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Assessment of Short Term Chloroquine-Induced Ototoxicity in Malaria Patients

By Vijayalakshmi Subramaniam & Ravi N Vaswani
Yenepoya University, India

Abstract- *Objective:* To evaluate the effects of chloroquine phosphate on cochlear function using clinical and audiometric studies when administered in regular doses and in the recommended regimens, for the treatment of malaria.

Study design and setting: Prospective, cohort, observational study, with convenience sampling, in a tertiary care hospital.

Methodology: All subjects proved or presumed to be suffering from malaria and who received chloroquine phosphate treatment were inducted into the study. Base line clinical examination with detailed ear examination was carried out. Audiometric evaluation was carried out prior to treatment. All patients were treated with chloroquine phosphate tablets (1200mg) stat followed by 600 mg every 12 hours for 4 doses and paracetamol on a qrn basis. The study endpoints were development of ototoxic symptoms/signs or completion of the course as prescribed by the treating physician. Upon achieving any of the endpoints, the clinical examination and audiometric test battery was repeated.

Keywords: *ototoxicity, chloroquine, malaria.*

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Results: Only 2 subjects showed a change in hearing thresholds on high frequency audiometry following administration of chloroquine. The Auditory Brainstem Response (ABR) and Otoaccoustic Emission (OAE) were also abnormal in these 2. All the others showed no change in clinical or audiometric profile following administration of chloroquine. Only one subject showed vestibular side effects in the form of giddiness and nystagmus which spontaneously resolved on completion of therapy.

Conclusions: Chloroquine is not significantly ototoxic when administered in regular doses for treatment of uncomplicated malaria. The ototoxic effects of chloroquine which are rarely encountered are fully reversible.

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I. Introduction

Chloroquine is a drug with wide spread clinical applications. It has long been used in the treatment or prevention of malaria. As it mildly suppresses the immune system, it is used in some autoimmune disorders, such as rheumatoid arthritis and lupus erythematosus. Chloroquine is in clinical trials as an investigational antiretroviral in humans with HIV/AIDS and as a potential antiviral agent against chikungunya fever.[1,2] The radio-sensitizing and chemo-sensitizing properties of chloroquine are beginning to be exploited in anticancer strategies in humans.[3,4] Ototoxicity due to chloroquine (cochlear and sometimes vestibular) has been reported by many. This is usually but not always, dose –dependent and reversible.[5,6]

Mangalore is endemic for malaria. Not just in numbers but also in terms of unusual presentations. Considering that many clinicians empirically prescribe chloroquine for febrile patients, it is one of the most prescribed drugs in this area. This cohort study was designed to investigate the effect of chloroquine on cochlear function using clinical and audiometric studies when used in the regular treatment of malaria.

II. Methods

This prospective, cohort, convenience sampling study comprised 30 patients to be treated with chloroquine phosphate at the Yenepoya Medical College Hospital, Mangalore. All patients (whether admitted or not) proved or presumed to be suffering from malaria who were to receive chloroquine phosphate treatment were included in the study after informed valid consent. Patients were excluded from the study if they had received a course of chloroquine, in the past seven days. Also, those suffering from complicated malaria, hearing disorders, receiving any other ototoxic drug (including quinine), baseline audiometry showing any form of hearing loss, history of allergy to chloroquine, those who refused participation in the study or those who were lost to follow-up were excluded from the study.

Before starting treatment with chloroquine, baseline clinical examination with detailed ear examination was carried out. Functional assessment of hearing was done using tuning fork tests. Pre-treatment audiometric evaluation comprised pure tone audiometry with high frequency audiogram, brain stem evoked response audiometry (BERA) and otoacoustic emissions. All patients enrolled in the study were administered chloroquine phosphate. The course consisted of a stat dose of chloroquine phosphate 1200 mg, followed by 600 mg every 12 hours for 4 doses. The only other medicine administered was paracetamol (acetaminophen) which was given only on qrn basis. No other anti malarial or antibiotic was administered, unless clinically determined and in such a case the subject was subsequently excluded from the study. The clinical examination and audiometric test battery was repeated upon completion of treatment.

Author α: Associate Professor in Otorhinolaryngology, Yenepoya Medical College, Yenepoya University, Mangalore, Karnataka, India.
e-mail: vijisubbu@gmail.com
Author σ: Professor in Internal Medicine, Yenepoya Medical College, Yenepoya University, Mangalore, Karnataka, India.
e-mail: mirdad365@gmail.com

The data obtained was tabulated and analysed for incidence, type, severity and course of chloroquine induced ototoxicity.

