

# Rifampin Greatly Reduces the Plasma Concentrations of Intravenous and Oral Oxycodone

Tuija H. Nieminen, M.D.,\* Nora M. Hagelberg, M.D., Ph.D.,† Teijo I. Saari, M.D., Ph.D.,\* Antti Pertovaara, M.D., Ph.D.,‡ Mikko Neuvonen, M.Sc.,§ Kari Laine, M.D., Ph.D.,|| Pertti J. Neuvonen, M.D., Ph.D.,# Klaus T. Olkkola, M.D., Ph.D.\*\*

**Background:** Oxycodone is a  $\mu$ -opioid receptor agonist that is metabolized mainly in the liver by cytochrome P450 3A and 2D6 enzymes. Rifampin is a strong inducer of several drug-metabolizing enzymes. The authors studied the interaction of rifampin with oxycodone. Their hypothesis was that rifampin enhances the CYP3A-mediated metabolism of oxycodone and attenuates its pharmacologic effect.

**Methods:** The protocol was a four-session, paired crossover. Twelve volunteers were given 600 mg oral rifampin or placebo once daily for 7 days. Oxycodone was given on day 6. In the first part of the study, 0.1 mg/kg oxycodone hydrochloride was given intravenously. In the second part of the study, 15 mg oxycodone hydrochloride was given orally. Concentrations of oxycodone and its metabolites noroxycodone, oxymorphone, and noroxymorphone were determined for 48 h. Psychomotor effects were characterized for 12 h by several visual analog scales. Analgesic effects were characterized by measuring the heat pain threshold and cold pain sensitivity.

**Results:** Rifampin decreased the area under the oxycodone concentration–time curve of intravenous and oral oxycodone by 53% and 86%, respectively ( $P < 0.001$ ). Oral bioavailability of oxycodone was decreased from 69% to 21% ( $P < 0.001$ ). Rifampin greatly increased the plasma metabolite–parent drug ratios for noroxycodone and noroxymorphone ( $P < 0.001$ ). Pharmacologic effects of oral oxycodone were attenuated.

**Conclusions:** Induction of cytochrome P450 3A by rifampin reduced the area under the oxycodone concentration–time curve of intravenous and oral oxycodone. The pharmacologic effects of oxycodone were modestly attenuated. To maintain adequate analgesia, dose adjustment of oxycodone may be necessary, when used concomitantly with rifampin.

OXYCODONE is a semisynthetic opioid receptor agonist widely used in the treatment of acute and chronic pain.<sup>1</sup> It has relatively high oral bioavailability of 60–80%,<sup>2</sup> and it is mainly metabolized in the liver by cytochrome P450 (CYP) enzymes. CYP3A-mediated *N*-demethylation to noroxycodone accounts for the major part of its oxidative

metabolism. A smaller fraction of oxycodone is *O*-demethylated to oxymorphone by CYP2D6. Both noroxycodone and oxymorphone are then further metabolized to noroxymorphone by CYP3A and CYP2D6.<sup>3,4</sup> While the oxidative metabolites are responsible for 50% of the urinary excretion, the reduced metabolites in total account for approximately 18% of the dose.<sup>4</sup> Less than 10% of the dose is excreted unchanged in the urine.<sup>2,5,6</sup> Although the metabolites show variable pharmacologic activity, it is the parent oxycodone that seems to be responsible for the central effects of oxycodone.<sup>4</sup>

The involvement of CYP enzymes in the metabolism of oxycodone makes it prone for drug interactions. So far, there is little information about the effects of different CYP inducers on the pharmacokinetics of oxycodone. CYP3A enzymes are strongly inducible, whereas CYP2D6 is hardly inducible. One case report suggests that concurrent rifampin enhances the elimination of oxycodone. Although the patient ingested 60 mg oxycodone daily, the urine screen for oxycodone was negative. Because high concentrations of noroxycodone were found in urine, the authors concluded that rifampin enhanced the *N*-demethylation of oxycodone.<sup>7</sup>

Rifampin (rifampicin) is an effective antimicrobial agent and a strong inducer of several drug-metabolizing enzymes both in liver and small intestine.<sup>8</sup> Rifampin has decreased the plasma concentrations of many CYP3A substrates, including methadone,<sup>9,10</sup> alfentanil,<sup>11</sup> diazepam,<sup>12</sup> midazolam,<sup>13</sup> triazolam,<sup>14</sup> buspirone,<sup>15</sup> simvastatin,<sup>16</sup> and atorvastatin,<sup>17</sup> but the extent of these interactions has been highly variable. Because the global use of oxycodone is increasing,<sup>18</sup> we found it important to study the possible interaction of rifampin with oxycodone. Our hypothesis was that rifampin enhances the CYP3A-mediated metabolism of oxycodone and attenuates its pharmacologic effect.

## Materials and Methods

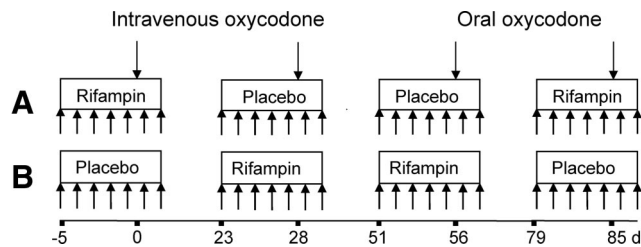
### Subjects

In view of previous studies<sup>2,5</sup> it was calculated that 10 subjects would be required to demonstrate a 30% difference in the area under the oxycodone plasma concentration–time curve (AUC) at level of significance  $P = 0.05$  and a power of 80%. Because we wanted to be prepared for dropouts, 12 healthy volunteers (7 women and 5 men; age range, 20–31 yr; weight range, 53–110 kg), were enrolled in the study after giving written informed consent. All subjects were genotyped for CYP2D6<sup>19</sup>; one was a poor CYP2D6 metabolizer, and the

\* Staff Anesthesiologist, † Chief of the Pain Clinic, \*\* Professor and Chairman, Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine, Turku University Hospital and the University of Turku, Turku, Finland. ‡ Professor, Institute of Biomedicine/Physiology, University of Helsinki, Helsinki, Finland. § Chemist, # Professor and Chairman, Department of Clinical Pharmacology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland. || Associate Professor, Department of Pharmacology, Drug Development and Therapeutics, University of Turku, Turku, Finland.

