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PHARMACOKINETICS AND DISPOSITION

Effects of terbinafine and itraconazole on the pharmacokinetics of orally administered tramadol

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Abstract
Background Tramadol is widely used for acute, chronic, and neuropathic pain. Its primary active metabolite is O-desmethyltramadol (M1), which is mainly accountable for the μ-opioid receptor-related analgesic effect. Tramadol is metabolized to M1 mainly by cytochrome P450 (CYP)2D6 enzyme and to other metabolites by CYP3A4 and CYP2B6. We investigated the possible interaction of tramadol with the antifungal agents terbinafine (CYP2D6 inhibitor) and itraconazole (CYP3A4 inhibitor).
Methods We used a randomized placebo-controlled crossover study design with 12 healthy subjects, of which 8 were extensive and 4 were ultrarapid CYP2D6 metabolizers. On the pretreatment day 4 with terbinafine (250 mg once daily), itraconazole (200 mg once daily) or placebo, subjects were given tramadol 50 mg orally. Plasma concentrations of tramadol and M1 were determined over 48 h and some pharmacodynamic effects over 12 h. Pharmacokinetic variables were calculated using standard non-compartmental methods.
Results Terbinafine increased the area under plasma concentration–time curve ($AUC_{0-\infty}$) of tramadol by 115 % and decreased the $AUC_{0-\infty}$ of M1 by 64 % ($P<0.001$). Terbinafine increased the peak concentration (C_{max}) of tramadol by 53 % ($P<0.001$) and decreased the C_{max} of M1 by 79 % ($P<0.001$). After terbinafine pretreatment the elimination half-life of tramadol and M1 were increased by 48 and 50 %, respectively ($P<0.001$). Terbinafine reduced subjective drug effect of tramadol ($P<0.001$). Itraconazole had minor effects on tramadol pharmacokinetics.
Conclusions Terbinafine may reduce the opioid effect of tramadol and increase the risk of its monoaminergic adverse effects. Itraconazole has no meaningful interaction with tramadol in subjects who have functional CYP2D6 enzyme.

Keywords Terbinafine · Itraconazole · Tramadol · *O*-desmethyltramadol · Interaction · Pharmacokinetics

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Introduction

Tramadol is a synthetic opioid analgesic with multiple pharmacological actions. It is widely used for acute, chronic, and neuropathic pain [1–4]. The primary metabolite is O-desmethyltramadol (M1), which is mainly accountable for the μ-opioid-related analgesia [5]. M1 has 700-fold affinity to μ receptors compared to tramadol, and therefore, tramadol is considered as an opioid prodrug [6]. The parent compound

tramadol suppresses also pain signals in the spinal cord by inhibiting the neuronal reuptake of serotonin (5-HT) and norepinephrine [7]. Orally administered tramadol is rapidly absorbed with an oral bioavailability of 66 %, and its elimination half-life is approximately 5 h [8, 9].

There are 5 main (M1–M5) and 19 minor (M6–M24) metabolites of tramadol that have been identified in humans [10]. Tramadol is metabolized to M1 primarily by cytochrome P450 (CYP)2D6 and to M2 by CYP2B6 and to lesser extent, by CYP3A4 according to in vitro studies [11]. There are data suggesting that extensive metabolizers (EM) of CYP2D6 have better analgesic effects of tramadol compared to poor metabolizers (PM) when given tramadol orally [12].

Terbinafine and itraconazole are antifungal agents widely used to treat skin and nail infections [13]. Terbinafine, unlike itraconazole, has been shown to inhibit CYP2D6 [14, 15]. In a study with healthy volunteers, CYP2D6-mediated formation of O-desmethylvenlafaxine from venlafaxine was decreased significantly with terbinafine pretreatment [16]. Itraconazole is a strong inhibitor of CYP3A4 and P-glycoprotein [17, 18]. In vitro studies suggest that itraconazole can inhibit also CYP2B6 [19].

Tramadol, terbinafine, and itraconazole are extensively used in clinical practice. Therefore, it is relevant to investigate the potential interaction of these two antimycotics with tramadol. Moreover, co-administration of tramadol with other CYP2D6 inhibitors is common [20]. We hypothesized that inhibition of CYP-mediated metabolism of tramadol leads to significant changes in the plasma concentrations of tramadol and M1, with possible pharmacodynamic changes.

