ORIGINAL CLINICAL RESEARCH REPORT

Predicting Unacceptable Pain in Cardiac Surgery Patients Receiving Morphine Maintenance and Rescue Doses: A Model-Based Pharmacokinetic-Pharmacodynamic Analysis

Sebastiaan C. Goulooze, MSc,* Elke H. Krekels, PhD,* Mohammed A. Saleh, MSc,* Sabine J. Ahlers, PhD, PharmD,† Pyry A. Välitalo, PhD,‡§ Eric P. van Dongen, MD, PhD,‖ Ron H. van Schaik, PhD,¶ Thomas Hankemeier, PhD,* Dick Tibboel, MD, PhD,# and Catherijne A. J. Knibbe, PharmD, PhD*,**

BACKGROUND: Optimal analgesic treatment following cardiac surgery is crucial for both patient comfort and successful postoperative recovery. While knowledge of both the pharmacokinetics and pharmacodynamics of analgesics is required to predict optimal drug dosing, models quantifying the pharmacodynamics are scarce. Here, we quantify the pharmacodynamics of morphine by modeling the need for rescue morphine to treat unacceptable pain in 118 patients after cardiac surgery.

METHODS: The rescue morphine event data were analyzed with repeated time-to-event (RTTE) modeling using NONMEM. Postoperative pain titration protocol consisted of continuous morphine infusions (median duration 20.5 hours) with paracetamol 4 times daily and rescue morphine in case of unacceptable pain (numerical rating scale ≥4).

RESULTS: Patients had a median age of 73 years (interquartile range [IQR]: 63–77) and median bodyweight of 80 kg (IQR: 72–90 kg). Most patients (55%) required at least 1 rescue morphine dose. The hazard for rescue morphine following cardiac surgery was found to be significantly influenced by time after surgery, a day/night cycle with a peak at 23:00 (95% confidence interval [CI], 19:35–02:03) each day, and an effect of morphine concentration with 50% hazard reduction at 9.3 ng·mL^{-1} (95% CI, 6.7–16).

CONCLUSIONS: The pharmacodynamics of morphine after cardiac surgery was successfully quantified using RTTE modeling. Future studies can be used to expand the model to better predict morphine's pharmacodynamics on the individual level and to include the pharmacodynamics of other analgesics so that improved postoperative pain treatment protocols can be developed. (Anesth Analg XXX;XXX:00–00)

KEY POINTS

- **Question:** Can morphine concentrations be related to the hazard of unacceptable pain following cardiac surgery using repeated time-to-event modeling?
- **Finding:** A model was developed that predicts the hazard of unacceptable pain using the morphine concentration, time after surgery, and time of day.
- **Meaning:** The low morphine concentrations that result from weaning may contribute to the high incidence of unacceptable pain following cardiac surgery.

GLOSSARY

AIC = Akaike information criterion; **Chr.Analg** = chronic use of analgesics; **CI** = confidence interval; **$EFF_{morphine}$** = exponential effect of morphine concentration; **ICU** = intensive care unit; **IQR** = interquartile range; **kbVHC** = kernel-based visual hazard comparison; **M3G** = morphine-3-glucuronide; **NRS** = numerical rating scale; **OPCIC** = optimization of procedural pain control in intensive care unit patients; **PK-PD** = pharmacokinetic-pharmacodynamic; **RSE** = relative standard error; **RTTE** = repeated time-to-event; **SNP** = single nucleotide polymorphism; **WDFY4** = WD repeat- and FYVE domain–containing protein 4

From the *Division of Systems Biomedicine and Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, the Netherlands; †Department of Clinical Pharmacy, Rijnstate Hospital, Arnhem, the Netherlands; ‡School of Pharmacy, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland; §Assessment of Medicinal Products Department, Finnish Medicines Agency, Kuopio, Finland; ‖Department of Anesthesiology and Intensive Care and Pain Management, St. Antonius Hospital, Nieuwegein, the Netherlands; ¶Department of Clinical Chemistry, Erasmus Medical Center, Rotterdam, the Netherlands; #Intensive Care and Department of Pediatric Surgery, Sophia's Children's Hospital, Rotterdam, the Netherlands; and **Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, the Netherlands.

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Adequate management of postoperative pain is crucial to ensure patient comfort and is associated with reduced risk of extended hospital stay and chronic postoperative pain.[1,2] The push toward increasingly faster postoperative recovery after cardiac surgery limits the extent to which analgesic treatment can be used to avoid postoperative pain, as this may delay transfer from the intensive care unit (ICU) to the ward.[3,4] However, inadequate management of postoperative pain is detrimental for patient comfort and increases the risk for chronic postoperative pain, which occurs in an estimated 30%–55% of patients after cardiac surgery.[1,2,5] Evidence-based management of postoperative pain following cardiac surgery should therefore strike a delicate balance between providing adequate analgesia when needed, and weaning from intravenous analgesia and subsequent extubation as early as possible.[1,2,6]

Postoperative pain titration protocols are commonly used to titrate toward adequate analgesia in the individual patient, but this cannot prevent the majority of patients from still experiencing moderate to extreme pain at some point after surgery.[1,7,8] This is in part due to the inherent reactionary nature of pain titration. In an ideal situation, increased analgesic requirements are predicted so that adequate analgesia can be administered before unacceptable pain occurs, for example, by increasing (background) analgesia during certain time frames (eg, directly after surgery or after weaning from intravenous analgesia) or in patient subgroups that are more likely to experience postoperative pain (eg, male/female patients or younger patients). This requires that we have quantitative knowledge of the pharmacokinetics and pharmacodynamics of analgesics used in patients after cardiac surgery, preferably on an individual level.

