



Published in final edited form as:

*Anesthesiology*. 2023 July 01; 139(1): 16–34. doi:10.1097/ALN.0000000000004567.

## Morphine and Hydromorphone Effects, Side Effects and Variability – a Crossover Study in Human Volunteers

Konrad Meissner, MD<sup>1,2,3</sup>, Albert Dahan, MD PhD<sup>2</sup>, Erik Olofsen, PhD<sup>2</sup>, Christine Göpfert, MD<sup>3,§</sup>, Jane Blood, RN BSN<sup>3</sup>, Johannes Wieditz, PhD<sup>1,4</sup>, Evan D. Kharasch, MD PhD<sup>5</sup>

<sup>1</sup>Klinik für Anästhesiologie, Universitätsmedizin Göttingen, Germany

<sup>2</sup>Department of Anaesthesiology, Leiden University Medical Center, The Netherlands

<sup>3</sup>Department of Anesthesiology, Washington University in St. Louis, St. Louis MO, USA

<sup>4</sup>Department of Medical Statistics, Universitätsmedizin Göttingen, Germany

<sup>5</sup>Department of Anesthesiology, Duke University, Durham NC, USA

### Abstract

**Background:** Balancing between opioid analgesia and respiratory depression continues to challenge clinicians in perioperative, emergency department and other acute care settings. Morphine and hydromorphone are postoperative analgesic standards. Nevertheless, their comparative effects and side effects, timing, and respective variabilities, remain poorly understood. We tested the hypothesis that intravenous morphine and hydromorphone differ in onset, magnitude, duration and variability of analgesic and ventilatory effects.

**Methods:** We conducted a randomized crossover study in healthy volunteers. Forty-two subjects received a 2-hour intravenous infusion of hydromorphone (0.05 mg/kg) or morphine (0.2 mg/kg) 1–2 weeks apart. We measured arterial opioid concentrations, analgesia in response to heat pain (maximally tolerated temperature, and verbal analog pain scores at discreet preset temperatures to determine half-maximum temperature effect), dark-adapted pupil diameter and miosis, end-expired CO<sub>2</sub>, and respiratory rate for 12 h after dosing.

**Results:** For morphine and hydromorphone, respectively: maximum miosis was less (3.9 [3.4,4.2] vs 4.6 mm [4.0,5.0], P<0.001; median and 25%–75% quantiles) and occurred later (3.1±0.9 vs 2.3±0.7 h after infusion start, P<0.001; mean ± SD); maximum tolerated temperature was less (49±2 vs 50±2°C, P<0.001); verbal pain scores at end-infusion at the most informative stimulus (48.2°C) were 82±4 and 59±3 (P<0.001); maximum end-expired CO<sub>2</sub> was 47 [45,50] and 48 mmHg [46,51] (P=0.007), and occurred later (5.5±2.8 vs 3.0±1.5 h after infusion start, P<0.001); respiratory nadir was 9±1 and 11±2 breaths/min (P<0.001) and occurred at similar

\*To whom correspondence should be addressed: Dr. Konrad Meissner, Klinik für Anästhesiologie, Universitätsmedizin Göttingen, Germany, konrad.meissner@med.uni-goettingen.de, Phone: +49 551 3967700.

§current address: Abt. Chronische Schmerztherapie, Kliniken Ostalb, Dalkinger Str. 8-12, 73479 Ellwangen, Germany

This investigation was conducted before the requirement for clinical trials registration.

The valuable technical assistance of Viktor Yermolenka BS, Senior Research Technician, Amber Francis and Karen Frey, Clinical Research Coordinators, Department of Anesthesiology, Washington University in St. Louis, St. Louis MO, USA is appreciated. The authors thank Andreas Leha PhD, Department of Medical Statistics, Universitätsmedizin Göttingen, Germany, for statistical advice.

times. Area under the temperature tolerance-time curve was less for morphine (1.8 [0.0,4.4]) than hydromorphone (5.4°C-h [1.6,12.1]  $P<0.001$ ). Inter-individual variability in clinical effects did not differ between opioids.

**Conclusions:** For morphine compared to hydromorphone, analgesia and analgesia relative to respiratory depression were less, onset of miosis and respiratory depression was later, and duration of respiratory depression was longer. For each opioid, timing of the various clinical effects was not coincident. Results may enable more rational opioid selection, and suggest hydromorphone may have a better clinical profile.

---

## INTRODUCTION

Acute postoperative pain that is insufficiently treated is a problem that afflicts a majority of surgical patients, and has remained so for decades. Acute postoperative pain causes suffering, is associated with surgical and non-surgical complications, and in its severe manifestations is associated with regret for having had surgery.<sup>1,2</sup> Acute postsurgical pain is also a risk factor for chronic postoperative pain, which affects 10–80% of patients.

While multimodal analgesia has become increasingly common, opioids remain the most efficacious systemic analgesics available for moderate to severe pain. Postoperative opioid use is challenged by side effects, ranging from unpleasant nausea and emesis, to respiratory depression which can be fatal.<sup>3,4</sup> The Anesthesia Patient Safety Foundation has continuously issued warnings regarding the dangers of postoperative respiratory complications.<sup>5</sup> Minimizing opioid toxicity remains an important priority for patients, clinicians, and hospital authorities.<sup>6,7</sup> While respiratory monitoring has been a recommended solution, this is only secondary prevention (detecting toxicity).<sup>8</sup> A better ideal is primary prevention; that is, preventing toxicity.<sup>9</sup> Confounding the goal of optimal analgesia, without untoward side effects, is the considerable and unpredictable inter- and intra-individual variability in opioid pharmacokinetics and pharmacodynamics, although the relative contribution of these to observed clinical variability is poorly understood. Variability may be a root cause of both inadequate opioid analgesia and toxicity.

Opioid selection is often based largely on pharmacokinetic differences, particularly the temporal profile of drug effect dissipation, with less consideration of risk-benefit differences between various opioids.<sup>10,11</sup> Opioid selection for acute pain treatment may be even less data-driven, as the pharmacokinetic differences between morphine and hydromorphone, arguably the two most commonly used opioids for acute pain in the United States, such as for patient controlled analgesia and emergency department use, are considered to be comparatively minor.<sup>12,13</sup> Numerous clinical outcome studies have evaluated some opioid side effects, and others have attempted to predict risk for respiratory depression for each patient.<sup>4,14</sup> Nevertheless, deep understanding of morphine and hydromorphone clinical pharmacology, including the various clinical effects and their relationship to each other, interindividual variability in these effects, and differences between the opioid, remains elusive.<sup>15</sup>

This investigation tested the hypothesis that IV morphine and hydromorphone differ significantly in drug effects and side effects and their interindividual variabilities. The

premise was that this could affect drug safety, and that, based on the identification of these factors, opioid selection can be made more rationally. The specific aims of the study were to define the onset, time course, and interindividual variability of morphine and hydromorphone analgesia, miosis, and respiratory depression, and to define the concentration-response relationships for these effects and their variability.

## MATERIALS AND METHODS

### Ethics and Subjects

After approval of the protocol by the Institutional Review Board of Washington University in St. Louis, this study was performed at the Washington University Clinical Research Unit. The study was performed according to the ethical principles for medical research involving human subjects (Declaration of Helsinki), and before the need for clinical trials to be registered. Subjects were enrolled and studied from October 2008 to August 2009.

Subjects were recruited by advertisement (institutional research website and flyers) and interested persons contacted study staff. Eligible subjects had to be 18–40 yr, body mass index 20–33 kg/m<sup>2</sup>, in good general health with no remarkable medical conditions, take no prescription or non-prescription drugs except for oral contraceptives, and have no history of drug abuse. A total of 51 healthy volunteers were enrolled into the study after providing written informed consent.

### Clinical protocol

The study was a single-center, double-blinded, randomized, balanced crossover of single-dose IV infusion of morphine or hydromorphone, with assessments of plasma concentrations, analgesic response to thermal stimulus, miosis, and respiratory effects. The order of drug administration was determined by simple randomization using a random number table (odds and evens), and there was a washout period of at least one week between sessions. Subjects arrived at the study site fasted, an intravenous catheter for drug administration and an arterial catheter for blood sampling were inserted, and subjects received an intravenous infusion of D5LR (125 mL/h). All subjects were monitored with a pulse oximeter, automated blood pressure cuff, and side-stream CO<sub>2</sub> monitor using a combined nasal and oral spoon sampler (Philips, Cambridge MA).

Hydromorphone and morphine were administered intravenously as 2-hour infusions (marked in gray in all time-related figures). Subjects received intravenous ondansetron (4 mg) for antiemetic prophylaxis prior to opioid administration. Initial dosing was 0.1 mg/kg for both opioids, intended to achieve target plasma concentrations of about 10 ng/ml hydromorphone and 50 ng/ml morphine, resulting in about a 5–6 mm maximum pupil diameter change. After the first seven subjects, it was obvious that the sedative and pupillary effects of the two opioids were unequal, and subject and observer blinding was not possible, and that the doses were not correctly chosen. Based on an assumed 4 to 5-fold potency difference,<sup>16</sup> the doses were revised to 0.05 mg/kg hydromorphone and 0.2 mg/kg morphine. Arterial blood samples were obtained for 12 hours after the start of the hydromorphone and morphine infusions. Plasma was separated and stored at –20°C for later analysis. Standard blood gas

analyses were obtained at baseline and after the first three hours. One hour after the drug infusion had finished, subjects were fed a standard breakfast, and had free access to food and water thereafter. Subjects received supplemental oxygen for saturations less than 94%.

Sample size was based on the following: To estimate an outcome parameter, based on interindividual variability of 50%,<sup>17</sup> and 15% error, would require 43 subjects. To compare two outcome means, for example two EC50s for two different effects in the same subject, or two EC50s for different drugs in the same subject, using a paired t-test, to detect a 25% difference with a 50% standard deviation and  $\alpha=0.05$  and 90% power requires 44 subjects.

## Measurements

At each time point during the 12 h, the following measurements were taken in order: 1) respiratory rate, peripheral SpO<sub>2</sub>, and end-expired CO<sub>2</sub> concentration, 2) dark-adapted pupil diameter (in triplicate) using an infrared pupillometer (Neuroptics, Irvine CA) as described before,<sup>18</sup> and 3) antinociception (response to heat pain). Two analgesia measurement models were implemented sequentially using a Peltier-type thermal stimulator and thermode applied to the forearm (Pathway, Medoc Advanced Medical Systems, Ramat Yishay, Israel). The first was the “method of limits” (a continuous increase from 32°C at 0.8°C/min until the maximally tolerable temperature was reached, at which point the subject pressed a button and the thermode cooled; the temperature cutoff was 52°C). Measurements were performed in triplicate, with the thermode moved between measurements. The mean of three temperatures was recorded as the result. The “ramp and hold method” was the single application of 6 different specific temperatures (41, 43, 44.8, 46.5, 48.2, and 50 °C, each applied once in random order), with the probe moved to different spots on the forearm after each measurement.<sup>19</sup> Subjects were asked to rate the pain at each temperature on a 0–100 verbal analogue scale (VAS). Subjects were instructed and familiarized to the procedures after enrollment and prior to their first study day. Pupil miosis was calculated as the baseline pupil diameter minus the diameter at each time point. All pain testing, subject assessments, and data recording were performed by a trained research technician, who was blinded to the identity of the opioid in each session. Arterial blood samples and measurements of ventilatory parameters and pupil diameter were taken every quarter hour for the first three hours, every half an hour for another two hours and every hour thereafter until 12 h. Temperature tolerance was measured every half hour for the first five hours and every hour thereafter. There were also measurements of pH, pCO<sub>2</sub>, pO<sub>2</sub>, HCO<sub>3</sub> for the first 3 hours every hour.

## Analytical methods

Hydromorphone analysis: Hydromorphone in plasma was quantified by solid phase extraction and stereoselective liquid chromatography–mass spectrometry. Plasma samples (250 µL) were diluted with 750 µL of 2% (v/v) ammonium hydroxide in water containing the internal standard deuterated hydromorphone (Cerilliant, Round Rock, TX), processed by solid phase extraction (Varian Bond-Elut Plexa, 30 mg), rinsed with 1 mL of water, and eluted with 1 mL of methanol. The samples were evaporated to dryness and reconstituted in 100 µL of mobile phase A (listed below). The Agilent 1100 series liquid chromatograph

with mass selective detector was used for analysis. Column: Agilent Zorbax XDB-C18, 5  $\mu\text{m}$ , 2.1  $\times$  100 mm with a guard cartridge Phenomenex AJO-4286 C18, 2.0  $\times$  4.0 mm, and a 0.5  $\mu\text{m}$  steel frit filter. Mobile phase A – 5 mM aqueous formic acid with 5% of 1:1 acetonitrile-methanol solution; mobile phase B - 1:1 acetonitrile-methanol. Flow rate 0.35 mL/min. Gradient timetable (percent B): 0–4 min - 0%, 4–5 min - gradient increase to 85%, 5–7 min - 85% with increasing flow rate to 0.4 mL/min at 7 min, 7–8 min - gradient return to 0% and 0.35 mL/min flow rate, 8–12 min - 0%. Injection volume 10  $\mu\text{L}$ . The approximate retention time of hydromorphone was 3.6 min. Quantitation was performed for the following ions (positive electrospray ionization): m/z 286 (hydromorphone), m/z 292 (hydromorphone-d6, internal standard). The calibration curve fit was performed with Microsoft Excel 2003 and SigmaPlot software for a quadratic curve with reciprocal X regression. Calibrated range was 0.2 – 200 ng/mL, limit of detection was below 0.1 ng/mL. Interday coefficients of variation were all less than 5% at 0.5, 2 and 10 ng/ml.