Materials and methods

Study participants

According to pre-study calculations based on a previous study with oral tramadol, ten subjects were required to demonstrate a 30 % difference in the area under the time–concentration curve (AUC) of tramadol at a level of significance of $P=0.05$ and power of 80 % [8]. Therefore, 12 healthy non-smoking volunteers (four males and eight females; age 20–31 years; weight 53–91 kg; body mass index 18.2–25.7 kg/m^2) were included in the study. All subjects were Caucasians of Finnish origin, and all were ascertained to be healthy by clinical examination, laboratory tests, and electrocardiogram. Urine screens for drugs and pregnancy tests for females were negative. Written informed consent was obtained from all subjects. The risk of participants developing drug abuse was estimated to be low as evaluated by answers to a Finnish translation of the Abuse Questions [21]. The subjects were forbidden to use any medications or herbal products for 14 days before and during the study. Drugs known to cause enzyme induction or inhibition and grapefruit juice were not allowed for 30 days before the study. Female subjects were instructed to use non-hormonal contraception for the entire duration of the study. Consumption of coffee, tea, alcohol, and cola drinks were not allowed during the study days. The study protocol was approved by the ethics committee of the Hospital District of Southwest Finland and the Finnish National Agency for Medicines. The study was registered in the EudraCT clinical trials register (EudraCT no.: 2009-016998-15) and was conducted according to the revised (2008) Declaration of Helsinki.

Study design

We used a randomized single-blinded crossover study design with three phases and a 6-week washout period between the phases. The long washout period was chosen because in a previous study, the CYP2D6 inhibitory effect of terbinafine persisted after 4 weeks [22]. The subjects were given in randomized order 250 mg terbinafine (Lamisil®; Novartis, Switzerland), 200 mg itraconazole (Sporanox®; Janssen-Cilag, Finland) or placebo orally at 07:00 a.m. for 5 days. In previous studies, this pretreatment regimen has produced significant CYP2D6 inhibition with terbinafine and CYP3A4 inhibition with itraconazole [16, 18]. A single oral dose of 50 mg tramadol (Tramal; Orion, Finland) was administered on day 4 at 08:00 a.m. (Supplementary Table 1). Tramadol was administered 1 h after the fourth dose of terbinafine, itraconazole, or placebo because we wanted to have the peak concentration of the pretreatment drug closer to the time of tramadol administration. The subjects were instructed to fast for 8 h before tramadol administration. Standard meals were served 4 and 8 h after the administration of tramadol. The hospital pharmacy (Pharmacy of the Hospital District of Southwest Finland, Turku, Finland) packed the study drugs according to a randomization list. Blood samples for the determination of plasma concentrations of tramadol and M1 were drawn from a cannulated forearm vein immediately before and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, and 48 h after tramadol administration. For the control of compliance, a blood sample for analysis of terbinafine and itraconazole concentrations was also taken before tramadol administration. Samples for determining whole blood 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) concentrations were taken prior to and 4 and 8 h after tramadol administration. Bioanalytical methods are described in detail in the supplementary material.

Pharmacokinetics

Peak plasma concentrations (C_{max}) and corresponding peak times (t_{max}) of tramadol and M1 were observed directly from the plasma concentration data. The linear trapezoidal method

was used when successive concentration values were increasing, and the logarithmic trapezoidal method was used when values were decreasing to determine the AUC. The individual terminal log–linear phases of the tramadol and M1 concentration curves were identified visually. The elimination rate constant (k_e) was determined by regression analysis of the log–linear part of the curve. The elimination half-life ($t_{1/2}$) was then calculated using the equation $t_{1/2}=\ln 2/k_e$. The pharmacokinetic data were analyzed by using the WinNonlin pharmacokinetic program (version 4.1; Pharsight, Mountain View, CA).

