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Itraconazole prevents terfenadine metabolism and increases risk of torsades de pointes ventricular tachycardia

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Summary. Terfenadine, a nonsedating H_1-selective antihistamine, is widely used in many countries. We report pharmacokinetic results in a patient who developed a prolonged QT-interval in ECG and symptomatic torsades de pointes ventricular tachycardia as a consequence of the interaction of itraconazole and terfenadine. Both drugs were taken in the recommended doses: terfenadine 60 mg b.d. and itraconazole 100 mg b.d.

Terfenadine metabolism was delayed by itraconazole, leading to an increased level of unmetabolised terfenadine. Seven weeks after the cessation of itraconazole treatment, terfenadine was rapidly metabolized to its active metabolite and did not prolong the QT-interval when given as a single provocation dose (120 mg).

The findings suggest that intraconazole in therapeutic doses inhibits terfenadine metabolism. It is also possible that unmetabolised terfenadine alone, without an increased level of its active metabolite, may cause torsades de pointes. The concomitant use of terfenadine and itraconazole (and ketoconazole) should be avoided.

Key words: Torsades de pointes, Terfenadine, Itraconazole; QT-interval, drug-interaction, pharmacokinetics, drug metabolism

Terfenadine, a selective H_1-receptor antagonist, is now widely used, since it is less sedating than older antihistamines. However, there are some alarming reports of a potentially dangerous adverse effect, torsades de pointes ventricular tachycardia. During overdosage [1, 2] or on simultaneous use of ketoconazole [3, 4] it has caused a prolonged QT-interval in the ECG, leading to torsades de pointes ventricular tachycardia. We have recently reported this complication as a result of concomitant use of terfenadine and itraconazole [5]. The aim of the present study was to assess terfenadine metabolism and its relationship to QT-prolongation in the ECG during a toxic interaction in a patient on combined terfenadine and itraconazole therapy.

Patients and methods

A 26-year-old female (152 cm, 43 kg) was admitted to hospital for syncopal episodes, which had started 10 h previously. She was otherwise healthy but had received several courses of antibiotic treatment for maxillary sinuitis during the past 8 months. She had not had antibiotics for the last 2 weeks. She also had received terfenadine 120 mg

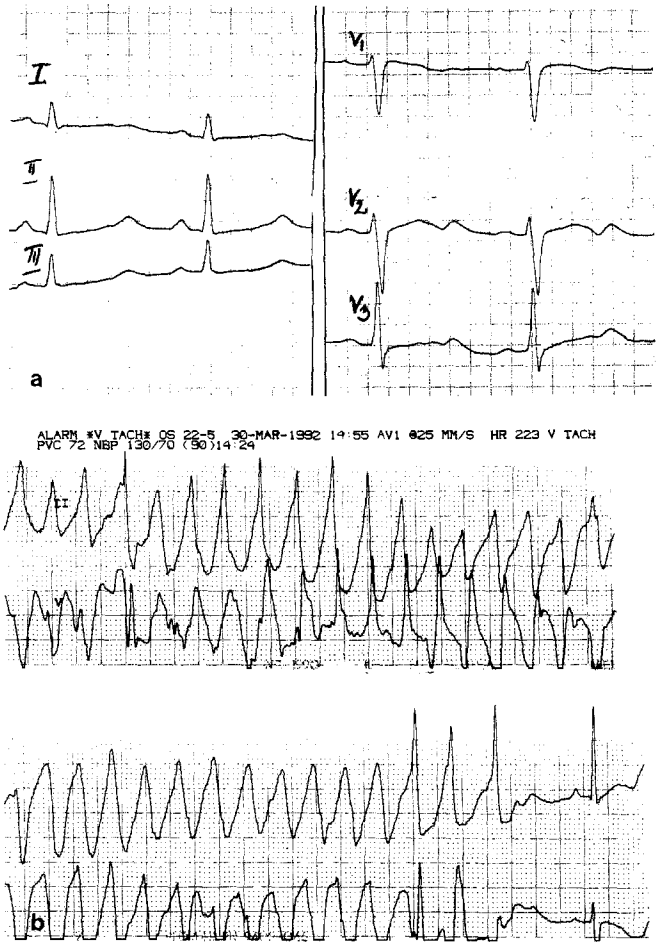

Fig. 1. **a** A QT-interval of 580 ms at the heart rate of 67 beats min^{-1} in admission ECG. **b** Torsades de pointes ventricular tachycardia

