Case Report

Atazanavir Induced First Degree Atrioventricular Block and Ventricular Tachycardia: A Case Report

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Atazanavir is one highly active antiretroviral therapy for naïve patients or patients with previous regimen failure. However, it seems that the protease inhibitor induces hyperlipidemia. Hyperbillirubinemia is the most common clinical adverse events but reports of cardiotoxicity due to atazanavir are scarce. The authors report a patient who had QT prolongation, first-degree atrioventricularblock, and ventricular tachycardia. After atazanavir/ritonavir discontinuation, this patient got better and had normal electrocardiography. Lopinavir/ritonavir was carefully reintroduced during hospitalization without any adverse drug reaction. Atazanavir induced cardiotoxicity has to be monitored when using protease inhibitors.

Keywords: *Atazanavir, first-degree atrioventricular block, ventricular tachycardia*

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Atazanavir (ATV), a protease inhibitor (PI), is a drug used as part of antiretroviral therapy for naïve patients or experienced patients on a failing regimen. ATV acts as protease enzyme blocking. It inhibits the cleavage of precursor proteins for viral maturation. Because of its long half-life, it is a once-daily regimen. The ATV or ATV/boosted with ritonavir(ATV/r) is a convenient medication that could improve patient adherence. Moreover, in contrast with other PIs, ATV has lesser effects on the patient's lipid profile. Therefore, they were widely used in the clinical practice[1,2]. Normally, hyperbilirubinemia is asymptomatically found in ATV use[2,3]. The most common adverse drug reactions are nausea (4-14%), vomiting (4%), jaundice/scleral icterus (5-7%), and rash (3-7%)[4,5]. However, post-marketing experience of the rare adverse events have been reported such as arthralgia, edema, pancreatitis, hyperglycemia, nephrolithiasis, and cardiovascular events including prolonged PR interval, first-degree AV block, prolonged QT interval, and Torsades de pointes[3]. The present report shows QT prolongation and first-degree AV block with ventricular tachycardia after administration of ATV/r combined with zidovudine and lamivudine in an experienced HIV patient.

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Case Report

A 58-year-old male patient who had been an HIV infected patient with right basal ganglion hemorrhage was admitted due to syncope. He also had dyslipidemia and chronic kidney disease at stage 3. His medication regimen prior to hospitalization included aspirin (300 mg per day), gemfibrozil (600 mg per day), rosuvastatin (10 mg per day), zidovudine (400 mg per day), lamivudine (300 mg per day), ATV (300 mg per day), and RTV (100 mg per day). At emergency room, he developed hypotension and his electrocardiography showed wide-complex tachycardia. The ventricular tachycardia developed and he was defibrillated. He also received intravenous amiodarone. ATV and RTV were stopped due to suspected QT prolongation agents. While admitted in the intensive care unit, the serial EKG showed ventricular tachycardia and turned to first-degree AV block with left anterior fascicular block on the first day. It became first-degree AV block without ventricular tachycardia a later day. The corrected QT intervals were 455, 508, and 400 milliseconds at two, three, and six day after ATV/r discontinuation. Considering a good clinical symptom and QT interval normalization,

the patient was carefully started on lopinavir/ritonavir (400/100 mg twice daily) with continued EKG monitoring. His condition was stable and no QT interval prolongation was noticed. He could be discharged and returned to follow-up at the out-patient HIV clinic without any adverse events.

Discussion

QT interval prolongation is a heart condition delayed repolarization period. This phenomenon is associated with ventricular tachycardia and torsade de pointes. It can cause sudden cardiac death[6]. The QT prolongation represents as congenital abnormality inherited in an autosomal dominant or recessive. The acquired long QT syndrome occurs only after the administration of certain medications[7] such as anti-arrhythmic agents, antimicrobial agents (macrolides and fluoroquinolones), anti-psychotic agents, and antiemetic agents (e.g. cisapride)[8,9]. Genetic mutations may make it more susceptible to drug-induced QT interval prolongation[7,8]. ATV has been approved by the US Food and Drug Administration (FDA) since June 2003, for use with other active agents as part of the highly active antiretroviral therapy (HAART)[1]. It has been reported to induce prolonged PR interval, first-degree AV block, prolonged QT interval, and Torsades de pointes by inhibiting a rectifier potassium current (Ikr) channel encoded by human ether-a-go-go related gene (HERG)[6,10]. Anson et al showed that lopinavir, nelfinavir, ritonavir, and saquinavir caused dose-dependent block of Ikr channels expressed in HEK293 cells in vitro. These findings suggested that PIs might be medications to induce QT prolongation and torsade de pointes[11]. Moreover, Soliman et al performed the study of the changes in corrected QT (cQT) after 12 and 24 months of randomization in PIs group (saquinavir, lopinavir, atazanavir, and other protease inhibitor/r), and non-nucleotide reverse transcriptase inhibitor (NNRTI) group. The different cQT between boosted PIs and the NNRTI group was significant level and discontinuation of PIs could reduce the prolonged duration. However, the clinical relevance of the different QT interval has to be confirmed in a further study[12].

