

Ventricular Tachycardia and Long QT Associated with Clarithromycin Administration in a Patient with HIV Infection

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Prolongation of the QT interval is associated with a high risk of serious ventricular tachyarrhythmias, usually *torsade de pointes* (TdP) polymorphic ventricular tachycardia, although monomorphic ventricular tachycardia may also develop. Both congenital and acquired forms have been reported, acquired forms being much more prevalent. An association between human immunodeficiency virus (HIV) infection and a higher rate of dilated cardiomyopathy has also been recognized. The severity of immunodeficiency seems to influence both the incidence and severity of cardiomyopathy. A higher prevalence of QT prolongation has been reported among hospitalized HIV-positive patients with HIV infection, possibly related to drugs prescribed for such patients or to an acquired form of long QT syndrome arising from HIV infection. We report a case of QT prolongation and development of ventricular arrhythmia in one HIV patient that started with intravenous clarithromycin and cotrimoxazole therapy.

Key words: Long QT. HIV. Clarithromycin. Ventricular tachyarrhythmias. Torsade de pointes.

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Taquicardia ventricular y QT largo asociados a la administración de claritromicina en un paciente afectado de infección por el VIH

Se conoce que la prolongación del intervalo QT está asociada con un alto riesgo a desarrollar arritmias ventriculares, frecuentemente taquicardias ventriculares polimórficas tipo *torsade de pointes* (TdP), aunque también de tipo monomórfico. Se han descrito formas primarias y secundarias, siendo éstas las más frecuentes. Por otra parte, existe relación entre la infección por el virus de la inmunodeficiencia humana (VIH) y una mayor incidencia de miocardiopatía dilatada. El grado de inmunodeficiencia parece influir tanto sobre la incidencia como sobre la gravedad de la cardiopatía. Se ha descrito una mayor prevalencia de QT largo entre pacientes hospitalizados positivos para el VIH, lo que podría estar en relación con diferentes tratamientos administrados, o asociado a una forma adquirida propia de este grupo de pacientes. Describimos un caso de prolongación del intervalo QT con inducción de arritmia ventricular en un paciente VIH positivo tras iniciar tratamiento con claritromicina y cotrimoxazol por vía intravenosa.

Palabras clave: QT largo. VIH. Claritromicina. Taquiarritmias ventriculares. Torsade de pointes.

CLINICAL CASE

The patient was a 30-year-old man in a methadone detoxication program with positive serology for the hepatitis C virus, without previous decompensations, and positive serology for human immunodeficiency virus (HIV), who had never received antiretroviral treatment or prophylaxis with cotrimoxazole. At the time of admission he had a viral load of 90 000 RNA co-

pies/ml and CD4+ lymphocyte index of 36. He was hospitalized for a 10-day episode of cough, mucopurulent expectoration, pleuritic chest pain, fever, and dyspnea. The chest radiograph showed an alveolar pattern in both bases compatible with bilateral pneumonia. Laboratory tests disclosed arterial gasometry: FiO₂, 50%; pO₂, 87 mm Hg; pCO₂, 29.5 mm Hg; pH, 7.46; total leukocytes, 9.1 · 10⁹/L with 7% unsegmented neutrophils; hemoglobin, 7.3 g/dL; hematocrit, 21%; MCV, 85 fl; creatinine, 2.4 mg/dL; sodium, 129 mEq/L, and potassium, 5.0 mEq/L. The ECG showed sinus rhythm with a heart rate of 100 beats/min, QRS axis 60° and corrected QT (QTc) 0.35 s. Two packs of concentrated red blood cells were transfused and kidney failure and hyponatremia were corrected by water replacement. Intravenous antibiotic treatment was be-

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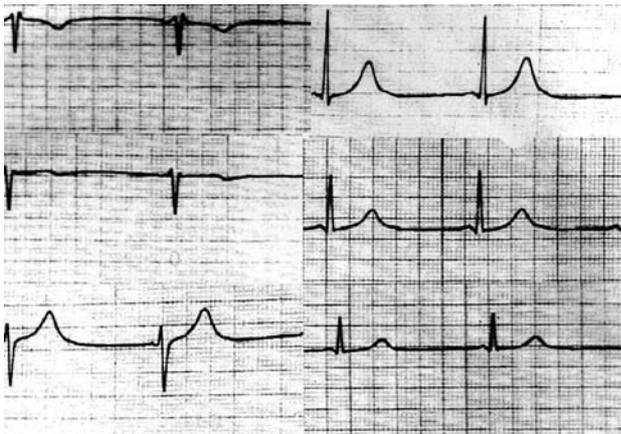


Fig. 1. Prolongation of the QT interval (QT/QTc=0.4 s/0.37 s) in our patient at the beginning of treatment with clarithromycin and cotrimoxazole.

