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ANESTHESIOLOGY

Morphine and Hydromorphone Effects, Side Effects, and Variability: A Crossover Study in Human Volunteers

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- All clinicians know that both morphine and hydromorphone are effective opioid analgesics. Their basic pharmacokinetics are also well-known and that hydromorphone may have a faster analgesic onset. However, a rigorous comparison of their relative impacts on a wide range of relevant "side effects" (beyond analgesia) has not been performed.

What This Article Tells Us That Is New

- This meticulously performed comparative volunteer study examined the onset, depth, and duration of drug effects on analgesia, pupil diameter, expired carbon dioxide, and respiratory rate, along with measured arterial opioid concentrations. They showed that the relationship between analgesia and respiratory depression differed between the two drugs, with morphine having "less analgesia" for any given degree of respiratory depression as well as a delayed onset and longer duration of respiratory depression. The authors suggest that hydromorphone may, as a result, have advantages in the clinical setting.

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. This study tested the hypothesis that IV morphine and hydromorphone differ in onset, magnitude, duration, and variability of analgesic and ventilatory effects.

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

Results: For morphine and hydromorphone, respectively, maximum miosis was less (3.9 [3.4 to 4.2] *vs.* 4.6 mm [4.0 to 5.0], $P < 0.001$; median and 25 to 75% quantiles) and occurred later (3.1 ± 0.9 *vs.* 2.3 ± 0.7 h after infusion start, $P < 0.001$; mean $\pm$ SD); maximum tolerated temperature was less (49 ± 2 *vs.* $50 \pm 2°C$, $P < 0.001$); 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_2 was 47 (45 to 50) and 48 mmHg (46 to 51; $P = 0.007$) and occurred later (5.5 ± 2.8 *vs.* 3.0 ± 1.5 h after infusion start, $P < 0.001$); and respiratory nadir was 9 ± 1 and 11 ± 2 breaths/min ($P < 0.001$), and occurred at similar times. The area under the temperature tolerance-time curve was less for morphine (1.8 [0.0 to 4.4]) than hydromorphone (5.4°C-h [1.6 to 12.1] $P < 0.001$). Interindividual 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.

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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 nonsurgical complications, and in its severe manifestations is associated with regret for having had surgery.[1,2] Acute postsurgical pain is also a risk factor for chronic postoperative pain, which affects 10 to 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.[3,4] The Anesthesia Patient Safety Foundation (Rochester, Minnesota) has continuously issued warnings regarding the dangers of postoperative respiratory complications.[5] Minimizing opioid toxicity remains an important priority for patients, clinicians, and hospital authorities.[6,7] While respiratory monitoring has been a recommended solution, this is only a secondary prevention (detecting toxicity).[8] A better ideal is primary prevention—that is, preventing toxicity.[9] Confounding the goal of optimal analgesia, without untoward side effects, is the considerable and unpredictable inter- and intraindividual 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.[10,11] 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.[12,13] Numerous clinical outcome studies have evaluated some opioid side effects, and others have attempted to predict risk for respiratory depression for each patient.[4,14] 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 opioids remain elusive.[15]

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 (St. Louis, Missouri), 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 Web site and flyers), and interested persons contacted study staff. Eligible subjects had to be 18 to 40 yr, have body mass index 20 to 33kg/m^2, be in good general health with no remarkable medical conditions, take no prescription or nonprescription 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 1 week between sessions. Subjects arrived at the study site fasted, an IVs catheter for drug administration and an arterial catheter for blood sampling were inserted, and subjects received an IV infusion of lactated Ringers in 5% dextrose (125 ml/h). All subjects were monitored with a pulse oximeter, automated blood pressure cuff, and sidestream carbon dioxide monitor using a combined nasal and oral spoon sampler (Philips, USA).

Hydromorphone and morphine were administered IV as 2-h infusions (marked in gray in all time-related figures). Subjects received IV ondansetron (4 mg) for antiemetic prophylaxis before 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- to 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 four- to fivefold

potency difference,[16] the doses were revised to 0.05 mg/kg hydromorphone and 0.2 mg/kg morphine. Arterial blood samples were obtained for 12 h 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 3 h. 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%[17] 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% SD 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 oxygen saturation measured by pulse oximetry, and end-expired carbon dioxide concentration; (2) dark–adapted pupil diameter (in triplicate) using an infrared pupillometer (Neuroptics, USA) as described before,[18] 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, Israel). The first was the "method of limits" (a continuous increase from 32°C at 0.8°C/sec 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 six 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.[19] Subjects were asked to rate the pain at each temperature on a 0 to 100 verbal analog scale. Subjects were instructed and familiarized with the procedures after enrollment and before 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 3 h, every half an hour for another 2 h, and every hour thereafter until 12 h. Temperature tolerance was measured every half hour for the first 5 h and every hour thereafter. There were also measurements of pH, $Paco_2$, Po_2, and bicarbonate for the first 3 h 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 2% (volume/volume) ammonium hydroxide in water containing the internal standard deuterated hydromorphone (Cerilliant, USA), processed by solid phase extraction (Varian Bond-Elut Plexa, USA; 30 mg), rinsed with 1 ml water, and eluted with 1 ml methanol. The samples were evaporated to dryness and reconstituted in 100 μl mobile phase A. An Agilent 1100 series liquid chromatograph with mass selective detector was used for analysis, with a Zorbax XDB-C18 column, 2.1 × 100 mm x 5 μm (Agilent, USA), Phenomenex (USA) guard cartridge AJO-4286 C18, 2.0 × 4.0 mm, and 0.5-μm steel frit filter. Mobile phase A − 5 mM aqueous formic acid with 5% 1:1 acetonitrile-methanol solution; mobile phase B – 1:1 acetonitrile-methanol. Flow rate 0.35 ml/min. Gradient timetable (percent B): 0 to 4 min - 0%, 4 to 5 min – gradient increase to 85%, 5 to 7 min – 85% with increasing flow rate to 0.4 ml/min at 7 min, 7 to 8 min – gradient return to 0% and 0.35 ml/min flow rate, 8 to 12 min - 0%. Injection volume was 10 μl. The approximate retention time of hydromorphone was 3.6 min. Quantitation was performed for the following ions (positive electrospray ionization): mass/charge 286 (hydromorphone), and m/z 292 (hydromorphone-d6, internal standard). The calibration curve fit was performed with Microsoft Excel 2003 (Microsoft, USA) and SigmaPlot (Inpixon, USA) software for a quadratic curve with reciprocal X regression. Calibrated range was 0.2 to 200 ng/ml, and the limit of detection was less than 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 an AB/Sciex 4000 QTRAP (AB/Sciex, USA) as described previously,[20] except that the calibration range was 0.1 to 100 ng/ml for morphine and morphine-6-glucuronide, and 2 to 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 mean ± SD, 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 mean ± SD whenever the assumption of normal distribution is reasonable, and by 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 were 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) values 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, verbal analog scale data were fitted to the following model.

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

T is the preselected temperatures 41°, 43°, 44.8°, 46.5°, 48.2°, and 50°C, T_{50} is the temperature giving a verbal analog scale of 50, and γ is a shape factor. NONMEM[18] (ICON Plc, Dublin, Ireland) was used to fit the data, assuming different T_{50} values at each time point, and one overall γ. Interindividual differences in T_{50} and γ were assumed to be lognormally distributed, and residual error was assumed to be normally distributed. Because we observed high values for γ (around 20), the following alternative model was chosen (it resulted in 70 points lower objective function values).

