

# Torsade De Pointes Caused By Concomitant Use Of Ketoconazole And Terfenadine

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## Abstract

A 47-year-old female developed frequent syncope eight days after the administration of oral ketoconazole and terfenadine for fungal infection and urticaria respectively. ECG at hospital admission showed prolonged QT interval and TDP. The patient had no previous history of syncope nor did she have other risk factors for TDP. Both ketoconazole and terfenadine were immediately discontinued, followed by intravenous infusion of isoprenaline (2.0 µg/min) to maintain the heart rate at 100 beats/min. TDP resolved after the management. QT interval returned to normal range within 5 days of admission. She had no recurrence in TDP or QT prolongation during the follow up of six months. Conclusions: Terfenadine prolongs QT interval and leads to life-threatening ventricular arrhythmia. This cardiac toxicity may be enhanced by concomitant use of liver enzyme inhibitor ketoconazole.

## INTRODUCTION

The introduction of non-sedating antihistamines, such as terfenadine, astemizole and cetirizine, has been a major advance in the treatment of human allergies. However, there have been ongoing concerns about the cardiac toxicities of these medications.<sup>1,2,3</sup> Although the incidence of cardiac arrhythmias caused by non-sedating antihistamines appears to be very low,<sup>3</sup> it can be significantly increased when these drugs are used in combination with other medications suppressing liver enzyme activity.

## CASE REPORT

A 47-year-old woman was admitted for frequent dizziness and blackouts. Past medical history included feet and hands fungal infection for which she was treated with oral ketoconazole 200 mg twice daily. Outpatient follow up including physical examination and liver function tests at 14 days of the therapy showed marked improvement in fungal infection with no obvious side effects from ketoconazole. At day 16 of the ketoconazole therapy, she suffered from urticaria in the arm and chest, for which she was prescribed with terfenadine 60 mg twice daily. Eight days after the combined use of ketoconazole and terfenadine, she experienced three episodes of syncope within 12 hours for which she was urgently admitted for further assessment. The patient had no previous history of syncope or any other risk factors for cardiac arrhythmias, such as cardiovascular

disease or electrolyte disturbances.

On examination, the patient was conscious but lethargic and pale. Her temperature was 36.7°C. Her respiration rate was 20 breaths/min, HR was 72 beats/min and regular, BP was 90/60 and 88/60 mm Hg in supine and standing position respectively. Both lungs were clear. Heart sounds were normal with no murmurs. The examinations on abdomen and limbs were unremarkable.

Complete blood cell count was normal. Serum biochemical profile showed no electrolyte disturbances or abnormal liver function. Two-dimensional and Doppler echocardiography showed no cardiac enlargement or dysfunction. However, her ECG showed a prolonged QT interval with corrected QT interval (QTc) of 0.54 sec. During the initial hours of admission, she experienced an episode of syncope and polymorphic ventricular tachycardia (torsade de pointes), which was confirmed by bedside ECG monitoring. The heart rate during tachycardia, which terminated spontaneously after three min of the attack, was 210 beats/min.

Both ketoconazole and terfenadine were immediately discontinued. Intravenous infusion of isoprenaline was commenced at a rate of 2.0 g/min to maintain the heart rate at 100 beats/min. During the first 24 hours of isoprenaline infusion, there were frequent ventricular ectopic beats but no further syncope or torsade de pointes attacks. Ventricular

ectopics resolved in the following 2 days along with a recovery of prolonged QT interval and QTc. The ECG on day 4 showed sinus rhythm (81 beats/min) with QT interval of 0.42 sec. She was then discharged, and was followed up in the outpatient clinic for six months with no further syncope events or QT prolongation.

### DISCUSSION

Ketoconazole was the first azoles that administered orally to treat systemic fungal infections. Although it is effective against several different types of fungi, it has largely been superseded by the triazoles, such as itraconazole and fluconazole, due to its liver toxicity, inhibition of androgen synthesis and interaction with many drugs as result of the inhibition of cytochrome P450 pathway.

Terfenadine is a non-sedating antihistamine, which is used for allergic reactions including hay fever, urticaria, insect bites and drug hypersensitivities. One of the most serious adverse effects of terfenadine is a form of polymorphic ventricular tachycardia known as torsade de pointes, which often leads to syncope and in severe cases, sudden cardiac death.<sup>1, 2</sup> In subjects without other risk factors of ventricular arrhythmias, the incidence of terfenadine-induced torsade de pointes is very low, perhaps in an order of 0.25 per million doses sold daily.<sup>3</sup>

Because terfenadine is mainly inactivated in the liver, drugs that suppress the liver P450 system will affect the normal metabolism of terfenadine and increase its plasma concentration. Ketoconazole forms a tight complex with the Fe<sup>3+</sup> form of the haem iron of CYP3A4 causing reversible non-competitive inhibition of the enzyme.<sup>4</sup> Its concomitant use with terfenadine is known to increase the risk of adverse effects of terfenadine including cardiac toxicity.<sup>5</sup> Our patient had no risk factors for cardiac arrhythmias. Eight days after the concomitant use of terfenadine and ketoconazole, she developed QT prolongation and torsade de pointes, which resolved after the cessation of both agents. The temporal relation of terfenadine administration and the occurrence of ventricular arrhythmias, and the subsequent resolution of the tachycardia support our hypothesis that the clinical presentation of the patient was the result of cardiac toxicity of terfenadine.

The mechanism by which terfenadine leads to torsade de pointes is not entirely clear, but animal studies have shown that terfenadine prolongs action potential duration, ventricular effective refractory period and QT interval on body surface ECG.<sup>6,7,8</sup> In humans, such as in our case,

terfenadine-induced torsade de pointes is often associated with QT interval prolongation, a leading cause of torsade de pointes.<sup>1</sup> Therefore, terfenadine-induced ventricular tachycardia in humans is likely due to the delay in ventricular repolarisation.

Terfenadine-induced ventricular arrhythmias require urgent medical attention. The most effective management is immediate discontinuation of the offending drug. Recovery of prolonged QT interval and stabilization of ventricular rhythm usually starts within 1-2 days of drug cessation. A common feature in drug-induced QT prolongation and torsade de pointes is bradycardia or a cardiac pause that precedes the onset of tachycardia.<sup>9, 10</sup> The pause that precipitates torsade de pointes may be due to sinus arrest or postextrasystolic pause.<sup>9</sup> Cardiac pacing or isoprenaline have been shown to shorten QT intervals and eliminate bradycardia or pause, the precipitating factors of torsade de pointes caused by either congenital or acquired long QT syndromes.<sup>11,12,13</sup>

### SUMMARY

This patient's ventricular arrhythmia is probably the result of the cardiac toxicity of terfenadine, which was enhanced by the concomitant use of a potent liver enzyme inhibitor ketoconazole. Since terfenadine is still used in some parts of the world to treat human allergies, clinicians should be aware of its cardiac adverse effects and be extremely cautious when it is used concomitantly with drugs affecting liver enzymes.

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