Population pharmacokinetic-pharmacodynamic modeling is a technique particularly suited for predictions of drug requirements by providing a dynamic and quantitative understanding of pain and analgesic therapy.[9] Repeated time-to-event modeling can be used to quantify the pharmacodynamics of analgesics by modeling the occurrence of the administration of rescue analgesia (eg, bolus dose of morphine).[10,11] Because rescue analgesia is administered in response to unacceptable pain, this approach puts a stronger focus on clinically relevant pain compared with modeling all changes in self-reported pain scores.

Although there exists a variety of postoperative pain protocols, with some relying on multimodal analgesia, morphine remains one of the most commonly used drugs to treat postoperative pain. While the pharmacokinetics of morphine are relatively well understood, the knowledge of its pharmacodynamics is limited. To quantify the pharmacodynamics of morphine after cardiac surgery, we performed a repeated time-to-event modeling analysis of rescue morphine data from a previously published study. This study included 118 patients after cardiac surgery that were treated with a standardized anesthesia and postoperative pain titration protocol, and data from this study were previously used to quantify the pharmacokinetics of morphine.[12,13]

METHODS

Clinical Study

This study is a secondary analysis of data obtained from the optimization of procedural pain control in intensive care unit patients (OPCIC) study.[12,13] This study was approved by the Institutional Review Board of the St. Antonius Hospital, Nieuwegein, and written informed consent was obtained before cardiac surgery from all subjects participating in the trial. The trial was registered at ClinicalTrials.gov before patient enrollment (NCT00558090, principal investigator: Catherijne A. J. Knibbe, date of registration: November 14, 2007). The study included 118 adult patients during their stay at the ICU after cardiac surgery.

All patients were treated according to a standardized postoperative pain titration protocol, which consisted of continuous intravenous infusions of morphine, and 4 times daily intermittent paracetamol at scheduled times. The pain was monitored using a numerical rating scale (NRS) that ranged from 0 to 10. All patients started on a continuous morphine infusion (2 $mg \cdot h^{-1}$), which was lowered and eventually stopped when the patient reported negligible pain levels (NRS ≤ 1). In case of unacceptable pain (NRS ≥ 4), additional rescue morphine was administered using bolus injections and, if patients were on continuous morphine infusion, the infusion rate was also increased by 0.5 $mg \cdot h^{-1}$. The first postoperative morning after surgery, patients received an additional bolus injection of morphine for procedural pain (ie, turning and/or chest drain removal) as part of the study protocol, for which patients were randomly assigned to receive either 2.5 or 7.5 mg morphine 30 minutes before the procedure. This planned bolus was given to all patients regardless of pain, and therefore not considered a rescue morphine dose in the pharmacokinetic-pharmacodynamic model. On leaving the

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This study is a secondary analysis of data from the OPCIC study, which is registered at clinicaltrials.gov (NCT00558090).

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Address correspondence to Catherijne A. J. Knibbe, PhD, PharmD, Division of Systems Biomedicine and Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Einsteinweg 55, 2333CC Leiden, the Netherlands. Address e-mail to c.knibbe@antoniusziekenhuis.nl.

ICU, patients who still received continuous intravenous morphine were switched to morphine as needed (intravenous or subcutaneous), and patient follow-up ended. Additional details about the study, patient demographics, and the pain titration protocol can be found in a previous publication.[13]

Population Pharmacokinetic Model

Morphine and morphine-3-glucuronide plasma concentrations were measured 4 times daily in all patients, resulting in an average of 8 samples per patient.[12] Concentrations were determined using high-performance liquid chromatography-tandem mass spectrometry with within-day coefficients of variation below 6% for morphine, and below 11% for morphine-3-glucuronide.[12] We used a previously published population pharmacokinetic model, which resulted from a nonlinear mixed-effects analysis of these pharmacokinetic observations. From this model, considering the individual patient's covariates, dosing history, and pharmacokinetic observations, we obtained the individual post hoc predicted plasma concentrations of morphine and morphine-3-glucuronide. We then used these concentrations as input for the repeated time-to-event model, without reestimating any of the parameters of the pharmacokinetic model (Figure 1).[14]

Pharmacokinetic-Pharmacodynamic Model Development

A repeated time-to-event model was used to characterize the hazard of (repeated) occurrences of rescue morphine administration between the start of the morphine infusion and the last available data record before leaving the ICU.[15] This hazard represents the expected number of rescue morphine doses per hour in an individual patient.[15] The input data for a repeated time-to-event model are the times at which a subject experiences an event, as well as the time at which the follow-up ends (ie, censoring data point). The likelihood of these data given the model is calculated according to[16]

$$P(\text{event}) = \text{hazard}(t) \times e^{-\text{cumh}(t)}$$

$$P(\text{censoring}) = e^{-\text{cumh}(t)}$$

where hazard (t) represents the hazard of an individual subject at the time of the event, and cumh (t) represents the cumulative hazard between the time of the previous event (or the time of follow-up start if the subject did not experience an event before time t) and the time t (the time of the event or the time of censoring).[16]

