Influence of itraconazole on the pharmacokinetics and electrocardiographic effects of astemizole

Romain A. Lefebvre, Achiel Van Peer[1] & Robert Woestenborghs[1]

Heymans Institute of Pharmacology, University of Gent Medical School and [1]Department of Drug Metabolism and Pharmacokinetics, Janssen Research Foundation, Beerse, Belgium

Aims The aim of this study was to investigate the influence of chronic itraconazole treatment on the pharmacokinetics and cardiovascular effects of single dose astemizole in healthy subjects was studied.

Methods Twelve male volunteers were taking orally 200 mg twice daily itraconazole or placebo for 14 days with a washout period of 4 weeks in between. Approximately 2 h after the morning dose of itraconazole or placebo on day 11, 10 mg astemizole was orally administered. The plasma concentrations of astemizole and desmethylastemizole were measured by radioimmunoassay up to 504 h after administration; electrocardiograms with analysis of the QT_c interval were recorded up to 24 h post administration.

Results Itraconazole treatment did not significantly change the peak concentration of astemizole (0.74 *vs* 0.81 ng ml^{-1}) but it increased the area under the curve from 0 to 24 h (5.46 to 9.95 ng ml^{-1} h) and from 0 to infinity (17.4 to 48.2 ng ml^{-1} h), and the elimination half-life (2.1 to 3.6 days). The systemic bioavailability of desmethylastemizole was also increased. The QT_c interval did not increase after astemizole administration and there was no difference in the QT_c intervals between the itraconazole and placebo session.

Conclusions Chronic administration of itraconazole influences the metabolism of single dose astemizole in normal volunteers without changes of cardiac repolarization during the first 24 h after astemizole administration. However, the reduction in astemizole clearance under concomitant administration of itraconazole may result in a marked increase in astemizole plasma concentrations and QT_c alterations during chronic combined intake of astemizole with itraconazole.

Keywords: itraconazole, astemizole, drug interaction

Introduction

In high doses, the H_1-receptor antagonists astemizole and terfenadine prolong the cardiac QT interval and can induce a potentially lethal ventricular arrhythmia, torsades de pointes [1]. Therapeutic doses of terfenadine and astemizole can be cardiotoxic, when combined with inhibitors of CYP3A4 such as azole antifungals. Both ketoconazole and itraconazole potently inhibit terfenadine metabolism in human liver microsomes with an IC_{50} in the 4–10 μM range [2] and alter the metabolism of terfenadine with accumulation of parent drug in healthy volunteers [3, 4]. Torsades de pointes ventricular tachycardia in patients on terfenadine plus ketoconazole or itraconazole have been reported [5, 6].

Whereas the major metabolite of astemizole, desmethylastemizole, contributes to the antihistamine effect [7], it is not yet clear whether it also contributes to the cardiotoxic effect. For the parent compound, *in vitro* observations compatible with the clinical arrhythmogenic effect such as inhibition of repolarization in Purkinje fibers and blockade of potassium channels in ventricular myocytes have been reported [8, 9]. In human liver microsomes, ketoconazole inhibits astemizole metabolism with an IC_{50} of 2.4 μM while itraconazole inhibits astemizole metabolism for 30% at 30 μM [10]. The aim of this study was to investigate the influence of chronic itraconazole treatment on the pharmacokinetics and cardiovascular effects of single dose astemizole in healthy volunteers.

Correspondence: Dr Romain A. Lefebvre, Heymans Institute of Pharmacology, University of Gent Medical School, De Pintelaan 185, B-9000 Gent, Belgium

Methods

Subjects

Twelve male Caucasian subjects (age range, 22–28 years; body weight range, 65.4–88.4 kg) gave written informed consent to participate in this study, which was approved by the Ethics Committee of the Gent University Medical School. The subjects were in good health as indicated by medical history, physical examination, including ECG and biochemical testing within 2 weeks prior to the start of the study. All subjects were non-smokers and none used chronic medication.

