



HAL
open science

Effects of itraconazole on the pharmacokinetics and pharmacodynamics of intravenously and orally administered oxycodone

Teijo I. Saari, Juha Grönlund, Nora M. Hagelberg, Mikko Neuvonen, Kari Laine, Pertti J. Neuvonen, Klaus T. Olkkola

► **To cite this version:**

Teijo I. Saari, Juha Grönlund, Nora M. Hagelberg, Mikko Neuvonen, Kari Laine, et al.. Effects of itraconazole on the pharmacokinetics and pharmacodynamics of intravenously and orally administered oxycodone. *European Journal of Clinical Pharmacology*, 2010, 66 (4), pp.387-397. 10.1007/s00228-009-0775-8 . hal-00555614

HAL Id: hal-00555614

<https://hal.science/hal-00555614>

Submitted on 14 Jan 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Effects of itraconazole on the pharmacokinetics and pharmacodynamics of intravenously and orally administered oxycodone

Teijo I. Saari · Juha Grönlund · Nora M. Hagelberg ·
Mikko Neuvonen · Kari Laine · Pertti J. Neuvonen ·
Klaus T. Olkkola

Received: 12 October 2009 / Accepted: 8 December 2009 / Published online: 14 January 2010
© Springer-Verlag 2010

Abstract

Background The aim of this study was to investigate the effects of the cytochrome P450 3A4 (CYP3A4) inhibitor itraconazole on the pharmacokinetics and pharmacodynamics of orally and intravenously administered oxycodone.

Methods Twelve healthy subjects were administered 200 mg itraconazole or placebo orally for 5 days in a four-session paired cross-over study. On day 4, oxycodone was administered intravenously (0.1 mg/kg) in the first part of the study and orally (10 mg) in the second part. Plasma concentrations of oxycodone and its oxidative metabolites were measured for 48 h, and pharmacodynamic effects were evaluated.

Results Itraconazole decreased plasma clearance (Cl) and increased the area under the plasma concentration–time curve (AUC_{0–∞}) of intravenous oxycodone by 32 and 51%, respectively ($P < 0.001$) and increased the AUC(0–∞) of orally administered oxycodone by 144% ($P < 0.001$). Most of the pharmacokinetic changes in oral oxycodone were seen in the elimination phase, with modest effects by itraconazole on its peak concentration, which was increased

by 45% ($P = 0.009$). The AUC(0–48) of noroxycodone was decreased by 49% ($P < 0.001$) and that of oxymorphone was increased by 359% ($P < 0.001$) after the administration of oral oxycodone. The pharmacologic effects of oxycodone were enhanced by itraconazole only modestly.

Conclusions Itraconazole increased the exposure to oxycodone by inhibiting its CYP3A4-mediated N-demethylation. The clinical use of itraconazole in patients receiving multiple doses of oxycodone for pain relief may increase the risk of opioid-associated adverse effects.

Keywords CYP enzymes · Intravenous/oral drug administration · Itraconazole · Opioid effects · Oxycodone · Pharmacodynamics · Pharmacokinetics

Introduction

Oxycodone is a semi-synthetic μ -opioid receptor agonist which is widely used in the treatment of both acute and chronic pain [1]. The oral bioavailability of oxycodone is over 60% and it is extensively metabolised by duodenal and hepatic cytochrome P450 (CYP) isoenzymes. Only 10% of the oxycodone dose is excreted unchanged in the urine [2–5]. The predominant metabolic pathway of oxycodone is CYP3A4-mediated N-demethylation to noroxycodone, while a small part of the oxycodone undergoes 3-O-demethylation to oxymorphone by CYP2D6 [5, 6]. Further oxidation of these metabolites via CYP2D6 (and CYP3A4) yields noroxymorphone [5, 6]. Although the metabolites possess μ -opioid receptor activity, the relative contribution of the different metabolites to the central opioid effects are still to discussion [6, 7].

The involvement of CYP enzymes in the metabolism of oxycodone makes it prone for drug interactions, and the

T. I. Saari (✉) · J. Grönlund · N. M. Hagelberg · K. T. Olkkola
Department of Anesthesiology, Intensive Care,
Emergency Care and Pain Medicine, University of Turku,
P.O. Box 52, Kiinamylynkatu 4-8,
FI-20520 Turku, Finland
e-mail: teijo.saari@tyks.fi

M. Neuvonen · P. J. Neuvonen
Department of Clinical Pharmacology, University of Helsinki,
Helsinki, Finland

K. Laine
Department of Pharmacology,
Drug Development and Therapeutics, University of Turku,
Turku, Finland

inhibition of CYP3A4 and CYP2D6 enzyme activities may impair the metabolism of oxycodone. It has been shown that the inhibition of CYP2D6 with quinidine increases noroxycodone concentration and blocks the formation of oxymorphone, while the oxycodone concentration remains unchanged [8]. Voriconazole, an effective inhibitor of several CYP enzymes, profoundly delays the elimination of oxycodone [9]. On the other hand, rifampicin, a strong inducer of CYP enzymes, effectively enhances the elimination of both oral and intravenous oxycodone [10].

Itraconazole is widely used in the treatment of superficial and invasive fungal infections [11, 12]. It is a potent and specific inhibitor of CYP3A and it has been the cause of clinically significant drug–drug interactions with many substrates of CYP3A [13–16]. Similar to quinidine, itraconazole is also a potent inhibitor of the efflux transporter P-glycoprotein [17]. We hypothesised that itraconazole might have the potential to increase the plasma concentrations of oxycodone via inhibition of the CYP3A-mediated metabolism of oxycodone. We have therefore investigated the possible effects of itraconazole on the pharmacokinetics and pharmacodynamics of both intravenous and oral oxycodone in healthy subjects.

Methods

Subjects

Based on data reported in published studies [3, 18], we calculated that ten subjects would be required to demonstrate a 30% difference in the area under the oxycodone plasma concentration–time curve (AUC) with a type I error of 5% and a statistical power of 80%. Written informed consent was obtained from 12 healthy non-smoking volunteers (five men and seven women, age range 22–39 years, body mass index range 20–28 kg/m²). Before entering the study, the volunteers were ascertained to be in good health based on a medical history, clinical examination, routine laboratory tests and electrocardiogram (ECG). The risk of participants developing aberrant opioid-related behaviour was estimated to be low as evaluated by the Finnish translation of the Abuse Questions [19]. Urine toxicology screens were negative. None of the volunteers was receiving any continuous medication, including contraceptive steroids, or natural products. Female subjects used safe non-hormonal contraception during the study. The study was conducted according to the revised Declaration of Helsinki, and it was approved by the Ethics Committee of the Hospital District of Southwest Finland and the Finnish National Agency for Medicines.

