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Research Article

Incidence of cardiac conduction disorders in patients with rheumatic disease receiving hydroxychloroquine

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ABSTRACT

Background: Hydroxychloroquine (HCQ) used for long-term management of rheumatic diseases. Prolonged use of antimalarials has been implicated in the development of conduction disorders particularly with chloroquine. Since limited data are available with HCQ, we studied electrocardiograms (ECG's) of 122 patients with rheumatic diseases treated with HCQ. This is the first study with large cohort evaluating conduction disorders in those receiving HCQ.
Methods: To evaluate cardiac conduction disorders in patients receiving HCQ as a part of their treatment, during 1-year follow-up and to note other related adverse reactions with a hypothesis to determine, how common are conduction disorders with HCQ. This is longitudinal prospective observational study over 1-year in the tertiary referral of south India. All patients who were started on HCQ (200-400 mg/day) as a part of their treatment were included. Patients with established cardiac diseases, electrolyte abnormalities and who were on drugs that cause conduction disorders were excluded. All ECG's were cross-checked by a cardiologist.
Results: A total of 276 patients were screened at baseline and 270 patients were enrolled in the study. Patients of rheumatoid arthritis, lupus, Sjogren's syndrome, undifferentiated connective tissue disease, palindromic rheumatism were included after satisfying respective classification criteria. The mean age is 38.85 (standard deviation [SD] 8.34) years. Females are 82.8% (n=101) and males are 17.2% (n=21). The baseline mean heart rate is 81.4 beats/min (SD=11.04), PR interval is 141.5 ms (SD=13.90), QRS is 84.8 ms (SD=13.90), QTc is 421.5 ms (SD=35.65). At 6 months, mean heart rate is 80.4 beats/min (SD=9.99), PR interval is 141.9 ms (SD=16-37), QRS is 81.5 ms (SD=11.82), QTc is 427.4 ms (SD=34.56). At the end of study period, mean heart rate is 81.8 beats/min (SD=9.49), PR interval is 140 ms (SD=21.33), QRS is 84.6 ms (SD=15.72), QTc is 422.7 ms (SD=36.2). During study period four events occurred. A young girl with lupus developed ventricular ectopics on hiking dose of HCQ from 200 mg to 400 mg with a cumulative drug intake of 9.8 g, which has resolved completely on stopping drug without any other intervention. A lupus patient died at home and the cause was not known. A 36-year-old male with rheumatoid arthritis of 4 years duration developed prolonged PR interval with 6 months of drug intake with cumulative was drug intake of 30.6 g with no available follow-up data. A 30-year-old female with undifferentiated arthritis developed skin rash which is pruritic, exfoliative with tiny blisters, 3 days after starting drug. The incidence of cardiac conduction defects in 1-year of follow-up in patients started on HCQ is 0.84.
Conclusion: This study highlights need for periodic cardiac evaluation of patients receiving long-term antimalarials. Reversibility of antimalarial toxicity is also highlighted in this study. Conduction disorders observed were similar to that expected in general population thus adding further evidence on safety of HCQ.

Keywords: Hydroxychloroquine, Myopathy, Cardiomyopathy, Conduction disorders

INTRODUCTION

Antimalarial drugs have been used for long term management of many connective tissue diseases. They have both anti-inflammatory and immunomodulatory properties. They have several other beneficial effects like photoprotection, antithrombotic effects, and favorable alteration of lipid profile. However, their long term use is associated with retinal

toxicity, the most common complication, neuromyotoxicity, skin rash, hyperpigmentation, hair depigmentation, and hearing defects. These adverse events can be associated with wide range of drug dosage, treatment duration. Cardiac toxicity is one of the rare fatal adverse events of their chronic usage and includes cardiac conduction disorders, complete heart blocks, cardiomyopathy, and congestive failure.[1-4] Hydroxychloroquine (HCQ) was also found to have favorable cardiac safety profile than chloroquine[5] which had led to increase use of former drug. The prognosis of antimalarial drug induced cardiotoxicity varies from partial or complete improvement, heart transplantation, and death. Nevertheless, these cardiac problems were underappreciated and incidence of cardiac toxicity due to HCQ has not been established.[6]

