

# Third-Degree Atrioventricular Block Due to Chloroquine Treatment

## Klorokin Tedavisine Bağlı Üçüncü Derece Atriyoventriküler Blok

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### Summary

A 67-year-old woman on long-term chloroquine treatment for rheumatoid arthritis presented with dizziness and syncope. Although her medical history revealed no cardiovascular disease, complete atrioventricular block was detected by electrocardiography. Chloroquine was discontinued. Three days later, complete atrioventricular block spontaneously resolved to sinus rhythm. Cardiac complications associated with chronic chloroquine use are uncommon, nevertheless, there have been several reports on potential life-threatening rhythm disturbances and/or cardiomyopathy. In our case, atrioventricular block was associated with chronic chloroquine use. Cardiac evaluation with electrocardiography must be done for conduction disorders in patients using chloroquine for rheumatic diseases. *Türk J Phys Med Rehab 2011;57:253-5.*

**Key Words:** Chloroquine, complete atrioventricular block, rheumatoid arthritis

### Özet

Romatoid artrit nedeniyle klorokin kullanan 67 yaşında kadın hasta, polikliniğimize baş dönmesi ve bayılma şikayetiyle başvurdu. Öncesinde kardiyak problemi olmayan hastanın çekilen elektrokardiyografisinde atriyoventriküler tam blok tespit edildi. Hastanın günlük klorokin alımı kesildi. Hastaneye yatışın 3. günü hastanın ritmi spontan olarak sinüs ritmine döndü. Klorokin kullanan kişilerde kardiyak komplikasyonlar nadir görülmesine rağmen klorokinin hayatı tehdit edici ritm bozuklukları, kardiyomyopatiler yaptığı çeşitli raporlarda belirtilmiştir. Bizim vakamızda, klorokin kullanımına bağlı atriyoventriküler tam blok gelişmişti. Romatolojik hastalıklar nedeniyle klorokin kullanması gereken hastalar, ileti bozuklukları açısından belirli periyotlarla elektrokardiyografi ile kontrol edilmelidir. *Türk Fiz Tıp Rehab Derg 2011;57:253-5.*

**Anahtar Kelimeler:** Klorokin, atriyoventriküler tam blok, romatoid artrit

### Introduction

Chloroquine, an antimalarial drug, is widely used in the treatment of connective tissue diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (1). Numerous toxic effects, such as skin disorders, blood dyscrasias, corneal deposits, encephalopathy, neuropathy, myopathy and impairment of auditory function are associated with prolonged high-dose use of chloroquine (2,3). However, cardiac toxicity is uncommon (4).

Long-term chloroquine treatment can produce cardiac toxicity, restrictive and hypertrophic cardiomyopathy as well as atrioventricular blocks (AVB) or other conduction disorders (3). Herein, we describe a patient with RA who developed third-degree AVB secondary to prolonged chloroquine treatment.

### Case Report

A 67-year-old woman without any previous cardiac symptoms was admitted to the hospital because of shortness of breath,

dizziness and syncope. Her medical history revealed RA since 1987 and treatment with chloroquine 155 mg p.o. daily (Emquine 155 mg tb, Merck Limited) and azathioprine (AZA) 50 mg p.o. daily. She had been taking chloroquine for three years and AZA for ten months, but not non-steroidal anti-inflammatory drugs. On admission, her blood pressure was 90/60 mmHg, and pulse rate was 30 beats/min. A 12-lead electrocardiogram revealed complete AVB (Figure 1). There was not any structural or functional abnormality on transthoracic echocardiography except for a mild mitral regurgitation (MR). Blood electrolyte levels and cardiac biochemical markers were normal. There was no systemic involvement of the RA. After initial evaluation, a temporary transvenous pacemaker was implanted via the right jugular vein, and chloroquine was discontinued. We detected an increase in creatine levels due to complete AVB. The blood creatine level was high (2.39 mg/dl) because of decreased cardiac output related with AVB. Therefore, 0.09% sodium chloride (NaCl) was administered intravenously. Coronary angiography was performed after the blood creatine level decreased below 1.5 mg/dl on the third day of hospitalization. In the coronary angiogram, noncritical plaques were observed in the left anterior descending artery and the right coronary artery. Three days later, complete AVB spontaneously resolved to sinus rhythm (Figure 2). Methotrexate 15 mg p.o. weekly was started instead of chloroquine and AZA treatment continued. The patient was discharged on the 4th hospital day. She was free of any symptoms and her electrocardiography was normal six weeks after discharge.

