H YDROMORPHONE is a semisynthetic derivative of morphine regarded as \( \mu \)-selective opioid agonist. Clinical studies demonstrate that hydromorphone is approximately five to seven times as potent as morphine, produces a shorter duration of analgesia, and generates comparable side effects at equianalgesic doses with those of morphine.\(^1,2\) Hydromorphone does not have an active, renally eliminated metabolite like morphine which might together with short-term analgesia be an advantage in pain therapy.\(^3\) Although hydromorphone has been used extensively for relief of severe pain since its introduction in 1926, its pharmacokinetics are not thoroughly studied in postoperative patient populations.

Adequate postoperative pain therapy still remains a major challenge in everyday clinical practice.\(^4,5\) Patient-controlled analgesia (PCA) is an effective method in postoperative pain therapy,\(^6\) but without background infusion too low plasma

What We Already Know about This Topic
- Safe and effective anesthesia and analgesia can be achieved with infusions based on pharmacokinetic models
- Population-based pharmacokinetic parameters can improve dosing strategies
- Available hydromorphone pharmacokinetics were determined in young healthy volunteers

What This Article Tells Us That Is New
- Target-controlled infusions based on published hydromorphone pharmacokinetic parameters underestimated observed plasma concentrations in 49 cardiac surgery patients receiving hydromorphone for postoperative pain management
- A new hydromorphone pharmacokinetic model with a smaller initial distribution volume and age-adjusted and body weight–adjusted pharmacokinetic parameters was developed, which may improve dosing in patients undergoing cardiac surgery
concentrations might result between subsequent bolus doses. In addition, bolus dosage used in PCA increases the risk for too high peak concentrations, which may predispose patients to serious adverse effects. To improve pain therapy, target-controlled infusion (TCI) systems have been introduced to continuously calculate the infusion rate needed to achieve and maintain a given therapeutic drug plasma concentration based on population pharmacokinetic parameters. Compared with the traditional bolus dosage which is typically used in PCA, TCI systems may provide more stable analgesia and better hemodynamic control. Also, smaller amounts of opioids may be administered with TCI, which reduces the frequency of adverse effects during postoperative pain therapy.

Therefore, PCA with TCI might be considered as a better option to get a more stable dosing scheme, avoiding too high peak concentrations on the one hand and inadequate pain therapy on the other. A recent study observed the usage of TCI-PCA using remifentanil in treating acute pain after uterine artery embolization, and previously alfentanil TCI has been shown to be comparable with morphine PCA in postoperative cardiac surgery patients regarding pain relief and adverse effects.

In current pain therapeutic practice, analgesics are administered using standard dosing guidelines, an approach that largely ignores inter- and intraindividual variability, although recent studies show that model-guided clinical practice may result in better patient care. Pharmacokinetic models with clinically acceptable accuracy are available for several opioids, but these models are at present only used intraoperatively in clinical practice. Published pharmacokinetic models of hydromorphone were determined in young healthy volunteers, but to our knowledge, there exists no pharmacokinetic model for hydromorphone based on a patient population undergoing cardiac surgery. Our primary aim was, therefore, to evaluate the pharmacokinetics of hydromorphone in cardiac surgery patients during postoperative pain therapy. For PCA with TCI, we used the pharmacokinetic model developed in healthy volunteers by Westerling et al. Our objective was to build up a new model incorporating covariates to further characterize hydromorphone pharmacokinetics. As a secondary aim, we tested whether intraoperative sufentanil dosing had an effect on postoperative hydromorphone pharmacokinetics.

Materials and Methods
This study was performed in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. The study was approved by the Institutional Review Board (Ethikkommission der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany), and it was registered to the EudraCT (Number: 2011-003648-31) and ClinicalTrials.gov (Identifier: NCT01490268) databases. CONSORT guidelines were followed, and the study was clinically monitored by the Center for Clinical Studies, Erlangen.

Patients
After receiving written informed consent, we enrolled 50 adult patients undergoing cardiac surgery involving thoracotomy in this study. Inclusion criteria were an age between 40 and 80 yr, American Society of Anesthesiologists physical status classification of 3 or less, and a left ventricular ejection fraction of at least 40%. Female subjects in child-bearing age were required to have safe contraception throughout the study. Patients having allergy to opioid drugs or a medical history of diabetes mellitus, renal, neurological, or psychiatric disease as well as patients with chronic inflammatory disease or chronic obstructive lung disease were excluded from the study. Further exclusion criteria were pregnancy, body mass index greater than 30 kg/m², participation in another clinical trial, drug abuse, psychological or emotional problems as well as the use of nonsteroidal antiinflammatory drugs, monoamineoxidase inhibitors, or pain therapy with opioids 14 days before the start of the study. Patients who were not cooperative or could not use PCA were also excluded.

