BRIEF REPORT

Ritonavir-Boosted Atazanavir, Methadone, and Ventricular Tachycardia: 2 Case Reports

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We describe 2 cases of symptomatic ventricular tachycardia associated with prolonged QT interval. Both patients were infected with the human immunodeficiency virus and were receiving treatment with ritonavir-boosted atazanavir and methadone. Discontinuation of atazanavir in both cases resulted in a reduction in the QT interval and cessation of arrhythmia. We concluded that atazanavir contributed to prolonged corrected QT interval and subsequent ventricular tachycardia.

The HIV type 1 (HIV-1) protease inhibitor atazanavir, pharmacologically boosted with ritonavir (ATVr), is recommended in combination with other antiretrovirals as first-line therapy for HIV-1 infection [1]. ATVr can be used in antiretroviral-naive patients receiving treatment with methadone, because ATVr is administered once per day and does not alter methadone concentrations [2].

Both methadone and protease inhibitors have the potential to prolong the QT interval [3, 4]. To date, there has been only 1 report of torsades de pointes ventricular tachycardia (VT) being associated with atazanavir [5], and that use of atazanavir did not include coadministration of methadone. However, little is known about the effects on the QT interval or the risk of VT with combined methadone and atazanavir treatment. We report 2 recent cases of symptomatic VT associated with prolonged QT interval in HIV-1–infected patients who had received both ATVr and methadone.

Case 1. A 47-year-old HIV-1–infected man, a former injection drug user, presented to the Mater Misericordiae University Hospital (Dublin, Ireland) in May 2007 with a fractured humerus sustained during a syncopal episode. He reported that syncopal episodes occurred several times per week over the previous months. He received a diagnosis of HIV-1 infection in 1991 and had been controlling his infection with antiretroviral treatment comprising ATVr (300 mg and 100 mg of atazanavir and ritonavir, respectively, per day), tenofovir (300 mg per day), and emtricitabine (200 mg per day) since 2004 (recent $CD4^+$ T cell count, 379 cells/μL; HIV-1 RNA level, <50 copies/mL). Other medications included methadone (120 mg per day), flurazepam (30 mg per day), and diazepam (10 mg 3 times per day).

Electrocardiograph at hospital admission revealed prolonged corrected QT interval (QTc) of 589 ms (figure 1*A*), and cardiac telemetry (figure 1*B*) revealed frequent episodes of sustained VT that coincided with subsequent syncopal episodes. There were no electrolyte abnormalities, and the trough atazanavir level (247 ng/mL) was therapeutic. Antiretroviral and benzodiazepine therapy was stopped, but methadone treatment was continued. Three days later, the QTc had decreased to 521 ms, with no further episodes of VT. When the patient was discharged from the hospital, methadone treatment was continued and benzodiazepine therapy was resumed; at follow-up in July 2007, his QTc was 461 ms.

In August 2007, the patient was readmitted to the hospital, and antiretroviral treatment comprising ritonavir-boosted fosamprenavir, tenofovir, and emtricitabine was commenced, with cardiac monitoring. QTc was unchanged (500 ms before antiretroviral initiation and 480 ms 3 days after antiretroviral initiation), and there have been no further symptomatic arrythmias. We, therefore, concluded that atazanavir contributed to prolonged QTc and subsequent VT.

Case 2. A 37-year-old HIV-1–infected man, a former injection drug user, presented to the emergency department at Mater Misericordiae University Hospital in May 2007 after a witnessed collapse, which lasted ~1 min and occurred several hours after the patient ingested 12 flurazepam tablets (30 mg each). The patient experienced an additional collapse in the hospital, during which an electrocardiograph revealed VT, and the patient underwent emergency electrical cardioversion. A subsequent electrocardiograph revealed a QTc of 541 ms (figure 1*C*) that persisted after correction of hypokalemia (potassium level, 2.7 mmol/L), with a QTc of 521 ms 1 day after presentation.

