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Nora M. Hagelberg, Tuija H. Nieminen, Teijo I. Saari, Mikko Neuvonen, Pertti J. Neuvonen, et al.. Voriconazole drastically increases exposure to oral oxycodone. *European Journal of Clinical Pharmacology*, 2008, 65 (3), pp.263-271. 10.1007/s00228-008-0568-5 . hal-00477928

HAL Id: hal-00477928

<https://hal.science/hal-00477928>

Submitted on 30 Apr 2010

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Voriconazole drastically increases exposure to oral oxycodone

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Received: 27 June 2008 / Accepted: 8 September 2008 / Published online: 3 October 2008
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Abstract

Objective We investigated the effect of voriconazole on the pharmacokinetics and pharmacodynamics of oxycodone.

Methods Twelve healthy subjects ingested either voriconazole or placebo for 4 days in a randomized, cross-over study. On day 3, they ingested 10 mg oxycodone. Timed plasma samples were collected for the measurement of oxycodone, noroxycodone, oxymorphone, noroxymorphone and voriconazole up to 48 h, and pharmacodynamic effects were recorded.

Results When voriconazole was taken at the same time as oxycodone, the mean area under the plasma concentration-time curve ($AUC_{0-\infty}$) of oxycodone increased 3.6-fold (range 2.7- to 5.6-fold), peak plasma concentration 1.7-fold and elimination half-life 2.0-fold ($p < 0.001$) when compared to placebo. The $AUC_{0-\infty}$ ratio of noroxycodone to oxycodone was decreased by 92% ($p < 0.001$), and that of oxymorphone increased by 108% ($p < 0.01$). Pharmacodynamic effects of oxycodone were modestly increased by voriconazole.

Conclusions Voriconazole inhibits the CYP3A-mediated N-demethylation of oxycodone, drastically increasing exposure to oral oxycodone. Clinically, lower doses of oxycodone may be needed during voriconazole treatment to avoid opioid-related adverse effects especially after repeated dosing.

Keywords Oxycodone · Voriconazole · Cytochrome P450 · CYP2D6 · CYP3A · Pharmacokinetics

Introduction

Oxycodone is a semi-synthetic μ -opioid receptor agonist widely used in the treatment of acute and chronic pain. The bioavailability of oxycodone is over 60% [1]. Oxycodone undergoes oxidative metabolism mainly in the liver by cytochrome P450 (CYP) 3A and 2D6 enzymes [2]. About 10% of the parent compound is excreted unchanged or as direct conjugates in urine. The majority of oxycodone is N-demethylated to noroxycodone predominantly via CYP3A, and less than 10% is O-demethylated to oxymorphone via CYP2D6. These metabolites undergo further oxidation through CYP3A to form noroxymorphone [2, 3].

Voriconazole is an antifungal agent clinically used in the treatment of disseminated fungal infections. The bioavailability of oral voriconazole is over 90% and its pharmacokinetics is nonlinear [4]. Voriconazole undergoes extensive hepatic oxidative metabolism via CYP2C19 and CYP3A, and possibly CYP2C9 [5, 6]. Less than 2% of voriconazole dose is excreted unchanged in urine. Voriconazole inhibits the enzyme activities of CYP3A, CYP2C19 and CYP2C9 but not CYP2D6 [7, 8].

Previous studies indicate that changes in CYP3A and CYP2D6 enzyme activities may impair the metabolism of oxycodone. Inhibition of CYP2D6 activity with quinidine

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increases noroxycodone concentration and blocks the formation of oxymorphone, but does not influence oxycodone concentration [9]. Competition of CYP2D6 and CYP3A enzyme activities with a single dose of tramadol has no effect on the clearance of oxycodone whereas indirect evidence suggests that ketoconazole influences the pharmacokinetics of oxycodone [10, 11]. Considering that the major metabolic pathway occurs via CYP3A enzymes, changes in CYP3A activity may be more relevant in terms of the clinical effects of oxycodone. A clinical case report suggests that the analgesic effect of oxycodone is diminished by concomitant treatment with rifampicin [12]. The aim of the present study was to investigate the effects of the CYP3A, CYP2C9 and CYP2C19 enzyme inhibitor voriconazole on the pharmacokinetics and pharmacodynamics of oxycodone in healthy subjects.

