Population Pharmacokinetics of Piritramide in Surgical Patients

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Background: Piritramide is a synthetic opioid used for postoperative analgesia in several European countries. The authors present a mixed-effects model of its population pharmacokinetics in patients undergoing surgery.

Methods: After institutional approval and informed patient consent was obtained, 29 patients who were classified as American Society of Anesthesiologists physical status I or II and aged 21–82 yr were enrolled in the study. They received 0.2 mg/kg piritramide as an intravenous bolus before anesthesia was induced. Central venous blood samples were drawn for as long as 48 h after administration of the drug. The plasma concentration of piritramide was determined by gas chromatography. The concentration–time data were analyzed by mixed-effects modeling. Target-controlled infusions and intermittent bolus regimens were simulated to identify a regimen suitable for patient-controlled analgesia based on population pharmacokinetics and published pharmacodynamic data.

Results: The pharmacokinetics of piritramide were described adequately by a linear three-compartment model. Patient age and weight were significant covariates. The values of the pharmacokinetic parameters are: $V_1 = 50.5 \text{ L}$, $V_2 = 150 \cdot (1 + 9.32 \cdot 10^{-3} \cdot (\text{age} - 47 \text{ yr}))$, $V_3 = 212 \cdot (1 + 6.37 \cdot 10^{-3} \cdot (\text{age} - 47 \text{ yr}))$, $CL = 0.56 \cdot (1 - 6.14 \cdot 10^{-3} \cdot (\text{age} - 47 \text{ yr})) \text{ L/min}$, $CL_{\text{int}} = 8.25 \cdot (1 + 2.02 \cdot 10^{-2} \cdot \text{(Wt - 74 kg)}) \text{ L/min}$, $CL_{\text{b}} = 0.80 \text{ L/min}$. The age of 47 yr and the weight of 74 kg refer to the median values for these factors in the patients studied. Rapid distribution, slow distribution, and elimination half-lives for the median patient are 0.05, 1.34, and 10.45 h, respectively. The context-sensitive half-time after a 24-h infusion is predicted at 10.5 h in a 75-yr-old patient compared with 7 h for the median patient.

Conclusions: Piritramide is distributed extensively and eliminated slowly. The pharmacokinetic profile of the drug allows for intermittent bolus administration even when constant effect compartment concentrations are desirable, e.g., for PLA. (Key words: Dosing adjustments; NONMEM; patient-controlled analgesia.)

PIRITRAMIDE (Dipidorol; Janssen, Beersel, Belgium), a synthetic opioid analgesic structurally related to meperidine, has been used for postoperative analgesia and sedation in the intensive care unit for more than 30 yr in several European countries. After a single intravenous or intramuscular injection of 15 mg, the originally reported therapeutic dose for postoperative analgesia in adults, pain can be relieved for 4–6 h. In a previous study, we evaluated the pharmacokinetics of piritramide in 10 male patients. In the current study, we used mixed-effects modeling to describe the pharmacokinetics in patients having surgery who were of both genders. There was a wide distribution of ages and weights, and we included the 10 patients described previously. Furthermore, we simulated plasma and effect compartment piritramide concentrations resulting from a computer-controlled infusion and intermittent bolus administration. These simulations were performed to better understand the clinical pharmacokinetics of piritramide (patient-controlled analgesia) and to determine how variability among patient subgroups might affect dosing recommendations.

Methods

Patients

The local ethics committee approved the study, and each patient gave written informed consent. We evalu-
ated 29 patients, including 10 studied previously, who were undergoing minor elective ophthalmologic or otorhinolaryngologic surgery. All patients were classified as American Society of Anesthesiologists physical status I or II based on their medical history and the results of physical examination, laboratory tests (complete blood cell count, blood chemistries [SMA 20]), and an electrocardiogram. None of them lost more than 300 ml blood during surgery.

