Cardiovasc Toxicol
DOI 10.1007/s12012-014-9274-y

Torsades de Pointes Induced by the Concomitant Use of Ivabradine and Azithromycin: An Unexpected Dangerous Interaction

Giuseppe Cocco · Paul Jerie

Abstract A 68-year-old man had a cardiac syncope. He was known to have a long QT-interval and was treated with ivabradine for paroxysmal sinusal tachycardia. In the last 5 days, azithromycin had been prescribed for sinusitis. An electrocardiogram showed torsades de pointes (TdP). Azithromycin is known to prolong the QT-interval. Ivabradine does not affect the QT-interval but has a conditional risk of TdP when taken with other drugs that block its metabolic breakdown. This case presents the specific problem of a patient with long QT who received two medications, which may interact and prolong the QT.

Keywords Pharmacodynamic toxicity · Torsades de pointes · Azithromycin · Ivabradine · Proarrhythmic effect

Clinical Case

We follow a 68-year-old man who recently had a cardiac syncope. Occasional bronchial hyperreactivity was known since childhood and was treated with salbutamol spray on need. When he was 18 year old, during a medical checkup for the military service, in his ECG, a long corrected QT-interval (QTc) was found. The QTc fluctuated between 490 and 560 ms. The patient was asymptomatic and refused genetic testing. An accurate family history did not detect cases of either severe arrhythmias or sudden death. The patient did not smoke, had never used illicit drugs and had a normal body weight. He jogged and had a good physical work capacity.

G. Cocco (✉) · P. Jerie
Cardiology Office, Postfach 119, Marktgasse 10A,
4310 Rheinfelden, Switzerland
e-mail: praxis@cocco.ch

Since 4 years, the patient complained of paroxysmal long-lasting palpitations, especially when jogging. He had never fainted. Cardiac anatomy and function were normal. Two 1-week dynamic-ECGs had detected a symptomatic, mostly exertional, sinusal tachycardia (up to 160 beats/min) with normal PR-value and a narrow QRS-morphology; there was no evidence for preexcitation or re-entry arrhythmias; rare (<1 %), isolated, supraventricular and ventricular premature beats were documented. A long QTc was confirmed (between 490 and 560 ms), and the maximal value was recorded at night during the sleep. The sinusal tachycardia was considered to be related to the known bronchial hyperreagibility. A therapy with the cardio-selective β-blocker bisoprololo was discontinued because of an asthmatic reaction. A therapy with diltiazem was also discontinued because of fatigue and ankles edema. The patient was treated with ivabradine 7.5 mg b.i.d. The drug was reasonably effective and well tolerated. In the 5 days preceding the syncope, his family physician had prescribed azithromycin for acute sinusitis. The syncope occurred without warning symptoms while the patient was walking in the garden. The patient had not used salbutamol in the preceding days. An ECG (Fig. 1) was recorded 30 min later and detected ventricular torsades de pointes (TdP). The patient was hospitalized. The pulmonary function was normal, and the arterial O_2-concentration was 98 % while he was breathing room air. Hematology, hepatic, renal function and serum electrolytes (Na^+, K^+, Ca^{++} and Cl^-) were normal. An infusion of magnesium sulfate was started, the TdP disappeared and the recovery was uneventful. During the follow-up, the patient remained asymptomatic. An ECG (Fig. 2) shows the known long QTc. The therapy with ivabradine was continued but the patient was instructed to avoid azithromycin and received a list of drugs, which are known to prolong the QT-interval