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Address correspondence to Dr. Nieminen: Department of Anesthesiology, Intensive Care, Emergency Care and Pain Medicine, Turku University Hospital, P.O. Box 52 (Kiinamylynkatu 4-8), FI-20520 Turku, Finland. tuija.nieminen@utu.fi. Information on purchasing reprints may be found at [www.anesthesiology.org](http://www.anesthesiology.org) or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.



**Fig. 1.** A four-session, paired, placebo-controlled, randomized (either sequence A or B), crossover study design at intervals of 4 weeks was used. Before oral or intravenous oxycodone administration, 12 volunteers were given in randomized order either 600 mg oral rifampin or placebo once daily at 8 PM for 7 days. Oxycodone was given on day 6 at 8 AM, 12 h after the fifth dose of rifampin or placebo. Two more doses of rifampin or placebo were given on days 6 and 7. Arrows pointing upward denote oral administration of rifampin or placebo. Arrows pointing downward denote the administration of oxycodone.

others were extensive metabolizers. The volunteers were ascertained to be in good health by medical history, clinical examination, and standard hematologic and blood chemistry test results. Urine toxicology and pregnancy test results were negative. None of the volunteers were receiving any continuous medication or were a smoker. The risk of participants to develop opioid abuse was considered low as assessed by the Finnish translation of the Abuse Questions.<sup>20</sup>

### Study Design

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. We used a four-session, paired, crossover study design (fig. 1). The volunteers were given in randomized order either 600 mg oral rifampin (Rimapen<sup>®</sup>; Orion, Espoo, Finland) or placebo once daily at 8 PM for 7 days. Oxycodone was administered on day 6, intravenously in the first part of the study and orally in the second part.

In the first part of the study, on two occasions at an interval of 4 weeks, all volunteers received 0.1 mg/kg intravenous oxycodone hydrochloride (Oxynorm<sup>®</sup>, 10 mg/ml; Mundipharma, Bard Pharmaceuticals Ltd., Cambridge, United Kingdom) on day 6 at 8 AM in 2 min, 12 h after the fifth dose of rifampin or placebo. Two more doses of rifampin or placebo were given on days 6 and 7. In the second part, the volunteers were given correspondingly 15 mg oral oxycodone hydrochloride (Oxynorm<sup>®</sup>, 10-mg and 5-mg capsules; Mundipharma, Bard Pharmaceuticals, Ltd.) with 150 ml warm water. Adherence with the rifampin/placebo-dosing schedule was assessed by use of mobile telephone text messages. The volunteers fasted for 8 h before the administration of oxycodone. They were given standard meals at 4 and 8 h after oxycodone. 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 were drawn into EDTA-containing tubes immediately before and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, and 48 h after administration of 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. Plasma was separated within 30 min and stored at  $-70^{\circ}\text{C}$  until oxycodone, noroxycodone, oxymorphone, and noroxymorphone concentrations were analyzed with a validated liquid chromatography tandem mass spectrometric method as described previously.<sup>21</sup> The lower limits of quantification were 0.1 ng/ml for oxycodone and oxymorphone and 0.25 ng/ml for noroxycodone and noroxymorphone. The interday coefficients of variation were less than 10% for all analytes at relevant plasma concentrations.