Study Design

The study was performed as a prospective open-label study. Each patient received benzodiazepines for premedication (either 20 mg temazepam or 1-2 mg flunitrazepam orally the night before and 10 mg diazepam orally 1 hour before induction of anesthesia). After the patients arrived in the anesthesia suite, an electrocardiograph, a pulse oximeter, and a noninvasive blood pressure monitor were attached to the patients. Thereafter an indwelling intravenous cannula for drug administration was placed in a forearm vein. A central venous catheter was inserted into a cubital vein of the contralateral arm and advanced 30-40 cm for intravenous access during the study. All blood samples were taken from this site. Immediately after preoxygenation by mask, the patients received 0.2 mg/kg pritiramide as an intravenous bolus. Before injection; 2, 4, 6, 8, 10, 15, 20, 30, and 45 min; and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h after injection, central venous blood samples were collected into heparin-prepared syringes. The blood samples were centrifuged immediately after collection, and the plasma was stored at -80°C until the assay. Ten minutes after injection of the opioid, anesthesia was induced with 0.3 mg/kg etomidate, which was followed by muscle relaxation with 1 mg/kg succinylcholine after precurarization with 1 mg pancuronium bromide. After endotracheal intubation, anesthesia was maintained with halothane (n = 17), isoflurane (n = 9), or enflurane (n = 1), as indicated clinically (0.75-1.5 minimum alveolar concentration), and with 65% nitrous oxide in oxygen. Two patients underwent conscious sedation with pritramid (0.2 mg/kg intravenous bolus) and droperidol, as clinically indicated.

Analysis of Pritiramide

We determined pritiramide concentrations using a sensitive and selective gas chromatographic assay similar to the method described in detail in another report.

Briefly, pritiramide and a structurally analogous compound serving as an internal standard (R4125, Janssen) were extracted from heparin-prepared plasma samples into n-heptane-isooamylalcohol (98.5/1.5 vol/vol) and, after evaporation, redissolved in 0.05 M sulfuric acid. The acid extract was washed with n-heptane-isooamylalcohol and centrifuged. Thereafter, the pH was adjusted to 10 with 25% ammonia. The extraction with n-heptane-isooamylalcohol was repeated twice, and the organic phases were combined. After evaporation to dryness, the residue was redissolved in 2-propanol. The samples were analyzed by gas chromatography with nitrogen-phosphorus-sensitive detection on a WCOT-fused silica capillary using OV-1 as the stationary phase. The limit of quantitation was 1.5 μg/l, and the assay was linear in the concentration range from 1.5 to 500 μg/l. Accuracy was 0.4-8.3% (relative error), and precision was 3.9-6.7% (coefficient of variation).

Pharmacokinetic Analysis

Two- and three-compartment models were fitted and compared using the Akaike information criterion. Parameters were specified for the models in terms of the volumes of distribution (V1,2; V1,2,3), the elimination clearance (Cl1), and the intercompartmental (distribution) clearance(s) (Cl2, Cl3, Cl4).

A multiplicative model was used to describe the interindividual variability in the pharmacokinetic parameters:

\[ \theta_{(n,i)} = \theta_{(n,m)} (1 + \eta_{(i)}) \]  

where \( \theta_{(n,i)} \) refers to the individual value of the respective pharmacokinetic parameter, \( \theta_{(n,m)} \) is the population mean of the parameter, and \( \eta \) varies randomly between individuals with a mean of zero and a diagonal variance-covariance matrix \( \Omega^2 \).

Because the concentration range covered two orders of magnitude, a multiplicative error model was chosen to model residual variability:

\[ C_{obs} = C_{exp}(1 + \epsilon) \]

where \( C_{obs} \) refers to the observed concentration, \( C_{exp} \), to the concentration predicted based on dose, time, and the individual pharmacokinetic parameters. \( \epsilon \) is normally distributed with a mean of zero and variance \( \sigma^2 \).

Covariates available were type of anesthesia, gender, age, and weight. The parameters were plotted against these covariates for visual inspection. Covariates were added one at a time and were kept in the model if they improved the goodness of the fit, as judged by the likelihood ratio criterion, with \( P < 0.01 \). For age and weight, the influence of covariates was expressed as
deviation per unit of the covariate from the median value in the study population:

\[
\theta_{(i,j)} = \theta_{(i,m)} \left[ 1 + \theta_{(i)} (Cov_{(i)} - Cov_{(median)}) \right]
\]

where \(\theta_{(i,j)}\) refers to the value of the respective pharmacokinetic parameter for the patient, \(\theta_{(i,m)}\) is the population mean of the parameter, \(\theta_{(i)}\) is the deviation from the population mean for one unit of the covariate, \(Cov_{(i)}\) is the individual value of that covariate, and \(Cov_{(median)}\) is the median value of the covariate in the study population. With these parameters, the population mean of the parameter equals the value for the median patient.

We tested for model misspecification by plotting the ratio of the measured and the predicted concentrations against observation time on a logarithmic scale.

We used the program system NONMEM, version IV, with the first-order method for all model fits and empirical Bayesian estimation of the individual parameters.

