Oxycodone clearance is markedly reduced with advancing age: a population pharmacokinetic study

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Editor’s key points

- This study analysed the effect of covariates on the pharmacokinetics of i.v. administered oxycodone using non-linear mixed effect modelling.
- The pharmacokinetics of oxycodone were best described by a two-compartmental model.
- The elimination of oxycodone is reduced with advancing age.

Background. Oxycodone is a μ-opioid receptor agonist, the global use of which has increased vigorously during the past decade. The pharmacokinetic data of oxycodone available for elderly are limited, and there appear to be only little data on the population pharmacokinetics of oxycodone.

Methods. We analysed 1272 plasma oxycodone samples of 77 individuals (range of age 19–89 yr) with non-linear mixed effect modelling. Inter- and intra-individual variability of the model was estimated for clearances and distribution volumes. The effect of covariates was studied with simulations.

Results. Data were best described with a two-compartment linear model. Lean body mass and age were found to be significant covariates for elimination clearance and the volume of the central compartment. The population estimates of elimination clearance, volume of the central compartment, and the volume of distribution at steady state for a reference individual (male 35 yr, 70 kg, 170 cm) were 51.0 litre h$^{-1}$, 134, and 258 litres, respectively. The elimination half-life of oxycodone showed an age-dependent increase. The context-sensitive half-time at steady state increased from 3.8 to 4.6 h between the age of 25 and 85 yr, respectively. Simulations of repetitive bolus dosing showed a 20% increase in oxycodone concentration in the elderly.

Conclusions. Age was found to be a significant covariate for oxycodone pharmacokinetics. In elderly patients, dosing should therefore be reduced and carefully titrated to avoid considerable accumulation of oxycodone and potentially hazardous side-effects.

Keywords: analgesics, opioid; intravenous, elderly; oxycodone; population pharmacokinetics

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Oxycodone is a semisynthetic opioid analgesic widely used in the treatment of both acute and chronic pain. Oxycodone is mainly used as an oral preparation but parenteral i.v. or i.m. oxycodone is a good alternative when the oral route is not feasible, for instance, in the immediate postoperative period. 1 2 The pharmacokinetics of oxycodone have been studied quite extensively but primarily from studies in healthy volunteers. Oxycodone is extensively metabolized, mainly by cytochrome P450 (CYP) 3A enzymes, but ~10% of the dose is metabolized by CYP2D6. 3 High individual variation in the pharmacokinetics has been attributed to the activity of these enzymes, which might be caused by genetic polymorphisms, 4 and the effect of enzyme inhibitors and inducers. 5-9

The dosing regimens for i.v. oxycodone are mainly based on studies conducted in young healthy volunteers, and the effects of individual patient covariates are largely unknown. Age, 10 11 gender, 10 12 and organ function 13 14 have been shown to affect the pharmacokinetics of oxycodone, but the findings of these studies are not consistent. Therefore, our aim was to study the population pharmacokinetics of i.v. oxycodone in an adult population covering a broad range of covariates to elucidate their effect on the overall variation in the pharmacokinetics of oxycodone.
Table 1 Summary of the study population. *Dose was given as a short infusion over 2 min. †For the present analysis, we used only the data from the i.v. administration of oxycodone in combination with oral placebo. ‡Knee arthroscopy or knee replacement surgery patients under spinal anaesthesia. F, female; M, male