Morphine and morphine glucuronides analysis: Plasma was analyzed using a AB/Sciex 4000 QTRAP as described previously,<sup>20</sup> except that the calibration range was 0.1–100 ng/mL for morphine and morphine-6-glucuronide, and 2–400 ng/mL for morphine-3-glucuronide.

Plasma samples were analyzed in batch shortly after the conclusion of the investigation.

### Statistical Analysis

Subject demographic data are reported as means  $\pm$  standard deviations, whereas pharmacokinetic and pharmacodynamic data are given as the median with 25% and 75% quantiles in brackets, respectively. All variables have been summarized by absolute and relative frequencies for categorical data, by means  $\pm$  standard deviation whenever the assumption of normal distribution is reasonable, and median and 25% and 75% quantiles otherwise.

Measured variables were summarized at each time point in each opioid group, and for maximum or minimum values across the entire 12 h experiment. Additionally, at each time point the differences between the two opioids were calculated per crossover session for the same subject, and the resulting differences analyzed. For each endpoint, linear mixed effect models were fitted including the nominal time in interaction with the opioid as fixed effects and the subject as random effect, to account for repeated measurements. Results are presented as the estimated marginal mean and the 25% and 75% quantiles, except where noted. All pairwise contrast tests have been conducted on the fit models to test for difference between the opioids at each time point. Resulting P-values were corrected for multiple testing using Tukey adjustment. Test results were reported as statistically significant if  $P < 0.05$ .

The areas under the curve (AUC) were computed with respect to baseline using the trapezoidal rule. Of note, for an expected effect below baseline (i.e. respiratory rate), the computed AUC rather corresponds to an “area over the curve”, and all values beyond return to the initial value were set to baseline, corresponding to a difference of 0. Interindividual variability is reported using coefficients of variation.

For the maximally tolerated temperature (“method of limits”), the endpoint was temperature. For the “ramp and hold” method using discrete temperatures, verbal pain scores were the endpoint, and the applied temperature was included in the linear mixed effect models as an additional fixed effect with full interaction. In addition, data were envisioned as a dose-response (temperature-pain rating) curve. At each time point, VAS data were fitted to the following model:

$$VAS = \frac{\left(\frac{T}{T_{50}}\right)^\gamma}{1 + \left(\frac{T}{T_{50}}\right)^\gamma} \cdot 100 \quad (1)$$

where T are the preselected temperatures 41, 43, 44.8, 46.5, 48.2, and 50 °C,  $T_{50}$  is the temperature giving a VAS of 50, and  $\gamma$  is a shape factor. NONMEM<sup>18</sup> was used to fit the data, assuming different  $T_{50}$  values at each time point, one overall  $\gamma$ , interindividual differences in  $T_{50}$  and  $\gamma$  were assumed to be lognormally distributed, residual error was assumed to be normally distributed. Because we observed high values for  $\gamma$  (around 20), the following alternative model was chosen (it resulted in 70 points lower objective function values):

$$VAS = \frac{e^{(T - T_{50}) \cdot \gamma}}{1 + e^{(T - T_{50}) \cdot \gamma}} \cdot 100 \quad (2)$$

where the standard error of the differences was estimated as the square root of the sum of squares of the standard errors of the hydromorphone and morphine  $T_{50}$ s. For  $T_{50}$ s, we state the mean with corresponding 95% CI instead of quantiles (as above), as the underlying data is model fit- based.

Mean model-derived  $T_{50}$  values for hydromorphone and morphine at each time point were compared using the log-likelihood test for statistical significance between a model of same or different means, using critical values of the chi-square distribution with one degree of freedom. Calculated P-values were adjusted for multiple comparisons using the Bonferroni correction.

All analyses were performed with the statistics software R (version 4.2.1, R Core Team 2022). For the determination of peak effects, a peak detection algorithm for time series of the R-package pracma of Borchers was employed,<sup>21</sup> which returns both peak time and the corresponding maximal effect. We used the R-package lme4 (version 1.1.21) for the mixed effect linear regression, and the R-package emmeans (version 1.4; for the estimation of marginal means and pairwise contrast tests).<sup>22</sup> For the computation of the AUCs the R-package DescTools of Signorelli et al. was employed.<sup>23</sup>

## RESULTS

### Demographic data

A total of 51 healthy volunteers (26 female, 25 male,  $28 \pm 6$  yr,  $73 \pm 13$  kg, body mass index  $24.7 \pm 3.4$  kg/m<sup>2</sup>) were enrolled in the study. After the first 11 study sessions, involving



seven subjects receiving 0.1 mg/kg hydromorphone and 0.1 mg/kg morphine (in random order, 4 completing both sessions and 3 completing one only), it became apparent that the effects of the two opioids were perceivable to study personnel, particularly sedation, were grossly unequal, and subject and observer blinding was impaired. The protocol was therefore modified and opioid doses were changed to 0.05 mg/kg hydromorphone and 0.2 mg/kg morphine. The CONSORT diagram for enrollment is shown in Figure 1. Supplemental Table 1 depicts the full scope of drug exposures. All available samples and measurements from the 51 subjects were analyzed, with the datasets complete except for any individual missed blood draws due to technical problems. A total of 42 subjects received both morphine (0.2 mg/kg) and hydromorphone (0.05 mg/kg) in a crossover fashion. Comparative statistics were executed on all subjects which completed both the 0.05 mg/kg hydromorphone and 0.2 mg/kg morphine sessions (n= 42, 24 female, 18 male). No subjects experienced any safety-relevant side effects.

A synopsis of plasma drug concentrations and clinical effects is given in Fig. 2. The individual curves are subsequently discussed and presented in detail.

### Plasma opioid concentrations

Arterial plasma opioid concentrations for the 42 paired subjects peaked at the end of the two-hour infusion. Maximum concentrations were 16.9 [14.8, 19.6] ng/mL for 0.05 mg/kg hydromorphone and 55.8 [48.6, 61.9] ng/mL for 0.2 mg/kg morphine (Figs. 2, 3), and then rapidly declined thereafter.

### Miosis

Baseline dark-adapted pupil diameters for the 42 paired sessions in subjects receiving both 0.05 mg/kg hydromorphone and 0.2 mg/kg morphine (n=42) were  $6.4 \pm 0.9$  and  $7.2 \pm 0.9$  mm, respectively. Pupils constricted to  $2.1 \pm 0.7$  and  $4.2 \pm 1.2$  mm at the end of the two-hour opioid infusion (Supplemental Figure 1), equivalent to miosis of  $4.3 \pm 0.7$  and  $3.0 \pm 1.2$  mm, respectively (Fig. 3A). Of note, miosis continued long after the steep decline in plasma concentrations after discontinuation of the opioid infusion. Time-specific pupillary effects of the two drugs differed significantly from each other, starting with the first measurement (15 min) until 3.5 hours after the discontinuation of the drug, with the most impressive difference during the infusion (Figs. 2, 4B). Overall maximum miosis was 4.6 mm [4.0, 5.0] after hydromorphone and 3.9 mm [3.4, 4.2] after morphine ( $P < 0.001$ ) and occurred at  $2.3 \pm 0.7$  and  $3.1 \pm 0.9$  h ( $P < 0.001$ ), respectively, after the start of the infusion (Figure 5). Interindividual variability in miosis, based on the coefficient of variation in maximum miosis, was 17% and 24% for hydromorphone and morphine, respectively. Area under the curve for miosis was significantly greater after hydromorphone (33 mm-h [26, 39]) than after morphine (25 mm-h [17, 33]) ( $P < 0.001$ , Figure 5). Interindividual variability in miosis, based on the area under the curve was 29% and 43% for hydromorphone and morphine, respectively. Miosis results for all subjects receiving either 0.05 mg/kg hydromorphone (n=44) or 0.2 mg/kg morphine (n=45) are shown in Supplemental Figure 2.

## Analgesia

Analgesia was tested using two different models of response to thermal pain. The “method of limits” determined the maximally tolerated temperature as temperature increased, and the “ramp and hold” method assessed verbal pain scores in response to six randomly applied discrete temperatures.

In the “method of limits”, the maximally tolerated temperature at the end of the infusion was  $49 \pm 2^\circ\text{C}$  for 0.05 mg/kg hydromorphone compared to  $48 \pm 2^\circ\text{C}$  for 0.2 mg/kg morphine for the 42 subjects receiving both opioids ( $P < 0.001$ , Figs. 2, 6A). The largest difference between the two drugs occurred at 30 min after the discontinuation of the opioid infusion, but remained significant throughout the infusion and until more than four hours after its discontinuation (Fig. 6B). Throughout the 12 h experiment, maximum tolerated temperature at any time was greater after hydromorphone ( $49.6 \pm 1.5^\circ\text{C}$ ) than after morphine ( $48.7 \pm 1.7^\circ\text{C}$ ,  $P < 0.001$ ) and occurred at 2.0 h [2.0, 2.6] and 2.5 h [1.5, 4.0] ( $P = 0.488$ ), respectively, after the start of the infusion (Figure 5). Interindividual variability in analgesia, based on the coefficient of variation in maximum tolerated temperature, was 3% for both opioids. The area under the curve for analgesia, based on maximum tolerated temperature, was significantly greater after hydromorphone ( $5.4^\circ\text{C}\cdot\text{h}$  [1.6, 12.1]) than after morphine ( $1.8^\circ\text{C}\cdot\text{h}$  [0.0, 4.4]) ( $P < 0.001$ , Figure 5). Interindividual variability in analgesia, based on the area under the curve was 95% and 145% for hydromorphone and morphine, respectively. Results for all subjects receiving either 0.05 mg/kg hydromorphone ( $n = 44$ ) or 0.2 mg/kg morphine ( $n = 45$ ) are shown in Supplemental Figure 3.

In the “ramp and hold” pain model using 6 randomly applied specific temperatures and verbal analogue scores for subjective pain intensity, subjects reported increasing pain scores with increasing temperature. Time-dependent data for both opioids at every time point are shown in Figure 7A, with the differences and significance testing results in Fig. 7B. Pain scores decreased during the opioid infusions, and then returned back to baseline. Consistent with the results for the “method of limits” protocol, the reduction in pain scores was greater for hydromorphone than morphine. Significant differences occurred most frequently around the time of peak plasma concentrations, and within the medium temperature range ( $45\text{--}48^\circ\text{C}$ ) (Fig. 7B). The greatest difference between opioids in pain scores was at  $48.2^\circ\text{C}$ . Pain scores at  $48.2^\circ\text{C}$  at the end of the infusion were  $59 \pm 3$  and  $82 \pm 4$  for hydromorphone and morphine, respectively ( $P < 0.001$ ). Hydromorphone analgesia persisted for 1–2 h after the end of the infusion, while morphine duration was difficult to assess because of the comparatively minimal effect. (Fig. 7). Results for all subjects receiving either 0.05 mg/kg hydromorphone ( $n = 44$ ) or 0.2 mg/kg morphine ( $n = 45$ ) are shown in Supplemental Figure 4.

In addition to analyzing pain scores over time, and comparing opioids, we also evaluated the stimulus-response (temperature-pain score) relationship at each time point, and for each drug, using a sigmoid Emax model (see equation 2). Figure 8A shows the sigmoid relationship between stimulus temperature and pain score at baseline. This analysis yielded the temperature at which half-maximal pain score occurred ( $T_{50}$ ) and the slope of the curve ( $\gamma$ ). With successive time points during and after the infusion, the curves were shifted down and to the right due to analgesia (e.g. Fig. 8B, 2 h after the start of the infusion), and then returned towards baseline after the end of the infusion (e.g. Fig 8C, 12 h after the start of



the infusion). Shifting of the curves yielded an apparent increase in the  $T_{50}$  (e.g. Fig. 8B). Differences between the stimulus-response curves for the two opioids are apparent in Fig. 8B. The time course of the  $T_{50}$  values, and for both opioids, is shown Fig. 9A and 9B, where increasing  $T_{50}$  represents analgesic effects. Peak analgesic effects occurred at the end of the 2 h hydromorphone infusion, and then declined.  $T_{50}$  at the end of the opioid infusion was  $44.7 \pm 0.4$  and  $46.5 \pm 0.5^{\circ}\text{C}$  for morphine and hydromorphone, respectively. Unlike after hydromorphone, changes in  $T_{50}$  after morphine were minimal, and appeared not to peak for several hours, and an accurate time of maximum effect was not possible to determine. The maximum  $T_{50}$  at any time during the entire experiment were  $46.6 \pm 0.3^{\circ}\text{C}$  at 3 h and  $45.4 \pm 0.4^{\circ}\text{C}$  at 2.5 h for hydromorphone and morphine, respectively. Fig 9B depicts the differences between the hydromorphone and morphine data.

Interindividual variability in analgesia for the two opioids was estimated by the interindividual variability in  $T_{50}$  and  $\gamma$ . Gamma was not significantly different between the two drugs ( $0.46 \pm 0.02$  and  $0.48 \pm 0.02$  for hydromorphone and morphine), and was singularly estimated as  $0.47 \pm 0.02$  (model estimate  $\pm$  standard deviation) in a combined model including both drugs. Interindividual variabilities (in the log domain) of  $T_{50}$  and  $\gamma$  were  $0.0022 \pm 0.0004$  and  $0.11 \pm 0.02$ , respectively, and were not significantly different between the two drugs ( $0.0023 \pm 0.0004$  and  $0.11 \pm 0.02$  for hydromorphone and morphine  $T_{50}$  respectively, and  $0.0019 \pm 0.0005$  and  $0.09 \pm 0.02$ , for hydromorphone and morphine  $\gamma$ , respectively).

