

# Patient-controlled Analgesia with Target-controlled Infusion of Hydromorphone in Postoperative Pain Therapy

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## ABSTRACT

**Background:** Patient-controlled analgesia (PCA) is a common method for postoperative pain therapy, but it is characterized by large variation of plasma concentrations. PCA with target-controlled infusion (TCI-PCA) may be an alternative. In a previous analysis, the authors developed a pharmacokinetic model for hydromorphone. In this secondary analysis, the authors investigated the feasibility and efficacy of TCI-PCA for postoperative pain therapy with hydromorphone.

**Methods:** Fifty adult patients undergoing cardiac surgery were enrolled in this study. Postoperatively, hydromorphone was applied intravenously during three sequential periods: (1) as TCI with plasma target concentrations of 1 to 2 ng/ml until extubation; (2) as TCI-PCA with plasma target concentrations between 0.8 and 10 ng/ml during the following 6 to 8 h; and (3) thereafter as PCA with a bolus dose of 0.2 mg until the next morning. During TCI-PCA, pain was regularly assessed using the 11-point numerical rating scale (NRS). A pharmacokinetic/pharmacodynamic model was developed using ordinal logistic regression based on measured plasma concentrations.

**Results:** Data of 43 patients aged 40 to 81 yr were analyzed. The hydromorphone dose during TCI-PCA was 0.26 mg/h (0.07 to 0.93 mg/h). The maximum plasma target concentration during TCI-PCA was 2.3 ng/ml (0.9 to 7.0 ng/ml). The NRS score under deep inspiration was less than 5 in 83% of the ratings. Nausea was present in 30%, vomiting in 9%, and respiratory insufficiency in 5% of the patients. The  $EC_{50}$  of hydromorphone for NRS of 4 or less was 4.1 ng/ml (0.6 to 12.8 ng/ml).

**Conclusion:** TCI-PCA with hydromorphone offered satisfactory postoperative pain therapy with moderate side effects. (ANESTHESIOLOGY 2016; 124:56-68)

PREVIOUS studies show that severe postoperative pain is still a widespread and underestimated problem.<sup>1-5</sup> The challenge in acute pain treatment is to individually titrate analgesics to the desired effect while minimizing the adverse effects. Patient-controlled analgesia (PCA) with systemic opioids approaches this therapeutic goal and provides better pain control and patient satisfaction than parenteral analgesia administered by medical staff.<sup>6</sup> Background basal infusion may be used in addition to bolus dosing to further improve pain therapy, but this approach may increase the risk of overdosing due to accumulation of the drug and therefore increase the risk of respiratory depression.

In current PCA practice, opioids are administered using standard dosing guidelines.<sup>7</sup> This approach largely ignores inter- and intraindividual variability, whereas model-guided clinical practice may result in better patient care.<sup>8,9</sup> Based on drug-specific population pharmacokinetic parameters, target-controlled infusion (TCI) systems avoid an

### What We Already Know about This Topic

- The titration of analgesics to effective but safe levels postoperatively remains problematic
- Background opioid infusions may help achieve better pain control but require appropriate infusion parameters

### What This Article Tells Us That Is New

- Using hydromorphone-specific pharmacokinetic parameters, accurate target-controlled infusions can be delivered
- Using combined target-controlled infusion with patient-controlled analgesia, satisfactory postoperative pain control can be delivered with moderate levels of opioid-related side effects

undershooting as well as high peak concentrations and reduce the risk of drug accumulation by continuously calculating the infusion rate needed to achieve and maintain the intended therapeutic drug concentration.<sup>10,11</sup>

Therefore, PCA combined with TCI (TCI-PCA) may improve pain control and patient satisfaction while reducing

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the risk of adverse events and inadequate pain therapy. In this secondary analysis of a recently published study regarding the pharmacokinetics of hydromorphone,<sup>12</sup> we investigated the feasibility and efficacy of the TCI-PCA concept for postoperative pain therapy in patients undergoing cardiac surgery with two commonly used opioid analgesics: sufentanil as intraoperative analgesic and hydromorphone for postoperative pain therapy. Our primary aim was to study whether the TCI-PCA approach provides satisfactory pain relief after cardiac surgery with thoracotomy. As a secondary aim, we investigated the pharmacodynamics of pain sensation by pharmacokinetic/pharmacodynamic modeling based on measured plasma concentrations of hydromorphone and sufentanil.

## Materials and Methods

The study was approved by the local institutional review board (Ethikkommission der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany), and it was registered in Germany with the European Clinical Trials Database: EudraCT Number 2011-003648-31; in the United States at ClinicalTrials.gov: NCT01490268, first registered on November 28, 2011, principal investigator: C.J., Department of Anesthesiology, University of Erlangen-Nuremberg, Erlangen, Germany. The study was clinically monitored by the Center for Clinical Studies, Erlangen, and the guidelines of Consolidated Standards of Reporting Trials (CONSORT)<sup>13</sup> were followed. The results of this study dealing with the pharmacokinetic modeling of hydromorphone have been published recently.<sup>12</sup>

### Patients

Fifty adult patients undergoing cardiac surgery involving thoracotomy were enrolled in this study after receiving written informed consent. To be considered for inclusion, the patients needed to meet the following criteria: 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%. Patients with 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 in female subjects in child-bearing age, body mass index greater than 30 kg/m<sup>2</sup>, participation in another clinical trial, drug abuse, psychological or emotional problems as well as the use of nonsteroidal antiinflammatory drugs, monoamine oxidase inhibitors, or pain therapy with opioids 14 days before the start of the study. Furthermore, patients who were not cooperative or could not use PCA were also excluded.

### Clinical Protocol

This study was conducted at the University Hospital Erlangen, Erlangen, Germany, during November 2011 and September 2012 and was of prospective, single-blinded,

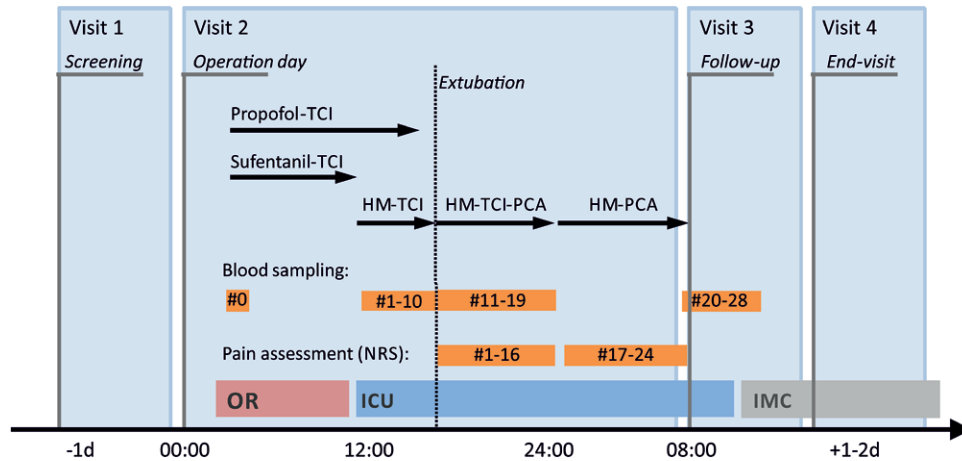
randomized, single-center design with two parallel arms. The clinical study protocol, drug dosing, and data management have been described in detail in our previous publication.<sup>12</sup> In brief, after a premedication with 7.5 mg midazolam *per os* (Dormicum®; Roche Pharma, Germany), anesthesia was induced and maintained with TCI of propofol (Disoprivan® 2%; AstraZeneca, Germany) as anesthetic and sufentanil (Sufenta®; Janssen-Cilag, Germany) as analgesic drug. For facilitating endotracheal intubation, a bolus dose of 0.15 mg/kg cisatracurium (Nimbex®; GlaxoSmithKline, Germany) was administered. Both propofol and sufentanil were administered by a TCI infusion device (Fresenius Orchestra® Base Primea; Fresenius Kabi, Germany). Propofol was administered as TCI using the pharmacokinetic model reported by Marsh *et al.*<sup>14</sup> and target plasma concentrations between 2.5 and 4 µg/ml. Sufentanil was administered as TCI using the pharmacokinetic model reported by Gepts *et al.*<sup>15</sup> The patients were randomized into two treatment groups with target sufentanil plasma concentrations of 0.4 (group 1) or 0.8 ng/ml (group 2). These target concentrations were kept constant during maintenance of anesthesia. After the end of the surgery, the patients were transferred to the intensive care unit (ICU) where the sufentanil infusion was discontinued while the propofol infusion was continued for further 2 to 3 h until weaning from mechanical ventilation with an infusion rate of 2.5 mg · kg<sup>-1</sup> · h<sup>-1</sup>.