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of individuals</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>I.V. oxycodone dose*</th>
<th>Sampling period (range)</th>
<th>No. of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nieminen and colleagues†</td>
<td>12 healthy subjects</td>
<td>20–31</td>
<td>F/M</td>
<td>0.1 mg kg⁻¹</td>
<td>15 min–48 h</td>
<td>15</td>
</tr>
<tr>
<td>Saari and colleagues¹</td>
<td>12 healthy subjects</td>
<td>22–39</td>
<td>F/M</td>
<td>0.1 mg kg⁻¹</td>
<td>15 min–48 h</td>
<td>15</td>
</tr>
<tr>
<td>Grönlund and colleagues⁵</td>
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<td>19–30</td>
<td>F/M</td>
<td>0.1 mg kg⁻¹</td>
<td>15 min–48 h</td>
<td>15</td>
</tr>
<tr>
<td>Liukas and colleagues¹⁰</td>
<td>41 patients</td>
<td>19–89</td>
<td></td>
<td>5 mg</td>
<td>5 min–24 h</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 2 Subject characteristics of the study population. CYP2D6, cytochrome P450 2D6; UM, ultrarapid metabolizer; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; LBM, lean body mass, Data are reported as number or as median (range)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (women/men)</td>
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</tr>
<tr>
<td>ASA physical status</td>
<td>47/17/11/2</td>
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<tr>
<td>CYP2D6 genotype (UM/EM/IM/PM)</td>
<td>2/66/4/5</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>29 (19–89)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73 (52–110)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 (148–189)</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>24.9 (18.3–33.5)</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>51.7 (40.5–75.3)</td>
</tr>
</tbody>
</table>

Methods

We pooled the data of 77 subjects receiving i.v. oxycodone from four previously conducted studies. Details of the individual studies are presented in Table 1 and the patient characteristic data of the subjects are presented in Table 2. The study protocols were approved by the ethics committee of the Hospital District of Southwest Finland and by the Finnish National Agency for Medicines, and they were registered in the EudraCT clinical trials register. The original studies were conducted in accordance with the latest version of the Declaration of Helsinki (amendment by the 52nd WMA General Assembly, Edinburgh, UK, October 2000). Written informed consent was obtained from all subjects and patients in all four studies. All oxycodone plasma concentrations from 1272 venous blood samples were analysed in the same laboratory with the liquid chromatography-tandem mass spectrometric (LC-MS/MS) method as described previously. There were three concentration values below the limit of quantification (0.1 ng ml⁻¹), and these values were omitted from the data set.

Non-linear mixed-effects modelling was performed using NONMEM (Version 7.1.2, ICON Development solutions, Ellicot City, MD, USA) driven by PLTTools graphical software (version 3.4.0, www.PLTsoft.com). The first-order conditional estimation method with interaction was used to fit the data throughout the analysis. The variability of the pharmacokinetic parameters was estimated using a log-normal model. For the i^th^ individual:

\[ \theta_i = \theta_{POP} \times e^{\eta_i} \]

in which \( \theta_i \) is the individual value of the parameter \( \theta \), \( \theta_{POP} \) the population value of this parameter, and \( \eta_i \) is a random variable with mean zero and variance \( \sigma^2_\eta \). For the intraindividual variability describing the residual errors, a mixed additive and constant coefficient of variation model was used:

\[ c_{ij} = c_{ij} \times (1 + \epsilon_{1ij}) + \epsilon_{2ij} \]

in which \( c_{ij} \) is the j^th^ measured concentration of the i^th^ individual, \( c_{ij} \) the corresponding predicted concentration and \( \epsilon_{1ij} \) and \( \epsilon_{2ij} \) are the random variables with mean zero and variances \( \sigma^2_1 \) and \( \sigma^2_2 \).

A basic structural model was determined first, and two- and three-compartment models with first-order elimination were fitted to the data to choose the model. Estimated parameters were volumes of distribution, and elimination and intercompartmental clearances (subroutines ADVAN3, ADVAN11, TRANS4). Interindividual variability was incorporated to the model and the structure of the residual error model was determined. The individual Bayesian estimates of the pharmacokinetic parameters were plotted independently against the following covariates: age, gender, weight, height, BMI, lean body mass (LBM), CYP2D6 genotype, presence of CYP3A/2D6 inhibitors/inducers in the medication, glomerular filtration rate (GFR), ASA classification status, serum urea, serum alanine amino transferase, serum alkaline phosphatase, serum aspartate aminotransferase, and urine creatinine. GFR was estimated by the modification of diet in renal disease study formula:

\[ GFR = 186 \times (\text{creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \]

