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Oxycodone concentrations are greatly increased by the concomitant use of ritonavir or lopinavir/ritonavir

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ABSTRACT

Purpose: This study was aimed to investigate the effect of antivirals ritonavir and lopinavir/ritonavir on the pharmacokinetics and pharmacodynamics of oral oxycodone, a widely used opioid receptor agonist used in the treatment of moderate to severe pain.

Methods: A randomized crossover study design with 3 phases at intervals of 4 weeks was conducted in 12 healthy volunteers. Ritonavir 300 mg, lopinavir/ritonavir 400/100 mg or placebo b.i.d. for 4 days was given to the subjects. On day 3, 10 mg oxycodone hydrochloride was administered orally. Plasma concentrations of oxycodone, noroxycodone, oxymorphone and noroxymorphone were determined for 48 h. Pharmacokinetic parameters were calculated with standard noncompartmental methods. Behavioural effects and experimental cold pain analgesia were assessed for 12 h. ANOVA for repeated measures was used for statistical analysis.

Results: Ritonavir and lopinavir/ritonavir increased the area under the plasma concentration–time curve of oral oxycodone by 3.0- (range 1.9- to 4.3-fold; $P<0.001$) and 2.6-fold (range 1.9- to 3.3-fold; $P<0.001$). The mean (\pm SD) elimination half-life prolonged after ritonavir and lopinavir/ritonavir from 3.6 ± 0.6 to 5.6 ± 0.9 h ($P<0.001$) and 5.7 ± 0.9 h ($P<0.001$), respectively. Both ritonavir ($P<0.001$) and lopinavir/ritonavir ($P<0.05$) increased the self-reported drug effect of oxycodone.

Conclusions: Ritonavir and lopinavir/ritonavir greatly increase the plasma concentrations of oral oxycodone in healthy volunteers and enhance its effect. When oxycodone is used clinically in patients during ritonavir and lopinavir/ritonavir treatment, reductions in oxycodone dose may be needed to avoid opioid-related adverse-effects.

Keywords: Oxycodone, Ritonavir, Lopinavir/ritonavir, Interaction, Pharmacokinetics, Pharmacodynamics

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INTRODUCTION

Pain is one of the most frequently reported symptoms associated with human immunodeficiency virus (HIV) infection. It has been estimated that in the developed world, depending on the stage of disease and study settings, 30–80% of people living with HIV/AIDS are affected with pain [1, 2]. Pain experienced by HIV patients can be acute or chronic, and it is usually multifactorial in origin. HIV-associated pain can be due to e.g. HIV itself, antiretroviral treatment, opportunistic infections, HIV-associated cancers, rheumatic conditions or peripheral polyneuropathy [3-5]. Unfortunately, these painful conditions are often under-recognised and -treated.

Oxycodone is a semi-synthetic opioid agonist, which is effective in treating acute, cancer-related and chronic pain [6, 7]. It is metabolized mainly via oxidative, but also via reductive pathways with only 10–14% being excreted in unchanged or conjugated forms in urine [8]. Oxycodone is principally a cytochrome P450 3A4/5 substrate, which makes it prone to the interactions with CYP3A inducers and inhibitors [9]. The main oxidative pathway includes N-demethylation to noroxycodone by CYP3A4/5 and further to noroxymorphone by CYP2D6 [9]. Approximately 11% of oxycodone is O-demethylated to oxymorphone by CYP2D6, which is further transformed to noroxymorphone by CYP3A4/5 and CYP2D6 [9]. Animal studies have given controversial results about the role of P-glycoprotein in the transport of oxycodone via blood-brain barrier (BBB) [10, 11]. However, the higher concentrations of oxycodone in rat and sheep brain tissue compared to plasma concentrations suggest that the influx protein is much more active than P-glycoprotein, which acts as an efflux protein limiting the concentrations of oxycodone in brain [12-14].

HIV protease inhibitors, such as ritonavir and lopinavir inflict the HIV-specific aspartic protease enzyme on processing the *gag* and *gag-pol* polyprotein precursor, which leads to the production of immature, non-infectious viral particles [15]. Ritonavir is a potent CYP3A, CYP2D6 and P-glycoprotein inhibitor [16-18]. It has been described to induce CYP1A2, CYP2B6, CYP2C9 and CYP2C19 [19, 20]. Difficult dosing regimens, the development of resistance and adverse effects have restricted the use of ritonavir as an independent part of HIV treatment [21]. Lopinavir/ritonavir is a combination preparation, where lopinavir is

combined with low-dose ritonavir to enhance its low bioavailability by favourable CYP3A inhibition [22].

Lopinavir/ritonavir has become a well-tolerated, effective and preferred protease inhibitor in the treatment of HIV. It is a substrate and inhibitor of CYP3A4 and to a lesser extent CYP2D6, and an inducer of CYP1A2, 2B6, 2C9 and 2C19 [23, 24] which makes it prone to cytochrome P450-mediated interactions.

In previous studies it has been shown, that CYP3A inhibitors voriconazole [25], itraconazole [26] and telithromycin [27] increased the concentrations of oxycodone and oxymorphone, but only minor changes have been observed in the pharmacological action of oxycodone following single doses in healthy volunteers. As HIV patients are often affected with moderate to severe pain, there is an obvious need for the concomitant use of antivirals and strong opioids, such as oxycodone. The aim of this study was to investigate the effects of ritonavir and lopinavir/ritonavir on the pharmacokinetics and effects of oxycodone in healthy volunteers.

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METHODS

Participants

The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland and by the Finnish National Agency for Medicines and was and was thereby reported to the EudraCT clinical trial register. In view of our previous studies, it was calculated, that 10 subjects would be required to detect a 30% difference in the area under the oxycodone concentration–time curves ($AUC_{0-\infty}$) at a level of significance $P = 0.05$ and power of 80% [25-27]. To allow a drop-out rate of 20%, we decided to recruit 12 subjects. Twelve healthy volunteers, four women and eight men (age 18–26 years; weight 52–84 kg) were studied according to the revised Declaration of Helsinki. Informed consent was obtained from all subjects before study screening. All participants were ascertained to be healthy by means of medical history and clinical examination, and they were tested for routine laboratory tests. Urine screens for drugs with abuse risk were negative and a 12-lead electrocardiogram (ECG) within normal limits. Pregnancy tests for women were negative. None of the participants were receiving any continuous medication including hormonal contraception and all were non-smokers. Women in need of contraception were instructed to use non-hormonal methods during the study.

Finnish translation of Abuse Questions [28] was used to assess risk for drug abuse. The consumption of any product with potential CYP3A effect such as herbal remedies or grapefruit juice was forbidden for 4 weeks and all other drugs for 2 weeks before and during the study. Consumption of coffee, tee, alcohol and cola drinks were not allowed in the study facility during the study days. Genotyping for CYP2D6 was conducted by a two-step multiplex primer extension method [29]. This method enables the detection of 11 most relevant polymorphic positions, the definition of whole-gene deletion, duplication and the allele combination in case of gene duplication.

