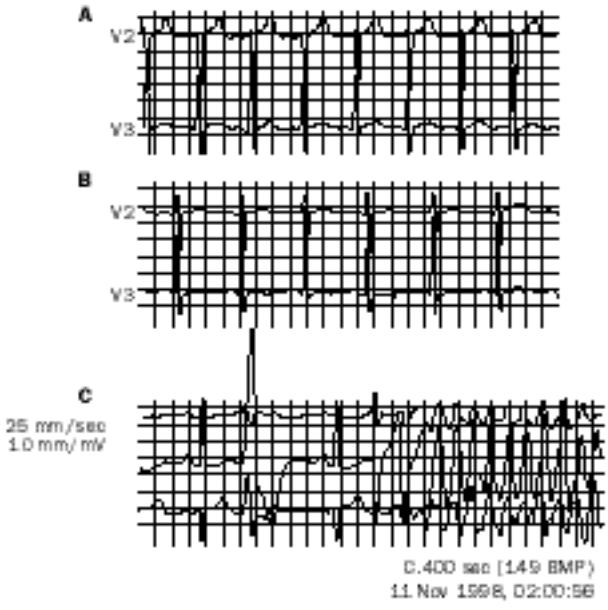
QT lengthening and life-threatening arrhythmias associated with fexofenadine

Y M Pinto, I C van Gelder, M Heeringa, H J G M Crijns

For clinicians treating patients with suspected or known QTc prolongation and ventricular arrhythmias, it is important to be aware of rare but life-threatening arrhythmogenic properties of some antihistamines. Fexofenadine, a histamine H1-receptor antagonist used for the treatment of seasonal allergic rhinitis, was approved by the FDA in December, 1996, with its main advantage being its proposed lack of effect on QTc time. Fexofenadine is the primary active derivative of terfenadine. Terfenadine was withdrawn because of its association with cardiac arrhythmias mainly in conjunction with macrolide antibiotics and antifungal medication. These adverse effects of terfenadine were known for several years but it was only withdrawn after the approval of fexofenadine, which was reported not to cause cardiotoxic reactions.[1]

A 67-year-old man was taken to the cardiac emergency room after syncope. He was known to have mild hypertension and mild left ventricular hypertrophy (septal thickness 13 mm) for 3 years. He also had unexplained itching. As a result, his anti-hypertensive medication (carvedilol) had been stopped 2 months earlier. He collapsed just before a visit to the dermatology department of our hospital to evaluate his itching. He had started to take fexofenadine 180 mg daily 2 months ago, and did not use any other medication. Upon admission, he had spontaneously recovered from his syncope during which he had broken a tooth, and was free from chest pain or palpitations. A first electrocardiogram (ECG) showed no other abnormalities than an abnormally long QTc time (table; figure A). The same day fexofenadine was discontinued, and QTc time shortened (figure B). 180 mg daily fexofenadine was restarted on day 6, whereafter QTc time increased again (table). On day 11, while taking



Electrocardiograms in hospital

A=V2 and V3 on admission, where heart rate is 95 and QTc is 532 ms. B=the same leads after discontinuation of fexofenadine for 4 days, when heart rate is 78 and QTc has shortened to 489 ms. C=polymorphic ventricular tachycardia that occurred after restarting fexofenadine. The event occurs at night, and is preceded by a long RR interval due to a premature ventricular beat and initiated by a short coupling interval.

Time relative to admission	QTc/HR	Fexofenadine
–3 months	494/76	not used
0 days	532/95	180 mg o d
6 days	489/78	Stopped for 5 days
11 days	512/85	Restarted for 5 days
24 days	482/83	Stopped second time
28 days	484/72	Cetirizine 10 mg daily

HR=heart rate.

QTc time as determined by the longest QT time divided by the square root of the RR interval

fexofenadine, he had a polymorphic ventricular tachycardia, which rapidly progressed to ventricular fibrillation (figure C). There were no electrolyte disturbances during his hospital stay (potassium 4·1 mmol/L, magnesium 0·76 mmol/L). He was successfully defibrillated, and fexofenadine was discontinued whereupon QTc time shortened again (table). Evaluation including magnetic resonance imaging, coronary angiogram with a cardiac biopsy, and perfusion scintigraphy did not show any abnormality other than ventricular hypertrophy.

Increased QTc interval during fexofenadine treatment was also reported to the Uppsala Monitoring Centre of WHO.[2] The temporal relation between the use of fexofenadine and the occurrence of lengthening of QTc interval in our patient, including positive withdrawal and rechallenge, strongly suggest a causal relation. That QTc tended to be beyond normal limits without use of the drug suggests that this particular patient was prone to a long QTc interval. The absence of a history of risk factors such as a familial history of arrhythmias, electrolyte disturbances, hypothermia, toxic substances, intensive weight reduction, and central nervous system damage, support this.

Clinical observations suggested that decreased metabolism of terfenadine may be the primary mechanism in patients with terfenadine-induced ventricular arrhythmia. This led to the idea that fexofenadine, which is the active metabolite of terfenadine, might not increase QTc interval.[3] This was further corroborated by clinical studies which failed to show an effect of fexofenadine on QTc in adult patients and children.[4] However, rare adverse drug reactions that rely on patients' susceptibility are not likely to be detected in these trials, because the number of patients included are small relative to the total number of patients exposed to the drug after marketing. An important illustration of this phenomenon is that arrhythmias associated with second-generation antihistamines were recognised only 10 years after they had been in wide clinical use.

The mechanism of drug-induced polymorphic ventricular tachycardia is not clear, but is thought to be related to an excessive delay of repolarisation producing marked QTc prolongation.[5] This case warns us that fexofenadine may increase QTc time and induce ventricular arrhythmias in susceptible patients. Use of this drug is steadily increasing since it is often used to replace its predecessor terfenadine, which was among the most frequently prescribed drugs in the United States. Pharmacoepidemiological studies are needed before a more definitive risk-benefit analysis can be made.

1 Markham A, Wagstaff AJ. Fexofenadine. *Drugs* 1998; **55:** 269–74.
2 Product Information: Allegra (R), fexofenadine. Hoechst Marion Rousell, Inc, Kansas City, MO, 1997.
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4 Simons FE, Bergma NJ Watson WT, Simons KJ. The clinical pharmacology of fexofenadine in children. *J Allergy Clin Immunol* 1996; **98:** 1062–64.
5 Faber TS, Zehender M, Just H. Drug-induced torsade de pointes. Incidence, management and prevention. *Drug Saf* 1994; **11:** 463–76.

Department of Cardiology, Thoraxcenter, University Hospital Groningen, 9713 G2 Groningen, Netherlands
(Y M Pinto e-mail: y.m.pinto@thorax.azg.nl)**; and The Netherlands Pharmacovigilance Foundation LAREB, 's Hertogenbosch, Netherlands**