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# The pharmacokinetics and metabolism of oxycodone after intramuscular and oral administration to healthy subjects

R. PÖYHIÄ[1], T. SEPPÄLÄ[2], K. T. OLKKOLA[1,3] & E. KALSO[1]
Departments of [1]Anaesthesia and [3]Clinical Pharmacology, Helsinki University and [2]Department of Biochemistry, National Health Institute, Helsinki, Finland

1 The pharmacokinetics and metabolism of oxycodone were studied in nine healthy young volunteers in a cross-over study. Each subject received oxycodone chloride once intramuscularly (0.14 mg $kg^{-1}$) and twice orally (0.28 mg $kg^{-1}$) at intervals of 2 weeks. A double-blind randomized pretreatment with amitriptyline (10–50 mg a day) or placebo was given prior to oral oxycodone.

2 The concentrations of oxycodone, noroxycodone and oxymorphone in plasma and the 24 h urine recoveries of their conjugated and unconjugated forms were measured by gas chromatography.

3 No differences were found between treatments in mean $C_{max}$ and AUC values of oxycodone which varied from 34 to 38 ng $ml^{-1}$ and from 208 to 245 ng $ml^{-1}$ h, respectively. The median $t_{max}$ of oxycodone was 1 h in all groups. The bioavailability of oral relative to i.m. oxycodone was 60%. The mean renal clearance of oxycodone was 0.07–0.08 l $min^{-1}$. The kinetics of oxycodone were unaffected by amitriptyline.

4 The mean ratio of the AUC(0,24 h) values of unconjugated noroxycodone to oxycodone was 0.45 after i.m. oxycodone and 0.6–0.8 after oral oxycodone. Plasma oxymorphone concentrations were below the limit of the assay. Eight to 14% of the dose of oxycodone was excreted in the urine as unconjugated and conjugated oxycodone over 24 h. Oxymorphone was excreted mainly as a conjugate whereas noroxycodone was recovered mostly in an unconjugated form.

**Keywords** oxycodone oxymorphone noroxycodone amitriptyline intramuscular oral pharmacokinetics metabolism

## Introduction

As an effective alternative to morphine for the treatment of moderate to severe postoperative or cancer pain oxycodone (14-hydroxy-7,8-dihydrocodeinone) has been used both parenterally and orally over 70 years. On a molar basis the analgesic potency of intravenous oxycodone in man is 1.6 times that of morphine (Kalso *et al.*, 1991) and about 10 times that of pethidine (Takki & Tammisto, 1973). Compared with morphine oxycodone has a longer analgesic action (Kalso *et al.*, 1991) which may be due to a slower elimination (Pöyhiä *et al.*, 1991). Oxycodone has a high efficacy not only after parenteral but also after oral administration when it is half as potent (Beaver *et al.*, 1978; Gilman *et al.*, 1985; Kalso & Vainio, 1990). In Finland oxycodone is commonly used intramuscularly for premedication before anaesthesia and for postoperative pain. However, the pharmacokinetics of oxycodone after oral and i.m. administration have not been studied in man.

Part of the analgesic effect of oxycodone has been attributed to active metabolites (Beaver *et al.*, 1978; Kalso *et al.*, 1990). Oxycodone is thought to be metabolized in animals by *N*- and *O*-demethylation and by glucuronidation, but differences exist between species (Ishida *et al.*, 1982). In man there are only few reports on the metabolism of oxycodone. According to Weinstein & Gaylord (1979) and Baselt *et al.* (1978) noroxycodone, free and conjugated oxycodone and oxymorphone are excreted in urine after a single oral dose of oxycodone. The contributions of oxymorphone and noroxycodone to the effects of oxycodone are not known.