Study protocol

The trial was a double-blind, placebo-controlled and randomized cross-over with two study phases. Itraconazole (200 mg as two 100 mg capsules twice daily) or matching

placebo was taken orally for 14 days with a washout period of 4 weeks. Medication was taken between 06.30 and 07.30 h immediately after breakfast and between 18.30 and 19.30 h immediately after dinner in the evening. Day 11 of each treatment period was spent in the experimental unit. The subjects took their morning itraconazole or placebo dose between 07.00 and 07.30 h immediately after a standardized breakfast and approximately 2 h later a 10 mg astemizole tablet was taken with 150 ml of water. A standardized meal was given 4 h after the astemizole dose, while the usual diet could be used from 8 h after the astemizole dose. Venous blood samples were collected in heparinized tubes through an indwelling heparin lock immediately before astemizole intake (15 ml) and 0.5, 1, 1.5, 2, 4, 6, 8 and 10 h (each time 10 ml) after astemizole intake. The subjects returned to the experimental unit to obtain blood samples by vein puncture 24 (day 12), 48 (day 13), 72 (day 14), 96 (day 15), 168 (day 18), 240 (day 21), 336 (day 25) and 504 (day 32) h (each time 10 ml) after astemizole intake. The plasma was separated within 2 h after collection and stored at -20°C until analyzed. The biochemical screen as performed before the study was repeated in the morning of day 9 and before (day 11), and 24 (day 12), 72 (day 14) and 504 (day 32) h after astemizole intake during each session.

Cardiovascular measurements

Before and 2, 4, 8 and 24 h after astemizole intake, the heart rate (pulse rate over 30 s) and blood pressure (phase I and V Korotkoff sounds) were recorded after 5 min rest in supine position. Twelve-lead ECGs were recorded at a paper speed of 25 mm s^{-1} using a Schiller Cardiovit AT-3, that provides the QT intervals corrected for heart rate (QT_c) according to Bazett's formula: $QT_c = QT/\sqrt{RR}$.

Astemizole and itraconazole assays

Plasma concentrations of astemizole and the antihistaminic moiety of astemizole plus desmethylastemizole were determined by radioimmunoassay [11]. As the antibody used reacts with both astemizole and desmethylastemizole, a first extraction at pH 7.8 allowed measurement of the sum of astemizole and desmethylastemizole (detection limit 0.10 ng ml^{-1}), while a subsequent extraction at pH 12.5 extracted astemizole alone (detection limit 0.05 ng ml^{-1}). The coefficients of variation were between 8.3 and 15.2% for astemizole and between 7.7 and 10.8% for astemizole plus desmethylastemizole. Itraconazole in plasma was determined by high performance liquid chromatography, with a detection limit of 0.020 μg ml^{-1}.

Pharmacokinetic analysis

Based on the individual plasma concentration-time data, the following parameters were determined for astemizole, and astemizole plus desmethylastemizole: peak concentration (C_{max}), time to peak concentration (t_{max}), elimination rate constant (λ_z) determined by linear regression of the ln-linear concentration-time curve, terminal half-life ($t_{1/2,z}$) defined as $0.693/\lambda_z$, the area under the plasma concentration-time curve from zero time up to 24 h calculated by the trapezoidal rule AUC(0,24 h) and the area under the plasma concentration-time curve extrapolated to infinity by use of the elimination rate constant (AUC). For desmethylastemizole, the AUC was obtained by subtracting the AUC of astemizole from that of astemizole plus desmethylastemizole.

Statistical analysis

Differences in t_{max} were analyzed by use of the non-parametric method of Koch [12] while all other pharmacokinetic parameters were statistically compared using analysis of variance for a two-period two-treatment cross-over design, with sequence, subjects (nested to sequence), period and treatment as factors. The 90% classical confidence intervals were calculated for the ratios of the C_{max} and AUCs between the two treatments (itraconazole and placebo) using the mean square error from the analysis of variance. Cardiovascular parameters between both treatments were compared by analysis of variance. All results are given as mean $\pm$s.d. with 95% confidence intervals (CI) of the mean difference.

Results

All subjects ended the study without serious adverse experiences or protocol violations. No concurrent medication was taken during the treatment periods. The laboratory screens before and during the study did not reveal clinically relevant deviations from normal ranges except for hypokalaemia (3.3 mmol l^{-1}) on day 11 of the itraconazole treatment period in volunteer 8. The volunteer received two doses of an oral potassium solution on day 11 and the potassium level was normalized by day 12.

The plasma concentrations of itraconazole, measured approximately 2 h post the morning dose of itraconazole were (μg ml^{-1}) 1.17 ± 0.48 on day 11, 1.38 ± 0.54 on day 12, 1.55 ± 0.72 on day 13 and 1.67 ± 0.69 on day 14. They progressively declined after ending the itraconazole treatment and the last measurable concentrations were found on day 25. Compared with the placebo session, the mean plasma concentrations of astemizole during itraconazole treatment were higher from 1.5 h after its administration and were measurable up to 72 h instead of up to 10 h. The C_{max} and the t_{max} of astemizole were not significantly different under placebo and itraconazole treatment (Table 1). Itraconazole treatment significantly increased the $t_{1/2,z}$ of astemizole and the AUC was nearly three times higher; the relative bioavailability was 277% with 90% classical confidence intervals of 236–318%. The plasma concentrations of desmethylastemizole were more elevated under itraconazole treatment from 72 h after astemizole administration. The C_{max} of desmethylastemizole did not differ between the placebo and itraconazole session, but the t_{max} significantly increased. The AUC increased from 119 ± 21 to 235 ± 40 ng ml^{-1} h under itraconazole treatment; the relative bioavailability was 197% with 90% classical confidence intervals of 178–217%.