## Ventilation

Ventilation was assessed using end-expired  $\text{CO}_2$ , respiratory rate and arterial blood gas analysis. End-expired  $\text{CO}_2$  for the 42 subjects receiving both 0.05 mg/kg hydromorphone and 0.2 mg/kg morphine increased from 39 mmHg [37, 42] and 39 mmHg [36, 41] at baseline to 45 mmHg [43, 48] and 42 mmHg [39, 45] mmHg at the end of the two-hour infusion, respectively, with significantly higher values for hydromorphone throughout the infusion and the one hour thereafter (Fig. 10). Overall maximum end-expired  $\text{CO}_2$  was greater after hydromorphone (48 mmHg [46, 51]) than after morphine (47 mmHg [45, 50]) ( $P=0.008$ ) (Figure 5). Maximum end-expired  $\text{CO}_2$  occurred much later after morphine ( $5.5 \pm 2.8$  h after the start of the infusion) than after hydromorphone ( $3.0 \pm 1.5$  h) ( $P<0.001$ ) (Figure 5). Interindividual variability, based on the coefficient of variation in respiratory effect for hydromorphone and morphine, respectively, was 7% and 12% for maximum end-expired  $\text{CO}_2$ , and 49% and 51% for the time to peak end-expired  $\text{CO}_2$ . Area under the curve for  $\text{CO}_2$  was 53 mmHg-h [30, 78] after hydromorphone and 49 mmHg-h [30, 79] after morphine ( $P=0.532$ , Figure 5). Interindividual variability in end-expired  $\text{CO}_2$ , based on the area under the curve was 63% and 60% for hydromorphone and morphine, respectively. Results for all subjects receiving either 0.05 mg/kg hydromorphone ( $n=44$ ) or 0.2 mg/kg morphine ( $n=45$ ) are shown in Supplemental Figure 5.

Respiratory rates for subjects receiving both 0.05 mg/kg hydromorphone and 0.2 mg/kg morphine decreased from  $17 \pm 3$  and  $17 \pm 3$  breaths.min<sup>-1</sup> at baseline to  $12 \pm 3$  and  $14 \pm 2$  breaths.min<sup>-1</sup> at the end of the two-hour infusion, with significantly lower values for hydromorphone throughout the infusion and the 4–5 hours thereafter (Figs. 2, 11) for time-

based paired comparisons. Overall respiratory rate nadir was  $11 \pm 2$  and  $9 \pm 1$  breaths.min<sup>-1</sup> after hydromorphone and morphine, respectively (Figs. 2, 5,  $P < 0.001$ ). The time to the respiratory rate nadir was not significantly different ( $P = 0.952$ ) between hydromorphone and morphine (2.4 h [1.2, 3.0] and 2.4 h [1.2, 3.0], respectively (Figure 5). Interindividual variability in minimum respiratory rate, based on the coefficient of variation, was 15 and 14% for hydromorphone and morphine, respectively. Area under the curve for respiratory rate was 47 min<sup>-1</sup>-h [23, 73] after hydromorphone and 44 min<sup>-1</sup>-h [20, 63] after morphine ( $P = 0.496$ , Figure 5). Interindividual variability in respiratory rate, based on the area under the curve was 58% and 63% for hydromorphone and morphine, respectively. Results for all subjects receiving either 0.05 mg/kg hydromorphone (n=44) or 0.2 mg/kg morphine (n=45) are shown in Supplemental Figure 6.

Arterial blood gas analyses (Table 1) revealed a well-buffered physiological response to respiratory depression with indistinguishable values for both pH and HCO<sub>3</sub><sup>-</sup>, over time and between groups. CO<sub>2</sub> partial pressure increased from baseline after both drugs, with a 1.9 mmHg (95% CI: [0.5, 3.4]) larger increase for 0.05 mg/kg hydromorphone compared to 0.2 mg/kg morphine ( $P = 0.010$ ).

Comparison of the magnitude and time course of various clinical effects for a particular opioid is facilitated by representation of all effects in a single figure panel, as is comparison of different drugs. Figure 2 shows mean data from Figures 3, 4, 6, 10, and 11 recapitulated in a single panel, for both hydromorphone and morphine.

## DISCUSSION

The present investigation evaluated the magnitude, time course, and variability of analgesic effects and side effects of a 2-hour morphine or hydromorphone infusion in human volunteers in a crossover design, using a comprehensive clinical phenotyping paradigm. Even though both drugs were introduced decades ago, data comparing analgesia and side effects in the same subjects for each opioid over time, and in comparison to each other, as well as interindividual variability, is still lacking.<sup>14</sup> We tested the hypothesis that intravenous morphine and hydromorphone differ significantly in drug effects and side effects and their interindividual variabilities.

The first major findings were the onset, magnitude, and duration of miotic, analgesic, and ventilatory effects of hydromorphone. Hydromorphone clinical effects were characterized by temporal coincidence. Miotic, analgesic and ventilatory effects had a rapid onset and peaked at or immediately after the end of the 2-hour intravenous infusion. The decline in clinical effects was also generally temporally coincident, although these effects persisted well after the steep decline in plasma concentrations. Miosis, analgesia, and respiratory rate essentially returned to baseline by the end of the 12-hour observation period, while end-expired CO<sub>2</sub> remained elevated compared with pre-drug values. Rapid onset of effect was similar to that after bolus dose hydromorphone, which had detectable analgesia in 5 min and peak effects between 10 and 20 min.<sup>24</sup> Rapid onset of hydromorphone analgesia and miosis has also been reported.<sup>25</sup>

The second major findings were the onset, magnitude, and duration of miotic, analgesic, and ventilatory effects of morphine. In contrast to hydromorphone, there were disparities in the various morphine clinical effects, both in timing and magnitude. Analgesia was not apparent until well into the first hour of the infusion, peaked at the end of the infusion, and declined thereafter. In contrast, miosis maximum occurred only after about 3.5 h, the decline in respiratory rate was greatest at 5 h, and end-expired CO<sub>2</sub> was maximal after 7 h. The magnitude of the ventilatory effects was greater than the magnitude of analgesia. The combination of delayed respiratory depression relative to analgesia (and miosis), and greater magnitude of respiratory depression compared with analgesia, is notable. Miosis, analgesia, and respiratory rate essentially returned to baseline by the end of the 12-h observation period, while end-expired CO<sub>2</sub> remained elevated compared with pre-drug values. Delayed onset of morphine clinical effects, relative to plasma concentration, was similar to that reported previously, as assessed by miosis or analgesia.<sup>26–28</sup> Delayed onset of maximum morphine analgesia (5 h) compared to miosis (2 h) has also been shown previously, albeit after much larger doses than used herein.<sup>27</sup> Morphine is known to transfer from plasma to the effect-site for miosis rather slowly.<sup>29</sup> Together these findings confirm the hypothesis that the magnitude and timing of analgesic and side effects differ significantly for morphine and for hydromorphone.

The third set of major findings was that the onset, magnitude, and duration of miotic, analgesic, and ventilatory effects were different between morphine and hydromorphone at the doses studied in our experimental volunteer model. Our hypothesis therefore was accepted. In general, hydromorphone compared with morphine had faster onset of analgesic, respiratory and miotic effects, and greater analgesia relative to respiratory depression, based on maximum effect and AUCs. Specifically, within-subjects comparisons for hydromorphone vs morphine AUC ratios were 2.56 [0.75,6.69] for temperature tolerance, 1.29 [1.11,1.79] for miosis, 1.09 [0.70,1.43] for end-expired CO<sub>2</sub>, and 1.11 [0.49,2.28] for respiratory rate. Similarly, the within-subjects AUC ratio of temperature tolerance to end-expired CO<sub>2</sub> was 0.104 [0.042,0.282] for hydromorphone and 0.040 [0.001,0.106] for morphine. Thus, the hydromorphone and morphine doses used had a 2.5-fold difference in analgesia, but minimal difference in respiratory side effects.

In contrast to the temporal coincidence of most effects, morphine respiratory depression was substantially delayed relative to analgesia, and was slower relative to that of hydromorphone. A delay (hysteresis) between blood concentration and clinical effect (EEG, analgesia, miosis), attributed to slow distribution to the effect site (presumably the central nervous system) has been well-described for morphine.<sup>30,31</sup> but is substantially less for hydromorphone.<sup>32</sup> The present results are generally consistent with these distribution differences between opioids. In contrast, the temporal discordance between end-expired CO<sub>2</sub> and other opioid effects for morphine was not anticipated. A mechanistic explanation is not apparent. Despite decades of use, few investigations have comprehensively evaluated the analgesic and other pharmacologic effects of various opioids in humans, and compared them.<sup>33</sup> The present investigation highlights the value of comprehensive quantitative clinical assessments in volunteers.

One generalized approach to compare the desirable vs side effects of drugs is to compare their therapeutic ratios within each subject based on the AUCs of the desirable and undesirable effects. The median ratio of AUCs for temperature tolerance to end-expired CO<sub>2</sub> (°C/mmHg) was 0.10 [0.04,0.29] for hydromorphone and 0.04 [0.00,0.11] for morphine (P=0.001), and the ratio of AUCs for temperature tolerance to respiratory rate (°C/breaths-min<sup>-1</sup>) was 0.15 [0.04,0.38] for hydromorphone and 0.04 [0.00,0.17] for morphine (P=0.022). Thus, the effect ratios of temperature tolerance to both measures of respiratory depression differed between hydromorphone and morphine. Analgesia relative to respiratory depression was 3- to 4-fold greater for hydromorphone than morphine. This further supports the conclusion that therapeutic benefit vs risk appears greater for hydromorphone than for morphine, at the doses studied. It is important to note, however, that these are single-dose AUC comparisons, not formal determinations of median effect (ED50), median toxicity (TD50) and therapeutic index (TD50/ED50). These would require formal dose-response studies.

The fourth major findings were the interindividual variabilities in the magnitude and onset of opioid effects and the differences between opioids. The hypothesis was that intravenous morphine and hydromorphone would differ in their interindividual variabilities. Interindividual variability in opioid effects, based on the coefficients of variation, were determined for analgesia, miosis, and respiratory depression. For analgesia, variation was 3% for both opioids based on maximum tolerated temperature, 95% and 145% for hydromorphone and morphine based on the area under the temperature curves, and was not significantly different between the two drugs based on T<sub>50</sub> and  $\gamma$ . For miosis, for hydromorphone and morphine, variation in peak effect was 17% and 24%, respectively, and 29% and 43% based on the areas under the curve. For respiratory depression from hydromorphone and morphine, variation was 7% and 12% for maximum end-expired CO<sub>2</sub>, 63% and 60% for areas under the CO<sub>2</sub> curve, 15% and 14% for minimum respiratory rate, and 58% and 63% based on the areas under the respiratory rate curve. Together, these observations do not support the hypothesis that morphine and hydromorphone differ in interindividual variability of their clinical effects.

A fifth major finding is that both pain models identified opioid analgesia, with increases in maximally tolerated temperature and T<sub>50</sub> (although the magnitude of analgesia was greater for hydromorphone in both models) without a change in  $\gamma$ . Increased T<sub>50</sub> without a change in  $\gamma$  was previously reported for remifentanyl.<sup>19</sup> We also observed considerable interindividual variation in temperature tolerance-time AUCs. There was not an obvious advantage to either the ramp and hold method or the method of limits in our investigation. The former has more sophisticated data analysis and modeling,<sup>19,34-36</sup> while the latter take less time to implement (3 vs 6 stimuli) and analyze.<sup>36-39</sup> The lack of an apparent advantage of the method of limits or a multi-level submaximal method for assessing opioid analgesia parallels that seen in quantitative sensory testing for neurologic pathophysiology.<sup>35,40</sup>

Another novel aspect of this investigation was the comprehensive phenotypic assessment of opioid disposition and clinical effects, including arterial plasma concentration, thermal analgesia (using 2 models), respiratory effects, and miosis. While it is common for studies to evaluate one or perhaps two clinical effects, with actual or often simulated

drug concentrations, few use this more comprehensive approach. In addition, studies often use predicted or modeled drug concentrations, but it is important to use actual measured drug concentrations, such as to confirm adequacy of dosing or in pharmacokinetic and/or pharmacodynamics modeling.<sup>41</sup>

The last major finding is the clinical implication for opioid analgesia and rational opioid selection. There are relatively few clinical studies directly comparing morphine and hydromorphone for acute pain.<sup>42</sup> There is said to be “clinical lore” that hydromorphone results in better pain control with fewer adverse effect than morphine.<sup>16,24</sup> When titrated or self-administered to analgesic effect, when evaluated based on analgesia or on analgesia relative to behavioral side effects (mood, sedation, sleep, drug liking) morphine and hydromorphone are generally considered comparable.<sup>24,43</sup> Based on analgesia and more relevant side effects (respiratory depression, nausea, vomiting, itch), hydromorphone is considered to be comparable,<sup>12,16,44–46</sup> or to have some advantage.<sup>4,7,13</sup> Nevertheless, it remains unknown and under discussion whether morphine or hydromorphone is inherently safer or clinically advantageous.<sup>4,15,26,47</sup> In contrast to these clinical outcomes studies, the present investigation, using more quantitative assessments, shows that hydromorphone confers greater analgesia relative to respiratory depression. This may allow for more rational opioid selection, and suggests that hydromorphone may be advantageous for acute pain.

