

Concise Report

Heart conduction disorders related to antimalarials toxicity: an analysis of electrocardiograms in 85 patients treated with hydroxychloroquine for connective tissue diseases

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Objective. The antimalarial agents chloroquine (CQ) and hydroxychloroquine (HCQ) are used in long-term treatment of connective tissue diseases (CTDs). A high incidence of heart conduction disorders, including bundle-branch block and incomplete or complete atrioventricular block, has been observed among patients treated with CQ. Since no data were available for HCQ, we studied electrocardiograms (ECGs) in 85 unselected patients with CTD treated with HCQ as the sole antimalarial.

Methods. Eighty-five unselected out-patients treated with HCQ for a minimum of 1 yr, and without established cardiac diseases had standard 12-lead ECGs.

Results. Two incomplete right bundle-branch blocks and one left bundle-branch block were observed. No atrioventricular block was observed. The mean PR interval was 137 ± 20 ms (range 99–188). The mean QTc interval was 410 ms (range 349–464). The mean heart rate was 73 beats/min (range 53–102).

Conclusion. PR interval, QTc interval and heart rate were not different from normal values. The rate of heart conduction disorders was similar to what is expected in the general population, and contrasted with prior results in CQ-treated patients. Our results add further evidence on the safety of HCQ compared with CQ.

KEY WORDS: Hydroxychloroquine, Antimalarials, Atrioventricular block, Electrocardiogram, Toxicity, Heart conduction disorders.

Antimalarial agents, chloroquine (CQ) and hydroxychloroquine (HCQ), are used in long-term treatment of connective tissue diseases (CTDs) and dermatological disorders, and are generally regarded as safe. However, rare but severe toxic effects may develop following prolonged use of these treatments. These side effects include retinopathy, neuropathy, vacuolar myopathy and/or cardiotoxicity [1], with both heart conduction disturbances and congestive heart failure [2].

To our knowledge, only one study systematically assessed heart conduction disorders in unselected patients with CTD exposed to antimalarials [3]. Five complete atrioventricular block (AVB) were observed among 112 patients [3]. The authors hypothesized for the first time that antimalarials were responsible for these heart conduction disorders [3, 4]. In this study published in 1981, CQ had been predominantly used. Currently, in order to reduce ocular toxicity [5], HCQ is preferentially prescribed. However, few data are available concerning its cardiac toxicity.

The high incidence of heart conduction disorders in the previous report and the lack of studies assessing such abnormalities in patients receiving HCQ as the sole antimalarial, prompted us to

study electrocardiograms (ECGs) in 85 unselected patients with CTD treated with HCQ.

Patients and methods

Patients

Eighty-five unselected out-patients (79 women and 6 men) routinely followed-up between January 2003 and January 2004 by three of us (N.C.C., Z.A., J.C.P.) in the Department of Internal Medicine at Pitié-Salpêtrière Hospital in Paris, France, the national referral centre for systemic lupus erythematosus (SLE) were included in the study. All the patients (i) were treated with HCQ sulphate (Plaquenil, Sanofi-Aventis, Paris, France) for a minimum of 1 yr, (ii) never received other antimalarials for their CTD, (iii) had no prior history of myocardial infarction or other established cardiac diseases, except for pericarditis, (iv) and provided their informed consent. These patients had ECG during longitudinal therapeutic monitoring including regular determination of blood HCQ concentration [6]. They represented about 15% of our current patients, and were presumed to be representative of our whole cohort. Ethical approval was obtained for blood HCQ assay, but was not required for ECG.

ECGs analysis

Resting standard 12-lead ECGs were recorded systematically when the patients were attending our department for the follow-up of their CTD. Measurement of PR, QT intervals and heart rate, and assessment of heart conduction disorders were performed by a trained cardiologist (J.S.H.) blinded to clinical characteristics of the patients. QT intervals were corrected for heart rate (QTc) according to Bazett's formula.

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Results

Patient characteristics

Seventy patients met the American College of Rheumatology (ACR) criteria for SLE, and 15 patients had other CTD. Additionally, 15 patients fulfilled the Sapporo criteria for definite antiphospholipid syndrome [7]. Mean age was 38 yrs (range 17–73). Regarding cardiovascular risk factors, 19 patients were active smokers and eight used to smoke previously, 13 were treated for hypertension and two were treated for hyperlipidaemia. Patients were receiving 200 mg of HCQ either twice ($n=77$) or once daily ($n=8$) for a mean of 7.9 yrs (range 1.0–23.7). The mean daily dosage was 6.4 mg/kg/day (range 3.2–10.8) and the mean cumulative dosage was 1090 g (range 70–3470), respectively. Mean blood HCQ concentrations was 977 ± 470 ng/ml. Other treatments at time of ECG included prednisone ($n=65$), 100 mg/day aspirin ($n=26$), oral anticoagulants ($n=11$), azathioprine ($n=5$), calcium channel blockers ($n=10$) and/or β -antagonists ($n=3$).