Pharmacodynamics

Subjective effects of tramadol were assessed with 100-mm-long visual analogue scales for the following items: drowsiness, performance, drug effect, relaxation, nausea and calmness. Digit symbol substitution test (DSST) [23] was used to evaluate possible psychomotor effects. Pupil size was measured using Cogan's pupillometer under constant lighting conditions [24]. The Maddox wing was used to measure the central coordination of the extra ocular muscles [25]. A cold pressor test [26] was used to evaluate the analgesic effect of tramadol. The subject immersed his or her hand up to the wrist into ice-cold water (0.5–2 °C). The cold pain threshold was defined by the time from the immersion to the first sensation of pain. Subjects reported the intensity of pain at 30 (CPI30) and 60 s (CPI60). Pharmacodynamic effects were evaluated before and 1, 2, 3, 4, 5, 6, 8, 10, and 12 h after the administration of tramadol. For each pharmacodynamic variable, the area under the response–time curve was determined by the linear trapezoidal rule for 12 h ($AUEC_{0–12}$).

CYP2D6 genotyping

The genotypes of the study subjects were not known at the time of recruiting process. Samples for determination of CYP2D6 genotype were taken in the first study session. The subjects were genotyped for CYP2D6*1 (wild type), *3, *4, *5, *6, *9, *10, and *41. Eight subjects were extensive CYP2D6 metabolizers (EM), five of whom had the CYP2D6*1/*1 genotype, two had CYP2D6*1/*4 and one had CYP2D6*1/*41 genotype. Four subjects were ultrarapid metabolizers (UM) with the CYP2D6*1/*1 genotype with gene duplication.

Statistical analysis

The primary outcome variables in this study were the area under plasma concentration–time curve ($AUC_{0-\infty}$) of tramadol and M1. Shapiro–Wilk's test was used to examine the normality of the data. Analysis of variance for repeated measurements was used to analyze the differences in the pharmacokinetic variables, except for t_{max}, which was analyzed with Wilcoxon's signed rank test. P values of <0.05 were regarded as statistically significant. Differences were considered clinically significant when 90 % confidence interval (CI) of the geometric mean ratio was outside of the commonly applied bioequivalence acceptance limits of 0.8–1.25. Data were log-transformed and reported as geometric mean ratios with CI of 90 %. Data were analyzed using SYST AT for Windows (ver. 10.2; Systat Software, Richmond, CA), SAS System 9.1.3 for Windows (SAS Institute, Cary, NC) and GraphPad Prism 5 for Windows (GraphPad Software, San Diego, CA) statistical programs.

Results

All subjects completed the study according to the study protocol. In the terbinafine phase, before tramadol administration, plasma terbinafine concentrations (mean±SD) were 214±211 ng/ml. Three subjects in the placebo phase and two subjects in the itraconazole phase had trace amounts of terbinafine from the previous terbinafine phase. In the itraconazole phase, the concentration of plasma itraconazole and hydroxy-itraconazole before tramadol administration were 129±60 and 147±78 ng/ml, respectively. In a previous study with pretreatment of 250 mg oral terbinafine daily or 100 mg oral itraconazole daily for 4 days resulted in terbinafine and itraconazole baseline concentrations of 698±143 and 136±38 ng/ml, respectively [14]. The observed differences in terbinafine and itraconazole concentrations are understandable because in the previous study, the concentrations were measured 2 h after the administration of terbinafine or itraconazole while in the present study, the baseline samples were taken before the administration of terbinafine or itraconazole. Almost all subjects experienced some mild or moderate adverse effects. After tramadol ingestion, 11 subjects reported adverse effects in the placebo phase, 9 in the terbinafine phase, and 9 in the itraconazole phase. The most common effects were drowsiness and dry mouth. There were no serious adverse effects.

Pharmacokinetics

Terbinafine pretreatment increased tramadol $AUC_{0-\infty}$ 2.1-fold and decreased M1 $AUC_{0-\infty}$ 64 % (geometric mean ratios 2.23; 90 % CI 1.85–2.69; $P<0.001$ and 0.36; 90 % CI 0.32–0.41; $P<0.001$, respectively) compared to placebo (Table 1; Figs. 1 and 2). Peak plasma concentration (C_{max}) of tramadol was increased 1.5-fold (geometric mean ratio 1.56; 90 % CI 1.33–1.82; $P<0.001$) and M1 C_{max} was decreased 78 % (geometric mean ratio 0.21; 90 % CI 0.17–0.24; $P<0.001$) by terbinafine

