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Transient cardiac arrhythmias related to lopinavir/ritonavir in two patients with HIV infection


A Department of Medicine, Cairns Base Hospital, PO Box 902, Cairns, Qld 4870, Australia.

B Department of Clinical, Immunology and Immunogenetics, Centre for Clinical Pharmacology and Infectious Diseases, Royal Perth Hospital, 2nd Floor North Block, Wellington Street, Perth, WA 6000, Australia.

C Cairns Sexual Health Service, Cairns Base Hospital, PO Box 902, Cairns, Qld 4870, Australia.

D Melbourne School of Population Health, Level 5, 207 Bouverie Street, The University of Melbourne, Vic. 3010, Australia.

E Department of Molecular Medicine and Surgery, D2:04, Karolinska Institute, Stockholm, 171 76, Sweden.

Abstract

A 42-year-old Thai man was administered the combination drugs lopinavir/ritonavir and abacavir/lamivudine. On day 3 he was admitted and his electrocardiogram demonstrated sinus arrest with junctional escape rhythm with a rate of 42 min⁻¹. Three days after stopping the medication he reverted to normal sinus rhythm. A 55-year-old Caucasian man was admitted to hospital with triple vessel disease. He had a permanent pace maker inserted 4 years previously for Mobitz type II AV
block detected on stress electrocardiogram, which developed 1 month after initiation of lopinavir/ritonavir. These two cases highlight the importance of considering lopinavir/ritonavir induced arrhythmias when dealing with HIV-positive individuals.

**Additional keyword:** antiretroviral therapy.

**Introduction**

The United States Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents panel considers lopinavir/ritonavir (co-formulated, given twice daily) as a preferred protease inhibitor (PI) for the treatment-naïve patient. Side-effects with antiretroviral (ARV) therapy are common; however, many side-effects improve over time with continued administration. We present two cases with severe cardiac arrhythmias occurring within 1 month of lopinavir/ritonavir initiation to create awareness about this uncommon but very serious adverse effect.

**Case 1**

A 53 kg, 42-year-old Northern Thai man who was a resident in Australia presented to the sexual health clinic with recent single dermatomal herpes zoster infection. He was also known to be Venereal Disease Research Laboratory (VDRL) positive, although no clinical evidence of syphilis on history or examination could be elucidated. In the medical examination for immigration he had been found to be antibody positive for HIV-1 infection. However, he had never received ARVs, or any primary or secondary prophylactic medications for opportunistic infections. He was unaware of any other medical condition. His HIV-1 viral RNA load at the first visit was 13 200 copies mL\(^{-1}\) and CD4 count 440 cells mL\(^{-1}\) (22%). CD4 count subsequently dropped to 390 cells mL\(^{-1}\) (22%) 4 months later. After
discussion the patient opted to commence ARV therapy. He was commenced on the combination of lopinavir/ritonavir tablets (400 mg/100 mg bd) plus a fixed dose combination of abacavir 600 mg and lamivudine 300 mg once daily. After three doses of lopinavir/ritonavir and two of abacavir/lamivudine, he presented to the clinic with ‘dizziness’, and on examination was found to be bradycardic. He was immediately referred to the Emergency Department where his electrocardiogram (ECG) was found to be suggestive of sinus arrest with junctional escape rhythm (Fig. 1A). Based on the temporal pattern of symptoms, related to initiation of ARV, an adverse drug reaction (ADR) was suspected and all ARVs were stopped. He was admitted to the hospital and he required cardiac monitoring for 72 h because of his variable pattern of supraventricular arrhythmias (Fig. 1B, C). He did not require any anticholinergic or sympathomimetic medications. During monitoring he had intermittent sinus bradycardia with wide rate variation and atrial fibrillation before returning to normal sinus rhythm. An echocardiogram demonstrated a structurally and functionally normal heart.

Furthermore, a mild anaemia with profound microcytosis was found. Due to his ethnicity, thalassemia and secondary hemochromatosis as a cause of his sick sinus syndrome was considered. However, iron studies and haemoglobin electrophoresis showed α thalassemia without evidence of iron overload.