ECGs findings

No AVB was observed. Only three minor heart conduction disorders were noticed, including two incomplete right bundle-branch blocks [2%; 95% confidence interval (CI): 0–8%] and one complete left bundle-branch block (1%; 95% CI: 0–6%). Additionally, repeated ECG performed 3 yrs later in both patients with incomplete right bundle-branch block remained unchanged despite continuation of HCQ. Echocardiograms did not show any signs of cardiomyopathy related to antimalarials, and were normal except for mild mitral regurgitation (probably explained by the presence of antiphospholipid antibodies in these patients). None of them had cardiovascular risk factors. These three patients were treated with HCQ for a mean of 4.6 yrs (range 1.1–9.8). The mean daily dosage was 5.2 mg/kg/day (range 4.2–6.4) and the mean cumulative dosage was 670 g (range 160–1430). Mean blood HCQ level was 1029 ng/ml (range 880–1119). These results were not different from those of the entire cohort.

The mean PR interval was 137 ± 20 ms (range 99–188). The mean QTc interval was 410 ms (range 349–464). The mean heart rate was 73 beats/min (range 53–102).

Discussion

In a recent review of the literature, we found 25 patients with congestive heart failure and 45 patients with heart conduction disturbances secondary to antimalarials long-term treatment (both manifestations were associated in 16 patients) [2]. Antimalarials were mainly given for lupus, either systemic or discoid, rheumatoid arthritis or malaria. Mean age of these patients was 51 yrs (range 27–81 yrs). Clinical and echocardiographic presentations of congestive heart failure often included a restrictive pattern and biventricular hypertrophy, and histological findings were essential for diagnosis. Heart conduction disorders seemed to progress slowly from bundle-branch block (including left anterior hemiblock) or 1st and 2nd AVB to complete AVB. In some cases, heart conduction disorders preceded congestive heart failure. Associated toxicity was frequent and included myopathy, retinopathy, neuropathy and/or skin colouration. Withdrawal of antimalarials was associated with regression of heart conduction disorders in only three cases, whereas 12 patients (80%) did not show any improvement. The apparent progressive evolution of the conduction abnormalities and the frequent absence of regression after withdrawal emphasize the importance of detection of these side effects.

To our knowledge, this is the first study that assessed electrocardiographic abnormalities in unselected patients with CTD treated with HCQ as the sole antimalarial. Only one case of QT interval prolongation has been reported after chronic

exposure to HCQ [8]. In our study, PR interval, QTc interval and heart rate were not different from those in a population of healthy young adults with a high proportion of women [9, 10].

Regarding heart conduction disorders, we did not find any AVB. We only observed two incomplete right bundle-branch blocks and one left complete bundle-branch block. These results were not statistically significantly different from what is expected in the general population [11, 12], although they are compatible with a small increase in the prevalence of bundle-branch blocks in our subjects. However, comparison is limited by the absence of data on expected prevalence of conduction disorders in young women and by the small size of our study, and therefore wide CIs. In any case, our results contrast with the only available study with a similar design [3]. Among 112 patients with acute disseminated lupus erythematosus ($n=103$) or chronic discoid lupus ($n=9$), 18 (17.5%) had heart conduction disorders (*vs* 3.6% in our study). These included five incomplete right bundle-branch-block, three incomplete and two complete left bundle-branch-block, two first degree AVB, one second degree AVB and five complete AVB [3]. There were strong evidences that complete AVB were related to cardiotoxicity of the treatment: they occurred in patients treated with CQ for many years, toxic retinopathy and/or biopsy proven toxic myopathy were associated in three cases, and myocardial involvement related to disease was unlikely since three patients had only discoid lupus erythematosus and two had SLE lasting for 9 and 20 yrs with no recent flare-up.

The use of HCQ in the present study, instead of CQ in the study by Godeau *et al.* [3] may explain these conflicting results since HCQ, which differs in structure from CQ only by the presence of a hydroxyl group at the end of the side chain [1], is considered safer than CQ especially for retina [5]. Indeed and in agreement with our results, whereas heart conduction disorders have been reported in 45 patients receiving long-term antimalarials, only two of these patients (4.5%) had been treated with HCQ without CQ [2, 13, 14]. Questions regarding other potential risk factors for cardiotoxicity remain largely unanswered. Similarly to retinal toxicity, it has been suggested that cardiotoxicity may be enhanced by renal insufficiency, older age, pre-existing cardiac disease, elevated per-kilogram daily dose of antimalarials and longer duration of treatment [3, 15–17]. However, in the literature [2], duration of antimalarials use varied widely in patients with cardiac toxicity, ranging from 3 months to 27 yrs, with a similarly wide range of cumulative dose of antimalarial drugs (270–9125 g), and the small number of case-reports that mentioned the weight and the creatinine level precludes any conclusion to be drawn. Thus, even if some other risk factors may facilitate the occurrence of cardiotoxicity of antimalarials, this rare condition remains largely unpredictable.

Regarding limitations of our study, our series is small, and a larger prospective study is required to allow more definitive conclusions. Additionally, we studied ECGs, but echocardiograms were not systematically assessed. Then, we cannot rule out the existence of cardiomyopathy in some patients, even if this seems improbable in the absence of any clinical symptoms.

In conclusion, even if our reassuring results should be confirmed by a larger study, they add further evidence on the safety of HCQ compared with CQ.

The authors have declared no conflict of interest.

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