Study design and drug dosing

We used a randomized, crossover study design with three phases at intervals of four weeks. During each phase, the volunteers were given 4 capsules or tablets b.i.d. at 7 a.m. and 7 p.m. for 4 days. The capsules and tablets were packed into sealed coded envelopes which contained either:

1. Two lopinavir/ritonavir 200 mg/50 mg tablets (Kaletra[®], Abbott Laboratories Ltd, Queenborough, UK) and two placebo capsules
2. Three ritonavir 100 mg capsules (Norvir[®], Abbott Laboratories Ltd, Queenborough, UK) and one placebo capsule
3. Four placebo capsules.

An oral dose of 10 mg oxycodone hydrochloride (Oxynorm[®] 10 mg capsule, Mundipharma, Bard Pharmaceuticals Ltd, Cambridge, UK) was administered on day 3 at 8 a.m. with 150 ml warm water. The participants arrived at the study facility one hour before oxycodone administration and were under supervision 12 hours after the dosing.

The volunteers fasted for 8 h before oxycodone hydrochloride administration and received a standard meal 4 and 8 h after dosing. Drinking was allowed only during the meals. Adherence to the pre-treatment medication schedule was ensured with mobile phone text messages, which the volunteers sent to the investigator after taking each dose of pre-treatment taken outside the study facility.

Sampling and determination of drug concentrations

In the study facility, a cubital vein was cannulated for blood sampling. The samples (10 ml each) were collected into EDTA containing tubes before and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 h after the oxycodone hydrochloride dose. Plasma was separated within 30 min and stored at -70°C until analysis.

Plasma concentrations of oxycodone, noroxycodone, oxymorphone and noroxymorphone were analyzed with the liquid chromatography–tandem mass spectrometric (LC–MS/MS) method as described earlier [30]. The lower limits of quantification (LLQ) were 0.1 ng/mL for oxycodone and oxymorphone, and 0.25 ng/mL for noroxycodone and noroxymorphone. The interday coefficient of variation was less than 6% for parent oxycodone and less than 13% for the metabolites at relevant plasma concentrations.

The concentrations of ritonavir and lopinavir just before and 2 h after the administration of the dose of pretreatment on the day 3 were determined with a LC–MS/MS method [31]. Saquinavir was used as internal standard. The LLQ was 0.1 µg/ml for ritonavir and 0.4 µg/ml for lopinavir. The interday CVs were < 5.4% and < 7.0% for ritonavir and lopinavir, respectively, at relevant concentrations (n=3).

Pharmacokinetic analysis

The pharmacokinetics of oxycodone and its metabolites were determined by standard noncompartmental methods using a pharmacokinetic program WinNonlin (version 4.1, Pharsight Corporation, Mountain View, CA, USA). The peak plasma concentrations (C_{\max}) and the corresponding C_{\max} times (t_{\max}) were observed directly from the data. The elimination rate constant (k_e) was determined by log-linear regression. The elimination half-life $t_{1/2}$ was calculated from $\ln 2/k_e$. The areas under the oxycodone, noroxycodone, oxymorphone and noroxymorphone concentration–time curves ($AUC_{0-\infty}$) were calculated by trapezoidal rule with extrapolation to infinity. Whenever k_e could not be estimated because of low plasma concentrations of the metabolite, AUC_{0-48} was used instead of $AUC_{0-\infty}$. The metabolite-to-parent drug AUC ratios (AUC_m/AUC_p) were calculated to compare the relative abundance of each metabolite.

Analysis of pharmacological effects

Behavioral effects

The behavioural measures were performed before and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 h after oxycodone as described earlier [32]. Subjective assessment of drowsiness, deterioration of performance, self-reported drug-effect, pleasantness and nausea or vomiting was quantified using visual analog scales (VAS) and scored 0–100. Attributes assessed included alert/drowsy, good/poor performance, no/strong drug effect, unpleasant/pleasant feeling and no/extreme nausea or vomiting [33]. Maddox wing test was used to estimate the central coordination of extraocular muscles [34]; digit symbol substitution test (DSST) to estimate the central processing of sensory information [35] and Cogan's pupillometry to measure pupil diameter [36]. All reported and observed adverse effects were recorded.

Experimental pain

The analgesic effect was studied in an experimental cold pressor test, which is sensitive to opioid effects [37]. The subjects placed their left hand up to the wrist into the ice water bath (temperature 0–2°C) for one minute and reported the first sensation of pain (cold pain threshold, CPT), which was measured in seconds with a stopwatch. The intensity of cold pain at 60 s (CPI) was assessed using numerical rating scale (NRS 0–100). The area under the drug effect–time curve (AUEC_{0–12}) from 0 to 12 hours was calculated with linear trapezoidal rule based on the observations by the use of the WinNonlin (version 4.1, Pharsight Corporation, Mountain View, CA, USA) software for all effect variables.

Statistics

The results are expressed as mean \pm SD, except for t_{\max} , where medians with minimum and maximum values are reported. In figures, for clarity, mean \pm SEM are given. Descriptive and comparative statistics were calculated with use of SYSTAT for Windows (version 10.2; Systat software, Richmond, CA, USA). The pharmacokinetic and pharmacodynamic variables were compared with the use of analysis of variance for repeated measures and a posteriori testing was performed with Tukey's test. Pharmacokinetic data was logarithmically transformed before statistical comparisons. Analysis of variance was used to determine the contributions of treatment, CYP2D6-genotype, gender, phase and sequence on overall variance. The t_{\max} was analyzed by Friedman's test and Wilcoxon signed rank test was used for pair wise comparisons. P was considered significant at the level of <0.05 . We also calculated geometric mean ratios with 90% confidence intervals (CI) for the pharmacokinetic parameters. Bioequivalence (i.e., the lack of an interaction) was concluded, if the 90% CI of the geometric mean ratios (coadministration/oxycodone alone) were within the acceptance limit of 0.8 to 1.25.

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RESULTS

All subjects completed the study.

Pharmacokinetic results

The pharmacokinetic results are presented in Figure 1 and Table 1. During the ritonavir and lopinavir phases, all of the calculated pharmacokinetic parameters for oxycodone were outside the bioequivalence acceptance limits (Table 1). Compared with placebo, ritonavir and lopinavir/ritonavir increased the oxycodone $AUC_{0-\infty}$ (geometric mean ratio) by 3.0-fold (90% CI 2.6, 3.4; $P<0.001$) and 2.6-fold (90% CI 2.3, 2.9; $P<0.001$), respectively. Ritonavir increased the geometric mean ratio of oxycodone C_{max} by 1.7-fold (90% CI 1.5, 2.0; $P<0.001$) and prolonged its elimination half-life from 3.6 ± 0.6 h to 5.6 ± 0.9 h ($P<0.001$). Lopinavir/ritonavir increased the geometric mean ratio of oxycodone C_{max} by 1.4-fold (90% CI 1.2, 1.7; $P<0.05$) and prolonged its elimination half-life to 5.7 ± 0.9 hours ($P<0.001$). Gender had no significant influence on the pharmacokinetic parameters of oxycodone.