At review in the sexual health clinic 2 weeks after the admission he was asymptomatic, and in normal sinus rhythm. He was administered tenofovir/emtricitabine and efavirenz, but did not tolerate efavirenz, and was thus switched to nevirapine. This combination was well tolerated.

HLA-B*5701 status was investigated, which has a well established association with abacavir-related hypersensitivity, but this was negative.

Case 2

A few months after the first case was presented, a 55-year-old Caucasian man was admitted to the hospital with angina. A coronary angiogram revealed triple vessel disease. He had a background history of HIV infection diagnosed 15 years earlier and had received various combinations of ARVs
in the past. There was no history of smoking, excessive alcohol intake, diabetes or hypertension. However, ARV-associated dyslipidaemia had been diagnosed 5 months ago. Furthermore, a permanent pacemaker (PPM) had been implanted 4 years previously due to Mobitz type II AV block detected on stress ECG (Fig. 2A). In retrospect, the arrhythmia seemed to have developed soon after re-introduction of lopinavir/ritonavir capsules. He was on this combination as a part of a regimen that also included didanosine and tenofovir. However, previously he had been on this particular combination for a year and did not have any significant cardiac symptoms. Before the reintroduction of lopinavir/ritonavir he was on a regimen containing atazanavir, abacavir and tenofovir. He had further changes in his regime and his current medication list included ritonavir, emtricitabine, tenofovir and fosamprenavir. Unlike our first case he did not have the potentially catastrophic presentation and had a normal baseline ECG. However, the history was suggestive of low output symptoms and palpitations with exertion, occurring within 1 month of lopinavir/ritonavir initiation. Documentation regarding bradycardia and palpitations were noted in medical clinic notes 3 months after initiation of this particular combination. Mobitz type II AV block was presumed as a cause of his symptoms. After PPM was implanted he remained symptom-free for 4 years until his recent presentation. An atrial arrhythmia associated with lopinavir/ritonavir was suspected in light of the recent presentation of the previous case and other reported cases. He did not demonstrate any pacing rhythm on more than 4 days of cardiac telemetric monitoring during two recent admissions (Fig. 2B).

**Discussion**

There are four previous reported cases of atrial arrhythmia in HIV-positive patients treated with lopinavir/ritonavir.2–4 Among them three cases were reported in Japanese individuals and one in a Spanish male. Kichuki et al. reported two Japanese male patients aged 22 and 60 years on ARVs who developed Mobitz type I, second degree AV block and sinus arrest with junctional escape rhythm, respectively, within 48 h of initiation of lopinavir/ritonavir. Rhythm abnormalities in both of these cases resolved and did not recur with cessation of the combination.2 Miwok et al. reported a 62-year-
old Japanese female who developed sinus arrest with junctional escape rhythm alternating with atrial flutter 4 days after initiating lopinavir/ritonavir. The atrial flutter was converted to normal sinus rhythm within 24 h of discontinuation of the medication.\textsuperscript{3} Jimenez \textit{et al.} reported a 50-year-old Spanish male with baseline ECG of partial right bundle and left anterior hemi block, who developed complete atrioventricular block and asystole 48 h after receiving lopinavir/ritonavir. Medication was ceased and a pacemaker was inserted.\textsuperscript{4}

Our patients did not have any previous history of cardiac disease, not even a family history of cardiac arrhythmia or sudden death. Similar to the other four cases described above, our first case developed serious atrial arrhythmias, which resolved after discontinuation of lopinavir/ritonavir. Unfortunately, in our second case these adverse effects were not realised and a pacemaker was implanted 6 months after reintroduction of lopinavir/ritonavir. His history is more convoluted as he was on a similar regimen for a year in the past without any notable cardiac adverse events. Ischemia as a contributor or facilitator for this conduction defect is a possibility; however, the stress ECG did not show any other signs of ischemia. Atazanavir has prospectively been shown not to affect the QTc interval and QTc dispersion in HIV-positive patients although a minor, but statistically significant, increase in PR and QRS intervals were observed.\textsuperscript{5} However, we do not consider Atazanavir as a cause of arrhythmia in our case as he was not on this medication when he developed symptoms and it persisted after 5 months of cessation of Atazanavir.

