Importance of hepatitis C coinfection in the development of QT prolongation in HIV-infected patients

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Abstract

Background: Case reports and unblinded studies suggest that human immunodeficiency virus (HIV) disease is associated with QT prolongation and torsade de pointes ventricular tachycardia. Hepatitis C coinfection is common in patients with HIV disease, and cirrhosis is also associated with QT prolongation. We therefore undertook a systematic analysis of the role of liver injury, nutritional state, and coinfection with hepatitis C in the etiology of QT prolongation in HIV disease.

Methods: We performed a blinded, controlled retrospective cohort study of 1648 patients over a 3-year period at a university-affiliated municipal hospital. All electrocardiograms were included if patients with HIV disease had measurements of CD4 count and viral load within 3 months and serum electrolytes within 30 days (n = 816). Control subjects were chosen randomly from the general medicine service (n = 832). QT interval was measured in lead II and corrected for heart rate by Bazett's formula (QTc).

Results: QTc was slightly but significantly longer in patients with HIV disease than in controls (443 ± 37 vs 436 ± 36 milliseconds, $P < .001$). Patients with hepatitis C had more pronounced QTc prolongation (452 ± 41 vs 437 ± 35 milliseconds, $P < .001$). CD4 count, HIV viral load, and HIV medications had no effect on QTc. When patients with hepatitis C were excluded from the analysis, there was no statistical difference between patients with HIV disease and controls (438 ± 34 vs 436 ± 36 milliseconds, $P = .336$). Multiple linear regression revealed that both HIV and hepatitis C infection predicted QTc prolongation, as did age, female sex, history of hypertension, use of opiates, low serum K^+ and albumin, and high AST. Hepatitis C coinfection nearly doubled the risk of QTc of 470 milliseconds or greater in patients with HIV disease (29.6% vs 15.8%, $P < .001$).

Conclusions: Human immunodeficiency virus and hepatitis C infections both independently prolong QTc. Coinfection with hepatitis C greatly increases the likelihood of clinically significant QTc prolongation in patients with HIV disease.
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1. Introduction

Human immunodeficiency virus (HIV) infection has significant effects on cardiac muscle [1,2]. Furthermore, QT prolongation and torsade de pointes have been reported in patients with HIV disease [3-8]. Because torsade may cause death in HIV-infected patients, analysis of possible causes of QT prolongation in HIV-infected patients is important from a clinical perspective.

Initially, case reports suggested that QT prolongation and torsade were associated with specific medications, particularly antibiotics such as pentamidine [3,5] and erythromycin [6]. In 1997, Kocheril et al [8] undertook a retrospective, unblinded analysis of the prevalence of QTc prolongation in 42 patients over a 6-month period at one institution and compared QTc, measured by hand, with computer-derived QTc of more than 34 000 electrocardiograms (ECGs) during

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the same period. They found that patients with HIV disease had an increased prevalence of QTc prolongation when compared to the overall ECG database (28.6% vs 7%, $P = .002$).

These reports and unblinded studies suggest that QT prolongation is associated with HIV disease, and that specific medications may cause QT prolongation and torsade de pointes in HIV-infected patients. No reports in the literature have analyzed other possible causes for QT prolongation in patients with HIV disease.

Patients with HIV disease are frequently coinfected with other organisms. Of particular interest is coinfection with hepatitis C, which is common in patients with HIV disease [9]. Hepatitis C per se, to our knowledge, has not been reported specifically to cause QT prolongation. However, cirrhosis, which is common in patients with hepatitis C and HIV disease, has been associated with QT prolongation [10-12].

To test in a rigorous fashion whether HIV disease is associated with QT prolongation, and to investigate the role of liver injury and coinfection as possible causes of QT prolongation in this patient population, we undertook a large, blinded, controlled study to evaluate QTc in both inpatients and outpatients followed at a university-affiliated municipal hospital over a 3-year period.

2. Methods

2.1. Patient and ECG selection

After approval of the protocol by the Committee on Clinical Investigation of Albert Einstein College of Medicine, we created a cohort of patients with ECGs from the database of Jacobi Medical Center, a university-affiliated municipal hospital in the Bronx. All patients with a diagnosis of HIV infection and a hospital or clinic visit between January 1, 1999, and December 31, 2001, were included in the cohort of HIV-infected patients if an ECG was performed (1) within 3 months of measurement of CD4 count, and (2) within 1 month of measurement of serum electrolytes.

The control group was selected from patients in the ECG database during the same period. Patients were chosen from 2 sources: admissions to the Internal Medicine inpatient service and visits to the outpatient Primary Care Clinic. To roughly match the number of ECGs from HIV-infected patients, we chose every 15th chronological ECG from patients on the inpatient service and every 14th ECG from the Primary Care Clinic. ECGs from control patients were included for analysis if serum electrolytes were measured within 1 month of the ECG.

For those patients with more than 1 ECG, only the most recent was used for analysis. ECGs were excluded in all patients with atrial fibrillation, atrial flutter, and left bundle branch block. ECGs with pacemaker activity were also excluded. Two ECGs were excluded a priori because visual inspection revealed that QTc could not be measured.

Following the above exclusions, the data set included 816 ECGs from HIV-infected patients (433 inpatients and 383 outpatients) and 832 ECGs from control patients (433 inpatients and 399 outpatients).

2.2. Other data collection

Following the choice of ECGs, and before measurements of QTc, the hospital database was searched for further information on each patient and entered in the spreadsheet. Height and weight, as well as blood pressure closest to the time of ECG, were included when available. CD4 count and viral load were also included. Charts were searched for diagnosis of hypertension, diabetes, cirrhosis, and hepatitis C infection. Echocardiographic measurements of ejection fraction (EF) and right ventricular systolic pressure (RVSP), as well as diagnosis of left ventricular hypertrophy (LVH), were included if echocardiograms were performed within 1 year of the ECG. The results of hepatitis C antibody tests and hepatitis C viral RNA were included when available. Liver function tests were included if done within 1 month of the ECG. Hemoglobin A_{1c} values were also included if done within 3 months of the ECG.

Hepatitis C infection was defined as either a history of hepatitis C noted in the chart or positive antibody test for hepatitis C in the hospital laboratory database.

2.3. Determination of QTc

We used a modification of the technique of Algra et al [13] (ie, measurement of a single QT interval from the limb leads) that is similar to the method of the International Long-QT Registry Research Group [14,15]. QT intervals were measured on each ECG using lead II, unless the end of the T wave could not be accurately determined, in which case lead I or III was used.

To increase accuracy of our measurements, the QT interval of each patient was measured in a blinded fashion by 2 investigators, and the average was used for analysis. For all ECGs in which the difference in QTc between the 2 readers was 40 milliseconds or less, the average QTc was used for analysis. For those ECGs where the difference in QTc measurements was greater than 40 milliseconds on the initial measurement, a specific QRS complex was chosen, independent measurements were again made, and the average used if the measurements were within 40 milliseconds. In 5 remaining cases, a third investigator determined the QTc. Thus, the concordance of final measurements between the 2 investigators was very high.

The QT corrected for heart rate (QTc) was calculated by Bazett's formula [QTc = QT/(RR)$^{1/2}$], using the RR interval before the measured QT, as in other studies [13-15]. All measurements were made in a blinded fashion.

2.4. Statistical methods

For statistical analysis, we used SPSS software (SPSS, Chicago, Ill). Univariate analyses were performed, using χ^2 tests, correlation coefficients, t tests, or analysis of variance as