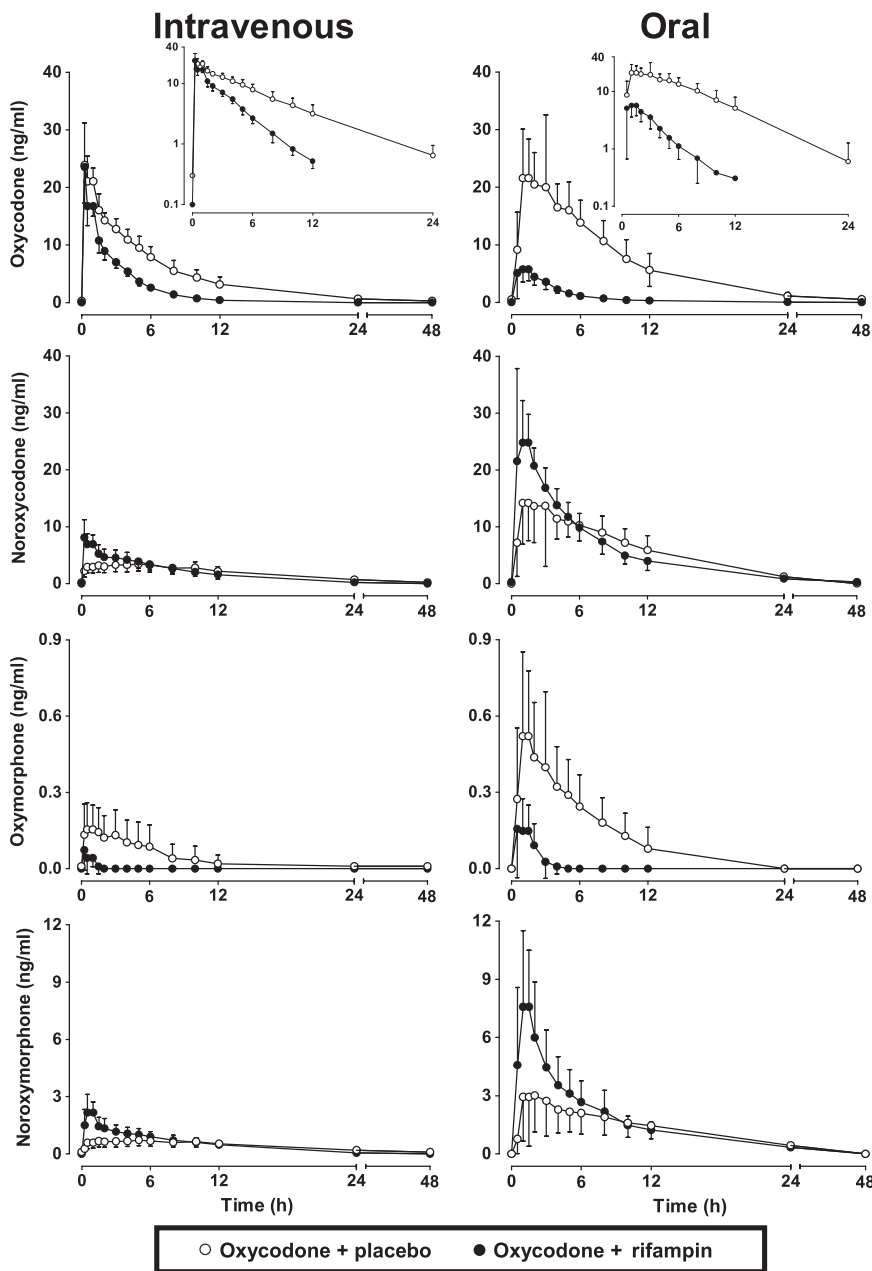
### Pharmacokinetic Analysis

The peak plasma concentrations ( $C_{\text{max}}$ ) and corresponding  $C_{\text{max}}$  times ( $t_{\text{max}}$ ) 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 ( $\text{AUC}_{0-\infty}$ ). 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 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 intravenous administration of oxycodone, plasma clearance (Cl) and steady state volume of distribution ( $V_{\text{ss}}$ ) of oxycodone were calculated by use of noncompartmental methods based on statistical moment theory. The oral bioavailability of oxycodone (F) was calculated as follows:  $F = [\text{AUC}_{0-\infty \text{ oral}} \cdot \text{Dose}_{\text{intravenous}}] / [\text{AUC}_{0-\infty \text{ intravenous}} \cdot \text{Dose}_{\text{oral}}]$ . After oral administration of oxycodone, we calculated the apparent clearance (Cl/F) and the apparent volume of distribution of oxycodone during elimination ( $V_z/F$ ). The pharmacokinetic data were analyzed using the WinNonlin pharmacokinetic program (version 4.1; Pharsight, Mountain View, CA). The metabolite-to-parent drug AUC ratios were calculated as indexes of metabolism through different metabolic pathways.

### Analysis of Pharmacologic Effects

Subjective effects of oxycodone were recorded with 100-mm visual analog scales from the following items:



**Fig. 2.** Plasma concentrations (mean  $\pm$  SD) of oxycodone and its metabolites in 12 volunteers following intravenous administration of 0.1 mg/kg and oral administration of 15 mg oxycodone hydrochloride after placebo or rifampin. The volunteers were given in randomized order either 600 mg oral rifampin or placebo once daily at 8 PM for 7 days. Oxycodone was given on day 6 at 8 AM, 12 h after the fifth dose of rifampin or placebo. Two more doses of rifampin or placebo were given on days 6 and 7. The oxycodone concentrations are shown both on an arithmetic and on a semilogarithmic plot (*inset*).

alert-drowsy, very good performance-very poor performance, no effects of the drug-very strong effects of the drug, unpleasant feeling-pleasant feeling.<sup>22</sup> The Maddox wing test was used to measure the effects of oxycodone on the coordination of extraocular muscles. The result was given in diopters.<sup>23</sup> The digit symbol substitution test was used to measure both cognitive and motor functions by recording the number of correct symbols substituted in 3 min.<sup>24</sup> Pupil diameter was measured using a Cogan pupillometer under stable lighting conditions.<sup>25</sup> These tests were performed before and 1, 2, 3, 4, 5, 6, 8, 10, and 12 h after the administration oxycodone. For each effect variable, the area under the response-time curve was determined by use of the trapezoidal rule for 12 h ( $AUC_{0-12}$ ).

Sensitivity to tactile stimuli was assessed with von Frey monofilaments (18011 Semmes-Weinstein Aesthesiometer Kit, Stoelting Co., Wood Dale, IL) before the administration of oxycodone and 2 h after dosing. The subject lay comfortably in a supine position with the eyes blindfolded while monofilaments of five strengths (0.23, 0.27, 1.63, 4.00, and 11.8 mN) and a sham filament (no stimulus) were applied to the tip of the right index finger. Each stimulus was randomly applied on the skin eight times at an interval of 5 s. The subjects rated each stimulus on a scale of 0-2 (0 = no stimulus, 1 = a possible stimulus, 2 = a definite stimulus). Tactile threshold was determined before and 2 h after the administration of oxycodone. For the analysis, scores 1 and 2 were pooled together. Tactile threshold was depicted