Study design

A four-session paired crossover study design was used. The volunteers were orally administered, in a randomised and balanced order, either 200 mg itraconazole (Sporanox; Janssen-Cilag S.p.A., Latina, Italy) or placebo once daily at 7 A.M. for 5 days. Oxycodone was administered on day 4, intravenously in the first part of the study and orally in the second part, and there was a wash-out interval of 4 weeks between the first and the second part of the study.

In the first part of the study, on two occasions, with an interval of 4 weeks, all volunteers received 0.1 mg/kg intravenous oxycodone hydrochloride (Oxynorm 10 mg/ml; Mundipharma, Bard Pharmaceuticals, Cambridge, UK), administered within a 2-min period, on day 4 at 8 A.M., 1 h after the fourth dose of itraconazole or placebo. One more dose of itraconazole or placebo was given on day 5. In the second part of the study, the volunteers were given correspondingly 10 mg of oral oxycodone hydrochloride (Oxynorm 10 mg capsules, Mundipharma, Bard Pharmaceuticals) with 150 ml of warm water. Blood samples were collected immediately before and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 h after administration of the oxycodone. An additional blood sample was drawn 0.25 h after intravenous oxycodone administration. In the first part of the study, another venous cannula was inserted into the opposite forearm for the intravenous administration of oxycodone. The behavioural and analgesic effects were evaluated prior to and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 h after the administration of oxycodone, except for heat-pain analgesia, which was assessed prior to and 1 h after oxycodone dosing. Adherence with the itraconazole/placebo-dosing schedule was assessed by use of mobile telephone text messages. The volunteers fasted for 8 h before the administration of oxycodone, and were given standard meals at 4 and 8 h after its administration. They were not allowed to smoke or to drink grapefruit juice during the study. Alcohol, coffee, tea and cola drinks were not permitted on test days.

Blood sampling and drug analysis

On the test days, a forearm vein of each subject was cannulated with a plastic cannula and timed blood samples (10 ml) were drawn into ethylenediaminetetraacetic acid-containing tubes. Plasma was separated within 30 min and stored at –70° C until analysis.

The plasma concentrations of itraconazole were quantified by high-performance liquid chromatography as described earlier [20]. The lower limit of quantification (LLQ) was 10 ng/ml. The interday coefficients of variation (CV) were 10.9, 5.7 and 4.1% at 40, 192 and 1200 ng/ml, respectively ($n=5$).

Plasma concentrations of oxycodone, noroxycodone, oxymorphone and noroxymorphone were analysed with the liquid chromatography tandem mass spectrometric method, as previously described [21]. The LLQ was 0.1 ng/ml for oxycodone and oxymorphone and 0.25 ng/ml for noroxycodone and noroxymorphone. The CV at 0.1, 5 and 100 ng/ml was 8.5, 3.5 and 2.5% ($n=11$), respectively, for oxycodone, and less than 10% for the rest of the analytes at relevant plasma concentrations.

Genotyping for CYP2D6 was performed using a two-step multiplex primer extension method [22]. The method allows the detection of 11 of the most relevant polymorphic positions, the assessment of whole-gene deletion and the duplication and allele composition of gene duplication.

Pharmacokinetic analysis

The peak plasma concentrations (C_{\max}) and corresponding times of C_{\max} (t_{\max}) of oxycodone and its metabolites were observed directly from the data. The areas under the oxycodone, noroxycodone, oxymorphone and noroxymorphone concentration–time curves were estimated by means of the trapezoidal rule with extrapolation to infinity [AUC(0– ∞)]. We used the linear trapezoidal rule when successive concentration values were increasing and the logarithmic trapezoidal rule when successive concentration values were decreasing after the peak concentration value. For oxidative metabolites of oxycodone, we calculated the area under the metabolite plasma concentration–time curve from 0 to 48 h [AUC(0–48)]. The metabolite-to-parent drug AUC ratios (AUC_m/AUC_p) were calculated as indexes of metabolism through different metabolic pathways. For each subject, the terminal log-linear phase of the oxycodone, noroxycodone, oxymorphone and noroxymorphone plasma concentration–time curve was identified visually, and the elimination rate constant (k_e) was determined by regression analysis. The elimination half-life ($t_{1/2}$) was then calculated from the following equation: $t_{1/2} = \ln 2/k_e$.

After the intravenous administration of oxycodone, plasma clearance (Cl) and steady-state volume of distribution (V_{ss}) of oxycodone were calculated by use of noncompartmental methods based on statistical moment theory. The oral bioavailability of oxycodone (F) was calculated as follows: $F = [AUC(0 - \infty)_{\text{oral}} \cdot \text{Dose}_{\text{intravenous}}] / [AUC(0 - \infty)_{\text{intravenous}} \cdot \text{Dose}_{\text{oral}}$. After the oral administration of oxycodone, we calculated the apparent clearance (Cl/F) and the apparent volume of distribution of oxycodone during elimination (V_z/F). Pharmacokinetic variables of oxycodone, noroxycodone, oxymorphone, noroxymorphone and itraconazole were determined using the WinNonlin pharmacokinetic program (version 4.1; Pharsight, Mountain View, CA).

Pharmacodynamic measurements

Behavioural effects Behavioural effects of oxycodone were assessed with 100-mm visual analogue scales for the following items: alert/drowsy, very good performance/very poor performance, no effects of the drug/very strong effects of the drug, unpleasant feeling/pleasant feeling [23]. The central co-ordination of extraocular muscles was evaluated using Maddox wing test, which measures horizontal heterophoria in diopters [24]. The central processing of sensory information was assessed with the digit symbol substitution test (DSST) [25]. The pupil size was measured with Cogan's pupillometry [26]. In addition, any adverse events spontaneously reported by the subjects were recorded.

Analgesic effects The cutaneous heat-pain threshold was determined using a feedback-controlled contact thermode (TSA-2; Medoc, Rehovot, Israel). This device delivers three heat-pain stimuli of slowly increasing (1°C/s) temperature to the right volar forearm. The size of the thermode was 30×30 mm. Heat increased linearly from a baseline temperature of 35°C until the subject reported the first sensation of pain by pressing a button. This temperature was recorded, and the temperature returned to baseline. The interval between the stimuli was approximately 30 s. To avoid sensitisation, testing site on the skin differed slightly. The heat-pain threshold was defined as the mean of the three temperature measurements.

The cold pressor test [27] was used to assess cold-pain sensitivity. The subject immersed his or her left hand up to the wrist in ice water at 0.5–2°C for 1 min. The latency in seconds from the immersion to the first sensation of pain was defined as the cold-pain threshold. During the immersion, the subject reported the intensity of cold pain at 30 s (CPI30) and 60 s (CPI60) using a numerical rating scale (NRS, 0=no pain, 100=maximum pain). If the pain became intolerable, the subject was allowed to withdraw his or her hand from the water. In such a case, the intensity and unpleasantness after withdrawal were recorded as maximum (100).

