Supplemental Digital Content 1: Pharmacokinetic/-dynamic modeling

Pharmacokinetic/-dynamic modeling was performed using NONMEM (Version 7.3, ICON Development solutions, Hanover, MD, USA). Interindividual variability of the pharmacokinetic parameters was estimated using log-normal distributions with mean zero and variance ω^2, and intra-individual variability was estimated using a proportional error model with mean of zero and variance σ_1^2. The first-order conditional estimation method with interaction was used for pharmacokinetic analyses. For hydromorphone, 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. Based on the individual Bayesian estimates of the pharmacokinetic parameters, selected covariates were incorporated to the basic structural model using linear relationships with centering on the median value of the covariate within the population. The influence of age and body weight on pharmacokinetic parameters was assessed by linear relationships, and also by an allometric power model for the effect of body weight. Model selection was based on changes of the NONMEM objective function value (OFV). An additional covariate parameter was included in the model, if the decrease in the NONMEM objective function value (ΔOFV) was at least 3.84 ($P < 0.05$) and if the 95% confidence interval of this additional parameter did not include zero. Subsequently, backward deletion analysis was performed and each covariate effect was tested again for significance. This time, a more conservative significance level of $P < 0.01$ was used, which corresponds to ΔOFV=6.6 for one degree of freedom.

For sufentanil we used a slightly different approach, as there were only post-infusion concentration data available, which may cause some bias in the estimates of the central

compartment of distribution and of the fast half-life. As we aimed only to obtain individual predictions of the sufentanil concentration for the pharmacodynamic modeling during pain assessment, the time course of the sufentanil plasma concentration was fitted using a simple two-exponential function: $C(t) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$

where t=0 was defined as the time of the first sample shortly before end of the sufentanil infusion. Individual posthoc estimates of the parameters A, B, α and β were obtained by population modeling as described above, and were used to calculate the individual time courses of the sufentanil plasma concentrations.

The pharmacodynamic model used an ordinal logistic regression approach to relate the probability of measuring a particular NRS score to the hydromorphone and sufentanil effect site concentrations:

$$P(pain \leq m) = \exp(Z_m)/(1+\exp(Z_m)) \tag{1}$$

Where $P(pain \leq m)$ is the probability that the NRS score would be equal to or smaller than m. Z_m is the logit function of the probability and links the effect with the drug concentrations:

$$Z_m = \sum_{i=0}^{m} a_i + b_1 \cdot C_{E,HM} + b_2 \cdot C_{E,SUF} \tag{2}$$

The parameters a_i define the cumulative probabilities $P(pain \leq m)$ if no drug is present, the parameters b_1 and b_2 assess the drug effects of hydromorphone and sufentanil, and $C_{E,HM}$ and $C_{E,SUF}$ are the effect site concentrations of hydromorphone and sufentanil, respectively. As the NRS scale has 11 levels from 0 to 10, one has therefore to estimate the parameters a_0, a_1, …a_{10}, b1 and b2. There are, however, two conditions to be considered. From the condition $P(pain \leq m) \leq P(pain \leq m+1)$ follows that $a_i \geq 0$ for i=1 to 10. From the condition $P(pain \leq 10) = 1$

follows that $\sum_{i=0}^{10} a_i = 1$, so that only a_0 to a_9 are to be estimated, whereas a_{10} is given by

$$a_{10} = 1 - \sum_{i=0}^{9} a_i .$$

The half-maximum effect-site concentrations $EC_{50,m}^{HM}$ and $EC_{50,m}^{SUF}$ that are needed for

P(pain≤m)=50% can be calculated from the condition Z_m=0. Thus, the half-maximum effect-

site concentration for hydromorphone without sufentanil is $EC_{50,m}^{HM} = -(\sum_{i=0}^{m} a_i)/b_1$, and for

sufentanil without hydromorphone $EC_{50,m}^{SUF} = -(\sum_{i=0}^{m} a_i)/b_2$. The half-maximum effect-site

concentration of hydromorphone in combination with a specific sufentanil concentration