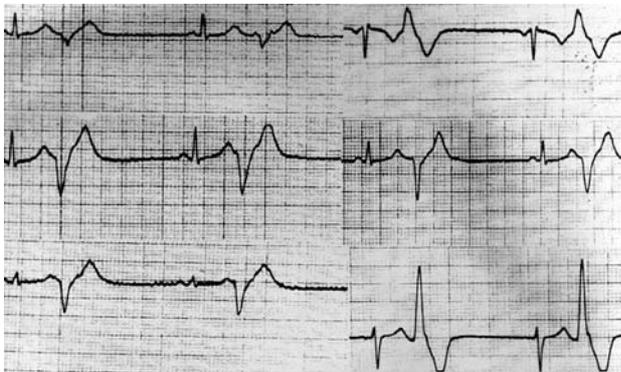


Fig. 2. Ventricular bigeminy with prolonged QT interval (QTc 0.58 s for a heart rate of 35 beats/min) 48 h after beginning antibiotic treatment.

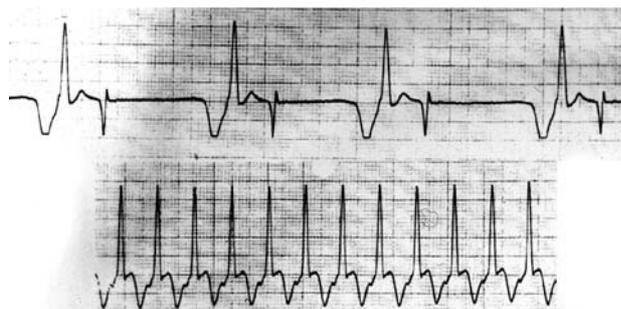


Fig. 3. Ventricular extrasystole in the form of ventricular bigeminy and monomorphic ventricular tachycardia with the same morphology of extrasystole in V2 in our patient.

gun with cefepime (2 g/8 h), clarithromycin (500 mg/12 h), and cotrimoxazole (trimethoprim 240 mg+sulfamethoxazole 1200 mg/6 h). Forty-eight hours after admission, the patient presented QT prolongation (QTc 0.58 s) (Figure 1) with a cardiac rhythm disorder in the form of ventricular bigeminy

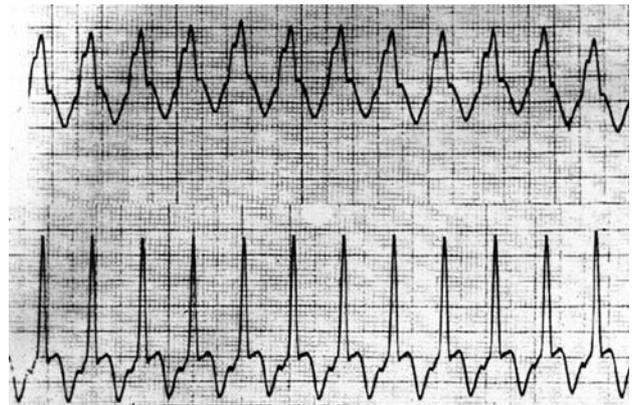


Fig. 4. Monomorphic VT with RBBB morphology documented in V1 and V2 72 h after admission and the initiation of antibiotic treatment with clarithromycin and cotrimoxazole.

(Figure 2) and a heart rate of 35 beats/min that was well tolerated hemodynamically. Twenty-four hours later he presented a self-limited episode of monomorphic ventricular tachycardia¹ documented in two leads (V1 and V2) with a morphology of right bundle-branch block (RBBB) and QRS 0.16 ms at a rate of 150 beats/min (Figures 3 and 4). Perfusion of clarithromycin and cotrimoxazole was discontinued but treatment with cefepime i.v. was maintained. The myocardial enzyme curve (CK, CK-mass, and myoglobin) was negative. The echocardiogram revealed a slightly dilated left ventricle (left ventricular end-diastolic diameter 62 mm and end-systolic diameter 48 mm) with slightly depressed function (EF 23%). After clarithromycin and cotrimoxazole were withdrawn, no new episodes of ventricular tachycardia were registered, although the prolonged QT persisted until day four, when it normalized (QTc 0.36 s).