Both ritonavir and lopinavir/ritonavir decreased the geometric mean ratio for noroxycodone AUC_{0-48} to 0.49 (90%CI 0.43, 0.58, $P<0.001$) and 0.44 (90%CI 0.38, 0.50; $P<0.001$), respectively. Ritonavir alone had no effect on oxymorphone but lopinavir/ritonavir increased geometric mean ratio for oxymorphone AUC_{0-48} by 2.7-fold (90%CI 2.0, 3.8; $P<0.05$). The geometric mean ratio for noroxymorphone AUC_{0-48} was 0.19 (90%CI 0.15, 0.24; $P<0.01$) after ritonavir and 0.24 (90%CI 0.16, 0.35; $P<0.01$) after lopinavir/ritonavir, respectively. Four subjects during ritonavir phase and three subjects during lopinavir/ritonavir phase had no detectable concentrations of noroxymorphone during the study period 0–48 hours.

Nine volunteers were classified as extensive metabolizers (EM). Three of them were homozygous for CYP2D6*1 allele and the rest of the genotypes were CYP2D6*1/4 ($n = 3$), CYP2D6*1/5 ($n = 2$) and CYP2D6*1/41 ($n=1$). Furthermore, there were two subjects with CYP2D6*1/1 x 2 genotype classified as ultrarapid metabolizer (UM) and one CYP2D6*10/*41 classified as intermediate metabolizer (IM). The IMs

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3 appeared to have lower oxymorphone AUC values than most of the extensive metabolizers during all phases
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10 After pre-treatment with ritonavir, plasma ritonavir concentrations (mean \pm SD) measured $\frac{1}{2}$ and 3 hours
11 after the morning dose on day 3, were 3.2 ± 1.6 μ g/ml and 8.7 ± 2.6 μ g/ml. After lopinavir/ritonavir pre-
12 treatment, the corresponding plasma lopinavir concentrations were 9.0 ± 2.0 μ g/ml and 11.3 ± 2.9 μ g/ml and
13 ritonavir concentrations 0.5 ± 0.3 μ g/ml and 1.0 ± 0.5 μ g/ml, respectively. All volunteers had measurable
14 values of ritonavir and ritonavir/lopinavir before the morning dose during active phases indicating
15 compliance to the dosing schedule.
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25 Pharmacodynamic results

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27 Results from behavioral and analgesic tests are shown in Fig. 2. The self-reported drug effect $AUEC_{0-12}$
28 increased significantly after ritonavir and lopinavir/ritonavir ($P < 0.001$ and < 0.05). Ritonavir increased also
29 nausea or vomiting as measured by VAS ($P < 0.01$), but no other statistically significant differences were
30 observed in the pharmacological response to oxycodone.
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38 The adverse effects reported are presented in Table 2. All three volunteers with vomiting were treated with 2
39 mg intravenous tropisetron 4, 8 or 12 h after oxycodone.
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DISCUSSION

This study convincingly demonstrates that short-term administration of ritonavir and lopinavir/ritonavir strongly inhibits the CYP3A-mediated N-demethylation of oxycodone, as reflected by an approximately 2–3-fold increase in oxycodone $AUC_{0-\infty}$ and decrease in noroxycodone AUC_{0-48} . When oxycodone was administered together with ritonavir or lopinavir/ritonavir, the mean concentration of oxycodone was still higher at 8 h than the C_{max} during the control phase. These pharmacokinetic changes were accompanied by enhanced self-reported drug-effect after both antiviral treatments.

Ritonavir has been shown to be a strong inhibitor of CYP3A both *in vitro* [38, 39] and *in vivo* [16, 18, 40, 41]. In the present study ritonavir caused a 3-fold mean increase of oxycodone $AUC_{0-\infty}$, which is somewhat smaller than that observed after the azole antimycotic voriconazole (3.6-fold increase in oxycodone $AUC_{0-\infty}$), but bigger than that observed for itraconazole (2.4-fold increase) and telithromycin (1.8-fold increase) [25–27]. It can be speculated, although it seems doubtful, that the interaction between oxycodone and ritonavir would have been stronger, if a larger ritonavir dose would have been used as recommended by the manufacturer. However, because we wanted to minimize possible adverse effects in healthy volunteers, 300 mg b.i.d. was used and the treatment lasted only four days. This could lead to bias, as the steady-state was not reached [21]. Ritonavir has been reported to cause an enzyme induction after approximately 2 weeks administration, which can diminish the inhibitory effects [42, 43].

Interestingly, lopinavir/ritonavir resulted in an almost equal alteration in oxycodone pharmacokinetics as compared to ritonavir. The clinically used maintenance dose of ritonavir is 600 mg b.i.d., which is recommended to be attained during 2 weeks to avoid adverse effects. During the 4-day pre-treatment our volunteers were given 300 mg of ritonavir b.i.d., which is three times higher than the dose of ritonavir during lopinavir/ritonavir phase. Still, the pharmacokinetics of oxycodone was very similar whether it was given together with ritonavir or lopinavir/ritonavir. A plausible explanation for the observed pharmacokinetic changes is the additional inhibitory effect by lopinavir. Lopinavir is a less potent inhibitor of CYP3A *in vitro* than ritonavir, but it might nonetheless contribute to net CYP3A inhibition *in vivo* during the treatment with

the combination of lopinavir and ritonavir. The dose-response curve for CYP3A inhibition by ritonavir can be so flat *in vivo* that despite a 3-fold dose reduction, it causes a maximal inhibition of CYP3A when combined with a 4-fold higher dose of lopinavir [44].

Ritonavir inhibits CYP2D6 *in vitro*, but to a lesser extent than it inhibits CYP3A [44, 45]. In the present study, oxymorphone concentrations were increased during both antiviral phases indicating the increased significance of compensatory oxycodone metabolic route via CYP2D6 during CYP3A inhibition. In a previous study, coadministration of oxycodone and telithromycin, an inhibitor of CYP3A and CYP2D6, shifted the metabolism of oxycodone towards the CYP2D6-mediated route increasing oxymorphone concentrations [27]. After lopinavir/ritonavir, the geometric mean ratio for oxymorphone AUC was increased by 2.7-fold. Earlier studies have reported CYP2D6 inhibition during lopinavir/ritonavir [17, 24]. The inhibition was not strong enough to totally hinder the compensation via CYP2D6-mediated route after CYP3A inhibition. The formation of oxymorphone has recently been shown to be dependent on CYP2D6 genotype [46]. In our study with only 12 healthy volunteers, there were 9 extensive, one intermediate, two ultrarapid but no poor metabolizers. In the present small-scale study these genotypes were not associated with changes in pharmacokinetic parameters of oxycodone or its metabolites.