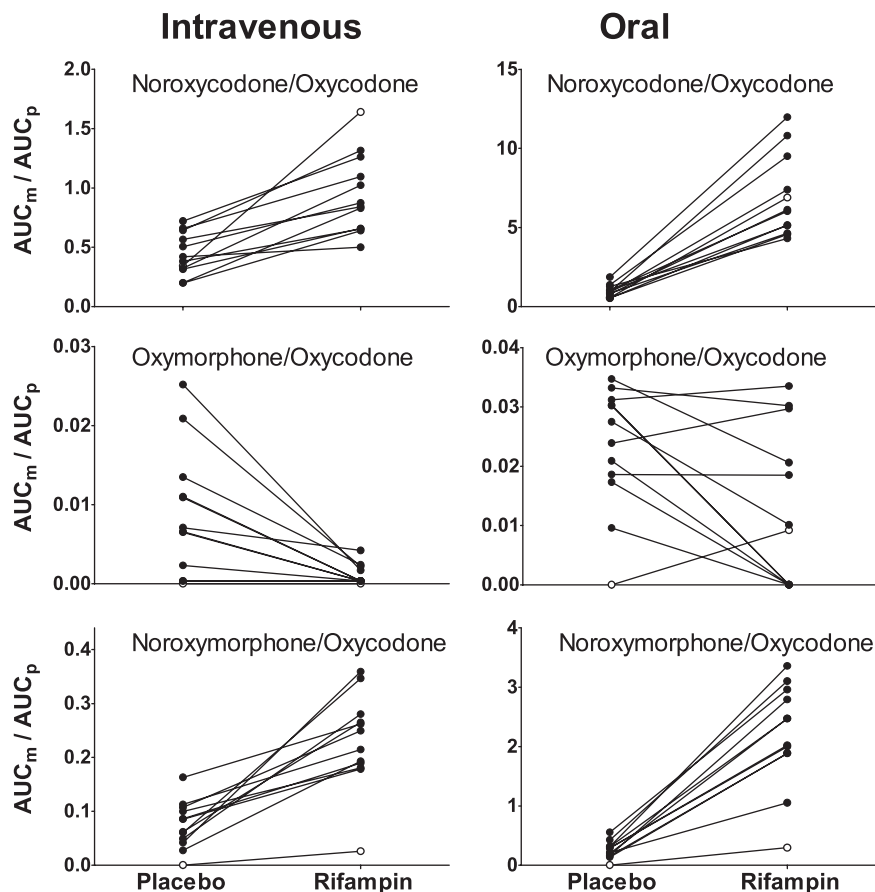


Fig. 3. Individual metabolite-to-parent drug area-under-the-curve (AUC) ratios ( $AUC_m/AUC_p$ ) following intravenous administration of 0.1 mg/kg and oral administration of 15 mg oxycodone hydrochloride after placebo or rifampin. The volunteers were given in randomized order either 600 mg oral rifampin or placebo once daily at 8 PM for 7 days. Oxycodone was given on day 6 at 8 AM, 12 h after the fifth dose of rifampin or placebo. Two more doses of rifampin or placebo were given on days 6 and 7. Each circle represents one subject. The subject with poor metabolism *via* CYP2D6 is depicted with an open circle.

from psychometric curve as the 50% detection rate of stimuli.

Cutaneous heat pain threshold was determined before the administration of and 1 h after the dosing of oxycodone. The thermode site on the skin was the same during both measurement sessions. During each session, cutaneous heat pain threshold was defined as the mean of three measurements, which were performed at 30-s intervals on three adjacent sites on the right forearm to avoid sensitization and hyperalgesia. A feedback-controlled contact thermode (TSA-2; Medoc Inc., Rehovot, Israel) was used to deliver three heat pain stimuli of slowly increasing ( $1^{\circ}\text{C}/\text{s}$ ) temperature on the right volar forearm. The size of the thermode was  $30 \times 30$  mm. Heat increased linearly from a baseline temperature of  $35^{\circ}\text{C}$  until the subject reported the first sensation of pain by pressing a button. This temperature was recorded, and after this, the temperature returned to baseline. The interval between the stimuli was approximately 30 s.

A cold pressor test was used to assess cold pain sensitivity. The subject immersed his or her left hand into ice water (temperature from  $0.5^{\circ}$  to  $2^{\circ}\text{C}$ ) up to the wrist for 1 min. The latency from the immersion to the first sensation of pain (in seconds) was defined as the cold pain threshold. During the immersion, the subject reported the intensity and unpleasantness of cold pain at 30 and 60 s using a numerical rating scale (0 = no pain

or unpleasantness, 100 = maximal pain or unpleasantness). If pain became intolerable, the subject was instructed to withdraw his or her hand from the water. In such case, the intensity and unpleasantness after withdrawal were reported as maximal (100). The cold pressor test was performed before and 1, 2, 3, 4, 5, 6, 8, 10, and 12 h after the dose of oxycodone. The AUC for cold pain was determined by the trapezoidal rule for 0–12 h.

#### Statistical Analysis

The results are expressed as mean  $\pm$  SD. The paired Student *t* test was used, except for  $t_{\text{max}}$ , cutaneous heat pain threshold, and tactile sensitivity. The values for  $t_{\text{max}}$  were compared by the use of Wilcoxon signed rank test. The values for heat pain threshold and tactile sensitivity were compared by use of analysis of variance for repeated measures. The statistical significance level was  $P < 0.05$ . Because pharmacokinetic drug interactions can also be assessed statistically by the same methods that are standard for the investigation of bioequivalence, we calculated geometric mean ratios (rifampin/control) with 90% confidence intervals for the parameter  $AUC_{0-\infty}$  of oxycodone. All data were analyzed by use of the statistical program SYSTAT for Windows (version 10.2; Systat Software, Richmond, CA).

