

## Prolonged QT Interval and Torsades de Pointes Associated with Atazanavir Therapy

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**We report, to our knowledge, the first documented case of torsades de pointes associated with atazanavir therapy. This case serves to highlight the need to monitor patients receiving atazanavir therapy who have risk factors for QT interval prolongation, such as female sex, bradycardia, electrolyte abnormalities, congestive heart failure, and a baseline prolonged QT interval.**

Since their first introduction in 1995, protease inhibitors have expanded the clinician's armamentarium in the ongoing battle against HIV infection. Despite the benefits of protease inhibitors, this class has been associated with a rare but potentially fatal toxicity—specifically, a prolonged QT interval syndrome that leads to torsades de pointes. This phenomenon has been described in association with lopinavir, nelfinavir, ritonavir, and saquinavir therapies [1].

In 2003, atazanavir was approved for use. Atazanavir offers an improved profile by decreasing pill burden, having fewer lipid-altering effects, and causing fewer gastrointestinal symptoms, yet maintaining relative potency. Studies that have evaluated atazanavir's safety profile revealed that there is evidence of asymptomatic PR prolongation and a dose-dependent QT interval prolongation, notably at a dose of 800 mg. However, at a dose of 400 mg, the effect on QT interval appears to be minimal [2]. Although the effect of QT interval prolongation has been observed in clinical trials, no tachyarrhythmias have been observed. We present the first reported case of torsades de pointes in association with atazanavir use.

**Case report.** Our patient is a 59-year-old woman who has congestive heart failure with an ejection fraction of 30% and HIV infection (CD4 cell count, 8 cells/ $\mu$ L; viral load, 750,000 copies/mL); she was undergoing hemodialysis and began receiving lamivudine (50 mg once per day), zidovudine (300 mg once per day), and atazanavir (400 mg once per day) therapies 1 month prior to her presentation. She presented with syncope. She complained of nausea, which had been continuous for 5 days, and shortness of breath, which had been slowly progressive during the month previous to presentation. A 12-lead electrocardiogram revealed a new prolonged QT<sub>c</sub> interval of 619 min. An electrocardiogram prior to initiation of antiretroviral therapy showed a QT<sub>c</sub> interval of 398 min.

The patient developed sustained ventricular tachycardia. She did not experience chemical conversion and was defibrillated to sinus bradycardia, with a heart rate of ~50 beats/min. Her QT interval prolongation worsened with the bradycardia, and she experienced torsades de pointes that reverted after additional defibrillation. Isoproterenol therapy was initiated to titrate her heart rate to 100 beats/min and decrease her QT interval.

During the patient's hospitalization, antiretroviral therapy and azithromycin therapy were ceased. Secondary to concern about QT prolongation, these therapies were not restarted. Amiodarone therapy, which was given for ventricular tachycardia, was also discontinued because of the same concern. The patient experienced no further ventricular tachyarrhythmias, and her QT<sub>c</sub> interval improved to 394 min. The patient was rechallenged with antiretroviral therapy, including lamivudine, zidovudine, and atazanavir. Within 2 days of antiretroviral therapy reinitiation, surveillance 12-lead electrocardiograms revealed lengthening of the QT<sub>c</sub> interval to 571 min. It was therefore concluded that the culprit for QT interval prolongation and torsades de pointes was atazanavir therapy. The patient's antiretroviral therapy was discontinued, and the QT interval normalized. She will be observed as an outpatient for antiretroviral therapy adjustments.

**Discussion.** Ventricular tachycardia and torsades de pointes, which are complications of drug-induced QT interval prolongation, are the most common reasons for the restriction and withdrawal of marketed drugs today [3]. During the period of 1975–2000, the US Food and Drug Administration removed 16 drugs from the market because of safety concerns; of these, 4 drugs were removed because of their association with QT interval prolongation associated with torsades de pointes [4]. Prolongation of the QT interval is attained by inhibiting the

Received 24 October 2006; accepted 5 December 2006; electronically published 1 February 2007.

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**Clinical Infectious Diseases** 2007;44:e67–e68

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1058-4838/2007/4406-00E3\$15.00

DOI: 10.1086/511875

repolarization cycle and efflux of potassium ions. HERG, a human ether a-go-go-related gene, encodes a potassium-channel protein that regulates a major repolarizing potassium current ( $I_{kr}$ ). A study of patients who experienced drug-induced arrhythmia found mutations in HERG that diminished potassium flux at baseline, rendering patients susceptible to QT interval prolongation [5]. Virtually all drugs that prolong the QT interval and cause torsades de pointes inhibit the  $I_{kr}$  through HERG inhibition [1, 3]. Anson et al. [1] reported in vitro data that suggested evidence of lopinavir dose-related blockage of the HERG potassium channels and  $I_{kr}$ . Similar results were found with nelfinavir, ritonavir, and saquinavir therapies.

Independent risk factors that can predispose a person to QT interval prolongation and torsades de pointes include older age, female sex, bradycardia, electrolyte abnormalities (including hypokalemia and hypomagnesemia), congestive heart failure, a baseline prolonged QT interval, and ion-channel polymorphisms [3]. Drug-drug interactions must also be considered. Inhibition of cytochrome p450 can decrease metabolism of the protease inhibitors, thus increasing the possibility of QT interval prolongation [1].

In summary, our patient had predisposing risk factors for the development of a prolonged QT interval and torsades de pointes. The patient's sex, age, and history of left ventricular dysfunction may have partly contributed to her prolonged QT

interval and torsades de pointes after she started receiving a protease inhibitor antiretroviral regimen. The prevalence of such adverse effects with the protease inhibitor class is unknown. Routine electrocardiogram screenings for all patients starting antiretroviral therapy is currently not recommended. However, patients who have underlying risk factors for drug-induced prolonged QT intervals may benefit from closer observation and baseline 12-lead electrocardiograms to monitor for abnormalities while receiving protease inhibitors.

## Acknowledgments

*Potential conflicts of interest.* T.L.: no conflicts.

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