The self-reported drug effect of oxycodone was significantly increased by both ritonavir and lopinavir/ritonavir. As well as oxycodone, also ritonavir was involved in the side-effects because approximately 25% of ritonavir users typically report nausea or vomiting [21]. Contrary to our previous studies, oxycodone reduced pain in the cold pressor test only in some subjects. As only a single dose of oxycodone was used in the current study in order to minimize the exposure of healthy volunteers to opioids, drug effect remained smaller compared to normal clinical setting. Moderate differences in drug concentrations do not necessarily affect the pharmacologic response because of the log-linear relationship between the drug concentration and effect. Furthermore, the power of this study was insufficient to show differences between ritonavir or lopinavir/ritonavir and placebo phases in pharmacodynamic parameters, because our primary interest was a change in the oxycodone AUC and the calculation of the sample size was based on that endpoint.

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The possibility of drug-drug interactions must be considered in the treatment of HIV-associated pain. In previous pharmacokinetic studies in healthy volunteers, for instance, the oral bioavailability of alfentanil was increased from 37% to 95% by steady-state ritonavir concentrations [18]. The acute administration of ritonavir reduced the clearance of intravenous fentanyl by 67% [16]. In HIV-negative subjects receiving buprenorphine/naloxone as opioid-replacement therapy, tipranavir/ritonavir reduced the formation of CYP3A4 dependent active metabolite norbuprenorphine, but the AUC of parent drug remained unchanged and no clinical opioid withdrawal symptoms were noted [47]. Contrary to the above mentioned studies, the concentrations of methadone have been decreased after ritonavir probably due to the induction of CYP2B6 [43]. Thus, the effect of ritonavir on important opioids can be opposite. Drug-drug interactions in HIV-associated pain management are not restricted only to opioids; concomitant administration of lopinavir/ritonavir caused a 46% reduction in the plasma concentrations of lamotrigine, which is an antiepileptic recommended as second or third line drug for the treatment of neuropathic pain [6]. The mechanism behind this interaction might be the induction in lamotrigine glucuronidation [48]. Theoretically, the induction of glucuronidation could have an influence on the metabolism of oxycodone and its metabolites, but these metabolic routes are of minor importance [49] and they were not investigated in this study. Additionally, it is unlikely, that short duration of ritonavir would have induced the glucuronidation of noroxycodone and oxymorphone significantly.

In conclusion, administration of lopinavir/ritonavir and ritonavir greatly increases plasma concentrations of oxycodone. Clinically, attention should be drawn to the concomitant use of oxycodone and ritonavir or lopinavir/ritonavir and oxycodone. Further studies are needed to extend the results to HIV or AIDS pain patients suffering from chronic pain.

The authors declare no conflicts of interest.

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For Peer Review

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Oxycodone concentrations are greatly increased by the concomitant use of ritonavir or lopinavir/ritonavir

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ABSTRACT

Purpose: This study was aimed to investigate the effect of antivirals ritonavir and lopinavir/ritonavir on the pharmacokinetics and pharmacodynamics of oral oxycodone, a widely used opioid receptor agonist used in the treatment of moderate to severe pain.

Methods: A randomized crossover study design with 3 phases at intervals of 4 weeks was conducted in 12 healthy volunteers. Ritonavir 300 mg, lopinavir/ritonavir 400/100 mg or placebo b.i.d. for 4 days was given to the subjects. On day 3, 10 mg oxycodone hydrochloride was administered orally. Plasma concentrations of oxycodone, noroxycodone, oxymorphone and noroxymorphone were determined for 48 h. Pharmacokinetic parameters were calculated with standard noncompartmental methods. Behavioural effects and experimental cold pain analgesia were assessed for 12 h. ANOVA for repeated measures was used for statistical analysis.

Results: Ritonavir and lopinavir/ritonavir increased the area under the plasma concentration–time curve of oral oxycodone by 3.0- (range 1.9- to 4.3-fold; $P<0.001$) and 2.6-fold (range 1.9- to 3.3-fold; $P<0.001$). The mean (\pm SD) elimination half-life prolonged after ritonavir and lopinavir/ritonavir from 3.6 ± 0.6 to 5.6 ± 0.9 h ($P<0.001$) and 5.7 ± 0.9 h ($P<0.001$), respectively. Both ritonavir ($P<0.001$) and lopinavir/ritonavir ($P<0.05$) increased the self-reported drug effect of oxycodone.

Conclusions: Ritonavir and lopinavir/ritonavir greatly increase the plasma concentrations of oral oxycodone in healthy volunteers and enhance its effect. When oxycodone is used clinically in patients during ritonavir and lopinavir/ritonavir treatment, reductions in oxycodone dose may be needed to avoid opioid-related adverse-effects.

Keywords: Oxycodone, Ritonavir, Lopinavir/ritonavir, Interaction, Pharmacokinetics, Pharmacodynamics

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INTRODUCTION

Pain is one of the most frequently reported symptoms associated with human immunodeficiency virus (HIV) infection. It has been estimated that in the developed world, depending on the stage of disease and study settings, 30–80% of people living with HIV/AIDS are affected with pain [1, 2]. Pain experienced by HIV patients can be acute or chronic, and it is usually multifactorial in origin. HIV-associated pain can be due to e.g. HIV itself, antiretroviral treatment, opportunistic infections, HIV-associated cancers, rheumatic conditions or peripheral polyneuropathy [3-5]. Unfortunately, these painful conditions are often under-recognised and -treated.

Oxycodone is a semi-synthetic opioid agonist, which is effective in treating acute, cancer-related and chronic pain [6, 7]. It is metabolized mainly via oxidative, but also via reductive pathways with only 10–14% being excreted in unchanged or conjugated forms in urine [8]. Oxycodone is principally a cytochrome P450 3A4/5 substrate, which makes it prone to the interactions with CYP3A inducers and inhibitors [9]. The main oxidative pathway includes N-demethylation to noroxycodone by CYP3A4/5 and further to noroxymorphone by CYP2D6 [9]. Approximately 11% of oxycodone is O-demethylated to oxymorphone by CYP2D6, which is further transformed to noroxymorphone by CYP3A4/5 and CYP2D6 [9]. Animal studies have given controversial results about the role of P-glycoprotein in the transport of oxycodone via blood-brain barrier (BBB) [10, 11]. However, the higher concentrations of oxycodone in rat and sheep brain tissue compared to plasma concentrations suggest that the influx protein is much more active than P-glycoprotein, which acts as an efflux protein limiting the concentrations of oxycodone in brain [12-14].