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

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} values. For T_{50} values, we state the mean with corresponding 95% CI instead of quantiles, 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; https://www.R-project.org/, accessed April 13, 2022). For the determination of peak effects, a peak detection algorithm for time series of the R-package pracma of Borchers was employed,[21] 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).[22] For the computation of the AUCs, the R-package DescTools of Signorelli was employed.[23]

Results

Demographic Data

A total of 51 healthy volunteers (26 female, 25 male, 28 ± 6 yr, 73 ± 13 kg, body mass index 24.7 ± 3.4 kg/m²) 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, four completing both sessions and three completing one only), it became apparent that the effects of the two opioids were perceivable to study personnel, grossly unequal, and subject as well as observer blinding were impaired. The protocol was therefore modified, and opioid doses were changed to 0.05 mg/kg hydromorphone and 0.2 mg/kg morphine. The Consolidated Standard of Reporting Trials diagram for enrollment is shown in figure 1. Supplemental Table 1 (https://links.lww.com/ALN/D119) 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 who 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 figure 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 2-h infusion. Maximum
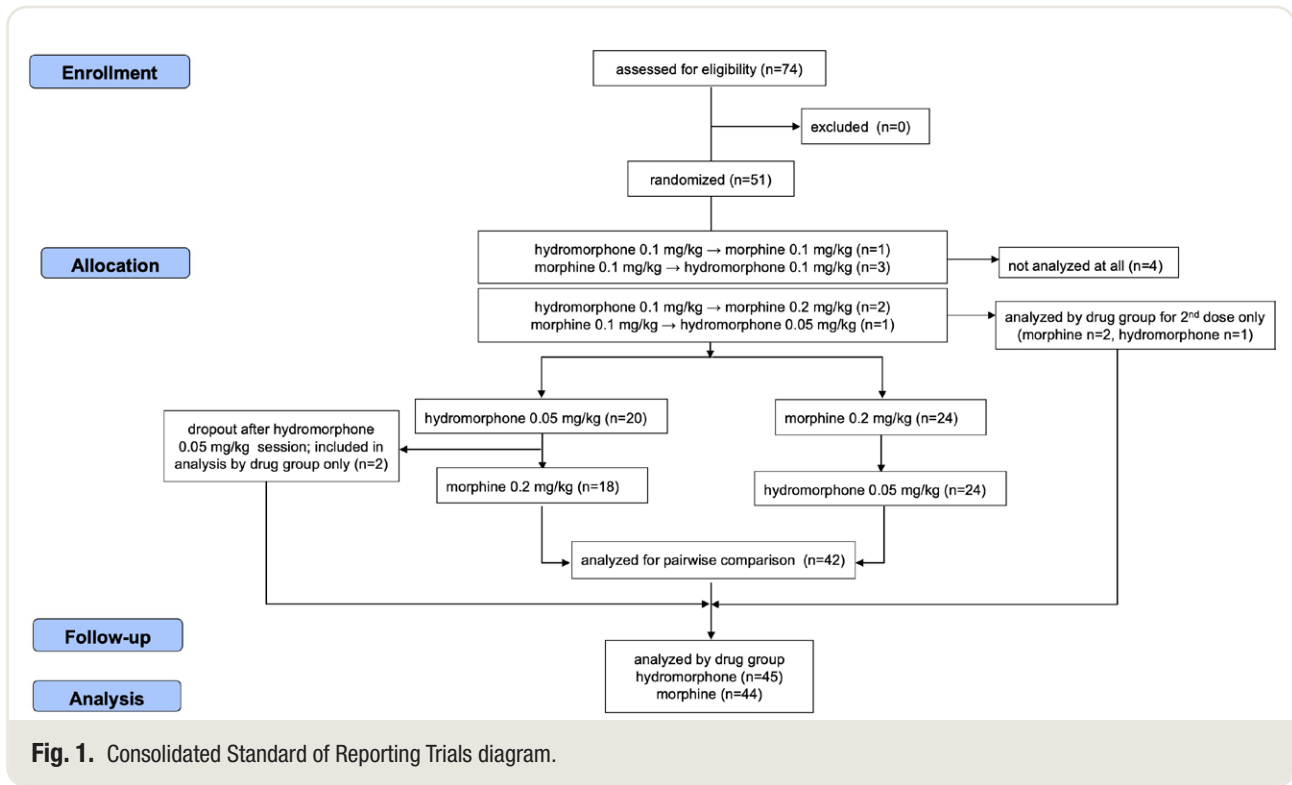
Fig. 1. Consolidated Standard of Reporting Trials diagram.

concentrations were 16.9 [14.8 to 19.6] ng/ml for 0.05 mg/kg hydromorphone and 55.8 [48.6 to 61.9] ng/ml for 0.2 mg/kg morphine (figs. 2 and 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 ± 0.9 and 7.2 ± 0.9 mm, respectively. Pupils constricted to 2.1 ± 0.7 and 4.2 ± 1.2 mm at the end of the 2-h opioid infusion (Supplemental Figure 1, https://links.lww.com/ALN/D113), equivalent to miosis of 4.3 ± 0.7 and 3.0 ± 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 h after the discontinuation of the drug, with the most impressive difference during the infusion (figs. 2 and 4B). Overall maximum miosis was 4.6 mm [4.0 to 5.0] after hydromorphone and 3.9 mm [3.4 to 4.2] after morphine ($P < 0.001$) and occurred at 2.3 ± 0.7 and 3.1 ± 0.9 h ($P < 0.001$), respectively, after the start of the infusion (fig. 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 to 39]) than after morphine (25 mm-h [17 to 33]; $P < 0.001$, fig. 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 (https://links.lww.com/ALN/D114).