Vasoactive drugs were infused goal directed depending on the clinical demand to maintain the hemodynamics in the normal range (mean arterial pressure of 70 to 90 mmHg). Dobutamine, noradrenaline, and glycerylnitrate infusions were routinely used. If the vasoactive control was insufficient, adrenalin was administered instead of dobutamine according to the standard operating procedures of the ICU.

During the study phases, patients were treated and monitored according to the standard protocols of the ICU. Invasive arterial blood pressure, peripheral arterial oxygen saturation, heart rate, and respiratory rate were measured continuously (Siemens SL 9000 XL Patient Monitor, Version VF 3.1-W; Siemens Medical Systems, Sweden). Adverse effects and administration of rescue medication were also 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). Laboratory data were determined regularly by blood gas analysis (ABL800 FLEX analyzer; Radiometer Medical ApS, Denmark), and the results were collected from the ICU documents.

### Hydromorphone Dosing

Immediately after discontinuation of sufentanil infusion in the ICU, hydromorphone (Palladon® inject; Mundipharma GmbH, Germany; 1 mg hydromorphone hydrochloride corresponding to 0.89 mg hydromorphone free base) was administered intravenously *via* a central venous catheter using three different dosing regimens (fig. 1): TCI,



**Fig. 1.** Diagram showing the phases during the clinical trial. Time course of the drug infusions, blood sampling, pain assessment, and patient flow is illustrated. HM = hydromorphone; ICU = intensive care unit; IMC = intermediate care unit; NRS = numerical rating scale; OR = operation room; PCA = patient-controlled analgesia; TCI = target-controlled infusion.

TCI-PCA, and PCA. The setup for hydromorphone administration as TCI and TCI-PCA was developed by the authors and consisted of a standard infusion pump (Braun Perfusor FM<sup>®</sup>; B. Braun, Germany), which was controlled by a laptop computer running a user-written control software (ivFeedPCA 1.1, Department of Anesthesiology, University Hospital Erlangen, Erlangen, Germany).<sup>12</sup> The typical dose of hydromorphone for postoperative pain therapy is 0.1 to 0.2 mg/h.<sup>16</sup> Assuming a hydromorphone clearance of 1.7 l/min,<sup>17,18</sup> this corresponds to a steady-state concentration of 1 to 2 ng/ml. TCI was based on a pharmacokinetic model published by Westerling *et al.*<sup>18</sup> As we expected different influences of residual concentrations of sufentanil on pain relief postoperatively, we started with target hydromorphone plasma concentrations of 2 and 1 ng/ml in treatment groups 1 and 2, respectively. In treatment group 2, the plasma target concentration was increased to 2.0 ng/ml 15 min before extubation to account for the decrease of the residual sufentanil effect. During TCI-PCA, minimum and maximum plasma target concentrations were 0.8 and 10 ng/ml, respectively. A push button was connected *via* the serial port to the laptop computer running the control system. The TCI-PCA algorithm is shown in figure S1 of Supplemental Digital Content 1, <http://links.lww.com/ALN/B222>. Patients were instructed to request an increase of the target by pressing the button, and the study anesthetist had to confirm the request. The step size for target increase was 0.2 ng/ml between 0.8 and 1 ng/ml, 0.5 ng/ml between 1 and 5 ng/ml, and 0.25 ng/ml between 5 and 10 ng/ml. A 15-min lockout time was used. Without any requests, the target was automatically reduced after 30 min until the patient either requested an increase of the target or the minimum target of 0.8 ng/ml was reached. The step size for target decrease was 0.5 ng/ml in the range of 10 to 5 ng/ml, 0.25 ng/ml in the range of 5 to 1 ng/ml, and 0.2 between 1 and 0.8 ng/ml. For TCI-PCA, the drug concentration in the syringe was 40 µg/ml Palladon<sup>®</sup>, and the maximal infusion

rate was 60 ml/h of Palladon<sup>®</sup> corresponding to 35.6 µg/min of hydromorphone base. TCI-PCA phase took place for 6 to 8 h after extubation.

During the night (*i.e.*, after TCI-PCA phase), hydromorphone was administered by conventional PCA (Graseby PCA 3300 PCA device; Smiths Medical Deutschland, 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). After PCA phase, pain therapy was continued according to the standard operating procedures of the ICU. Hydromorphone infusion-related parameters were automatically stored by the control system.

### Vital Signs Assessment

The study personnel assessed the invasive arterial blood pressure, peripheral arterial oxygen saturation, and heart rate at 15, 30, 45, 60, 90, 120, 150, 210, 270, 330, and 390 min after start of TCI-PCA. During the PCA phase, the nursing staff assessed the vital signs every hour until the end of the PCA phase.

### Pain Assessment and Rescue Therapy

Patients were asked to evaluate their pain at rest and under deep inspiration by using the 11-point numerical rating scale (NRS, 0 = no pain, 10 = maximum pain).<sup>19</sup> NRS was evaluated when the hydromorphone TCI-PCA was started and at 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, and 390 min thereafter. During the PCA phase, the nursing staff asked the patients every 1 to 2 h to evaluate their pain. If the maximum target concentration of 10 ng/ml was reached and the patient still expressed continuing severe pain (5 or greater at rest on the 11-point NRS) 1 g acetaminophen (given IV twice daily as a short infusion) was administered as a rescue medication, and if necessary, additional dipyrone could be administered as a continuous infusion with an infusion rate of 100 mg/h.

### Sedation Assessment

Sedation was assessed using a Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Scale, based on the assessment of responsiveness in the original Observer's Assessment of Alertness/Sedation Scale.<sup>20</sup> The MOAA/S scores were defined as following: 0 = no response to painful trapezius squeeze, 1 = response only after painful trapezius squeeze, 2 = response only after mild prodding or shaking, 3 = response after name is called loudly and/or repeatedly, 4 = lethargic response to name spoken in normal tone, and 5 = immediate response to name spoken in normal tone (alert). MOAA/S scores were evaluated at 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, and 300 min after start of TCI-PCA. During the PCA phase, the nursing staff assessed the sedation level using the Richmond Agitation Sedation Scale<sup>21</sup> in addition to pain evaluation. We further estimated the residual propofol concentration at the time of extubation, using the propofol infusion data and parameters from the pharmacokinetic model reported by Marsh *et al.*<sup>14</sup>

### Adverse Events Assessment

Respiratory rate was monitored continuously as a measure of dynamic opioid effect<sup>22</sup> during the study phases. The study personnel assessed the respiratory rate at 15, 30, 45, 60, 90, 120, 150, 210, 270, 330, and 390 min after start of TCI-PCA. During the PCA phase, the nursing staff assessed the respiratory rate every hour until the end of the PCA phase.