Different repeated time-to-event models were fitted with NONMEM 7.3 (ICON plc, Dublin, Ireland) using the stochastic approximation expectation-maximization method to estimate the parameters that maximize the likelihood followed by an expectation-only step of the importance sampling method to obtain an objective function value suitable for hypothesis testing.[17] The CTYPE = 3 option was set, meaning that the NONMEM's convergence test considers all model parameters. Mu-referencing was used in the model code.[18] Competing models were compared using the objective function value (–2 times log likelihood) for nested models or the Akaike information criterion (AIC) for nonnested models.[19] The visual evaluation of repeated time-to-event models is challenging due to the fact that the event and censoring data cannot be directly visually compared with the model-predicted hazard. Therefore, we used the kernel-based visual hazard comparison (kbVHC) as a model evaluation tool, which compares a kernel-based nonparametric hazard estimate of the data with the mean hazard of the repeated time-to-event model over time.[20] While the nonparametric hazard estimate may be smoother than the model-predicted hazard, the model-predicted hazard should display a similar trend of the hazard over time with the nonparametric hazard estimate. CV_{target}, the parameter that controls the smoothness of the nonparametric hazard estimate of the kbVHC, was set to 25%.[20]

Structural Hazard Model

Constant hazard, Gompertz and Weibull models were tested to describe the effect of time after surgery on the hazard for requiring rescue morphine doses.[15] In addition, a circadian or day/night variation of the hazard rate was explored, drug effect models based on E_{max}, sigmoid E_{max}, or exponential functions (with and without effect compartment) to characterize the effects of morphine and/or morphine-3-glucuronide on the hazard.[14] To characterize the unexplained interindividual variability of the hazard, a log-normally distributed frailty term was included in all tested models. A significance level of .05 was used when comparing nested models using the likelihood ratio test. For nonnested models, we used the AIC, where the difference in AIC corresponds to stronger evidence to prefer the model with the lower AIC.

Covariate Model

After the structural hazard model was developed, an exploratory covariate analysis was performed to identify covariates that would characterize interindividual variability of the hazard rate for rescue morphine. Covariates considered included patient demographics, perioperative and postoperative conditions, and a limited set of single nucleotide polymorphisms (SNPs) that have previously been reported to be associated with morphine's pharmacokinetics or pharmacodynamics.[21,22] Potential covariates were first preselected using the Empirical Bayesian Estimates correlation test[23] and then tested in the repeated time-to-event model using the likelihood ratio test in a stepwise

