Atazanavir Causing CNS Toxicity? Unexplained Neurological Symptoms in Two Patients Recently Started on Atazanavir

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Abstract
To date only one published case report exists of the HIV protease inhibitor atazanavir (ATV) causing central nervous system (CNS) side effects. We report two such cases of patients experiencing disabling CNS side effects shortly after starting ATV-containing regimens whose symptoms only resolved after withdrawing the drug.

Case
A 39-year-old, homosexual man from the Philippines was diagnosed with HIV (no resistance mutations, CD4 count 315 cells/µl, HIV viral load 120,033 copies/ml) and hepatitis B (HBV) infections (HBV e antigen negative, HBV DNA 2349 IU/ml). Three months after diagnosis he was started on a one-pill combination regimen of tenofovir, emtricitabine and efavirenz (TDF/FTC/EFV). After 10 days he developed a widespread erythematous rash without mucosal involvement and TDF/FTC/EFV was stopped immediately. Routine biochemistry and hematology blood tests done at this time were all within normal limits and he was started on a new regimen of TDF/FTC and ritonavir-boosted atazanavir (ATV/r; 300 mg/100 mg) once daily.

He returned to the clinic 2 weeks later complaining of weakness, mild headache, agitation and difficulty sleeping in the first week of taking his new regimen. This had progressed and after the second week, 4 hours after taking his antiretrovirals in the morning he became disoriented in time and place, described severe vertigo and became tremulous. These episodes occurred for 5 consecutive days and lasted approximately 3 hours each time.

He tried taking his antiretrovirals at night; his partner reported that 3 hours after taking the medication he woke up from sleep completely disoriented and complained of nausea and extreme vertigo rendering him unable to walk. The patient stopped his antiretrovirals of his own volition after this night-time episode. He was seen in clinic 48 hours later by which time he was completely asymptomatic; he was apyrexial and all other vital signs were within normal limits. Routine biochemistry and hematology blood tests done at this time were all within normal limits and he was started on a new regimen of TDF/FTC and ritonavir-boosted atazanavir (ATV/r; 300 mg/100 mg) once daily.

A second patient was an Ecuadorian woman diagnosed with HIV at diagnosis (CD4 count 315 cells/µl) and hepatitis B (HBV) infections (HBV e antigen negative, HBV DNA 2349 IU/ml). Three months after diagnosis she was started on a one-pill combination regimen of tenofovir, emtricitabine and efavirenz (TDF/FTC/EFV). After 10 days she developed a widespread erythematous rash without mucosal involvement and TDF/FTC/EFV was stopped immediately. Routine biochemistry and hematology blood tests done at this time were all within normal limits and she was switched back to her previous regimen of TDF, 3TC and LPV/r and seen 1 week later, by which time her symptoms had subsided completely.

Discussion
To our knowledge there is only one published case report of similar side effects in a patient taking ATV. In this case the patient had a 3-year history of ATV, 3TC and TDF use and was admitted to hospital for objective vertigo, nausea and sweating triggered by postural changes. He was diagnosed as having lithiasis of his posterior semicircular canal, possibly related to his ATV use [1].

It is well known that ATV/r is associated with renal lithiasis and there have been reports of ATV-associated choledocholithiasis [2-4]. We can postulate that our patients may have had semicircular canal lithiasis causing similar symptoms, though the short duration between onset and starting the drug and the complete resolution of symptoms after stopping the drug make this mechanism less likely.

It is known that cerebro-spinal fluid (CSF) concentrations of ATV are usually 100-fold lower than plasma concentrations. If CSF concentrations are a reasonable surrogate marker for antiretroviral drug levels in the brain we should expect lower levels of CNS toxicity [5,6]. This has however been refuted by a recent US study examining antiretroviral neurotoxicity using sensitive indices of neural damage and there have been reports of ATV-associated choledocholithiasis [2-4]. We can postulate that our patients may have had semicircular canal lithiasis causing similar symptoms, though the short duration between onset and starting the drug and the complete resolution of symptoms after stopping the drug make this mechanism less likely.

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prior to employing investigative methods for assessing the cause of vertigo such as using the Dix Hallpike manoeuvre to aid in the diagnosis of benign paroxysmal positional vertigo. A MRI may also have been useful in the first patient to exclude diffuse CNS involvement. A further limitation is that ATV levels may have been helpful in both cases to ascertain if toxic serum concentrations of the drug could provide an explanation for the symptoms.

**Conclusion**

Our cases demonstrate possible treatment-limiting CNS side effects in patients recently started on ATV. Clinicians should consider withdrawing ATV in patients taking the drug if such symptoms occur without another clear aetiology.

**References**