III. Results

Within the data collection period, 45 patients with a definitive or presumed diagnosis of malaria were to be given chloroquine phosphate. Of these 6 were excluded on account of discharging ears with clinical diagnosis of chronic suppurative otitis media (CSOM) and abnormal audiometry. Furthermore, 9 patients were lost to follow up. Thus a total of 30 patients in the age range of 14-58 years were included in the study, of which 28 were males and 2 were females.

None of the patients had any ear abnormality on clinical examination before treatment. None of the subjects reported diminished hearing or tinnitus following therapy. Tuning fork tests did not reveal any form of hearing loss prior to or after treatment with chloroquine. Hearing thresholds on pure tone audiometry were reported to be normal in all subjects prior to and after treatment with chloroquine. However, high frequency audiogram revealed bilateral mild hearing loss at 12 kHz in one subject and bilateral mild to moderate hearing loss at 8 kHz in another following treatment, not accountable to any other obvious cause.

ABR was normal in all subjects prior to treatment. Abnormal wave V latency was observed in the 2 subjects who had high frequency hearing loss. OAEs were found to be abnormal only in the 2 subjects who reported high frequency hearing loss following treatment. A follow- up audiogram after one month of therapy was found to be normal. Only one patient reported giddiness on the second day of therapy. He was found to have spontaneous nystagmus, fast component to the left. His symptoms and nystagmus disappeared spontaneously on completion of treatment.

IV. Discussion

Drugs that induce ototoxicity have been a well-recognised cause of cochlear hearing loss. Ototoxicity because of classic antimalarial drugs such as quinine have been well established for many years. It manifests as both auditory and vestibular dysfunction, and it is typically mild to moderate, bilateral and symmetric; hearing is usually restored after cessation of the drug.[9] Despite reports of chloroquine resistance, it is the most widely used anti malarial in the world. It is also being used widely in the treatment of rheumatoid arthritis and other connective tissue diseases. Ototoxicity is a rare but well-established side effect of hydroxychloroquine when used in rheumatoid arthritis, idiopathic pulmonary hemosiderosis and other connective tissue diseases. Sensorineural hearing loss following chloroquine therapy has been reported to be dependent on dose and duration of treatment and observed to be reversible by many [5,6,7,8] while some have reported it to be irreversible.[10,11] Chloroquine sulphate was found to be highly toxic in guinea pigs when administered in single doses in excess of 40mg/kg. The spiral organ was assessed in segments each of 100 outer hair cells in length and the percentage of damaged inner and outer hair cells for each segment was calculated. No evidence was found to suggest that chloroquine causes permanent damage to the hair cells.[12]

This study was conducted to evaluate the effects of chloroquine on cochlear function when used in regular doses for the treatment of malaria in Mangalore which is endemic for malaria, not just in numbers, but also in terms of unusual presentations, mixed and occult infections. Apart from baseline clinical examination with detailed ear examination including functional assessment of hearing by way of tuning fork tests, all subjects enrolled into the study were subjected to an audiometric test battery comprising of pure tone and high frequency audiometry, brain stem evoked response audiometry and otoacoustic emissions. Ototoxicity has been reported to be generally detected by high frequency auditory testing before it can be detected by conventional audiometric procedures.[13] While brain-evoked response audiometry has been reported to be the most sensitive test in detecting early manifestations of cochlear injury caused by chloroquine when still in a reversible stage[2], transient evoked acoustic emissions have been proposed recently as a better way of monitoring hearing loss produced by ototoxicity and can be suggested as an alternative to monitor hearing loss.[14,15,16]

Only 2 out of the 30 subjects studied developed hearing loss in the high frequencies after chloroquine therapy. The follow up audiogram of these individuals showed that the ototoxic effects of chloroquine were reversible. The sole subject who developed vestibular side effects in the form of giddiness and nystagmus had spontaneous resolution of symptoms on completion of therapy. This shows that chloroquine is not significantly ototoxic when used in regular doses in the treatment of uncomplicated malaria. Ototoxic effects if any are reversible in nature.

V. Conclusion

Chloroquine may be used safely in regular doses in the treatment of uncomplicated malaria as ototoxic side effects are very rare and reversible in nature. Audiometric evaluation could be performed prior to and after therapy in patients at-risk for ototoxicity, receiving therapy in order to document and monitor hearing loss due to chloroquine.

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