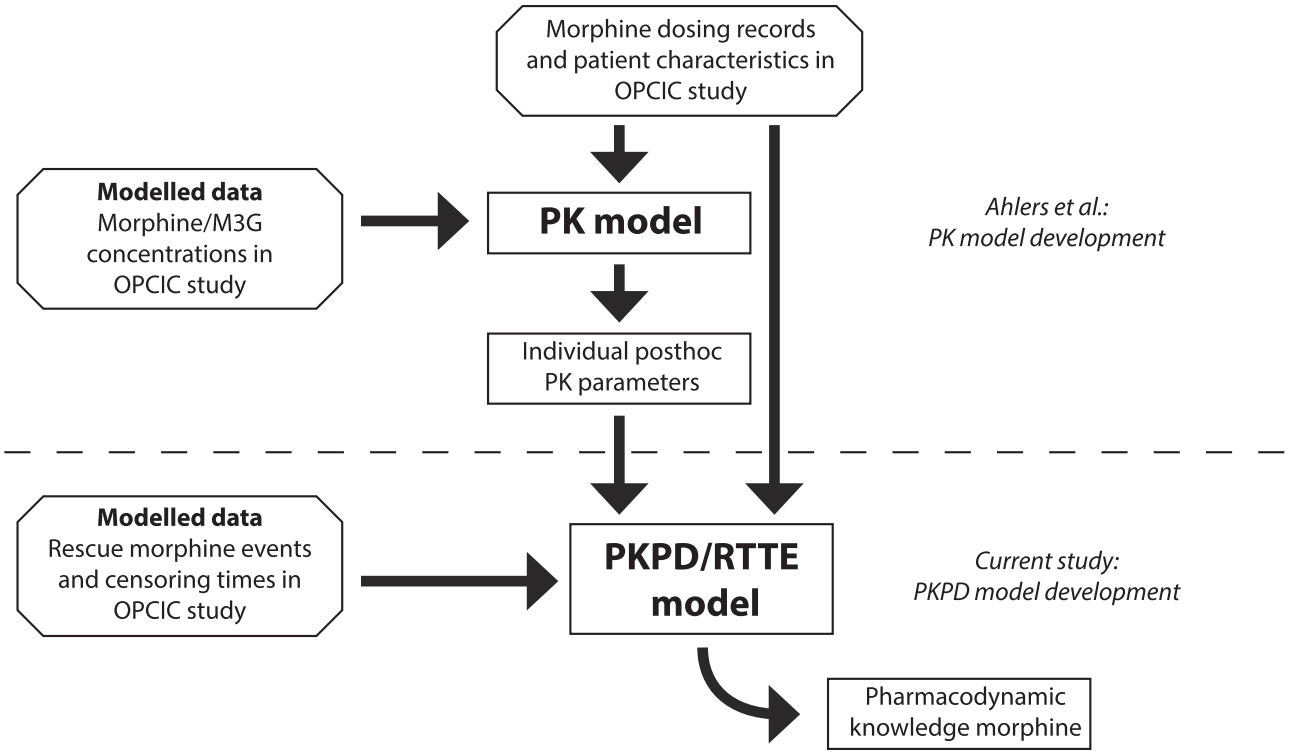

Figure 1. Flow chart showing how the observed data from the OPCIC study feeds into the current repeated time-to-event modeling analysis of rescue morphine after cardiac surgery. The upper part of the figure illustrates the nonlinear mixed-effects or population PK modeling analysis of OPCIC PK data by Ahlers et al,[12] which provided the individual post hoc estimated PK parameters. These PK parameters, and the morphine dosing records, are used in the current PK-PD analysis to obtain morphine and M3G concentrations over time, which are used in the RTTE analysis of the OPCIC rescue morphine data. M3G indicates morphine-3-glucuronide; OPCIC, optimization of procedural pain control in intensive care unit patients; PK-PD, pharmacokinetic-pharmacodynamic; RTTE, repeated time-to-event.

forward inclusion procedure ($\alpha = .05$), followed by a backward elimination ($\alpha = .01$) procedure.[24]

RESULTS

Clinical Study

The median follow-up of the 118 included subjects undergoing cardiac surgery was 42 hours (range, 16–247 hours). Patients had a median age of 73 years (interquartile range [IQR]: 63–77), median bodyweight of 80 kg (IQR: 72–90 kg). Most patients were taken off continuous morphine infusion between 12 and 24 hours after surgery. The median total duration of continuous morphine infusion during follow-up was 20.5 hours, with 83% of patients receiving <24 hours of morphine infusion.

During ICU stay, a total of 155 events of rescue morphine administration were observed. The majority of patients (55%) received at least 1 dose of rescue morphine, while 8% received rescue morphine on more than 3 occasions (Figure 2B). Figure 2A shows the follow-up of patients and occurrence of morphine rescue doses over time together with the period during which morphine infusion was given. A relatively large number of rescue morphine events occurred between 24 and 48 hours after surgery. The majority of rescue morphine events (ie, 74%) occurred after the morphine infusion was stopped (Figure 2). The median number of NRS scores collected in each patient was 8 (IQR: 6–11), with 64% of the scores indicating negligible pain (NRS ≤ 1), and 9% of the scores indicating unacceptable pain (NRS ≥ 4).

Pharmacokinetic-Pharmacodynamic Modeling

Model development started with a base model with a constant hazard over time, and additional parameters were added to the model in a stepwise manner if this addition significantly improved the fit of the rescue morphine event data (Supplemental Digital Content 1, Table S1, http://links.lww.com/AA/D211). Adding an exponential effect of morphine concentration ($EFF_{morphine}$) significantly improved the fit of the data ($P < .001$), and performed better than (sigmoid) E_{max} models. Going from a constant hazard to a Gompertz model, where the hazard declines exponentially over time from a baseline HAZ_{base} with an estimated slope HAZ_{slope}, further improved the model ($P < .001$). To reduce a bias observed in the kbVHC, a circadian or day/night variation of the hazard was also included in the model by estimating the parameters $CIRC_{amp}$ and $CIRC_{shift}$, and fixing $CIRC_{period}$ to 24 hours (Table) ($P < .05$). Including an effect of morphine-3-glucuronide on the hazard did not improve the model any further ($P > .05$).