Table 1 Pharmacokinetic parameters of tramadol and its primary metabolite O-desmethyltramadol (M1) after oral administration of 50 mg tramadol on the fourth day of pretreatment with oral placebo, terbinafine (250 mg once daily) or itraconazole (200 mg once daily) in 12 healthy volunteers

Parameter	Placebo	Terbinafine	*P* value	Itraconazole	*P* value	Geometric mean ratio (90 % CI)	
						Terbinafine/placebo	Itraconazole/placebo
Tramadol							
$AUC_{0-\infty}$ (ng h/ml)	1033±407	2219±630	<0.001	1174±602	0.19	2.23 (1.85–2.69)	1.11 (1.00–1.23)
C_{max} (ng/ml)	140±37	215±46	<0.001	162±48	0.08	1.56 (1.33–1.82)	1.16 (1.02–1.32)
$t_{1/2}$ (h)	4.3±0.7	6.4±1.3	<0.001	4.7±0.9	0.02	1.47 (1.34–1.62)	1.10 (1.03–1.17)
t_{max} (h)	1.5 (0.5–3)	1.5 (1–3)	0.751	1.5 (1–3)	0.629		
CL/F (l/min)	0.92±0.32	0.40±0.08	<0.001	0.83±0.29	0.18	0.45 (0.37–0.54)	0.90 (0.81–1.00)
O-desmethyltramadol (*M1*)							
$AUC_{0-\infty}$ (ng h/ml)	433±76	158±30	<0.001	521±79	0.004	0.36 (0.32–0.41)	1.20 (1.10–1.32)
C_{max} (ng/ml)	46±10	10±2	<0.001	51±11	0.14	0.21 (0.17–0.24)	1.11 (1.00–1.24)
$t_{1/2}$ (h)	4.9±0.7	7.4±1.4	<0.001	5.3±0.9	0.06	1.50 (1.36–1.64)	1.08 (1.02–1.14)
t_{max} (h)	2 (1–5)	2 (1.5–10)	0.046	2 (1–3)	0.18		
AUC_m/AUC_p	0.47±0.17	0.07±0.02	<0.001	0.51±0.18	0.25	0.16 (0.14–0.19)	1.09 (0.99–1.17)

Data are shown as arithmetic mean±standard deviation (SD) and as the geometric mean ratios with the 90 % confidence interval (CI) in parenthesis—except for t_{max}, which is given as median and range

$AUC_{0-\infty}$ area under plasma concentration time curve extrapolated to infinity, C_{max} peak plasma concentration, $t_{1/2}$ terminal elimination half-life, t_{max} time to peak concentration, *CL/F* apparent oral clearance, V_z/F apparent volume of distribution, AUC_m/AUC_p $AUC_{0-\infty}$ of *O*-desmethyltramadol/$AUC_{0-\infty}$ of tramadol

pretreatment. Terminal elimination half-life ($t_{1/2}$) of tramadol was prolonged from 4.3±0.7 to 6.4±1.3 h (geometric mean ratio 1.47; 90 % CI 1.34–1.62; $P<0.001$) and the ratio of M1 to tramadol (AUC_m/AUC_p) was markedly reduced by terbinafine (geometric mean ratio 0.16; 90 % CI 0.14–0.19; $P<0.001$).

Itraconazole pretreatment increased M1 $AUC_{0-\infty}$ 1.2-fold (geometric mean ratio 1.20; 90 % CI 1.10–1.32; $P=0.004$) and $t_{1/2}$ 1.1-fold (geometric mean ratio 1.10; 90 % CI 1.03–1.17; $P=0.02$). Other parameters did not have statistically significant changes after pretreatment with itraconazole.

CYP2D6 genotyping

Among the four subjects with the CYP2D6 UM genotype, the AUC ratio of M1 to tramadol was 68 % higher and the apparent oral clearance of tramadol was 46 % higher than that among the eight EM subjects in the placebo phase. Pretreatment with terbinafine diminished the effect of UM genotype, as the AUC ratio of M1 to tramadol was increased only 37 % and the apparent oral clearance was increased only 25 %.

Pharmacodynamics

The $AUEC_{0-12h}$ of subjective drug effect of tramadol was significantly reduced after terbinafine treatment compared to placebo (95 % CI −267.5 to −49.5; $P<0.001$). There were no other statistically significant differences in the pharmacodynamic effects of tramadol between the three phases (Fig. 3). Tramadol did not affect whole blood 5-HT or 5-HIAA concentrations in the placebo, terbinafine, or itraconazole phase.