In summary, the present investigation shows that the magnitude and time course of the analgesic, respiratory and miotic effects of morphine differ significantly, as they do for hydromorphone, and in different ways between the two opioids. In contrast, there was little difference between opioids in the magnitude of interindividual variability in clinical effects. In general, at the doses studied, hydromorphone compared with morphine had a faster onset of effects and greater analgesia relative to respiratory depression, and morphine respiratory depression was delayed relative to analgesia. These results suggest that hydromorphone may have clinical advantages compared with morphine for treating acute pain in perioperative, emergency department and other acute care settings.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## FUNDING STATEMENT:

Funded by grants from the Foundation for Barnes-Jewish Hospital (St. Louis MO, USA) (to Konrad Meissner), the National Institutes of Health (Bethesda MD, USA) Grants K24-DA00417, R01-DA14211 and R01-DA042985 (to Evan D. Kharasch), and National Institutes of Health Grant UL1-TR000448 to the Washington University in St Louis Institute of Clinical and Translational Sciences

## CONFLICTS OF INTEREST:

The Anesthesia & Pain Research Unit of the Department of Anesthesiology, Leiden University Medical Center received/receives funding from AMO Pharma Ltd. (United Kingdom), Bedrocan BV (The Netherlands), Grünenthal GmbH (Germany) and Medtronic (USA), MSD Nederland BV (The Netherlands).

KM – none,

AD received consultancy and/or speaker fees from Enalare Therapeutics Inc. (USA), Grünenthal BV (The Netherlands), Medasense Biometrics Ltd. (Israel), Trevena Inc. (USA), MSD Nederland BV.,

EO – none,

CG – none,

JB – none,

JW – none,

EDK – none.

## Data availability statement

The raw data supporting the conclusions of this article as well as the full trial protocol will be made available by the authors, upon reasonable request.

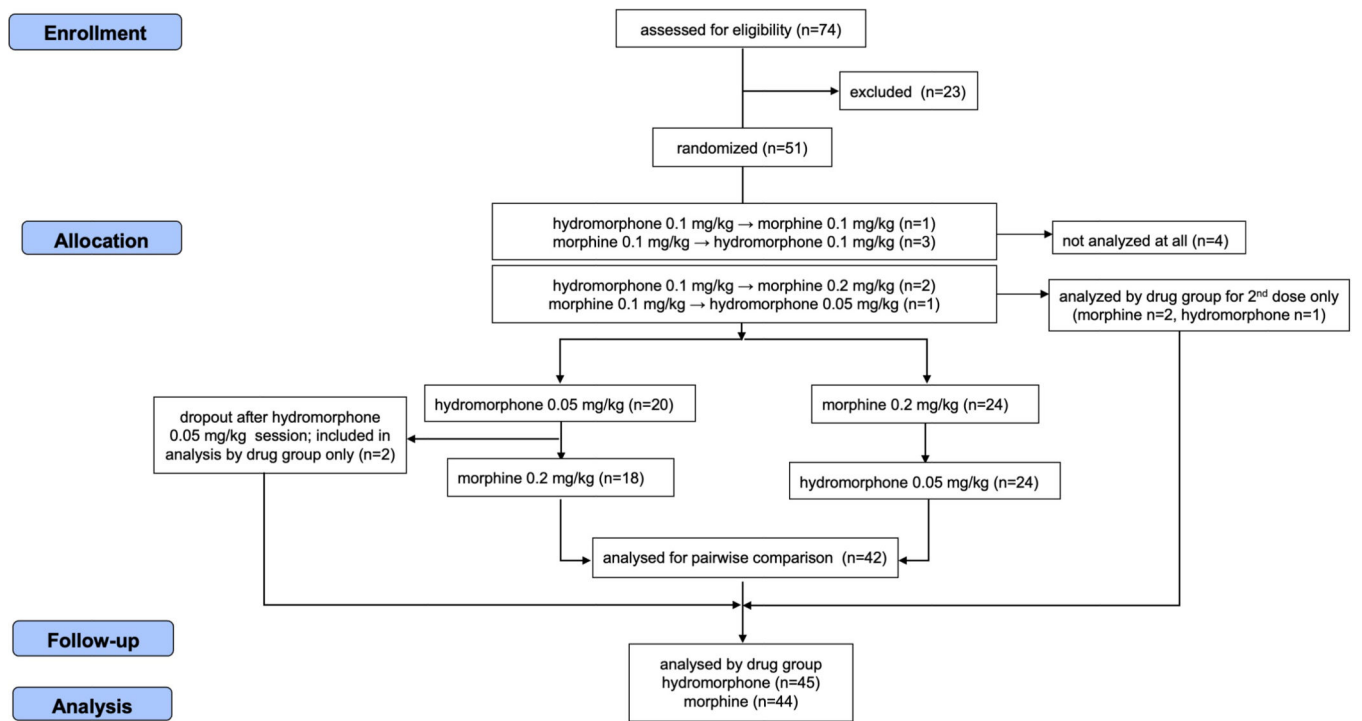
## REFERENCES

1. Turan A, Leung S, Bajracharya GR, Babazade R, Barnes T, Schacham YN, Mao G, Zimmerman N, Ruetzler K, Maheshwari K, Esa WAS, Sessler DI: Acute Postoperative Pain Is Associated With Myocardial Injury After Noncardiac Surgery. *Anesth Analg* 2020; 131: 822–829 [PubMed: 32665475]
2. Schwenkglens M, Gerbershagen HJ, Taylor RS, Pogatzki-Zahn E, Komann M, Rothaug J, Volk T, Yahiaoui-Doktor M, Zaslansky R, Brill S, Ullrich K, Gordon DB, Meissner W: Correlates of satisfaction with pain treatment in the acute postoperative period: results from the international PAIN OUT registry. *Pain* 2014; 155: 1401–1411 [PubMed: 24785269]
3. Epstein RH, Dexter F, Lopez MG, Ehrenfeld JM: Anesthesiologist staffing considerations consequent to the temporal distribution of hypoxemic episodes in the postanesthesia care unit. *Anesth Analg* 2014; 119: 1322–33 [PubMed: 25185590]
4. Urman RD, Khanna AK, Bergese SD, Buhre W, Wittmann M, Le Guen M, Overdyk FJ, Di Piazza F, Saager L: Postoperative opioid administration characteristics associated with opioid-induced respiratory depression: Results from the PRODIGY trial. *J Clin Anesth* 2021; 70: 110167
5. Weinger MB: Dangers of Postoperative Opioids. *APSF Newsletter* 2006; 21: 61–67
6. Driver CN, Laporta ML, Bergese SD, Urman RD, Di Piazza F, Overdyk FJ, Sprung J, Weingarten TN: Frequency and Temporal Distribution of Postoperative Respiratory Depressive Events. *Anesth Analg* 2021; 132: 1206–1214 [PubMed: 33857962]
7. Khanna AK, Saager L, Bergese SD, Jungquist CR, Morimatsu H, Uezono S, Ti LK, Soto R, Jiang W, Buhre W: Opioid-induced respiratory depression increases hospital costs and length of stay in patients recovering on the general care floor. *BMC Anesthesiol* 2021; 21: 88 [PubMed: 33743588]
8. Bolden N, Posner KL, Domino KB, Auckley D, Benumof JL, Herway ST, Hillman D, Mincer SL, Overdyk F, Samuels DJ, Warner LL, Weingarten TN, Chung F: Postoperative Critical Events Associated With Obstructive Sleep Apnea: Results From the Society of Anesthesia and Sleep Medicine Obstructive Sleep Apnea Registry. *Anesth Analg* 2020; 131: 1032–1041 [PubMed: 32925320]
9. Bateman JT, Saunders SE, Levitt ES: Understanding and countering opioid-induced respiratory depression. *Br J Pharmacol* 2021
10. Belcher AW, Khanna AK, Leung S, Naylor AJ, Hutcherson MT, Nguyen BM, Makarova N, Sessler DI, Devereaux PJ, Saager L: Long-Acting Patient-Controlled Opioids Are Not Associated With More Postoperative Hypoxemia Than Short-Acting Patient-Controlled Opioids After Noncardiac Surgery: A Cohort Analysis. *Anesth Analg* 2016; 123: 1471–1479 [PubMed: 27607476]
11. Shafer SL, Varvel JR: Pharmacokinetics, pharmacodynamics, and rational opioid selection. *Anesthesiology* 1991; 74: 53–63 [PubMed: 1824743]
12. Spenard S, Gelinas C, E DT, Tremblay-Racine F, Kleiber N: Morphine or hydromorphone: which should be preferred? A systematic review. *Arch Dis Child* 2021