The area under the response–time curve for 12 h [AUC(0–12)] for all pharmacodynamic variables except for the heat pain test was determined using the trapezoidal rule.

Statistical analysis

Differences in pharmacokinetic and pharmacodynamic variables between the itraconazole and placebo phases were analysed using paired Student's *t* test except for t_{\max} , which was analysed with Wilcoxon signed-ranks test. The

contributions of oxycodone and itraconazole to overall variance in heat- and cold-pain thresholds and cold-pain intensity were analysed by analysis of variance. The possible association of plasma concentration of oxycodone with pharmacological effect was calculated using Pearson's product-moment correlation coefficient. Pearson's product-moment correlation coefficient was also used to investigate the possible relationship between the ratio of the AUC(0–∞) of oxycodone during the itraconazole phase to AUC(0–∞) of oxycodone during the control phase and the AUC(0–48) of itraconazole. All data were analysed using the statistical program SYSTAT for Windows (ver. 10.2; SystatSoftware, Richmond, CA). The results are expressed as mean±standard deviation (SD) or median (range) whenever appropriate. *P* values<0.05 were considered to be statistically significant.

Results

Genotyping

In terms of metabolism mediated through CYP2D6, seven subjects were considered to be extensive metabolisers: four with the CYP2D6*1/*1 genotype, two with the CYP2D6*1/*4 genotype and one with the CYP2D6*1/*41 genotype. One subject was an ultrarapid metaboliser through CYP2D6 metabolism, with the CYP2D6*1/*1 genotype and gene duplication. Three of the remaining four subjects were considered to be intermediate metabolisers (CYP2D6*4/*41 genotype), and one was a poor metaboliser (CYP2D6*4/*4 genotype). The intermediate and poor metabolisers appeared to have higher oxycodone and noroxycodone AUC values and lower oxymorphone AUC values than extensive metabolisers during both study phases (Fig. 2). The statistical significance of these observations was not tested because of the small group sizes.

Pharmacokinetics

Oxycodone Itraconazole decreased the plasma Cl of intravenous oxycodone by 32% (*P*<0.001) and increased its *t*_{1/2} from 3.8 h to 5.5 h (*P*=0.016) (Fig. 1; Table 1). The AUC(0–∞) of intravenous oxycodone was increased 1.5-fold (*P*=0.009) following itraconazole administration, and itraconazole also increased the mean *C*_{max} and AUC(0–∞) of oral oxycodone by 1.4-fold (*P*=0.009) and 2.4-fold (*P*<0.001), respectively. The AUC(0–∞) of oral oxycodone was increased in all subjects by itraconazole, the greatest increase being 3.4-fold. The *t*_{1/2} of oral oxycodone was prolonged from 4.0 h to 5.9 h (*P*=0.007), and the oral bioavailability was increased from 55 to 82% (*P*<0.001) by itraconazole (Fig. 1; Table 2).

Noroxycodone Itraconazole decreased the *C*_{max} of noroxycodone by 64% after the administration of intravenous oxycodone and by 71% after the administration of oral oxycodone compared to the control values (Fig. 1; Tables 1 and 2). The AUC(0–48) of noroxycodone was decreased by 54 (*P*<0.001) and 49% (*P*<0.001) after the intravenous and oral administration of oxycodone, respectively. The corresponding metabolite-to-parent drug AUC ratios (AUC_m/AUC_p) were decreased by 69 and 78% (*P*<0.001), respectively (Fig. 2).

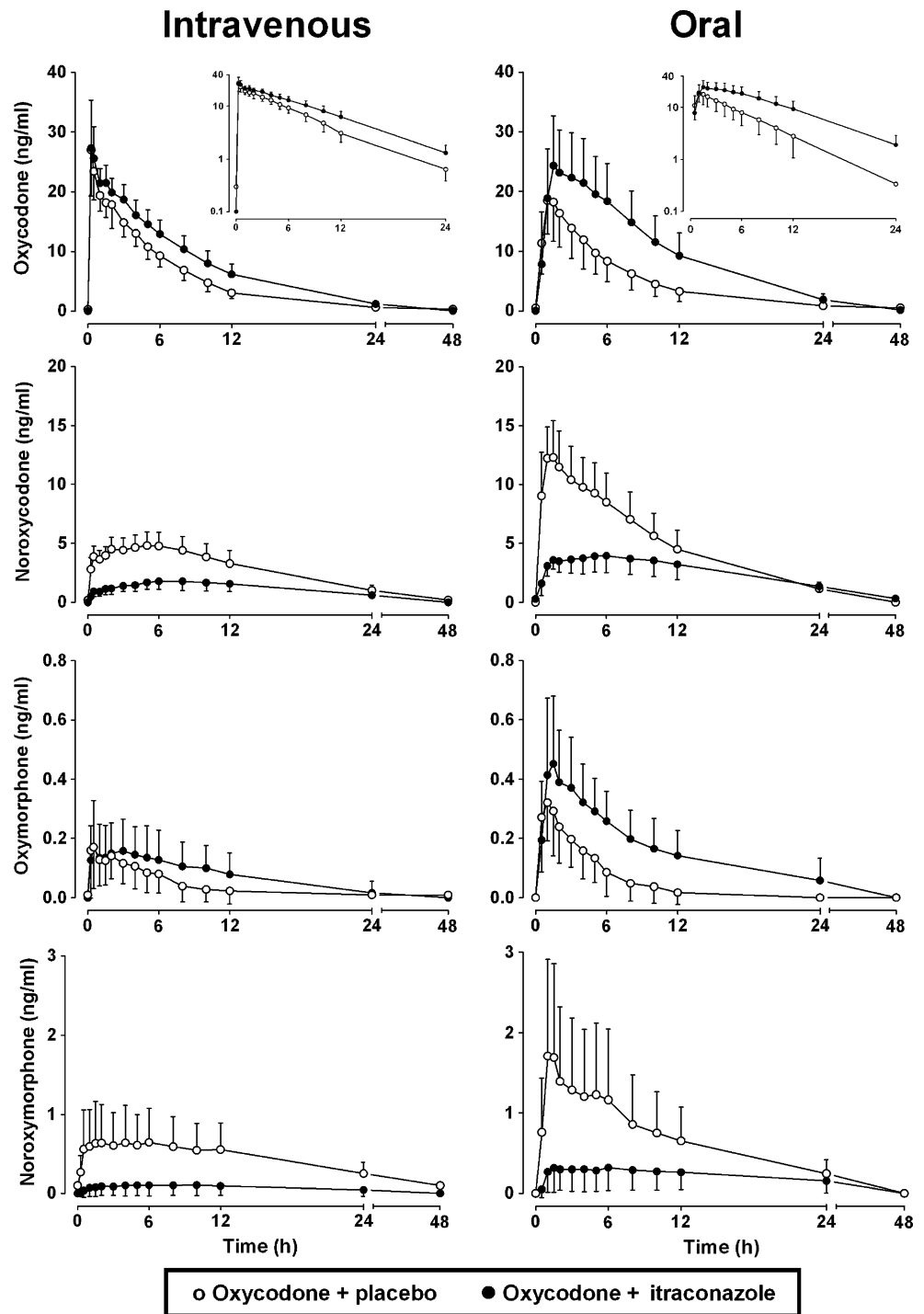
Oxymorphone and Noroxymorphone Itraconazole increased the *C*_{max} of oxymorphone by nearly 1.5-fold in the oral part of the study. The mean AUC(0–48) of oxymorphone was significantly greater after itraconazole pre-treatment (Fig. 1; Tables 1 and 2) in both phases of the study: 2.6-fold (*P*=0.034) after intravenous and 4.6-fold (*P*=0.001) after oral oxycodone. Itraconazole decreased the AUC(0–48) of noroxymorphone by approximately 80% following the intravenous and oral administration of oxycodone. Intravenous oxycodone produced no quantifiable oxymorphone concentrations in two subjects after administration of placebo and itraconazole. Noroxymorphone was not quantified in seven subjects after itraconazole and intravenous oxycodone. Following itraconazole and oral oxycodone administration, all of the measured noroxymorphone concentrations of four of the subjects were below the LLQ.