METHODS

This is a longitudinal 1-year prospective observational study conducted in a tertiary hospital of south India between 2012 and 2013. All patients with rheumatic diseases who will be started on HCQ as a part of their treatment, and those who provided written informed consent were included in this study. The dose of drug given is between 200 mg and 400 mg. A 12 lead electrocardiogram (ECG) at the baseline, at 6 months and at 12 months was done. Echocardiography, serum electrolytes, anti-Ro antibodies were done on occurrence of cardiac event. Patients with established cardiac diseases, those who were on drugs which can cause conduction abnormalities, those who refused consent were excluded. On occurrence of a cardiac event, HCQ was stopped. Assessment of heart rate, PR interval, QRS duration and QTc by Bazett's formula was done by cardiologist. The sample size of 122, calculated by Nielsen Landauer formula based on the study done by Costedoat-Chalumeau et al.[7] This study was approved by Institute Ethics Committee.

RESULTS

A total of 276 patients were screened at baseline and only 270 patients were enrolled in study. Among six patients who were excluded in study, one had baseline prolonged PR interval, two had established cardiac diseases, and two did not give consent. Patients with Rheumatoid arthritis who had satisfied 1987 American College of Rheumatology (ACR) criteria, lupus who satisfied ACR criteria for lupus, and Sjogren's syndrome who satisfied Sjögren's International Collaborative Clinical Alliance criteria, undifferentiated connective tissue, and palindromic rheumatism were included in this study. All the patients were on HCQ throughout the study period. The other drugs which the patients were receiving include prednisolone in 106, methotrexate in 108, azathioprine in 2, cyclophosphamide in 2, and sulfasalazine in 6. Those who had completed 1-year of study period include 50% early rheumatoid arthritis (n=61), 45.1% chronic rheumatoid arthritis (n=55), two were systemic lupus erythematosus, two were Sjogren's, and one each was undifferentiated connective tissue and palindromic rheumatism.

During the 1-year study period, four events occurred. A 17-year girl with lupus of 4 months, developed ventricular ectopic on hiking dose of HCQ from 200 mg to 400 mg with a cumulative drug intake of 9.8 g. This has resolved completely on stopping drug without any intervention. A lupus patient died at home and the cause was not known. A 36 year male with rheumatoid arthritis of 4 years developed prolonged PR interval, with 6 months of drug intake and total drug dose of 30.6 g. No follow-up data are available. A 30 year female with undifferentiated arthritis developed skin rash which is pruritic, exfoliative with tiny blisters, 3 days after starting drug, and total drug dose is 800 mg. The incidence of cardiac conduction defects in 1-year of follow-up in patients started on HCQ is 0.84.

DISCUSSION

Long-term treatment with chloroquine is associated with conduction disorders and cardiac failure. Reports of cardiac toxicity with increased use of HCQ available though the exact incidence of antimalarial cardiac toxicity is not known. This study was undertaken with the objective to evaluate the incidence of cardiac conduction disorders. To our knowledge, this is the first largest study evaluating cardiac conduction disorders in patients who were on HCQS. Antimalarial drugs accumulate in lysosomes, increase intracellular pH and interfere with mitochondrial metabolism. Conduction disorders are common initial manifestations, which may progress slowly to heart failure. They have the potential of reversibility on stopping the drug.[8] In our study, we had proved reversibility on stopping the drug without any intervention. In view of their potential for reversibility, regular screening with 12 lead ECGs should be considered. Evidence of toxicity by antimalarial drugs comes from the demonstration of vacuolization of myocytes and myelin bodies by histopathology. However, from the literature, biopsy was not performed in more than 50% of reported cases of antimalarial induced cardiac toxicity.

Parameter	Baseline (SD)	6 months	12 months
Heart rate (beats/min)	81.4 (11.04)	80.4 (9.99)	81.8 (9.49)
PR interval (ms)	141.5 (13.90)	141.9 (16.37)	140 (21.33)
QRS duration (ms)	84.8 (3.90)	81.5 (11.82)	84.6 (15.72)
QTc interval (ms)	421.5 (35.65)	427.4 (34.56)	422.7 (36.2)

We did not find other rare toxicities with HCQ like retinal toxicity. The reported incidence of conduction abnormalities from this study did not differ from the incidence in normal healthy population which has added evidence on safety of HCQ.[9]

CONCLUSION

Cardiac side effects with HCQ were rarely reported. Conduction disorders observed were similar to that expected in the general population, which adds evidence on safety of HCQ.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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