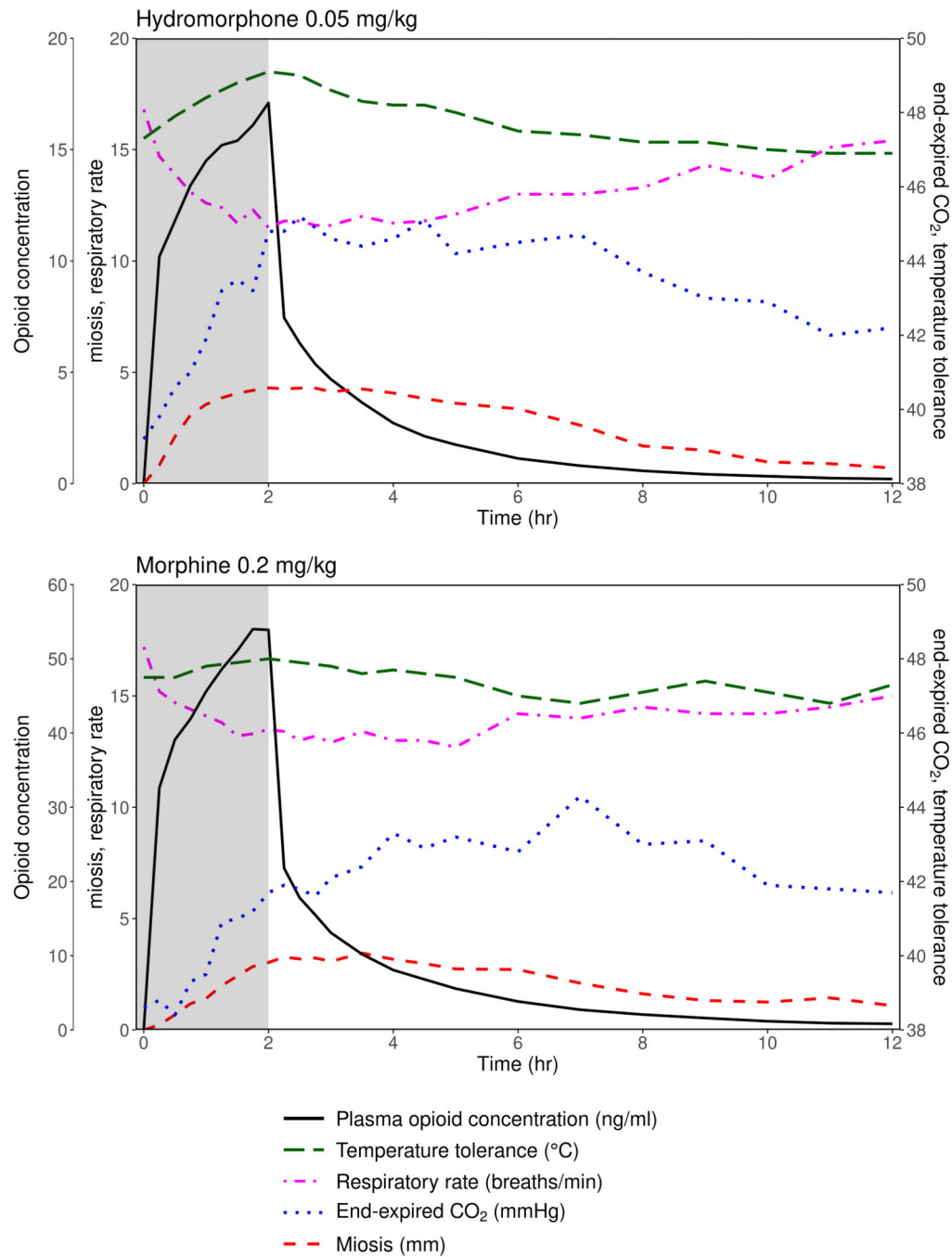


13. Felden L, Walter C, Harder S, Treede RD, Kayser H, Drover D, Geisslinger G, Lotsch J: Comparative clinical effects of hydromorphone and morphine: a meta-analysis. *Br J Anaesth* 2011; 107: 319–28 [PubMed: 21841049]
14. Khanna AK, Bergese SD, Jungquist CR, Morimatsu H, Uezono S, Lee S, Ti LK, Urman RD, McIntyre R Jr., Tornero C, Dahan A, Saager L, Weingarten TN, Wittmann M, Auckley D, Brazzi L, Le Guen M, Soto R, Schramm F, Ayad S, Kaw R, Di Stefano P, Sessler DI, Uribe A, Moll V, Dempsey SJ, Buhre W, Overdyk FJ, Collaborators PRO-irDIPmbcG: Prediction of Opioid-Induced Respiratory Depression on Inpatient Wards Using Continuous Capnography and Oximetry: An International Prospective, Observational Trial. *Anesth Analg* 2020; 131: 1012–1024 [PubMed: 32925318]
15. Roth JV: Opioid-Induced Respiratory Depression: Is Hydromorphone Safer Than Morphine? *Anesth Analg* 2021; 132: e60 [PubMed: 33723198]
16. Hong D, Flood P, Diaz G: The side effects of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg* 2008; 107: 1384–9 [PubMed: 18806056]
17. Levy G: Predicting effective drug concentrations for individual patients. Determinants of pharmacodynamic variability. *Clin Pharmacokinet* 1998; 34: 323–33 [PubMed: 9571304]
18. Kharasch ED, Walker A, Hoffer C, Sheffels P: Intravenous and oral alfentanil as in vivo probes for hepatic and first-pass cytochrome P450 3A activity: noninvasive assessment by use of pupillary miosis. *Clin Pharmacol Ther* 2004; 76: 452–66 [PubMed: 15536460]
19. Cortinez LI, Hsu YW, Sum-Ping ST, Young C, Keifer JC, Macleod D, Robertson KM, Wright DR, Moretti EW, Somma J: Dexmedetomidine pharmacodynamics: Part II: Crossover comparison of the analgesic effect of dexmedetomidine and remifentanil in healthy volunteers. *Anesthesiology* 2004; 101: 1077–83 [PubMed: 15505442]
20. Meissner K, Avram MJ, Yermolenka V, Francis AM, Blood J, Kharasch ED: Cyclosporine-inhibitable blood-brain barrier drug transport influences clinical morphine pharmacodynamics. *Anesthesiology* 2013; 119: 941–53 [PubMed: 23851346]
21. Borchers HW: *pracma: Practical Numerical Math Functions*, 2021
22. Bates D, Machler M, Bolker BM, Walker SC: Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software* 2015; 67: 1–48
23. Signorelli A: *DescTools: Tools for descriptive statistics*. R package version 0.99.44, 2021
24. Coda B, Tanaka A, Jacobson RC, Donaldson G, Chapman CR: Hydromorphone analgesia after intravenous bolus administration. *Pain* 1997; 71: 41–8 [PubMed: 9200172]
25. Westerling D, Bjork H, Svedman P, Høglund P: Analgesic and Nonanalgesic Effects of Intravenous Hydromorphone - Relation to Plasma Concentrations in Healthy Volunteers. *Pain Research and Management* 1996; 1: 313012
26. Kharasch ED: Intraoperative methadone: rediscovery, reappraisal, and reinvigoration? *Anesth Analg* 2011; 112: 13–6 [PubMed: 21173206]
27. Skarke C, Darimont J, Schmidt H, Geisslinger G, Lotsch J: Analgesic effects of morphine and morphine-6-glucuronide in a transcutaneous electrical pain model in healthy volunteers. *Clin Pharmacol Ther* 2003; 73: 107–21 [PubMed: 12545149]
28. Sarton E, Olofsen E, Romberg R, den Hartigh J, Kest B, Nieuwenhuijs D, Burm A, Teppema L, Dahan A: Sex differences in morphine analgesia: an experimental study in healthy volunteers. *Anesthesiology* 2000; 93: 1245–54; discussion 6A [PubMed: 11046213]
29. Lotsch J, Skarke C, Schmidt H, Grosch S, Geisslinger G: The transfer half-life of morphine-6-glucuronide from plasma to effect site assessed by pupil size measurement in healthy volunteers. *Anesthesiology* 2001; 95: 1329–38 [PubMed: 11748388]
30. Lotsch J: Pharmacokinetic-pharmacodynamic modeling of opioids. *J Pain Symptom Manage* 2005; 29: S90–103 [PubMed: 15907650]
31. Groenendaal D, Freijer J, Rosier A, de Mik D, Nicholls G, Hersey A, Ayrton AD, Danhof M, de Lange EC: Pharmacokinetic/pharmacodynamic modelling of the EEG effects of opioids: the role of complex biophase distribution kinetics. *Eur J Pharm Sci* 2008; 34: 149–63 [PubMed: 18467078]
32. Jeleazcov C, Ihmsen H, Saari TI, Rohde D, Mell J, Fröhlich K, Krajinovic L, Fechner J, Schwilden H, Schuttler J: Patient-controlled Analgesia with Target-controlled Infusion of Hydromorphone in Postoperative Pain Therapy. *Anesthesiology* 2016; 124: 56–68 [PubMed: 26556729]

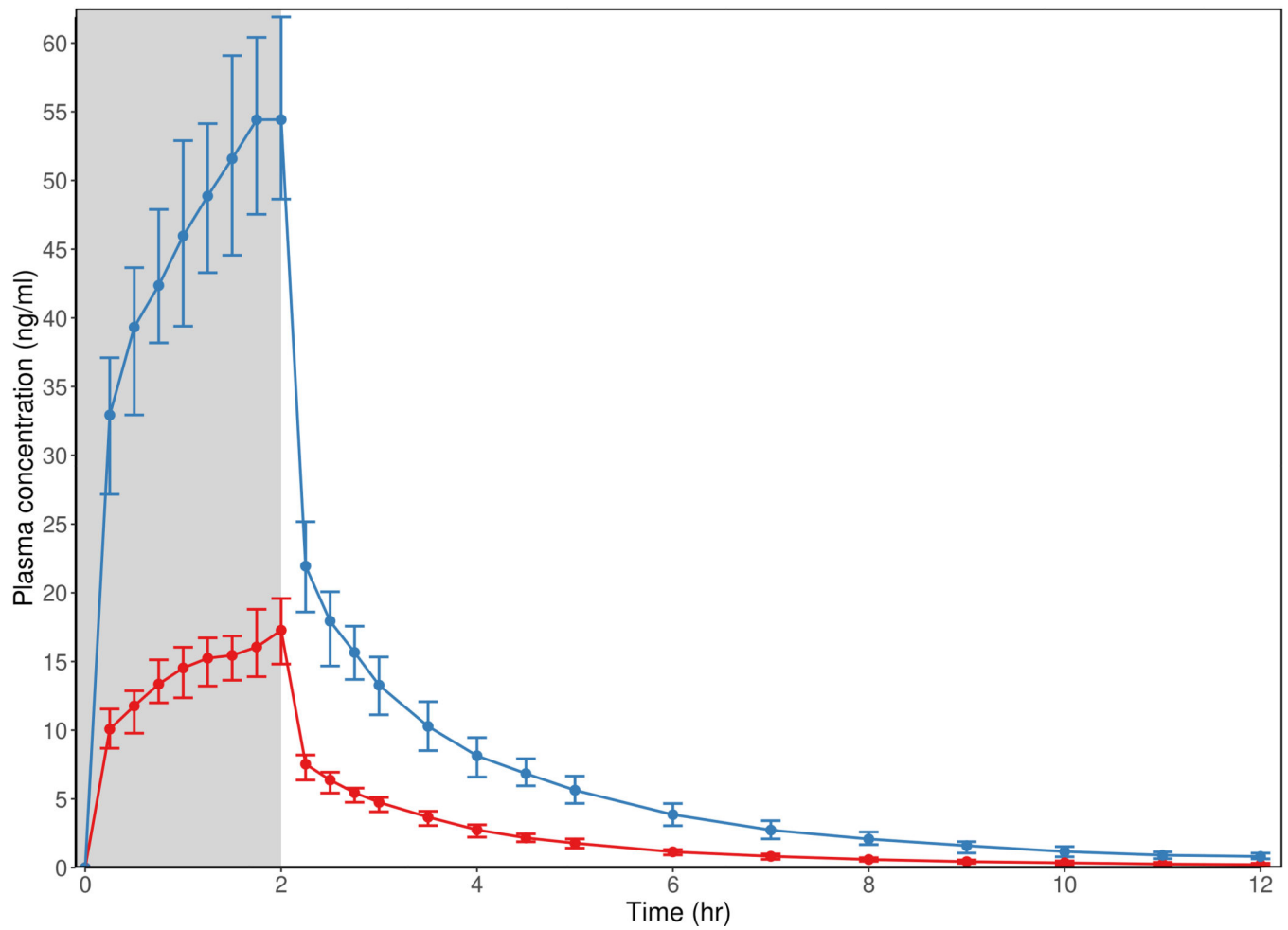
33. Schulte H, Sollevi A, Segerdahl M: Dose-dependent effects of morphine on experimentally induced cutaneous pain in healthy volunteers. *Pain* 2005; 116: 366–374 [PubMed: 15982813]
34. Yarnitsky D, Sprecher E: Thermal testing: normative data and repeatability for various test algorithms. *Journal of the Neurological Sciences* 1994; 125: 39–45 [PubMed: 7964887]
35. Moloney NA, Hall TM, Doody CM: Reliability of thermal quantitative sensory testing: a systematic review. *J Rehabil Res Dev* 2012; 49: 191–207 [PubMed: 22773522]
36. Olesen AE, Andresen T, Staahl C, Drewes AM: Human experimental pain models for assessing the therapeutic efficacy of analgesic drugs. *Pharmacol Rev* 2012; 64: 722–79 [PubMed: 22722894]
37. Staahl C, Olesen AE, Andresen T, Arendt-Nielsen L, Drewes AM: Assessing analgesic actions of opioids by experimental pain models in healthy volunteers - an updated review. *Br J Clin Pharmacol* 2009; 68: 149–68 [PubMed: 19694733]
38. Brennum J, Arendt-Nielsen L, Horn A, Secher NH, Jensen TS: Quantitative sensory examination during epidural anaesthesia and analgesia in man: effects of morphine. *Pain* 1993; 52: 75–83 [PubMed: 8446440]
39. Siebenga P, Okkerse P, van Amerongen G, Doll RJ, Mentink A, Hay J, Groeneveld GJ: Pharmacodynamic evaluation: pain methodologies, *Drug Discovery and Evaluation: Methods in Clinical Pharmacology*. Edited by Hock FJ, Gralinski MR. Switzerland, Springer Nature, 2020, pp pp 95–125
40. Kemler MA, Reulen JP, van Kleef M, Barendse GA, van den Wildenberg FA, Spaans F: Thermal thresholds in complex regional pain syndrome type I: sensitivity and repeatability of the methods of limits and levels. *Clin Neurophysiol* 2000; 111: 1561–8 [PubMed: 10964065]
41. Avram MJ: Presenting Data versus Predictions as Basic Scientific Information: Target-controlled Infusions versus Microgram per Kilogram per Minutes. *Anesthesiology* 2011; 114: 723–723
42. Chang AK, Bijur PE, Meyer RH, Kenny MK, Solorzano C, Gallagher EJ: Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: a randomized clinical trial. *Ann Emerg Med* 2006; 48: 164–72 [PubMed: 16857467]
43. Rapp SE, Egan KJ, Ross BK, Wild LM, Terman GW, Ching JM: A multidimensional comparison of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg* 1996; 82: 1043–8 [PubMed: 8610865]
44. Dinges HC, Otto S, Stay DK, Baumlein S, Waldmann S, Kranke P, Wulf HF, Eberhart LH: Side Effect Rates of Opioids in Equianalgesic Doses via Intravenous Patient-Controlled Analgesia: A Systematic Review and Network Meta-analysis. *Anesth Analg* 2019; 129: 1153–1162 [PubMed: 30418234]
45. Shanthanna H, Paul J, Lovrics P, Vanniyasingam T, Devereaux PJ, Bhandari M, Thabane L: Satisfactory analgesia with minimal emesis in day surgeries: a randomised controlled trial of morphine versus hydromorphone. *Br J Anaesth* 2019; 122: e107–e113 [PubMed: 31027915]
46. Rodrigues S, Shin D, Conway M, Smulski S, Trenker E, Shanthanna H, Vanniyasingam T, Thabane L, Paul J: Hydromorphone versus morphine: a historical cohort study to evaluate the quality of postoperative analgesia. *Can J Anaesth* 2021; 68: 226–234 [PubMed: 33170454]
47. Khanna AK, Urman RD, Overdyk FJ: In Response. *Anesth Analg* 2021; 132: e61