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 ± 2°C for 0.05 mg/kg hydromorphone compared to 48 ± 2°C for 0.2 mg/kg morphine for the 42 subjects receiving both opioids ($P < 0.001$, figs. 2 and 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 4 h after its discontinuation (fig. 6B). Throughout the 12-h experiment, maximum tolerated temperature at any time was greater after hydromorphone (49.6 ± 1.5°C) than after morphine (48.7 ± 1.7°C, $P < 0.001$) and occurred at 2.0 h [2.0 to 2.6] and 2.5 h [1.5 to 4.0] ($P = 0.488$), respectively, after the start of the infusion (fig. 5). Interindividual variability in
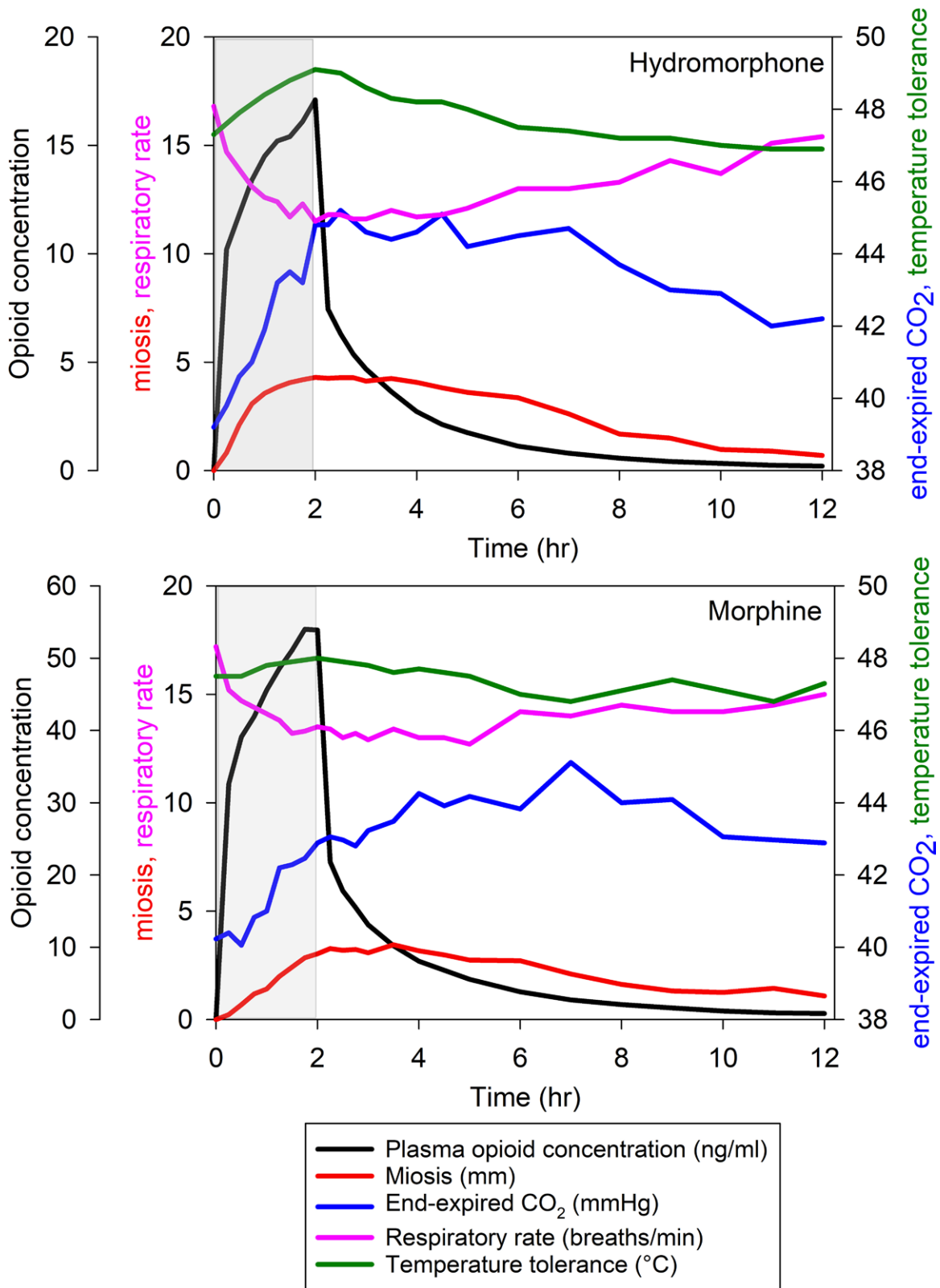
Fig. 2. Summary of opioid concentrations and effects. Results are the arithmetic means for 42 subjects receiving 0.05 mg/kg hydromorphone (*upper*) and 0.2 mg/kg morphine (*lower*) as a 2-h infusion (*gray bar*), replotted from the data in figures 3, 4, 6, 10, and 11.
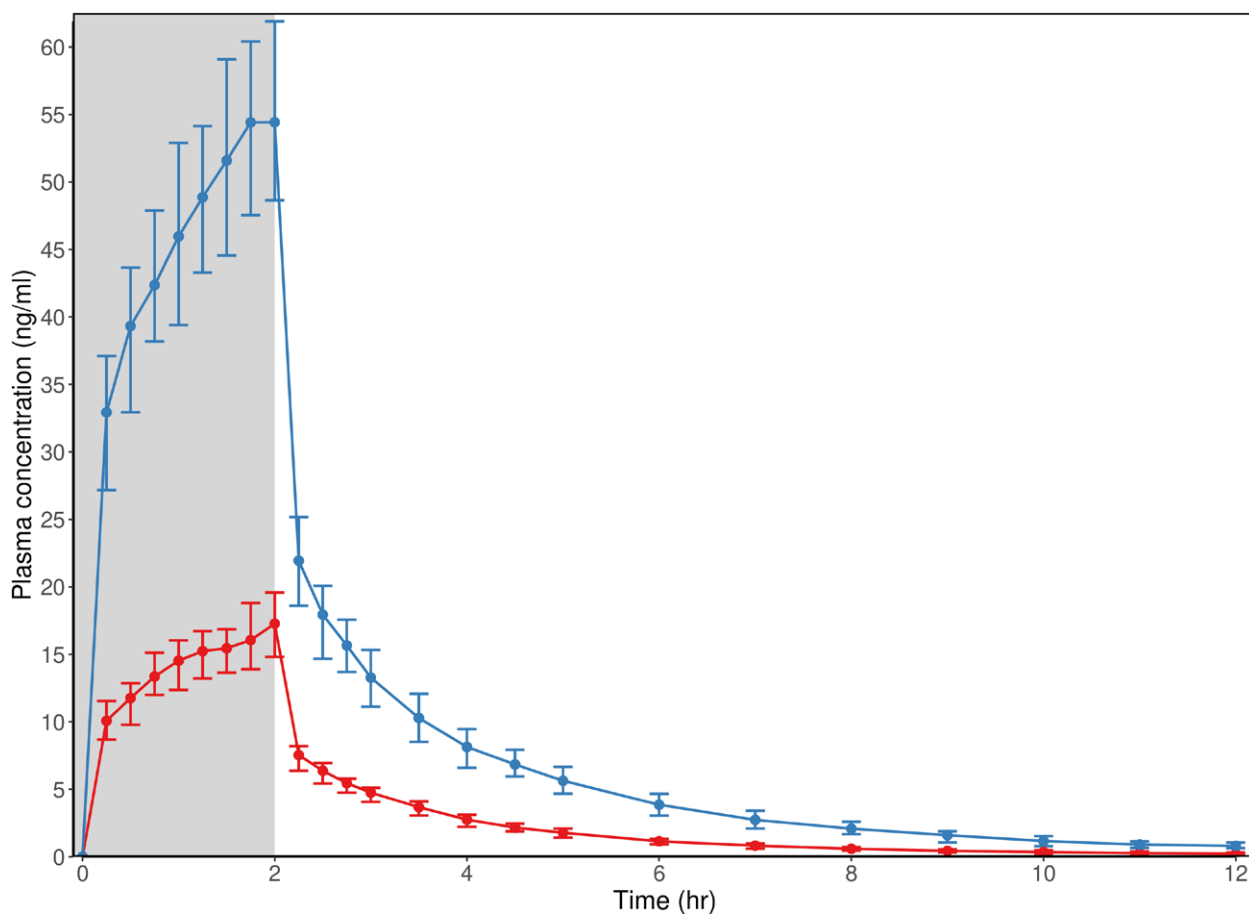
Fig. 3. Plasma concentrations of morphine and hydromorphone. Data are shown for 42 subjects who received both 0.2 mg/kg morphine (*blue*) and 0.05 mg/kg hydromorphone (*red*) on separate occasions in a crossover fashion. Opioids were administered as a 2-h infusion (*gray*). Results are shown as the marginal mean and the 25% and 75% quantiles (*whiskers*).

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°C–h [1.6 to 12.1]) than after morphine (1.8°C–h [0.0 to 4.4]; $P < 0.001$; fig. 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 (https://links.lww.com/ALN/D115).

In the "ramp and hold" pain model using six randomly applied specific temperatures and verbal analog 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 figure 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° to 48°C) (fig. 7B). The greatest difference between opioids in pain scores was at 48.2°C. Pain scores at 48.2°C at the end of the infusion were 59 ± 3 and 82 ± 4 for hydromorphone and morphine, respectively ($P < 0.001$). Hydromorphone analgesia persisted for 1 to 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 (https://links.lww.com/ALN/D116).

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
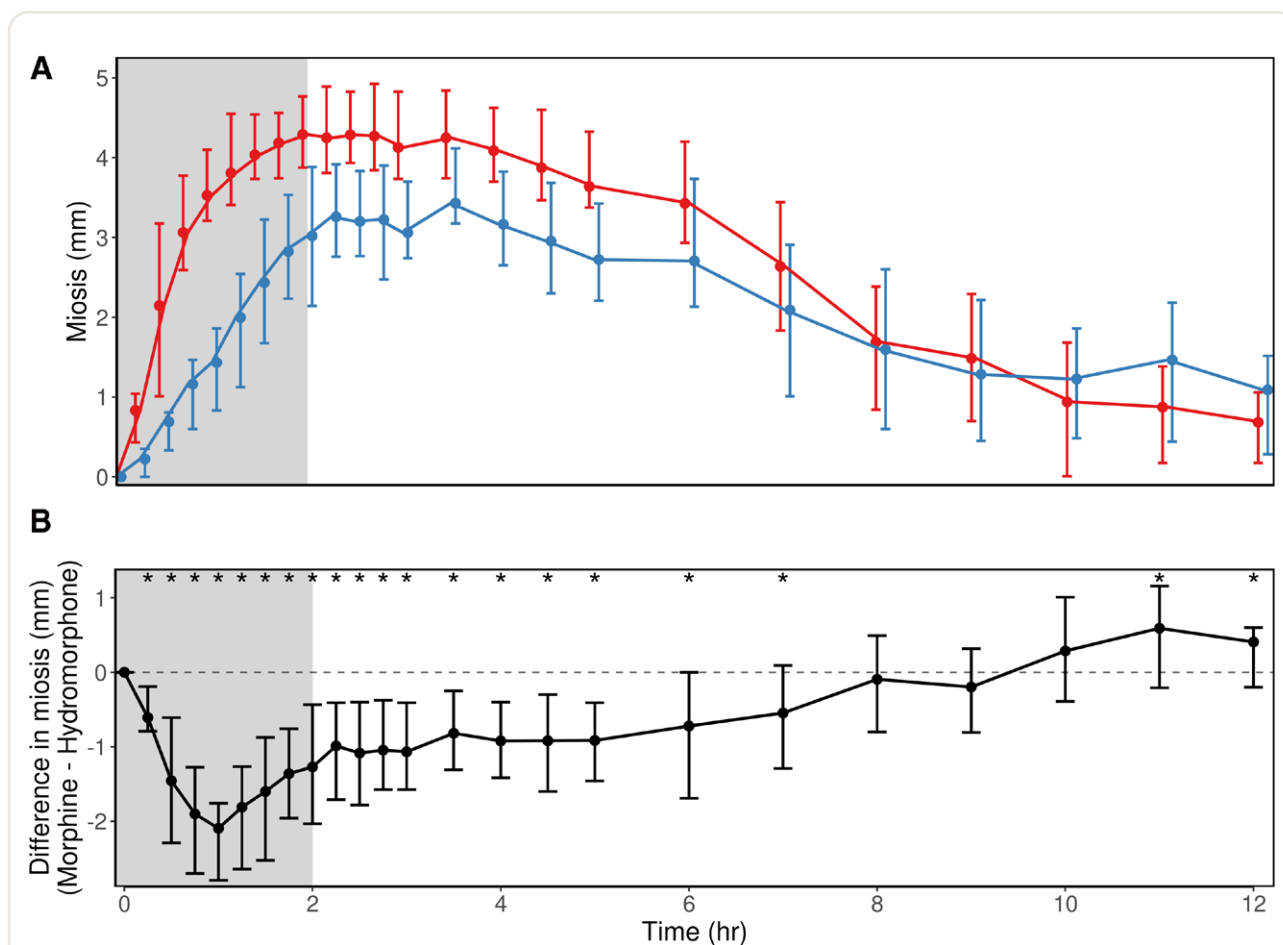
Fig. 4. Morphine and hydromorphone effects on pupil diameter. Miosis of subjects receiving 0.2 mg/kg morphine (n = 42, *blue*) and 0.05 mg/kg hydromorphone (n = 42, *red*). Results are the marginal mean and 25% and 75% quantiles (*whiskers*). Opioids were administered as a 2-h infusion (*gray*). (*A*) 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.