Published online: 27 August 2014

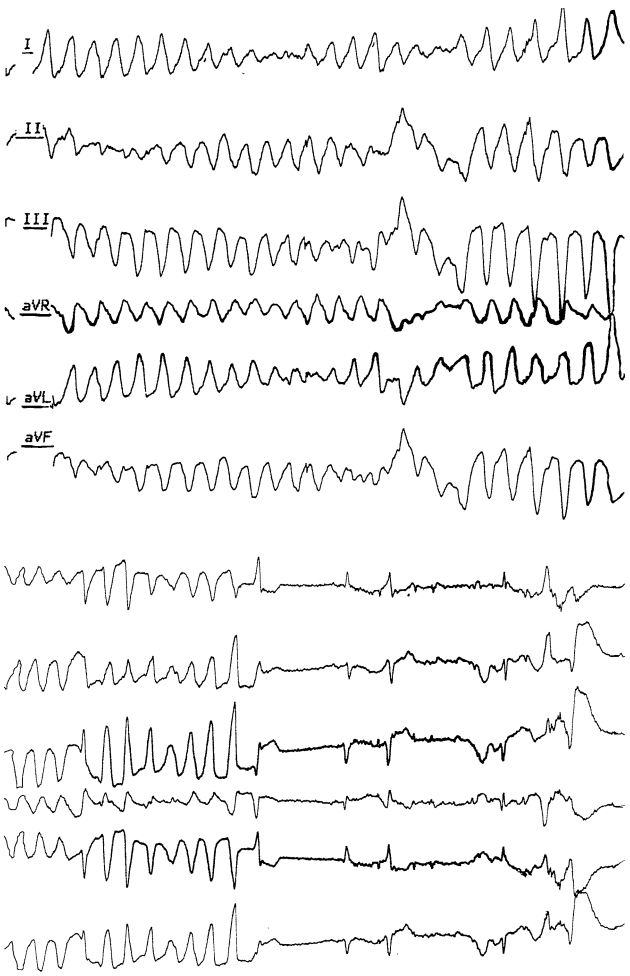

Fig. 1 ECG recorded 30 min. after the syncope, showing TdP. The paper speed is 25 mm/s, and the amplitude is 10 mm/mV. The heart rate is >150/min, and one recognizes the typical aspect of the ventricular TdP

and predispose to the risk of TdP. Till now, the TdP did not recur.

QT-interval

The best method to measure the QTc-interval is not yet established. Despite Simonson's warning in 1961 that Bazett's QT correction formula could not be recommended, this formula is still the most popular, even if it seems that other formulas, such as the Fridericia's formula, should be more accurate [1]. In the ECG shown in Fig. 2, the QTc was: 532 ms according to the software (Marquette Hellige, CardioSys V6.73); 549 ms with the Bazett's formula; and 524 ms with the Fridericia's formula. With any formula, the patient's QT is long (between 524 and 549 ms).

Discussion

In recent years, many "old" drugs had to include "black box" warning because of proarrhythmic effects [2, 3]. Cardiac diseases and the cardiovascular side effects of drugs are essentially multifactorial problems involving interactions between many proteins, dependent on highly organized cell, tissue and organ structures. This is one reason why the cardiovascular side effects of medications are often unanticipated. Since 2005, new drugs have to undergo a "thorough QT study" (TQT) [4]. However, even TQT studies may fail to detect proarrhythmic effects before medications are used in clinical practice. Drug-induced prolongation of the QTc is a relevant adverse event especially in patients with several cardiovascular conditions and often under polytherapy. Some drugs are particularly important because interactions with frequently used medications can increase the risk of TdP. One interaction involves the co-prescription of a medication that prolongs the QTc with another one that increases the plasma concentration of the first drug (pharmacokinetic interaction). Another interaction involves the co-administration of medications, each with prolonging effects on the QTc (pharmacodynamic interaction). Estimating the risk of these interactions is difficult. Most of what is known about drug-induced QTc prolongation derives from reports.

It is known that the macrolide antibiotic azithromycin may prolong the QT [5]. Thus, one might assume that in this patient with preexisting long QTc, azithromycin induced TdP and ivabradine was an innocent bystander.

Ivabradine is a selective I*f*-inhibitor and thus reduces heart rate in patients who are in sinus rhythm. It was found that, by reducing heart rate, ivabradine expectedly prolongs the QT-interval, but after appropriate correction for heart rate, it lacks a significant effect on ventricular repolarization [6]. From the known pharmacology, for obvious reasons, ivabradine should not be co-administered with drugs, which have known rate-lowering or QT-prolonging effects, but it was assumed that the drug has no direct torsadogenic potential. However, there are no absolutes and, as Bernard Shaw wrote "The golden rule is that there is no golden rule." After oral administration, the hepatic clearance of ivabradine accounts for 80 % of its total clearance, and the other 20 % is cleared through the kidneys; the cytochrome P450 3A4 (CYP3A4) isoform is mainly involved in its metabolism [7, 8], and numerous potential interactions can arise with CYP3A4 inhibitors and inducers. Indeed, recently ivabradine has been added to the list of medicines with conditional risk of TdP because there is substantial evidence that it is associated with TdP when taken with other drugs that block its metabolic breakdown [9].

In this patient, at risk because of a preexisting long QT, ivabradine did not induce severe bradycardia and did not