HIV protease inhibitors, such as ritonavir and lopinavir inflict the HIV-specific aspartic protease enzyme on processing the *gag* and *gag-pol* polyprotein precursor, which leads to the production of immature, non-infectious viral particles [15]. Ritonavir is a potent CYP3A, CYP2D6 and P-glycoprotein inhibitor [16-18]. It has been described to induce CYP1A2, CYP2B6, CYP2C9 and CYP2C19 [19, 20]. Difficult dosing regimens, the development of resistance and adverse effects have restricted the use of ritonavir as an independent part of HIV treatment [21]. Lopinavir/ritonavir is a combination preparation, where lopinavir is

combined with low-dose ritonavir to enhance its low bioavailability by favourable CYP3A inhibition [22].

Lopinavir/ritonavir has become a well-tolerated, effective and preferred protease inhibitor in the treatment of HIV. It is a substrate and inhibitor of CYP3A4 and to a lesser extent CYP2D6, and an inducer of CYP1A2, 2B6, 2C9 and 2C19 [23, 24] which makes it prone to cytochrome P450-mediated interactions.

In previous studies it has been shown, that CYP3A inhibitors voriconazole [25], itraconazole [26] and telithromycin [27] increased the concentrations of oxycodone and oxymorphone, but only minor changes have been observed in the pharmacological action of oxycodone following single doses in healthy volunteers. As HIV patients are often affected with moderate to severe pain, there is an obvious need for the concomitant use of antivirals and strong opioids, such as oxycodone. The aim of this study was to investigate the effects of ritonavir and lopinavir/ritonavir on the pharmacokinetics and effects of oxycodone in healthy volunteers.

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METHODS

Participants

The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland and by the Finnish National Agency for Medicines and was and was thereby reported to the EudraCT clinical trial register. In view of our previous studies, it was calculated, that 10 subjects would be required to detect a 30% difference in the area under the oxycodone concentration–time curves ($AUC_{0-\infty}$) at a level of significance $P = 0.05$ and power of 80% [25-27]. To allow a drop-out rate of 20%, we decided to recruit 12 subjects. Twelve healthy volunteers, four women and eight men (age 18–26 years; weight 52–84 kg) were studied according to the revised Declaration of Helsinki. Informed consent was obtained from all subjects before study screening. All participants were ascertained to be healthy by means of medical history and clinical examination, and they were tested for routine laboratory tests. Urine screens for drugs with abuse risk were negative and a 12-lead electrocardiogram (ECG) within normal limits. Pregnancy tests for women were negative. None of the participants were receiving any continuous medication including hormonal contraception and all were non-smokers. Women in need of contraception were instructed to use non-hormonal methods during the study.

Finnish translation of Abuse Questions [28] was used to assess risk for drug abuse. The consumption of any product with potential CYP3A effect such as herbal remedies or grapefruit juice was forbidden for 4 weeks and all other drugs for 2 weeks before and during the study. Consumption of coffee, tee, alcohol and cola drinks were not allowed in the study facility during the study days. Genotyping for CYP2D6 was conducted by a two-step multiplex primer extension method [29]. This method enables the detection of 11 most relevant polymorphic positions, the definition of whole-gene deletion, duplication and the allele combination in case of gene duplication.

Study design and drug dosing

We used a randomized, crossover study design with three phases at intervals of four weeks. During each phase, the volunteers were given 4 capsules or tablets b.i.d. at 7 a.m. and 7 p.m. for 4 days. The capsules and tablets were packed into sealed coded envelopes which contained either:

1. Two lopinavir/ritonavir 200 mg/50 mg tablets (Kaletra[®], Abbott Laboratories Ltd, Queenborough, UK) and two placebo capsules
2. Three ritonavir 100 mg capsules (Norvir[®], Abbott Laboratories Ltd, Queenborough, UK) and one placebo capsule
3. Four placebo capsules.

An oral dose of 10 mg oxycodone hydrochloride (Oxynorm[®] 10 mg capsule, Mundipharma, Bard Pharmaceuticals Ltd, Cambridge, UK) was administered on day 3 at 8 a.m. with 150 ml warm water. The participants arrived at the study facility one hour before oxycodone administration and were under supervision 12 hours after the dosing.

The volunteers fasted for 8 h before oxycodone hydrochloride administration and received a standard meal 4 and 8 h after dosing. Drinking was allowed only during the meals. Adherence to the pre-treatment medication schedule was ensured with mobile phone text messages, which the volunteers sent to the investigator after taking each dose of pre-treatment taken outside the study facility.

Sampling and determination of drug concentrations

In the study facility, a cubital vein was cannulated for blood sampling. The samples (10 ml each) were collected into EDTA containing tubes before and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 h after the oxycodone hydrochloride dose. Plasma was separated within 30 min and stored at -70°C until analysis.

Plasma concentrations of oxycodone, noroxycodone, oxymorphone and noroxymorphone were analyzed with the liquid chromatography–tandem mass spectrometric (LC–MS/MS) method as described earlier [30]. The lower limits of quantification (LLQ) were 0.1 ng/mL for oxycodone and oxymorphone, and 0.25 ng/mL for noroxycodone and noroxymorphone. The interday coefficient of variation was less than 6% for parent oxycodone and less than 13% for the metabolites at relevant plasma concentrations.

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The concentrations of ritonavir and lopinavir just before and 2 h after the administration of the dose of pretreatment on the day 3 were determined with a LC–MS/MS method [31]. Saquinavir was used as internal standard. The LLQ was 0.1 µg/ml for ritonavir and 0.4 µg/ml for lopinavir. The interday CVs were < 5.4% and < 7.0% for ritonavir and lopinavir, respectively, at relevant concentrations (n=3).

Pharmacokinetic analysis

The pharmacokinetics of oxycodone and its metabolites were determined by standard noncompartmental methods using a pharmacokinetic program WinNonlin (version 4.1, Pharsight Corporation, Mountain View, CA, USA). The peak plasma concentrations (C_{max}) and the corresponding C_{max} times (t_{max}) were observed directly from the data. The elimination rate constant (k_e) was determined by log-linear regression. The elimination half-life $t_{1/2}$ was calculated from $\ln 2/k_e$. The areas under the oxycodone, noroxycodone, oxymorphone and noroxymorphone concentration–time curves ($AUC_{0-\infty}$) were calculated by trapezoidal rule with extrapolation to infinity. Whenever k_e could not be estimated because of low plasma concentrations of the metabolite, AUC_{0-48} was used instead of $AUC_{0-\infty}$. The metabolite-to-parent drug AUC ratios (AUC_m/AUC_p) were calculated to compare the relative abundance of each metabolite.