We used the program RECOV\# to calculate context-sensitive half-times (CST)\# and 50% decrement times of the effect compartment concentration (DTEC\_{50}). Context-sensitive half-time refers to the time it takes, after cessation of an infusion designed to instantaneously obtain and then maintain a certain target concentration in the plasma, to decrease to 50% of this concentration. Fifty percent decrement time of the effect compartment concentration refers to the time it takes, after cessation of an infusion designed to obtain a certain target concentration in the effect compartment as fast as possible without overshoot and then to maintain it, to decrease to 50% of this concentration. The CST can be calculated from the kinetic microconstants, which were determined in this study. Calculation of the DTEC\_{50} (the more important value, because the effect, which is directly related to the concentration in the effect compartment, is targeted when a drug is administered in a clinical setting), requires an additional rate constant, \(k_{50}\). This rate constant governs the speed of equilibration of the effect compartment with the central compartment. All pharmacodynamic parameters used for the simulations (\(k_{50} = 0.041 \text{ min}^{-1}, EC_{50} = 12.1 \mu g/l\) and \(\gamma = 1.9\)) were taken from Kietzmann et al.\# The EC\_{50} used refers to severe pain (using a visual analog score rating of 75 on a scale from 0 [no pain] to 100 [worst imaginable pain]).

Simulations of target-controlled infusions and intermittent bolus applications were performed using STANPUMP\# and IVA-SIM.\#0

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\# The program was written by Steven Shafer, Department of Anesthesiology, Stanford University, Palo Alto, California.

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Results

Of the 29 patients studied, 14 were men and 15 were women. Their ages ranged from 21 to 82 yr (median, 47 yr). Their weights ranged from 49 to 93 kg (median, 74 kg). The total number of observations in these patients was 570. The plasma concentration time course was described best with a three-compartment model. Figure 1 shows the measured plasma concentrations for all patients and the model predictions based on the population mean of the parameters and a plot of the ratio of measured and predicted concentrations based on the individual doses and the mean population parameters versus time on a logarithmic scale. The line drawn at \(y = 1\) represents a perfect prediction.

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**Table 1. Pharmacokinetic Parameters of Piritramide**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Covariates [population mean (% CV)]</th>
<th>Full Model [population mean (% CV)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (L)</td>
<td>50.9 (46)</td>
<td>50.5 (49)</td>
</tr>
<tr>
<td>Central (V&lt;sub&gt;c&lt;/sub&gt;)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapidly equilibrating (V&lt;sub&gt;s&lt;/sub&gt;)</td>
<td>162 (36)</td>
<td></td>
</tr>
<tr>
<td>Slowly equilibrating (V&lt;sub&gt;d&lt;/sub&gt;)</td>
<td>230 (38)</td>
<td></td>
</tr>
<tr>
<td>Clearance (L/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic (Cl&lt;sub&gt;1&lt;/sub&gt;)</td>
<td>0.53 (26)</td>
<td></td>
</tr>
<tr>
<td>Rapid distribution (Cl&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>7.2 (46)</td>
<td></td>
</tr>
<tr>
<td>Slow distribution (Cl&lt;sub&gt;d&lt;/sub&gt;)</td>
<td>0.76 (32)</td>
<td></td>
</tr>
<tr>
<td>Derived parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of distribution at steady state (V&lt;sub&gt;d&lt;/sub&gt;)[L]&lt;sup&gt;*&lt;/sup&gt;</td>
<td>442.9</td>
<td>412.5</td>
</tr>
<tr>
<td>Fractional coefficients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.81</td>
<td>0.79</td>
</tr>
<tr>
<td>B</td>
<td>0.12</td>
<td>0.13</td>
</tr>
<tr>
<td>C</td>
<td>0.07</td>
<td>0.08</td>
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<tr>
<td>Half-lives (h)&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α</td>
<td>0.056</td>
<td>0.048</td>
</tr>
<tr>
<td>β</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>γ</td>
<td>11.9</td>
<td>10.4</td>
</tr>
<tr>
<td>Improvement in −2 log likelihood</td>
<td></td>
<td>57</td>
</tr>
</tbody>
</table>

* Calculated from the values for the median subject (74 kg, 47 yr).

The interindividual variability of the parameters in the population has been expressed as percent coefficient of variation (% CV), which can be obtained by taking the square root of ω<sup>2</sup> and multiplying it by 100. The residual error was 12.7% for the model without covariates and 12.4% for the full model. The residual error under the population model without accounting for unexplained interindividual variability (predictions with structural and fixed effect parameters) was 33.9% for the model without covariates and 29.4% for the model with covariates. The standard errors of the parameter estimates (% of mean) ranged between 5 and 18% for the structural parameters, between 32 and 45% for the parameters relating covariates to structural parameters, and between 32 and 54% for the variance parameters.