Previously, only one case report of 59-year-old female HIV infected patient with congestive heart failure who had been received ATV 400 mg per day combined with zidovudine and lamivudine for a month, experienced a QT interval prolongation that developed to ventricular arrhythmias and torsades de pointes[13]. In contrast with the present case, no underlying cardiac or coronary diseases were diagnosed, precipitating to the prolonged QT interval. Additionally, bradycardia, hypoglycemia, high body mass index, intracranial trauma, hypomagnesemia, hypokalemia, and drug-drug interaction except hypercholesterolemia, which is a factor to predispose to QT prolongation, were not detected in the present case. However, the authors cannot exclude the unknown factors of ion channel polymorphism and congenital long QT syndrome recognized as predisposing factors[6,7,10]. Fortunately, the present case could successfully re-challenge lopinavir/r without any cardiac conditions. Although in vitro study showed the PIs can block HERG channels and may induce QT prolongation, the clinical evidence is hard to absolutely indicate cardiotoxicity as a class effect. This issue needs to be studied.

In conclusion, ATV induced QT interval prolongation is a rare adverse drug reaction but this is a serious condition that cause death. The present case had no obviously predisposing cardiac factors or electrolyte imbalance for QT interval prolongation. However, the hypercholesterolemia and unknown potassium channels polymorphism were ignored. The re-challenge of lopinavir/r or other PIs might be successful because the cardiologic class effect is unknown. However, monitoring the EKG monitor closely by the cardiologist during reintroduction is required.

Potential conflicts of interest

None.

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First degree atrioventricular block และ ventricular tachycardia ชักนำโดยยาอะตาซานาเวีย: รายงานผู้ป่วย 1 ราย

วิชัย สันติมาลีวรกุล, สุทธิพร ภัทรชยากุล, ศรัญญู ชูศรี, พรรณทิพย์ ฉายากุล

อะตาซานาเวียเป็นยาต้านไวรัสเอชไอวีประสิทธิภาพสูงตัวหนึ่ง สำหรับผู้ป่วยผู้ไม่เคยใช้ยามาก่อน หรือ ในผู้ป่วยผู้ล้มเหลวจากยาสูตรอื่น และดูเหมือนเป็นยาชักนำภาวะไขมันเกินกว่าปกติน้อยที่สุดในกลุ่มโปรตีเอส อินฮิบิเตอร์ ภาวะบิลลิรูบินในเลือดมากกว่าปกติเป็นผลข้างเคียงคลินิกพบบ่อยที่สุด แต่รายงานภาวะพิษต่อหัวใจเนื่องจากยาอะตาซานาเวียเป็นสิ่งน่าตกใจ ผู้นิพนธ์รายงานผู้ป่วย 1 ราย ผู้มีภาวะ QT prolongation, first degree atrioventricular block และ ventricular tachycardia หลังจากระงับใช้ยาอะตาซานาเวีย/ริโทรนาเวีย ผู้ป่วยดีขึ้น และคลื่นไฟฟ้าหัวใจปกติ เริ่มให้ยาโลปินาเวีย/ริโทรนาเวียใหม่ด้วยความระมัดระวังระหว่างอยู่โรงพยาบาล โดยปราศจากผลข้างเคียงใด ยาอะตาซานาเวียชักนำภาวะพิษต่อหัวใจต้องมีการตรวจเตือนในยุคใช้ยา ยากลุ่มโปรตีเอส อินฮิบิเตอร์ อย่างแพร่หลาย