## Discussion

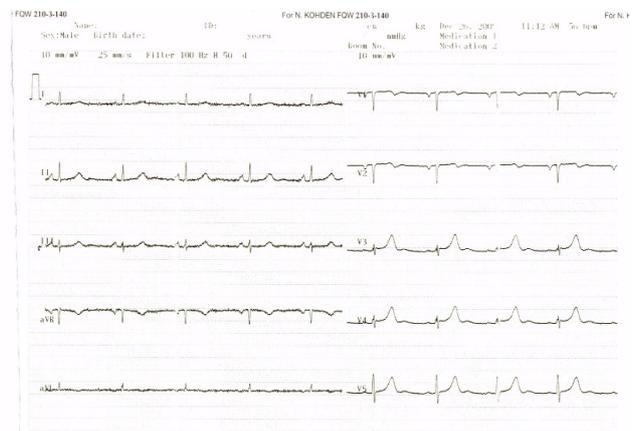
Until recently, chloroquine was the most widely used antimalarial drug in the treatment of connective tissue diseases (1). Cardiac complications are uncommon, but there have been several reports on potential life-threatening rhythm disturbances associated with chronic chloroquine use; these include conduction abnormalities, complete AVB, QT interval prolongation and torsades de pointes (3,5,6). Major arrhythmias caused by chronic chloroquine use have been related to a significant reduction in the cardiac rate, increases in the action potential duration and refractory period of Purkinje fibers (7).

The usual electrocardiographic abnormality is fascicular block which can lead to advanced types of AVB, generally

associated with syncope. Among 279 RA patients on chloroquine therapy, Jurik and Moller (8) have found only four cases of first-degree AVB. Ihenacho et al. (9) have described 12 AVB cases among 30 patients with no other potential cause for conduction disease, and chronic chloroquine use resulting in cardiac disorders has also been described. Cervera et al. (3) have shown in their study 12 cases of cardiac toxicity secondary to long-term chloroquine treatment in systemic autoimmune diseases. Some authors have reported that the doses of chloroquine in these patients ranged between 600 and 2281 g. However, Verny et al. (10) have notified that the total dose of chloroquine received (100 to 2.500 g) and the time interval between the starting of treatment and the occurrence of these abnormalities (2 to 30 years) are extremely variable. Costedoat-Chalumeau et al. (18) evaluated electrocardiograms of 85 rheumatology patients using hydroxychloroquine. The patients were treated with hydroxychloroquine for a mean of 7.9 yrs. The mean cumulative dose was 1090 g. No AVB was observed. Only three minor heart conduction disorders were noticed, including two incomplete right bundle-branch blocks and one complete left bundle-branch block. Echocardiographies did not show any signs of cardiomyopathy related to antimalarials. These three patients were treated with hydroxychloroquine for a mean of 4.6 yrs. The mean cumulative dose was 670 g. In our case, the dose of chloroquine was quite low and the duration of the therapy was short (total dose was 169 g and three years, respectively). To the best of our knowledge, in the literature, there is not any case of complete heart block in this dose and duration. Besides, our patient had shown no evidence of AVB prior to her chloroquine treatment. In addition, our patient had no structural or functional abnormalities except mild MR on echocardiographic examination. Finally, she had only noncritical plaques on the coronary angiogram. However, in many reported cases, secondary causes of conduction disturbances were not excluded such as coronary artery disease or myocardial dysfunction in angiography or echocardiography examination. In previous reports, chloroquine had been taken for many years before the development of heart block, which was irreversible and required pacemaker implant (11-13). Conversely, we suggest that this patient's transient AVB was related to her chloroquine therapy. Rather than the irreversible block seen in



**Figure 1.** ECG shows complete atrioventricular block whilst the patient was taking chloroquine. The patient had a ventricular escape rhythm (rate of 30 beats/min) and an atrial rate of 86 beats/min.



**Figure 2.** ECG shows a return to sinus rhythm after discontinuation of chloroquine.

long-term chloroquine therapy, this reversible block may have been due to a profound calcium channel blockade consequent to therapy with chloroquine.

The mechanism for this effect is unclear but long-term chloroquine use can cause skeletal myopathy. Swanson and Samani (14) have reported a patient with acute, reversible type II (Wenkebach) heart block due to chloroquine treatment and they have suggested that conduction delay may be due to a related cardiomyopathy and fibrosis affecting the interventricular septum. The authors have suggested another explanation that the reversible, acute-onset block seen in their patient may be associated with chloroquine's actions on intracellular calcium. Supportingly, it has been reported in several studies that chloroquine decreases the slow calcium channel current, behaving like a calcium channel blocker. Chloroquine and its derivatives have been shown to prevent the release of intracellular calcium after ligand-binding by blocking the inositol trisphosphate receptor which is a second messenger responsible for the release of calcium into the cytosol (14-16).

Arrhythmia is an important cause of mortality in RA and may be secondary to ischaemia, conduction abnormalities due to rheumatoid nodules, amyloidosis or congestive heart failure (17). However, whether these conduction disturbances are diseases related or should be related to drugs used in the treatment of RA remains to be determined. Although histological studies were not performed, it is possible that our patient could have minor abnormalities of the cardiac conduction system that predated her chloroquine treatment. However, intensive investigations did not reveal another underlying cause for conduction disturbances; the AVB was probably due to chloroquine-related cardiac toxicity in the present case.

As a result, we have asserted that the transient AVB in our patient was related to her chloroquine therapy. It should be kept in mind that cardiac abnormalities such as conduction disorder or cardiomyopathy because of chloroquine may cause cardiotoxic effects not only in high doses but also in therapeutic doses. Consequently, cardiac evaluation including electrocardiography and echocardiography must be done for conduction disorders before starting long-term treatment with chloroquine and cardiac assessment may be periodically warranted in patients during antimalarial therapy.

#### Conflict of Interest:

Authors reported no conflicts of interest.

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