There was no significant difference in the QT_c intervals after astemizole intake during treatment with placebo or itraconazole (Figure 1). In the two conditions, the QT_c intervals at 2, 4 and 8 h were decreased *vs* the basal value.

Table 1 Mean (±s.d.) pharmacokinetic parameters of astemizole and desmethylastemizole during treatment with placebo or itraconazole in 12 healthy male subjects.

	Placebo	*Itraconazole*	*95% CI of the mean difference*
Astemizole			
t_{max} (h)	1.3±0.5	1.7±0.3	0.14 to 0.61
C_{max} (ng ml^{-1})	0.74±0.34	0.81±0.29	−0.10 to 0.24
AUC(0,24 h) (ng ml^{-1} h)	5.46±1.98	9.95±3.41**	3.82 to 6.42
$t_{1/2,z}$ (days)	2.1±0.8	3.6±1.0**	0.90 to 2.16
AUC (ng ml^{-1} h)	17.4±8.1	48.2±16.7**	28.02 to 46.01
Desmethylastemizole			
t_{max} (h)	27.9±36.9	195±107**	100.2 to 233.85
C_{max} (ng ml^{-1})	0.37±0.14	0.41±0.11	−0.05 to 0.14
AUC (ng ml^{-1} h)	119±21	235±40**	86.64 to 144.11

**$P<0.01$: Significantly different from the value during treatment with placebo.

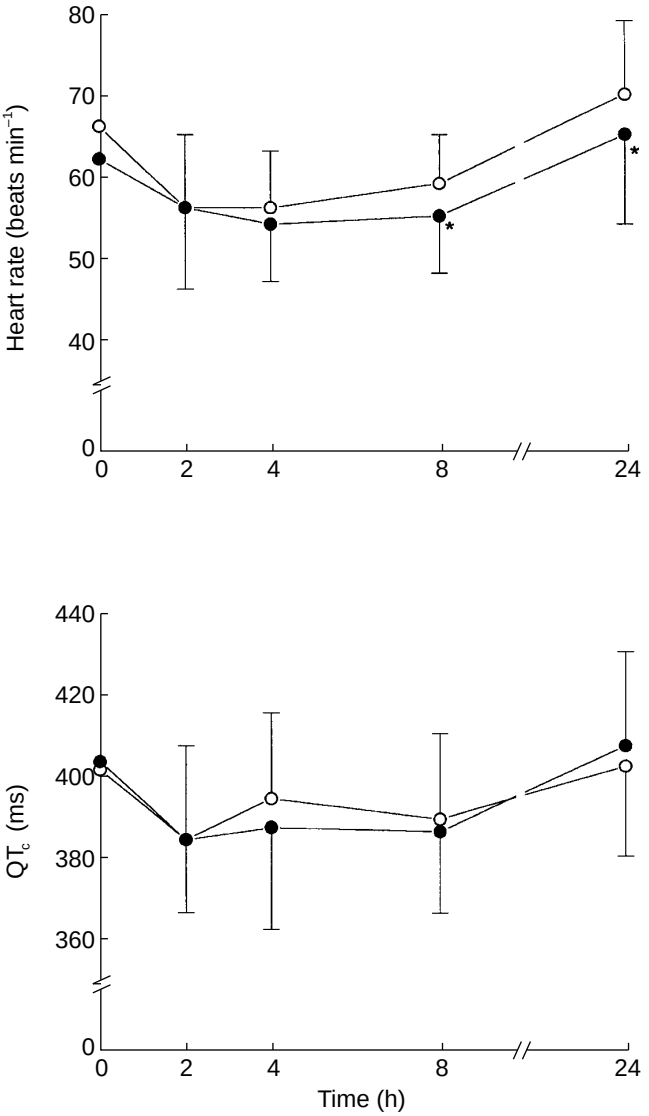

Figure 1 Mean (±s.d.) heart rate and QT_c intervals for 0 to 24 h after oral administration of a 10 mg astemizole dose during treatment with placebo (○) or itraconazole (●) to 12 healthy male subjects.
*$P<0.05$: Significantly different from the value during treatment with placebo.