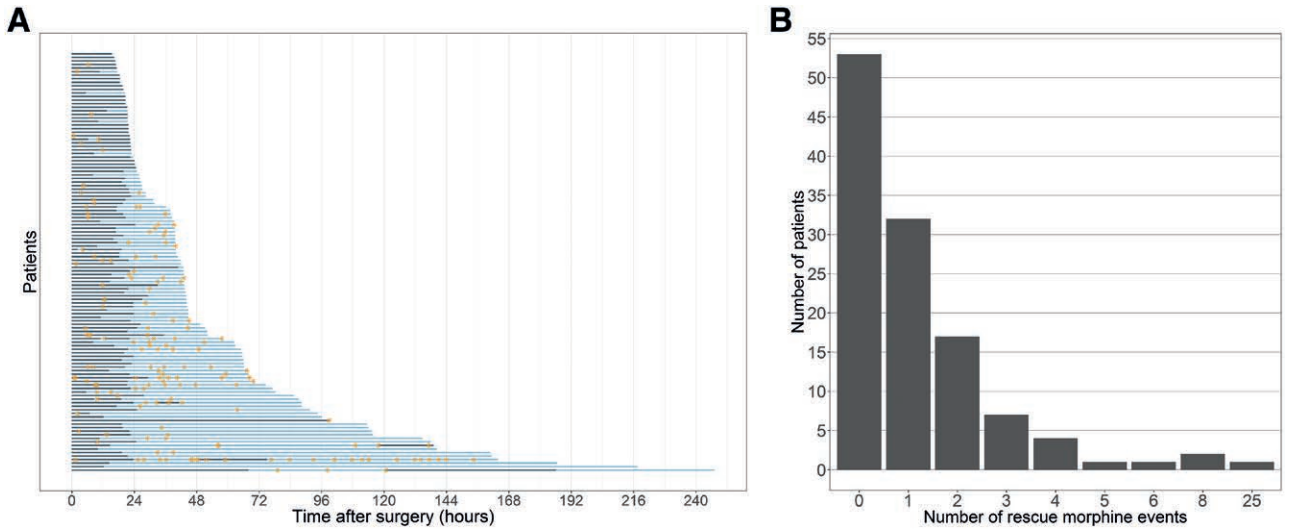

Figure 2. Overview of rescue morphine event data. A, Overview of follow-up time (horizontal lines) and rescue morphine administration (orange stars) of 118 patients included in the study. The black part of the horizontal line indicates the time during which a patient received a continuous morphine infusion while the blue part of the horizontal line indicates the absence of a continuous morphine infusion during follow-up. The ends of the horizontal lines indicate the censoring time of each patient. B, Overview of the number of rescue morphine events experienced by individual patients.

Interindividual variability was identified for the base hazard of the Gompertz model and could not be precisely estimated for any other model parameter.

In the covariate analysis, 3 statistically significant covariates were identified, that is, the genotype for the WD repeat- and FYVE domain–containing protein 4 (WDFY4) gene was found as covariate for the slope of the exponential relationship between morphine concentration and the hazard (COV_{WDFY4}), while sex and a history of chronic analgesic use were found as covariates on the hazard for requiring rescue morphine (COV_{sex} and $COV_{analgesics}$, respectively), see Table. More specifically, the slope of the exponential relationship between morphine concentration and the hazard was reduced by 82% (95% confidence interval [CI], 49–120) in patients with the WDFY4 SNP (rs17011183, $P < .001$, 11% of study population), women (25% of study population) had an estimated 63% (95% CI, 34–79) lower hazard than men ($P = .003$) and patients with a history of chronic use of analgesics (16% of study population) had a 121% (95% CI, 11–342) higher hazard ($P = .007$). Final parameter estimates can be found in Table and the NONMEM model code in Supplemental Digital Content 2, Information, http://links.lww.com/AA/D258. After the development described above, the individual hazard of a patient is defined as

$$\text{Hazard}_i = e^{\left(HAZ_{base} + HAZ_{slope} \times \text{time}_{since\ start}\right)} \times \left(1 + CIRC_{amp} \times \sin\frac{2\pi \times \left(\text{time}_{clock} + CIRC_{shift}\right)}{CIRC_{period}}\right) \times e^{\left(\left(EFF_{morphine} + WDFY4 \times COV_{WDFY4}\right) \times C_{mor}\right)} \times e^{\left(sex \times COV_{sex} + \text{analgesic use} \times COV_{analgesics}\right)} \times e^{(\eta i)}$$

where Hazard_i = individual hazard estimate of subject i; HAZ_{base} = natural log base hazard of Gompertz model; HAZ_{slope} = slope natural log base hazard of Gompertz model; $\text{time}_{since\ start}$ = hours since patient started initial morphine infusion; $CIRC_{amp}$ = relative amplitude of circadian hazard variation; time_{clock} = time in hours since last midnight; $CIRC_{shift}$ = shift of circadian hazard variation; $CIRC_{period}$ = period of circadian hazard variation; $EFF_{morphine}$ = slope of exponential morphine effect; WDFY4 = 1 if patient has the WDFY4 SNP and 0 otherwise; COV_{WDFY4} = additive covariate effect of WDFY4 SNP on slope of morphine effect; C_{mor} = morphine concentration in $ng \cdot mL^{-1}$; sex = 0 if male and 1 if female; COV_{sex} = natural log covariate effect of female sex on base hazard; analgesic use = 1 if patient is using analgesic chronically and 0 otherwise; $COV_{analgesics}$ = natural log covariate effect of history of analgesic use on base hazard; ηi = post hoc estimate of the individual frailty term of subject i. Due to the complexity of this equation, the different hazard functions that form the final model are illustrated in Figure 3 and Supplemental Digital Content 3, Figure S1, http://links.lww.com/AA/D259 (the latter with inclusion of the precision of the parameter estimates).

Figure 4 shows the model evaluation of the final model using the kbVHC method,[20] in which the nonparametric hazard estimate (representing the observations) is compared with the mean hazard of the model (representing model predictions). The figure shows for the nonparametric hazard estimate of the data a drop in the hazard for morphine rescue between 12 and 18 hours, and an elevated hazard between 24 and 40 hours, which is the period after most morphine infusions are stopped. A similar pattern is seen in

Table. Parameter Estimates and RSE of Final Pharmacokinetic-Pharmacodynamic Model of Rescue Morphine in Patients After Cardiac Surgery