Analysis of pharmacological effects

Behavioral effects

The behavioural measures were performed before and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 h after oxycodone as described earlier [32]. Subjective assessment of drowsiness, deterioration of performance, self-reported drug-effect, pleasantness and nausea or vomiting was quantified using visual analog scales (VAS) and scored 0–100. Attributes assessed included alert/drowsy, good/poor performance, no/strong drug effect, unpleasant/pleasant feeling and no/extreme nausea or vomiting [33]. Maddox wing test was used to estimate the central coordination of extraocular muscles [34]; digit symbol substitution test (DSST) to estimate the central processing of sensory information [35] and Cogan’s pupillometry to measure pupil diameter [36]. All reported and observed adverse effects were recorded.

Experimental pain

The analgesic effect was studied in an experimental cold pressor test, which is sensitive to opioid effects [37]. The subjects placed their left hand up to the wrist into the ice water bath (temperature 0–2°C) for one minute and reported the first sensation of pain (cold pain threshold, CPT), which was measured in seconds with a stopwatch. The intensity of cold pain at 60 s (CPI) was assessed using numerical rating scale (NRS 0–100). The area under the drug effect–time curve (AUEC_{0–12}) from 0 to 12 hours was calculated with linear trapezoidal rule based on the observations by the use of the WinNonlin (version 4.1, Pharsight Corporation, Mountain View, CA, USA) software for all effect variables.

Statistics

The results are expressed as mean \pm SD, except for t_{\max} , where medians with minimum and maximum values are reported. In figures, for clarity, mean \pm SEM are given. Descriptive and comparative statistics were calculated with use of SYSTAT for Windows (version 10.2; Systat software, Richmond, CA, USA). The pharmacokinetic and pharmacodynamic variables were compared with the use of analysis of variance for repeated measures and a posteriori testing was performed with Tukey's test. Pharmacokinetic data was logarithmically transformed before statistical comparisons. Analysis of variance was used to determine the contributions of treatment, CYP2D6-genotype, gender, phase and sequence on overall variance. The t_{\max} was analyzed by Friedman's test and Wilcoxon signed rank test was used for pair wise comparisons. P was considered significant at the level of <0.05 . We also calculated geometric mean ratios with 90% confidence intervals (CI) for the pharmacokinetic parameters. Bioequivalence (i.e., the lack of an interaction) was concluded, if the 90% CI of the geometric mean ratios (coadministration/oxycodone alone) were within the acceptance limit of 0.8 to 1.25.

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RESULTS

All subjects completed the study.

Pharmacokinetic results

The pharmacokinetic results are presented in Figure 1 and Table 1. During the ritonavir and lopinavir phases, all of the calculated pharmacokinetic parameters for oxycodone were outside the bioequivalence acceptance limits (Table 1). Compared with placebo, ritonavir and lopinavir/ritonavir increased the oxycodone $AUC_{0-\infty}$ (geometric mean ratio) by 3.0-fold (90% CI 2.6, 3.4; $P<0.001$) and 2.6-fold (90% CI 2.3, 2.9; $P<0.001$), respectively. Ritonavir increased the geometric mean ratio of oxycodone C_{max} by 1.7-fold (90% CI 1.5, 2.0; $P<0.001$) and prolonged its elimination half-life from 3.6 ± 0.6 h to 5.6 ± 0.9 h ($P<0.001$).

Lopinavir/ritonavir increased the geometric mean ratio of oxycodone C_{max} by 1.4-fold (90% CI 1.2, 1.7; $P<0.05$) and prolonged its elimination half-life to 5.7 ± 0.9 hours ($P<0.001$). Gender had no significant influence on the pharmacokinetic parameters of oxycodone.

Both ritonavir and lopinavir/ritonavir decreased the geometric mean ratio for noroxycodone AUC_{0-48} to 0.49 (90%CI 0.43, 0.58, $P<0.001$) and 0.44 (90%CI 0.38, 0.50; $P<0.001$), respectively. Ritonavir alone had no effect on oxymorphone but lopinavir/ritonavir increased geometric mean ratio for oxymorphone AUC_{0-48} by 2.7-fold (90%CI 2.0, 3.8; $P<0.05$). The geometric mean ratio for noroxymorphone AUC_{0-48} was 0.19 (90%CI 0.15, 0.24; $P<0.01$) after ritonavir and 0.24 (90%CI 0.16, 0.35; $P<0.01$) after lopinavir/ritonavir, respectively. Four subjects during ritonavir phase and three subjects during lopinavir/ritonavir phase had no detectable concentrations of noroxymorphone during the study period 0–48 hours.

Nine volunteers were classified as extensive metabolizers (EM). Three of them were homozygous for CYP2D6*1 allele and the rest of the genotypes were CYP2D6*1/4 ($n = 3$), CYP2D6*1/5 ($n = 2$) and CYP2D6*1/41 ($n=1$). Furthermore, there were two subjects with CYP2D6*1/1 x 2 genotype classified as ultrarapid metabolizer (UM) and one CYP2D6*10/*41 classified as intermediate metabolizer (IM). The IMs

appeared to have lower oxymorphone AUC values than most of the extensive metabolizers during all phases (data not shown).

After pre-treatment with ritonavir, plasma ritonavir concentrations (mean \pm SD) measured $\frac{1}{2}$ and 3 hours after the morning dose on day 3, were 3.2 ± 1.6 μ g/ml and 8.7 ± 2.6 μ g/ml. After lopinavir/ritonavir pre-treatment, the corresponding plasma lopinavir concentrations were 9.0 ± 2.0 μ g/ml and 11.3 ± 2.9 μ g/ml and ritonavir concentrations 0.5 ± 0.3 μ g/ml and 1.0 ± 0.5 μ g/ml, respectively. All volunteers had measurable values of ritonavir and ritonavir/lopinavir before the morning dose during active phases indicating compliance to the dosing schedule.

Pharmacodynamic results

Results from behavioral and analgesic tests are shown in Fig. 2. The self-reported drug effect $AUEC_{0-12}$ increased significantly after ritonavir and lopinavir/ritonavir ($P < 0.001$ and < 0.05). Ritonavir increased also nausea or vomiting as measured by VAS ($P < 0.01$), but no other statistically significant differences were observed in the pharmacological response to oxycodone.

The adverse effects reported are presented in Table 2. All three volunteers with vomiting were treated with 2 mg intravenous tropisetron 4, 8 or 12 h after oxycodone.

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DISCUSSION

This study convincingly demonstrates that short-term administration of ritonavir and lopinavir/ritonavir strongly inhibits the CYP3A-mediated N-demethylation of oxycodone, as reflected by an approximately 2–3-fold increase in oxycodone $AUC_{0-\infty}$ and decrease in noroxycodone AUC_{0-48} . When oxycodone was administered together with ritonavir or lopinavir/ritonavir, the mean concentration of oxycodone was still higher at 8 h than the C_{max} during the control phase. These pharmacokinetic changes were accompanied by enhanced self-reported drug-effect after both antiviral treatments.