We have studied the pharmacokinetics of oxycodone after single intramuscular and oral doses in young healthy volunteers. Because tricyclic antidepressants are commonly used in patients given narcotic analgesics for cancer pain and since they may affect the

Correspondence: Dr Reino Pöyhiä, Department of Anaesthesia, University of Helsinki, Haartmaninkatu 4, SF-00290 Helsinki, Finland

glucuronidation of morphine (Yue *et al.*, 1990), a randomized double-blind pretreatment with amitriptyline and placebo was included in order to study the possible effect of a tricyclic antidepressant on the pharmacokinetics of oxycodone.

## Methods

### *Subjects*

Nine healthy students (five females and four males), aged 21–26 years and weighing 55–78 kg, gave written informed consent and volunteered for the trial. Prior to the study ECG, blood glucose, serum creatinine, serum $Na^+$ and $K^+$, serum GPT and GOT, haemoglobin and haematocrit were found to be normal in all subjects. They were in good physical and mental health and were taking no medicine prior to the study. The study was approved by the Institutional Ethics Committee.

### *Trial design*

The subjects participated in three test sessions at 2-week intervals. They were asked to refrain from coffee, tea and cola beverages for 12 h before each session. During the first session 0.14 mg $kg^{-1}$ of oxycodone hydrochloride ($\approx$ 0.11 mg $kg^{-1}$ of free base, (Oxanest®, Leiras-Huhtamäki Ltd, Helsinki)) was injected (i.m.) into the vastus lateralis muscle. During the following sessions 0.28 mg $kg^{-1}$ of oxycodone chloride ($\approx$ 0.22 mg $kg^{-1}$ free base) was given orally. Prior to the oral administration of oxycodone subjects received oral placebo or amitriptyline in a randomized double-blind order for 4 days. The doses of amitriptyline were 10 mg on day 1, 10 mg + 10 mg on day 2 and 10 mg + 25 mg on day 3, 25 mg + 25 mg on day 4 and 25 mg in the morning 1 h before the session. After the administration of oxycodone the subjects remained supine for 5 h and thereafter a light standard meal was served. For blood sampling an intravenous cannula (Venflon® 2, Viggo, Sweden) was inserted under local anaesthesia into a cubital vein, through which blood was taken before administration of oxycodone and thereafter at 15, 30, 45 and 60 min and 1.5, 2, 3, 4, 6, 8, 12 and 24 h. Blood was collected into heparinized, ice-chilled tubes and centrifuged immediately at 3500 rev $min^{-1}$ for 10 min. Plasma was separated and stored at −70° C until analyzed. Urine was collected for 24 h and stored at −70° C pending analysis.

### *Assay of oxycodone, noroxycodone and oxymorphone*

Plasma oxycodone concentrations were measured by gas chromatography as described by Kalso *et al.* (1990). The lower assay limit of the method was 3 ng $ml^{-1}$ and the intraday coefficient of variation (CV) was 7% (52 ng $ml^{-1}$, $n = 10$). Plasma noroxycodone was measured as a heptafluorobutyric acid anhydride derivative as described by Weinstein & Gaylord (1979) with the following modifications. Toluene was used for extraction and flurazepam served as internal standard. The limit of quantification was 1 ng $ml^{-1}$ and the intraday variation % CV was 8% (30 ng $ml^{-1}$, $n = 7$).

Plasma oxymorphone was assayed by h.p.l.c. with electrochemical detection. Plasma (1 ml) was extracted with 5 ml butylacetic acid and 1 ml 0.5 M NaOH containing naltrexone as internal standard. After mixing and centrifuging the organic layer was transferred to another test tube, mixed and centrifuged with 75 µl 0.1 M perchloric acid. 50 µl of the acid layer was injected into the h.p.l.c. (Kontron pump 420, Tegmenta ag, Switzerland). Separation was achieved isocratically at room temperature using a 100 × 3.2 mm Velosep RP-18 (Brownlee Labs, USA; 3 µm) column and a mobile phase (pH 3.4, 1.5 ml $min^{-1}$) which consisted of 15% (v/v) acetonitrile and 0.05 M monochloracetic acid, 0.005 M heptanesulphonic acid and 0.005 M tetraethylamine. A coulometric detector with a dual electrode (Esa Coulochem Model 5100 A) was used with upstream oxidation at 0.2 V and downstream oxidation of the eluate at 0.5 V. The assay limit was 0.5 ng $ml^{-1}$ and the CV % was less than 5% at 2.2 ng $ml^{-1}$ ($n = 8$).