**Table 1. Pharmacokinetic Parameters of Oxycodone and Its Metabolites in Volunteers after Intravenous Administration of Oxycodone Following Placebo (Control) or Oral Rifampin**

Parameter	Control Phase	Rifampin Phase
<b>Oxycodone</b>		
Cl, l/min	0.90 ± 0.16	1.91 ± 0.29*
V <sub>ss</sub> , l	307 ± 57	372 ± 68*
AUC <sub>0-∞</sub> , μg · min · ml <sup>-1</sup>	7.3 ± 1.8	3.3 ± 0.5*
t <sub>1/2</sub> , h	3.7 ± 0.9	2.4 ± 0.5*
<b>Noroxycodone</b>		
C <sub>max</sub> , ng/ml	3.4 ± 1.2	8.4 ± 2.8*
t <sub>1/2</sub> , h	6.7 ± 1.6	4.5 ± 0.6*
t <sub>max</sub> , h	4.0 (0.5–8.0)	0.25 (0.25–1.5)*
AUC <sub>0-∞</sub> , μg · min · ml <sup>-1</sup>	3.1 ± 1.2	3.1 ± 1.0
AUC <sub>m</sub> /AUC <sub>p</sub>	0.44 ± 0.18	0.94 ± 0.34*
<b>Oxymorphone</b>		
C <sub>max</sub> , ng/ml	0.17 ± 0.12	0.07 ± 0.08*
t <sub>max</sub> , h	0.5 (0.25–3.0)	0.25 (0.25–0.25)
AUC <sub>0-∞</sub> , μg · min · ml <sup>-1</sup>	0.065 ± 0.068	0.003 ± 0.005*
AUC <sub>m</sub> /AUC <sub>p</sub>	0.01 ± 0.01	0.001 ± 0.001*
<b>Noroxymorphone</b>		
C <sub>max</sub> , ng/ml	0.7 ± 0.3	2.2 ± 0.9*
t <sub>max</sub> , h	5.0 (0.5–10.0)	0.5 (0.5–1.5)*
t <sub>1/2</sub> , h	12.5 ± 5.6	6.8 ± 1.1*
AUC <sub>0-∞</sub> , μg · min · ml <sup>-1</sup>	0.82 ± 0.33	0.98 ± 0.31
AUC <sub>m</sub> /AUC <sub>p</sub>	0.12 ± 0.06	0.32 ± 0.06*

Twelve volunteers were given in randomized order either 600 mg oral rifampin or placebo once daily at 8:00 PM for 7 days. Oxycodone hydrochloride, 0.1 mg/kg, was given on day 6 at 8:00 AM, 12 h after the fifth dose of rifampin or placebo. Two more doses of rifampin or placebo were given on days 6 and 7. The results are given as mean ± SD, except for t<sub>max</sub> data, which are given as median and range.

\* Significantly different ( $P < 0.05$ ) from control.

AUC<sub>0-∞</sub> = area under the oxycodone, noroxycodone, oxymorphone, or noroxymorphone plasma concentration–time curve; AUC<sub>m</sub>/AUC<sub>p</sub> = metabolite-to–parent drug area under plasma concentration–time curve ratio; Cl = plasma clearance of oxycodone; C<sub>max</sub> = maximum plasma concentration; t<sub>1/2</sub> = elimination half-life; t<sub>max</sub> = time to maximum plasma concentration; V<sub>ss</sub> = steady state volume of distribution.

## Results

Our pharmacokinetic results after placebo are well in line with the previous information on the pharmacokinetics of intravenous and oral oxycodone. Rifampin affected the pharmacokinetics of both intravenously and orally administered oxycodone (figs. 2 and 3, tables 1 and 2). The plasma concentrations of parent oxycodone were greatly decreased, particularly after its oral administration (fig. 2), and also the oxycodone-associated effects were reduced by rifampin.

### Pharmacokinetics of Parent Oxycodone

Rifampin decreased the AUC<sub>0-∞</sub> of intravenous oxycodone by 53%, increased the mean plasma Cl by 2.2-fold, and decreased its t<sub>1/2</sub> from 3.7 to 2.4 h (fig. 2 and table 1). Rifampin decreased the mean AUC<sub>0-∞</sub> and C<sub>max</sub> of oral oxycodone by 86% and 63%, respectively (fig. 2 and table 2). The geometric mean ratios with 90% confidence intervals for AUC<sub>0-∞</sub> (rifampin/control) were 0.47 (0.42–0.52) and 0.14 (0.12–0.16) for intravenous and oral oxycodone, respectively. The mean oral bioavailabil-

**Table 2. Pharmacokinetic Parameters of Oxycodone and Its Metabolites in Volunteers after Oral Administration of Oxycodone Following Placebo (Control) or Oral Rifampin**