Clinical Protocol
The study was of prospective, single-blinded, randomized, single-center design with two parallel arms and was conducted in the University Hospital of Erlangen, Germany, during November 2011 to September 2012. After premedication with 7.5 mg of midazolam p.o. (Dormicum®; Roche Pharma, Grenzach-Wyhlen, Germany), anesthesia was induced and maintained with continuous infusions of propofol (Disoprivan® 2%; AstraZeneca, Wedel, Germany) as anesthetic and sufentanil (Sufenta®; Janssen-Cilag, Neuss, Germany) as analgesic drug. Intubation was facilitated with 0.15 mg/kg of cisatracurium (Nimbex®; GlaxoSmithKline, München, Germany). Propofol was administered as TCI based on the pharmacokinetic model by Marsh et al. targeting plasma concentrations between 2.5 and 4 µg/ml. Sufentanil was administered as TCI based on the pharmacokinetic model by Gepts. The patients were randomized into two treatment groups with target sufentanil plasma concentrations of 0.4 ng/ml (group 1) or 0.8 ng/ml (group 2). These target concentrations were kept constant throughout the anesthesia period after induction of anesthesia, when the sufentanil target concentrations were 0.4–1.5 ng/ml. The cardiopulmonary bypass circuit was primed with 500 ml of Ringer’s solution, 500 ml of 6% hydroxyethyl starch 130/0.4 (Voluven®; Fresenius Kabi, Bad Homburg, Germany), and 500 ml of 10% mannitol supplemented with 5,000 international units of heparin and 2 g of tranexamic acid. The bypass was conducted using normothermia, nonpulsatile blood flow, and ω-stat pH management. After the surgery, the patients were transferred to the intensive care unit (ICU) where the sufentanil infusion was discontinued, whereas the
propofol infusion was continued with an infusion rate of 2.5 mg·kg⁻¹·h⁻¹ for further 2–3 h until weaning from mechanical ventilation.

**Hydromorphone Dosing**

Throughout the study period in the ICU, hydromorphone (Palladon® inject; Mundipharma GmbH, Limburg, Germany; consisting of hydromorphone hydrochloride, 1 mg corresponding to 0.89 mg of hydromorphone-free base) was administered intravenously via a central venous catheter using three different dosing regimens, namely TCI, TCI as PCA (TCI-PCA), and PCA (fig. 1). For TCI and TCI-PCA, hydromorphone was administered using a setup which was developed by the authors for experimental use in this study. It consisted of a standard infusion pump (Braun Perfusor FM®; B. Braun, Melsungen, Germany) which was controlled by a laptop computer running a user-written control software (ivFeedPCA 1.1; Department of Anesthesiology, University Hospital, Erlangen, Germany); see Supplemental Digital Content 1, http://links.lww.com/ALN/A971, which is a brief description of the infusion system. The drug concentration in the syringe was 40 µg/ml of Palladon®. The maximal infusion rate was 60 ml/h equal to 40 µg/min of Palladon® corresponding to 35.6 µg/min of hydromorphone base.

**Hydromorphone TCI.** Immediately after arrival at the ICU, sufentanil infusion was discontinued and hydromorphone administration was commenced. Before extubation, hydromorphone was administered using TCI based on a pharmacokinetic model published by Westerling et al.²⁰ with a plasma target concentration of 2.0 ng/ml in treatment group 1 and 1.0 ng/ml in treatment group 2. In treatment group 2, the target concentration was increased to 2.0 ng/ml 15 min before extubation to account for the decrease of the residual sufentanil effect.

**Hydromorphone TCI-PCA.** After extubation, hydromorphone dosing was switched from TCI to TCI-PCA starting with the same plasma target concentration used at the end of TCI phase. To facilitate TCI-PCA, we connected a push-button via the serial port to the laptop computer running the control system, allowing the patient to communicate with the system. Patients were instructed to express inadequate analgesia by requesting an increase of the plasma concentration target by pressing the button. The study anesthetist confirmed the request after which the control system increased the target in steps of 0.5 ng/ml until a target concentration of 5 ng/ml was reached, after which the target was increased in steps of 0.25 ng/ml until the maximum target concentration of 10 ng/ml was reached. A 15-min lockout time was used. Pressing the button during the lockout time leads to a request without an increase in the target concentration. Without any requests, the control system was programmed to reduce the target after 30 min until the patient either requested an increase in the target concentration or a preset minimum plasma target concentration of 0.8 ng/ml was reached. Plasma target was decreased in steps of 0.5 ng/ml in the concentration range of 10 to 5 ng/ml after which the decrease was 0.25 ng/ml. The last decrease from 1.0 to 0.8 ng/ml was 0.2 ng/ml; similarly, the first increase after reaching the lowest target was 0.2 ng/ml. TCI-PCA phase took place for 6–8 h after extubation.

**Hydromorphone PCA.** After TCI-PCA phase (i.e., during the night), pain therapy was continued with conventional PCA (Graseby PCA 3300 PCA device; Smiths Medical Deutschland, Kirchseeon, Germany), delivering 0.2 mg (0.5 ml)
bolus doses of hydromorphone hydrochloride in 1 min with a lockout time of 10 min. PCA was continued until 8:00 AM next morning (first postoperative day). Thereafter, the pain therapy was continued according to the standard operating procedures of the ICU.

During these three study phases, patients were treated and monitored according to the normal ICU protocols. Arterial blood pressure, oxygen saturation (SpO₂), and heart rate were measured continuously (Siemens SL 9000 XL Patient Monitor; Siemens Medical Systems, Solna, Sweden). The study anesthetist recorded vital values in case report forms. Hydromorphone infusion–related parameters were automatically stored by the control system. In addition, patients were regularly asked to evaluate their pain at rest and under deep inspiration using the 11-point numerical rating scale (0 = no pain, 10 = maximum pain).²³ If the maximum target concentration of 10 ng/ml was reached and the patient still expressed continuing severe pain (≥25 at rest on the 11-point numerical rating scale), 1 g of acetaminophen (given intravenously twice daily as a short infusion) was administered as a rescue medication, and if necessary, an additional dipyrone could be administered as a continuous infusion at an infusion rate of 100 mg/h. Adverse effects and administration of rescue medication were recorded throughout the study from the beginning of intraoperative sufentanil dosing until the end of follow-up period (32 h after discontinuation of hydromorphone PCA).