Urine samples were analyzed both directly (unconjugated oxycodone and its metabolites) and after a 20 h incubation at 37° C with β-glucuronidase (*Helix pomatia* Juice, IBF Biotechnics, France) and 50% v/v acetic acid (conjugation products).

### *Pharmacokinetic analysis*

Peak plasma concentrations ($C_{max}$) and peak times ($t_{max}$) of oxycodone were noted directly from the data. The elimination rate constant ($\lambda_z$) was determined by linear regression of the terminal log-linear data. Hence, the terminal elimination half-life ($t_{½,z}$) was calculated from $\ln 2/\lambda_z$. Assuming that the i.m. dose was 100% bioavailable, the systemic clearance of oxycodone was calculated from $Dose_{im}/AUC_{im}$, and oral availability from $AUC_{oral}/AUC_{im}$, normalized for dose. AUC values were calculated using the linear trapezoidal rule for increasing drug concentrations, and the logarithmic trapezoidal rule for post-peak concentrations. Extrapolation to infinity was done using the last observed value divided by $\lambda_z$. The ratio of AUC(0, 24 h) values of noroxycodone and oxycodone was calculated to assess the effect of the mode of administration on the production of the noroxycodone metabolite. The relative availability of the two oral doses was calculated from the ratio of AUC values.

The urinary recoveries of unconjugated and conjugated oxycodone, noroxycodone and oxymorphone were calculated. Renal clearance values ($CL_R$) of unconjugated oxycodone and unconjugated noroxycodone were calculated from the 24 h urine recovery divided by AUC(0,24 h).

### *Statistical analysis*

The pharmacokinetic parameters and the urinary recoveries after the different treatments were compared by analysis of variance for repeated measurements (ANOVA). Where significant differences were disclosed ($P < 0.05$), Student's *t*-test for paired data was used to compare the i.m. and oral values. Renal clearances of oxycodone and noroxycodone were compared using Student's *t*-test for paired data. Data are presented as mean values with standard deviations.

Kruskal-Wallis analysis of variance was used to compare $t_{max}$ values, which are presented as median values with range.

## Results

The mean pharmacokinetic parameters of oxycodone after i.m. and oral administration are shown in Table 1. $C_{max}$, $t_{max}$ and AUC values were similar after all treatments. Allowing for the difference in i.m. and oral dosage the oral bioavailability was 60%. $t_{½,z}$ values were independent of dose. Significantly ($P < 0.01$) more noroxycodone was found in plasma after oral compared with i.m. administration (Figure 1 and Table 1). The renal clearances of oxycodone and noroxycodone were independent of route of administration. The $CL_R$ of noroxycodone was significantly ($P < 0.01$) higher than that of oxycodone. Plasma concentrations of oxymorphone were below the limit of assay. Oxycodone and noroxycodone kinetics were unaffected by amitriptyline pretreatment.