Materials and methods

Subjects

Twelve healthy non-smoking subjects, including six women and six men (age range 19–25 years and weight range 50–95 kg), participated in the study after giving written informed consent. The general health of the subjects was good as assessed by their medical history, clinical examination, routine laboratory tests and an ECG. The risk for participants of developing aberrant opioid-related behaviour was estimated low as evaluated by the Finnish translation of the Abuse Questions [13]. Urine toxicology screens were negative. The subjects consented to abstain from any medication for 2 weeks and any products with known effects on CYP enzyme activity for 4 weeks prior to the study. Female subjects used safe non-hormonal contraception during the study, as hormonal contraceptives were not allowed. The Ethics Committee of the Hospital District of Southwest Finland, Finland, and the National Agency of Medicines, Finland, approved the study protocol. The study was conducted according to the revised Declaration of Helsinki.

Study outline

The study was conducted in a placebo-controlled, randomized, cross-over design with two phases. The wash-out interval was 4 weeks. The subjects took either voriconazole (voriconazole phase) or placebo (control phase) in a randomized order for 4 days. On day 3, the subjects received a single dose of oxycodone. Blood samples were collected immediately before, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24 and 48 h after oxycodone administration. 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.

Study drug administration

Dosing of voriconazole (Vfend 200 mg tablet; Pfizer, Sandwich, UK) was as follows: 400 mg at 7 P.M. on day 1, 400 mg at 7 A.M. and 200 mg at 7 P.M. on day 2, and 200 mg at 7 A.M. and 7 P.M. on days 3 and 4. Voriconazole and placebo were self-administered by the subjects except for day 3 when they were administered by the investigators. Adherence with the dosing schedule was assessed using mobile phone text messages. The subjects sent a mobile phone text message to one of the investigators after taking each dose. If no text message was received within 15–20 min after scheduled dosing time, the investigator contacted the subject by phone and reminded him/her to take the dose. On day 3, 1 h after voriconazole or placebo dosing, an oral dose of oxycodone hydrochloride 10 mg (Oxynorm; Mundipharma, Bard Pharmaceuticals, Cambridge, UK) was administered in the study facility with 150 ml of water. During both phases, the subject fasted overnight before the administration of oxycodone and continued fasting until a standardized lunch was served 4 h after oxycodone dosing.

Blood sampling and drug analysis

In the study facility, a forearm vein was cannulated for collecting timed blood samples (10 ml) into ethylenediaminetetraacetic acid containing tubes. Plasma was separated within 30 min of sampling and stored at -70°C until analysis.

Plasma concentration of voriconazole was determined by high-performance liquid chromatography [14, 15]. The lower limit of quantification (LLQ) was 20 ng/ml. The interday coefficients of variation (CV) were 9.7 and 1.6% at 1,031 and 9,654 ng/ml respectively ($n=6$).

Plasma concentrations of oxycodone, noroxycodone, oxymorphone and noroxymorphone were analysed with the liquid chromatography tandem mass spectrometric method as previously described [16]. 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, 4.9 and 99 ng/ml was 7.0, 1.8 and 2.0% ($n=6$) respectively for oxycodone, and less than 15% for the rest of the analytes at relevant plasma concentrations.

Genotyping for *CYP2D6* was performed using a two-step multiplex primer extension method [17]. The method allows the detection of 11 of the most relevant polymorphic positions, the assessment of whole-gene deletion and duplication and the allele composition of gene duplication.

Pharmacokinetic measurements

Pharmacokinetic variables of oxycodone, noroxycodone, oxymorphone and noroxymorphone were determined using the WinNonlin pharmacokinetic program (version 4.1; Pharsight, Mountain View, California). The peak plasma concentration (C_{max}) and time to maximum concentration (t_{max}) were observed directly from the data. The area under the plasma concentration-time curve with extrapolation to infinity ($AUC_{0-\infty}$) was calculated by the trapezoidal rule. The linear trapezoidal rule was used for successive increasing concentration values, and the logarithmic trapezoidal rule for decreasing concentration values. Individual terminal log-linear phases of plasma concentration-time curves were identified visually, and the elimination rate constant (K_e) was determined by regression analysis. The elimination half-life ($t_{1/2}$) was calculated using the following equation: $t_{1/2} = \ln 2 / K_e$. The apparent clearance (CL/F) and apparent volume of distribution during elimination (V_z/F) were calculated. Metabolite-to-parent drug AUC ratios (AUC_m/AUC_p) were calculated to compare the relative abundance of each metabolite.