**Blood Sampling**

Timed blood samples of 4 ml each were drawn for the pharmacokinetic measurements from an arterial line (radial or brachial) into ethylenediaminetetraacetic acid–containing tubes (S-Monovette® Kalium EDTA; Sarstedt, Nürnbrecht, Germany). A zero sample was drawn before the start of anesthesia in the operating room. At ICU, blood samples were drawn at 1, 3, 5, 7, 10, 30, 60, 120, and 240 min after the start of hydromorphone infusion and shortly before extubation. Further samples were drawn at 15, 45, 90, 150, 210, 270, 330, and 390 min after the start of hydromorphone TCI-PCA. During the first postoperative day, blood samples were drawn immediately before the stop of hydromorphone PCA and 1, 15, 30, 60, 120, 180, 240, and 300 min after the stop of hydromorphone PCA. After each sample was collected, the arterial catheter was flushed with 2 ml of heparinized NaCl solution. The samples were kept on ice, and plasma was separated within 15 min and stored at −70°C until analysis. The samples were analyzed within 2 months after sampling.

**Hydromorphone Drug Analysis**

Total plasma concentrations of hydromorphone were determined using a validated liquid chromatography–tandem mass spectrometric method as recently described.²⁴ The lower limit of quantification was 78 pg/ml, and the interday coefficients of variation for hydromorphone were 3.7, 4.7, and 2.6% at concentrations of 0.078, 1.0, and 5.0 ng/ml, respectively (n = 10 in each group). We did not recognize any interference by any concomitantly used drugs or their metabolites with the assay used to determine drug concentrations, and we have previously shown that no stability-related problems were observed during long-term storage at −70°C.²⁴

**Data Analysis**

For modeling, the infusion rates of hydromorphone-free base obtained from the control device were used. Nonlinear mixed-effects modeling was performed using NONMEM (Version 7.2.0; ICON Development Solutions, Ellicott City, MD). The first-order conditional estimation method with interaction was used throughout the analysis. Interindividual variability was assumed to follow a log-normal distribution: \( θ = θ_{pop} \cdot e^{η_i} \), where \( θ \) is the individual value of the parameter \( i \) in the \( j \)th individual, \( θ_{pop} \) is the population value of this parameter, and \( η_i \) is a random variable with mean zero and variance \( σ_η^2 \). For the intraindividual variability describing the residual errors, a proportional error model was used: \( ε_{ij} = c_{ij} \cdot (1 + ε_{ij}) \) in which \( c_{ij} \) is the \( i \)th measured concentration of the \( j \)th individual, \( cp_{ij} \) is the corresponding predicted concentration, and \( ε_{ij} \) is a random variable with mean zero and variance \( σ^2 \).

**Model Development**

Modeling was performed sequentially: A basic structural model was determined first, fitting two- and three-compartment models with first-order elimination to the data. Estimated parameters were apparent volumes of distribution, and elimination and intercompartmental clearances.

The individual Bayesian estimates of the pharmacokinetic parameters were used for the detection of covariate effects. One has, however, to consider that the variance of individual Bayesian estimates is shrinking toward zero as the quantity of information at the individual level diminishes. This phenomenon, called shrinkage, has been shown to blur the relationships between random effects and covariates, so that diagnostic plots of individual parameter estimates versus covariates could be misleading.²⁵ Therefore, we assessed η-shrinkage to assure the informativeness of the individual Bayesian estimates. η-Shrinkage was calculated as 1 − SD (η)/o where η are the individual Bayesian estimates of interindividual variance and o is the population model estimate of the corresponding SD. The individual Bayesian estimates of the pharmacokinetic parameters were plotted independently against the following covariates: age, sex, weight, height, body mass index, and lean body mass. Linear regression analysis was used as a first test for covariate effects. Subsequently, selected covariates were incorporated into the basic structural model using linear relationships...
with centering on the median value of the covariate (COV) within the population:

$$\theta_{POP} = \theta_{TV} \cdot [1 + \theta_{COV} \cdot (\text{COV} - \text{Median (COV)})]$$

where $\theta_{TV}$ is the typical value of the parameter in the population and $\theta_{COV}$ quantifies the covariate effect. For the effect of body weight (BW), we tested a linear model where all clearances and volumes were linearly proportional to BW: $\theta_{POP} = \theta_{TV} \times \text{(BW / 70)}$, and also an allometric power model: $\theta_{POP} = \theta_{TV} \times \text{(BW / 70)}^{\text{PBW}}$, where the power for body weight (PBW) is a scaling exponent. A PBW of 0.75 was used for all clearances and PBW of 1 for all volumes.26 Model selection was primarily based on changes of the NONMEM objective function value ($\Delta$OFV). One additional covariate parameter was included in the model, if the decrease in the NONMEM $\Delta$OFV was at least 3.84 ($P < 0.05$) and if the 95% CI of this additional parameter did not include zero. Subsequently, backward deletion analysis was performed, and each covariate effect was tested again for significance by fixing the corresponding parameter $\theta_{COV} = 0$. This time, a more conservative significance level of $P$ value less than 0.01 was used, which corresponds to $\Delta$OFV = 6.6 for one degree of freedom.