This is related to the decrease of heart rate (Figure 1) observed at these moments increasing the RR interval in the formula of QT_c. Systolic and diastolic blood pressure did not change manifestly during the course of the measurement.

Discussion

The aim of this study was to examine the influence of chronic treatment of itraconazole on the pharmacokinetics and electrocardiographic effects of single dose astemizole. Itraconazole is a broad spectrum antifungal for oral administration in doses of 100 to 400 mg daily [13, 14]; the maximal dose was tested in this study. Itraconazole was taken immediately after breakfast and dinner as the oral absorption is maximal immediately after a main meal [15]. During chronic dosing, steady state plasma concentrations are reached after 1–2 weeks; at the 15th day of chronic dosing with 200 mg twice daily, the mean itraconazole plasma concentrations rose from 1.4 μg ml^{-1} (trough) to 1.8 μg ml^{-1}, 4 h after intake [16]. The plasma concentrations from day 11 till 14 of itraconazole treatment in our subjects were measured approximately 2 h post the morning dose of itraconazole and were in the range of the steady state trough concentrations. As maximal plasma concentrations of astemizole are reached within 1 h after oral dosing [17], administration of astemizole 2 h after the morning dose of itraconazole on day 11 meant that maximal astemizole concentrations were reached when the itraconazole plasma concentrations were approaching their maximal values.

The plasma concentrations and pharmacokinetic parameters of astemizole plus desmethylastemizole (not shown) after single oral intake of 10 mg astemizole during the placebo session were comparable with those reported before [17]. Treatment with itraconazole did not significantly change the C_{max} of astemizole but clearly increased the AUC and the $t_{1/2,z}$ illustrating that itraconazole, although having a lower inhibition potency *in vitro* than ketoconazole [10], *in vivo* inhibits astemizole metabolism. Also the AUC of the major antihistaminic active metabolite desmethylastemizole was clearly increased, showing that the inhibition also occurs at further steps in the metabolism of astemizole. This is comparable with the inhibition of terfenadine metabolism by e.g. erythromycin, where both the first and

second step of metabolism are inhibited [18]. The increased bioavailability of astemizole, following a single dose, under chronic itraconazole administration did not cause a change of the QT_c interval. The QT_c intervals under astemizole plus placebo did not increase, confirming previous results with chronic dosing of 10 mg daily in healthy volunteers [19]. The QT_c intervals actually decreased on the 2 measurement days, in correlation with the decrease of heart rate. The latter might be related to acclimatization to the experimental unit; some fluctuations in heart rate during 24 h recordings in healthy volunteers are also observed in other studies [see e.g. 20]. Long term itraconazole treatment can be accompanied by hypokalaemia [21], and hypokalaemia may prolong cardiac repolarization and precipitate ventricular arrhythmias [22]. Although hypokalaemia was indeed observed in one volunteer under itraconazole, the QT_c before administration of astemizole on day 11 was not different between the itraconazole and placebo session; in the volunteer with hypokalaemia on day 11, the QT_c interval was 400 ms.

Notwithstanding its influence on the pharmacokinetics of astemizole and desmethylastemizole, repeated intake of 200 mg itraconazole twice daily did thus not influence the cardiographic effects of single dose astemizole. However, it cannot be excluded that cardiac effects might occur in susceptible individuals. Also, no ECG recordings were taken more than 24 h after astemizole administration, so that the possible cardiac effects of the maximum concentrations of desmethylastemizole were not assessed. Furthermore, the reduction in astemizole clearance may result in a threefold increase in astemizole plasma concentrations, and a twofold increase in the plasma concentrations of desmethylastemizole during chronic astemizole intake when it would be combined with high doses of itraconazole. As a consequence, combined intake of astemizole and itraconazole should be absolutely avoided. In view of the increase of the $t_{1/2,z}$ of astemizole under concomitant administration of itraconazole to 3.6 days, the steady state astemizole concentration and the maximal alteration in QT_c may be achieved about 2 weeks after initiating the combined therapy.

In conclusion, chronic itraconazole treatment changes the pharmacokinetics of single dose astemizole in healthy volunteers but this does not alter cardiac repolarization in the first 24 h after astemizole administration.

The authors acknowledge the help of D. Roelant and D. Van Roosbroeck in the astemizole and itraconazole assays, and of A. Daems and S. Van de Poel in the pharmacokinetic analysis.