**Figure 1:**  
Consort diagram.

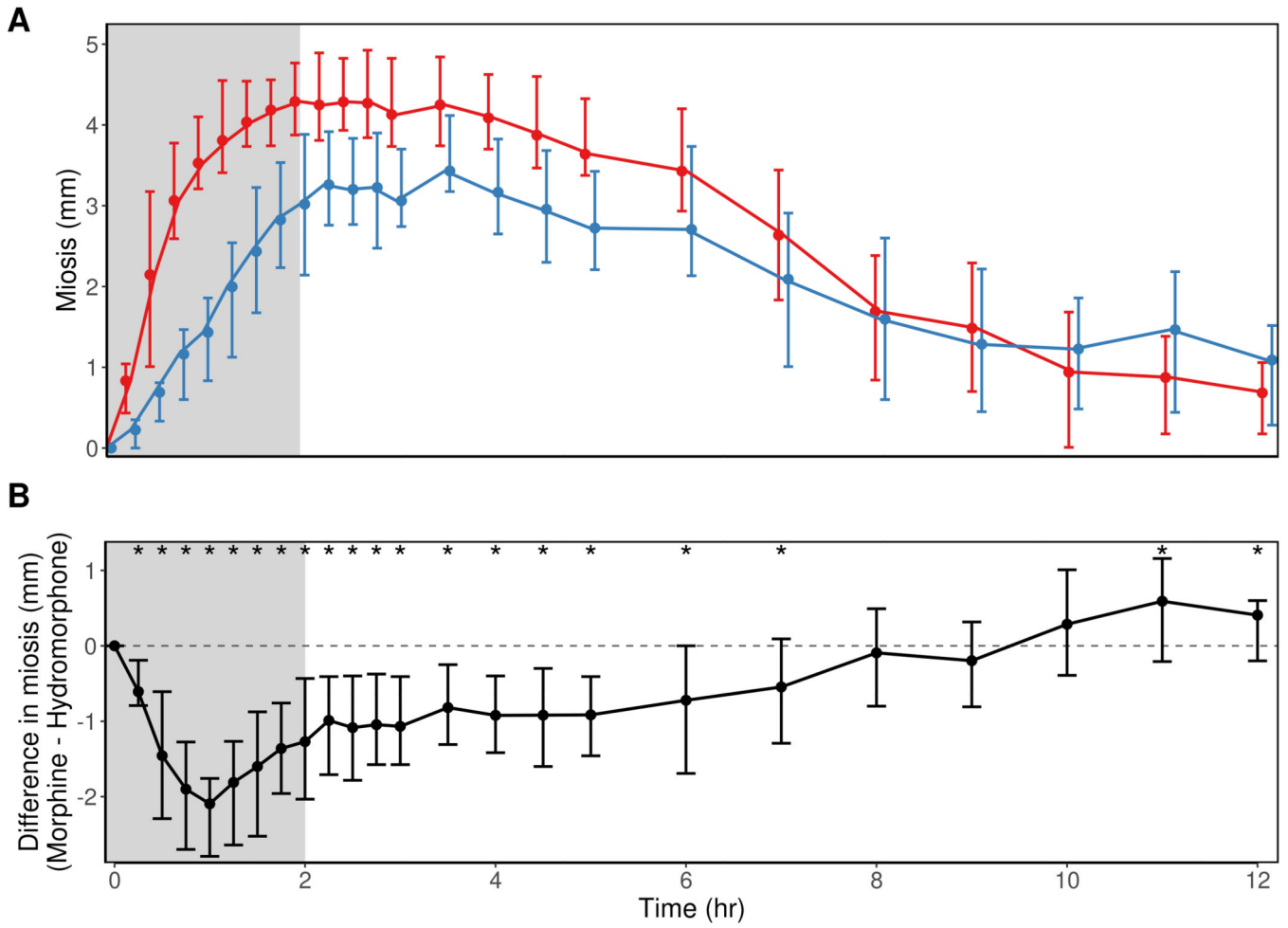


**Figure 2. Summary of opioid concentrations and effects.** Results are the arithmetic means for 42 subjects receiving 0.05 mg/kg hydromorphone (upper panel) and 0.2 mg/kg morphine (lower panel) as a 2 h infusion (grey bar), replotted from the data in Figures 3, 4, 6, 10, and 11



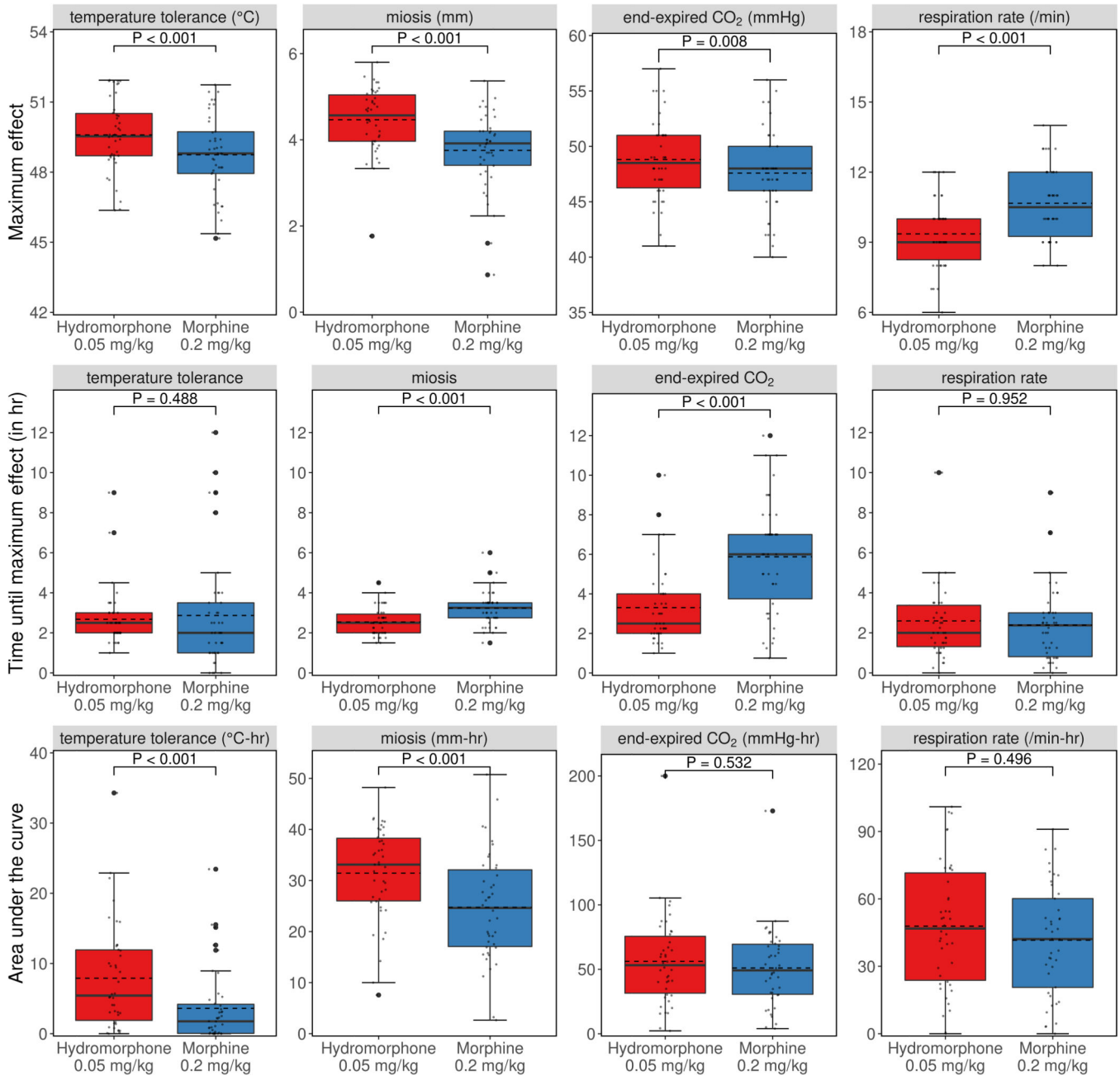
**Figure 3. Plasma concentrations of morphine and hydromorphone.**

Data are shown for 42 subjects that received both 0.2 mg/kg morphine (blue) and 0.05 mg/kg hydromorphone (red) on separate occasions in a crossover fashion. Opioids were administered as a 2 h infusion (gray). Results are shown as the marginal mean and the 25% and 75% quantiles (whiskers)



**Figure 4: Morphine and hydromorphone effects on pupil diameter.**  
: Miosis of subjects receiving 0.2 mg/kg morphine (n=42, blue) and 0.05 mg/kg hydromorphone (n=42, red). Results are the marginal mean and 25–75% quantiles (whiskers). Opioids were administered as a 2 h infusion (gray). (A) Results for each opioid (B) Pairwise differences between opioids. Asterisks indicate significant differences between the two opioid treatments after Tukey adjustment in pairwise contrast tests on a linear mixed effect model for miosis.





**Figure 5: Morphine and hydromorphone clinical effects.**

(Top row) Maximum drug effect, (middle row) time to maximum drug effect, (bottom row) area under the effect-time curve. Clinical effects are analgesia (maximum tolerated temperature), miosis, end-expired carbon dioxide, and minimum respiratory rate. Results are for 42 subjects receiving 0.2 mg/kg morphine and 0.05 mg/kg hydromorphone (individual values displayed as small dots). Dashed lines are the mean, solid lines are median. The lower and upper ends of the box correspond to the 25th and 75th percentiles, defining the interquartile range (IQR). The whiskers extend from 25th and 75th percentiles to the smallest and largest values, but no further than 1.5 \* IQR from its origin, with data points

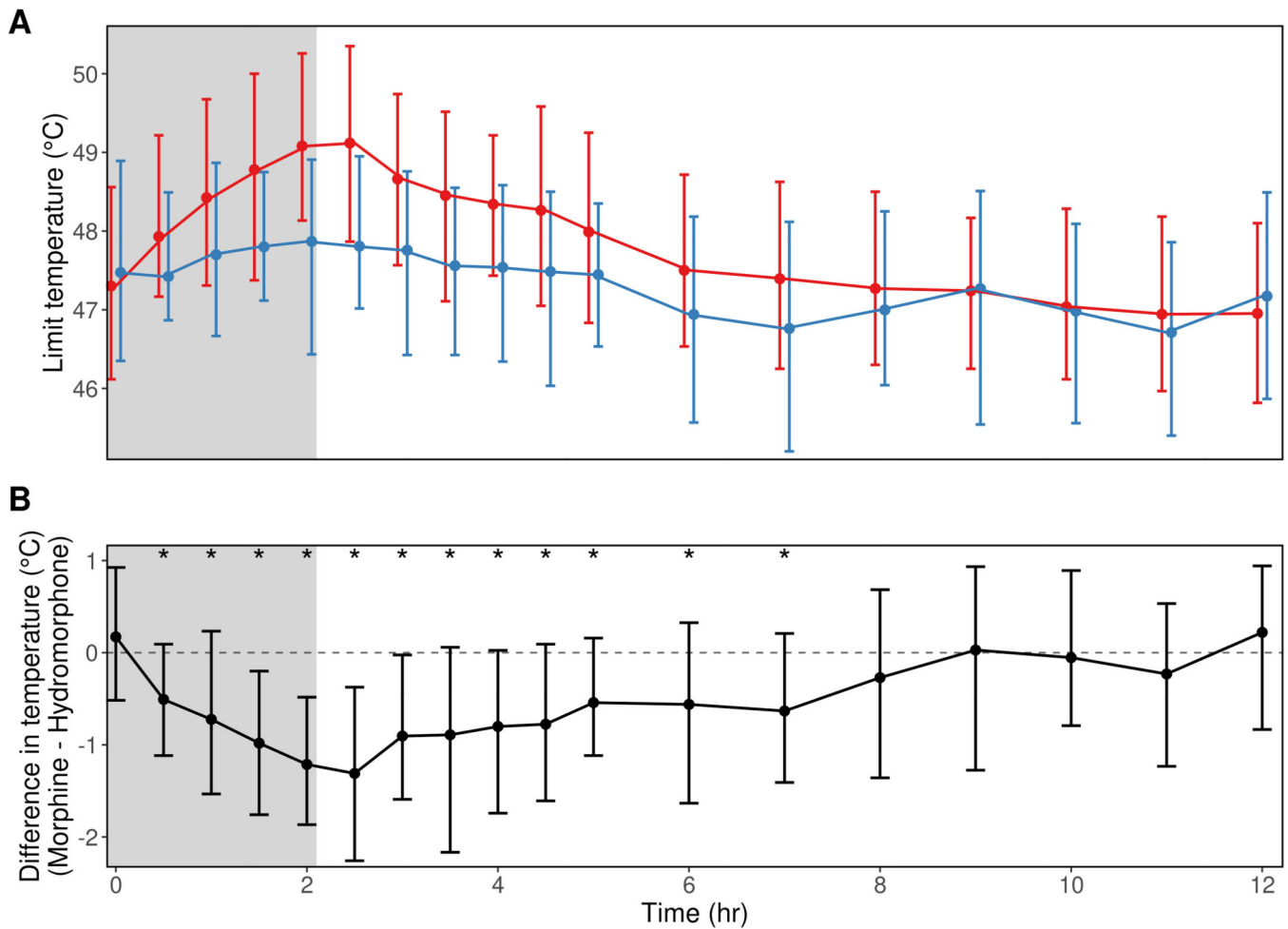
lying further out defined as outliers (enlarged dots). Pairwise tests for equality of medians used Wilcoxon signed-rank tests. The corresponding P values are stated at the top in the respective panel.