Parameter	Control Phase	Rifampin Phase
<b>Oxycodone</b>		
C <sub>max</sub> , ng/ml	26.1 ± 11.0	8.3 ± 2.2*
t <sub>max</sub> , h	1.5 (1.0–5.0)	1.0 (0.5–3.0)*
AUC <sub>0-∞</sub> , μg · min · ml <sup>-1</sup>	10.7 ± 3.4	1.5 ± 0.6*
Cl/F, l/min	1.35 ± 0.36	10.13 ± 3.43*
V <sub>z</sub> /F, l	477 ± 85	2,067 ± 511*
t <sub>1/2</sub> , h	3.8 ± 0.9	2.3 ± 1.3*
F	0.69 ± 0.10	0.21 ± 0.07*
<b>Noroxycodone</b>		
C <sub>max</sub> , ng/ml	17.7 ± 10.10	31.0 ± 8.3*
t <sub>max</sub> , h	1.5 (1.0–5.0)	1.0 (0.5–2.0)*
AUC <sub>0-∞</sub> , μg · min · ml <sup>-1</sup>	9.8 ± 3.4	9.3 ± 2.4
AUC <sub>m</sub> /AUC <sub>p</sub>	0.97 ± 0.39	6.88 ± 2.58*
t <sub>1/2</sub> , h	5.6 ± 1.1	4.3 ± 0.7*
<b>Oxymorphone</b>		
C <sub>max</sub> , ng/ml	0.61 ± 0.34	0.23 ± 0.16*
t <sub>max</sub> , h	1.0 (0.5–5.0)	1.0 (0.5–2.0)
AUC <sub>0-∞</sub> , μg · min · ml <sup>-1</sup>	0.24 ± 0.13	0.02 ± 0.02*
AUC <sub>m</sub> /AUC <sub>p</sub>	0.023 ± 0.010	0.015 ± 0.012
<b>Noroxymorphone</b>		
C <sub>max</sub> , ng/ml	3.9 ± 2.5	8.6 ± 3.6*
t <sub>max</sub> , h	1.5 (1.0–4.0)	1.0 (0.5–2.0)*
AUC <sub>0-∞</sub> , μg · min · ml <sup>-1</sup>	2.39 ± 1.11	2.95 ± 1.08*
AUC <sub>m</sub> /AUC <sub>p</sub>	0.25 ± 0.14	2.19 ± 0.88*
t <sub>1/2</sub> , h	7.8 ± 1.5	6.6 ± 1.0*

Twelve volunteers were given in randomized order either 600 mg of oral rifampin or placebo once daily at 8:00 PM for 7 days. Oxycodone hydrochloride, 15 mg, was given on day 6 at 8:00 AM, 12 h after the fifth dose of rifampin or placebo. Two more doses of rifampin or placebo were given on days 6 and 7. The results are given as mean ± SD, except for t<sub>max</sub> data, which are given as median and range.

\* Significantly different ( $P < 0.05$ ) from control.

AUC<sub>0-∞</sub> = area under oxycodone, noroxycodone, oxymorphone, or noroxymorphone plasma concentration–time curve extrapolated to infinity; AUC<sub>m</sub>/AUC<sub>p</sub> = ratio of AUC<sub>0-∞</sub> of metabolite to that of oxycodone; Cl/F = apparent oral clearance; C<sub>max</sub> = maximum concentration; F = oral bioavailability; t<sub>1/2</sub> = elimination half-life; t<sub>max</sub> = time to maximum concentration; V<sub>z</sub>/F = apparent volume of distribution during elimination.

ity of oxycodone was decreased from 69% to 21% by rifampin. The intervention sequence (placebo–rifampin or rifampin–placebo) had no effect on the observed rifampin-associated changes in the pharmacokinetics of oxycodone.

### Pharmacokinetics of Oxycodone Metabolites

Rifampin increased the C<sub>max</sub> of noroxycodone by 2.7-fold after intravenous oxycodone and by 2.0-fold after oral oxycodone compared with the control values (figs. 2 and 3, tables 1 and 2). The corresponding metabolite-to–parent drug AUC ratios (AUC<sub>m</sub>/AUC<sub>p</sub>) were increased 2.4-fold and 7.6-fold, respectively.

Rifampin reduced the AUC<sub>0-∞</sub> of oxymorphone to approximately 5–10% of the corresponding control value after intravenous and oral administration of oxycodone. Intravenous oxycodone produced no detectable oxymorphone concentrations in two subjects after placebo and in eight subjects after rifampin. After rifampin and