Concentrations of conjugated oxycodone and noroxycodone could not be assayed in eight of the urine samples because of interfering peaks in the chromatograms. Measurement of unchanged oxycodone, noroxycodone and oxymorphone was possible in all samples. The 24 h urinary recovery of unconjugated oxycodone was 8.4 ± 2.7% (mean ± s.d.) of the i.m. dose, 5.5 ± 2.5% of the oral dose after pretreatment with placebo and 6.1 ± 2.1% of the oral dose after pretreatment with amitriptyline (NS). Corresponding recoveries of conjugated oxycodone were 5.6 ± 3.4%,

**Table 1** Pharmacokinetic parameters of oxycodone (OX) and noroxycodone (NOR) after 0.14 mg $kg^{-1}$ of oxycodone chloride i.m. and 0.28 mg $kg^{-1}$ of oxycodone chloride orally (p.o.) in nine healthy volunteers pretreated with placebo or amitriptyline (ami). $t_{max}$ values are expressed as medians with ranges; other parameters are expressed as mean values with s.d. Statistically significant differences between i.m. and oral routes are marked as follows: $^{x}P < 0.05$, $^{y}P < 0.01$

| | | *Treatment* | | |
|---|---|---|---|---|
| *Parameter* | *i.m.* | *p.o. (+ placebo)* | *p.o. (+ ami)* | F-*test* |
| a) *Oxycodone* | | | | |
| $C_{max}$ (ng $ml^{-1}$) | 34 ± 10 | 38 ± 14 | 35 ± 9 | NS |
| $t_{max}$ (h) | 1.0 (0.5–1.5) | 1.0 (0.5–1) | 1.0 (0.5–4) | |
| AUC (ng $ml^{-1}$ h) | 208 ± 49 | 245 ± 84 | 240 ± 52 | NS |
| $t_{½,z}$ (h) | 4.89 ± 0.77 | 5.12 ± 1.65 | 4.65 ± 1.58 | NS |
| CL (l $min^{-1}$) | 0.78 ± 0.2 | | | |
| $CL_R$ (l $min^{-1}$) | 0.07 ± 0.02 | 0.08 ± 0.03 | 0.08 ± 0.03 | NS |
| Bioavailability | 1* | 0.60 ± 0.20† | 0.59 ± 0.12† | |
| b) *Noroxycodone* | | | | |
| $C_{max}$ (ng $ml^{-1}$) | 4 ± 0.87 | 14.78 ± 6.69$^{y}$ | 14.33 ± 6.36$^{y}$ | < 0.001 |
| $t_{max}$ (h) | 1.75 (0.75–5) | 0.75 (0.25–2) | 1.5 (0.5–3) | |
| AUC(0, 24) ratio NOR to OX | 0.45 ± 0.23 | 0.64 ± 0.24$^{x}$ | 0.78 ± 0.41$^{y}$ | < 0.001 |
| $CL_R$ | 0.19 ± 0.08 | 0.34 ± 0.19 | 0.19 ± 0.09 | NS |

* assumed.
† relative to i.m.