The second case did not demonstrate any pacing rhythm on cardiac telemetric monitoring during two recent admissions. Repeat stress ECG to look for precipitation of arrhythmias was not justifiable in the acute clinical setting but he denied having palpitations in his day to day activities since PPM insertion. This raises the question of whether the arrhythmogenic effect is more marked with lopinavir/ritonavir combination rather than low-dose ritonavir used in isolation, which is part of his current regimen.

Although HIV-1 related cardiotoxicity has been reported in the literature,\textsuperscript{6} it may not be applicable in our cases because of the lack of features of cardiomyopathy and mitochondrial toxicity. Furthermore,
in the first case, lack of history of preceding ARV therapy, the rapidity of onset in relation to ART initiation, and the temporal profile of improvement in signs and symptoms with cessation of lopinavir/ritonavir was indicative of transient cardiac arrhythmic effect of the particular combination. The role of PIs, including lopinavir/ritonavir, in blocking human ether-a-go-go-related gene potassium channels, predisposing individuals to QT prolongation especially in the setting of various co-medications is well known. PIs prolong QTc and are metabolised by CYP3A4 in the liver, but this does not apply to our cases as there was no evidence of ventricular arrhythmia or QTc prolongation.

HCN4 and SCN5A are recognised genes associated with sinus node dysfunction that are genetically polymorphic. SCN5A gene provides instructions for making a sodium channel that is abundant in the cardiac muscle and certain haplotypes have been described only in Asian populations. Hyperpolarisation activated cyclic nucleotide-gated potassium channel 4, also known as HCN4, is a human gene which codes for the α subunit of the cyclin nucleotide gated cation channel. This channel is thought to contribute to the pacemaker current in the sinus node. We have not specifically looked for genetic polymorphisms in these two target genes in our cases. In view of the recent depth elucidation of genetic polymorphisms in these genes in relation to cardiac arrhythmias, we hypothesise that genotype-specific triggers in combination with the pharmacologic effects of drugs like lopinavir/ritonavir may be important in the predisposition to arrhythmias. Future investigations are warranted in well-phenotyped patients who develop cardiac arrhythmias temporally associated with lopinavir/ritonavir initiation.

**Conclusion**

The use of lopinavir/ritonavir is expanding globally due to the recent formulation of the heat stable tablet and the increased need for other options to treat non-nucleoside reverse transcriptase inhibitor-resistant HIV in resource-poor settings. Cardiac arrhythmias are potentially life-threatening adverse events that have been rarely described in the first few weeks of lopinavir/ritonavir therapy. Although there are no proven mechanisms for the arrhythmogenic properties of lopinavir/ritonavir, our two cases
together with the four previously reported ones highlight the need to further elucidate in particular pharmacogenetic mechanisms or other pharmacodynamic reasons for these arrhythmias in order to select who should not be prescribed this combination. The role of genes known to be responsible for atrial conduction defects had not been investigated in our cases, although testing for HCN4 and SCN5A genes may be useful. The clustering of case reports in an Asian population points towards a possible link between ethnicity and this adverse event. Our cases, both of which occurred within 1 month of lopinavir/ritonavir initiation, and in particular the second case where an association between lopinavir/ritonavir and the ensuing arrhythmia was not initially entertained illustrate the need for increased awareness and vigilance for this potentially fatal adverse event.

**Conflict of interest**

This work has been conducted with no financial support. None of the authors have any conflict of interest.

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Fig. 1. Electrocardiograms of case 1 illustrating (A) sinus arrest with junctional rhythm; (B) atrial fibrillation; (C) sinus bradycardia.
Fig. 2. Electrocardiograms of case 2 illustrating (A) Mobitz type II AV block (4 years earlier) and (B) normal sinus rhythm (at present).