

Torsade de Pointes Associated With Rupatadine

To the Editor:

We have read with great interest the recent article by Nombela et al¹ in which the authors refer to a case of torsade de pointes and directly associated it with treatment with rupatadine, a recent H₁ antihistamine and platelet-activation factor antagonist. However, we would like to offer the following observations.

After contacting the authors, we were able to confirm this was an adverse event—previously reported by the Spanish Pharmacovigilance System (Sistema Español de Farmacovigilancia [SEFV]) to the marketing authorization holder—that occurred in 2006. The marketing authorization holder included this in the last update report on product safety,² as stipulated by drug vigilance regulations.

Second, the SEFV report describes 2 drugs suspected of adverse reactions and attributes the possible cause of the adverse event to their interaction: rupatadine 10 mg/d and sertraline (an antidepressant belonging to the selective serotonin reuptake inhibitor class) 40 mg twice a day during the 6 previous months. The article published by Nombela et al inexplicably overlooks this fact.

Third, and also according to the information provided by the SEFV itself, the patient presented a prolonged QTc interval of 580 ms during 2 previous ECGs (in 2001 and 2003), conducted for cataract surgery and a cholecystectomy, respectively.

Finally, as the marketing authorization holders of rupatadine, we would like to present the assessment conducted when this occurred and described in the safety report² delivered to the health authorities.

A randomized, blinded, parallel-group and placebo- and moxifloxacin-controlled QT/QTc study was conducted with 160 healthy volunteers, and showed that 10 mg/d and 100 mg/d (10 times the therapeutic dose) of rupatadine up to reaching the stationary equilibrium state did not modify the QTc interval on ECG, nor did the main metabolites. There were no differences between men and women and no serious or unexpected events were recorded.³

As known, rupatadine is mainly metabolized by CYP3A4, a cytochrome P450 isoenzyme. Sertraline can inhibit this isoenzyme but, according to the available information, is a less powerful inhibitor than many other drugs, as demonstrated by studies conducted with the concomitant administration of terfenadine (a withdrawn second-generation anti-H₁), in which terfenadine concentrations did not increase. The manufacturer has pointed out that sertraline very mildly inhibits the CYP3A4 isoenzyme and that this has no clinical importance.⁴ In the same line, and according to a review of clinically significant interactions, the inhibition of CYP3A4 by sertraline is practically nil.⁵ In view of all this, we consider it unlikely that sertraline increased rupatadine concentrations and even less likely that it led to concentrations high enough to have induced the aforementioned torsade de pointes, since sertraline is a weak inhibitor of CYP3A4 and rupatadine has been shown to be safe at doses 10 times higher than the treatment doses.³

Sertraline, like many other antidepressants, is metabolized by the cytochrome P450 (CYP) 2D6

isoenzyme.⁴ In vitro studies of pharmacokinetic interactions have shown that rupatadine inhibits CYP2D6 at concentrations of 0.5 μ mol (210 ng/mL), approximately 100 higher times than therapeutic concentrations (1.9 [1.2] ng/mL after administration of multiple 10 mg/d doses) and, thus, it was concluded that it would be improbable that such a mechanism of interaction would have clinical relevance.⁶

Thus, it is unlikely that the concomitant administration of rupatadine could have caused QT-interval prolongation and torsade de pointes, which were probably induced by sertraline. In contrast to rupatadine, evidence exists that sertraline does in fact alter ECG: a prolonged QT interval and ventricular tachycardia (including torsade de pointes-type arrhythmias) have been reported during various safety assessments after marketing sertraline,⁴ in addition to a placebo-controlled double-blind study in which 1 of 8 patients who received sertraline 200 mg/d showed a clinically significant prolonged QT segment at the end of the study compared to basal state.⁷

In conclusion, we believe that the causal role of rupatadine as the only catalyst of the arrhythmia, as the letter suggests, is biased and debatable, since in this case other factors are also involved, such as the combined treatment with sertraline and 2 previous episodes of a prolonged QTc interval.

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Response

To the Editor:

We have read with great interest the issues raised by Ramón Fité-Mora and thank him for his timely clarifications. We would like to offer some comments regarding his letter and our article.¹ The yellow card sent from our center to the Spanish Pharmacovigilance System (Sistema Español de Farmacovigilancia) described all the drugs that the patient took at the time of arrhythmia onset, among them sertraline and rupatadine. The purpose of this card is to report a suspected adverse drug reaction.² We consider it appropriate to report this possible adverse effect, due to the recent marketing of this drug in Spain and the relevance of the clinical event.

We would like to emphasize the temporal relationship between the time of rupatadine administration and symptom onset. The patient had already been receiving treatment with sertraline for several months without arrhythmic problems being recorded, even with previous electrocardiograms indicating a prolonged QT interval. Indeed, as we mentioned in the original article, the patient had been examined by the neurology service for previous syncopal symptoms, without a conclusive and definitive diagnosis. However, after starting rupatadine, the diagnosis was clear, since the patient presented presyncopal symptoms with 2 episodes of syncope, one of them in which ventricular tachycardia was recorded. We consider that a previous syncopal episode cannot be compared to the definitive diagnosis of the case. Again, the temporal relationship between the suspension of both drugs was the factor that normalized the QT interval and led to the disappearance of the ventricular arrhythmia.

As described, the patient presented a prolonged QT interval on previous electrocardiograms, so we emphasize that the final diagnosis was aborted sudden death due to torsade de pointes secondary to idiopathic long QT syndrome and exacerbated by rupatadine treatment. We agree that it would have been better to have made the combined administration of rupatadine and sertraline more explicit.

Finally, we do not consider that rupatadine was the cause of arrhythmia onset, rather, given a long QT syndrome substrate, a long list of factors can induce torsade de pointes, among which is recently initiated medication.^{3,4} Thus, the association, rather than a causal link, between rupatadine and the symptoms is clear, although other influencing factors also exist.

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