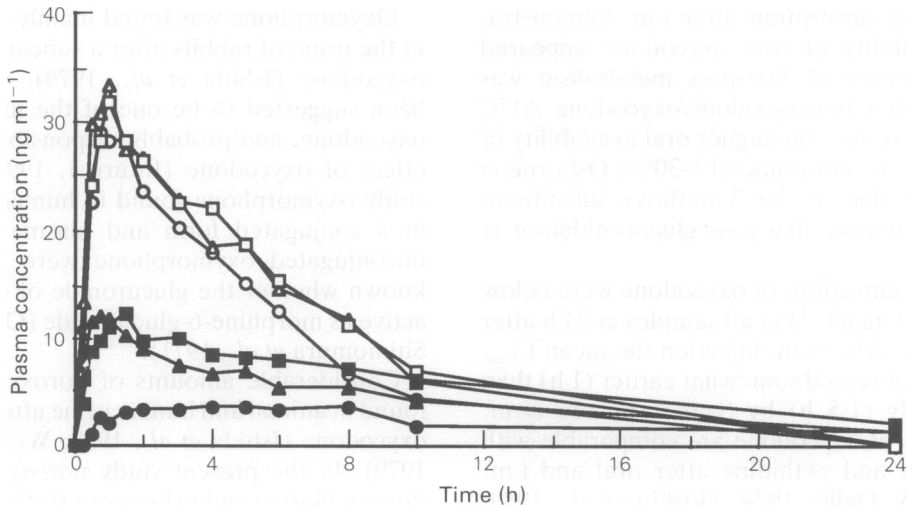


**Figure 1** Mean (± s.d.) plasma concentrations of oxycodone (OX) and noroxycodone (NOR) after 0.14 mg $kg^{-1}$ of oxycodone chloride i.m. and 0.28 mg $kg^{-1}$ of oxycodone chloride orally in nine healthy volunteers pretreated with placebo or amitriptyline (ami). ○ OX i.m, △ OX orally + placebo, □ OX orally + ami, ● NOR i.m., ▲ NOR orally + placebo, ■ NOR orally + ami.

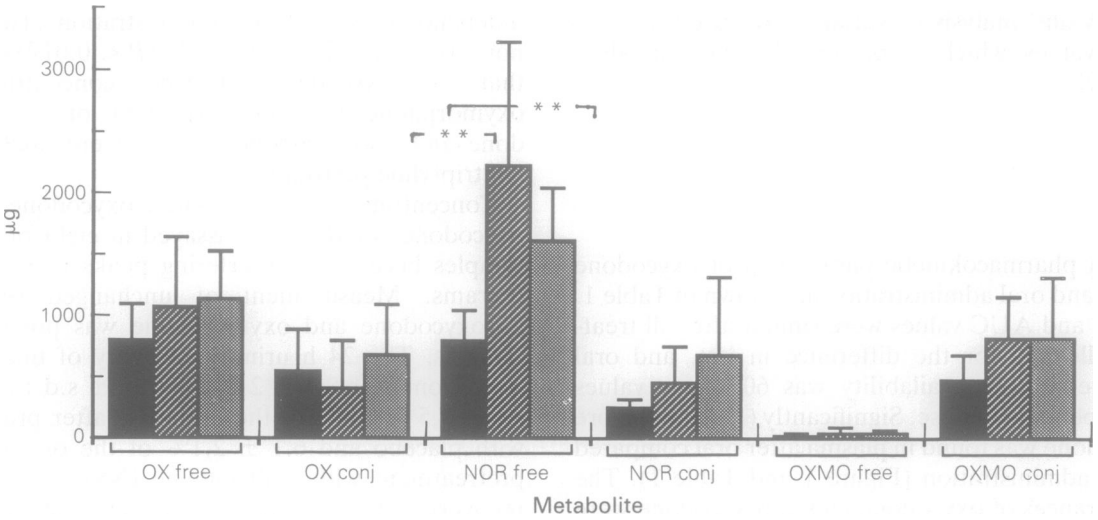


**Figure 2** 24 h excretion (mean ± s.d.) of unconjugated (free) and conjugated (conj) oxycodone (OX), noroxycodone (NOR) and oxymorphone (OXMO) after 0.14 mg $kg^{-1}$ of oxycodone chloride i.m. (■) and 0.28 mg $kg^{-1}$ oxycodone chloride orally (p.o.) in nine healthy volunteers pretreated with placebo (▨) or amitriptyline (ami, □). Significantly ($P < 0.01$) more unconjugated than conjugated noroxycodone and conjugated than unconjugated oxymorphone was excreted. Statistically significant differences between i.m. and oral routes are marked as follows: $^{**}P < 0.01$.

2.3 ± 5.5% and 3.5 ± 1.7%, respectively. Noroxycodone was found mostly in unconjugated form and oxymorphone as conjugated material in urine (Figure 2). The excretion of noroxycodone was significantly ($P < 0.01$) increased after oral administration of oxycodone compared with i.m. administration. Amitriptyline did not affect the excretion of oxycodone or its metabolites.

At the end of two sessions one of the volunteers received dehydrobenzperidole (1.25 mg intramuscularly) with metoclopramide (10 mg orally) and once metoclopramide (20 mg intramuscularly) with cyclizine (75 mg orally) for nausea and vomiting. Other participants did not have any significant side effects and they did not receive any medication.