**Model Evaluation and Validation**

Criteria for goodness-of-fit were diagnostic plots (measured concentrations vs. population predictions and vs. individual predictions, conditional weighted residuals vs. time and vs. population predictions). In addition, we calculated the prediction error (PE$_i$) and the absolute prediction error (APE$_i$):

$$\text{PE}_i = \frac{c_{m,ij} - c_{p,ij}}{c_{p,ij}} \cdot 100\%$$

$$\text{APE}_i = \frac{|c_{m,ij} - c_{p,ij}|}{c_{p,ij}} \cdot 100\%$$

where $c_{m,ij}$ is the $j$th measured concentration of the $i$th individual, and $c_{p,ij}$ is the corresponding predicted concentration. PEs were calculated for individual and population predictions, and goodness-of-fit was assessed by the median values of PE$_i$ (MDPE) and APE$_i$, (MDAPE). Because PEs will probably be biased if they are determined from the same data that were used for model estimation, we also performed a cross-validation.27 For this purpose, we constructed 10 test sets and 10 corresponding estimation sets. Each test set contained the data of five randomly selected patients; the corresponding estimation set contained the data of the remaining 44 patients. As our study population consisted of 49 patients, the last test set contained only four patients. The random selection of the test subjects was performed without replacement, so that the test sets were disjoint. The final model was then fitted to each of the 10 estimation sets, and the PEs PE$_i^a$ and APE$_i^a$ were estimated in the corresponding test set using the population parameter estimates obtained from the estimation set in this run. Finally, MDPE and MDAPE were calculated from the PEs in each test set. Bootstrap analysis was performed to analyze the stability of the model parameter estimates and obtain nonparametric CIs of the final population model parameters.27 It uses a Monte Carlo simulation to repeatedly resample from the observed data with replacement, generating new sets of data which have the same size as the original data set. Using the final model and the original data set, we conducted bootstrap resampling analysis with 1,000 replicates for validation of the model.

**Simulations**

Using the estimated parameters from the final model, we carried out several simulations to further evaluate the pharmacokinetic findings. To show the effect of age on dosing, we computed the infusion rates necessary to maintain a defined target concentration. We further calculated the time needed for a 50% decrease in plasma concentration after continuous infusion (context-sensitive half-time)28 for different ages. To compare the plasma concentration profiles between different study phases, we simulated the concentration–time curve for each patient based on the original hydromorphone infusion rates and the individual pharmacokinetic parameters. These individual predictions were used to estimate the median, minimum, and maximum concentrations in TCI-PCA and PCA phases. Simulations were performed with Matlab® R2010b (MathWorks, Natick, MA).

**Statistical Analysis**

Data are presented as median with range or as mean ± SD if not stated otherwise. To capture patterns in the data, smoother lines were added in the figures using locally weighted scatterplot smoothing. The accuracy of the hydromorphone TCI was assessed by the MDPE. Biometric and dosing data between the dosing groups were tested with Mann–Whitney test. Statistical analysis was performed with R, version 2.15.29 using Rstudio environment for R, version 0.97.248.30

**Results**

We recruited 50 patients of which one was excluded during anesthesia because the operation was prolonged unexpectedly. From the remaining 49 patients (age range, 40–81 yr, 36 men and 13 women) included in the study, 26 and 23 patients received a TCI of sufentanil with target concentrations of 0.4 and 0.8 ng/ml, respectively (table 1). The two sufentanil dosing groups did not differ regarding the patient characteristics and procedural times (table 1).

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Explorative Data Analysis

Before pharmacokinetic analysis, we excluded those concentration measurements that were considered outliers from the dataset. These values were either above the upper limit of quantification of the assay used for drug concentration measurement (two samples) or had unclear information regarding the sampling time (two samples). Furthermore, seven measurements were excluded for being below the lower limit of quantification. Thus the pharmacokinetic modeling was based on 1,194 of 1,205 measured concentrations. Total sufentanil and hydromorphone doses and infusion times are summarized in table 2. For intra-operative sufentanil TCI and also during hydromorphone TCI, two predefined target concentrations were used, which explains the statistical differences between the doses given during these phases. There were no significant differences between the sufentanil dosing groups with respect to the total amount of hydromorphone administrated during TCI-PCA and PCA phases. Hydromorphone plasma concentrations were higher than predicted by the pharmacokinetic model by Westerling et al.20 used for delivering TCI (MDPE = 58.3%), especially at the beginning of the TCI phase (figs. 2 and 3). All observed individual hydromorphone plasma concentrations versus time are shown in figure 4.

Pharmacokinetic Model Development

A two-compartment model was first tested (OFV = −220.1), but it showed a significantly worse fit than a three-compartment model (OFV = −365.1; ΔOFV = −145.0), thus a three-compartment model was chosen for further model development. The regression analysis of the individual Bayesian pharmacokinetic estimates indicated a significant influence of age on the elimination clearance and on the central volume of distribution (fig. 5). BW showed a clear effect on elimination clearance and only a weak effect on central volume of distribution (fig. 5). Linear scaling of all parameters with BW improved the

Table 1. Descriptive Statistics of the Study Population

<table>
<thead>
<tr>
<th>Sufentanil Dosing Group</th>
<th>0.4 ng/ml</th>
<th>0.8 ng/ml</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, men/women</td>
<td>18/8</td>
<td>18/5</td>
<td>36/13</td>
</tr>
<tr>
<td>Age, yr</td>
<td>66 (48–81)</td>
<td>65 (40–77)</td>
<td>67 (40–81)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>83 (55–104)</td>
<td>80 (63–100)</td>
<td>80 (55–104)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173 (156–189)</td>
<td>171 (157–180)</td>
<td>172 (156–189)</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>61 (45–74)</td>
<td>60 (50–69)</td>
<td>64 (45–74)</td>
</tr>
<tr>
<td>Duration of anesthesia, h</td>
<td>4.7 (3.2–5.6)</td>
<td>5.0 (3.9–7.4)</td>
<td>4.7 (3.2–7.4)</td>
</tr>
<tr>
<td>Intubation time, h</td>
<td>7.9 (6.7–24.2)</td>
<td>8.7 (6.7–14.9)</td>
<td>8.3 (6.7–24.2)</td>
</tr>
<tr>
<td>Duration of surgery, min</td>
<td>194 (41–247)</td>
<td>194 (156–335)</td>
<td>191 (41–335)</td>
</tr>
<tr>
<td>Bypass time, min</td>
<td>69 (33–108)</td>
<td>85 (33–206)</td>
<td>76 (33–206)</td>
</tr>
<tr>
<td>Aortic clamping time, min</td>
<td>39 (20–70)</td>
<td>50 (24–133)</td>
<td>44 (20–133)</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>10 (6–16)</td>
<td>10 (6–17)</td>
<td>10 (6–17)</td>
</tr>
</tbody>
</table>

No statistically significant differences among the drug groups were noted. Data are described as median (range), except sex, which is shown as a ratio of men/women.