Table 1. QT-intervals and plasma levels of terfenadine and its active metabolite: **a** After treatment with terfenadine 60 mg b.d. and itraconazole 100 mg b.d.; **b** Just before and after a single dose of 120 mg terfenadine. N.D., Not detected (< 5 ng/ml)

Hours since the last dose of terfenadine	Terfenadine ng · ml^{-1}	Active metabolite ng · ml^{-1}	QT ms	HR beats · min^{-1}	QTc ms
a 11	–	–	580	67	613
19	28	160	580	62	589
36	28	90	510	57	497
60	12	55	500	51	461
72	ND	49	–	–	–
84	ND	39	450	56	435
b 0	ND	0	440	49	398
2	ND	586	440	55	421
4	ND	548	460	53	432
6	ND	242	440	60	440
8	ND	124	430	55	411
10	ND	66	440	54	417
24	ND	13	420	52	391

per day in four or five 10–14 day courses, without any problems. She had been taking oral contraceptive pills (gestodene 75 μg and ethinyloestradiol 30 μg) for the last two years. Her family did not have a history of syncopal attacks or sudden death.

Before the hospital admission she had been taking terfenadine 60 mg b.d. (Teldanex, Astra, Finland) for 11 days for sinuitis. For the last three days she had also been taking itraconazole 100 mg b.d. (Sporanox, Janssen Pharmaceutica, Belgium) for vaginitis. Her ECG on admission showed a QT-interval of 580 ms at a heart rate of 67 beats · min^{-1} (Fig. 1 a). Neither physical examination nor serum electrolyte measurements revealed abnormal findings. During the 5 h in hospital, repeated episodes of torsades de pointes ventricular tachycardia were documented (Fig. 1 b), two of them associated with syncope. Terfenadine and itraconazole were discontinued. No further arrhythmias were detected 20 h after the last doses of terfenadine and itraconazole. The QT-interval became normal within 3 days. Serum samples were taken 19, 36, 60, 72 and 84 h after the last dose of terfenadine and were kept frozen for the determination of terfenadine and its metabolite.

Her liver function was normal, according to laboratory tests. Exercise test, echocardiogram, 24-h ambulatory ECG monitoring, antimyosin scanning and electrophysiological tests were all normal when studies 1 week after the cessation of terfenadine and itraconazole use. The ECGs of her family members showed normal QT-intervals.

Provocation study

7 weeks later a provocation test, with the consent of the patient, was performed in hospital. A single dose of 120 mg terfenadine was given, and serum samples were taken just before and after 2, 4, 6, 8, 10 and 24 h. The samples were frozen and the concentrations of terfenadine and its active metabolite were analysed by radioimmunoassay (Marion Merrell Dow Ltd, Uxbridge, UK). The detection limit of the method was 5 ng · ml^{-1}. An ECG was taken, with one exception, at the same time as the serum samples.

All ECGs were recorded at 50 mm · s^{-1}. The QT-interval was measured from the beginning of the QRS-complex to the point were the line parallelling the descending limb of the T-wave or TU-complex crossed the isoelectric line. The U wave was included in the QT-interval if it merged into an unified TU-complex in most of the leads. At the time of the QT-prolongation, the U-components of TU-complexes were large and bizarre, as is the usually case in drug-induced torsades de pointes ventricular tachycardia [6]. The QTc-interval was calculated from the formula $QTc = QT/\sqrt{RR}$ were QT and RR (the distance between the tops of two consequent R-waves) are measured in seconds [7]. A QTc-interval longer than 0.44 s is usually considered abnormal.

Antipyrine and debrisoquine tests

Oral antipyrine test (15 mg · kg^{-1}) was performed 7 weeks after the last dose of itraconazole (24 h after the provocation dose of terfenadine). The concentration of plasma antipyrine at 6, 9, 12, 18 and 24 h was measured by HPLC, and its half-life, clearance and apparent volume of distribution were calculated. Debrisoquine 10 mg (Declinax, Hoffman La-Roche, Switzerland) was given on empty stomach, 24 h after the antipyrine, and urine was collected for 6 h. The concentrations of debrisoquine and 4-hydroxydebrisoquine in urine were measured by HPLC and the debrisoquine metabolic ratio was determined [8].

Results

After the combined use of itraconazole and terfenadine, the concentration of unmetabolised terfenadine was high (28 ng · ml^{-1} at both 19 and 36 h) and the drug could be detected up to 60 h after the last dose of terfenadine (Table 1 a). The concentration of the active metabolite of terfenadine in serum at 19 h was 160 ng · ml^{-1} and the half-life of the metabolite was about 36 h. The QT-interval in the ECG gradually shortened and reached the normal range within 3 days, when no unmetabolised terfenadine was found in serum.