$C_{E,SUF}$ was calculated by

$$EC_{50,m}^{HM} = -(\sum_{i=0}^{m} a_i + b_2 \cdot C_{E,SUF})/b_1$$

Whereas equation (1) defines a cumulative probability that pain is smaller or equal than a

defined level, one is usually interested in the probability to observe exactly a defined pain

level. This probability P(pain=m) can be determined from the cumulative probabilities:

P(pain=m) = P(pain ≤m) - P(pain ≤m-1)   (3)

with P(pain=0) = P(pain≤0) and P(pain=10)=1 - P(pain≤9)

If one uses the original NRS data, there are 10 parameters a_0, a_1, … a_9 to be estimated, which

may be difficult if the incidence of a specific NRS score in the data is low. It may also be

questionable to discriminate clearly between two adjacent NRS scores. Therefore, we tested

also models where two or more adjacent NRS scores were merged to one pain level.

The effect site concentrations of hydromorphone and sufentanil were calculated based on the individual model predictions of the plasma concentrations $C_{P,HM}$ and $C_{P,SUF}$ of hydromorphone and sufentanil:

$$\frac{dC_{E,HM}}{dt} = k_{e0,HM} \cdot (C_{P,HM} - C_{E,HM})$$

$$\frac{dC_{E,SUF}}{dt} = k_{e0,SUF} \cdot (C_{P,SUF} - C_{E,SUF})$$

The rate constants $k_{e0,HM}$ and $k_{e0,SUF}$ which assess the time delay (hysteresis) between the plasma concentration of the drug and the analgesic effect are also to be estimated from the time course of the NRS rating. As the NRS ratings were measured in intervals of 15 to 30 min and as there were only slow changes in the plasma concentrations of hydromorphone and sufentanil, $k_{e0,HM}$ and $k_{e0,SUF}$ may not be estimated reliably. Therefore, we tested two approaches: 1) to estimate both $k_{e0,HM}$ and $k_{e0,SUF}$ and 2) to fix the values of $k_{e0,HM}$ and $k_{e0,SUF}$ to values from the literature. For sufentanil we chose a value of $k_{e0,SUF} = 0.11$ min^{-1} which was reported by Scott et al.[29] For hydromorphone, Coda et al.[38] reported a time to peak effect in the range of 10 to 20 min, whereas Angst et al.[39] reported a time to peak effect of approximately 40 min. We therefore chose $k_{e0,HM}$ such that a time to peak effect of 20 min was obtained when using the hydromorphone pharmacokinetics determined in this study. Interindividual variability of the pharmacodynamic parameters was estimated assuming log-normal distributions. Residual intra-individual variability is not defined for logistic regression models. Pharmacodynamic analyses were performed using the Laplacian method.

Model Evaluation and Validation

Pharmacokinetic models: We calculated the prediction error (PE_{ij}) and the absolute prediction error (APE_{ij}) to evaluate the goodness of fit:

$$PE_{ij} = \frac{c_{m,ij} - c_{p,ij}}{c_{p,ij}} \cdot 100\%$$

$$APE_{ij} = \frac{\left|c_{m,ij} - c_{p,ij}\right|}{c_{p,ij}} \cdot 100\%$$

where $c_{m,ij}$ is the jth measured concentration of the ith individual, and $c_{p,ij}$ is the corresponding predicted concentration. Prediction errors were calculated for individual and population predictions, and goodness of fit was assessed by the median values of PE_{ij} (MDPE) and APE_{ij} (MDAPE). Goodness of fit was also assessed by visual inspection of the following plots: measured concentrations vs. population (PRED) and individual predictions (IPRED), conditional weighted residuals (CWRES) vs. PRED and CWRES vs. time. Bootstrap analysis was performed to analyze the stability of the model and to obtain nonparametric confidence intervals of the final population model parameters. From the observed data, 1000 new data sets with the same number of individuals as the original data set were generated by resampling with replacement, and the final model was fitted to these new data sets.

