

SERIOUS ARRHYTHMIA INDUCED BY TERFENADINE-ERYTHROMYCIN INTERACTIONS

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ABSTRACT

Since the introduction of our local manufacturing of terfenadine, we have observed and expressed our concern about a small but increasing number of serious ventricular arrhythmias associated with the use of this non-sedating antihistamine. In January 1997 a case of torsade de pointes ventricular tachycardia was detected in a previously healthy woman taking terfenadine with erythromycin. Electrocardiography revealed QT interval prolongation and QRS widening. One hour after emergency room admission, her arrhythmia degenerated to ventricular fibrillation and she died of cardiac arrest. Episodes of torsade de pointes are most likely the result of the quinidine-like action of terfenadine. Dosage restriction and awareness of the clinical conditions and drug interactions capable of inhibiting the metabolism of terfenadine are essential for prevention of this serious reaction.

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INTRODUCTION

Antihistamines are frequently taken by patients and often prescribed for relief of symptoms due to allergy and viral upper respiratory tract infections, such as the common cold. However, excessive sedation has been a limiting factor for many of the older antihistamines.^{1,4} Terfenadine is metabolized extensively by hepatic first-pass metabolism, and after usual doses it cannot be detected in plasma unless very sensitive mass spectrometric assays are used. A specific hepatic cytochrome P-450 enzyme, CYP3A4 converts terfenadine to an acid metabolite (terfenadine carboxylate) that can be readily detected in plasma and is considered to be the active antihistamine (Fig.1).^{2,3}

There have been several reports of serious ventricular arrhythmias associated with two non-sedating antihistamines, i.e., terfenadine and astemizole. In 1990 a case of torsade de pointes ventricular tachycardia was described in a woman taking terfenadine with the antifungal

agent ketoconazole. In this case and other cases of intentional overdose, terfenadine concentrations in plasma were detectable and were associated with QT interval prolongation on the electrocardiogram and syncope or cardiac arrest.⁵⁻⁷

The concentration-response relationships for terfenadine and terfenadine carboxylate, and quinidine carboxylate and quinidine have been compared. No significant block of potassium current was seen after terfenadine carboxylate at concentrations up to 5 $\mu\text{mol/L}$. An almost complete block of potassium current was seen with quinidine 0.83 $\mu\text{mol/L}$ and terfenadine 1.0 $\mu\text{mol/L}$. The terfenadine and quinidine concentrations producing half-maximal block are 0.15 and 0.18 $\mu\text{mol/L}$, respectively.^{1,7,8}

An understanding of the mechanism of torsade de pointes and the pharmacological characteristics of terfenadine should allow physicians to anticipate clinical conditions that place patients at risk of developing this potentially lethal syndrome in which polymorphic ventricular tachycardia occurs in the setting of QT interval

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prolongation.^{9,11} It often includes certain predisposing factors; e.g. antiarrhythmic drugs (quinidine), hypokalemia and bradycardia.

Quinidine and several antiarrhythmic drugs such as sotalol and N-acetyl procainamide have in common the ability to block potassium currents. The same pertains to conditions such as hypothyroidism and electrolyte disorders, especially hypokalemia or hypomagnesemia.⁸

Recent studies have found that drugs such as erythromycin or ketoconazole interact to cause elevated concentrations of terfenadine (0.02 to 0.1 $\mu\text{mol/L}$) and that these elevated concentrations are closely associated with prolongation of the QT interval.^{5,10-12}

Case report

A 45 year old woman presented to our emergency room (ER) after losing consciousness while working at home. Relatives who brought her in explained that she was a healthy person, who would occasionally consume acetaminophen tablets for headaches. One week prior to her ER admission, she visited a family physician for treatment of cold and a sore throat. She was placed on terfenadine (60 mg every twelve hours), erythromycin (400 mg every eight hours) and acetaminophen (325 mg every six hours).

Upon admission her vital signs were: blood pressure 110/60 mmHg, pulse 70 beats/min and regular, and respiration 18/min. Electrolytes were as follows: Na^+ : 140 mEq/L, K^+ : 3.4 mEq/L, and CO_2 20 mEq/L. EKG showed normal sinus rhythm. However, she was placed on the cardiac monitor when occasional PVC's (premature ventricular contractions) were observed.

The QRS complexes appeared wide and bizarre in appearance and the QT interval was prolonged. 15 minutes

later she suddenly developed ventricular fibrillation with no pulse or blood pressure. Immediate electrical defibrillation with 200, 300, and 360 Joules with 5 second intervals was given. Standard doses of epinephrine, lidocaine, sodium bicarbonate and a total of eight unsuccessful electroshock attempts could never get her heart back to perform.

DISCUSSION

This patient presented to the ER after passing out for an unknown reason. Upon examination, a similar episode occurred with simultaneous documentation of a dysrhythmia which was interpreted as ventricular tachycardia. The possibility that this may be a toxic effect of terfenadine is perhaps the most important consideration.

Failure to recognize torsade de pointes could result in the institution of inappropriate treatment that may worsen the situation. This quinidine-like effect of terfenadine is due to a self-terminating episode of ventricular tachycardia that appears as QRS complexes twisting around the isoelectric line on the electrocardiogram (Fig. 2).

Usually, the arrhythmia terminates spontaneously after a few beats to several minutes, but as in this patient it may degenerate into ventricular fibrillation. Because the characteristic morphology may alternate with runs of monomorphic ventricular tachycardia, it may be misdiagnosed unless one examines several EKG recordings. It is of diagnostic importance that torsade de pointes almost always occurs in the setting of a prolonged QT interval (QT is prolonged to 0.60 seconds or more).