LBM was estimated by James equation:

\[ \text{LBM in males} = 1.10 \times \text{WT} - 120 \times \left(\frac{\text{HT}}{\text{WT}}\right)^2 \]

\[ \text{LBM in females} = 1.07 \times \text{WT} - 148 \times \left(\frac{\text{WT}}{\text{HT}}\right)^2 \]
Linear regression analysis was used as a first test to covariate effects. Subsequently, selected covariates were incorporated to the basic structural model using linear relationships with centering around mean value of the covariate within the population:

\[ u_{\text{POP}} = u_{\text{TV}} + u_{\text{COV}} \times \left[ \text{Cov} - \text{mean(Cov)} \right] \]

in which \( u_{\text{TV}} \) is the typical value of the parameter. In addition to linear models, we also tested power and allometric models. The covariate parameter was included in the model, if the decrease in the NONMEM objective function value (\( \Delta \text{OFV} \)) was at least 3.84 (\( P < 0.05 \)) and the 95% confidence interval of the additional parameter (estimated \( +1.96 \times \text{SE} \)) did not include zero.

Model selection was based on a visual inspection of goodness-of-fit plots [measured concentrations (\( C_p \)) vs population (\( \text{PRED} \)) and individual predictions (\( \text{IPRED} \)), conditional weighted residuals (\( \text{CWRES} \)) vs \( \text{PRED} \), and \( \text{CWRES} \) vs time after administration]. Prediction error (PE) was used to assess the goodness of fit. This was defined as: \( \left| (C_p - \text{PRED} \text{ or IPRED}) / \text{IPRED} \text{ or PRED} \right| \times 100\% \). Both median PE (MDPE) and median absolute PE (MDAPE) were calculated. Visual predictive checks were performed to evaluate the predictability of the model. This was performed by simulating 1000 data sets. Using the final model and the original data set, bootstrap resampling analysis with 1000 replicates (by subject with replacement) was conducted for validation of the model and to obtain non-parametric confidence intervals of the final population model parameters.

To estimate the effect of covariates on the pharmacokinetics of oxycodone, we performed several simulations. A bolus dosing with 5 mg of i.v. oxycodone followed by repeated doses of 3 mg of i.v. oxycodone (at 30, 60, 120, 180, and 240 min) was simulated using the estimated pharmacokinetic parameters of the final model. The dosing regimen which may be seen as typical for the postoperative use of oxycodone in the immediate postoperative care was based on a previous clinical trial. We further calculated the time for a 50% decrease in concentration after continuous infusion (context-sensitive half-time).

### Results

Based on the concentration–time curves of the original data, a two-compartment and a three-compartment model were tested, since it seemed that the elimination phase showed...
at least a two-phase behaviour. The objective function value for a three-compartment model was better ($\Delta$OFV = -31), but NONMEM could not determine the covariance matrix. There was bias in the residual plots and we could not obtain stable estimates for the three-compartment model. Therefore, a two-compartment model with first-order elimination was chosen, particularly as the residual plots with this model did not show any systematic bias for the terminal elimination phase.

The individual Bayesian pharmacokinetic estimates showed that age, body weight, kidney function (as measured with GFR), and CYP2D6 genotype had an influence on the elimination clearance and the volume of the central compartment. The effect of weight on the elimination clearance was best modelled with a linear additive model, when LBM was incorporated to the model ($\Delta$OFV = -16). A power model and proportional models were also tested, but the resulting fit was poorer ($\Delta$OFV = +36.7 for the power model, and $\Delta$OFV = +71.1 for the proportional model). At the next step, renal function, which was estimated by the GFR, was incorporated to the elimination clearance ($\Delta$OFV = -6.5). Since the formula for GFR incorporates the effect of age and sex, we tested separately the effect of these covariates on the model. Sex did not improve the fit, but age appeared to be superior to the GFR ($\Delta$OFV = -12.5). Finally, incorporation of LBM into the $V_1$ improved the fit significantly ($\Delta$OFV = -30.5). There was a trend of subjects carrying a CYP2D6*4/*4 genotype to have lower elimination clearance than those with other genotypes. However, when incorporated into the model, the improvement in the fit by this effect was not statistically significant, and it was discarded.

