

CONFLICTS OF INTEREST

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Alberto Garay,^a Albert Ariza-Solé,^{a,*} Emad Abu-Assi,^b Victòria Lorente,^a José C. Sánchez-Salado,^a and Ángel Cequier^a

^aServicio de Cardiología, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

^bServicio de Cardiología, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, A Coruña, Spain

*Corresponding author:

E-mail address: aariza@bellvitgehospital.cat (A. Ariza-Solé).

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Symptomatic Bradycardia and Heart Failure Triggered by Ivabradine in a Patient Receiving Antiretroviral Therapy



Bradycardia sintomática e insuficiencia cardíaca precipitadas por ivabradina a una paciente que recibe tratamiento antirretroviral

To the Editor,

Thanks to advances in highly effective antiretroviral therapy (ART), human immunodeficiency virus (HIV) infection has become a chronic disease. HIV-infected patients now have a life-expectancy close to that of the general population and are increasingly affected by cardiovascular diseases, mainly ischemic heart disease and heart failure.¹ ART includes drugs that are unfamiliar to most physicians, and patients sometimes do not recall the details of their medication; moreover, cardiologists are not always thoroughly familiar with their patients' ART or its possible interactions with drugs used routinely in cardiology, thereby increasing safety risks.

We present the case of a 50-year-old woman with a history of essential hypertension and acute myocardial infarction, chronic heart disease with a residual left ventricular ejection fraction of 30%, and virologically and immunologically stable HIV infection (viral load < 20 copies/mL and 1069 CD4 lymphocytes/mL). Her ART included atazanavir, ritonavir, and tenofovir-emtricitabine. She was also taking carvedilol (12.5 mg/12 h), eplerenone (25 mg/24 h), ramipril (2.5 mg/24 h), and aspirin (100 mg/24 h). During an outpatient consultation, her cardiologist decided to add ivabradine (5 mg/12 h) to her regular treatment in order to improve heart rate control. Within 48 h of starting this treatment, the patient developed a general malaise, intense asthenia, and dyspnea at rest. She presented to the emergency room, where a physical examination revealed blood pressure of 80/60 mmHg, a heart rate of 45 bpm, general hypoventilation, and bilateral crackles in the lung bases. Analytical explorations gave normal results for a complete blood count, renal function, and sodium and potassium levels. A plain chest x-ray revealed signs of heart failure, and an electrocardiography examination detected sinus bradycardia at 45 bpm. After admission, the patient's treatment for heart failure was reinforced

and ivabradine was withdrawn. The symptoms disappeared and the patient was released from hospital after 72 h. None of the electrocardiogram traces showed evidence of QT interval prolongation.

Patients infected with HIV often take protease inhibitors, among them ritonavir and nelfinavir, that are also potent inhibitors of cytochrome P450 3A4 (CYP3A4).² Ivabradine is metabolized exclusively via this route, and therefore coadministration with protease inhibitors can considerably increase its plasma concentration, resulting in the development of excessive bradycardia, hypotension, and heart failure. Because of this interaction—described in the summary of product characteristics of protease inhibitors and ivabradine—combined treatment with these drugs is contraindicated. In any event, we have found no other report of a case similar to the one described here.

Other drugs frequently used in cardiology that are contraindicated in conjunction with protease inhibitors are amiodarone (except with atazanavir), flecainide, propafenone, rivaroxaban, lovastatin, simvastatin, and lercanidipine.^{3,4} Coadministration with apixaban and ticagrelor should also be avoided because interactions with protease inhibitors can increase the serum concentrations of these drugs.⁵

Cardiologists who treat patients infected with HIV should have a thorough knowledge of their patients' ART regimens and the possible interactions with the drugs they commonly prescribe. On its website, GESIDA (*Grupo de Estudio del SIDA de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica* [AIDS Study Group, Spanish Society of Infectious Diseases and Clinical Microbiology]) provides numerous very useful action guidelines; of particular relevance to cardiologists is the "*Documento de consenso sobre alteraciones metabólicas y riesgo cardiovascular en pacientes con infección por el VIH (Febrero 2014)*" (Consensus document on metabolic alterations and cardiovascular risk in patients infected with HIV [February 2014]).⁶

José M. Romero-León,* María C. Gálvez-Contreras, and Luis F. Díez-García

Unidad de Enfermedades Infecciosas, Servicio de Medicina Interna, Complejo Hospitalario Torrecárdenas, Almería, Spain

* Corresponding author:

E-mail address: peperomeroleon@hotmail.com

(J.M. Romero-León).

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