Pharmacodynamic measurements

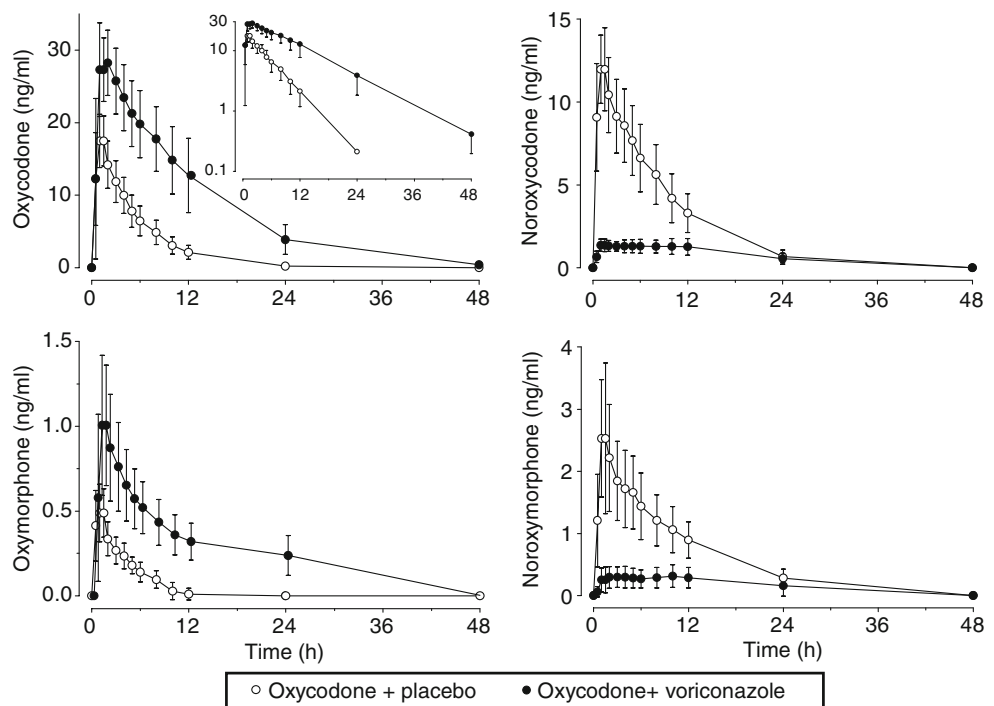
Behavioural effects Behavioural effects of oxycodone were assessed with 100-mm visual analogue scales for the

following items: alert/drowsy, good performance/poor performance, no drug effect/strong drug effect, unpleasant feeling/pleasant feeling, no nausea/extreme nausea or vomiting [18]. Central co-ordination of extraocular muscles was evaluated using Maddox wing test, which measures horizontal heterophoria in diopters [19]. Central processing of sensory information was assessed with the digit symbol substitution test (DSST) [20]. The pupil size was measured with Cogan’s pupillometry [21]. In addition, any adverse events spontaneously reported by the subjects were recorded.

Analgesic effects 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. Heat-pain threshold was defined as the mean of the three temperature measurements.

Cold pressor test [22] was used to assess cold-pain sensitivity. The subject immersed his or her left hand into ice water of 0.5–2°C up to the wrist for 1 min. The latency in seconds from the immersion to the first sensation of pain

Fig. 1 Mean plasma concentrations (± SD) of oxycodone, noroxycodone, oxymorphone and noroxymorphone after an oral dose of 10 mg of oxycodone hydrochloride during the placebo phase (open circles, control) or voriconazole phase (closed circles) in 12 healthy subjects. The inset depicts the same data on a semilogarithmic scale. The dose of voriconazole was 400 mg twice daily on the first day followed by five further doses of 200 mg of voriconazole at 12-h intervals



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 or unpleasantness, 100=maximum

pain or unpleasantness). 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).

Table 1 Pharmacokinetic parameters of oxycodone and its primary and secondary oxidative metabolites after oral administration of 10 mg of oxycodone hydrochloride following pre-treatment with placebo (control) and oral voriconazole in 12 healthy volunteers. The dose of voriconazole

was 400 mg twice daily on the first day followed by five further doses of 200 mg of voriconazole at 12-h intervals. Values are mean \pm standard deviation. Percent of control was calculated individually for each subject, and the mean and range of these individual values are reported