Itraconazole The plasma concentration profile of itraconazole was similar during both phases (Fig. 3). The mean plasma trough concentration of itraconazole just before the administration of oxycodone was 68 ng/ml (range 10–127 ng/ml) in the first part and 81 ng/ml (range 38–138 ng/ml) in the second part of the study. The values for AUC(0–48) of itraconazole were 6718±3438 ng ml⁻¹ h in the first part of the study and 7304±3949 ng ml⁻¹ h in the second part. In the control phase, no plasma itraconazole concentrations were detectable on the test days. There was no significant linear correlation between the plasma concentration of itraconazole and any of the itraconazole-induced changes observed in the pharmacokinetic or pharmacodynamic parameters.

Pharmacodynamics

Behavioural effects Following the oral administration of oxycodone, self-reported alertness, drug effect and deterioration of performance were significantly increased after the administration of itraconazole compared with placebo based on the AUC(0–12) (*P*<0.05). No other behavioural differences were observed (Fig. 4). Although itraconazole appeared to increase the perceived subjective drug effect and drowsiness during the immediate period following the

Fig. 1 Mean plasma concentrations (\pm standard deviation, SD) of oxycodone, noroxycodone, oxymorphone and noroxymorphone after an intravenous (0.1 mg/kg) or oral (10 mg) dose of oxycodone hydrochloride on day 4 of the placebo (*open circles*, control) or itraconazole phase (*filled circles*) in 12 healthy subjects. The *inset* depicts the same data on a semilogarithmic scale. The volunteers received either 200 mg of oral itraconazole or placebo once daily for 5 days



intravenous administration of oxycodone in the first part of the study, no statistically significant differences were observed ($P=0.052$). There was a statistically significant linear correlation between the behavioural effects and plasma oxycodone concentration ($P<0.05$ for all variables).

Analgesic effects Oral oxycodone did not increase the heat pain threshold in all subjects ($P=0.521$) and the magnitude

of this change was not affected by itraconazole pre-treatment ($P=0.630$). The maximum effect of oxycodone on the cold pain threshold and cold pain intensity scores were observed 1–2 h after oxycodone administration. Itraconazole did not enhance the analgesic effect of intravenous or oral oxycodone on cold pain intensity and unpleasantness when compared to placebo, and it also did not alter heat pain analgesia.

Table 1 Pharmacokinetic parameters of oxycodone and its primary and secondary oxidative metabolites after the intravenous administration of 0.1 mg/kg oxycodone hydrochloride on day 4 of the oral pretreatment with placebo or itraconazole (200 mg daily) to 12 healthy volunteers

Parameter	Placebo	Itraconazole	95% CI of the difference between the phases	<i>P</i> value
Oxycodone				
Cl (l min ⁻¹ kg ⁻¹)	12.3±2.8	8.2±1.6	-6.27, -2.37	<0.001
% of control (range)	100	68 (42–110)		
V _{ss} (l kg ⁻¹)	3.3±0.5	3.3±0.3	-0.28, 0.47	0.597
% of control (range)	100	98 (71–150)		
AUC(0–∞) (ng ml ⁻¹ h)	139±31	210±185	41.1, 101	<0.001
% of control (range)	100	151 (116–182)		
t _{1/2} (h)	3.8±1.3	5.5±1.6	0.32, 2.84	0.016
% of control (range)	100	142 (105–177)		
Noroxycodone				
C _{max} (ng/ml)	5.1±0.9	1.9±0.7	-3.8, -2.47	<0.001
% of control (range)	100	36 (27–62)		
t _{max} (h)	5.0 (0.5–8.0)	7.0 (3.0–12.0)		<0.001
AUC(0–48) (ng ml ⁻¹ h)	78.2±22.5	37.5±15.5	-57.1, -24.3	<0.001
% of control (range)	100	46 (36–66)		
AUC _m /AUC _p	0.57±0.18	0.18±0.09	-0.51, -0.27	<0.001
% of control (range)	100	31 (21–43)		
Oxymorphone				
C _{max} (ng/ml)	0.19±0.15	0.21±0.14	-0.14, 0.1	0.711
% of control (range)	100	94 (0–161)		
t _{max} (h)	0.25 (0–6.0)	0.5 (0–5.0)		0.427
AUC(0–48) (ng ml ⁻¹ h)	0.88±0.83	2.2±1.9	0.11, 2.59	0.034
% of control (range)	100	259 (0–493)		
AUC _m /AUC _p	0.014±0.011	0.019±0.011	-0.01, 0.002	0.174
% of control (range)	100	18 (0–36)		
Noroxymorphone				
C _{max} (ng/ml)	0.63±0.55	0.12±0.15	-0.84, -0.17	0.005
% of control (range)	100	15 (0–44)		
t _{max} (h)	3.5 (0–12)	0 (0–12)		0.108
AUC(0–48) (ng ml ⁻¹ h)	10.9±8.8	2.5±3.2	-14.0, -2.8	0.005
% of control (range)	100	16 (0–44)		

95% CI, 95 % Confidence interval; Cl, plasma clearance; V_{ss}, steady-state volume of distribution; AUC(0–∞), area under the plasma concentration–time curve extrapolated to infinity; AUC(0–48), area under the plasma concentration–time curve 0 to 48 h after oxycodone administration; t_{1/2}, elimination half-life; C_{max}, peak plasma concentration; t_{max}, time to peak plasma concentration; AUC_m/AUC_p, ratio of AUC of metabolite to AUC of oxycodone

Data are given as mean ± standard deviation (SD) (median and range for t_{max}). Percentage of control was calculated individually for each subject; mean and range of these individual values are reported

Discussion

Our results clearly show that itraconazole affected the metabolism oxycodone administered intravenously and orally, particularly the latter. After intravenous oxycodone administration, itraconazole reduced the mean plasma Cl of oxycodone by 32%. Because the values for V_{ss} remained essentially unaffected, the change in Cl was associated with a significant prolongation of the t_{1/2}. After oral administration of itraconazole, the C_{max} of oxycodone was increased 1.5-fold and the AUC(0–∞) by 2.4-fold. These changes

resulted from an increase in the oral bioavailability of oxycodone and a decrease in its plasma Cl.