Respiratory insufficiency was defined with respect to clinical symptoms such as dyspnea, respiratory rate less than 10 or greater than 25 breaths/min, evident use of accessory muscles, paradoxical breathing, and gas exchange abnormalities such as reduction in ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen ( $P_{aO_2}/F_{IO_2}$ ) less than 200 mmHg and increase in partial pressure of carbon dioxide ( $P_{aCO_2}$ ) above 50 mmHg.<sup>23</sup> Nausea and vomiting were recorded at the time of occurrence by the study personnel during the TCI-PCA phase and by the nursing staff during the PCA phase overnight. The ICU anesthetist in charge was responsible for the diagnosis of respiratory insufficiency and treatment of adverse events after consulting the study anesthetist.

### Blood Sampling

Arterial blood samples were drawn during all study phases. The blood sampling for hydromorphone has been described in detail in our recent publication.<sup>12</sup> For measurement of sufentanil, a blank sample was drawn before the start of anesthesia in the operating room. Further blood samples were drawn shortly before stop of the sufentanil infusion, at 1, 3, 5, 7, 10, 30, 60, 120, and 240 min after start of hydromorphone infusion, and shortly before extubation. The last sufentanil sample was drawn at the end of the TCI-PCA phase, 390 min after the start of hydromorphone TCI-PCA.

The samples were kept on ice and plasma was separated within 15 min and stored at  $-70^{\circ}\text{C}$  until analysis. Plasma

concentrations of hydromorphone were determined using a validated liquid chromatography-tandem mass spectrometric method as recently described.<sup>24</sup> 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). Plasma concentrations of sufentanil were determined using a validated liquid chromatography-tandem mass spectrometric method.<sup>25</sup> The lower limit of quantification of sufentanil was 5 pg/ml, and the interday coefficients of variation were 10.12, 4.0, and 6.3%, at concentrations of 5, 250, and 2,500 pg/ml, respectively ( $n = 16$  to 20 in each group).

### Pharmacokinetic/Pharmacodynamic Modeling

In order to assess the concentration-effect relation for the analgesic effect of hydromorphone, we performed a sequential pharmacokinetic/pharmacodynamic modeling, including the residual sufentanil concentrations from intraoperative analgesia. In the first step, a pharmacokinetic model for hydromorphone was developed from the measured plasma concentrations and the infusion rates obtained from the TCI devices. The pharmacokinetic modeling of hydromorphone has been published recently.<sup>12</sup> The decline of the sufentanil concentrations during TCI and TCI-PCA of hydromorphone was modeled by a two-exponential function. The individual predicted hydromorphone and sufentanil concentrations were then used for the pharmacodynamic analysis. Pharmacodynamic modeling was performed using the pain rating under deep inspiration. As pain was measured not on a continuous interval scale but on a discrete ordinal scale (NRS), we used an ordinal logistic regression model relating the probability of measuring a particular NRS score to the hydromorphone and sufentanil concentrations.<sup>26</sup> Details of the pharmacokinetic/pharmacodynamic modeling are given in Supplemental Digital Content 1, <http://links.lww.com/ALN/B222>. Supplemental Digital Content 2, <http://links.lww.com/ALN/B223>, contains a NONMEM control file for the pharmacodynamic analysis together with demo data.

### Statistical Analysis

The primary endpoint in this analysis was the assessment of postoperative pain using the NRS. Data are presented as median (range) or as mean  $\pm$  SD if not stated otherwise. Data were tested for normal distribution using Shapiro-Wilk test. Differences between the two sufentanil target groups regarding patient characteristics, doses, and infusion times were identified using the Mann-Whitney test. Comparisons between TCI-PCA and PCA phases were performed with the Wilcoxon test. The pain ratings were characterized by the distribution of the raw data and also by the distribution of the transition, that is, the difference between two consecutive ratings. The time course of the pain rating data was further analyzed by a generalized linear model for repeated measurements with the factors "sufentanil group"

(0.4 or 0.8 ng/ml target concentration), “period” (TCI-PCA or PCA), and “time” (nested in “period”), using an ordinal logistic regression. Statistical analysis was performed with R (Version 3.0.3)<sup>27</sup> using Rstudio (Version 0.98.501)<sup>28</sup> and SPSS (IBM, SPSS Statistics, Version 21.0, USA), and a *P* value less than 0.05 was considered significant.

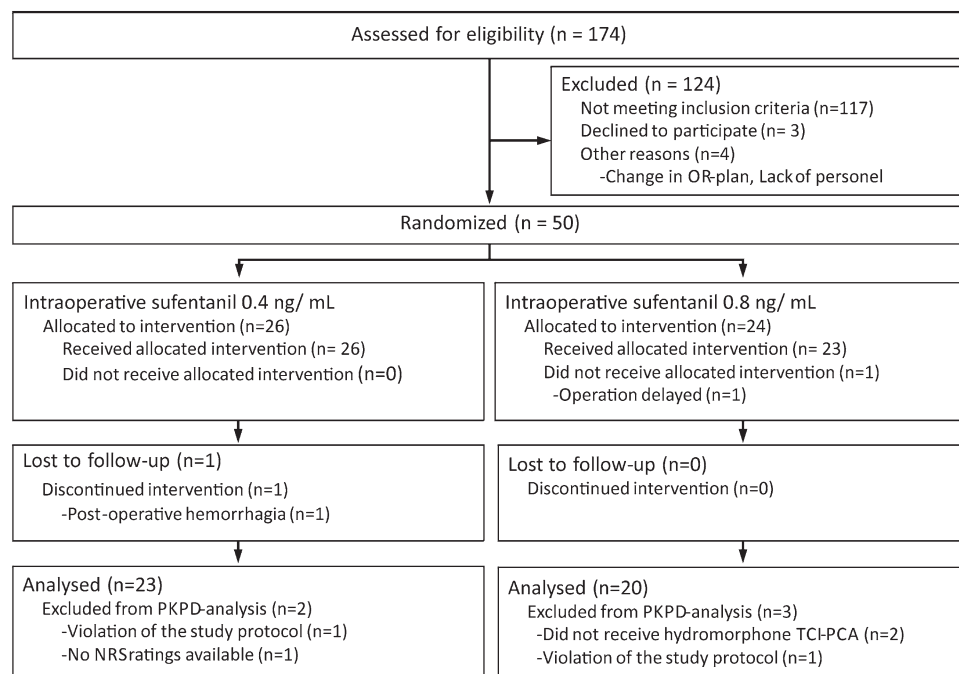
## Results

We recruited 50 patients, of which 1 was excluded during the anesthesia because the operation was prolonged unexpectedly. Overall, 1,194 hydromorphone and 518 sufentanil concentration measurements were obtained from 49 and 47 patients, respectively. Pharmacodynamic analysis could be performed in 43 patients with 615 NRS measurements (fig. 2); all descriptive statistics are reported for those 43 patients. Figure 3 visualizes the simulated concentration time profile of hydromorphone and sufentanil and the assessed NRS scores during inspiration in one representative patient. The two sufentanil dosing groups did not differ significantly regarding the patient characteristics and procedural times (table 1). Total sufentanil and hydromorphone doses and infusion times are summarized in table 2. The use of two predefined target concentrations for intraoperative sufentanil TCI and postoperative hydromorphone TCI explains the statistical differences between the doses given during these phases.