After a single provocation dose of 120 mg terfenadine (without itraconazole) no unmetabolized terfenadine was detectable (< 5 ng · ml^{-1}) in serum at any time points. The concentration of the metabolite, however, was high (peak concentration 586 ng · ml^{-1} at 2 h), although it declined rapidly. The ECG did not show significant prolongation of the QT-interval (Table 1 b).

The half-life of antipyrine was 17.0 h, clearance 0.49 ml × min^{-1} kg^{-1} and volume distribution 0.63 l × kg^{-1}. The ratio of debrisoquine and 4-hydroxydebrisoquine in urine was 0.31, i.e. the subject was an extensive metaboliser of debrisoquine.

Discussion

Terfenadine, a nonsedating antihistamine, has turned out to be well tolerated and safe in worldwide use [9]. However, in cases of overdosage, it has been shown to cause

torsades de pointes ventricular tachycardia associated with a prolonged QT-interval in the ECG [1, 2]. A similar complication has been reported as a consequence of an overdose of astemizole, another H_1-selective antihistamine [10–12]. Torsades de pointes ventricular tachycardia has also occurred during concomitant terfenadine and ketoconazole therapy [3, 4].

Our patient was small (152 cm, 43 kg), but she had previously taken the same dose of terfenadine without any problems. Routine laboratory tests did not reveal any abnormalities in her liver function. The debrisoquine phenotyping test was performed to find out if her phenotype was abnormal, but she turned out to be an extensive metaboliser of debrisoquine, as are most Caucasian subjects. An intrinsic cardiac disorder causing a prolonged QT-interval was also ruled out.

An overdose was excluded since the level of the active metabolite was not elevated, as confirmed by several serum level measurements during the toxic episode. The first serum sample, taken 19 h after the last dose of terfenadine and itraconazole, showed a distinct elevation of unmetabolised terfenadine to 28 $ng \cdot ml^{-1}$ (normally < 5 $ng \cdot ml^{-1}$). The level of the active metabolite of terfenadine was somewhat high (160 $ng \cdot ml^{-1}$) considering the 19 h delay from the last tablet. However, the concentration of the active metabolite was not toxic since its peak level is normally 250–300 $ng \cdot ml^{-1}$ at steady state during treatment with terfenadine 60 mg b.d. [9].

Seven weeks after the last dose of itraconazole, after a single dose of 120 mg terfenadine, no parent drug was detected and the serum level of the active metabolite remained within the range obtained in a study with healthy subjects (471 ($\pm$ 162) $ng \cdot ml^{-1}$) [9]. The somewhat high peak level of the metabolite (586 $ng \cdot ml^{-1}$) was probably due to the small size of the patient. However, since the clearance of antipyrine was relatively low, it might indicate a significant risk of an interaction for several weeks after the use of itraconazole. This fits well with the long half-life of itraconazole. The patient also used contraceptive pills but they are not known to interfere with terfenadine metabolism, and she was still taking them at the time of the provocation test. Thus, the simultaneous use of itraconazole had most probably caused the increased toxicity of terfenadine in our patient.

Terfenadine normally undergoes first pass metabolism in the liver to its active metabolite leaving no detectable parent drug in serum. This extensive first-pass metabolism makes it vulnerable to an interaction with other medications that are acted upon by the same cytochrome P 450 enzyme [9]. Ketoconazole has previously been shown to delay terfenadine metabolism [13]. In contrast, fluconazole is claimed not to delay terfenadine metabolism (Cantilena LR, Honig P, unpublished data).

On the basis of our case, it is possible that unmetabolised terfenadine alone might lead to a long QT-syndrome without producing a toxic level of its active metabolite. Support for this view is given by a report of a patient who had torsades de pointes after treatment with terfenadine and ketaconazole [3]. In that case unmetabolised terfenadine was also detected (57 $ng \cdot ml^{-1}$) but higher than expected level of its active metabolism was taken as a hint of possible overdose [9]. However, keto- and itraconazole may also slow the elimination of the active metabolite. In our patient the half-life of the metabolite (36 h) was more than twice normal.

There are now there reports of symptomatic torsades de pointes ventricular tachycardia after concomitant use of terfenadine and keto- or itraconazole, both drugs being taken in recommended doses [3–5]. In all cases the concomitant use has continued for at least three days. Terfenadine is available in many countries without prescription. Since the use of itra- and ketoconazole is increasing, it is essential that the arrhythmogenic effect of the interaction is well recognized, and that concomitant use of these drugs and terfenadine is avoided.

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