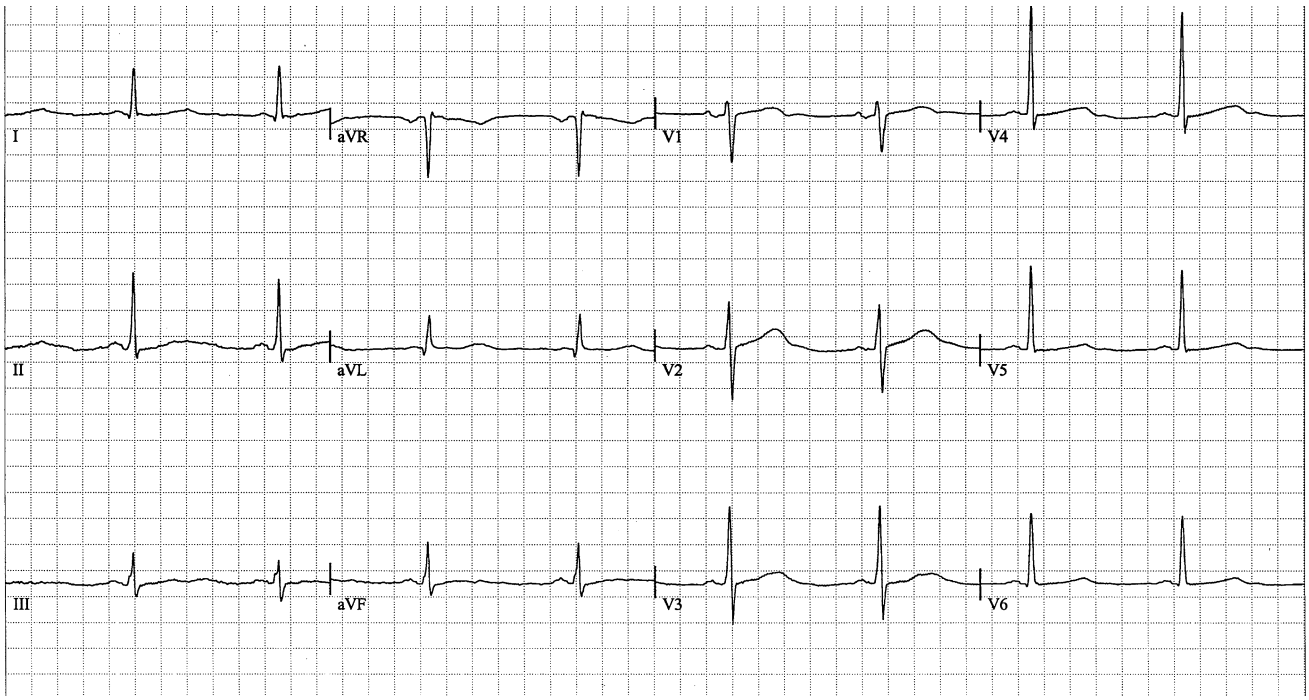

Fig. 2 ECG with a long corrected QT-Interval. 68-year-old male patient. The long QTc had been known since more than 20 years and fluctuates between 490 and 560 ms. This ECG is recorded while he is treated with ivabradine. The paper speed is 25 mm/s, and the amplitude is 10 mm/mV. It is of some note that his PR war rather short (122 ms), but there is no evidence for pre-excitation. The software (Marquette Hellige, CardioSys V6.73) offers a QTc-interval of 532 ms. Using the Bazett's form the value is 549 ms, and using the Fridericia's formula, it is 524 ms. Whatever the formula used, the QTc-interval is abnormally long (524–549 ms)

affect the QTc. However, when azithromycin was co-administered, TdP and syncope resulted. This case presents the specific problem of a patient with long QT with the co-prescription of two drugs, which may interfere and prolong the QT. It is at present unlikely to fully understand why ivabradine has a dangerous additive potential, when co-administered with other medications which affect the QTc. Whatever the explanation we find for the unexpected interaction, the side-effect had life-threatening effects on the involved patient.

References

1. Luo, S., Michler, K., Johnston, P., & Macfarlane, P. W. (2004). A comparison of commonly used QT correction formulae: The effect of heart rate on the QTc of normal ECGs. *Journal of Electrocardiology, 37*, 81–90. doi:10.1016/j.jelectrocard.2004.08.030.
2. www.torsades.org.
3. Liu, B. A., & Juurlink, D. N. (2004). Drugs and the QT interval. Caveat doctor. *New England Journal of Medicine, 351*, 1053–1056.
4. International conference on Harmonisation. (2005). *Guidance on E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs* (Vol. 70, pp. 61134–61135). Availability. Notice. Fed Regist.
5. http://drugs.com/azithromycin.html.
6. Cargnoni A., Ceconi C., Stavroula G., Ferrari R. (2006). Heart rate slowing by if current inhibition. In J. Camm & M. Tendera (Eds.), *Advances in Cardiology* (Vol. 43, pp. 31–44). Basel: Karger. doi:10.1159/000095404.
7. Vlase, L., Popa, A., Neag, M., Muntean, D., & Leucuta, S. E. (2010). Pharmacokinetic interactions study between ivabradine with fluoxetine or metronidazole in healthy volunteers. *Farmacia, 58*, 471–477.
8. Portoles, A., Terleira, A., & Calvo, A. (2006). Effects of hypericum perforatum on ivabradine pharmacokinetics in healthy volunteers: An open-label, pharmacokinetic interaction clinical trial. *Journal of Clinical Pharmacology, 46*, 1188–1194.
9. https://crediblemeds.org/blog/nelfinavir-and-ivabradine-added-list-drugs-avoid/.