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 (γ). 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 toward 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 figure 8B. The time course of the T_{50} values, and for both opioids, is shown figure 9, A and B, 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 ± 0.4 and 46.5 ± 0.5°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} values at any time during the entire experiment were 46.6 ± 0.3°C at 3 h and 45.4 ± 0.4°C at 2.5 h for hydromorphone and morphine, respectively. Figure 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 γ. The γ value was not significantly different between the two drugs (0.46 ± 0.02 and 0.48 ± 0.02 for hydromorphone and morphine), and was singularly estimated as 0.47 ± 0.02 (model estimate ± SD) in a combined model including both drugs. Interindividual variabilities (in the log domain) of T_{50} and γ were 0.0022 ± 0.0004 and 0.11 ± 0.02, respectively, and were not significantly different between the two drugs (0.0023 ± 0.0004 and 0.11 ± 0.02 for hydromorphone and morphine T_{50}, respectively, and
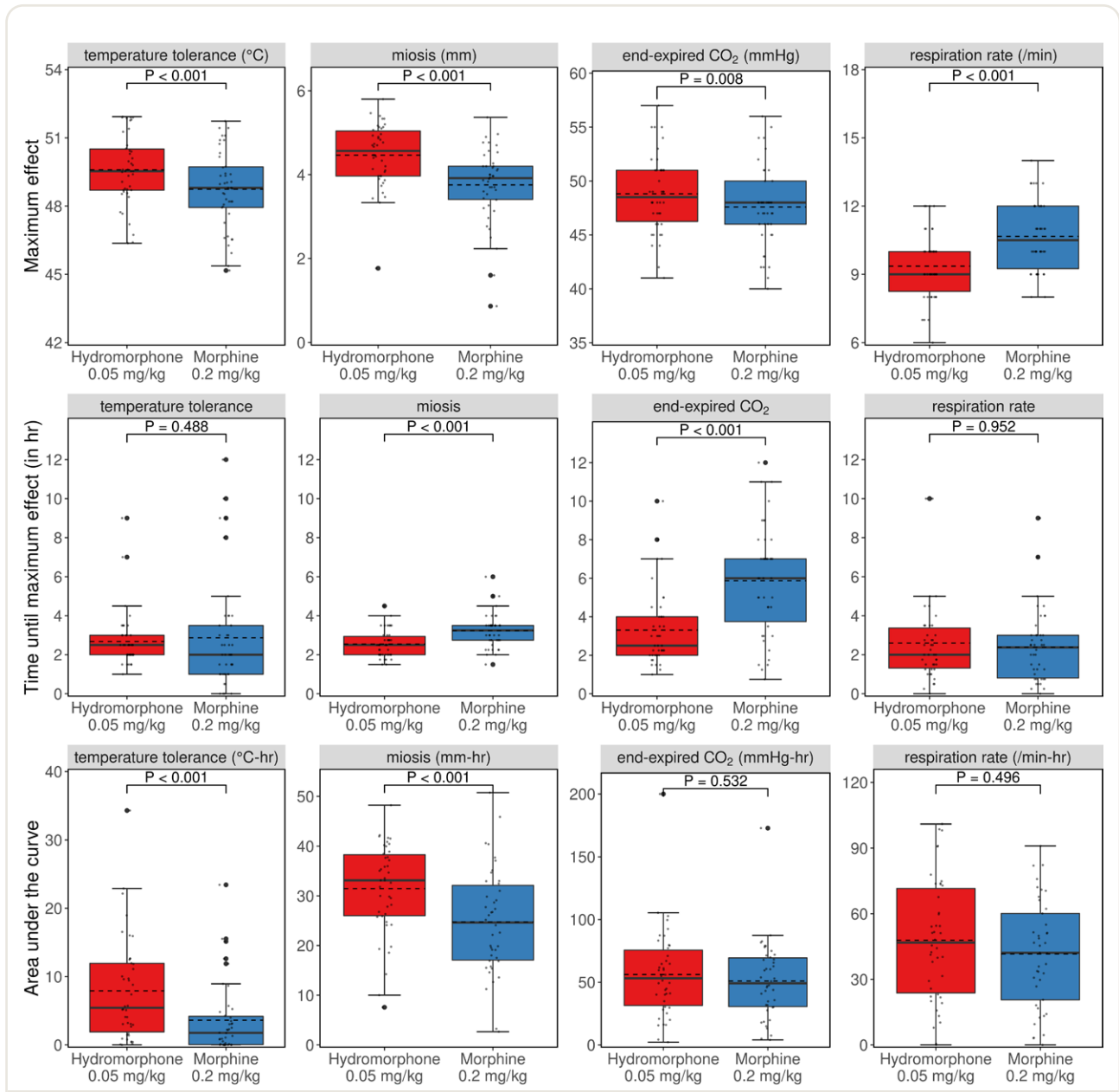
Fig. 5. Morphine and hydromorphone clinical effects. (*Top*) Maximum drug effect, (*middle*) time to maximum drug effect, and (*bottom*) area under the effect-time curve. Clinical effects are analgesia (maximum tolerated temperature), miosis, end-expired carbon dioxide, and minimum respiratory rate. 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, and *solid lines* are the median. The lower and upper ends of the box correspond to the 25th and 75th percentiles, defining the interquartile range. The *whiskers* extend from 25th and 75th percentiles to the smallest and largest values, but no further than 1.5 * interquartile range 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.

0.0019 ± 0.0005 and 0.09 ± 0.02 for hydromorphone and morphine γ, respectively).