Pharmacodynamic models: The standard goodness of fit diagnostics such as plots of measured vs. predicted values could not be directly performed as the pharmacodynamic model did not predict a pain level but probabilities to observe defined pain levels. One can, however, determine a "predicted value" by selecting as model prediction that pain level with the highest probability. Using this as "model prediction" we counted the percentage of correct NRS

predictions. Additionally, we calculated the predicted overall probability to observe a defined

pain level of m within the observation period as $P(\text{pain} = m) = \dfrac{\sum\limits_{i=1}^{N} P_i(\text{pain} = m)}{\sum\limits_{i=1}^{N} \sum\limits_{j=1}^{M} P_i(\text{pain} = j)}$

where $P_i(\text{pain}=m)$ is the predicted probability for the ith measurement to observe a pain level

of m, N is the total number of pain measurements, and M is the number of pain levels. The

difference of measured and predicted pain levels was further plotted vs. time as "heat map"

showing the density distribution on a grey scale.

In order to assess the significance of hydromorphone and sufentanil on the pharmacodynamic

model, we compared the NONMEM OFV of the full model with the OFV of the reduced

models with $b_1=0$ (no analgesic effect of hydromorphone) and/or $b_2=0$ (no analgesic effect of

sufentanil). Using the final model and the original data set, bootstrap analysis with 1000

replicates was conducted for validation of the pharmacodynamic model. The reliability of the

pharmacodynamic parameter estimates was further assessed by likelihood profiling. For this

purpose, the parameter to be assessed was fixed at particular values around its final population

estimate and the corresponding OFV was determined. The plot of the OFV vs. the parameter

values helps to identify problems with parameter estimability (e.g. in case of a very flat

profile). As the change of the OFV follows approximately a chi-square distribution with one

degree of freedom, nonparametric 95% and 99% confidence intervals of the parameter are

defined by those areas of the likelihood profile where $\Delta OFV < 3.84$ and <6.63, respectively.

Table S1. Hydromorphone pharmacokinetic parameters obtained from the final population model, as reported in a previous publication.[12]

Parameters	Model Parameters	Estimate	SE (RSE%)
θ_1 (l/min)	$CL_1=\theta_1\cdot(BW/70)\cdot(1+\theta_7\cdot(age-67))$	1.01	0.046 (4.6)
θ_2 (l)	$V_1=\theta_2\cdot(BW/70)\cdot(1+\theta_8\cdot(age-67))$	3.35	0.29 (8.6)
θ_3 (l/min)	$CL_2=\theta_3\cdot(BW/70)$	1.47	0.23 (16)
θ_4 (l)	$V_2=\theta_4\cdot(BW/70)$	13.9	2.9 (21)
θ_5 (l/min)	$CL_3=\theta_5\cdot(BW/70)$	1.41	0.13 (9.2)
θ_6 (l)	$V_3=\theta_6\cdot(BW/70)$	145	13.2 (9.1)
θ_7		-0.015	0.0053 (35.5)
θ_8		-0.028	0.0072 (25.9)

RSE, relative standard error; BW, bodyweight.