Table 2. Lengths of Infusion and Total Amount of Drug Infused during Each Study Phase

<table>
<thead>
<tr>
<th>Sufentanil Dosing Group</th>
<th>0.4 ng/ml</th>
<th>0.8 ng/ml</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufentanil TCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of infusion, h</td>
<td>5.1 (3.8–6.3)</td>
<td>5.6 (4.5–7.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>Amount dosed, mg</td>
<td>0.18 (0.14–0.23)</td>
<td>0.38 (0.30–0.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hydromorphone TCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of infusion, h</td>
<td>3.0 (2.0–5.3)</td>
<td>3.1 (1.9–6.2)</td>
<td>0.23</td>
</tr>
<tr>
<td>Amount dosed, mg</td>
<td>1.2 (0.8–2.4)</td>
<td>0.8 (0.5–2.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hydromorphone TCI-PCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of infusion, h</td>
<td>6.6 (3.9–6.8)</td>
<td>6.5 (3.1–6.8)</td>
<td>0.24</td>
</tr>
<tr>
<td>Amount dosed, mg</td>
<td>2.0 (0.4–6.1)</td>
<td>0.75 (0.3–5.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hydromorphone PCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of PCA, h</td>
<td>9.2 (5.4–10.6)</td>
<td>8.5 (5.8–11.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Amount dosed, mg</td>
<td>1.6 (0.6–4.6)</td>
<td>1.8 (0–6.2)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Amounts are reported as median (range). PCA = patient-controlled analgesia; TCI = target-controlled infusion.
fit significantly ($\Delta$OFV = −38.9), whereas the improvement of fit when using the allometric power model was smaller ($\Delta$OFV = −35.1). Adding the age effect to elimination clearance and central volume of distribution resulted in a further improvement of the model ($\Delta$OFV = −26.9). When compared with the basic model without covariates, the inclusion of age and BW reduced the interindividual variability of $\text{CL}_1$ and $\text{V}_1$ by more than 50% from 0.11 and 0.092 to 0.049 and 0.035, respectively. No sex effect was observed. There was also no significant effect of sufentanil dosing. The final model was tested with backward deletion analysis, and each covariate effect was tested again for significance. Deletion of age effect on $\text{CL}_1$ and $\text{V}_1$ resulted in a poorer fit ($\Delta$OFV = 11.4 and 9.5, respectively); similarly, the effect of weight scaling was shown to be significant ($\Delta$OFV = 44.7). Thus, the final pharmacokinetic model was as follows:

$$
\text{CL}_1 = \theta_1 \left( \frac{\text{BW}_{70}}{70} \right) \cdot (1 + \theta_7 \cdot (\text{Age} - 67))
$$

$$
\text{V}_1 = \theta_2 \left( \frac{\text{BW}_{70}}{70} \right) \cdot (1 + \theta_8 \cdot (\text{Age} - 67))
$$

$$
\text{CL}_2 = \theta_3 \left( \frac{\text{BW}_{70}}{70} \right)
$$

$$
\text{V}_2 = \theta_4 \left( \frac{\text{BW}_{70}}{70} \right)
$$

$$
\text{CL}_3 = \theta_5 \left( \frac{\text{BW}_{70}}{70} \right)
$$

$$
\text{V}_3 = \theta_6 \left( \frac{\text{BW}_{70}}{70} \right)
$$

with BW given in kg and age given in years. Table 3 shows the population pharmacokinetic parameter estimates of the final model.

**Model Evaluation**

Pharmacokinetic parameters were estimated with acceptable precision. Quality-of-fit was good with low PEs for population predictions (MDPE = −5.0%, MDAPE = 21.0%) as well as for individual post hoc predictions (MDPE = 1.2%, MDAPE = 9.5%) and with randomly and homogeneously distributed conditional weighted residuals (fig. 6). In the cross-validation, the median values of MDPE and MDAPE in the 10 test sets were −5.5% (range, −14.4 to 14.8%) and 22.3% (range, 16.1–30.0%), respectively. Figure 7 indicates that there were no significant changes of hydromorphone
pharmacokinetics within the study periods as the concentrations were adequately described by the model throughout all phases (TCI, TCI-PCA, and PCA) without a significant bias. Bootstrap analysis with 1,000 replications was performed to evaluate parameter uncertainty. Median and 95% CIs of the bootstrap distributions showed an acceptable agreement between population and bootstrap parameters (table 3).

**Simulations**

We performed several simulations to evaluate the effect of age using the estimated pharmacokinetic parameters of the final model. Table 4 shows the pharmacokinetic parameters of hydromorphone in different ages as predicted by the final model. Figure 8 displays the hydromorphone infusion rate needed to maintain a constant hydromorphone plasma concentration of 3 ng/ml for 5 h in three different age groups (40, 60, and 80 yr old). The total doses, including the loading dose, were 1.76, 1.48, and 1.20 mg for 40-, 60-, and 80-yr-old subjects. The loading doses for these subjects were 17.6, 12.0, and 6.4 µg, respectively. The context-sensitive half-times for these three individuals are depicted in figure 9. There is a remarkable increase in context-sensitive half-times from 26 min in a 40-yr-old patient to 84 min in an 80-yr-old patient. Our simulations indicated that the peak hydromorphone concentrations were considerably higher during PCA phase than during TCI-PCA phase (median, 27.1 vs. 6.67 ng/ml, respectively), and more low concentrations were seen in the PCA phase compared with TCI-PCA phase (minimum, 0.91 vs. 1.33 ng/ml; lower quartile, 1.7 vs. 2.7 ng/ml, respectively). The median hydromorphone concentration during TCI-PCA was 3.04 ng/ml (range, 1.33–6.67 ng/ml).

