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Letter to the Editor

Serious QT interval prolongation with ranolazine and amiodarone

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To the Editor:

QT interval prolongation is an adverse drug reaction (ADR) associated with some antiarrhythmic and non-antiarrhythmic drugs. This ADR can lead to ventricular tachyarrhythmia and *Torsade de Pointes* (TdP) [1].

We report the case of a 78 year-old woman who developed an unusual episode of TdP in the context of the use of ranolazine and amiodarone. In June 2010, the patient was admitted to the emergency department because of worsening angina, dyspnoea and orthopnea. Three days before she was prescribed ranolazine of 375 mg/12 h by her family doctor. Blood tests did not show any electrolyte abnormality, but the ECG tracing showed slow atrial fibrillation (AF) with nodal rhythm (50 bpm), bigeminism and frequent ventricular extrasystoles. She stayed under observation, and few hours later, developed two episodes of polymorphic nonsustained ventricular tachycardia (NSVT), thereafter intravenous amiodarone was started. Despite of the amiodarone, the NSVT evolved to polymorphic sustained ventricular tachycardia (*Torsade de Pointes*) that required a 200 J cardiac defibrillation. The ECG showed a narrowing QRS complex, nodal rhythm (50 bpm) and prolonged QTc interval (580 msec).

The past medical history of the patient included diabetes, dyslipidemia, hypertension, severe chronic renal failure (GFR: 28 ml/min), AF, ischemic heart disease and heart failure. She had been admitted to the hospital throughout the previous 6 months for several episodes of acute heart failure secondary to rapid AF and/or angina. She was in treatment with aspirin, topiramate, simvastatin, furosemide, omeprazole, acenocoumarol, nitro-glycerine, hydralazine, glicazide and allopurinol.

In the current hospitalization, the patient was admitted in the intensive care unit. None significant injury was found in heart catheterization. The echocardiogram showed a slightly dilated and hypertrophied left ventricle with inferior hypocinesia, a severe mitral valve regurgitation, and an ejection fraction of 37%, similar to the one recorded in January-2010. Finally, her cardiac rhythm in AF was recovered with low doses of β-blockers. The QT interval was gradually normalized, without new arrhythmic events. Ranolazine and amiodarone were withdrawn.

TdP is related to the QT interval prolongation usually due to the inhibition of the rapid outward potassium currents (IKr)[1]. Amiodarone is a multichannel antiarrhythmic drug with the lowest incidence rate of TdP. (< 1%) [1,2]. However some clinical conditions (e.g., electrolyte disorders, bradycardia and concomitant administration of drugs with high proarrhythmic risk) and concomitant use of amiodarone have been associated to an increased of the risk of TdP [3,4]. Moreover amiodarone is metabolized by cytochrome P-450 (CYP3A4)[4]. The interaction profile of this drug is mainly associated with its inhibitory activity, but amiodarone is also a substrate of CYP3A4. Therefore drugs that inhibit this isoenzyme could increase the concentration of amiodarone. It has been suggested that the concomitant use of amiodarone and metronidazol could produce cardiac toxicity due to CYP3A4 inhibition [5].

Ranolazine is a new second-line drug recommended in patients with stable angina inadequately controlled or intolerant to first-line drugs. Ranolazine produces myocardial relaxation through inhibition of the delayed current of sodium. Its use should be avoided in severe renal impairment due to a 2-fold AUC increase [6,7]. Ranolazine has a theoretical risk of developing TdP due to the inhibition of IKr channels in high doses and therefore the enlargement of QT interval. Pivotal clinical studies of ranolazine showed 2 cases of TdP (placebo and ranolazine group, one each) [6,8]. Thus, its use is contraindicated in patients with high risk of QT interval prolongation, and it is not recommended to be used in association with other QT interval prolonging drugs such as class Ia and III antiarrhythmic; except amiodarone [6].

In addition, ranolazine is a substrate of cytochrome P-450 (CYP 3A4), and has been reported as a mild inhibitor of CYP3A4 and P-glycoprotein; for this reason its interaction profile includes a warning about increased concentrations of simvastatin, and suggests a careful use with other substrates of CYP3A4 [6]. Recently, it has published a case of high plasma concentrations of tacrolimus (substrate of CYP3A4) attributed to the inhibition of cytochrome P-450 induced by ranolazine [9].

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A recent study has shown the efficacy of ranolazine + amiodarone in the treatment of supraventricular arrhythmia and it has been suggested that the combination of these two drugs does not increase the risk of arrhythmic events [10]. However it should be highlighted that all patients with high cardiac risk or with prior exposure to ranolazine were excluded. Thus, the safety of this combination remains unclear and some large studies are currently ongoing [11].

In our case, the patient had cardiac risk factors that could contribute to the appearance of TdP, despite this, the strong temporal relation between ranolazine + amiodarone administration and the TdP episode suggests a potential causal relationship. Moreover an inappropriate use of ranolazine (the patient's severe renal impairment was overlooked) could increase the exposure to the drug. This high ranolazine plasma concentration may have affected the metabolism of intravenous amiodarone, and this drug interaction could have produced QT interval prolongation and TdP. The feasible inhibition of potassium channels due to amiodarone and ranolazine together should not be excluded.

The case described herein together with the current knowledge about these drugs suggests that amiodarone + ranolazine should be only prescribed in patients without cardiac and/or renal risk factors. Ranolazine is a new drug; thereby its interaction profile and the potential risk of TdP remain unknown. Clinicians should be aware of this possible interaction, keeping in mind that sometimes the inappropriate use of drugs could precipitate a serious ADR.

Contributions of authors statement

EM and ALA have recovered the patient's complete medical history, upon the request of the Spanish Pharmacovigilance System (SPvS). MT identified and assessed the described cases in the SPvS database. She searched literature related Ranolazine safety and wrote the first draft. EM, GC and AF have contributed to the first draft with relevant comments. GC, AF and MT made corrections to the final version.

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