Figure S1. Flow-diagram showing the algorithm for the TCI-PCA control system.
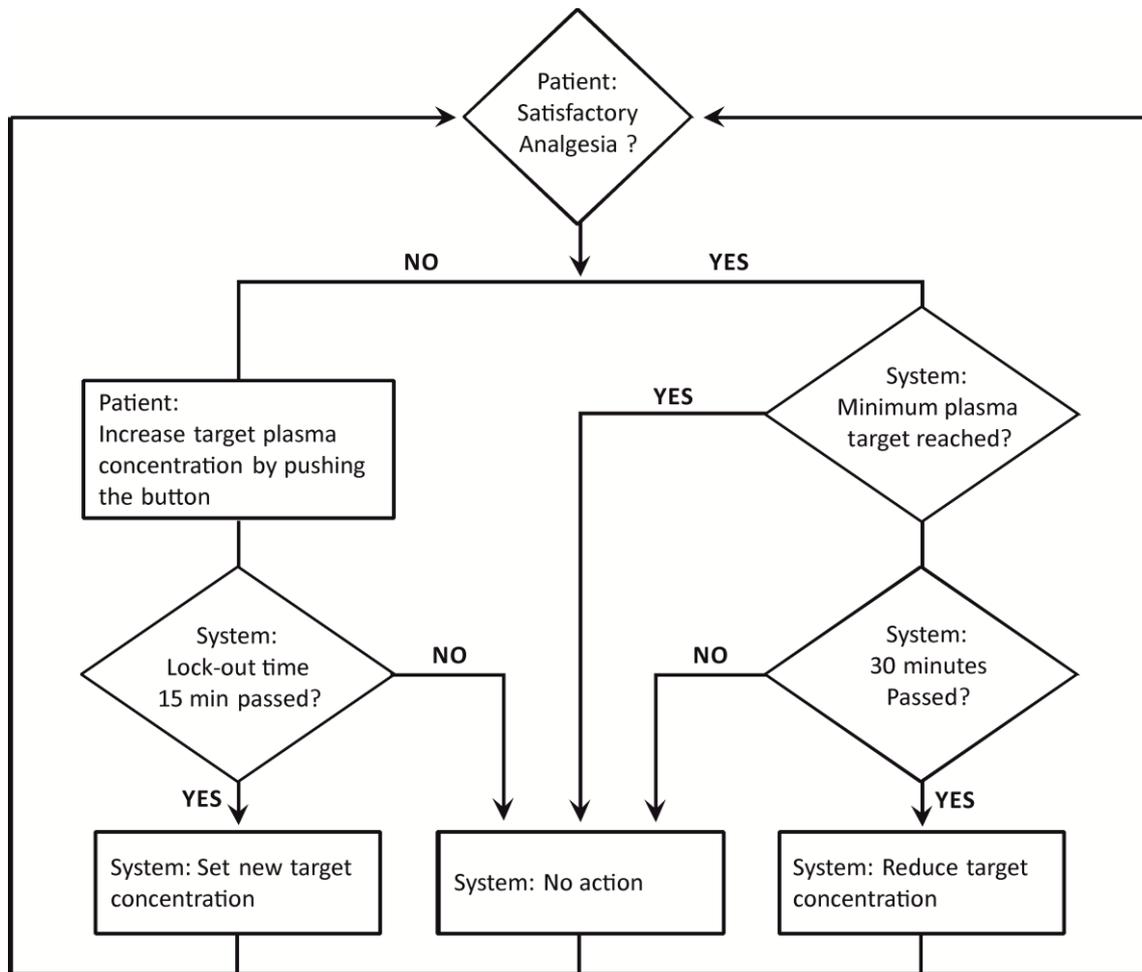
Figure S2. Prediction errors of the two-exponential function for the declining sufentanil

concentrations. MDPE, median prediction error; MDAPE, median absolute prediction error.