Author Manuscript

Author Manuscript

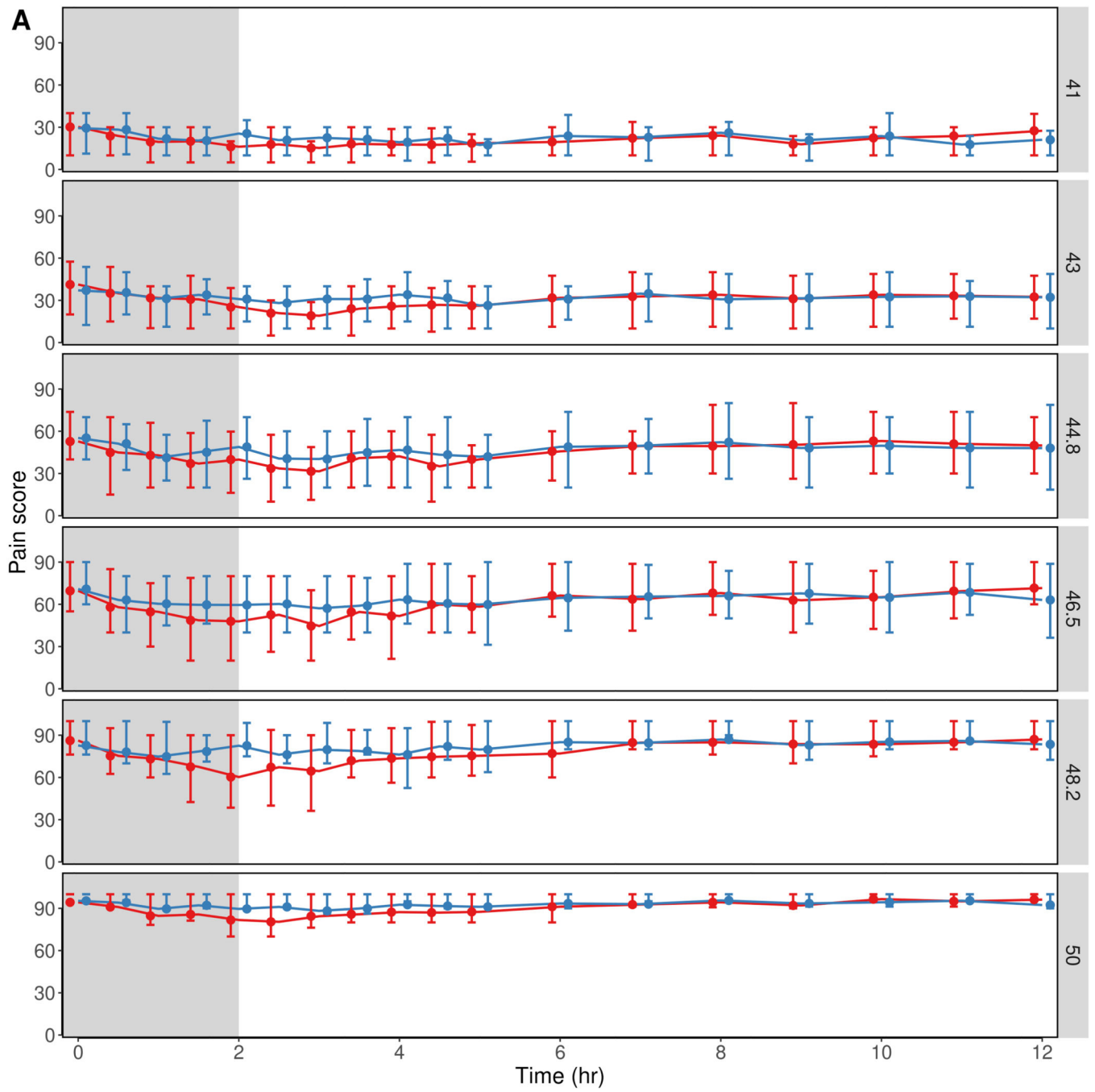
Author Manuscript

Author Manuscript



**Figure 6: Morphine and hydromorphone analgesia.**

Shown is the maximally tolerated temperature (“method of limits”, mean of three measurements) for subjects receiving 0.2 mg/kg morphine (n=42, blue) and 0.05 mg/kg hydromorphone (n=42, red). Results are the marginal mean and the 25% and 75% quantiles (whiskers). Opioids were administered as a 2 h infusion (shaded area). (A) Results for each opioid. (B) Pairwise differences between opioids. Asterisks indicate significant differences between the two opioid treatments after Tukey adjustment in pairwise contrast tests on a linear mixed effect model for the maximal limit temperature.

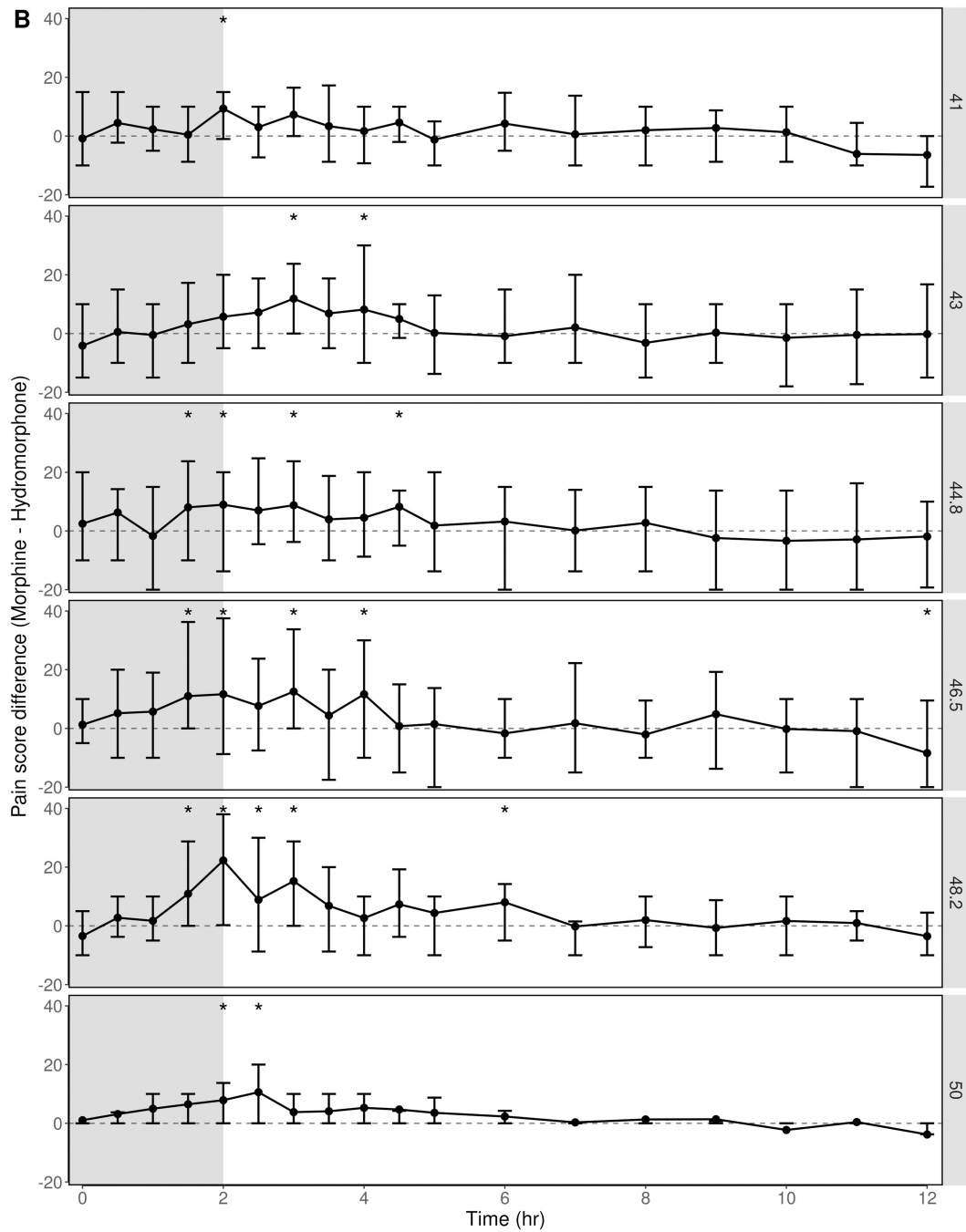


Author Manuscript

Author Manuscript

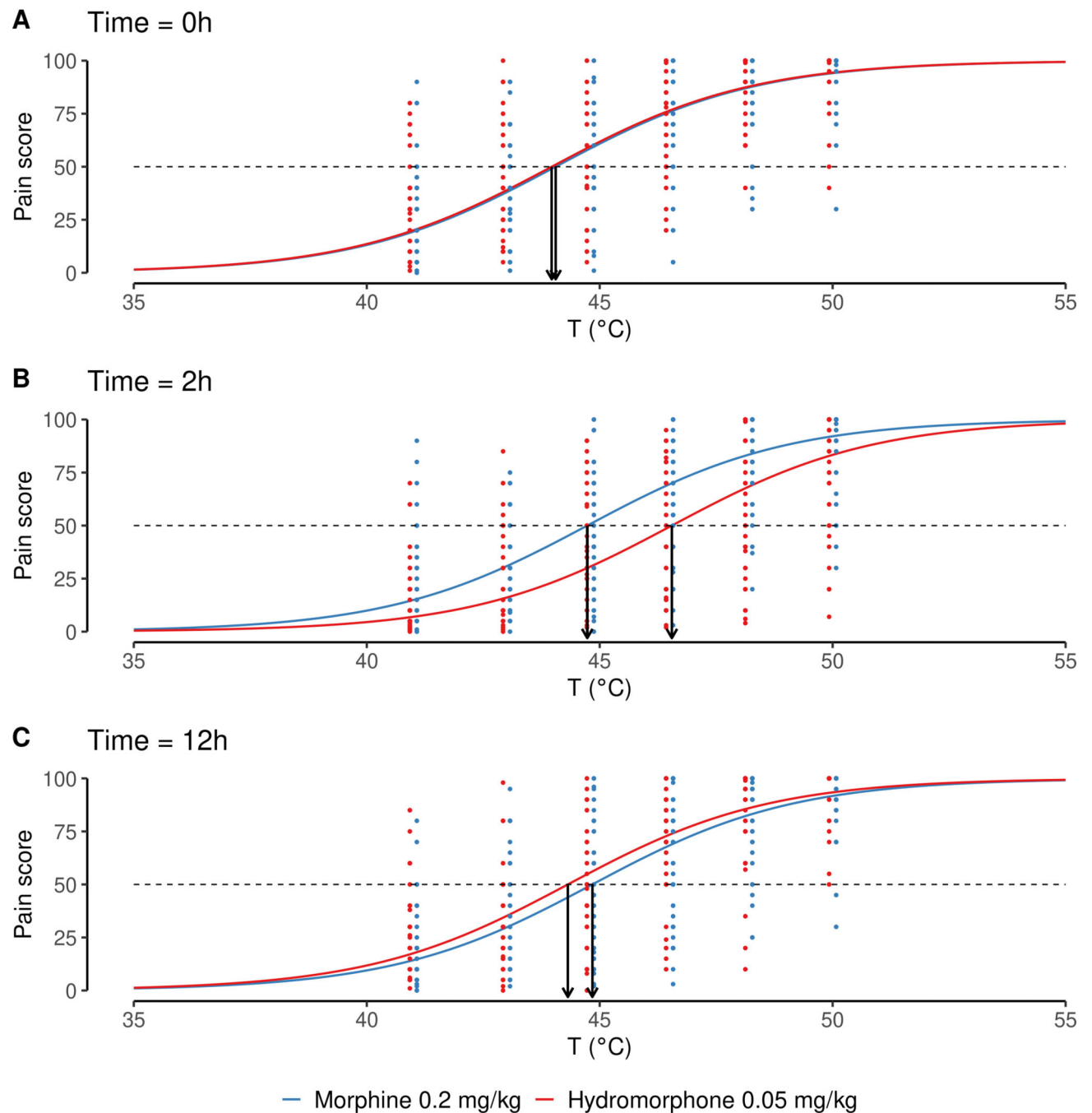
Author Manuscript

Author Manuscript



**Figure 7: Morphine and hydromorphone analgesia.**

Subjects (n=42) received 0.2 mg/kg morphine (blue) and 0.05 mg/kg hydromorphone (red). Shown are self-reported verbal pain scores (0–100) over time at six specific discrete temperatures (“ramp and hold” method). Results are the marginal mean and the 25% and 75% quantiles (whiskers). (A) Results for each opioid. (B) Pairwise differences between opioids. Asterisks indicate significance between the two opioids after Tukey adjustment in pairwise contrast tests on a linear mixed effect model for VAS.