**Coadministered Drugs and Hemodynamics**

On the average, patients had three substrates for cytochrome P450 (CYP) 3A enzyme in their home medication and these were paused 1 day before the anesthesia. None of the patients was taking any CYP inhibitors or inducers preoperatively. During anesthesia, all patients received three CYP3A

![Fig. 5. Plot of the individual Bayesian estimates of the elimination clearance (A and B) and central volume of distribution (C and D) against age and body weight for a three-compartment model without covariates. Each data point represents one subject. The solid black line was obtained by linear regression analysis; $r^2$ is the corresponding regression coefficient.](image-url)
Hydromorphone is commonly used in postoperative pain therapy, but its pharmacokinetics are not thoroughly studied in this patient population. Previous literature describes models based on small datasets in young healthy volunteers.\textsuperscript{18–20} Our primary aim was to evaluate the pharmacokinetics of hydromorphone in cardiac surgery patients during postoperative pain therapy and to develop a new model incorporating covariates to better characterize hydromorphone pharmacokinetics.

The plasma concentrations of hydromorphone were best described using a three-compartment model with first-order elimination incorporating the effects of age and BW. We tested the two-compartment model also, but this model was discarded because of the poorer fit. The final model described the pharmacokinetics of hydromorphone in the given population with satisfactory precision as judged with goodness-of-fit plots. Similarly, the random and homogeneous distribution of conditional weighted residuals indicates that the error model could describe the variance of the data accurately. The stability of the final model was further established by the bootstrap analysis, which produced narrow CIs for the parameter estimates. The cross-validation indicated a satisfactory predictability of the final model.

Table 3. Pharmacokinetic Parameters Obtained from the Final Population Model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Model Parameters</th>
<th>Estimate</th>
<th>SE (RSE%)</th>
<th>Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\theta_1) (l/min)</td>
<td>(CL_1)</td>
<td>1.01</td>
<td>0.046 (4.6)</td>
<td>1.01</td>
<td>0.93–1.08</td>
</tr>
<tr>
<td>(\theta_2) (l)</td>
<td>(V_1)</td>
<td>3.35</td>
<td>0.29 (8.6)</td>
<td>3.4</td>
<td>2.85–4.01</td>
</tr>
<tr>
<td>(\theta_3) (l/min)</td>
<td>(CL_2)</td>
<td>1.47</td>
<td>0.23 (16)</td>
<td>1.66</td>
<td>1.34–2.10</td>
</tr>
<tr>
<td>(\theta_4) (l)</td>
<td>(V_2)</td>
<td>13.9</td>
<td>2.9 (21)</td>
<td>23.4</td>
<td>8.99–61.7</td>
</tr>
<tr>
<td>(\theta_5) (l/min)</td>
<td>(CL_3)</td>
<td>1.41</td>
<td>0.13 (9.2)</td>
<td>1.15</td>
<td>0.55–1.63</td>
</tr>
<tr>
<td>(\theta_6) (l)</td>
<td>(V_3)</td>
<td>145</td>
<td>13.2 (9.1)</td>
<td>141</td>
<td>122–162</td>
</tr>
<tr>
<td>(\theta_7)</td>
<td>-0.015</td>
<td>0.0053 (35.5)</td>
<td>-0.0016</td>
<td>-0.024 to -0.0067</td>
<td></td>
</tr>
<tr>
<td>(\theta_8)</td>
<td>-0.028</td>
<td>0.0072 (25.9)</td>
<td>-0.024</td>
<td>-0.044 to -0.0065</td>
<td></td>
</tr>
</tbody>
</table>

Interindividual variability

| \(\omega^2\) \(CL_1\) | 0.049 | 0.013 (27) | 0.047 | 0.025–0.073 |
| \(\omega^2\) \(V_1\) | 0.035 | 0.045 (130) | 0.020 | 0.012–0.077 |
| \(\omega^2\) \(CL_2\) | 0.20 | 0.12 (64) | 0.18 | 0.014–0.53 |
| \(\omega^2\) \(V_2\) | 0.10 | 0.15 (151) | 0.17 | 4.0×10^{-5} – 0.20 |
| \(\omega^2\) \(CL_3\) | 0.14 | 0.055 (40) | 0.17 | 0.047–0.35 |
| \(\omega^2\) \(V_3\) | 0.13 | 0.045 (33) | 0.17 | 0.089–0.45 |

Intraindividual variability

| \(\sigma^2\) | 0.038 | 0.0008 (2.1) | 0.039 | 0.03–0.05 |

CL\(_1\) = elimination clearance; CL\(_{2,3}\) = intercompartmental clearances; RSE = relative standard error; \(V_1\) = central volume of distribution; \(V_{2,3}\) = peripheral volumes of distribution.

Discussion

Hydromorphone is commonly used in postoperative pain therapy, but its pharmacokinetics are not thoroughly studied in this patient population. Previous literature describes models based on small datasets in young healthy volunteers.\textsuperscript{18–20} Our primary aim was to evaluate the pharmacokinetics of hydromorphone in cardiac surgery patients during postoperative pain therapy and to develop a new model incorporating covariates to better characterize hydromorphone pharmacokinetics.