Parameters (Units)	Submodel	Estimate (RSE)
Gompertz hazard	$e^{(HAZ_{base}+HAZ_{slope}\times time_{since\ start})}$	
HAZ_{base} (h^{-1})		−2.89 (11%)
HAZ_{slope} (h^{-1})		−0.0134 (46%)
Circadian rhythm	$1+CIRC_{amp}\times\sin\frac{2\pi\times(time_{clock}+CIRC_{shift})}{CIRC_{period}}$	
$CIRC_{amp}$ (-)		0.307 (40%)
$CIRC_{shift}$ (h)		7.18 (23%)
$CIRC_{period}$ (h)		24 fixed
Morphine effect	$e^{((EFF_{morphine}+WDFY4\times COV_{WDFY4})\times C_{mor})}$	
$EFF_{morphine}$ ($mL\cdot ng^{-1}$)		−0.0744 (20%)
COV_{WDFY4} ($mL\cdot ng^{-1}$)		0.0609 (26%)
Covariates on base hazard	$e^{(sex\times COV_{sex}+analgesicUse\times COV_{analgesics})}$	
COV_{sex} (-)		−0.98 (29%)
$COV_{analgesics}$ (-)		0.794 (45%)
Interindividual variability	$e^{(\eta i)}$	
Frailty ω^2 (-)		0.523 (35%)

The final hazard model is $Hazard_i = e^{(HAZ_{base}+HAZ_{slope}\times time_{since\ start})}$

$$\times\left(1+CIRC_{amp}\times\sin\frac{2\pi\times(time_{clock}+CIRC_{shift})}{CIRC_{period}}\right)$$

$$\times e^{((EFF_{morphine}+WDFY4\times COV_{WDFY4})\times C_{mor})}\times e^{(sex\times COV_{sex}+analgesic\ use\times COV_{analgesics})}\times e^{(\eta i)}.$$

where $Hazard_i$ = individual hazard estimate of subject i; HAZ_{base} = natural log base hazard; HAZ_{slope} = slope natural log base hazard; $time_{since\ start}$ = hours since patient started initial morphine infusion; $CIRC_{amp}$ = relative amplitude of circadian hazard variation; $time_{clock}$ = time in hours since last midnight; $CIRC_{shift}$ = shift of circadian hazard variation; $CIRC_{period}$ = period of circadian hazard variation; $EFF_{morphine}$ = slope of exponential morphine effect; WDFY4 = 1 if patient has the WDFY4 SNP and 0 otherwise; COV_{WDFY4} = additive covariate effect of WDFY4 SNP on slope of morphine effect; C_{mor} = morphine concentration in $ng\cdot mL^{-1}$; sex = 0 if male and 1 if female; COV_{sex} = natural log covariate effect of female sex on base hazard; analgesic use = 1 if patient is using analgesic chronically and 0 otherwise; $COV_{analgesics}$ = natural log covariate effect of history of analgesic use on base hazard; ηi = post hoc estimate of the individual frailty term of subject i; Frailty ω^2 = variance of frailty term.

Abbreviations: $EFF_{morphine}$, exponential effect of morphine concentration; RSE, relative standard error; WDFY4, WD repeat- and FYVE domain–containing protein 4.

the mean of the individual hazard predictions of the final model, confirming the goodness of fit. The kernel bandwidth is predominantly low (<10 hours) in the first 48 hours of the study, which indicates a good time resolution of the kernel hazard estimate to show changes in the hazard over time (Figure 4B). Later in the study, the kernel bandwidth increases above 10 hours, which results in a smoother kernel hazard estimate that is less likely to show variations in the hazard over time. As the number of subjects in follow-up decrease toward the end of the postoperative follow-up, the 95% CI of the nonparametric hazard estimate increases in width (Figure 4).

DISCUSSION

There is a lack of pharmacodynamic knowledge of analgesics to support improved pain-management protocols. In this study, we quantified the pharmacodynamics of morphine following cardiac surgery in 118 patients using repeated time-to-event modeling of rescue morphine dosing data. Through the development of a pharmacodynamic model, we were able to quantify the concentration-effect relationship of morphine in this population with good precision and identified a significant influence of time after surgery and a day-night difference in need for rescue morphine (Supplemental Digital Content 3, Figure S1, http://links.lww.com/AA/D259). The model was evaluated using the kbVHC, which compares the model predictions with a nonparametric hazard rate, which indicated that the model characterized the observed rescue morphine data well (Figure 4). The kbVHC is an internal model validation tool, and it would be valuable to also externally validate the model with a new data set.

With the model correctly describing the observed rescue morphine doses in these patients after cardiac surgery, we here compare the model parameters that affected the hazard for rescue morphine over time with literature values. The morphine concentration, which reduced the hazard of rescue morphine by 50% in our model, was estimated at 9.3 $ng\cdot mL^{-1}$ (95% CI, 6.7–16), which corresponds with the reported therapeutic window of morphine (9–80 $ng\cdot mL^{-1}$).[25] The Gompertz function that characterizes the decrease of the hazard after surgery is consistent with observations that average pain levels after cardiac surgery slowly decrease during the week after surgery.[26,27] We also identified a day/night variation of the hazard rate in this study, with the highest hazard around 23:00 (95% CI, 19:35–02:03). Other pain studies have found day/night or circadian variations in a variety of experiments and clinical settings, but the direction of these patterns was context-dependent.[28]

Because a direct relationship between morphine and a lower hazard for rescue morphine was found, it seems that slower weaning or alternative strategies are needed to reduce the occurrence of unacceptable pain following cardiac surgery when the continuous infusion of morphine is stopped. Possible alternative strategies include the use of multimodal analgesic regimens and/or the use of oral, epidural, or intrathecal opioids.[29,30] Data from studies where such alternative analgesic regimens are used can be used to extend the current model to also quantify the pharmacodynamics of other analgesics, so that this knowledge may ultimately be used to improve postoperative pain protocols. This extension would also expand the applicability of the model, because the current model does not apply to institutions that do not use morphine as a first-line analgesic.

