularis and as the planum semilunatum are structures that produce endolymph, a fluid that bathes the apical regions of hair cells (ciliary tips).^{23,36} Vascular lesions or degenerative processes in these structures, caused by an accumulation of CQ in melanocytes, can lead to changes in the composition of the endolymph and secondary damage to sensory cells.²³

The exact mechanism induced by HCQ in the IE is not fully understood. All articles that try to explain its effects^{7,11,14,37} mention existing hypotheses about the impact of CQ (basically, cochlear damage caused by ischemia). Because these drugs have similar structures and derive from the same compound, it is reasonable to assume that there may be similar ototoxic properties. Therefore, it is assumed that CQ and HCQ can affect the peripheral auditory system; more specifically, the cochlea.

Concerning the associations between pharmacological factors and audiological consequences, attempts were made to establish a relationship between the route of administration, dosage, or treatment duration with the severity of the hearing impairment presented by the research population. It should be noted that the rate of absorption of a drug depends, to a certain degree, on its route of administration. Oral absorption rates vary and depend on a few factors, but there may be a decrease in absorption due to the characteristics of the medication. In general, intramuscular administration leads to faster absorption than oral administration, especially with aqueous solutions.³⁸ However, no differences were found among the articles regarding the route of administration and the degree of hearing impairment. In general, severe and profound hearing losses occurred in studies administering the drugs orally¹³ and in those that used the intramuscular route.^{5,17-19}

Similarly, no association was established between dosages and degrees of hearing loss. In the two articles in which two children were given doses of less than 200 mg per day, the authors reported profound⁵ and severe¹⁸ hearing loss; the same severity reported by articles that used much higher doses. Additionally, no association was established between treatment duration and the degree of hearing loss. Only two articles^{3,6} described longer treatment times, and in one,⁶ the degree of hearing loss is not even mentioned.

All selected studies were observational, and there was a low level of evidence. According to the GRADE system,²⁸ all selected articles fall into category C and are classified as low evidence documents. However, in general, the studies followed the checklist items of the STROBE initiative,²⁷ in whole or in part. There was inconsistency in the information presented in one article¹⁵ regarding design. Studies must adequately describe the design of their work for a proper understanding of methodological procedures. Four articles presented their variables clearly and completely,^{3,6,13,15} while the other four described them partially.^{5,17-19}

Most of the publications included in this review are case reports or case series,^{3,5,6,13,15,18} presenting inconsistent and under-structured methodologies. In general, the sample

sizes are smaller, and more information is needed, especially in the descriptions of the results. Overall, there is a need for more detailed information and appropriate design choices so that better evidence can be produced.

A pattern of incomplete audiological information also stands out, especially in the description of assessments (e.g., equipment, type of stimuli, and method of performance) and the results of these tests (e.g., characterizations of the type, degree, and laterality of hearing loss). Only one article¹⁷ presented a system for classifying the degrees of severity, based on the type of hearing loss. The rest did not describe how the averages were calculated or explain the severity of hearing losses. Four studies presented auditory imaging tests.^{3,5,13,18} However, when they were obtained, only pure tone audiometry and BERA imaging were shown. These audiograms were not described or explored in the texts, leaving the interpretation of the exams up to the reader.

The number of selected articles in this review was small. This probably occurred due to the exclusion criterion about hearing loss caused by diseases (SLE and RA mainly). This led to the exclusion of many studies, since most research that describes CQ or HCQ-induced ototoxicity includes patients with these underlying conditions in population samples. In the same manner, the difficulty in establishing greater associations between the degree of hearing impairment and other issues, such as dosage and route of administration, may also be due to the small sample sizes in the selected research.

Another point to be highlighted is the fact that none of the studies performed audiological assessments before issuing pharmacological prescriptions. All tests were performed only after using the drugs and receiving hearing loss complaints. Therefore, there were no previous results with which a comparison could be made, as the American Academy of Audiology recommends.³¹

Since CQ and HCQ are effective drugs in the treatment of diseases such as malaria and SLE (in their different presentations) and are being investigated as potentially useful drugs in the treatment of other conditions, it is evident that we need studies with adequate designs that aim to further identify CQ and HCQ ototoxic mechanisms.

Final Comments

The present literature review led us to conclude that CQ and HCQ are capable of inducing hearing impairment in their users. The most common finding was sensorineural hearing loss, most likely due to cochlear damage. No differences were found regarding the ototoxic properties of the two drugs. Further studies with greater methodological rigor are needed for the continued clarification of the subject.

Declarations

No funding was received for conducting this study. This study did not involve human or animal subjects. All data generated or analyzed during this study are included in this published article.

Conflict of Interests

The authors have no conflict of interests to declare.

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