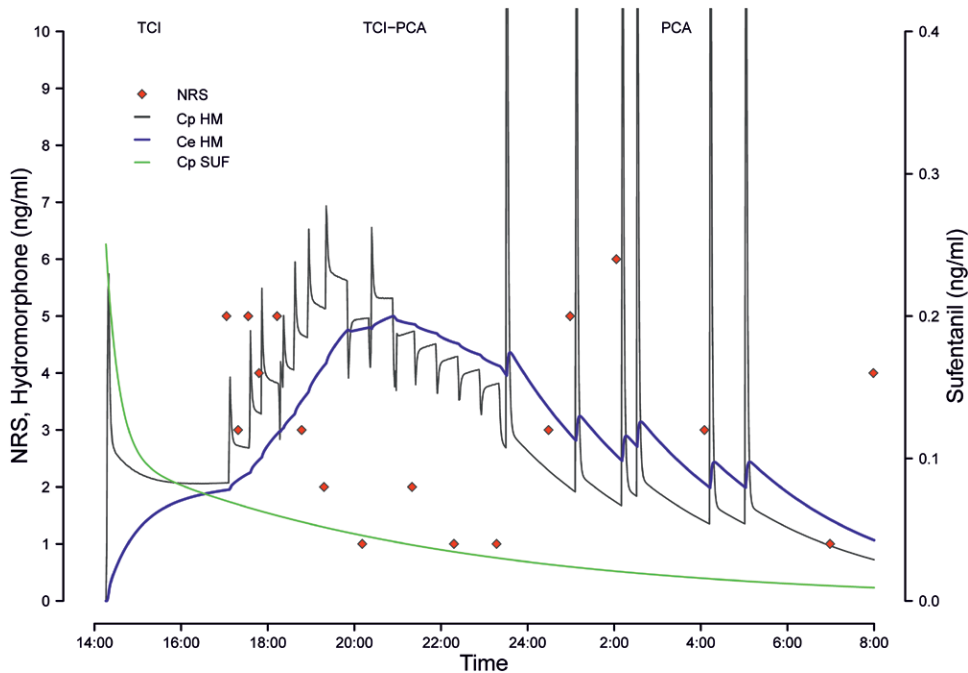
### Efficacy of Pain Therapy

Figure 4 shows the distribution of the NRS scores at rest and under inspiration during the TCI-PCA and the PCA

phases. As the time of pain assessment during PCA was not as standardized as during TCI-PCA, pain ratings during PCA were grouped in intervals of 2 h. During TCI-PCA, the NRS scores at rest stayed at a median of 0 during the first hour (measurements 1 to 5), then increased to a median of 2, and decreased again to a median of 1 where they remained until the end of the observation period (fig. 4A). At the beginning of TCI-PCA shortly after extubation, the NRS scores under inspiration were also low with a median of 0 (fig. 4B). During the following 60 min, the NRS scores increased to a median value of 3 where they remained until the end of the TCI-PCA phase. During the PCA phase, the median pain rating at rest further decreased to 0 and increased again at the end of the PCA phase (fig. 4C), whereas the median value of the pain under inspiration stayed at 3 for most of the time (fig. 4D). Furthermore, the distribution of NRS scores was more condensed at the end of TCI-PCA phase and more dispersed at the beginning of TCI-PCA and again toward the end of PCA. The analysis with the generalized model revealed that time and sufentanil group had a significant effect on the pain measurement at rest ( $P < 0.0001$  and  $P = 0.014$ , respectively), whereas the period (TCI-PCA vs. PCA) had no effect ( $P = 0.53$ ). For the pain under inspiration, there was a similar significant time effect ( $P < 0.0001$ ), but sufentanil ( $P = 0.12$ ) and period ( $P = 0.24$ ) had no effect. The median NRS score at rest during TCI-PCA was 2 (0 to 5) in sufentanil group 1 and 0 (0 to 4) in sufentanil group 2 ( $P = 0.049$ ). During PCA, the median NRS score at rest was 2 (0 to 5) in group 1 and 0 (0 to 5) in group 2 ( $P = 0.25$ ). For pain under inspiration, the corresponding



**Fig. 2.** Assessment, randomization, and follow-up of the patients. NRS = numerical rating scale; OR = operation room; PKPD = pharmacokinetic/pharmacodynamic; TCI-PCA = patient-controlled analgesia with target-controlled infusion.



**Fig. 3.** Pain sensation and concentration time profiles of predicted hydromorphone and sufentanil in a representative patient. Hydromorphone concentration axis (*i.e.*, left y-axis) is limited to 10 ng/ml although the maximum predicted hydromorphone plasma concentration during the patient-controlled analgesia (PCA) study phase was 17.6 ng/ml. Ce HM = hydromorphone effect-site concentration; Cp HM = hydromorphone plasma concentration; Cp SUF = sufentanil plasma concentration; NRS = numerical rating scale ratings under inspiration; TCI = target-controlled infusion; TCI-PCA = PCA with TCI.

**Table 1.** Descriptive Statistics of the Patients Used for Pharmacodynamic Analysis (n = 43)

	Sufentanil Dosing Group		Total
	0.4 ng/ml	0.8 ng/ml	
Sex (male/female)	16/7	15/5	31/12
Age (yr)	67 (48–81)	66 (40–77)	66 (40–81)
Weight (kg)	85 (58–104)	79 (63–100)	79 (58–104)
Height (cm)	175 (156–189)	172 (157–180)	173 (156–189)
Duration of anesthesia (min)	273 (189–312)	283 (235–444)	276 (189–444)
Intubation time (min)	475 (413–624)	509 (411–732)	487 (411–732)
Duration of surgery (min)	184 (41–244)	190 (156–335)	185 (41–335)
Bypass time (min)	69 (33–105)	80 (33–206)	74 (33–206)
Aortic clamping time (min)	39 (20–70)	50 (24–133)	43 (20–133)
Length of ICU stay (h)	23 (6.9–73)	22 (4.4–119)	22 (4.4–119)
Length of hospital stay (d)	9 (6–16)	9 (6–17)	9 (6–17)

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 males/females.

ICU = intensive care unit.

scores during TCI-PCA were 3 (0 to 6) in group 1 and 2 (0 to 5) in group 2 ( $P = 0.47$ ). During PCA, the median NRS score under inspiration was 3 (0 to 7) in group 1 and 2 (0 to 5) in group 2, respectively ( $P = 0.10$ ).

Figure 5A shows the frequency of all observed NRS scores under inspiration. Overall, 34% of the NRS ratings under inspiration were 1 or less, 49% were between 2 and 4, and only 17% were 5 or greater. The transition, that is, the difference between two consecutive NRS ratings, showed a narrow distribution around 0 (fig. 5B), also indicating a

relatively smooth time course of the pain rating without sudden changes.