Although the objective function of the model was reduced by 57 by the addition of covariates, the residual error under the population model, disregarding unexplained interindividual variability in the parameters, differed by only 4.5% between the model without and the model including covariates (33.9% vs. 29.4%).

Figure 4 depicts the CST and DTEC<sub>50</sub> for patients of different ages. After 24 h of continuous administration, the average CST was 7 h and exceeded that of all other opioids commonly used for anesthesia. Elderly patients will have a considerably prolonged CST (10.5 h for a 75-yr-old patient). Because of the large equilibration half-time to plasma (approximately 17 min), the DTEC<sub>50</sub> is greater than that of the CST for short procedures. The absolute value of the DTEC<sub>50</sub> is 3.3 h for infusions to reach pseudo-steady state lasting less than 1 h.

Figure 5 shows a target-controlled infusion simulated to achieve and maintain an effect compartment concentration of 35 µg/L, which corresponds to 90% of the maximum analgesic effect for severe postoperative pain (visual analog score = 75; range, 0–100).<sup>9</sup> The initial bolus administered, which is based on the volume of distribution at peak effect, V<sub>dpe</sub><sup>11</sup> is shown in the inset.

As is apparent in this plot, the relation between body weight and the size of the initial bolus of piritramide is nonlinear.

The final maintenance rate will be reached after approximately 20 h and equals on average 1.2 mg/h. Failure to adjust for age dependence of clearance results in underprediction or overprediction of less than 15% of the mean target concentration in the adult population.

Figure 6 shows the cumulative doses as determined by target-controlled infusion. With the exception of the initial bolus, the cumulative doses up to 1, 4, 12, and 24 h were similar for adult patients of different ages or weights.

Because piritramide is used frequently in patient-controlled analgesia pumps, an intermittent bolus dosing regimen aimed at achieving and maintaining at least 90% of the maximal analgesic effect for severe pain and increasing the effect compartment concentration by 1 EC<sub>50</sub> with every single bolus was simulated (fig. 7A). The size of the initial and the repetitive bolus doses was 10 and 3.34 mg, respectively. More than 80% of the maximal effect compartment concentration was reached 10 min after an intravenous bolus. Although the plasma...
first-order algorithm was used. High interindividual variability also adversely affects the performance of the first-order method. As shown in figure 1, the individual concentration time courses differed little in the population studied, which translates into relatively minor interindividual variability in the pharmacokinetic parameters. The size of the central volume of distribution, approximately 50 l, appears to be large compared with that of other opioids. The most likely reasons for this difference is the sampling site (arterial vs. central venous) and the

**Discussion**

We evaluated the population pharmacokinetics of the phenylpiperidine opioid piritramide, which is used commonly as a postoperative analgesic in Germany and other European countries.

As with nearly all other opioids, a three-compartment model adequately describes the concentration time course of the substance. Although the application of the first-order algorithm implemented in NONMEM has been criticized in the data rich situation, it performed well in the current analysis. This might be attributed to the structure of the data we examined. Each individual was represented by nearly the same number of samples, excluding unbalanced data as a source of error when the

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Fig. 2. The individual Bayesian estimates of the rapid distribution clearance ($Cl_r$) as a function of weight (dots). The linear relation between $Cl_r$ and weight (line) is estimated by linear regression.

Fig. 3. The individual Bayesian estimates of the peripheral volumes of distribution ($V_p$, $V_q$) and elimination clearance ($Cl_t$) as a function of age (dots). The linear relations between $V_p$, $V_q$, and age, and $Cl_t$ and age (lines) are estimated by linear regression.
large volume of distribution at steady state ($V_{ss}$), which exceeds body weight approximately six times and is one of the largest values reported for opioids, which is quite similar to that of methadone ($6.1 \pm 2.41$ kg). As a consequence, the amount of drug in the body at steady state will be high for a given concentration compared with other opioids.