The plasma concentrations of hydromorphone were best described using a three-compartment model with first-order elimination incorporating the effects of age and BW. We tested the two-compartment model also, but this model was discarded because of the poorer fit. The final model described the pharmacokinetics of hydromorphone in the given population with satisfactory precision as judged with goodness-of-fit plots. Similarly, the random and homogeneous distribution of conditional weighted residuals indicates that the error model could describe the variance of the data accurately. The stability of the final model was further established by the bootstrap analysis, which produced narrow CIs for the parameter estimates. The cross-validation indicated a satisfactory predictability of the final model.

The plasma concentrations of hydromorphone were near the lower limit of quantification at the end of the observation period although we used a recently developed very sensitive method to determine hydromorphone concentrations.\textsuperscript{24} This suggests that at the doses used in this study, it is unlikely that a longer sampling period during elimination of the phase would have given more information.

Age was found to be a significant covariate for hydromorphone elimination clearance and central volume of distribution in this patient group. Age-related changes in hydromorphone clearance were reflected in elimination half-lives, as our results demonstrate that it was prolonged by 28% in the 80-yr-old subject compared with a 40-yr-old (table 4). The half-lives and the apparent volume of distribution at steady state were comparable with previously published studies\textsuperscript{18–20} (table 5), whereas our study population showed a significantly smaller volume of the central compartment (5.87 l vs. 16.1–42.7 l). The distinct overshoot of the hydromorphone concentration, which was observed shortly after start of the infusion, can be mainly explained by the large central volume of distribution in the Westerling model. The smaller estimate of this parameter in our study may be explained not only by the different study populations (young healthy volunteers vs. elderly cardiac patients) but also by differences in blood sampling during the initial phase.\textsuperscript{31} Westerling \textit{et al.}\textsuperscript{20} used venous samples and the first sample was taken 5 min after start of infusion, whereas we...
analyzed arterial samples taken at 1, 3, and 5 min after start of infusion. The value of elimination clearance in our patient group was smaller than reported previously. However, the expected value for elimination clearance for a 30-yr-old subject as predicted by our final model would be 1.67 l/min, which is approximately the same as reported in the healthy volunteer studies. This further demonstrates the strong effect of age on the pharmacokinetics of hydromorphone. We used a linear relationship between age and pharmacokinetic parameters, and the model structure may produce irrational results when used outside the supporting patient data (e.g., a negative value of V₁ if the age is greater than 102 yr). Therefore, the results of the present model should be extrapolated carefully.

Fig. 6. Goodness-of-fit plots. Measured hydromorphone concentrations versus the individual Bayesian predictions (A) and versus the population predictions (B) as obtained with the final pharmacokinetic model. Conditional weighted residuals versus time (C) and versus population-predicted plasma hydromorphone levels (D), respectively. The solid black line in A and B is the line of identity (measured = predicted). The blue line represents the smoother. MDAPE = median absolute prediction error; MDPE = median prediction error.

With respect to the effect of BW, it has been proposed that from a theoretical point of view, the allometric power model may be in general more reasonable than the simple linear scaling. For our data, however, the linear weight scaling was slightly better than the allometric model. One reason for this finding may be that the range of BW in our study population was narrow (55–104 kg), whereas the allometric power model may be more appropriate if one aims for a valid model over a very broad range, e.g., including children and adults. From a practical point of view, the linear weight scaling has the advantage that the dosing to achieve a defined drug concentration can be more easily determined in mg/kg or mg·kg⁻¹·min⁻¹.

It should be emphasized that age and BW may not be the only factors affecting hydromorphone pharmacokinetics in the postoperative period, but other covariates as, for example, the residual effects of anesthesia and operative treatment among other factors may have an impact. As hydromorphone is a drug with an intermediate hepatic extraction ratio of 0.51 in healthy volunteers, hepatic blood flow and cardiac output are expected to have an impact on hydromorphone clearance. A decreased cardiac output in our study population may also be in part responsible for the finding of a smaller clearance compared...
Population Pharmacokinetics of Hydromorphone

with studies in young volunteers. As our patients typically received vasoactive drugs particularly at the beginning of the ICU therapy, changes in cardiac output within the study period cannot be ruled out. Although cardiac output was not measured, the blood pressure data indicated that there were no relevant changes in the hemodynamics that may affect the pharmacokinetics of hydromorphone. Similarly, figure 7 shows that the final model, which assumes that pharmacokinetics did not change throughout the study period, was able to describe all phases (TCI, TCI-PCA, and PCA) with similar precision and no bias. However, it should be emphasized that mean arterial pressure is not a direct measure for liver blood flow, and changes in the splanchnic blood flow may not be displayed in these data. Further studies are warranted to elucidate the effect of hemodynamic status on the hydromorphone pharmacokinetics.

Another important issue is the effect of coadministered drugs on the pharmacokinetics of hydromorphone, which is metabolized by CYP3A and to a lesser extent by CYP2C9 enzymes.33 Hence, concomitantly administered drugs interacting with these enzymes may affect the pharmacokinetics of hydromorphone. Our patients received several substrates for CYP3A during the study, but no CYP inhibitors or inducers were administered before or during the study. Previous studies have shown that the inhibition of the CYP3A-mediated metabolism of hydromorphone is compensated by other metabolic pathways,33 making it plausible to assume that our analysis is not significantly affected by CYP-mediated drug–drug interactions.

As the elimination clearance of hydromorphone was reduced with advancing age, smaller doses should be used in the elderly in the perioperative setting to avoid unwanted drug effects. For clinical practice, the effects of age and BW allow the dosing to be adjusted to the individual patient. We simulated three different infusion schemes necessary to maintain a hydromorphone concentration of 3 ng/ml in 40-, 60- and 80-yr-old patients. If normalized to weight, the total doses required for a dosing period of 5 h are approximately 32% higher in the youngest age group compared with the elderly.