References

1 Smith SJ. Cardiovascular toxicity of antihistamines. *Otolaryngol Head Neck Surg* 1994; **111**: 348–354.

2 Jurima-Romet M, Crawford K, Cyr T, Inaba T. Terfenadine metabolism in human liver. In vitro inhibition by macrolide antibiotics and azole antifungals. *Drug Metab Dispos* 1994; **22**: 849–857.

3 Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC, Cantilena LR. Terfenadine-ketoconazole interaction. Pharmacokinetic and electrocardiographic consequences. *JAMA* 1993; **269**: 1513–1518.

4 Honig PK, Wortham DC, Hull R, Zamani K, Smith JE, Cantilena LR. Itraconazole affects single-dose terfenadine pharmacokinetics and cardiac repolarization pharmacodynamics. *J Clin Pharmacol* 1993; **33**: 1201–1206.

5 Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR. Torsades de pointes occurring in association with terfenadine use. *JAMA* 1990; **264**: 2788–2790.

6 Pohjola-Sintonen S, Viitasalo M, Toivonen L, Neuvonen P. Itraconazole prevents terfenadine metabolism and increases risk of torsades de pointes ventricular tachycardia. *Eur J Clin Pharmacol* 1993; **45**: 191–193.

7 Desager J-P, Horsmans Y. Pharmacokinetic-pharmacodynamic relationships of H_1-antihistamines. *Clin Pharmacokin* 1995; **28**: 419–432.

8 Adamantidis MM, Lacroix DL, Caron JF, Dupuis BA. Electrophysiological and arrhythmogenic effects of the histamine type 1-receptor antagonist astemizole on rabbit Purkinje fibers: clinical relevance. *J Cardiovasc Pharmacol* 1995; **26**: 319–327.

9 Berul CI, Morad M. Regulation of potassium channels by nonsedating antihistamines. *Circulation* 1995; **91**: 2220–2225.

10 Lavrijsen K, Van Houdt J, Meuldermans W, Janssens M, Heykants J. The interaction of ketoconazole, itraconazole and erythromycin with the *in vitro* metabolism of antihistamines in human liver microsomes. *Allergy* 1993; **48**: (Supplement): 34.

11 Woestenborghs R, Geuens I, Michiels M, Hendriks R, Heykants J. Radioimmunoassay procedures for astemizole and metabolites in plasma. *Drug Developm Res* 1986; **8**: 63–69.

12 Koch GG. The use of non-parametric methods in the statistical analysis of the two-period change over design. *Biometr* 1972; **28**: 577–584.

13 Grant SM, Clissold SP. Itraconazole. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in superficial and systemic mycoses. *Drugs* 1989; **37**: 310–344.

14 Dollery C. *Therapeutic drugs*, Supplement 1. Edinburgh: Churchill Livingstone, 1992: 14–17.

15 Van Peer A, Woestenborghs R, Heykants J, Gasparini R, Cauwenbergh G. The effect of food and dose on the oral systemic availability of itraconazole in healthy subjects. *Eur J Clin Pharmacol* 1989; **36**: 423–426.

16 Hardin T, Graybill J, Fetchik R, Woestenborghs R, Rinaldi M, Kuhn J. Pharmacokinetics of itraconazole following oral administration to normal volunteers. *Antimicrob Agents Chemother* 1988; **32**: 1310–1313.

17 Heykants J, Van Peer A, Woestenborghs R, Jageneau A, Vandenbussche G. Dose-proportionality, bioavailability, and steady-state kinetics of astemizole in man. *Drug Developm Res* 1986; **8**: 71–78.

18 Honig PK, Woosley RL, Zamani K, Conner DP, Cantilena LR. Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. *Clin Pharmacol Ther* 1992; **52**: 231–238.

19 Craft TM, Vandenbussche G, De Cree J, Griffiths JV. ECG studies with astemizole. *Human Toxicol* 1987; **6**: 527–528.

20 Démolis P, Annane D, Duhazé P, Giudicelli JF. Systemic, regional and cerebral hemodynamic effects of a new angiotensin converting enzyme inhibitor, imidapril, in healthy volunteers. *Fundam Clin Pharmacol* 1994; **8**: 80–89.

21 Tester-Dalderup CBM. Antifungal drugs. In *Meyler's side effects of drugs*, ed Dukes MNG, 12th ed. Amsterdam: Elsevier, 1992: 672–686.

22 Napolitano C, Priori SG, Schwartz PJ. Torsade de pointes. Mechanisms and management. *Drugs* 1994; **47**: 51–65.

(*Received 10 May 1996, accepted 30 October 1996*)