Fig 1 (a) Goodness of fit plots for the final population model. Measured vs predicted oxycodone concentrations for the individual empirical Bayes estimates (left) and the population model (right). MDPE, median prediction error; MDAPE, median absolute prediction error. The line of identity is plotted in green. (b) CWRES vs time and predicted plasma oxycodone levels, respectively.
Table 3 shows the population pharmacokinetic parameter estimates of the final model.

Pharmacokinetic parameters were estimated with a reasonable precision (Table 3). Elimination clearance and the volumes of the compartments could be estimated with the lowest variability, whereas the intercompartmental clearance was the most variable parameter. Interindividual variability was estimated with good precision (Table 3). A good quality of fit was seen between the observed and the population or the individual predicted plasma oxycodone concentrations (Fig. 1A). The PEs were small for both individual and population predictions (MDPE 0.9% and −2.7%, MDAPE 5.9% and 19.1%, respectively), and the CWRES were randomly and homogenously distributed (Fig. 1a).

Bootstrap analysis with 1000 replications were performed to evaluate parameter uncertainty. Median and 95% confidence intervals of these analyses are shown in Table 3, showing a good agreement between the population and the bootstrap parameters. The model predictions were confirmed with the visual predictive check plot (Fig. 2) and there were no apparent deviations between the model and original data.

To illustrate the effect of covariates on the pharmacokinetics of oxycodone (Fig. 3), we performed several simulations for three typical individuals of different ages (Table 4). The chosen values of LBM in these individuals were based on the values in our study populations. The decrease in the elimination clearance of oxycodone with advancing age is reflected in the elimination half-life, which increased with increasing age. Correspondingly, a significant increase in the time needed for a 50% decrease in concentration after continuous infusion of variable length (context-sensitive half-time) was seen in the elderly (Fig. 4A).

The predicted time course after repeated bolus dosing of oxycodone showed that oxycodone may accumulate in the elderly compared with a young adult (Fig. 4B). The predicted peak concentrations were also much higher in the elderly.

Discussion

The plasma concentrations of oxycodone were best described using a two-compartment model with first-order elimination. Previously, one- and two-compartment models have been used to describe the pharmacokinetics of oxycodone. However, different routes of administration were investigated in these studies, which probably accounts for the differences between the models. The pharmacokinetics of i.v. oxycodone in children was best described with a two-compartment model, which is in accordance with our results. We tested the three-compartment model also, but as we did not get stable estimates, this model was discarded. Furthermore, the residual plots with the two-compartment model did not show any systematic bias for the terminal elimination phase which would indicate the need for a third compartment. The plasma concentrations of oxycodone were near the lower limit of quantification at the end of the observation period and a very sensitive method was used. This suggests that it is unlikely that the sampling period was too short to allow identification of a potential third compartment.

Our results demonstrate that the elimination of oxycodone is reduced with advancing age. Changes in oxycodone clearance were also reflected in elimination
half-life, as our simulations show that it was prolonged up to 30% in the elderly. The population values of the pharmacokinetic variables obtained in this study were in accordance with the parameters obtained in earlier studies with healthy subjects and patients.\(^{15 23 24}\) Similarly, the results in the population pharmacokinetic study conducted in children\(^{20}\) were comparable with ours, as the elimination clearance standardized to a 70 kg person using allometric scaling in that study was 55.3 litre h\(^{-1}\) (vs 51.0 litre h\(^{-1}\) with our final model).

The final model could describe the pharmacokinetics of i.v. oxycodone in the given population with satisfactory precision as judged with goodness-of-fit plots. Similarly, the random and homogeneous distribution of CWRES indicate that the error model could describe the variance of the data accurately. The suitability of the final model was further establised by the visual predictive check, which captured the data well.