Parameter	Control phase	Voriconazole phase	95% CI of difference between the phases
Oxycodone			
C_{max} (ng/ml)	18.1 \pm 4.0	30.5 \pm 5.1***	10.3 to 14.5
% of control (range)	100	172 (140–224)	
t_{max} (h)	1.0 (0.5–1.5)	1.5 (1.0–4.0)*	
$AUC_{0-\infty}$ (μ g min/ml)	6.1 \pm 1.6	21.8 \pm 6.2***	12.4 to 19.1
% of control (range)	100	361 (268–563)	
CL/F (l/min)	1.58 \pm 0.51	0.46 \pm 0.20***	–1.34 to –0.91
% of control (range)	100	29 (18–37)	
V_z/F (l)	474 \pm 139	266 \pm 62***	–265 to –152
% of control (range)	100	57 (44–78)	
$t_{1/2}$ (h)	3.5 \pm 0.6	7.1 \pm 1.0***	3.1 to 4.1
% of control (range)	100	203 (144–246)	
Noroxycodone			
C_{max} (ng/ml)	12.6 \pm 2.3	1.6 \pm 0.5***	–12.3 to –9.7
% of control (range)	100	13 (9–21)	
t_{max} (h)	1.0 (0.5–1.5)	1.8 (1.0–12.0)*	
$AUC_{0-\infty}$ (μ g min/ml)	6.5 \pm 1.9	2.1 \pm 0.9***	–5.5 to –3.3
% of control (range)	100	33 (19–63)	
AUC_m/AUC_p	1.07 \pm 0.19	0.09 \pm 0.02***	–1.09 to –0.87
% of control (range)	100	8 (7–12)	
$t_{1/2}$ (h)	5.3 \pm 1.0	10.9 \pm 2.7***	4.1 to 7.2
% of control (range)	100	208 (141–304)	
Oxymorphone			
C_{max} (ng/ml)	0.52 \pm 0.18	1.06 \pm 0.41***	0.32 to 0.75
% of control (range)	100	208 (133–332)	
t_{max} (h)	1.0 (0.5–1.5)	1.0 (0.5–1.5)	
$AUC_{0-\infty}$ (μ g min/ml)	0.150 \pm 0.046	1.046 \pm 0.523***	0.575 to 1.217
% of control (range)	100	727 (352–1,722)	
AUC_m/AUC_p	0.026 \pm 0.009	0.052 \pm 0.031**	0.010 to 0.042
% of control (range)	100	208 (90–480)	
$t_{1/2}$ (h)	3.6 \pm 0.5	23.1 \pm 11.9 ($n=9$)**	10.4 to 28.4 ($n=9$)
% of control (range)	100	627 (210–1,159)	
Noroxymorphone			
C_{max} (ng/ml)	2.8 \pm 1.2	0.34 \pm 0.23***	–3.1 to –1.8
% of control (range)	100	11 (0–18)	
t_{max} (h)	1.5 (1.0–3.0)	5.0 (1.0–10.0)	
$AUC_{0-\infty}$ (μ g min/ml)	1.70 \pm 0.47	0.86 \pm 0.76***	–1.22 to –0.46
% of control (range)	100	47 (0–112)	
AUC_m/AUC_p	0.299 \pm 0.121	0.040 \pm 0.030***	–0.32 to –0.20
% of control (range)	100	12 (0–28)	
$t_{1/2}$ (h)	8.9 \pm 2.4	28.3 \pm 15.2 ($n=9$)**	8.3 to 32.3
% of control (range)	100	368 (149–790)	

CI Confidence interval, C_{max} maximum concentration, t_{max} time to maximum concentration, $AUC_{0-\infty}$ area under plasma concentration-time curve extrapolated to infinity, CL/F apparent clearance, V_z/F apparent volume of distribution, $t_{1/2}$ terminal elimination half-life, AUC_m/AUC_p metabolite-to-parent drug area under plasma concentration-time curve ratio

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

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 voriconazole and placebo phases were analysed using Student's *t*-test except for t_{max} , which was analysed with Wilcoxon signed-ranks test. The contributions of oxycodone and voriconazole 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 $AUC_{0-\infty}$ of oxycodone during voriconazole phase to $AUC_{0-\infty}$ of oxycodone during the control phase and the AUC_{0-48} of voriconazole. All data were analysed using the statistical program SYSTAT for Windows (version 10.2; SystatSoftware, Richmond, CA). The results are expressed as mean \pm SD or median (range) whenever appropriate. *P* values <0.05 were considered as statistically significant.

Results

Pharmacokinetics

Oxycodone Voriconazole greatly increased plasma concentrations of the parent oxycodone. During the voriconazole phase, the mean $AUC_{0-\infty}$ of oxycodone increased 3.6-fold (range 2.7- to 5.6-fold; $p<0.001$), the mean C_{max} of oxycodone 1.7-fold (range 1.4- to 2.2-fold; $p<0.001$) and the mean $t_{1/2}$ 2.0-fold (range 1.4–2.5-fold; $p<0.001$) compared to the placebo phase. The mean plasma concentration of oxycodone at 24 h in the voriconazole phase was approximately at the same level as at 8–10 h after placebo. Voriconazole decreased CL/F of oxycodone by 71% and V_z/F by 43% (Fig. 1, Table 1).