Ritonavir has been shown to be a strong inhibitor of CYP3A both *in vitro* [38, 39] and *in vivo* [16, 18, 40, 41]. In the present study ritonavir caused a 3-fold mean increase of oxycodone $AUC_{0-\infty}$, which is somewhat smaller than that observed after the azole antimycotic voriconazole (3.6-fold increase in oxycodone $AUC_{0-\infty}$), but bigger than that observed for itraconazole (2.4-fold increase) and telithromycin (1.8-fold increase) [25-27]. It can be speculated, although it seems doubtful, that the interaction between oxycodone and ritonavir would have been stronger, if a larger ritonavir dose would have been used as recommended by the manufacturer. However, because we wanted to minimize possible adverse effects in healthy volunteers, 300 mg b.i.d. was used and the treatment lasted only four days. This could lead to bias, as the steady-state was not reached [21]. Ritonavir has been reported to cause an enzyme induction after approximately 2 weeks administration, which can diminish the inhibitory effects [42, 43].

Interestingly, lopinavir/ritonavir resulted in an almost equal alteration in oxycodone pharmacokinetics as compared to ritonavir. The clinically used maintenance dose of ritonavir is 600 mg b.i.d., which is recommended to be attained during 2 weeks to avoid adverse effects. During the 4-day pre-treatment our volunteers were given 300 mg of ritonavir b.i.d., which is three times higher than the dose of ritonavir during lopinavir/ritonavir phase. Still, the pharmacokinetics of oxycodone was very similar whether it was given together with ritonavir or lopinavir/ritonavir. A plausible explanation for the observed pharmacokinetic changes is the additional inhibitory effect by lopinavir. Lopinavir is a less potent inhibitor of CYP3A *in vitro* than ritonavir, but it might nonetheless contribute to net CYP3A inhibition *in vivo* during the treatment with

the combination of lopinavir and ritonavir. The dose-response curve for CYP3A inhibition by ritonavir can be so flat *in vivo* that despite a 3-fold dose reduction, it causes a maximal inhibition of CYP3A when combined with a 4-fold higher dose of lopinavir [44].

Ritonavir inhibits CYP2D6 *in vitro*, but to a lesser extent than it inhibits CYP3A [44, 45]. In the present study, oxymorphone concentrations were increased during both antiviral phases indicating the increased significance of compensatory oxycodone metabolic route via CYP2D6 during CYP3A inhibition. In a previous study, coadministration of oxycodone and telithromycin, an inhibitor of CYP3A and CYP2D6, shifted the metabolism of oxycodone towards the CYP2D6-mediated route increasing oxymorphone concentrations [27]. After lopinavir/ritonavir, the geometric mean ratio for oxymorphone AUC was increased by 2.7-fold. Earlier studies have reported CYP2D6 inhibition during lopinavir/ritonavir [17, 24]. The inhibition was not strong enough to totally hinder the compensation via CYP2D6-mediated route after CYP3A inhibition. The formation of oxymorphone has recently been shown to be dependent on CYP2D6 genotype [46]. In our study with only 12 healthy volunteers, there were 9 extensive, one intermediate, two ultrarapid but no poor metabolizers. In the present small-scale study these genotypes were not associated with changes in pharmacokinetic parameters of oxycodone or its metabolites.

The self-reported drug effect of oxycodone was significantly increased by both ritonavir and lopinavir/ritonavir. As well as oxycodone, also ritonavir was involved in the side-effects because approximately 25% of ritonavir users typically report nausea or vomiting [21]. Contrary to our previous studies, oxycodone reduced pain in the cold pressor test only in some subjects. As only a single dose of oxycodone was used in the current study in order to minimize the exposure of healthy volunteers to opioids, drug effect remained smaller compared to normal clinical setting. Moderate differences in drug concentrations do not necessarily affect the pharmacologic response because of the log-linear relationship between the drug concentration and effect. Furthermore, the power of this study was insufficient to show differences between ritonavir or lopinavir/ritonavir and placebo phases in pharmacodynamic parameters, because our primary interest was a change in the oxycodone AUC and the calculation of the sample size was based on that endpoint.

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The possibility of drug-drug interactions must be considered in the treatment of HIV-associated pain. In previous pharmacokinetic studies in healthy volunteers, for instance, the oral bioavailability of alfentanil was increased from 37% to 95% by steady-state ritonavir concentrations [18]. The acute administration of ritonavir reduced the clearance of intravenous fentanyl by 67% [16]. In HIV-negative subjects receiving buprenorphine/naloxone as opioid-replacement therapy, tipranavir/ritonavir reduced the formation of CYP3A4 dependent active metabolite norbuprenorphine, but the AUC of parent drug remained unchanged and no clinical opioid withdrawal symptoms were noted [47]. Contrary to the above mentioned studies, the concentrations of methadone have been decreased after ritonavir probably due to the induction of CYP2B6 [43]. Thus, the effect of ritonavir on important opioids can be opposite. Drug-drug interactions in HIV-associated pain management are not restricted only to opioids; concomitant administration of lopinavir/ritonavir caused a 46% reduction in the plasma concentrations of lamotrigine, which is an antiepileptic recommended as second or third line drug for the treatment of neuropathic pain [6]. The mechanism behind this interaction might be the induction in lamotrigine glucuronidation [48]. Theoretically, the induction of glucuronidation could have an influence on the metabolism of oxycodone and its metabolites, but these metabolic routes are of minor importance [49] and they were not investigated in this study. Additionally, it is unlikely, that short duration of ritonavir would have induced the glucuronidation of noroxycodone and oxymorphone significantly.

In conclusion, administration of lopinavir/ritonavir and ritonavir greatly increases plasma concentrations of oxycodone. Clinically, attention should be drawn to the concomitant use of oxycodone and ritonavir or lopinavir/ritonavir and oxycodone. Further studies are needed to extend the results to HIV or AIDS pain patients suffering from chronic pain.

The authors declare no conflicts of interest.

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For Peer Review

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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), oral ritonavir or lopinavir/ritonavir in 12 healthy volunteers.