The patient had received a diagnosis of HIV-1 infection in

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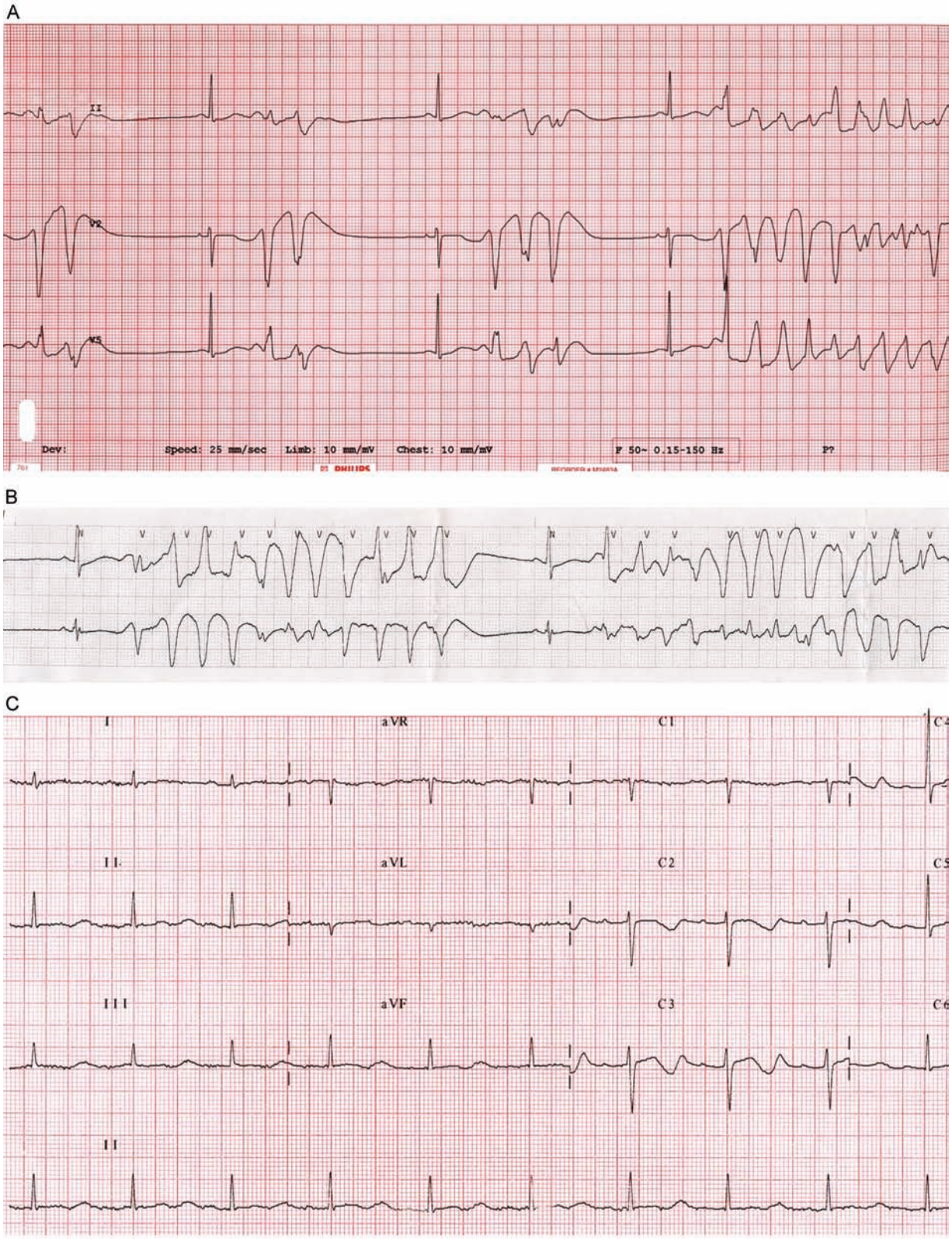

Figure 1. *A,* Electrocardiograph revealing prolonged QT interval and ventricular tachycardia. *B,* Cardiac telemetry revealing ventricular tachycardia. *C,* Electrocardiograph with prolonged QT interval after electrical cardioversion.

2001, and his condition had been stable with antiretroviral therapy comprising ATVr (300 mg and 100 mg of atazanavir and ritonavir, respectively, per day), abacavir (600 mg per day), and lamivudine (300 mg per day) since January 2007 ($CD4^+$ T cell count, 432 cells/μL; HIV-1 RNA level, 152 copies/mL). Other medications included methadone (80 mg per day) and diazepam (5 mg 3 times per day). All antiretrovirals were discontinued (methadone was maintained), and QTc decreased to 468 ms and 408 ms at 3 and 5 days after admission, respectively. Because the QT interval had returned to normal, we rechallenged with ATVr, with cardiac monitoring, which resulted in an increase in QTc (mean QTc during 6 days of follow-up, 431 ms; range, 421–441 ms). We again concluded that atazanavir contributed to the prolonged QT interval and subsequent VT.

Discussion. Prolongation of the QT interval to >500 ms confers increased risk of torsades de pointes VT [6]. These 2 recent cases demonstrate prolonged QTc and life-threatening VT in HIV-1–infected patients given treatment with ATVr and methadone. Drug-induced torsades de pointes is caused by suppression of cardiac myocyte repolarization of potassium currents, regulated by human ether-a-go-go–related gene *(HERG)* ion channels, which are blocked by protease inhibitors in vitro [3]. High-dose methadone (>200 mL per day) prolongs the QT interval [4], and atazanavir inhibits the repolarizing potassium current in vitro [7], although it did not prolong the QTc in 1 clinical study [8]. Further research is needed to determine the effect of concomitant administration of atazanavir and methadone on repolarization of the potassium current and the resultant effects on the QT interval.

In both cases described here, we believe that concomitant exposure to ATVr and methadone likely contributed to prolonged QTc, which resulted in torsades de pointes. In both cases, discontinuation of ATVr resulted in a significant reduction of the QT interval; in the second case, the reduction was to a level that permitted safe rechallenge under close monitoring and resulted in QT interval prolongation to a level that is considered to be borderline (431 ms) in an adult male [9].

In contrast to the case of VT described by Ly and Ruiz [5], which occurred in an elderly patient with congestive cardiac failure who was undergoing hemodialysis, our 2 cases differ significantly because they occurred in younger patients receiving methadone who had normal renal function and no history of cardiac disease and who would not normally be candidates for routine cardiac monitoring. Subsequent to these 2 cases, a third patient from our clinic, who had been prescribed methadone and atazanavir, was admitted to another hospital with a similar presentation [10]. Although there are important potential confounders, such as a benzodiazepine overdose in our case 2, we could find no reports of flurazepam affecting the QT interval. Nevertheless, this number of cases presenting so close together raises concerns that VT may occur with increasing frequency in patients who are prescribed atazanavir and methadone, which underlines the urgent need for increased pharmacovigilance of a population not known for health vigilance and the need for further research into this serious condition.

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