Itraconazole greatly decreased the formation of both CYP3A-dependent metabolites of oxycodone, as evidenced by the decrease in the AUC_m/AUC_p ratios of noroxycodone and noroxymorphone, which explains the observed changes in oxycodone pharmacokinetics. Because CYP3A is expressed both in the gut wall and in the liver, the inhibition of CYP3A by itraconazole can occur at both sites. Accordingly, it is not surprising that itraconazole increased the mean AUC(0–∞) of oral oxycodone by 2.4-fold

Table 2 Pharmacokinetic parameters of oxycodone and its primary and secondary oxidative metabolites after the oral administration of 10 mg immediate-release oxycodone hydrochloride on day 4 of the oral pretreatment with placebo or itraconazole (200 mg daily) to 12 healthy volunteers

Parameter	Placebo	Itraconazole	95% CI of the difference between the phases	<i>P</i> value
Oxycodone				
C_{\max} (ng/ml)	18.8±5.8	26.8±7.6	2.2, 13.6	0.009
% of control (range)	100	145 (117–185)		
t_{\max} (h)	1.0 (0.5–1.0)	1.5 (1.0–4.0)		0.558
AUC(0–∞) (ng ml ⁻¹ h)	119±53	268±92	85.7, 213.6	<0.001
% of control (range)	100	244 (151–338)		
Cl/F (l min ⁻¹ kg ⁻¹)	1.7±0.9	0.7±0.3	-1.6, -0.42	0.002
% of control (range)	100	43 (30–46)		
V_z/F (l kg ⁻¹)	0.54±0.22	0.34±0.08	-0.34, -0.06	0.007
% of control (range)	100	67 (43–85)		
$t_{1/2}$ (h)	4.0±1.6	5.9±1.5	0.6, 3.2	0.007
% of control (range)	100			
F	0.55±0.12	0.82±0.11	0.27, 0.37	<0.001
% of control (range)	100	156 (127–222)		
Noroxycodone				
C_{\max} (ng/ml)	13.3±2.6	4.1±1.2	-10.9, -7.5	<0.001
% of control (range)	100	29 (19–44)		
t_{\max} (h)	1.5 (0.5–4.0)	4.0 (1.0–10.0)		0.016
AUC(0–48) (ng ml ⁻¹ h)	139±43	72.6±27.7	-97.1, -36.3	<0.001
% of control (range)	100	51 (34–80)		
AUC _m /AUC _p	1.3±0.7	0.30±0.17	-1.44, -0.62	<0.001
% of control (range)	100	22 (14–31)		
Oxymorphone				
C_{\max} (ng/ml)	0.36±0.17	0.49±0.23	-0.03, 0.36	0.112
% of control (range)	100	148 (77–265)		
t_{\max} (h)	1.0 (0.5–1.5)	1.5 (0–3.0)		0.166
AUC(0–48) (ng ml ⁻¹ h)	1.5±1.0	4.8±2.7	1.52, 4.99	0.001
% of control (range)	100	459 (148–1285)		
AUC _m /AUC _p	0.01±0.01	0.02±0.01	-0.01, 0.004	0.274
% of control (range)	100	111 (0–263)		
Noroxymorphone				
C_{\max} (ng/ml)	1.8±1.3	0.38±0.33	-2.23, -0.6	0.001
% of control (range)	100	17 (0–29)		
t_{\max} (h)	1.5 (0.5–6.0)	1.5 (0–8.0)		0.141
AUC(0–48) (ng ml ⁻¹ h)	10.9±8.8	2.5±3.2	-14.0, -2.8	0.005
% of control (range)	100	29 (0–55)		

Cl/F, Apparent oral clearance; V_z/F , apparent volume of distribution during elimination; F=oral bioavailability;. Other parameters are defined in footnote of Table 1

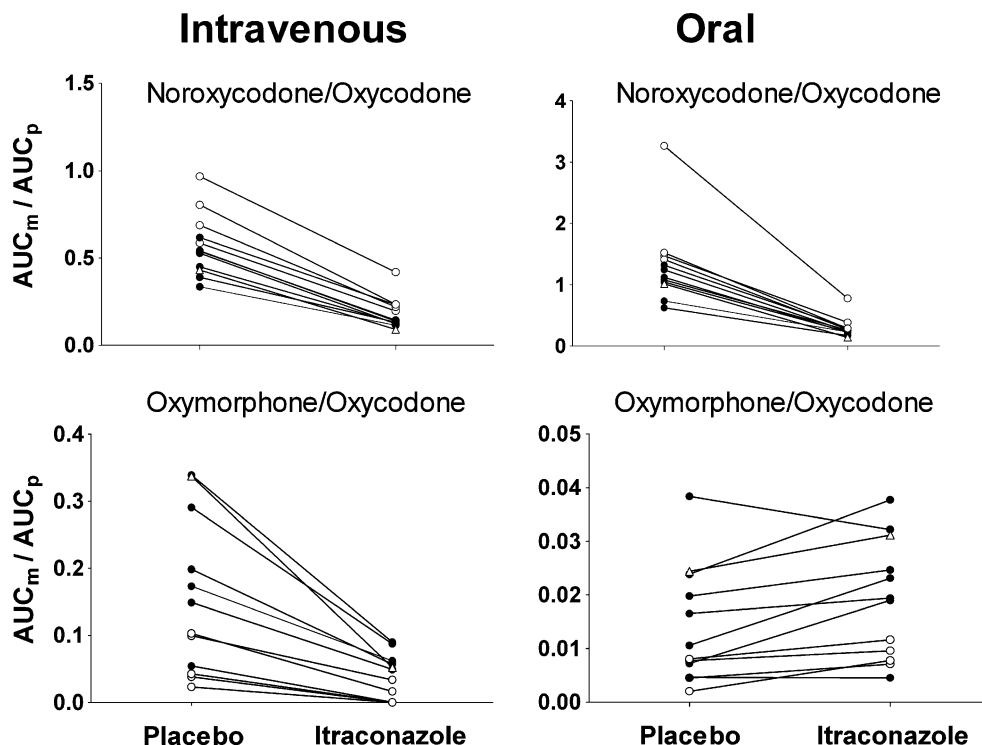
Data are given as mean ± SD (median and range for t_{\max}). Percentage of control was calculated individually for each subject; mean and range of these individual values are reported