Ventilation

Ventilation was assessed using end-expired carbon dioxide, respiratory rate, and arterial blood gas analysis. End-expired

carbon dioxide for the 42 subjects receiving both 0.05 mg/kg hydromorphone and 0.2 mg/kg morphine increased from 39 mmHg [37 to 42] and 39 mmHg [36 to 41] at baseline to 45 mmHg [43 to 48] and 42 mmHg [39 to 45] mmHg at the end of the 2-h infusion, respectively, with significantly higher values for hydromorphone throughout the infusion and the 1 h thereafter (fig. 10). Overall maximum
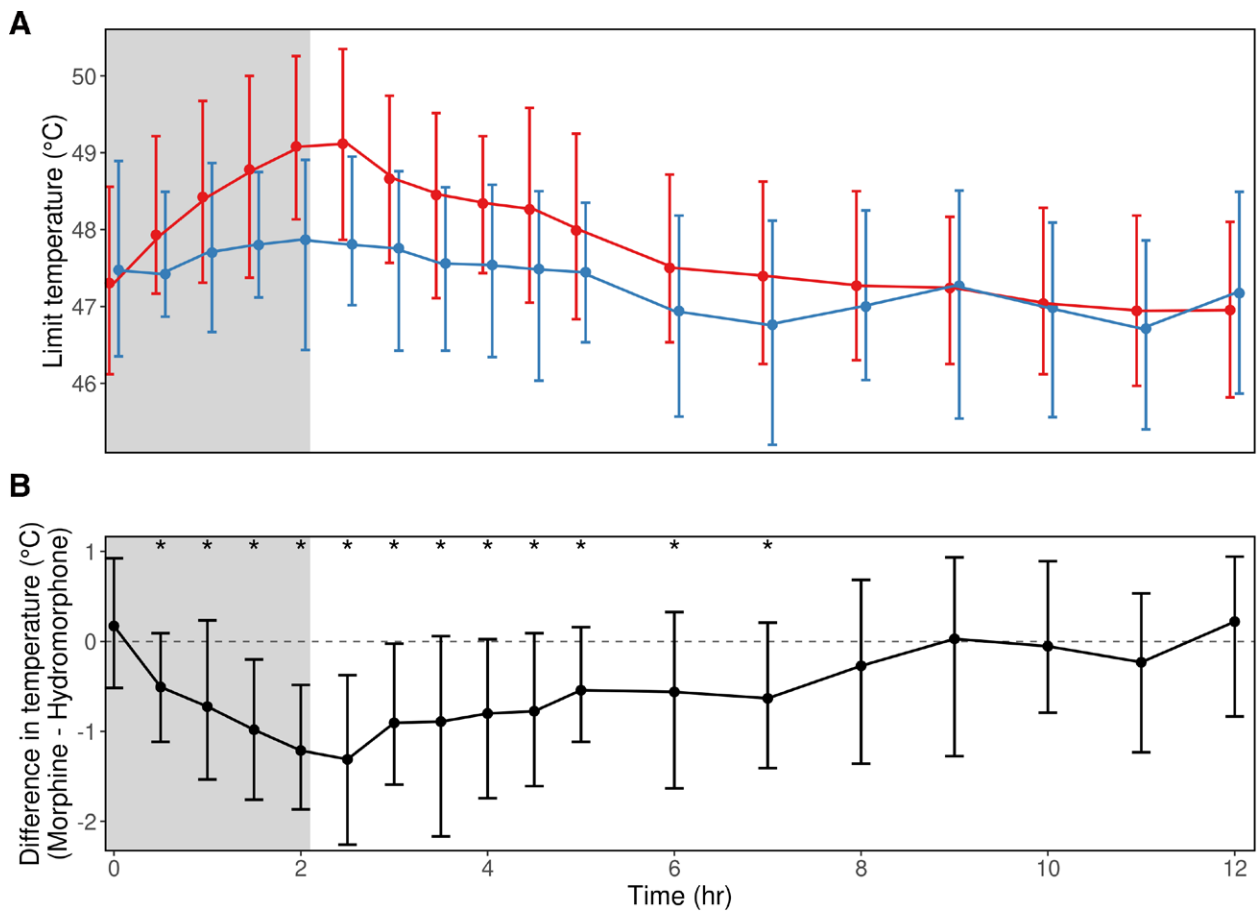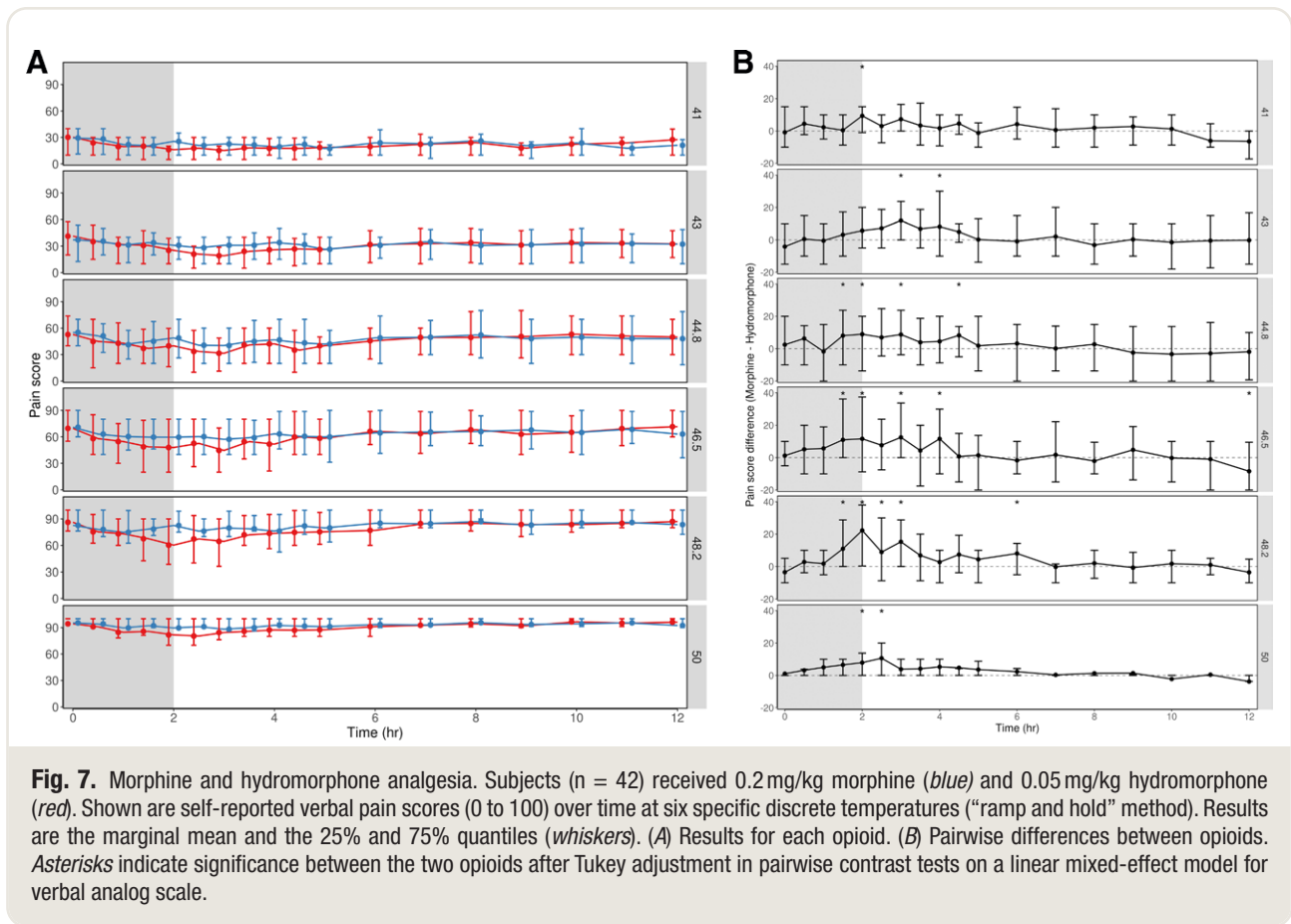
Fig. 6. Morphine and hydromorphone analgesia. Shown is the maximally tolerated temperature ("method of limits," mean of three measurements) for subjects receiving 0.2 mg/kg morphine (n = 42, *blue*) and 0.05 mg/kg hydromorphone (n = 42, *red*). Results are the marginal mean and the 25% and 75% quantiles (*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.

end-expired carbon dioxide was greater after hydromorphone (48 mmHg [46 to 51]) than after morphine (47 mmHg [45 to 50]; $P = 0.008$) (fig. 5). Maximum end-expired carbon dioxide occurred much later after morphine (5.5 ± 2.8 h after the start of the infusion) than after hydromorphone (3.0 ± 1.5 h; $P < 0.001$; fig. 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 carbon dioxide, and 49% and 51% for the time to peak end-expired carbon dioxide. Area under the curve for carbon dioxide was 53 mmHg-h [30 to 78] after hydromorphone and 49 mmHg-h [30 to 79] after morphine ($P = 0.532$; fig. 5). Interindividual variability in end-expired carbon dioxide, 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 (https://links.lww.com/ALN/D117).