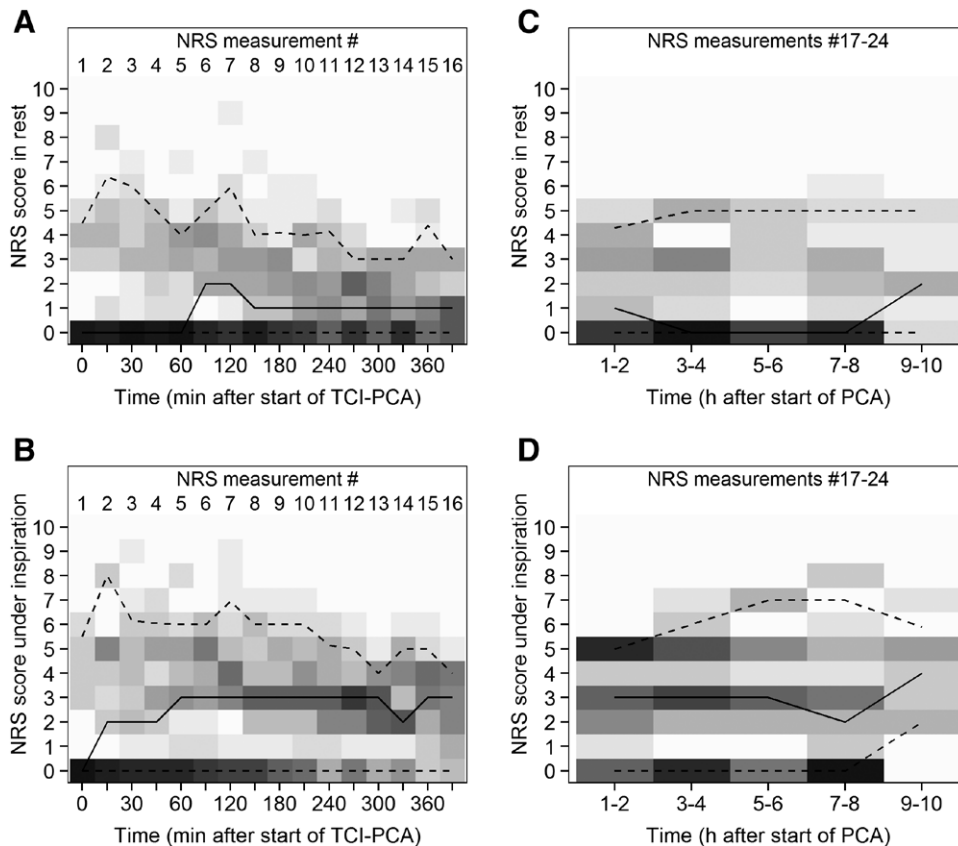
The hydromorphone doses administered during the TCI-PCA and PCA phases were 0.26 mg/h (0.07 to 0.93 mg/h) and 0.19 mg/h (0 to 0.61 mg/h), respectively ( $P = 0.023$ ). The median number of total requests for a target increase during TCI-PCA was 0.9 (0 to 3.6) requests per hour, and the median number of negatively answered requests was 0.15 (0 to 2.0) requests per hour. The median number of total bolus requests during the PCA phase was 1.3

**Table 2.** Lengths of Infusion and Total Amount of Drug Infused during Each Study Phase in Patients Used for Pharmacodynamic Analysis (n = 43)

	Sufentanil Dosing Group		P Value
	0.4 ng/ml	0.8 ng/ml	
Sufentanil TCI			
Length of infusion (h)	5.1 (3.8–6.6)	5.1 (4.5–7.6)	0.28
Amount dosed (mg)	0.18 (0.14–0.23)	0.36 (0.30–0.47)	< 0.0001
Hydromorphone TCI			
Length of infusion (h)	3.1 (2.0–5.3)	3.1 (1.8–6.2)	0.75
Amount dosed (mg)	1.2 (0.9–2.4)	0.8 (0.5–2.5)	0.015
Hydromorphone TCI-PCA			
Length of infusion (h)	6.6 (3.9–6.8)	6.5 (3.1–6.8)	0.18
Amount dosed (mg)	2.0 (0.5–6.1)	0.7 (0.3–5.3)	0.14
Hydromorphone PCA			
Length of PCA (h)	9.2 (5.4–10.6)	8.4 (5.8–11.5)	0.36
Amount dosed (mg)	1.6 (0.6–4.6)	1.6 (0–6.2)	0.60

Amounts are reported as median (range).

PCA = patient-controlled analgesia; TCI = target-controlled infusion; TCI-PCA = PCA combined with TCI.

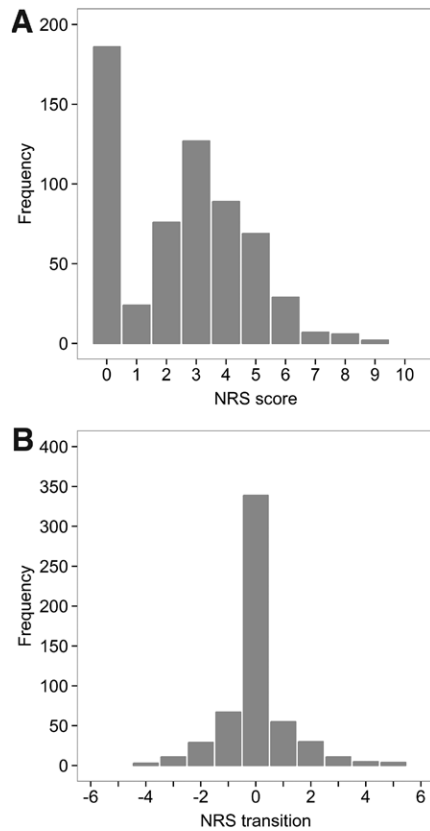


**Fig. 4.** Numerical rating scale (NRS) ratings during patient-controlled analgesia with target-controlled infusion (TCI-PCA) (A and B) and PCA (C and D), respectively. The solid black line represents the median and the dotted lines the 5th and 95th percentiles. Shading intensity corresponds to frequency density.

(0 to 26) requests per hour ( $P < 0.001$ ) compared with that during TCI-PCA. The median number of negatively answered bolus requests during the PCA phase was 0.42 (0 to 23) requests per hour ( $P = 0.012$ ) compared with that during TCI-PCA.

**Sedation**

Shortly after extubation at start of TCI-PCA, the median MOAA/S score was 4 (3 to 5) and the patients were cooperative. MOAA/S score increased to 5 (3 to 5) within the following 30 min and remained at this value until the end of the



**Fig. 5.** Distributions of the numerical rating scale (NRS) ratings under inspiration (A) and of the NRS transitions (B), that is, the difference between two consecutive NRS ratings under inspiration.

observation period. The simulated propofol concentration at the time of extubation was 0.59  $\mu\text{g/ml}$  (0.22 to 1.35  $\mu\text{g/ml}$ ).

### Rescue Therapy, Safety, and Adverse Effects

No rescue medications were required during the active study phase (TCI, TCI-PCA, and PCA). Two patients received dipyrone infusion during the TCI-PCA phase by a misunderstanding. These patients were excluded from the pharmacodynamic analysis (fig. 2). Adverse events are summarized in table 3. Nausea and vomiting were the most frequently adverse events. They were observed in 13 and 4 patients, respectively, and were treated with ondansetron.

Three patients developed respiratory insufficiency requiring noninvasive ventilation with a face mask: two patients during the TCI-PCA phase and one patient during the PCA phase (table 3). Because of no patient therapy requests, the system automatically reduced the hydromorphone target concentration from 1.5 to 1.25 ng/ml in both patients during the TCI-PCA phase.

Six patients had shivering during the TCI phase. All 43 patients received dobutamine; noradrenaline and glycerylnitrate were administered to 31 and 27 patients, respectively. Adrenalin was needed for hemodynamic control in two patients and amiodarone as an antiarrhythmic for two patients.

### Respiration and Hemodynamics

During TCI-PCA, respiratory frequency was  $14.0 \pm 2.2 \text{ min}^{-1}$  and peripheral arterial oxygen saturation was  $98.0 \pm 1.9\%$ . The mean values of heart rate during TCI, TCI-PCA, and PCA were  $88 \pm 11$ ,  $91 \pm 12$ , and  $94 \pm 11 \text{ min}^{-1}$ , respectively. The mean values of mean arterial blood pressure during TCI, TCI-PCA, and PCA were  $80 \pm 11$ ,  $77 \pm 10$ , and  $87 \pm 14 \text{ mmHg}$ , respectively.