compared with the 1.5-fold increase after intravenous oxycodone. Another explanation for the pharmacokinetic changes could be the inhibition of P-glycoprotein. Itraconazole is a potent inhibitor of P-glycoprotein [28]. If oxycodone were a substrate for P-glycoprotein, inhibition of intestinal P-glycoprotein would increase its oral bioavailability and concentrations. Moreover, inhibition of brain capillary endothelium P-glycoprotein would increase the penetration of oxycodone to the site of action in the

brain and increase the opioid effects. Animal data on the role of P-glycoprotein in the pharmacokinetics of oxycodone is controversial [29, 30]. In addition, there are no human data suggesting that oxycodone would be a substrate for P-glycoprotein. Therefore, it seems likely that the observed pharmacokinetic changes were caused entirely by the inhibition of CYP3A.

Following a single intravenous dose of oxycodone, itraconazole did not change the pharmacodynamic response

Fig. 2 The ratio of area under plasma concentration–time curve of metabolites to parent drug (AUC_m/AUC_p), for noroxycodone (*top panel*) and oxymorphone (*bottom panel*) after administration of the intravenous (0.1 mg/kg) and oral (10 mg) dose of oxycodone hydrochloride on day four of the placebo or itraconazole phase. The volunteers were given, in randomised order, either 200 mg of oral itraconazole or placebo once daily for 5 days. Each *circle* represents one subject. *Open triangle* Ultrarapid cytochrome P450 (CYP) 2D6 metaboliser, *open circles* intermediate and poor CYP 2D6 metabolisers



to oxycodone. However, after a single oral dose of oxycodone, the inhibition of CYP3A with itraconazole increased oxycodone-induced drowsiness, drug effect and deterioration of performance. Oxycodone also increased the heat pain threshold and decreased the cold pain sensitivity, but these changes were not altered by itraconazole. The minor effect of itraconazole on oxycodone-induced pharmacological response despite the clear changes in its pharmacokinetics is

well in line with the log-linear relationship between drug concentration and effect and the relatively small dose of oxycodone used in our study [31, 32].

Azole antimycotics are known to have significant interactions with several substrates of CYP3A [15, 16, 33–35]. With respect to other substrates of CYP3A, itraconazole has been found to decrease the mean plasma Cl of intravenous midazolam by 69% and increase the AUC (0–∞) of oral midazolam by 660% [14]. Compared to midazolam, we found that the effect of itraconazole on the pharmacokinetics of intravenous and oral oxycodone was much smaller. This difference is plausible because, unlike midazolam, the elimination of oxycodone is not solely dependent on CYP3A enzymes as oxycodone is also metabolised by CYP2D6 [5, 6]. The smaller effect of itraconazole on oral oxycodone is also explained by the higher bioavailability of oxycodone as compared to midazolam [10, 14].

To date, there is rather little information available on the pharmacokinetics of oxycodone in terms of the effect of drugs inhibiting CYP enzymes. Recent results obtained by our group show that the concentrations of oral oxycodone are profoundly increased by another antimycotic, voriconazole, which caused a 3.6-fold increase in the AUC(0–∞) of oxycodone [9]. Voriconazole thus appears to be a somewhat stronger inhibitor of CYP3A than itraconazole.

Both itraconazole and voriconazole [9] cause much greater changes in the pharmacokinetics of oxycodone than quinidine, an inhibitor of CYP2D6 and P-glycoprotein [8].

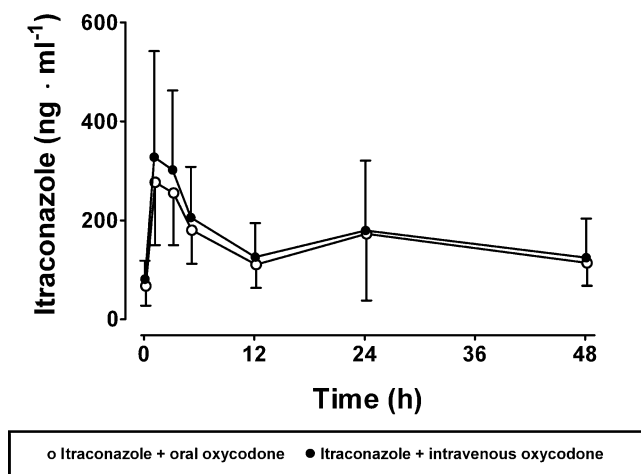
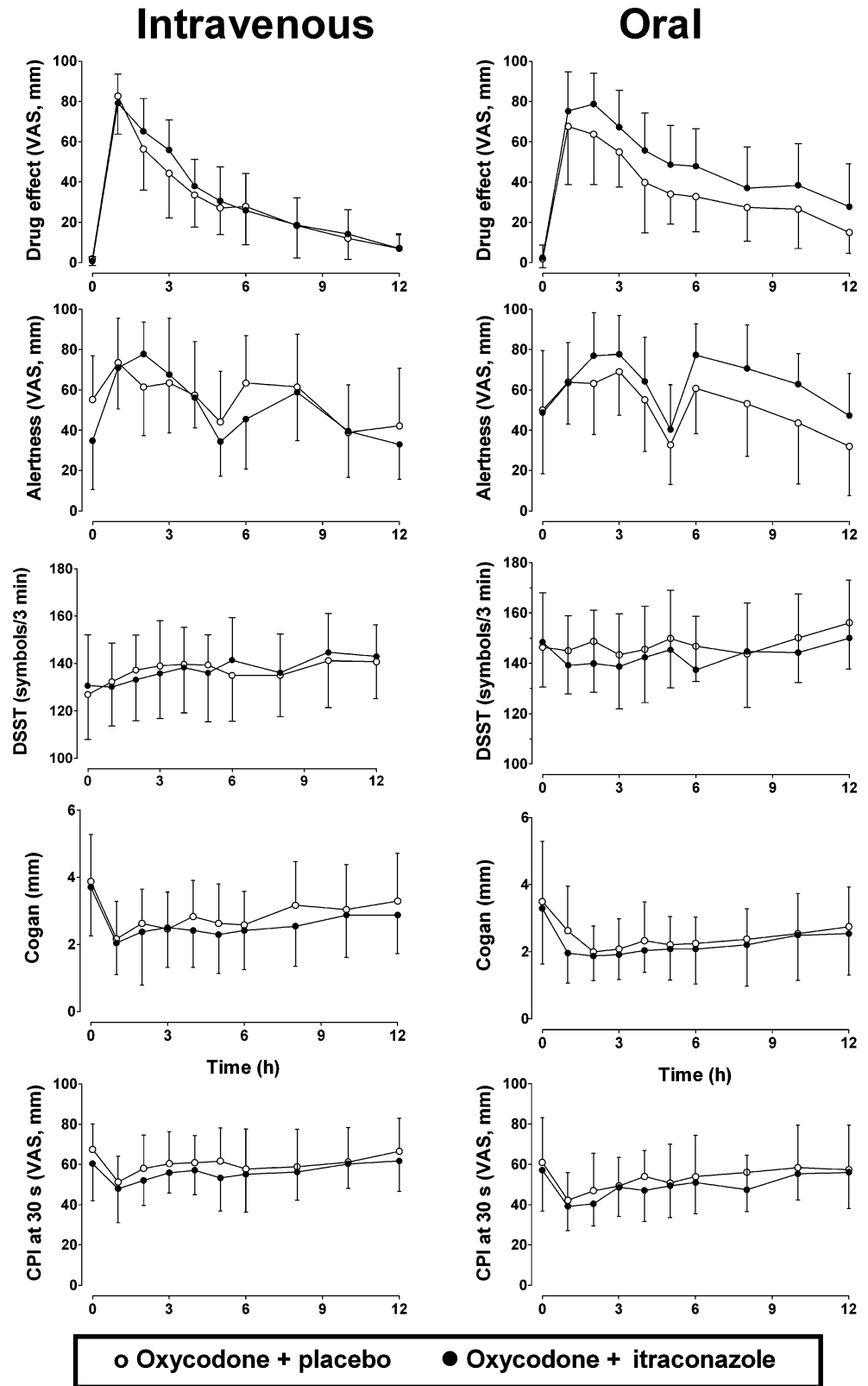