A

Individual predictions

MDPE: 0.1 %
MDAPE: 5.3 %

B

Population predictions

MDPE: -0.5 %
MDAPE: 29.5 %
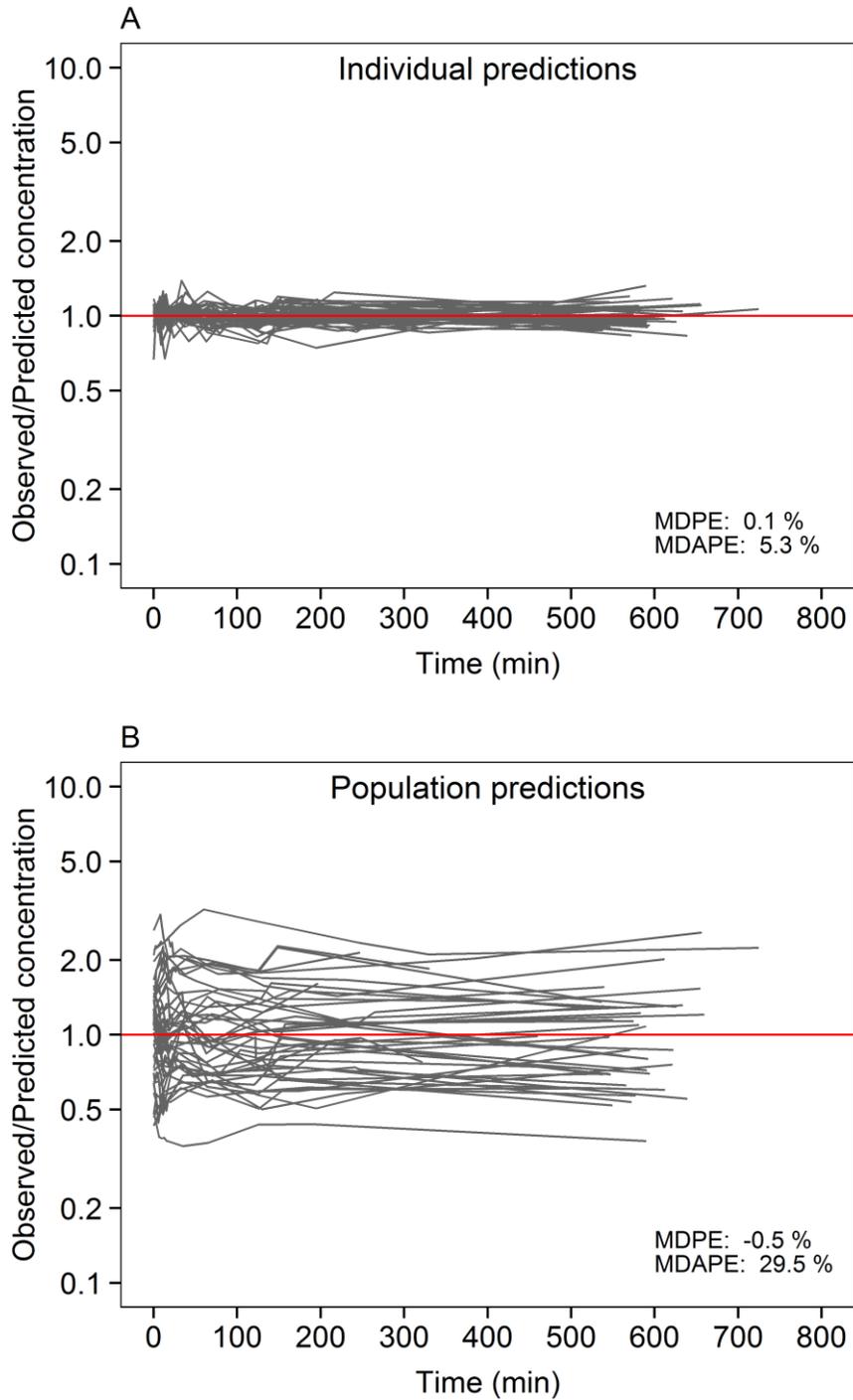
Figure S3. Log-likelihood profiles of the pharmacodynamic parameters. Critical values of the objective function value are shown as red and blue dotted line for $p<0.05$ and $p<0.01$, respectively. OFV, objective function value.