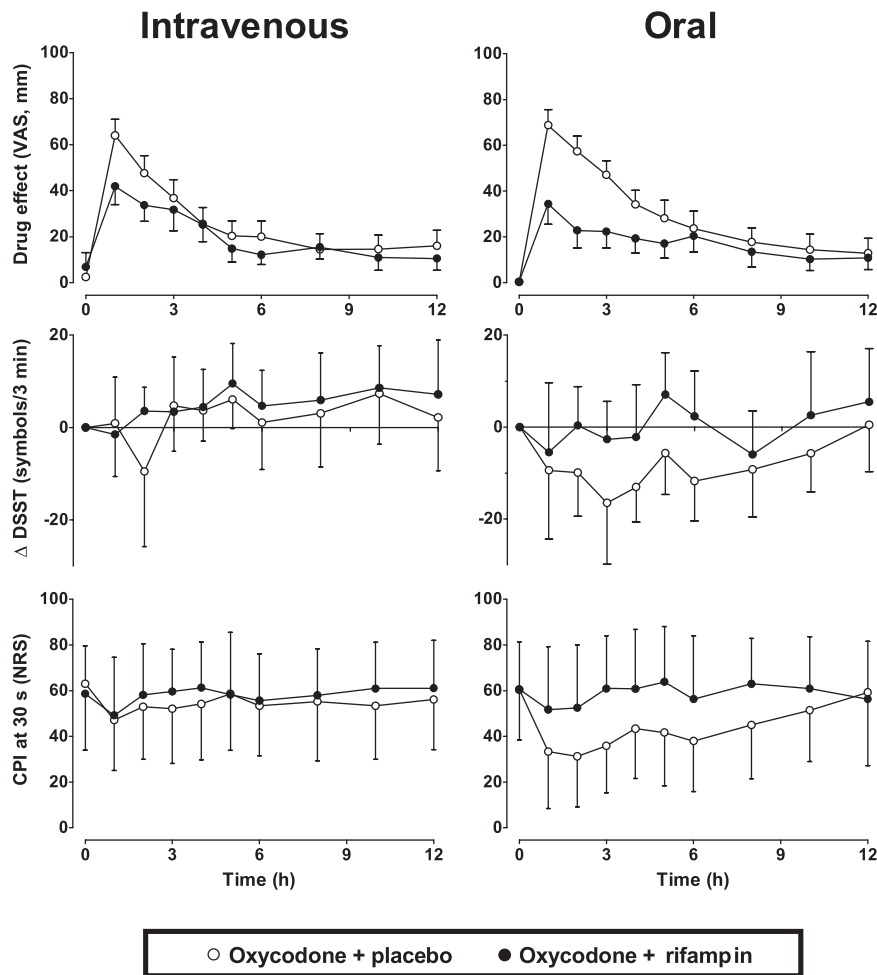


Fig. 4. Mean ( $\pm$ SD) of self-reported drug effect (visual analog scale [VAS]), change from initial value in digit symbol substitution test ( $\Delta$  DSST), and cold pain intensity (CPI) in 30 s following intravenous administration of 0.1 mg/kg and oral administration of 15 mg oxycodone hydrochloride after placebo or rifampin. The volunteers were given in randomized order either 600 mg of oral rifampin or placebo once daily at 8 PM for 7 days. Oxycodone was given on day 6 at 8 AM, 12 h after the fifth dose of rifampin or placebo. Two more doses of rifampin or placebo were given on days 6 and 7.

oral oxycodone, five of the subjects had every measured oxycodone concentration below the lower limit of quantification. Rifampin increased the  $C_{max}$  of noroxycodone more than twofold in both the intravenous and the oral part of the study. The corresponding metabolite-to-parent drug AUC ratios increased 2.4-fold after intravenous and 9.6-fold after oral oxycodone.

#### Pharmacologic Effects

After the oral administration of oxycodone, self-reported drowsiness, drug effect, and deterioration of performance were less pronounced after rifampin than after placebo as judged by  $AUC_{0-12}$ . Rifampin attenuated the miotic effect of intravenous oxycodone and decreased the oxycodone-associated heterotropia after oral oxycodone (fig. 4 and table 3).

Oxycodone decreased cold pain sensitivity after intravenous and oral administration (fig. 4 and table 3). During the control phase, oxycodone increased the heat pain threshold from  $44.9^\circ \pm 2.1^\circ$  to  $46.0^\circ \pm 2.6^\circ$  after oral dosing of oxycodone, and from  $43.9^\circ \pm 1.9^\circ$  to  $45.1^\circ \pm 2.3^\circ$  after intravenous dosing. Rifampin attenuated the increase in  $AUC_{0-12}$  of cold pain threshold, decrease in  $AUC_{0-12}$  of cold pain intensity, and unpleas-

antness after oral but not after intravenous administration of oxycodone.

#### Discussion

Rifampin greatly increased the formation of both CYP3A-dependent metabolites of oxycodone as evidenced by the increased values for metabolite-to-parent drug AUC ratios of noroxycodone and noroxycodone. The changes were more pronounced after oral administration of oxycodone because rifampin increased the first-pass metabolism in the intestinal wall and in the liver and enhanced the elimination of oxycodone. The results are in good agreement with our previous studies on the effect of rifampin on the pharmacokinetics of midazolam,<sup>26</sup> triazolam,<sup>14</sup> and ropivacaine<sup>27</sup> considering the relative contribution of CYP3A in their metabolism.

Another explanation for the observed pharmacokinetic changes especially after oral oxycodone could be the induction of the P-glycoprotein. Rifampin is known to induce P-glycoprotein, which is a membrane efflux transporter found in the intestinal wall and brain capillary endothelium.<sup>28</sup> Several opioids, such as loperamide,<sup>29</sup> alfentanil,<sup>30</sup> fentanyl,<sup>31</sup> morphine,<sup>32</sup> and metha-

**Table 3. Results (Mean ± SD) of the Different Tests Measuring the Effects of Oxycodone**

Pharmacodynamic Test	Intravenous Oxycodone		Oral Oxycodone	
	Control Phase	Rifampin Phase	Control Phase	Rifampin Phase
VAS scale: alert–drowsy, mm · h	585 ± 173	587 ± 242	634 ± 253	734 ± 210*
VAS scale: very good–very poor performance, mm · h	479 ± 154	429 ± 193	586 ± 177	472 ± 232*
VAS scale: no drug effect–very strong effect, mm · h	298 ± 231	229 ± 192	348 ± 211	202 ± 225*
VAS scale: unpleasant–very pleasant feeling, mm · h	825 ± 156	767 ± 182	744 ± 230	780 ± 230
Maddox wing test, diopters · h	91.3 ± 43.6	91.9 ± 47.7	105.5 ± 58.9	92.2 ± 54.5*
Cogan pupillometry, mm · h	40.2 ± 11.9	44.1 ± 13.7*	41.0 ± 13.2	45.0 ± 14.0
DSST, symbols/3 min · h	1,659 ± 205	1,645 ± 249	1,687 ± 213	1,753 ± 201
CPT, s · h	258 ± 182	249 ± 157	402 ± 182	309 ± 186*
CPI 30, NRS units · h	649 ± 248	698 ± 224	523 ± 233	704 ± 265*
CPU 30, NRS units · h	704 ± 199	777 ± 205	574 ± 211	778 ± 195*
CPI 60, NRS units · h	869 ± 207	879 ± 189	710 ± 215	909 ± 194*
CPU 60, NRS units · h	883 ± 170	930 ± 136	763 ± 181	959 ± 137*
Tactile threshold, mN	−0.15 ± 0.50	0.07 ± 0.40	0.04 ± 0.28	0.10 ± 0.29
Heat pain threshold, °C	1.26 ± 1.3	1.32 ± 0.8	1.09 ± 1.42	0.22 ± 0.87