Respiratory rates for subjects receiving both 0.05 mg/kg hydromorphone and 0.2 mg/kg morphine decreased from 17 ± 3 and 17 ± 3 breaths.min^{-1} at baseline to 12 ± 3 and 14 ± 2 breaths.min^{-1} at the end of the 2-h infusion, with significantly lower values for hydromorphone throughout the infusion and the 4 to 5 h thereafter (figs. 2 and 11) for time-based paired comparisons. Overall respiratory rate nadir was 11 ± 2 and 9 ± 1 breaths.min^{-1} after hydromorphone and morphine, respectively (figs. 2 and 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 to 3.0] and 2.4 h [1.2 to 3.0], respectively (fig. 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^{-1}-h [23 to 73] after hydromorphone and 44 min^{-1}-h [20 to 63] after morphine ($P = 0.496$; fig. 5). Interindividual variability in respiratory rate, based on the area under the curve, was 58%

Fig. 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 to 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 verbal analog scale.

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 (https://links.lww.com/ALN/D118).

Arterial blood gas analyses (table 1) revealed a well-buffered physiologic response to respiratory depression with indistinguishable values for both pH and bicarbonate, over time and between groups. Carbon dioxide partial pressure increased from baseline after both drugs, with a 1.9 mmHg (95% CI, 0.5 to 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 current investigation evaluated the magnitude, time course, and variability of analgesic effects and side effects of a 2-h 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, are still lacking.[14] We tested the hypothesis that IV 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-h IV 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-h observation period, while end-expired carbon dioxide remained elevated compared with predrug 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.[24] Rapid onset of hydromorphone analgesia and miosis has also been reported.[25]
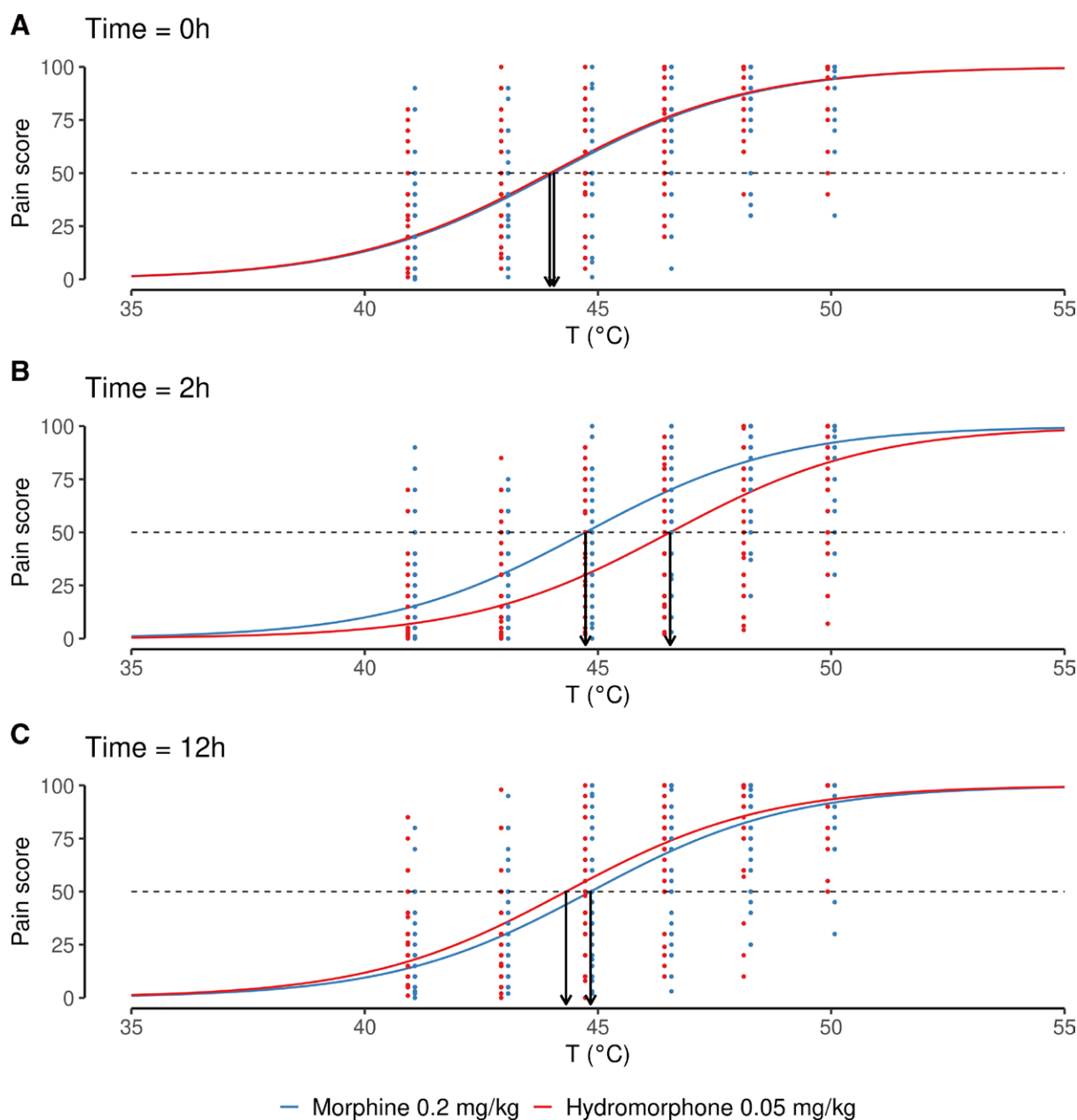
Fig. 8. Morphine and hydromorphone analgesia. Subjects (n = 42) received 0.2 mg/kg morphine (*blue*) and 0.05 mg/kg hydromorphone (*red*). Results are self-reported verbal pain scores (0 to 100) at six specific discrete temperatures. Shown is the relationship between thermal stimulus temperature and 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 (*C*) 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.

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, in both 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 carbon dioxide 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, are notable.
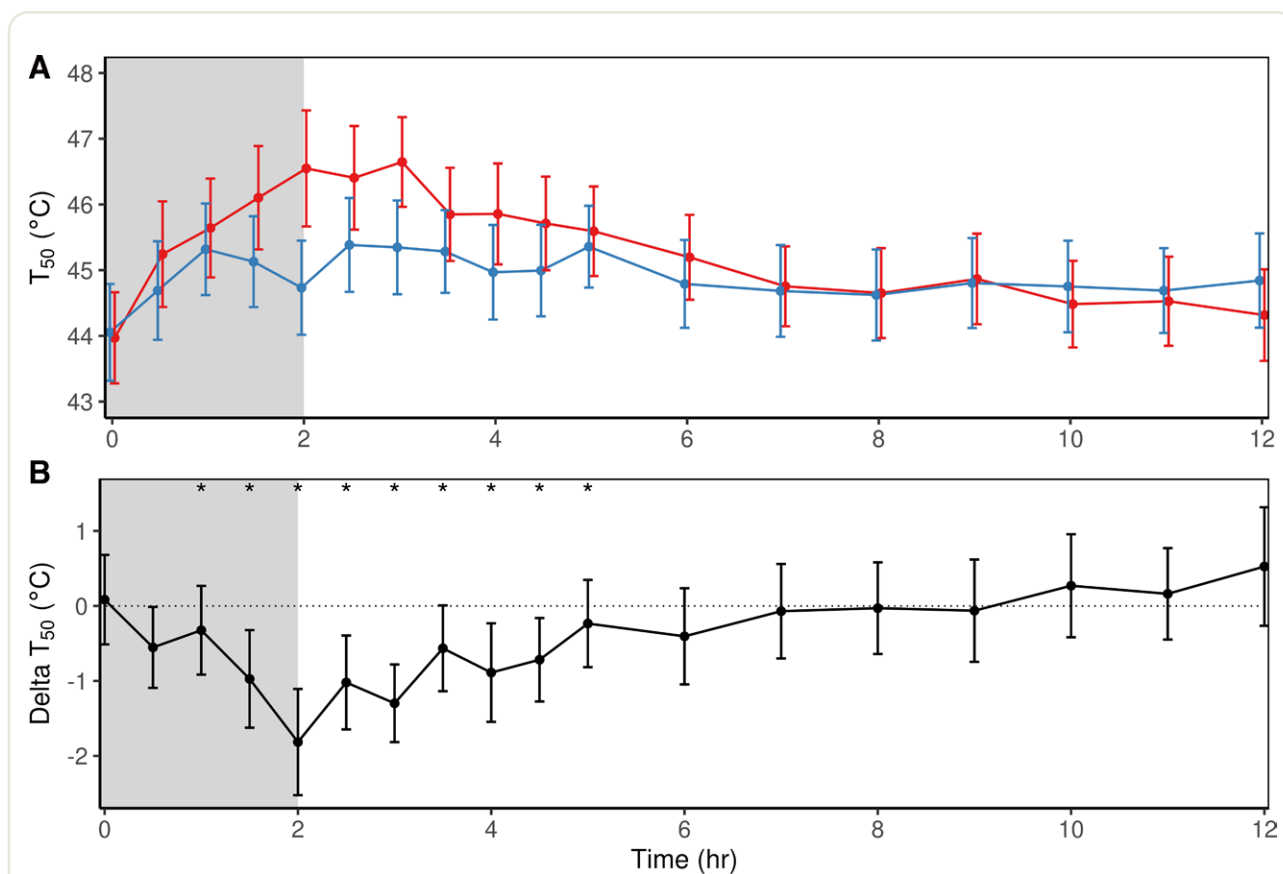
Fig. 9. Morphine and hydromorphone analgesia. Shown is the half-maximal temperature (T_{50}) over time for all 42 subjects receiving 0.05 mg/kg hydromorphone (*red curve, panel A*), 0.2 mg/kg morphine (*blue curve, panel A*), and the difference between the two (*black curve, panel B*). Results are the marginal mean with corresponding 95% CI (*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 1 degree of freedom. Calculated *P* values were adjusted for multiple comparisons using the Bonferroni correction. *Asterisks* denote significantly different values ($P < 0.05$).