Parameter	Control phase	Ritonavir phase [geometric mean ratio (90% CI)]	Lopinavir/ritonavir phase [geometric mean ratio (90% CI)]
Oxycodone			
C _{max} (ng/ml)	20.2 ± 6.8	34.1 ± 7.3*** [1.74 (1.55–1.95)]	27.7 ± 7.2* [1.38 (1.17–1.66)]
t _{max} (h)	1.5 (0.5–1.5)	1.5 (0.5–5.0)	2.5 (0.5–5.0)*
AUC _{0–∞} (µg·min/ml)	6.8 ± 2.3	19.6 ± 4.6*** [2.95 (2.57–3.39)]	17.3 ± 4.3*** [2.57 (2.34–2.88)]
t _{1/2} (h)	3.6 ± 0.6	5.6 ± 0.9*** [1.55 (1.45–1.62)]	5.7 ± 0.9*** [1.58 (1.48–1.66)]
Noroxycodone			
AUC _{0–48} (µg·min/ml)	7.6 ± 2.1	3.8 ± 1.4*** [0.49 (0.43–0.58)]	3.4 ± 1.5*** [0.44 (0.38–0.50)]
Oxymorphone			
AUC _{0–48} (µg·min/ml)	2.19 ± 1.77	2.8 ± 2.42 [1.07 (0.60–1.90)]	5.0 ± 2.2* [2.69 (1.95–3.80)]
Noroxymorphone			
AUC _{0–48} (µg·min/ml)	1.65 ± 0.63	0.27 ± 0.26** [0.19 (0.15–0.24)]	0.03 ± 0.03** [0.24 (0.16–0.35)]

The results are given as mean ± SD and geometric mean ratio (90% CI), except for t_{max}, which is given as mean and range.
Significantly different *(P<0.05), **(P<0.01) or ***(P<0.001) from the control phase.
C_{max} = maximum concentration, t_{max} = time to maximum concentration, AUC_{0–∞} = area under plasma concentration–time curve extrapolated to infinity, AUC_{0–48} = area under plasma concentration–time curve from zero to 48 hours, t_{1/2} = elimination half-life.

Table 2. Adverse effects in 12 healthy volunteers after placebo, ritonavir and lopinavir/ritonavir pre-treatment and during test days, after placebo, ritonavir and lopinavir/ritonavir and oral oxycodone hydrochloride 10 mg.

Adverse effect	Pre-treatment			Test days		
	<i>Placebo</i>	<i>Ritonavir</i>	<i>Lopinavir/ ritonavir</i>	<i>Placebo</i>	<i>Ritonavir</i>	<i>Lopinavir/ ritonavir</i>
Dizziness	0	0	0	5	5	7
Itching	0	0	0	4	4	4
Tiredness	0	0	0	2	0	0
Diarrhoea	0	2	3	0	0	0
Abdominal Irritation	0	3	3	0	0	0
Nausea	0	0	3	4	4	2
Vomiting	0	0	0	2	2	1

(n=number of subjects)

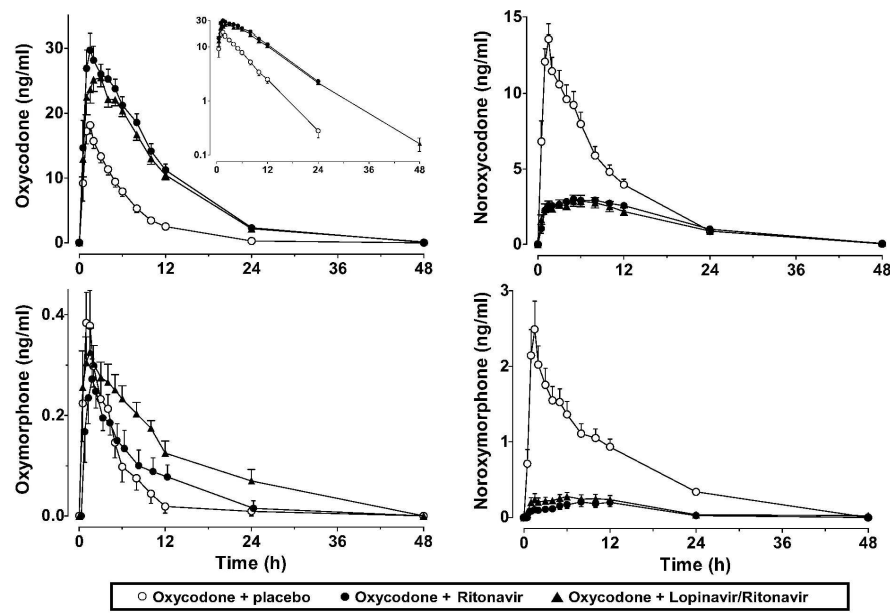


Fig. 1. Plasma concentrations (mean ± SEM) of oxycodone and its metabolites in 12 healthy volunteers after administration of placebo (control), ritonavir (RIT, 300 mg b.i.d.) or lopinavir/ritonavir (LPV/r, 400/100 mg b.i.d.) for four days. Oxycodone hydrochloride (10 mg per os) was given on day 3 at 8 a.m. with 150 ml of warm water. For clarity, SEMs were used instead of SDs. SEMs can be converted into SDs by multiplying it with square root of 12 (3.46). Time = 0 refers to the time of oxycodone administration.

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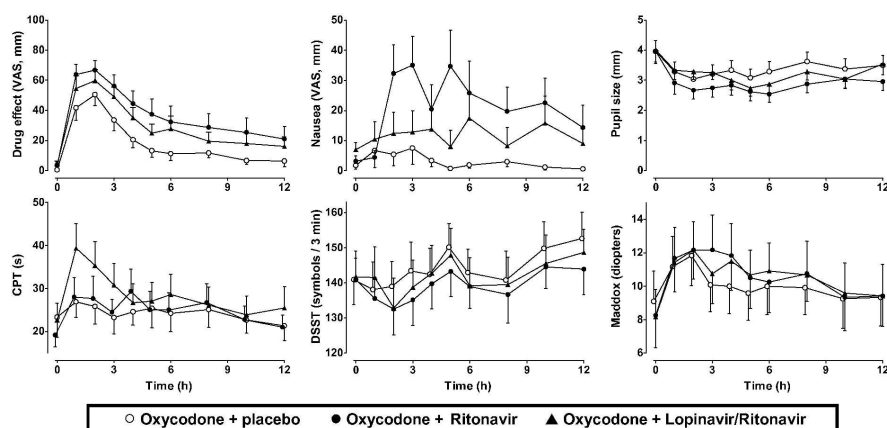


Fig. 2. Pharmacodynamic parameters in 12 healthy volunteers after administration of placebo (control), ritonavir (RIT, 300 mg b.i.d.) or lopinavir/ritonavir (LPV/r, 400/100 mg b.i.d.) for four days. Oxycodone hydrochloride (10 mg per os) was given on day 3 at 8 a.m. with 150 ml of warm water. The figures are presented as mean (\pm SEM) of self-reported drug effect and nausea (VAS 0–100), pupil size (mm), cold pain threshold (CPT in seconds,) value in Digit Symbol Substitution test (DSST) and value in co-ordination of the extraocular muscles (diopters) in 12 healthy volunteers. For clarity, SEMs were used instead of SDs. SEMs can be converted into SDs by multiplying it with square root of 12 (3.46). Time = 0 refers to the time of oxycodone administration.

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