### Pharmacokinetic Modeling and Simulation

The pharmacokinetic analysis of hydromorphone has been reported previously.<sup>12</sup> In short, we found that a three-compartment model with body weight and age as covariates best described the data. All clearances and volumes of distribution were scaled proportional to body weight. The elimination clearance and the central volume of distribution decreased with age. The parameters of the final pharmacokinetic model of hydromorphone are repeated in table S1 of the Supplemental Digital Content 1, <http://links.lww.com/ALN/B222>. The prediction errors were small for the population parameters (median prediction error [MDPE] = 5.0%; median absolute prediction error [MDAPE] = 21.0%), as well for the individual Bayesian estimates (MDPE = 1.2%, MDAPE = 9.5%).<sup>12</sup> The declining sufentanil concentrations could be well described by a two-exponential function (see fig. S2 of Supplemental Digital Content 1, <http://links.lww.com/ALN/B222>). The small prediction errors of MDPE = 0.1% and MDAPE = 5.3% indicated that the individual predictions were appropriate to calculate the individual sufentanil concentrations at the times of NRS measurement.

During TCI-PCA, the maximum target concentration varied between 0.9 and 7.0 ng/ml with a median of 2.3 ng/ml. The median value of the individually predicted hydromorphone concentration during this phase was 2.8 ng/ml (0.8 to 7.0 ng/ml) in group 1 and 1.6 ng/ml (0.9 to 8.9 ng/ml) in group 2 ( $P = 0.31$ ). During PCA, the individually predicted plasma concentrations of hydromorphone in the two groups were 1.7 ng/ml (0.1 to 54.1 ng/ml) and 1.7 ng/ml (0.1 to 33.0 ng/ml), respectively.

### Pharmacodynamic Modeling and Simulation

As there were only few pain ratings with an NRS score of 6 or greater and also only few pain ratings with an NRS score of 1 (fig. 5A), we did not build a logistic model with 11 levels from 0 to 10 but merged adjacent pain scores to reduce the number of levels. The tested model with highest resolution contained five levels: (0, 1), 2, 3, 4, and (5, 6, 7, 8, 9, 10). However, the resulting probability curves to observe a defined pain level overlapped strongly so that the probabilities to observe NRS scores of 2, 3, and 4 were almost identical in a hydromorphone concentration range around 3 ng/ml. Therefore, we merged the NRS scores further so that the final pharmacodynamic model contained three levels: pain level 1 (“no or very weak pain”) with NRS scores of



**Table 3.** Adverse Effects in Patients Used for Pharmacodynamic Analysis (n = 43)

Adverse Events	No. Patients	No. Incidents	Study Phase*
Nausea	13 (30%)	20	1/5/3/11
Vomiting	4 (9%)	5	0/1/1/3
Respiratory insufficiency	3 (7%)	3	0/2/1/0
Patients with respiratory insufficiency			
Patient number	8	14	50
Target concentrations of sufentanil TCI, hydromorphone TCI (ng/ml)	0.4, 2	0.8, 1	0.8, 1
Main symptoms	Rr 7 breaths/min, PaCO <sub>2</sub> 57 mmHg, PaO <sub>2</sub> /Fio <sub>2</sub> 195 mmHg	Rr 26 breaths/min, PaO <sub>2</sub> /Fio <sub>2</sub> 162 mmHg	Dyspnea, PaO <sub>2</sub> /Fio <sub>2</sub> 158 mmHg
Start of NIV after extubation (min)	93	141	545
NIV duration (min)	84	100	45
Study phase*	0/1/0/0	0/1/0/0	0/0/1/0
Target concentration of hydromorphone TCI-PCA (ng/ml)	1.5	1.5	—
Predicted effect concentrations of hydromorphone (ng/ml), sufentanil (ng/ml), and propofol (μg/ml)	2.19, 0.06, 0.3	1.9, 0.09, 0.34	2.4, 0.07, 0.07
NRS under deep inspiration, MOAA/S or RASS	0, 4	4, 5	3, -1

\* Number of patients during TCI/TCI-PCA/PCA/follow-up phases.

MOAA/S = Modified Observer's Assessment of Alertness/Sedation Scale; NIV = noninvasive ventilation; NRS = numerical rating scale; PaCO<sub>2</sub> = partial pressure of carbon dioxide; PaO<sub>2</sub>/Fio<sub>2</sub> = ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen; PCA = patient-controlled analgesia; RASS = Richmond Agitation Sedation Scale; Rr = respiratory rate; TCI = target-controlled infusion.

0 and 1, pain level 2 ("mild to moderate pain") with NRS scores of 2, 3, and 4, and pain level 3 ("severe pain") with NRS scores of 5 or greater. The observed probabilities for these three pain levels were 34, 49, and 17% (fig. 5A). Figure 6 shows the individually predicted effect-site concentrations of hydromorphone (fig. 6A) and sufentanil (fig. 6B) together with the distribution of these pain levels during TCI-PCA (fig. 6C). The equations for the final pharmacodynamic model were as following:

$$P(\text{pain} \leq 1) = \exp(Z_1) / (1 + \exp(Z_1)),$$

$$P(\text{pain} \leq 4) = \exp(Z_2) / (1 + \exp(Z_2)),$$

$$P(\text{pain} = [2, 3, 4]) = P(\text{pain} \leq 4) - P(\text{pain} \leq 1),$$

$$P(\text{pain} > 4) = 1 - P(\text{pain} \leq 4),$$

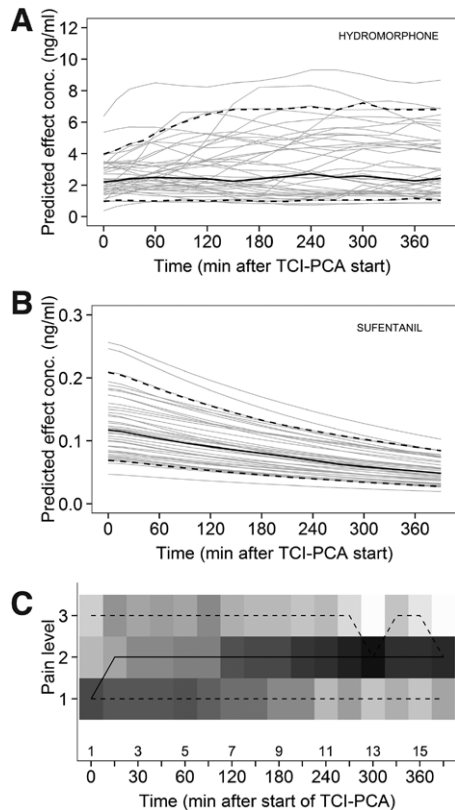
$$Z_1 = a_0 + b_1 \times C_{E, \text{HM}} + b_2 \times C_{E, \text{SUF}},$$

$$Z_2 = a_0 + a_1 + b_1 \times C_{E, \text{HM}} + b_2 \times C_{E, \text{SUF}}.$$

The parameters  $a_i$  define the probabilities of pain if no drug is present, the parameters  $b_1$  and  $b_2$  assess the drug effects of hydromorphone and sufentanil, and  $C_{E, \text{HM}}$  and  $C_{E, \text{SUF}}$  are the effect-site concentrations of hydromorphone and sufentanil, respectively (see Supplemental Digital Content 1, <http://links.lww.com/ALN/B222>). The effect-site equilibration rate constants  $k_{e0, \text{HM}}$  and  $k_{e0, \text{SUF}}$  could not be estimated reliably. Therefore, we fixed  $k_{e0, \text{HM}}$  to a value of  $0.015 \text{ min}^{-1}$  corresponding to a time to peak effect of 20 min

(see Supplemental Digital Content 1, <http://links.lww.com/ALN/B222>). For  $k_{e0, \text{SUF}}$  we chose a value of  $0.11 \text{ min}^{-1}$  as reported in the literature.<sup>29</sup> The likelihood profiles indicated no problems with parameter identification (see fig. S3 in Supplemental Digital Content 1, <http://links.lww.com/ALN/B222>). Table 4 summarizes the results obtained for the final pharmacodynamic model. The effect of pain treatment with both hydromorphone and sufentanil was significant as the objective function value increased by 44.1 ( $P < 0.0001$ ) if  $b_1$  was fixed to 0 (*i.e.*, no effect of hydromorphone) and by 99.4 ( $P < 0.0001$ ) if  $b_2$  was fixed to 0 (*i.e.*, no effect of sufentanil).