Noroxycodone Voriconazole decreased the mean C_{max} of noroxycodone by 87% ($p<0.001$) and its $AUC_{0-\infty}$ by 67% ($p<0.001$; Fig. 1, Table 1). The AUC_m/AUC_p ratio was decreased by 92% ($p<0.001$; Fig. 2, Table 1). The mean $t_{1/2}$ of noroxycodone was prolonged by 2.1-fold, to 10.9 from 5.3 h ($p<0.001$).

Oxymorphone Voriconazole increased the C_{max} of oxymorphone by 108% ($p<0.001$) and $AUC_{0-\infty}$ by 7.3-fold ($p<0.001$), on the average (Fig. 1, Table 1). The $AUC_m/$

AUC_p ratio was increased by 108% (Fig. 2, Table 1) and the mean $t_{1/2}$ prolonged 6.6-fold, by 19.5 h.

Noroxymorphone Voriconazole decreased the C_{max} of noroxymorphone by 89% and the $AUC_{0-\infty}$ by 53% (Fig. 1, Table 1). The AUC_m/AUC_p ratio was decreased

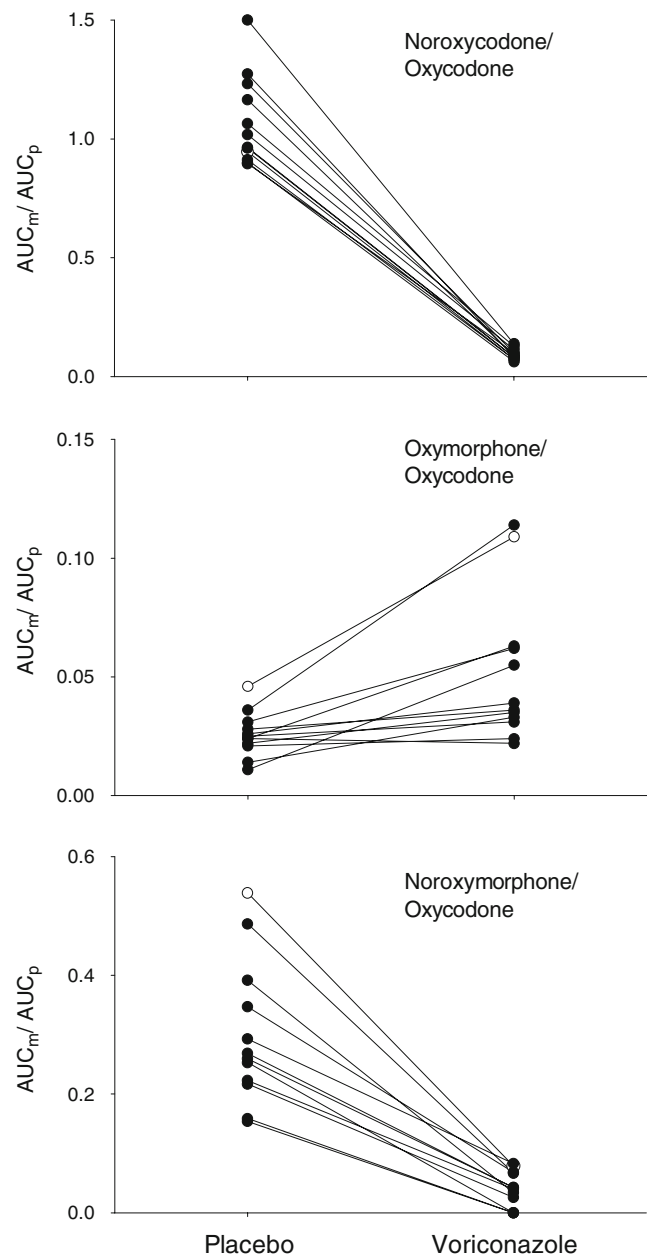


Fig. 2 Individual metabolite-to-parent drug AUC ratios (AUC_m/AUC_p) after an oral dose of 10 mg of oxycodone hydrochloride reflecting the relative abundance of each metabolite during the control and voriconazole phases. Each circle represents one subject. The subject with ultrarapid metabolism via CYP2D6 is depicted with an open circle. The dose of voriconazole was 400 mg twice daily on the first day followed by five further doses of 200 mg of voriconazole at 12-h intervals