Another option to reduce the occurrence of unacceptable pain events would be to adjust the timing

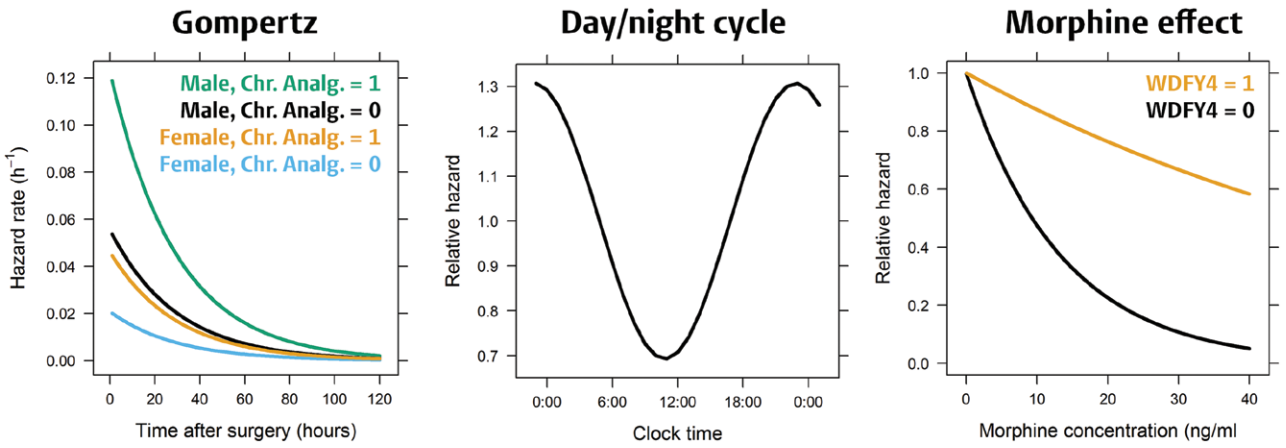

Figure 3. Visual illustration of the different submodels (ie, Gompertz hazard, day/night cycle, and morphine effect) of the final repeated time-to-event model, including the covariates sex, Chr.Analg, and WDFY4 genotype. The hazard of a typical individual (without interindividual variability) can be obtained by multiplying the Gompertz hazard (left panel) with the relative hazards from the other 2 panels. Chr.Analg = indicator whether or not patient chronically used analgesics before the study, indicated by a value of 1 or 0, respectively. WDFY4 = 1 indicates patients with the rs17011183 polymorphism in at least 1 allele of the WDFY4 gene. An adaptation of this figure that includes uncertainty of the model parameter is provided in Supplemental Digital Content 3, Figure S1, http://links.lww.com/AA/D259. Chr.Analg indicates chronic use of analgesics; WDFY4, WD repeat- and FYVE domain–containing protein 4.