**Figure 8: Morphine and hydromorphone analgesia.**

Subjects ( $n=42$ ) received 0.2 mg/kg morphine (blue) and 0.05 mg/kg hydromorphone (red). Results are self-reported verbal pain scores (0–100) at six specific discrete temperatures. Shown is the relationship between thermal stimulus temperature and verbal pain scores. Data points represent individual data, and lines represent the population NONMEM model fits to a sigmoidal Emax model determined by nonlinear regression. Also shown are the half-maximal temperature ( $T_{50}$ , arrow). Results are shown for (A) before (0 h), (B) 2 h after



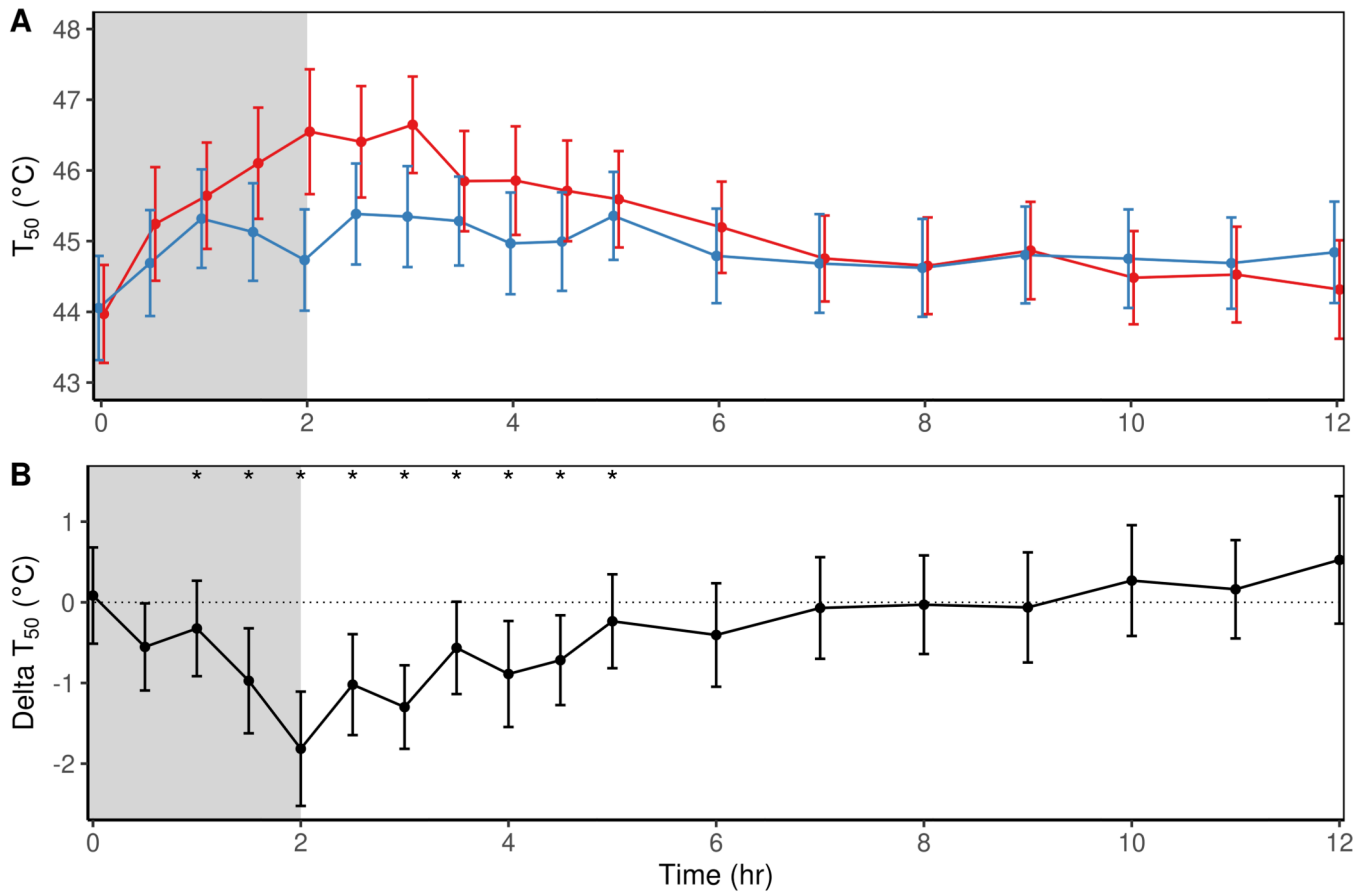
the start, and 12 h after the start of the opioid infusion.  $T_{50}$  values at all time points and for both drugs are shown in Figure 9.

Author Manuscript

Author Manuscript

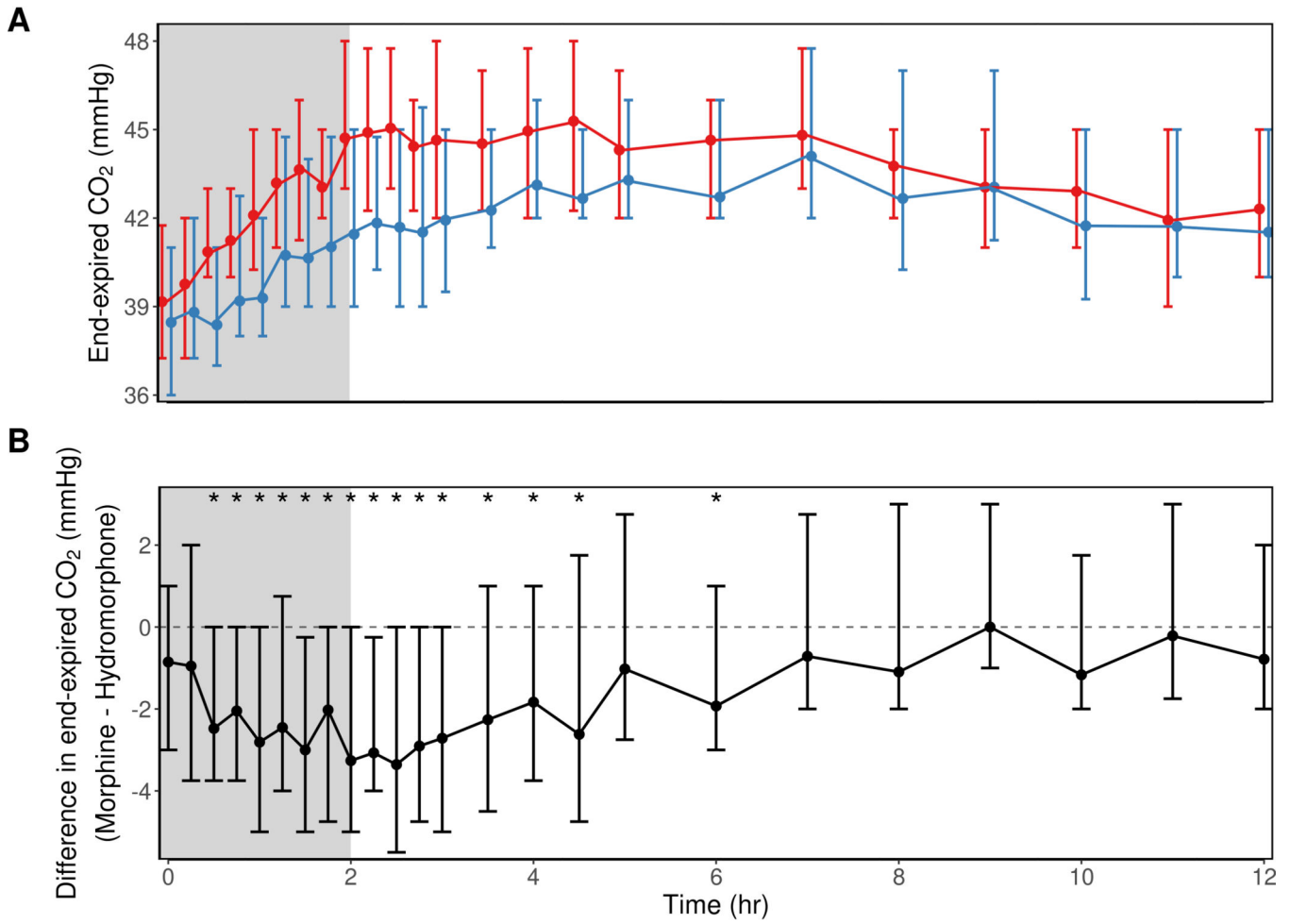
Author Manuscript

Author Manuscript



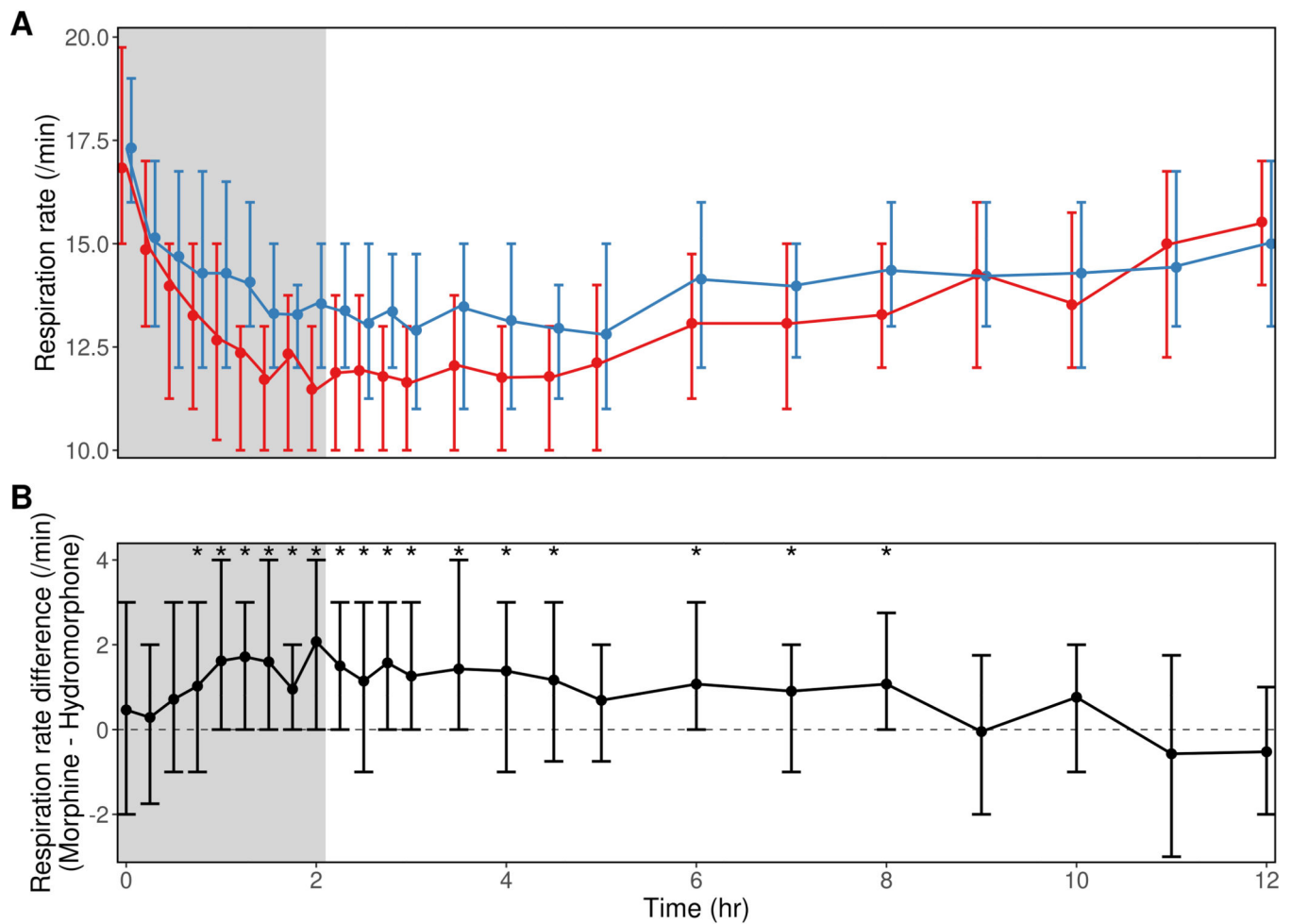
**Figure 9: Morphine and hydromorphone analgesia.**

Shown is the half-maximal temperature ( $T_{50}$ ) over time for all 42 subjects receiving 0.05 mg/kg hydromorphone (red curve, upper panel), 0.2 mg/kg morphine (blue curve, upper panel), and the difference between the two (black curve, lower panel). Results are the marginal mean with corresponding 95% confidence intervals (whiskers). Mean model-derived  $T_{50}$  values for hydromorphone and morphine at each time point were compared using the log-likelihood test for statistical significance between a model of same or different means, using critical values of the chi-square distribution with one degree of freedom. Calculated P values were adjusted for multiple comparisons using the Bonferroni correction. Asterisks denote significantly different values ( $P < 0.05$ ).



**Figure 10: Ventilatory effects of opioids.**

Shown is the end expired CO<sub>2</sub> in subjects receiving 0.2 mg/kg morphine (n=42, blue) and 0.05 mg/kg hydromorphone (n=42 red). Results are shown as the marginal mean and the 25% and 75% quantiles (whiskers). Opioids were administered as a 2 h infusion (shaded area). (A) Results for each opioid. (B) Pairwise differences between opioids. Asterisks indicate significant differences between the two opioid treatments after Tukey adjustment in pairwise contrast tests on a linear mixed effect model for etCO<sub>2</sub>.



**Figure 11: Ventilatory effects of opioids.**

Shown is the respiratory rate of subjects receiving both 0.2 mg/kg morphine (n= 42, blue) and 0.05 mg/kg hydromorphone (n=42, red). Results are shown as the marginal mean and the 25% and 75% quantiles (whiskers). Opioids were administered as a 2 h infusion (shaded area). (A) Results for each opioid. (B) Pairwise differences between opioids over time since start of opioid (2 h infusion, shaded area). Asterisks indicate significant differences between the two opioid treatments after Tukey adjustment in pairwise contrast tests on a linear mixed effect model for respiration rate.

**Blood gas analyses.**

**Table 1:**

Opioid infusion occurred from 0 to 2 hours. Results are subjects receiving both morphine and hydromorphone infusions (n=42). Results are the mean ± standard deviation

Time (h)	pH		pCO <sub>2</sub> (mmHg)		pO <sub>2</sub> (mmHg)		HCO <sub>3</sub> (mmol/L)	
	Hydromorphone (0.05 mg/kg)	Morphine (0.2 mg/kg)	Hydromorphone (0.05 mg/kg)	Morphine (0.2 mg/kg)	Hydromorphone (0.05 mg/kg)	Morphine (0.2 mg/kg)	Hydromorphone (0.05 mg/kg)	Morphine (0.2 mg/kg)
0	7.41±0.03	7.41±0.02	39±4	39±3	102±14	104±13	25±2	25±2
1	7.37±0.03	7.39±0.03	44±5	43±5	100±16	103±13	26±2	26±2
2	7.36±0.04	7.37±0.02	46±6	44±4	101±14	105±13	26±2	26±2
3	7.36±0.03	7.38±0.02	46±5	44±4	102±15	103±12	26±2	27±2