Twelve volunteers were given in randomized order either 600 mg of oral rifampin or placebo once daily at 8:00 PM for 7 days. Oxycodone hydrochloride (0.1 mg/kg intravenously or 15 mg orally) was given on day 6 at 8:00 AM, 12 h after the fifth dose of rifampin or placebo. Two more doses of rifampin or placebo were given on days 6 and 7. Tactile threshold, measured with von Frey filaments, is given as a difference of the values before and 2 h after oxycodone administration. Heat pain threshold is given as a difference of the values before and 1 h after oxycodone. All other variables represent areas under the response–time curves from 0 to 12 h.

\* Significantly different ( $P < 0.05$ ) from control.

CPI 30 = cold pain intensity in 30 s; CPI 60 = cold pain intensity in 60 s; CPT = cold pain threshold; CPU 30 = cold pain unpleasantness in 30 s; CPU 60 = cold pain unpleasantness in 60 s; DSST = digit symbol substitution test; NRS units = numerical rating scale units (numeric value for pain, 0–100); VAS = visual analog scale.

done,<sup>33</sup> are substrates for P-glycoprotein. If oxycodone were a P-glycoprotein substrate, induction of intestinal P-glycoprotein would decrease its oral bioavailability and concentrations. Similarly, induction of brain capillary endothelium P-glycoprotein would decrease oxycodone penetration to the effect site in the brain and decrease its pharmacologic effects. On the basis of animal data, the role of P-glycoprotein in the pharmacokinetics of oxycodone seems to be of minor importance,<sup>34</sup> though this issue is controversial.<sup>35</sup> In humans, quinidine, which is a P-glycoprotein and CYP2D6 inhibitor, did not change the effects of oxycodone.<sup>36</sup>

Inhibition of CYP2D6 by quinidine blocks the production of the active metabolite oxymorphone from oxycodone.<sup>36</sup> Interestingly, in the current study also rifampin seemed to reduce the formation of oxymorphone, as judged by means of the metabolite–to–parent drug AUC ratio. This is logical because rifampin shifted the metabolism of oxycodone toward the CYP3A-mediated route to noroxycodone, and the metabolism of oxymorphone *via* CYP3A was also accelerated. Although some studies have suggested that rifampin may somewhat increase the activity of CYP2D6,<sup>37,38</sup> this enzyme is generally considered not to be inducible.

Oxymorphone has been used in the treatment of post-operative pain,<sup>39</sup> low back pain,<sup>40</sup> and cancer-related pain.<sup>41</sup> Its binding affinity for  $\mu$ -opioid receptors is higher than that of oxycodone.<sup>4</sup> The role of oxymorphone in the analgesic effects of oxycodone, however, has not systematically been investigated.<sup>4,36</sup> In the current study, plasma concentrations of oxymorphone were generally very low,

which is in agreement with the findings of previous studies,<sup>4,36</sup> and five subjects had plasma oxymorphone concentrations below the lower limit of quantification after rifampin and oral oxycodone. Considering these findings and the fact that we assessed the analgesic effect of oxycodone on experimental but not clinical pain, any conclusions about the role of oxymorphone in the analgesic effects of oxycodone would be highly speculative.

Oxycodone increased heat pain threshold and decreased cold pain sensitivity, supporting the findings of previous studies.<sup>42–44</sup> These effects seemed to be pain specific because oxycodone did not affect tactile sensitivity. Pharmacologic effects were not measured until 60 min after oxycodone dosing, which is a limitation of our study because we may have missed differences in the effects of oxycodone especially after intravenous administration. The changes in pupil diameter and behavioral test results were consistent with the well-known clinical effects of opioids. Induction of CYP3A with rifampin decreased oxycodone-induced drowsiness, drug effect, and deterioration of performance, and attenuated oxycodone-induced pain relief in the cold pressor test. These findings are in line with previous clinical observation of poor analgesic effect of oxycodone when used concomitantly with rifampin.<sup>7</sup>

Rifampin is an effective inducer of many CYP enzymes both *in vitro* and in humans.<sup>8</sup> Rifampin induced methadone withdrawal symptoms in 70% of opioid-addicted patients given maintenance therapy with methadone, a substrate of CYP3A and CYP2B6.<sup>9,45</sup> The concomitant administration of rifampin together with oral midazo-

lam<sup>26</sup> and triazolam<sup>14</sup> has resulted in an approximately 95% reduction in the exposure to these hypnotics and a total loss of the hypnotic action. In the current study, the influence of rifampin on the pharmacologic effects of a single dose of oxycodone was rather modest. It is possible that the reduction of opioid effects after rifampin might have been of greater magnitude had we used a protocol with multiple doses of oxycodone.

The interaction of orally administered oxycodone with rifampin is clearly of clinical significance. It is reasonable to assume that other strong inducers of CYP3A, such as carbamazepine and phenobarbital, may also substantially reduce the therapeutic effect of oxycodone. Because the concomitant use of rifampin with oxycodone may attenuate its analgesic effect, dose adjustments or a switch to another method of analgesia may be necessary. Discontinuation of rifampin may result in excessive unwanted effects of opioids. Further studies are needed to investigate the possible effect of other CYP3A inducers on the pharmacology of oxycodone in patients.

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