Fig. 3 Mean plasma concentrations (\pm standard deviation, SD) of itraconazole in 12 healthy subjects on the fourth and fifth days (0–24 and 24–48 h) of itraconazole (200 mg daily). *Open* and *closed circles* refer to the phases when oxycodone was given orally or intravenously, respectively

Fig. 4 Mean (\pm SD) self-reported drug effect, alertness, number of digits substituted in 3 min (*DSST*), pupil size (*Cogan*) and cold pain intensity at 30 s (*CPI30*) after an intravenous (0.1 mg/kg) or oral (10 mg) dose of oxycodone hydrochloride on day 4 of the placebo phase (*open circles*, control) or itraconazole phase (*filled circles*) in 12 healthy subjects. The volunteers ingested—in randomised order—either 200 mg itraconazole or placebo once daily for 5 days. *VAS* Visual analogue scale



This difference reflects the fact that the CYP3A-mediated N-demethylation of oxycodone to noroxycodone is about sevenfold higher than the CYP2D6-mediated O-demethylation to oxymorphone [6]. The effects of CYP2D6 inhibitors on oxycodone pharmacokinetics are even further alleviated by the compensatory increase in the CYP3A-dependent production of noroxycodone [8].

There were seven extensive and one ultrarapid metaboliser through CYP2D6 among the test subjects. The subject with an ultrarapid CYP2D6 genotype appeared to have higher oxymorphone concentrations and lower oxycodone concentrations than the extensive, intermediate and poor metabolisers, respectively. Itraconazole appeared to cause a smaller increase in oxycodone concentrations in this single subject than in the others, suggesting that the CYP2D6 genotype may modulate the outcome of interaction between itraconazole and oxycodone. However, this conclusion is highly speculative due to the small number of subjects with the various genotypes in our study. Nevertheless, it cannot be ruled out that the inhibition of CYP3A enzymes in patients given oxycodone would have more clinical consequences in poor metabolisers through effects on metabolism mediated by CYP2D6 because these individuals have a lower capability to shift the metabolism of oxycodone towards the CYP2D6 pathway than other types of metabolisers.

To ensure the safety of the subjects, we administered only a low single dose of oxycodone. In the clinical setting, patients with cancer-related or chronic pain often receive much higher multiple doses of oxycodone. Thus, it is possible that in clinical practice the effect of itraconazole on the pharmacokinetics and pharmacodynamics of oral oxycodone may be more pronounced than that observed in this study. The clinical situation is also complicated by several confounding factors, such as age, concurrent diseases and concomitant medication. Indeed, both age and possible renal or liver dysfunction can greatly influence the pharmacokinetics and pharmacodynamics of oxycodone [4, 36, 37]. Consequently, the results of our study may not be directly applicable to all patients.

In conclusion, we found that itraconazole strongly inhibited the elimination of oxycodone among our small group of subjects by decreasing its CYP3A-mediated N-demethylation. As a result, the concentrations of oxycodone, especially after its oral administration, are greatly increased. This increase is reflected as only moderate changes in the behavioral effects of oxycodone. Dose adjustments of oxycodone may therefore be necessary during itraconazole treatment to avoid opioid-related adverse effects, especially when multiple doses of oxycodone are given orally.

Acknowledgements We want to thank Mrs. Elina Kahra (Medical laboratory technologist, Clinical Pharmacology, TYKSLAB, Hospital District of Southwest Finland, Turku, Finland) for her skillful technical assistance.

Financial Support Turku University Hospital research fund EVO 13821, Turku, Finland; Finnish Society of Anaesthesiologists, Helsinki, Finland; Finnish Association for the Study of Pain, Helsinki, Finland and Sigfrid Juselius Foundation, Helsinki, Finland