## Discussion

Assuming complete absorption after i.m. administration the bioavailability of oral oxycodone appeared to be 60%. A degree of first-pass metabolism was indicated by a higher noroxycodone/oxycodone AUC ratio after the oral route. The higher oral availability of oxycodone relative to morphine (19–30%; Osborne *et al.*, 1990) may be due to the 3-methoxy substituent which prevents extensive first-pass glucuronidation at this position.

The plasma concentrations of oxycodone were below the limit of assay (3 ng $ml^{-1}$) in all samples at 24 h after the drug was given. After i.m. injection the mean $C_{max}$ of oxycodone was observed somewhat earlier (1 h) than reported previously (1.5 h) by Saarialho-Kere *et al.* (1989). $t_{max}$ values of oxycodone are comparable with those of morphine and pethidine after oral and i.m. injection (Brunk & Delle, 1974; Hoskin *et al.*, 1989; Laitinen *et al.*, 1975; Mather & Tucker, 1975; Mather *et al.*, 1975; Osborne *et al.*, 1990; Stanski *et al.*, 1978). The clearance of oxycodone observed in this study was similar to that in surgical patients given oxycodone i.v. (Pöyhiä *et al.*, 1991). A somewhat longer $t_{1/2,z}$ of oxycodone after i.m. and oral administration (4.9–5.1 h) compared with that after i.v. administration ($t_{1/2,z}$ 3.7 h) may be explained by prolonged absorption of a fraction of the dose.

In animals, *O*- and *N*-demethylation, *N*-oxidation and 6-keto reduction have been shown to be the main metabolic pathways of oxycodone (Ishida *et al.*, 1982). Although the 14-OH-group of oxycodone is glucuronidated, this route is not as important in the metabolism of oxycodone as it is for morphine where extensive *O*-glucuronidation occurs at the 3 and 6 positions (Ishida *et al.*, 1982; Säwe *et al.*, 1981). This is supported by the present findings with respect to urinary recovery of free and conjugated oxycodone. In addition, no effect of amitriptyline was seen on the kinetics or metabolism of oxycodone, in contrast to a marked inhibitory effect of amitriptyline on the glucuronidation of morphine observed *in vitro* (Yue *et al.*, 1990).

Oxymorphone was found mainly in conjugated form in the urine of rabbits after a subcutaneous injection of oxycodone (Ishida *et al.*, 1979). Oxymorphone has been suggested to be one of the main metabolites of oxycodone, and probably responsible for the analgesic effect of oxycodone (Inturrisi, 1990). In the present study oxymorphone found in human urine was mostly in a conjugated form and plasma concentrations of unconjugated oxymorphone were neglible. It is not known whether the glucuronide of oxymorphone is as active as morphine-6-glucuronide (Osborne *et al.*, 1988; Shimomura *et al.*, 1971).

Considerable amounts of noroxycodone have been found in animal and human urine after administration of oxycodone (Ishida *et al.*, 1982; Weinstein & Gaylord, 1979). In the present study noroxycodone concentrations in plasma and urine were significantly higher after oral than i.m. administration of oxycodone suggesting a prominent role of *N*-dealkylation in the first-pass metabolism of oxycodone.

The $CL_R$ of oxycodone was similar to that of morphine ($\approx 0.1$ l min$^{-1}$; Gare & Walsh, 1991). It was independent of the route of administration of oxycodone and of pretreatment with amitriptyline.

In conclusion, these data suggest that oxycodone is extensively *N*-dealkylated during the first-pass and its oral bioavailability is approximately 60%. Over 24 h 8–14% of the total dose is excreted as free and conjugated oxycodone; noroxycodone is excreted mostly unconjugated and oxymorphone mainly in conjugated form. We detected no effect of amitriptyline on the pharmacokinetics of oxycodone.

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