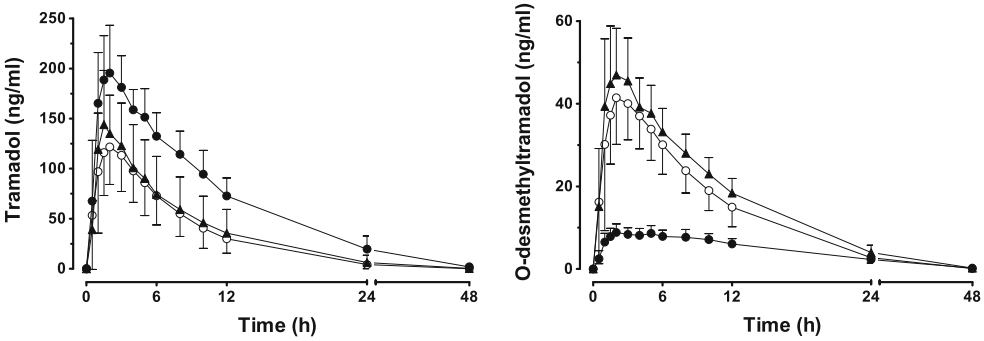

Fig. 1 Mean plasma (± SD) concentrations of tramadol and O-desmethyltramadol in 12 healthy volunteers after 50 mg oral tramadol on the fourth day of pretreatment with placebo (*open circles*), terbinafine 250 mg once daily (*filled circles*) or itraconazole 200 mg once daily (*filled triangles*)