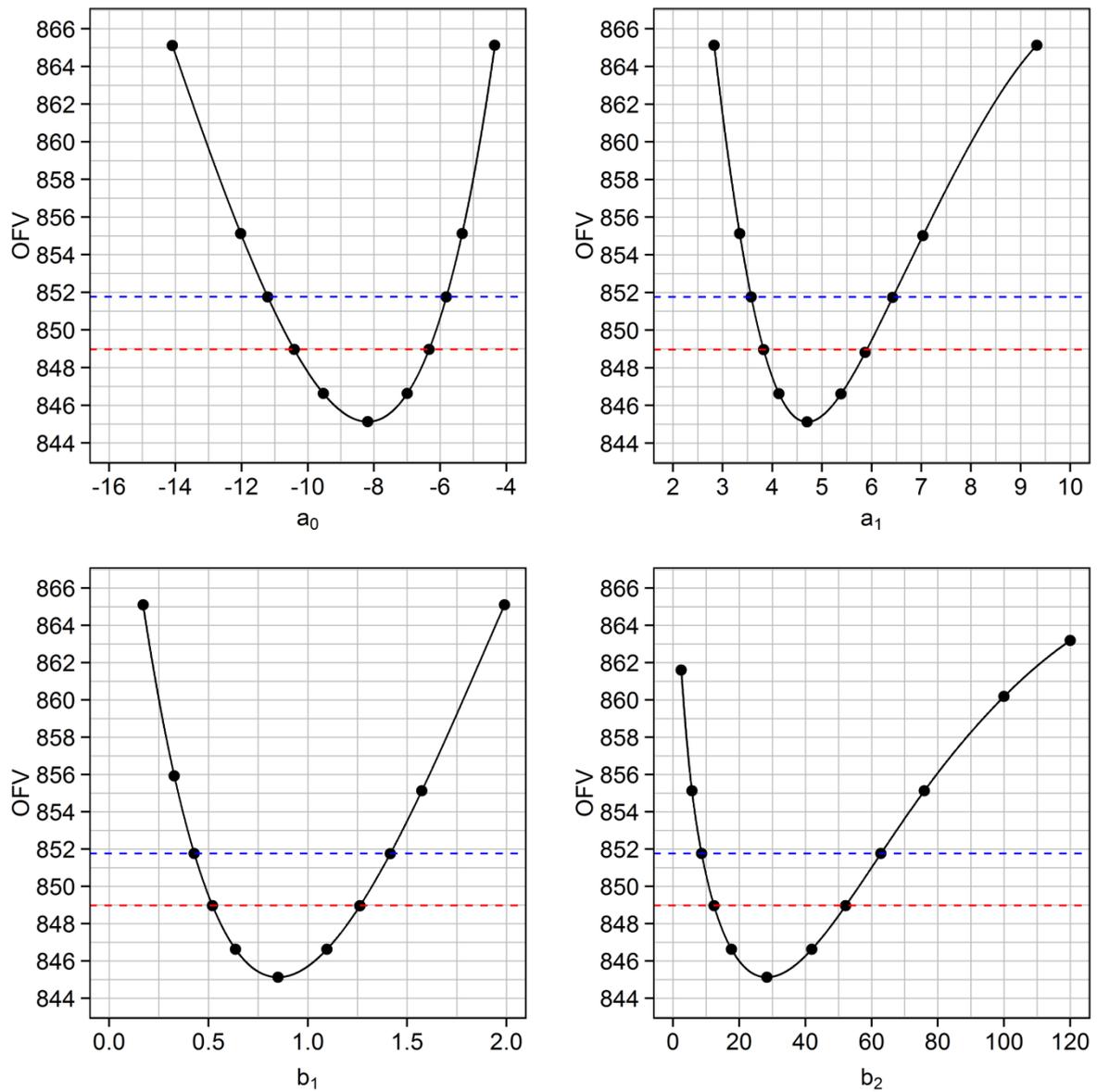
Figure S4. Probabilities of different numerical rating scale values under inspiration as a function of hydromorphone concentration (A-C). Individual predictions are shown in gray, population predictions in black. P, probability; NRS, numerical rating scale.
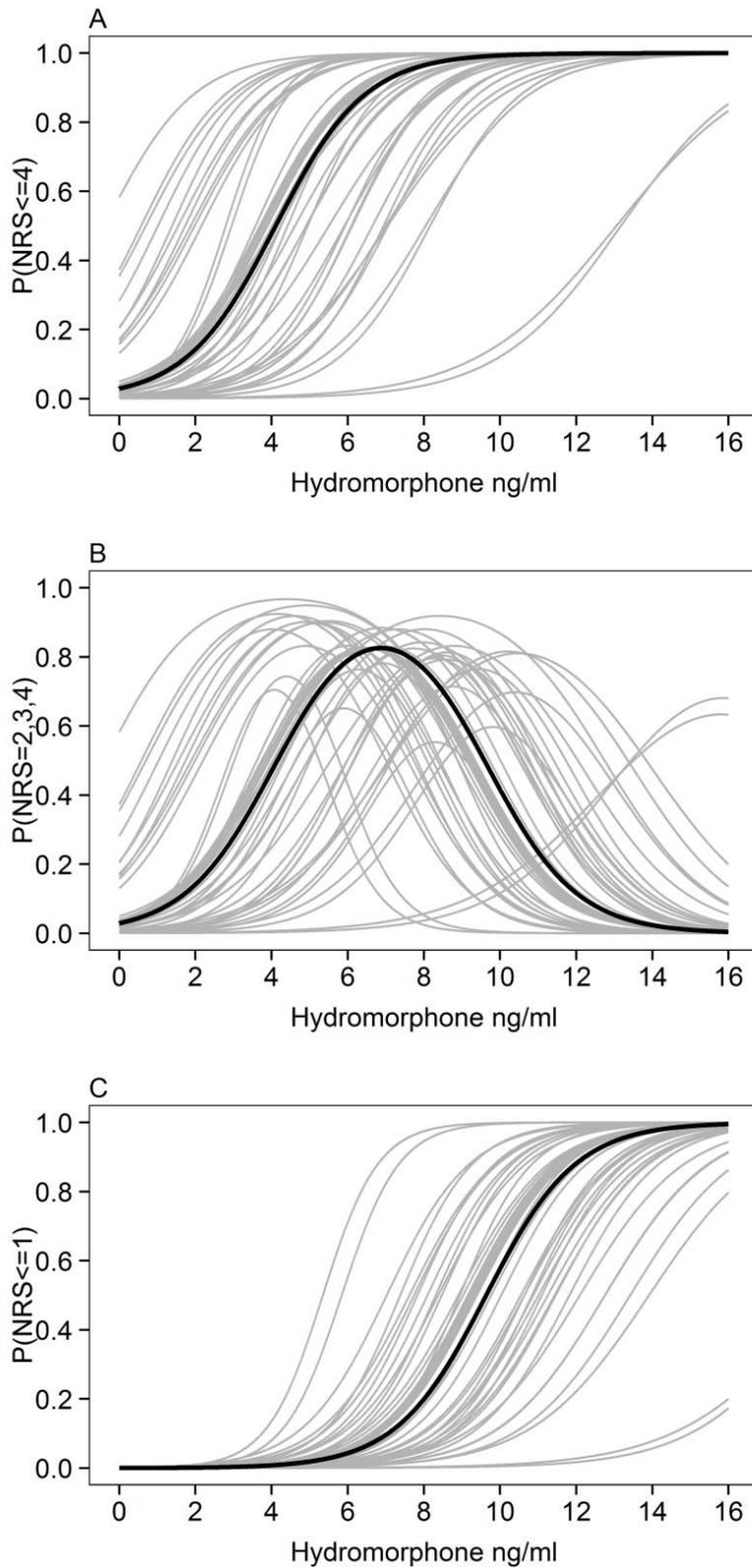
Figure S5. Distributions of the differences between predicted and measured pain levels under inspiration. The solid black line represents the median, and shading intensity corresponds to frequency density. DV, dependent variable; IPRED, individual predictions; PPRED, population predictions; NRS, numerical rating scale; TCI-PCA, patient controlled analgesia with target controlled infusion.