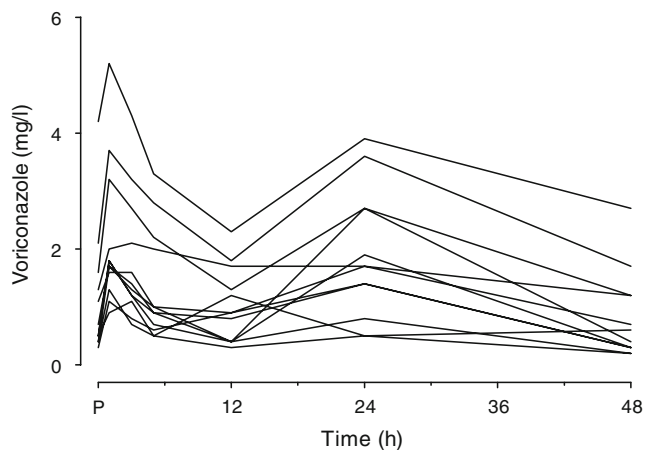


Fig. 3 Individual plasma concentrations of voriconazole in 12 healthy subjects. The dose of voriconazole was 400 mg twice daily on the first day followed by five further doses of 200 mg of voriconazole at 12-h intervals. *P* refers to the time point of the last dose of voriconazole before the administration of oxycodone

by 88% (Fig. 2). The $t_{1/2}$ of noroxymorphone was prolonged by 19.4 h.

Plasma voriconazole There was about a 5- to 10-fold interindividual variation in the AUC_{0-48} of voriconazole (Fig. 3). However, there was no significant linear correlation between the plasma concentration of voriconazole and any of the voriconazole-induced changes observed in the pharmacokinetic or pharmacodynamic parameters.

***CYP2D6* genotyping** Eleven subjects were classified as extensive metabolizers (EM). Five of them were homozygous for *CYP2D6*1* allele, four had the genotype *CYP2D6*1/*4*, one had genotype *CYP2D6*1/*3* and one had *CYP2D6*1/*6*. One subject was classified as an ultrarapid metabolizer (UM) having a *CYP2D6*1/*1×2* genotype. The subject with UM *CYP2D6* genotype had approximately 50% lower values for oxycodone C_{max} and $AUC_{0-\infty}$ than the rest of the volunteers. This subject differed distinctly from the others also in regard to the plasma concentrations of oxymorphone and noroxymorphone (Fig. 2).

Pharmacodynamics

Behavioural effects Voriconazole increased oxycodone-induced AUC_{0-12} for heterophoria ($p < 0.05$) and miosis ($p < 0.001$) when compared to placebo. Voriconazole also appeared to increase the perceived subjective drug effect, but the difference was not statistically significant ($p = 0.076$). No other behavioural differences were observed (Fig. 4). There was a statistically significant linear correlation between the behavioural effects and plasma oxycodone concentration (for heterophoria $p < 0.05$ and for all other variables $p < 0.001$).

Analgesic effects Oxycodone increased the heat-pain threshold ($p < 0.05$) and cold-pain threshold ($p < 0.05$), and