All pharmacodynamic parameters were characterized by a large interindividual variability (see fig. S4 in Supplemental Digital Content 1, <http://links.lww.com/ALN/B222>). The typical population values (95% CI of the individual estimates) of EC<sub>50</sub> for NRS of 4 or less and NRS of 1 or less were 4.1 ng/ml (0.6 to 12.8 ng/ml) and 9.6 ng/ml (5.9 to 18.3 ng/ml) for hydromorphone and 0.12 ng/ml (0.01 to 0.79 ng/ml) and 0.29 ng/ml (0.04 to 1.42 ng/ml) for sufentanil, respectively. During the observation period, the predicted residual sufentanil concentrations were around 0.1 ng/ml (fig. 6B). Simulation of the pain probabilities using the final pharmacodynamic model revealed that a concomitant sufentanil concentration of 0.1 ng/ml reduced the median EC<sub>50</sub> of hydromorphone by 3.3 ng/ml (fig. 7). The percentage of correct individual predictions by the final model was 83%. The individually predicted probabilities for a pain level of 1, 2, or 3 within the observation period were 34, 48, and 18%, respectively, being nearly identical to the observed probabilities. The plot of the difference between the observed and the predicted pain level *versus* time showed a good agreement for the individual predictions and an



**Fig. 6.** Time courses of the effect-site concentrations of hydromorphone (A) and sufentanil (B) and measured pain levels (C) during the patient-controlled analgesia with target-controlled infusion (TCI-PCA). Pain levels of 1, 2, and 3 correspond to numerical rating scale ratings of (0 to 1), (2 to 4), and (5 to 10) under inspiration, respectively. Effect-site concentrations were calculated using the individual parameters obtained in pharmacokinetic analysis and equilibration rate constants ( $k_{e0}$ ) of 0.015 and 0.11  $\text{min}^{-1}$  for hydromorphone and sufentanil, respectively. The *solid black line* represents the median and the *dotted lines* the 5th and 95th percentiles. Shading intensity corresponds to frequency density.

acceptable agreement for the population predictions (see fig. S5 in Supplemental Digital Content 1, <http://links.lww.com/ALN/B222>).

## Discussion

Patient-controlled analgesia with systemic opioids has been shown to provide better pain control than parenteral “nurse-administered” analgesia<sup>6</sup> and is nowadays a commonly used treatment of postoperative pain.<sup>7</sup> In clinical practice, the 11-point NRS is a widely used answer format for assessing pain intensity postoperatively.<sup>19,30</sup> A recently published analysis of postoperative pain in relation to pain-related interference with mood and activity identified NRS scores of 0 to 2, 3 to 4, and 5 to 10 for mild, moderate, and severe pain, respectively.<sup>31</sup> In this study, postoperative TCI of hydromorphone followed by TCI-PCA of hydromorphone was feasible for postoperative pain therapy and revealed effective pain relief at rest and during inspiration during the first 10 h after

cardiac surgery with thoracotomy. During the mean time of 6.5 h of TCI-PCA study phase, the assessed pain intensity at rest indicated a high degree of patient comfort, showing mild pain with an average NRS of 1. Furthermore, the level of pain intensity during inspiration was moderate with an average NRS of 3. There were no significant differences in NRS scores during inspiration between patients who had intraoperative sufentanil TCI target concentrations of 0.4 or 0.8 ng/ml. As depicted in figure 4, the dispersion of NRS scores became more condensed with ongoing TCI-PCA therapy, indicating that patients titrated themselves to a satisfactory level of pain intensity independent of their residual intraoperative opioid concentrations. Moreover, the frequency of abrupt changes in pain intensity was low as indicated by the difference between consecutive NRS ratings, which showed a narrow distribution around 0 (fig. 5B). However, the time resolution of 15 to 30 min for NRS assessment may have contributed in part to this smooth time profile of pain sensation.

The feasibility of the TCI-PCA concept for postoperative pain therapy has also been shown in a previous study that compared remifentanyl TCI-PCA with morphine PCA for the treatment of acute pain after uterine artery embolization.<sup>32</sup> The patients in the TCI-PCA group showed lower NRS scores and a lower number of treatment requests than patients in the PCA group during the first 4 h after surgery. The authors concluded a more effective pain therapy with remifentanyl TCI-PCA than with morphine PCA.

Recently published Practice Guidelines for Postanesthetic Care by the American Society of Anesthesiologists Task Force on Postanesthetic Care concluded that extensive and proactive evaluation of pain intensity should be performed during emergence and recovery.<sup>33</sup> In our study, we assessed pain intensity every 15 min during first hour after extubation and every 30 min afterward until the end of the TCI-PCA study phase. Concurrently to NRS assessment, the MOAA/S scores were also evaluated. A patient request for increasing the hydromorphone target concentration was positively answered by the TCI-PCA system after the predefined lockout time of 15 min. In addition, for safety reasons and with respect to the experimental design of the TCI-PCA algorithm, the study anesthetist had to confirm the patient request and release the positive answer of the TCI-PCA system after clinical evaluation of the patient. This complies with a vigilant dose titration to ensure an adequate pain treatment while avoiding adverse effects such somnolence or suppression of spontaneous breathing.<sup>33</sup> However, during the TCI-PCA phase, two patients (5%) developed respiratory insufficiency without somnolence with temporary need of noninvasive ventilatory support *via* face mask. The respiratory insufficiency observed in one patient who showed depression of respiratory rate and hypercarbia could have been induced by the opioid effect, whereas in the other patient, atelectasis formation might have induced the observed tachypnea and reduced arterial oxygenation

**Table 4.** Pharmacodynamic Parameters of the Final Population Model

Parameters	Estimate	SE (RSE%)	Bootstrap	
			Median	95% CI
$a_0$	-8.19	0.73 (8.9)	-8.13	-12.0 to -5.50
$a_1$	4.70	0.51 (11)	4.70	3.76 to 6.16
$b_1$ (ng/ml)	0.85	0.14 (16)	0.85	0.38 to 1.51
$b_2$ (ng/ml)	28.4	7.8 (27)	29.0	6.38 to 66.1
$k_{e0, HM}$ (min <sup>-1</sup> )	0.015 (fixed)	—	0.015 (fixed)	—
$k_{e0, SUF}$ (min <sup>-1</sup> )	0.11 (fixed)	—	0.11 (fixed)	—
Interindividual variability				
$\omega^2 a_0$	0.052	0.047 (90)	0.044	0.00001 to 0.13
$\omega^2 a_1$	0.16	0.082 (51)	0.15	0.039 to 0.31
$\omega^2 b_1$	0.13	0.13 (103)	0.11	0.00004 to 0.31
$\omega^2 b_2$	2.53	0.81 (32)	2.51	1.04 to 6.49
$\omega^2 k_{e0, HM}$	0 (fixed)	—	0 (fixed)	—
$\omega^2 k_{e0, SUF}$	0 (fixed)	—	0 (fixed)	—

HM = hydromorphone; RSE = relative standard error; SE = standard error; SUF = sufentanil.