DISCUSSION

In the case of our patient the ECG at time of admission showed a normal QT. There was no personal history of syncope or a family history of sudden death, which excluded congenital causes of long QT. The electrolyte disorders, anemia, and kidney failure were corrected when the arrhythmia appeared, so that possible causes of long QT that must be considered in our patient had to have been related with HIV and the drugs administered.

A greater prevalence of long QT in hospitalized patients with HIV infection compared to other patients has been reported. After excluding treatment with drugs that can cause long QT, the possibility of an acquired form of long QT syndrome associated with HIV was contemplated, the causal mechanism of which could be myocarditis, a subclinical myocardopathy due to HIV, or an autonomic neuropathy

due to the virus *per se*. There are no studies correlating QT duration with the stage of disease due to HIV.²⁻⁴

The appearance of long QT in relation to different drugs has been reported, among them class I_a and III antiarrhythmics, psychotropics, antihistamines, antifungals, and diverse antimicrobial agents like pentamidine i.v., chloroquine, amantadine, erythromycin, and cotrimoxazole. With respect to cotrimoxazole, numerous side effects have been described, most of which affect the skin, hematopoietic and gastrointestinal systems, and the kidney. Cardiotoxicity in the form of the appearance of long QT and *torsades de pointes* has been described in a patient after the oral administration of a tablet of cotrimoxazole (160 mg of trimethoprim and 800 mg of sulfamethoxazole). It has been attributed to an idiosyncratic reaction similar to that induced in patients treated with quinidine. The fact that the arrhythmia appeared after 72 h of treatment in our patient excludes this mechanism. In a prospective, nonrandomized study, the incidence of QT lengthening and ventricular arrhythmias in patients with HIV treated with intravenous pentamidine (16 patients) or cotrimoxazole (11 patients) was compared. In the group treated with cotrimoxazole, no differences in the duration of QT were observed before and during treatment. The results of this study do not indicate an increase in ventricular extrasystoles, non-sustained or sustained ventricular tachycardia associated with cotrimoxazole treatment in patients with HIV.⁶

With regard to macrolides, the appearance of long QT and ventricular arrhythmias in patients treated with erythromycin has been widely described. The mechanisms involved are similar to class I_a and III antiarrhythmic agents. Erythromycin inhibits the fast potassium current channel (I_{Kr}) in the myocyte, impeding the outflow of potassium from the myocytes of the ventricular myocardium and prolonging the transmembrane action potential (PAT) in Purkinje fibers, thus delaying repolarization and originating QTc lengthening.^{7,8} The appearance of these effects is influenced by the rate of infusion of the drug, which indicates a relation with its plasma concentration. For that reason, it is recommended that erythromycin be administered very slowly.^{8,9} Other macrolides like roxithromycin and azithromycin seem to be less arrhythmogenic in comparative studies *in vitro*.¹⁰

In the case of our patient the macrolide given was clarithromycin. The cases of two patients who developed QT prolongation and *torsades de pointes* after the administration of clarithromycin have been reported.¹¹ In Spain this complication has not been reported previously. Since the structure of clarithromycin is similar to that of erythromycin, its arrhythmogenic properties are similar, with the active metabolite 14(R)-hydroxy-clarithromycin acting on I_{Kr} to prolong the QT inter-

val.¹¹ The presence of cardiac anomalies favors the appearance of arrhythmias,¹² as does the presence of hepatic disorders, since the metabolism of the drug is mainly hepatic and only 20% is eliminated by the kidney. In our patient the clear temporal relation between prolongation of the QTc interval and the induction of arrhythmia 48 h after beginning treatment, the development of ventricular tachycardia just after finalizing the last dose administered, and the progressive normalization of the ECG after discontinuing the drug suggests that it was the trigger factor. No ventricular arrhythmias have been identified in patients treated with cefepime.

CONCLUSIONS

HIV-positive patients can present lengthening of the QT interval and ventricular arrhythmias. This may be due to the viral infection *per se* and could be potentiated by the action of different drugs that act as triggers of the disorder. When the causal agent is discontinued (in our case clarithromycin), the duration of QT reverts to its initial state. Based on these observations, we recommend electrocardiographic follow-up and correction of the electrolyte disorders in patients with HIV infection who are treated with drugs that can induce prolongation of the QT interval.

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