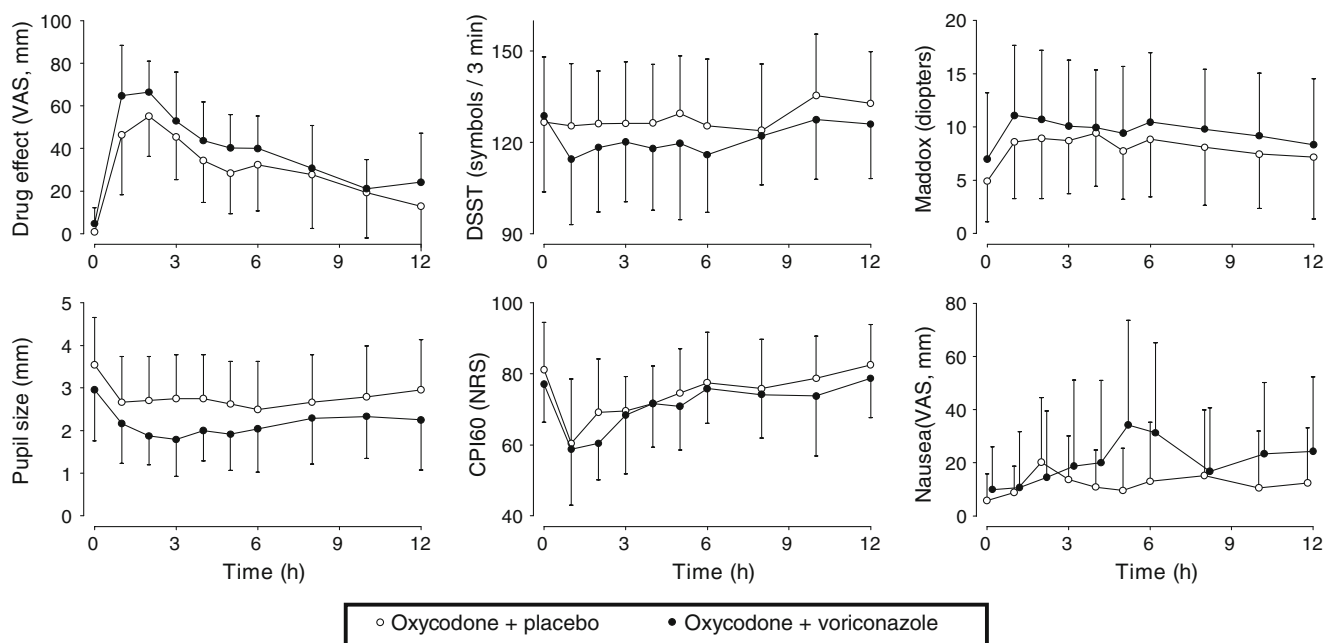


Fig. 4 Mean (\pm SD) self-reported drug effect, number of digits substituted in 3 min (*DSST*), heterophoria (*Maddox*), pupil size, cold-pain intensity at 60 s (*CPI60*), and nausea after an oral dose of 10 mg of oxycodone hydrochloride during the placebo phase (*open circles*,

control) or voriconazole phase (*closed circles*) in 12 healthy subjects. The dose of voriconazole was 400 mg twice daily on the first day followed by five further doses of 200 mg of voriconazole at 12-h intervals

decreased the mean AUC_{0-12} for cold-pain intensity at 60 s ($p < 0.001$). However, voriconazole did not alter the effect of oxycodone on any of these pharmacodynamic variables (Fig. 4). Except for heat-pain threshold, there was a statistically significant linear correlation between the analgesic effect and plasma oxycodone concentration ($p < 0.001$).

Adverse events All subjects completed the study. Eight of the 12 subjects experienced adverse events on day 3. Adverse events were headache ($n=5$), nausea ($n=3$), vomiting ($n=1$), dizziness ($n=2$), extreme fatigue ($n=1$) and itch ($n=1$). Three subjects received paracetamol (1,000 mg) for headache 12 h after oxycodone dosing, and one received tropisetron 2 mg iv for nausea 5 h after dosing. All cases of nausea or vomiting were reported during the voriconazole phase. Number of reports of headache did not differ between voriconazole and control phases.

Discussion

This study indicates that voriconazole profoundly inhibited the CYP3A-catalyzed N-demethylation of oxycodone in all subjects, detected as an average 3.6-fold increase in oxycodone $AUC_{0-\infty}$ and 92% decrease in the AUC_m/AUC_p ratio of noroxycodone. Although voriconazole enhanced some of the behavioural effects of a single oral dose of oxycodone, the analgesic effects of oxycodone were not significantly affected by voriconazole. It is plausible to assume that the observed pharmacokinetic changes are due to a marked decrease in the first-pass metabolism and plasma clearance of oxycodone because both the C_{max} , $AUC_{0-\infty}$ and $t_{1/2}$ of oxycodone were greatly increased by voriconazole, and these changes were accompanied by drastic changes in the metabolite-to-oxycodone ratios.

Previous human studies have shown that voriconazole alters the pharmacokinetics of several drugs metabolized by CYP3A, including oral hypnotics [23–25] and opioids [26–28]. Voriconazole decreases the clearance of alfentanil by 83% [26] and that of fentanyl by 23% [27], and increases the AUC_{0-24} of R-methadone by 47% [28]. In the present study, following oral administration of oxycodone the plasma clearance could not be calculated, but voriconazole increased the exposure to oxycodone by 3.6-fold as judged by the mean value for oxycodone $AUC_{0-\infty}$. While voriconazole strongly decreased the plasma concentration of noroxycodone, the concentration of oxymorphone was substantially (on average 7.3-fold) increased. As studies in human liver microsomes suggest that voriconazole does not affect CYP2D6 activity [6, 7], the increase in plasma

concentration of oxymorphone probably reflects a compensatory reaction to the inhibition of CYP3A. The compensatory increase in the CYP2D6-mediated route of metabolism (O-demethylation) could not replace the CYP3A-mediated N-demethylation of oxycodone, which resulted in a markedly delayed elimination of oxycodone. Interestingly, voriconazole did not increase oxycodone concentrations to the same extent as those of midazolam. This is most likely due to the differences in the bioavailability of oxycodone and midazolam. Because oxycodone has a higher bioavailability than midazolam, it is somewhat less prone to the effects of other drugs affecting CYP enzymes during absorption and during first-pass metabolism [29, 30].