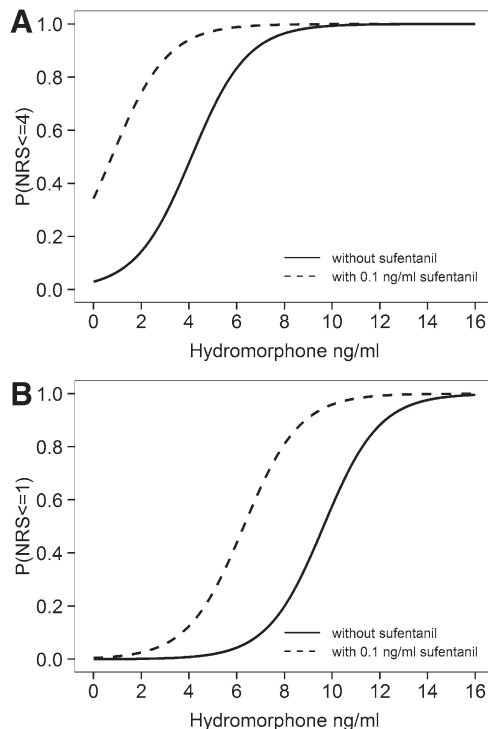
efficiency (table 3). However, the TCI-PCA system automatically reduced the hydromorphone target concentration to a previous level in both patients because of no patient therapy requests. These results are comparable with the mean incidence of respiratory adverse events with PCA that range between 1.2% (hypoventilation) and 11.5% (oxygen

desaturation).<sup>7,34</sup> Furthermore, with TCI-PCA, only five (12%) and one (2%) patients showed nausea and vomiting, respectively (table 3). These values are clearly below the mean incidence of 32 and 21% for nausea and vomiting, respectively, which have been reported in a 2005 published meta-analysis on adverse events of PCA.<sup>35</sup>

In our study, PCA was used because of practical limitations in carrying out the study overnight and because we were unaware if the TCI-PCA concept is efficient in this vulnerable patient population. Therefore, the comparison between TCI-PCA and PCA is limited not only by the different duration (6.5 and 8 h for TCI-PCA and PCA, respectively) but also by their sequential arrangement and pain assessment protocol. Although the median pain ratings did not differ between TCI-PCA and PCA, the CI became wider during the last 4 h of PCA (fig. 4), which might indicate that analgesia was less smooth.

The median hydromorphone doses were slightly higher during TCI-PCA than during PCA (0.26 and 0.19 mg/h, respectively). This may be mainly caused by the higher need of opioids during the titration period to the desired level of pain intensity within first 2 to 4 h after extubation. However, the median number of pain treatment requests per hour was significantly lower during TCI-PCA than during PCA. Furthermore, the range of the simulated hydromorphone plasma concentrations was much larger during PCA (0.1 to 54.1 ng/ml) than during TCI-PCA (0.8 to 8.9 ng/ml). This more narrow concentration range during TCI-PCA might be a benefit, as it may avoid overdosing as well as underdosing. Furthermore, targeting effect-site concentration in future applications instead of plasma concentration should also lead to a fast responsive effect-site concentration in response to titration of hydromorphone.

Considering the time profile of NRS scores in figure 4, the transition between residual analgesic effect of intraoperative sufentanil and postoperative pain relief with TCI-PCA



**Fig. 7.** The interaction between hydromorphone and sufentanil on the probabilities ( $P$ ) for a numerical rating scale (NRS) pain rating under inspiration 4 or less (A) and 1 or less (B), respectively. Population predictions of hydromorphone alone are shown with *solid lines*. The *dashed lines* show the corresponding analgesic effect if a sufentanil concentration of 0.1 ng/ml is present.

took place within first 2 h after extubation. The lower NRS scores at the beginning indicated either a residual sedative effect or a residual analgesic effect from intraoperative analgesia. Simulated propofol concentrations at the time of extubation were low with a median value of 0.59 µg/ml (0.22 to 1.35 µg/ml). After extubation, the median MOAA/S score was 4 (3 to 5), and the patients were cooperative, which suggests that the presence of a residual analgesic component was more likely than a residual sedation effect.

In our study, we used the 11-point NRS instead of a visual analog scale<sup>36</sup> because it is easily administered without the need for additional devices or writing materials. In addition, it provides sufficient discriminatory information for titrating opioid medication to incremental pain relief as well as information regarding the direction and the degree of change from one level of pain intensity to another. However, this pain measurement scale has been shown to have interval characteristics and therefore cannot be used to perform mathematical calculations for pharmacodynamic modeling, which require pain scores that exhibit ratio properties.<sup>37</sup> Therefore, we used an ordinal logistic regression model for the analysis of NRS scores. The pharmacodynamic model related the probability of measuring a particular NRS score to the hydromorphone and sufentanil effect-site concentrations. As depicted in figure S4 of Supplemental Digital Content 1, <http://links.lww.com/ALN/B222>, the typical hydromorphone EC<sub>50</sub> values for the probability of observing NRS of 4 or less and NRS of 1 or less were 4.1 and 9.6 ng/ml, respectively.

Previous studies investigated the analgesic effect of systemic hydromorphone with experimental pain models in healthy volunteers, having subjective pain reports and stimulus-related brain-evoked potentials<sup>38</sup> or pupil size<sup>18</sup> as analgesic effect indicators. Another previous study in healthy volunteers used visual analog scale to investigate the pharmacodynamics of orally administered sustained release of hydromorphone.<sup>39</sup> Therefore, the comparison of our pharmacodynamic results with previous findings is difficult.

The pharmacodynamic interaction between residual sufentanil and postoperative hydromorphone effect becomes evident when one considers not only the time profile of the merged NRS values in figure 6C, which were more condensed at a pain level of 1 for sufentanil concentrations above 0.1 ng/ml and increased afterward to a pain level of 2, but also the significant improvement in goodness of fit of the final pharmacodynamic model due to sufentanil effect. This implies the need for the sufentanil concentrations to be incorporated into the final pharmacokinetic/pharmacodynamic model. Thus, a concomitant sufentanil concentration of 0.1 ng/ml reduced the median EC<sub>50</sub> of hydromorphone by 3.3 ng/ml (fig. 7).

In conclusion, TCI-PCA with hydromorphone offered satisfactory pain relief after cardiac surgery with thoracotomy. The primary goal of NRS of 4 or less during inspiration, which is considered as a threshold value of acceptable

pain intensity during physical exacerbation<sup>37</sup> has been achieved with this pain therapy. Whereas the frequency of respiratory adverse events during TCI-PCA was comparable to values reported for PCA, the observed mean rates of nausea and vomiting were lower than values described in the literature. Finally, the pharmacokinetic/pharmacodynamic modeling based on plasma concentrations of postoperative hydromorphone and residual intraoperative sufentanil was able to describe the observed probabilities of pain levels.

## Acknowledgments

The authors thank Rainer Knoll (Department of Anesthesiology, University of Erlangen-Nürnberg, Erlangen, Germany) for conducting the drug analysis. The authors also thank Marie-Aline Kunz, M.Sc., Katharina Schmidt, M.Sc., Julian Peter, cand.med., Marco Lerch, cand.med., Eleana Acosta, cand.med., Tina Gräbner, cand.med., and Andreas Knipper cand.med. (Department of Anesthesiology, University of Erlangen-Nürnberg), for their assistance in data collection, and Gabriele Göhring-Waldeck (Department of Anesthesiology, University of Erlangen-Nürnberg) for her invaluable help in patient recruitment and study organization.

This work was supported by a grant from the German Federal Ministry of Education and Research, Berlin, Germany (Bundesministerium für Bildung und Forschung, grant no.: FKZ 13EX1015B).

## Competing Interests

The authors declare no competing interests.

## Reproducible Science

Full protocol available at: [christian.jeleazcov@kfa.imed.uni-erlangen.de](mailto:christian.jeleazcov@kfa.imed.uni-erlangen.de). Raw data available at: [christian.jeleazcov@kfa.imed.uni-erlangen.de](mailto:christian.jeleazcov@kfa.imed.uni-erlangen.de).

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