Elimination clearance is approximately 560 ml/min, which is similar to that for fentanyl. However, because of the high volume of distribution, only a small fraction of the entire amount in the body will be cleared for each unit of time, which translates into long CSTs compared with other phenylpiperidine opioids. Context-sensitive half-times are even longer in elderly persons because of a higher $V_{ss}$ and a lower elimination clearance, leading to a greater amount in the body for a given concentration, which is then eliminated more slowly compared with that in the median patient. As shown in figure 4, the DTEC$_{50}$ considerably exceeds the CST after short-term administration. Because the pseudo-steady-state infusion is simulated with the plasma concentration as a target to obtain the CST and with the effect compartment concentration as a target to obtain the DTEC$_{50}$, the initial bolus doses will be dissimilar. Within the context of well-stirred compartment models, an arbitrary plasma concentration can be reached instantaneously with the injection of a bolus dose equal to the product of a desired target concentration and the volume of distribution of the central compartment ($V_C$). Because the effect compartment can be accessed only through the plasma compartment, this approach is not possible when a certain target concentration is desired in the effect compartment. In this case, the target concentration must be multiplied by the apparent volume of distribution at the time of peak effect ($V_{d,pe}$), when the concentrations are equal in the central and the effect compartment after a bolus dose is given. This volume must always be larger than $V_C$, and the smaller the $k_{co}$ becomes, the larger the difference between $V_C$ and $V_{d,pe}$ will be. When the same target concentrations are aimed for in plasma and in the effect compartment, the respective initial bolus size will be several times larger for small $k_{co}$ drugs when targeting the effect compartment, as is the case with piritramide. Further, for drugs with a small $k_{co}$, the decrease in the effect compartment concentrations considerably lags behind the decrease in the plasma concentrations. Both factors lead to large differences in the CST and the more clinically relevant DTEC$_{50}$ after short ad-

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**Fig. 4.** Context-sensitive half-times and 50% decrement times of the concentration in the effect compartment of piritramide in patients of different ages and weighing 74 kg (the median weight of the population).

**Fig. 5.** Simulation of a target-controlled infusion designed to achieve and maintain an effect compartment concentration of 35 μg/l (90% of the maximum analgesic effect for severe pain) for the median patient (age, 47 yr; weight, 74 kg) and patients of different ages and weights. The initial bolus dose to achieve the target concentration without exceeding those values for different patient weights is shown in the inset.
ministration periods to pseudo-steady state. The differences are less pronounced at times that are longer than the plasma-effect compartment equilibration time after a bolus dose. We were surprised to find a linear relation between the rapid distribution clearance and weight rather than the usual correlation of the central volume of distribution and weight. Furthermore, when we simulated the effect of weight on the bolus size to achieve a predetermined concentration in the effect compartment, we found a nonlinear relation. Therefore, a dosing recommendation on a milligrams-per-kilogram basis would result in greater concentrations than desired in heavier patients.

We used the information in figure 6 to derive a simple and useful dosing recommendation that starts with a 50 kg patient: 7.5 mg + 0.1 mg for every additional kilogram up to 75 kg; beyond that, a fixed dose of 10 mg is recommended regardless of the patient’s body weight. The peripheral volumes of distribution and the elimination clearance depended on patient age. Weight and age were not correlated in our study population. Body composition changes during the physiologic aging process, leading to a decrease in total body water and muscle mass and an increase in total body fat, even when a person’s gross weight does not change. This cannot be compensated for by calculating lean body mass and body fat according to standard formulas, which do not include age as an independent variable. Because piritramide is lipophilic, it will accumulate considerably in fat, leading to apparently increased peripheral volumes of distribution in elderly persons.

We expected to find the age dependence of the elimination clearance. Keeping in mind that the renal clearance is negligible and hepatic plasma flow equals approximately 950 ml/min, the hepatic extraction ratio of the drug should be approximately 0.6. Changes of liver blood flow will alter the clearance of piritramide. Cardiac output, and therefore hepatic perfusion, is thought...
to decrease by approximately 1% per year beyond the age of 30 yr, as long as aging coincides with reduced physical activity, a requirement that is certainly fulfilled in most Western countries. Furthermore, hepatic function per se might be reduced in the elderly.\textsuperscript{15}

Failure to adjust for age dependence of clearance will result in underprediction or overprediction of the target concentration of less than 15% in adults who are aged 25–75 yr. We believe that the magnitude of this effect does not require that the maintenance dose be adjusted for patient age.

Simulations of target-controlled infusions within the therapeutic range allow us to compare immediately the amounts to be administered for a certain constellation of covariates. Although we did not obtain pharmacodynamic data in the current study, we decided to include simulations of computer-controlled infusions to desired effect and effect compartment rather than plasma concentrations.