Conflict of Interest None

References

- Mucci-LoRusso P, Berman BS, Silberstein PT, Citron ML, Bressler L, Weinstein SM, Kaiko RF, Buckley BJ, Reder RF (1998) Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain: A randomized, double-blind, parallel-group study. *Eur J Pain* 2:239–249
- Silvasti M, Rosenberg P, Seppälä T, Svartling N, Pitkanen M (1998) Comparison of analgesic efficacy of oxycodone and morphine in postoperative intravenous patient-controlled analgesia. *Acta Anaesthesiol Scand* 42:576–580
- Pöyhiä R, Seppälä T, Olkkola KT, Kalso E (1992) The pharmacokinetics and metabolism of oxycodone after intramuscular and oral administration to healthy subjects. *Br J Clin Pharmacol* 33:617–621
- Kirvelä M, Lindgren L, Seppälä T, Olkkola KT (1996) The pharmacokinetics of oxycodone in uremic patients undergoing renal transplantation. *J Clin Anesth* 8:13–18
- Lalovic B, Phillips B, Risler LL, Howald W, Shen DD (2004) Quantitative contribution of CYP2D6 and CYP3A to oxycodone metabolism in human liver and intestinal microsomes. *Drug Metab Dispos* 32:447–454
- Lalovic B, Kharasch E, Hoffer C, Risler L, Liu-Chen LY, Shen DD (2006) Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: Role of circulating active metabolites. *Clin Pharmacol Ther* 79:461–479
- Zwisler ST, Enggaard TP, Noehr-Jensen L, Pedersen RS, Mikkelsen S, Nielsen F, Brosen K, Sindrup SH (2009) The hypoalgesic effect of oxycodone in human experimental pain models in relation to the CYP2D6 oxidation polymorphism. *Basic Clin Pharmacol Toxicol* 104:335–334
- Heiskanen T, Olkkola KT, Kalso E (1998) Effects of blocking CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. *Clin Pharmacol Ther* 64:603–611
- Hagelberg NM, Nieminen TH, Saari TI, Neuvonen M, Neuvonen PJ, Laine K, Olkkola KT (2009) Voriconazole drastically increases exposure to oral oxycodone. *Eur J Clin Pharmacol* 65:263–271
- Nieminen T, Hagelberg N, Saari TI, Laine K, Neuvonen PJ, Olkkola KT (2009) Rifampin greatly reduces the plasma concentrations of intravenous and oral oxycodone. *Anesthesiology* 110:1371–1378
- Baran R, Hay RJ, Garduno JI (2008) Review of antifungal therapy and the severity index for assessing onychomycosis: part I. *J Dermatolog Treat* 19:72–81
- Gafter-Gvili A, Vidal L, Goldberg E, Leibovici L, Paul M (2008) Treatment of invasive candidal infections: systematic review and meta-analysis. *Mayo Clin Proc* 83:1011–1021
- Varhe A, Olkkola KT, Neuvonen PJ (1994) Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. *Clinical Pharmacol Ther* 56:601–607
- Olkkola KT, Ahonen J, Neuvonen PJ (1996) The effects of the systemic antimycotics, itraconazole and fluconazole, on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. *Anesth Analg* 82:511–516
- Kaukonen KM, Olkkola KT, Neuvonen PJ (1997) Itraconazole increases plasma concentrations of quinidine. *Clin Pharmacol Ther* 62:510–517

16. Backman JT, Kivistö KT, Olkkola KT, Neuvonen PJ (1998) The area under the plasma concentration-time curve for oral midazolam is 400-fold larger during treatment with itraconazole than with rifampicin. *Eur J Clin Pharmacol* 54:53–58
17. Wang E, Lew K, Casciano CN, Clement RP, Johnson WW (2002) Interaction of common azole antifungals with P-glycoprotein. *Antimicrob Agents Chemother* 46:260–265
18. Pöyhkä R, Olkkola KT, Seppälä T, Kalso E (1991) The pharmacokinetics of oxycodone after intravenous injection in adults. *Br J Clin Pharmacol* 32:516–518
19. Michna E, Ross EL, Hynes WL, Nedeljkovic SS, Soumekh S, Janfaza D, Palombi D, Jamison RN (2008) Predicting aberrant drug behavior in patients treated for chronic pain. *J Pain Symptom Manage* 28:250–258
20. Gubbins PO, Gurley BJ, Bowman J (1998) Rapid and sensitive high performance liquid chromatographic method for the determination of itraconazole and its hydroxy-metabolite in human serum. *J Pharm Biomed Anal* 16:1005–1012
21. Neuvonen M, Neuvonen PJ (2008) Determination of oxycodone, noroxycodone, oxymorphone, and noroxymorphone in human plasma by liquid chromatography-electrospray-tandem mass spectrometry. *Ther Drug Monit* 30:333–340
22. Sistonen J, Fuselli S, Levo A, Sajantila A (2005) CYP2D6 genotyping by a multiplex primer extension reaction. *Clin Chem* 51:1291–1295
23. Bond A, Lader M (1974) The use of analogue scales in rating subjective feelings. *Br J Med Psychol* 47:211–218
24. Hannington-Kiff JG (1970) Measurement of recovery from outpatient general anaesthesia with a simple ocular test. *Br Med J* 3:132–135
25. Stone BM (1984) Pencil and paper tests—sensitivity to psychotropic drugs. *Br J Clin Pharmacol* 18[Suppl 1]:15S–20S
26. Cogan DG (1941) Simplified entopic pupillometer. *Am J Ophthalmol* 24:1431–1433
27. Wolff BB, Kantor TG, Jarvik ME, Laska E (1966) Response of experimental pain to analgesic drugs. 1. Morphine, aspirin, and placebo. *Clin Pharmacol Ther* 7:224–238
28. Jalava KM, Partanen J, Neuvonen PJ (1997) Itraconazole decreases renal clearance of digoxin. *Ther Drug Monit* 19:609–611
29. Boström E, Simonsson USH, Hammarlund-Udenaes M (2005) Oxycodone pharmacokinetics and pharmacodynamics in the rat in the presence of the P-glycoprotein inhibitor PSC833. *J Pharm Sci* 94:1060–1066
30. Hassan HE, Myers AL, Lee IJ, Coop A, Eddington ND (2007) Oxycodone induces overexpression of P-glycoprotein (ABCB1) and affects paclitaxel's tissue distribution in Sprague Dawley rats. *J Pharm Sci* 96:2494–2506
31. Koltzenburg M, Pokorny R, Gasser UE, Richarz U (2006) Differential sensitivity of three experimental pain models in detecting the analgesic effects of transdermal fentanyl and buprenorphine. *Pain* 126:165–174
32. Sarton E, Olofsen E, Romberg R et al (2000) Sex differences in morphine analgesia: An experimental study in healthy volunteers. *Anesthesiology* 93:1245–1254
33. Varhe A, Olkkola KT, Neuvonen PJ (1996) Effect of fluconazole dose on the extent of fluconazole-triazolam interaction. *Br J Clin Pharmacol* 42:465–470
34. Jalava KM, Olkkola KT, Neuvonen PJ (1997) Itraconazole greatly increases plasma concentrations and effects of felodipine. *Clin Pharmacol Ther* 61:410–415
35. Jalava M, Olkkola KT, Neuvonen PJ (1998) Fluconazole, but not itraconazole decreases the metabolism of losartan to E-3174. *Eur J Clin Pharmacol* 53:445–449
36. Tallgren M, Olkkola KT, Seppälä T, Höckerstedt K, Lindgren L (1997) Pharmacokinetics and ventilatory effects of oxycodone before and after liver transplantation. *Clin Pharmacol Ther* 61:655–661
37. Liukas A, Kuusniemi K, Aantaa R, Virolainen P, Neuvonen M, Neuvonen PJ, Olkkola KT (2008) Plasma concentrations of oral oxycodone are greatly increased in the elderly. *Clin Pharmacol Ther* 84:462–467