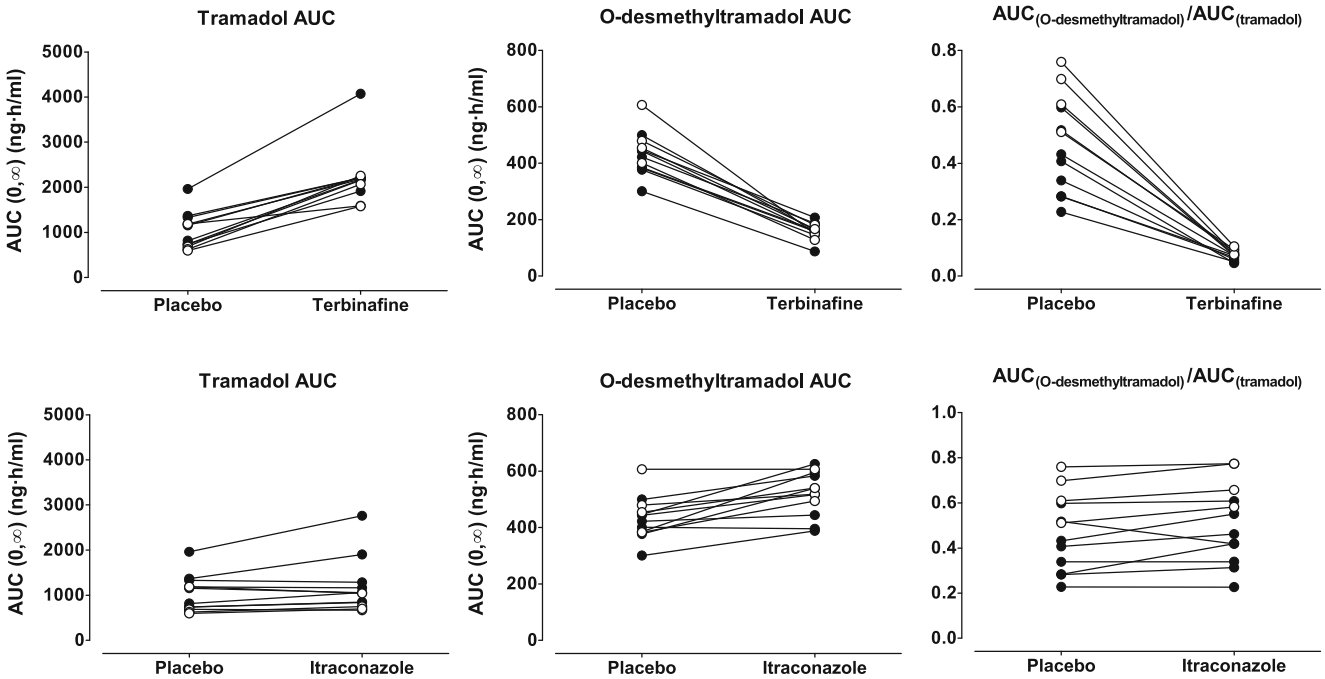

Fig. 2 Individual values of the area under plasma concentration–time curve extrapolated to infinity ($AUC_{0-\infty}$) for tramadol and O-desmethyltramadol and the O-desmethyltramadol to tramadol ratio after 50 mg oral tramadol following pretreatment with placebo, terbinafine of itraconazole. Four subjects with UM CYP2D6 genotype (*open circles*) and eight with EM CYP2D6 genotype (*filled circles*) are shown

Discussion

In this study, oral pretreatment with the strong CYP2D6 inhibitor terbinafine clearly decreased the conversion of tramadol to M1. All subjects, irrespective of their EM or UM CYP2D6 genotype, had a similar trend in the concentrations of tramadol and M1 (Fig. 2). The CYP3A4 inhibitor itraconazole had only a slight effect on the pharmacokinetics of tramadol in the subjects with CYP2D6 UM or EM genotype, which were not likely clinically relevant.

The mean M1 $AUC_{0-\infty}$ was 18 % higher in ultrarapid compared to extensive metabolizers in the placebo phase (Fig. 2); however, the difference was not statistically significant due to the low number of subjects in each genotype group. This finding is consistent with the crucial role of CYP2D6 in the metabolism of tramadol to M1 in individuals

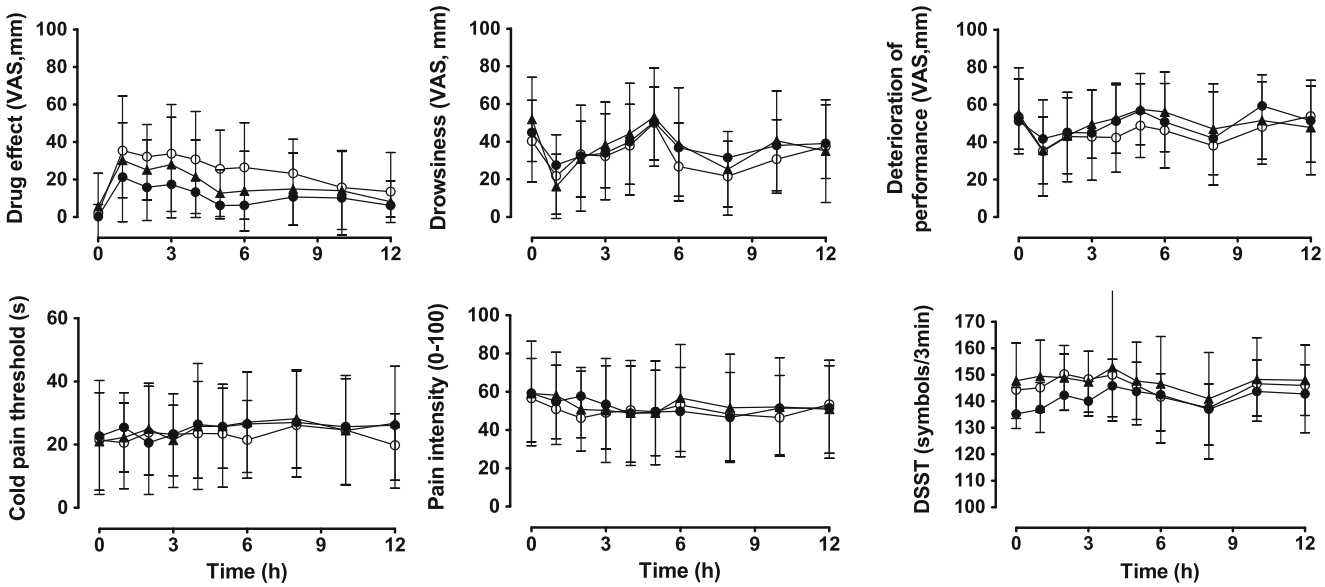

Fig. 3 Self-reported visual analogue scale (VAS) scores (mean±SD) of drug effect, drowsiness, and deterioration of performance, cold pain threshold, and cold pain intensity at 60 s and number of digits substituted in 3 min (DSST) after an oral dose of 50 mg of tramadol on the fourth day of pretreatment with placebo (*open circles*), terbinafine (*filled circles*), or itraconazole (*filled triangles*)