In a clinical setting, drug doses are calculated to achieve a certain effect rather than a certain concentration. With the exception of effects described by indirect response models, models involving physiologic counterregulation, and models involving tolerance development, a certain effect compartment concentration predicts a corresponding magnitude of effect. Therefore, targeting a certain effect compartment concentration is equivalent to targeting a certain magnitude of effect and is essential to obtain clinically relevant dosing information. Because the simulation time (24 h) is less than the sampling time, we did not have to extrapolate beyond the range of our observations, which has been identified as a potential source of error.\textsuperscript{17} Nevertheless, readers should be aware of two potential problems with the simulations. First, the $k_{eo}$ was taken from another study and might not match the kinetic parameter set and may distort the predictions. However, the $k_{eo}$ was estimated from a venous concentration–time course and the time course of postoperative analgesia during and after a 30-min intravenous infusion of piritramide. Therefore, because the current simulations aimed for analgesic effect compartment concentrations using venous kinetic parameters and a venous $k_{eo}$ for analgesia, we do not consider this to be an important error. Second, the simulations were based on the assumption that piritramide does not have active metabolites. Failure to account for an active metabolite of piritramide would invariably lead to erroneous dosing recommendations. However, because the pharmacodynamic data were well described with a sigmoid $E_{\text{max}}$ model that assumed piritramide as the sole active compound,\textsuperscript{9} and there is no evidence for relevant $\mu$-agonistic metabolites of piritramide or any other phenylpiperidine opioid in the literature, this possibility appears to be very unlikely.

The following points must be made when the results of the simulations are interpreted. The high equilibration half-life of 17 min ($k_{eo} = 0.041 \text{ min}^{-1}$) in addition to a high central volume of distribution requires the administration of a large loading dose to rapidly achieve effective concentrations, making the drug unsuitable for intraoperative use, when rapid termination of drug effect is desired. However, for postoperative pain therapy, this burden turns into an asset. The initial loading dose can be administered as an intravenous bolus and will achieve analgesic concentrations for several hours and avoid toxic (respiratory depressant) concentrations in the effect compartment. This can be inferred directly from the $V_{dlc}$ concept.\textsuperscript{11,14} A small $k_{eo}$ leads to a late peak effect. The later the peak effect, the lower the peak concentration will be in the effect compartment compared with the peak concentration in plasma. Therefore, a small $k_{eo}$ protects the effect compartment from transiently high plasma concentrations after an intravenous bolus dose. As suggested before, this bolus should be adjusted according to patient weight. Thereafter, as judged by the simulation of a computer-controlled infusion and an intermittent bolus scheme, no further corrections regarding weight and age are necessary for pharmacokinetic reasons. This seems to be a paradox when we consider the change of the peripheral volumes of distribution and elimination clearance in the elderly. However, the decreased amount eliminated per unit of time is offset by the increased amount distributed into the peripheral compartments before steady state is reached, leading to similar dosing requirements to achieve the respective target concentration.

The error from this approach will be less than 15% of the desired concentration at any time, and it is easily surpassed by interindividual variability resulting from unidentified causes. This makes the drug simple to use, as long as the $k_{eo}$ is accounted for when additional drug is administered after a bolus dose, which should not occur before 10 min after the most recent injection. The same considerations hold true when the lock-out interval is determined for a patient-controlled analgesia pump.

Because no concentration–effect relation has been established for adverse effects, especially respiratory depression, we cannot calculate the maximum safe concentration and therefore maximal cumulative doses per time interval. However, a suggestion of how to distribute
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a cumulative 24-h dose necessary to achieve and maintain an arbitrary concentration can be inferred from our data. Twenty-five percent of the 24-h dose should be allowed for in the first hour, 40% in the first 4 h, and 65% in the first 12 h.

Whether aging leads to increased sensitivity to opioid-induced analgesia, respiratory depression, or both has not been determined conclusively. Two studies clearly proved increased sensitivity of elderly persons to the electroencephalographic slowing effect of opioids.13,18 No conclusive evidence has been presented so far that elderly persons are more sensitive to the respiratory depressant effects of opioids19,20 or require lower opioid concentrations for pain relief.20 Therefore, we cannot recommend dosing adjustments for pharmacodynamic reasons in the elderly based on unequivocal scientific evidence. This question requires additional studies. In conclusion, piritramide shows favorable pharmacokinetics for intermittent bolus administration when relatively constant effect compartment concentrations are desirable, such as for patient-controlled analgesia. With the exception of the loading dose, which should be corrected for patient weight, no further dose adjustments seem to be necessary. As can be seen from the findings of this study, a statistically significant relation between a parameter and a covariate does not a priori imply dose adjustments for a segment of the population.

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