Intensified treatment with antiarrhythmic drugs in this situation can lead to further prolongation of the QT interval, worsening of the dysrhythmia, and death.

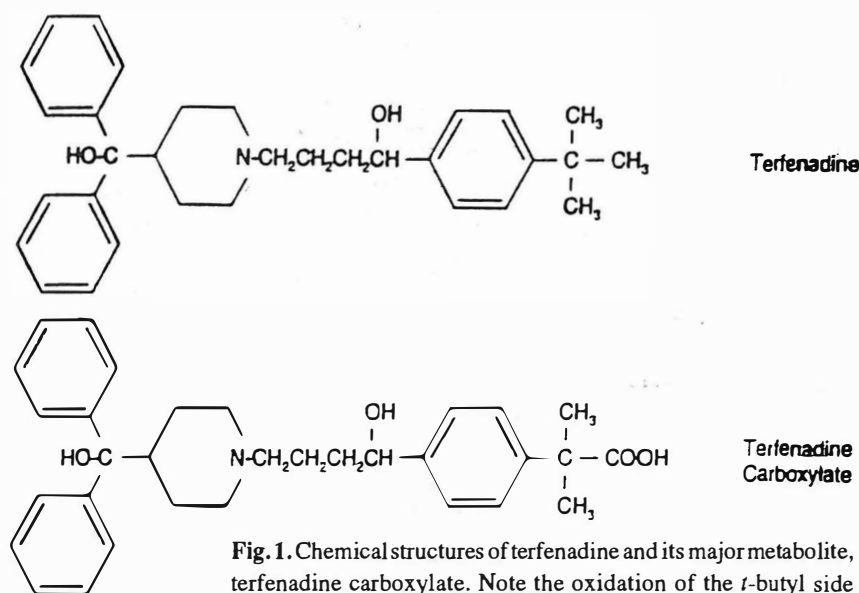


Fig. 1. Chemical structures of terfenadine and its major metabolite, terfenadine carboxylate. Note the oxidation of the *t*-butyl side chain of terfenadine to form the acid (asterisk).

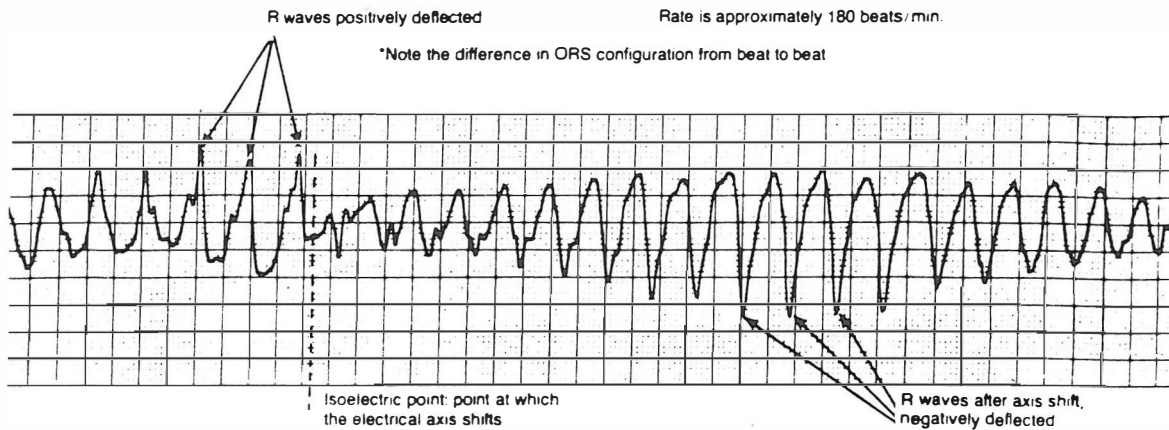


Fig. 2. Torsade de pointes; R waves positively deflected. Rate is approximately 180 beats/min. Note the difference in QRS configuration from beat to beat.

Treatment consists of removing the predisposing cause (i.e., quinidine, tricyclic anti-depressants, phenothiazines and terfenadine) and suppressing the arrhythmia until the QT interval returns to normal. Electrical defibrillation is indicated for prolonged episodes during which a pulse cannot be detected; however, there is a high rate of recurrence.

The definitive treatment for torsades is overdrive atrial pacing to increase the heart rate and shorten the QT interval. If atrioventricular block is present, ventricular pacing will be needed. In the interim, rapid control of the arrhythmia may be obtained by administering isoproterenol by intravenous bolus (100 to 200 µg) or by infusion. Electrolyte disorders such as hypokalemia and hypomagnesemia must be properly corrected as they may worsen the condition.

Subjects with torsade de pointes associated with terfenadine therapy, such as our patient, have many characteristics in common with the quinidine-induced syndrome. The almost identical potency of terfenadine and quinidine for block of potassium channels suggests that the arrhythmias and some of the deaths previously reported may have been caused by excessive levels of the parent compound. Torsade de Pointes has been a recognized complication of many drugs (antiarrhythmics, neuroleptics, antihistamines,...).

To prevent this form of life-threatening toxicity, physicians must be aware of the potential interaction between terfenadine and other drugs and patients must be instructed to limit dosage to that recommended in the manufacturer's labeling. The ability of terfenadine—but not its metabolite—to block potassium channels suggests that terfenadine carboxylate should be evaluated by our local manufacturers as an antihistamine with less potential than terfenadine for causing torsade de pointes.

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