with fully functional CYP2D6 enzyme. It is reasonable to assume that the interaction of tramadol with terbinafine and other CYP2D6 inhibitors would be minimal in subjects with the CYP2D6 PM genotype. On the other hand, it can be speculated that itraconazole and other strong CYP3A4 inhibitors could have a more pronounced, even clinically significant, effect on the pharmacokinetics of tramadol in CYP2D6 PM subjects than that seen in the present study in the UM and EM subjects.

Many opioid drugs, including morphine [27], fentanyl [28], and alfentanil [29], are substrates of P-glycoprotein (P-gp), which is an efflux transporter, e.g. in the intestinal wall and blood–brain barrier [30]. However, tramadol does not seem to be a substrate for P-gp [31]. Organic anion-transporting polypeptide (OATP) has possibly an influence on the pharmacokinetics of tramadol, but there is no strong evidence to support this [31]. Moreover, there is no evidence that terbinafine or itraconazole inhibits or induces OATP. Tzvetkov et al. [32] reported that the hepatic reuptake of M1, but not of tramadol, is mediated by organic cation transporter (OCT)1 suggesting that OTC1 may affect plasma concentrations of M1 and thus opioidergic efficacy. With respect to the genotype results, CYP2D6 inhibition by terbinafine pretreatment seems to be the most reasonable explanation for the decreased M1 and increased tramadol concentrations. Similar results have been reported previously, suggesting that CYP2D6 genotype seems to determine the variability in M1 concentrations [33].

Terbinafine pretreatment decreased significantly the $AUEC_{0\text{-}12h}$ of the subjective pharmacodynamic drug effect ($AUEC_{0\text{-}12h}$). Also, in our previous studies, the $AUEC_{0\text{-}12h}$ of drug effect has produced consistent results after a single dose of oral or intravenous tramadol and it has been the most sensitive parameter to detect pharmacodynamic consequences of opioid interactions [8, 34, 35]. These pharmacodynamic measurements were still somewhat underpowered to demonstrate this interaction because the effects of tramadol were quite minimal even in the placebo phase. Furthermore, the lack of double blinding may have an effect on these results.

Tramadol is known to inhibit the neuronal reuptake of 5-HT and norepinephrine [7]. Studies with selective serotonin reuptake inhibitors have shown that inhibition of 5-HT reuptake can decrease the concentrations of 5-HT in the whole blood and that this may compromise hemostasis [36–38]. In our study, 5-HT and 5-HIAA levels in the whole blood were not affected by a single dose of tramadol. Using a study setting with multiple and higher doses of tramadol could have led to changes in 5-HT and 5-HIAA levels.

In a previous study, CYP2D6 extensive metabolizers had higher M1 concentrations and augmented analgesia in the cold pressor test compared to poor metabolizers when given tramadol 100 mg intravenously [39]. Therefore, it could be extrapolated that the inhibition of tramadol conversion to M1 caused by terbinafine could lead to reduced analgesic effect, although the cold pressor test of this study could not detect it. In patients using weak opioid analgesics, it would be recommended to choose an antifungal medication like itraconazole that does not have the CYP2D6 interaction potential, because not only tramadol but also codeine is a prodrug activated by CYP2D6 [5, 40]. However, the strong CYP3A4 inhibiting effect of azole antifungal agents needs to be considered in their concomitant use with drugs that are dependent on CYP3A4.

In conclusion, terbinafine pretreatment decreased significantly the conversion of tramadol to M1. Therefore, concomitant use of terbinafine and tramadol should be avoided due to reduced μ-opioid receptor-related analgesia and possibly increased risk of serotonergic effects, especially when higher doses of tramadol are used. It should be remembered that all drugs used in this study may have different dosing regimen depending on the indication. No clinically significant interaction was found between itraconazole and tramadol in the present study, in which all subjects had functional CYP2D6 enzyme.

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