An age-dependent decrease in the elimination clearance was seen in our results, confirming the results obtained earlier with non-compartmental methods.\(^{10}\) There was also an association of GFR with the population pharmacokinetics of oxycodone, but the model including age was superior and was therefore preferred. Although the influence of GFR probably reflects the ‘physiological’ changes associated with advancing age, one has to consider that GFR was not measured but estimated using a formula including age.\(^{17}\) Also oxidative drug metabolism in the liver may be slightly slowered along with advanced age. However, a recent report found no difference in the pharmacokinetic parameters with advancing age.\(^{11}\) The difference could be related to the differences in the sample populations, since deviant liver or kidney function as judged with laboratory values was an exclusion criteria in the earlier study. Also the study of Villesen and coworkers\(^{11}\) had quite a small sample size with only eight patients (aged 59–86 yr), and no young patients were included, that is, only historical controls were used. The reduced clearance in the present study led to a longer elimination half-life and also to prolonged context-sensitive half-time in the elderly (Table 4, Fig. 4a). Although oxycodone is not commonly used as a continuous infusion, there are clinical situations where this might be relevant. When comparing the typical 85-yr-old with the typical 60-yr-old, it is obvious that the difference in the context-sensitive half-time was relatively small (Fig. 4a). This was caused by the circumstance that LBM and corresponding central volume of distribution and the volume of distribution at steady state were smaller in the 85-yr-old.

We could also demonstrate a relevant age effect for the expected concentration after repeated i.v. dosing of oxycodone (Fig. 4a). The decrease in drug clearance in combination with the smaller central volume of distribution causes an accumulation of oxycodone and higher peak concentrations in the elderly patients which may cause unwanted side-effects. These results suggest that smaller doses and possibly longer dosing intervals should be used in the elderly in the perioperative setting to avoid unwanted drug effects.

It has recently been hypothesized that the differences in the effects of coadministered drugs on the pharmacokinetics of oxycodone are attributable to the genetic polymorphisms in the CYP2D6. The individual estimates of our model suggested the influence of the CYP2D6 genotype on the elimination clearance of oxycodone as the subjects with poor metabolizer genotype displayed a decreased elimination clearance. However, the effect of the CYP2D6 genotype was not incorporated into the model, since the improvement of fit was not statistically significant. This may be due to the use of a single bolus of oxycodone in the original studies. The plasma concentrations of oxymorphone and noroxymorphone were, on the average, too low for pharmacokinetic characterization and the possible effect of the CYP2D6 genotypes on the formation of these CYP2D6-dependent metabolites to be evident. Also, the number of poor metabolizers in our population was quite small for the reliable characterization of the influence of this genotype on the metabolism of oxycodone. Thus, the effect of genetic polymorphisms of CYP2D6 remains to be elucidated in future studies.
Compartmental methods assume instantaneous mixing of the drug in the central compartment which is a simplification of the reality but as the first samples were drawn 5 min after dosing, it is unlikely that this phenomenon caused model misspecification in our study. It has been shown that there is a considerable difference in concentrations between venous and arterial samples during the first moments after administration, and this may cause model misspecification in our study. Intercompartmental clearance describes the transfer of drug from the circulation to the periphery at the early stages of distribution phase, and the imprecision in the estimates for intercompartmental clearance may also be due to a relatively scarce sampling during the initial distribution phase, as in 30 individuals of our study population, the first samples were drawn 15 and 30 min after the bolus dose.

We used a linear relationship between covariates and pharmacokinetic parameters. This model structure may produce irrelevant results (e.g. negative values) when used outside the supporting data patient characteristics and therefore the results of the present model should be extrapolated carefully. However, our simulations (Fig. 3) show that even for extreme values of age and LBM, clearance will still be in a reasonable range.

In conclusion, the mean population values of the pharmacokinetic variables obtained in this study were in accordance with the parameters obtained in earlier studies. However, the influence of age and LBM on the pharmacokinetics of oxycodone should be considered when oxycodone is administered i.v. Dosing based on pharmacokinetic data from healthy young volunteers may lead to excessive accumulation of oxycodone in the elderly and result in potentially hazardous side-effects, if the dose is not reduced and carefully titrated.

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Declaration of interest

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