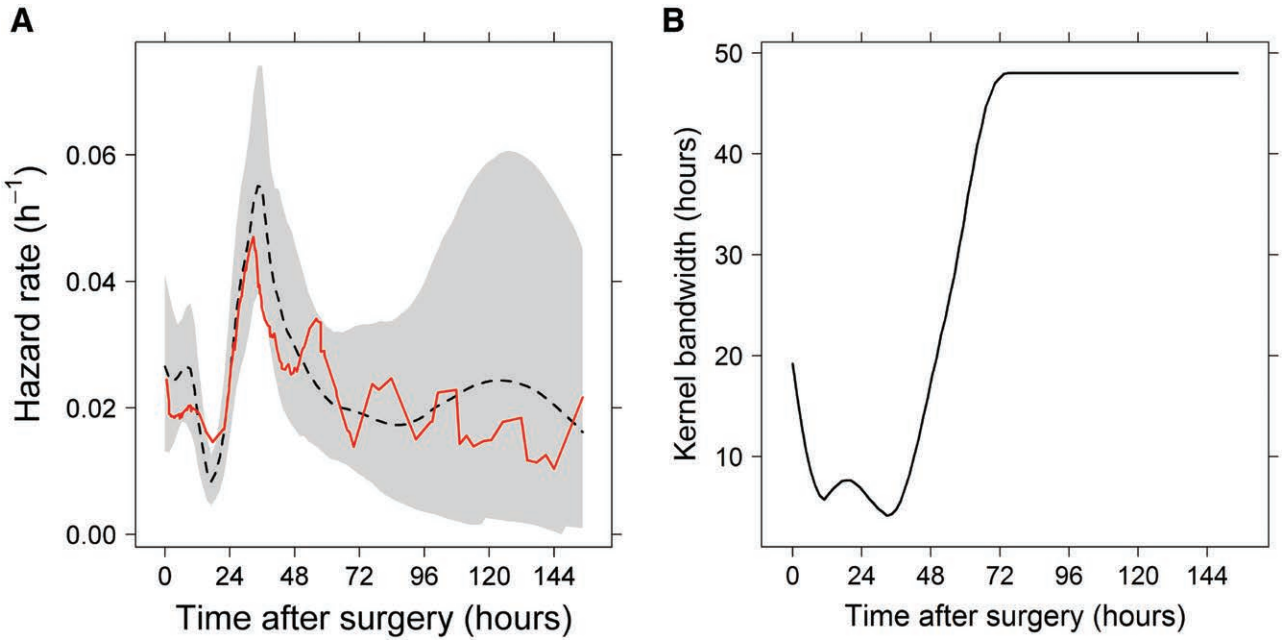

Figure 4. kbVHC of the final PK-PD model. A, Model evaluation of the final PK-PD model by visual comparison of the nonparametric hazard and the model-predicted hazard using the kbVHC.[20] The solid red line depicts the mean of the model-predicted individual hazard estimates of all noncensored individuals while the black dashed line and the gray shaded area depict the kernel estimate of the hazard rate in the data and its 95% confidence interval. B, Local bandwidth over time used to generate the kernel hazard estimate in (A). The higher the kernel bandwidth, the smoother the kernel estimate of the hazard rate becomes. PK-PD indicates pharmacokinetic-pharmacodynamic; kbVHC, kernel-based visual hazard comparison.

and doses of the pain titration protocol, because many unacceptable pain events that occurred after cessation of the morphine infusion might have been avoided if the morphine infusion was stopped more gradually. Additionally, the risk of unacceptable pain levels might be higher when weaning is initiated in the late afternoon or evening, because this would cause morphine concentrations to be low when the hazard for requiring rescue morphine is at the peak of its day/night cycle around 23:00 (95% CI, 19:35–02:03).

From the patient characteristics that we tested as covariates, 3 emerged as significant predictors of increased risk for unacceptable pain: male sex, a history of chronic analgesia use, and WDFY4 genotype. One or more of these covariates could theoretically be

used to individualize analgesic treatment, for example, by providing more aggressive analgesia to males to compensate for a higher baseline risk of unacceptable pain. However, it is important to note that the covariates identified here would need to be further validated in external data sets before the implementation of pain protocol adjustments based on these covariates in the clinic can be considered. This is due to the exploratory nature of the covariate search in this study, which resulted in wide CIs of the covariate effects (Supplemental Digital Content 3, Figure S1, http://links.lww.com/AA/D259) and increased the chance that false-positive covariates were identified among correlated covariates.[31]

Although we investigated a wide range of possible predictors of morphine requirements, we did not study potential psychological variables that are known to play an important role in pain perception.[32–34] We also did not incorporate the potential morphine-sparing effect of paracetamol in the model, because pharmacokinetic data of paracetamol were not collected during the clinical study, and all subjects received the same paracetamol doses.[35] Proteomics and metabolomics data would have also been valuable for their potential prognostic value for postoperative pain treatment, and might also provide insight into the mechanisms that underlie the considerable between-subject differences in morphine requirements.[36,37] Finally, the adverse effects of morphine, such as the occurrence of ventilatory depression over time, were not systematically recorded in this study. If they were, the adverse events could also have been analyzed with repeated time-to-event modeling, which could have allowed predictions of analgesia protocols that optimize the benefit-risk profiles of morphine.[38]

In conclusion, we used repeated time-to-event modeling to quantify the pharmacodynamics of morphine in the treatment of postoperative pain following cardiac surgery. The model adequately described the observed data and allowed us to quantitatively explain a period of increased unacceptable pain, which occurred after continuous infusions of intravenous morphine were stopped in most patients. Our findings suggest that slower weaning and/or use of alternative strategies might be needed to reduce the occurrence of unacceptable pain following cardiac surgery. The capacity of the model to propose improved postoperative pain-management protocols can be further enhanced in future studies by (1) inclusion of the pharmacodynamics of drugs used in other (multimodal) postoperative pain-management protocols, (2) inclusion of the adverse effects of analgesic treatment, and (3) validation of the prediction of the pharmacodynamics of morphine on the individual level.

DISCLOSURES

Name: Sebastiaan C. Goulooze, MSc.
Contribution: This author helped design the pharmacometrics study, perform the pharmacometrics study, interpret the results, and write the article.
Name: Elke H. Krekels, PhD.
Contribution: This author helped design the pharmacometrics study, perform the pharmacometrics study, interpret the results, and write the article.
Name: Mohammed A. Saleh, MSc.
Contribution: This author helped perform the pharmacometrics study and interpret the results.
Name: Sabine J. Ahlers, PhD, PharmD.
Contribution: This author helped design and conduct the clinical study, design the pharmacometrics study, and interpret the results.
Name: Pyry A. Välitalo, PhD.
Contribution: This author helped design the pharmacometrics study, perform the pharmacometrics study, and interpret the results.
Name: Eric P. van Dongen, MD, PhD.
Contribution: This author helped design and conduct the clinical study and interpret the results.
Name: Ron H. van Schaik, PhD.
Contribution: This author helped design and conduct the clinical study and interpret the results.
Name: Thomas Hankemeier, PhD.
Contribution: This author helped design the pharmacometrics study and interpret the results.
Name: Dick Tibboel, MD, PhD.
Contribution: This author helped design the clinical study, design the pharmacometrics study, and interpret the results.
Name: Catherijne A. J. Knibbe, PharmD, PhD.
Contribution: This author helped design the clinical study, design the pharmacometrics study, perform the pharmacometrics study, interpret the results, and write the article.
This manuscript was handled by: Ken B. Johnson, MD.

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