Miosis, analgesia, and respiratory rate essentially returned to baseline by the end of the 12-h observation period, while end-expired carbon dioxide remained elevated compared with predrug values. Delayed onset of morphine clinical effects, relative to plasma concentration, was similar to that reported previously, as assessed by miosis or analgesia.[26–28] 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.[27] Morphine is known to transfer from plasma to the effect site for miosis rather slowly.[29] 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 *versus* morphine AUC ratios were 2.56 [0.75 to 6.69] for temperature tolerance, 1.29 [1.11 to 1.79] for miosis, 1.09 [0.70 to 1.43] for end-expired carbon dioxide, and 1.11 [0.49 to 2.28] for respiratory rate. Similarly, the within-subjects AUC ratio of temperature tolerance to end-expired carbon dioxide was 0.104 [0.042 to 0.282] for hydromorphone and 0.040 [0.001 to 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 (electroencephalogram, analgesia, miosis), attributed to slow distribution to the effect
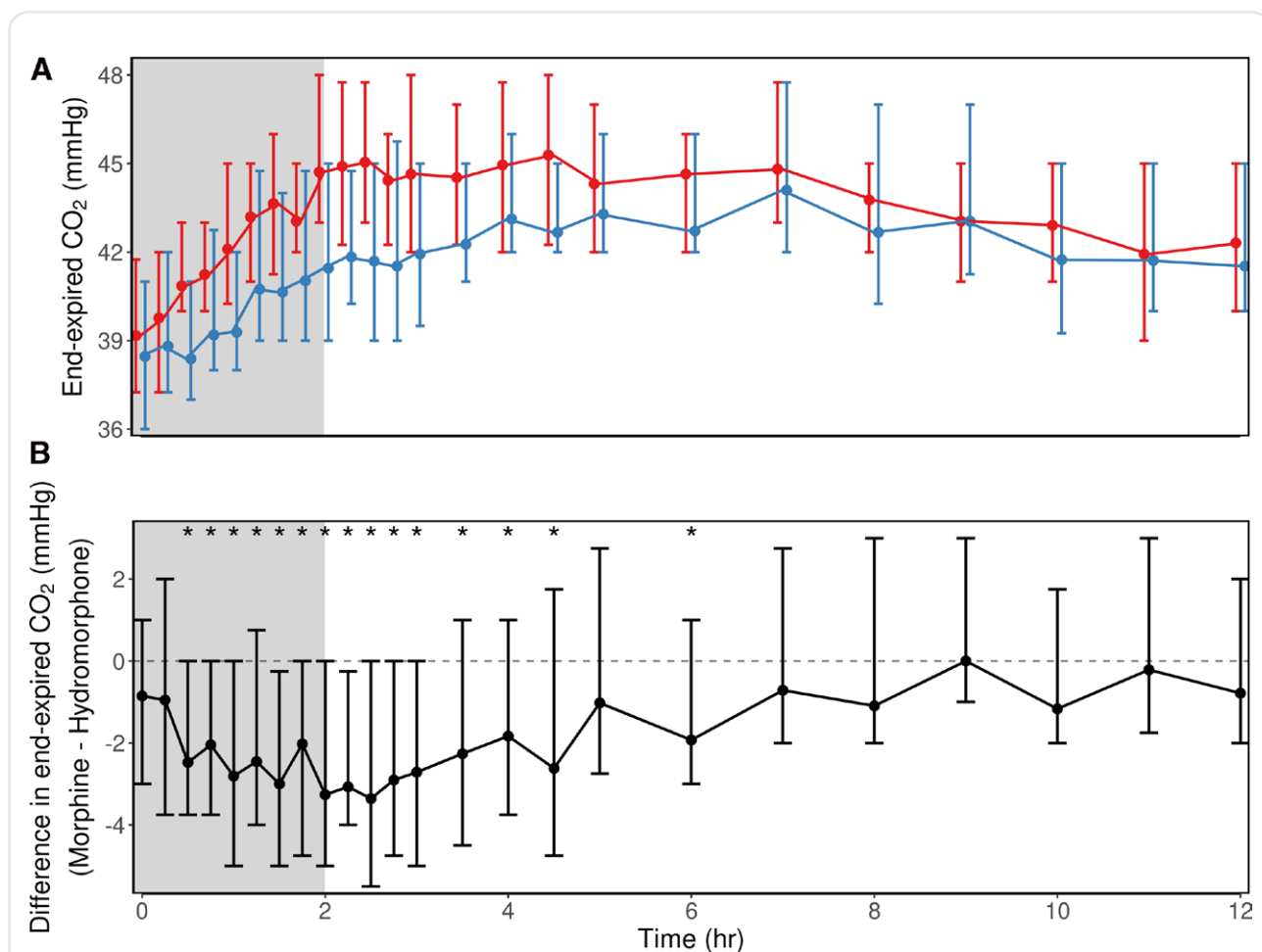
Fig. 10. Ventilatory effects of opioids. Shown is the end expired carbon dioxide in subjects receiving 0.2 mg/kg morphine (n = 42, *blue*) and 0.05 mg/kg hydromorphone (n = 42, *red*). Results are shown as the marginal mean and the 25% and 75% quantiles (*whiskers*). Opioids were administered as a 2-h 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 end-tidal carbon dioxide.

site (presumably the central nervous system), has been well-described for morphine.[30,31] but is substantially less for hydromorphone.[32] The current results are generally consistent with these distribution differences between opioids. In contrast, the temporal discordance between end-expired carbon dioxide 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.[33] The current investigation highlights the value of comprehensive quantitative clinical assessments in volunteers.