Because elimination half-live is a poor measure of recovery in the clinical setting, we estimated the time required for a 50% decrease in hydromorphone plasma concentration after a constant infusion of variable length (fig. 9) to further evaluate the effect of age on the hydromorphone pharmacokinetics. This context-sensitive half-time was markedly prolonged with advancing age. The oldest patients in our data set had approximately 70% longer context-sensitive half-times after 6 h constant infusion than the youngest. This means that the adjustment of pharmacokinetics can help to avoid misdosing, but differences with respect to the recovery time cannot be overcome.

The concentration data suggested that higher peak concentrations were observed during the PCA phase compared with the TCI-PCA phase. Several possible reasons can be assumed having caused this, but the different dosing regimens seem to be the most plausible explanation for higher peaks during PCA phase. We simulated the predicted concentration–time course for each patient in our study population based on our final model to get individual predictions for comparison. The predictions indicate that during the PCA phase significantly

Fig. 7. Semilogarithmic plot showing the residual errors of the individual (A) and population fit (B), expressed as measured and predicted concentration versus time. Each gray line represents one subject, and different phases of the study are indicated in the graph. The blue line represents the smoother. PCA = patient-controlled analgesia; TCI = target-controlled infusion.
PERIOPERATIVE MEDICINE

large fluctuation in concentrations was seen, and conversely TCI-PCA produced more stable concentration–time profile. During the PCA phase, the highest predicted concentrations were almost four times higher than in the TCI-PCA phase. Similarly, the median concentrations might have been too low during the PCA compared with the concentrations in the range of 2–3 ng/ml observed when patient reported satisfactory pain therapy during TCI-PCA. These results should be confirmed in future studies, but lower peak concentrations during TCI-PCA are beneficiary when considering the incidence of adverse effects because it has been shown that high opioid concentrations predispose patients to, e.g., respiratory depression.34

During the postoperative pain therapy, large interindividual variation is observed regarding the various aspects of nociception. It has been discussed whether high intraoperative administration of opioids increases postoperative pain and opioid consumption.35,36 We, therefore, divided our patient population into two groups to investigate the effect of intraoperative sufentanil dosing on the pharmacokinetics of hydromorphone during postoperative pain therapy. Our results indicate that intraoperative sufentanil administration may present no carryover effect on the immediate postoperative pain therapy with hydromorphone because the pharmacokinetic parameter estimates and the amounts of hydromorphone dosed were similar in both groups during TCI-PCA and PCA phases.

Clinical practice has shown that effective and safe anesthesia can be achieved with infusion schemes based on pharmacokinetic models because titration of the target concentration may help to manage the problem of interindividual variability of pharmacokinetics and pharmacodynamics.8,13 The use of population-based pharmacokinetic parameters is likely to further improve the dosing strategies during the perioperative pain therapy. We present here a patient-derived population pharmacokinetic model for hydromorphone, an opioid analgesic that is often used in postoperative and palliative pain therapy. Our model indicates that age and BW show

Table 4. Pharmacokinetic Parameters of Hydromorphone for Subjects with a Body Weight of 70 kg and Different Ages as Predicted by the Final Population Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>40 yr</th>
<th>60 yr</th>
<th>80 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CL}_1$, l/min</td>
<td>1.42 (0.91–2.26)</td>
<td>1.12 (0.71–1.78)</td>
<td>0.82 (0.52–1.30)</td>
</tr>
<tr>
<td>$V_1$, l</td>
<td>5.87 (4.10–8.70)</td>
<td>4.00 (2.79–5.92)</td>
<td>2.13 (1.48–3.15)</td>
</tr>
<tr>
<td>$\text{CL}_2$, l/min</td>
<td>1.47 (0.60–3.66)</td>
<td>1.47 (0.60–3.66)</td>
<td>1.47 (0.60–3.66)</td>
</tr>
<tr>
<td>$V_2$, l</td>
<td>13.9 (6.94–26.7)</td>
<td>13.9 (6.94–26.7)</td>
<td>13.9 (6.94–26.7)</td>
</tr>
<tr>
<td>$\text{CL}_3$, l/min</td>
<td>1.41 (0.66–2.90)</td>
<td>1.41 (0.66–2.90)</td>
<td>1.41 (0.66–2.90)</td>
</tr>
<tr>
<td>$V_3$, l</td>
<td>145 (70–321)</td>
<td>145 (70–321)</td>
<td>145 (70–321)</td>
</tr>
<tr>
<td>$T_{1/2\alpha}$, min</td>
<td>0.90 (0.38–1.47)</td>
<td>0.66 (0.28–1.08)</td>
<td>0.39 (0.17–0.63)</td>
</tr>
<tr>
<td>$T_{1/2\beta}$, min</td>
<td>10.2 (2.5–40.3)</td>
<td>10.4 (2.4–41.7)</td>
<td>10.7 (2.4–44.9)</td>
</tr>
<tr>
<td>$T_{1/2\gamma}$, min</td>
<td>147 (56–391)</td>
<td>168 (64–458)</td>
<td>204 (76–547)</td>
</tr>
</tbody>
</table>

CI s were calculated from simulated data for 1,000 cases, based on the estimated interindividual variances.

$\text{CL}_1$ = elimination clearance; $\text{CL}_{2,3}$ = intercompartmental clearances; $T_{1/2\alpha}$ = fast half-life; $T_{1/2\beta}$ = intermediate half-life; $T_{1/2\gamma}$ = terminal half-life; $V_1$ = central volume of distribution; $V_{2,3}$ = peripheral volumes of distribution.
a strong influence on the pharmacokinetics of hydromorphone, which should be considered when hydromorphone is used in pain therapy.

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**Competing Interests**

The authors declare no competing interests.

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