In the present study both voriconazole and oxycodone were administered orally. The extent of interaction might have been of different magnitude had either of these drugs been given parenterally. For example, the pharmacokinetic interactions between fluconazole and oral midazolam [31], and fluconazole and oral cyclosporine A or tacrolimus [32], were stronger when both the CYP inhibitor and the substrate (victim) drug were taken orally as compared with the intravenous route of inhibitor administration. Similarly, if the substrate drug (e.g. midazolam) has a significant first-pass metabolism, its intravenous administration can reduce the extent of interaction with orally administered CYP inhibitors (e.g. erythromycin) [29]. However, further studies are needed on the significance of the route of administration for the metabolic interactions of oxycodone.

The interindividual variation in the extent of voriconazole-oxycodone interaction was considerable. In one of our study subjects the AUC of oxycodone was increased more than six-fold. Considering the relatively narrow therapeutic range of oxycodone, a six-fold increase in plasma oxycodone concentration may cause serious adverse effects when increased plasma concentrations occur unexpectedly. In the present study, all cases of nausea or vomiting after oxycodone dosing occurred during the voriconazole phase. It is reasonable to assume that in a patient population using oxycodone, the interindividual variations in the pharmacokinetics and extent of interaction would be even greater than those observed in our study in young, healthy subjects.

Polymorphism of CYP2D6 has been shown to influence the metabolism of several opioid substrates of CYP2D6 such as codeine [33], tramadol [34] and methadone [35]. Genetic alterations in CYP2D6 enzyme activity have also been suggested to influence the pharmacokinetic profile [36] and clinical effects [37–39] of oxycodone. In the present study, one of the subjects was an ultrarapid metabolizer via CYP2D6. Although it is impossible to make conclusions based on one subject, he had distinctly lower oxycodone concentrations than the rest of the group. Consistent with the UM phenotype, his oxycodone metab-

olism produced much more oxycodone and noroxycodone than the others. However, as evidenced by the parallel course of the lines connecting the values for AUC_m/AUC_p ratios during the placebo and voriconazole phases in Fig. 2, the magnitude of the voriconazole-oxycodone interaction was similar in the subject with UM phenotype and the others.

Previous studies have indicated that oxycodone metabolites do not significantly contribute to the behavioural effects of oxycodone [3, 9]. In the present study, there was a linear correlation between the oxycodone plasma concentration and pharmacological response, except for analgesia in the heat-pain test. The analgesic effect of oxycodone was not influenced by voriconazole. This probably reflects the high interindividual variability in opioid sensitivity [40], gender differences in opioid responses [41] or the relatively small dose of oxycodone used in the study. Small differences in drug concentrations do not necessarily affect drug responses because of the log-linear relationship between the drug concentration and effect.

Several opioids such as morphine and methadone are substrates for the efflux transporter P-glycoprotein [42, 43]. Theoretically, voriconazole could inhibit the P-glycoprotein function in the intestinal wall, increasing the oral bioavailability of oxycodone. Similarly, an inhibition of P-glycoprotein at the blood-brain barrier could increase the penetration of oxycodone into the brain. However, the present pharmacodynamic results do not support this possibility, and are in agreement with the results of an animal study, in which the potent P-glycoprotein inhibitor PSC833 did not increase the brain concentrations of oxycodone [44].

In conclusion, voriconazole strongly inhibits the CYP3A-mediated N-demethylation of oxycodone, producing a profound increase in exposure to oral oxycodone. This increase is reflected as a modest change in the behavioural effects of oxycodone. Clinically, lower doses of oxycodone may be needed during voriconazole treatment to avoid opioid-related adverse effects especially after repeated dosing.

Acknowledgements We thank Mrs. Elina Kahra for technical assistance and Professor Antti Pertovaara for the use of the TSA-2. The study was supported by the EVO grant 13821 of the Hospital District of Southwest Finland. All experiments comply with the current laws in Finland, where the research was performed. There are no conflicts of interest.

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