One generalized approach to compare the desirable *versus* 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 carbon dioxide (°C/ mmHg) was 0.10 [0.04 to 0.29] for hydromorphone and

0.04 [0.00 to 0.11] for morphine (P = 0.001), and the ratio of AUCs for temperature tolerance to respiratory rate (°C/breaths-min^{-1}) was 0.15 [0.04 to 0.38] for hydromorphone and 0.04 [0.00 to 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 three- to fourfold greater for hydromorphone than morphine. This further supports the conclusion that therapeutic benefit *versus* 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
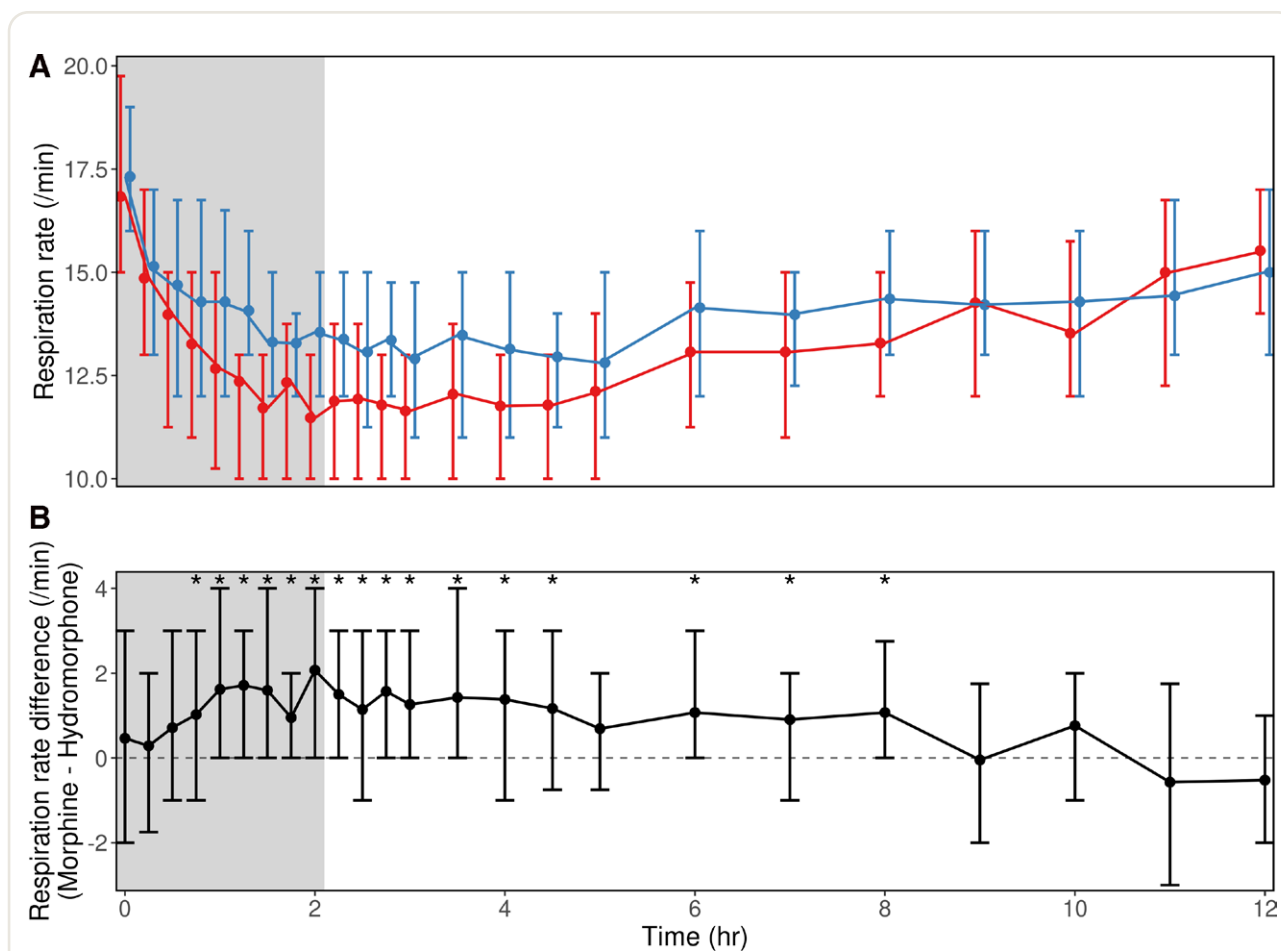
Fig. 11. Ventilatory effects of opioids. Shown is the respiratory rate of subjects receiving both 0.2 mg/kg morphine (n = 42, *blue*) and 0.05 mg/kg hydromorphone (n = 42, *red*). Results are shown as the marginal mean and the 25% and 75% quantiles (*whiskers*). Opioids were administered as a 2-h infusion (*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.

Table 1. Blood Gas Analyses

	pH		Paco$_2$ (mmHg)		Po$_2$ (mmHg)		HCO$_3$ (mmol/l)	
Time (h)	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

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

and the differences between opioids. The hypothesis was that IV 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, was 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_{50} and γ. For miosis, for hydromorphone and morphine, variation in peak effect was 17% and 24%, respectively, and 29% and 43% based on the AUC. For respiratory depression from hydromorphone and morphine, variation was 7% and 12% for maximum end-expired carbon dioxide, 63% and 60% for areas under the carbon dioxide 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_{50} (although the magnitude of analgesia was greater for hydromorphone in both models) without a change in γ. Increased T_{50} without a change in γ was previously reported for remifentanil.[19] 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,[19,34–36] while the latter take less time to implement (three *vs.* six stimuli) and analyze.[36–39] The lack of an apparent advantage of the method of limits or a multilevel submaximal method for assessing opioid analgesia parallels that seen in quantitative sensory testing for neurologic pathophysiology.[35,40]

Another novel aspect of this investigation was the comprehensive phenotypic assessment of opioid disposition and clinical effects, including arterial plasma concentration, thermal analgesia (using two 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.[41]

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.[42] There is said to be "clinical lore" that hydromorphone results in better pain control with fewer adverse effect than morphine.[16,24] 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.[24,43] Based on analgesia and more relevant side effects (respiratory depression, nausea, vomiting, itch), hydromorphone is considered to be comparable,[12,16,44–46] or to have some advantage.[4,7,13] Nevertheless, it remains unknown and

under discussion whether morphine or hydromorphone is inherently safer or clinically advantageous.[4,15,26,47] In contrast to these clinical outcomes studies, the current 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 current 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.

Competing Interests

The Anesthesia & Pain Research Unit of the Department of Anesthesiology, Leiden University Medical Center (Leiden, The Netherlands) received or receives funding from AMO Pharma Ltd. (London, United Kingdom), Bedrocan BV (Veendam, The Netherlands), Grünenthal GmbH (Aachen, Germany), Medtronic (Dublin, Ireland), and MSD Nederland BV (Haarlem, The Netherlands). Dr. Dahan received consultancy and/or speaker fees from Enalare Therapeutics Inc. (Princeton, New Jersey) and

Grünenthal BV (Breukelen, The Netherlands), and reports being chair of the scientific advisory board of MyCB1 (Steinheim, Germany). The other authors declare no competing interests

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Supplemental Digital Content

Supplemental Figure 1: Morphine and hydromorphone effects on pupil diameter, https://links.lww.com/ALN/D113
Supplemental Figure 2: Morphine and hydromorphone effects on pupil diameter, https://links.lww.com/ALN/D114
Supplemental Figure 3: Morphine and hydromorphone analgesia, https://links.lww.com/ALN/D115
Supplemental Figure 4: Morphine 0.2 mg/kg (n = 44) *versus* hydromorphone 0.05 mg/kg (n = 45) analgesia, https://links.lww.com/ALN/D116
Supplemental Figure 5: Ventilatory effects of opioids, https://links.lww.com/ALN/D117
Supplemental Figure 6: Ventilatory effects of opioids, https://links.lww.com/ALN/D118
Supplemental Table 1, https://links.lww.com/ALN/D119

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Eckenhoff, Eakins, and the Inklings of a New Profession

James Eckenhoff, M.D. (1915 to 1996), Dean of the Northwestern University School of Medicine and Past Editor-in-Chief of Anesthesiology, surveyed the rise of anesthesiology as a medical discipline in his 1977 Rovenstine Memorial Lecture. During his address, Eckenhoff referenced two famous paintings by Thomas Eakins (1844 to 1916), master of Realism, to highlight the state of anesthesia and surgery in the late-19th century United States. Eakins, who was fascinated by medicine and the human form, had enrolled in surgery classes taught by the magnetic Samuel Gross, M.D., at Jefferson Medical College. *The Gross Clinic* (1875, *left*) was Eakins' unfiltered depiction of Gross at work, with natural skylight illuminating the surgeon's furrowed brows and bloody hands. In the scene, the doctors still donned street clothes, and a junior surgeon, W. Joseph Hearn, M.D., delivered anesthesia using an ether-soaked cloth. Fourteen years later, Eakins' *The Agnew Clinic* (1889, *right*), a portrait of renowned University of Pennsylvania surgeon D. Hayes Agnew, M.D., would show greater progress in surgery than anesthesia. There were glimmers of asepsis—white gowns, surgical drapes, and sterilized instruments. Anesthetic delivery was also cleaner, via ether cone, but the anesthetist, Ellwood Kirby, M.D., was still a young surgery resident. It would take several more decades for anesthesiology to become professionalized as an independent medical specialty in the United States. (Artwork from the Philadelphia Museum of Art. Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology, Schaumburg, Illinois.)

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