ANESTHESIOLOGY

Benefit and Risk Evaluation of Biased μ-Receptor Agonist Oliceridine *versus* Morphine

Albert Dahan, M.D., Ph.D., C. Jan van Dam, M.D., Marieke Niesters, M.D., Ph.D., Monique van Velzen, Ph.D., Michael J. Fossler, Pharm.D., Ph.D., Mark A. Demitrack, M.D., Erik Olofsen, Ph.D.

ANESTHESIOLOGY 2020; 133:559–68

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Classical opioid analgesics engage two distinct transduction pathways after μ-opioid receptor activation, the G-protein–coupled signaling pathway and the β-arrestin pathway
- The G-protein pathway is primarily involved in analgesia, reward, and liking, while the β-arrestin pathway is involved in adverse effects such as respiratory depression
- Oliceridine is a μ-opioid receptor agonist that selectively engages the G-protein–coupled signaling pathway with reduced activation of the β-arrestin pathway

What This Article Tells Us That Is New

- Utility functions were developed from population pharmacokinetic–pharmacodynamic analyses of oliceridine and morphine concentration–effect relationships in 29 healthy male volunteers
- The utility function was defined as the probability of providing analgesia, an increase in hand withdrawal latency of 50% or more, minus the probability of producing respiratory depression, a decrease of the ventilatory response to hypercapnia of at least 25%
- Over the clinically relevant concentration range, oliceridine had a higher probability of providing analgesia than producing respiratory depression, while morphine had a higher probability of producing respiratory depression than providing analgesia

ABSTRACT

Background: To improve understanding of the respiratory behavior of oliceridine, a μ-opioid receptor agonist that selectively engages the G-protein–coupled signaling pathway with reduced activation of the β-arrestin pathway, the authors compared its utility function with that of morphine. It was hypothesized that at equianalgesia, oliceridine will produce less respiratory depression than morphine and that this is reflected in a superior utility.

Methods: Data from a previous trial that compared the respiratory and analgesic effects of oliceridine and morphine in healthy male volunteers (n = 30) were reanalyzed. A population pharmacokinetic–pharmacodynamic analysis was performed and served as basis for construction of utility functions, which are objective functions of probability of analgesia, P(analgesia), and probability of respiratory depression, P(respiratory depression). The utility function = P(analgesia ≥ 0.5) − P(respiratory depression ≥ 0.25), where analgesia ≥ 0.5 is the increase in hand withdrawal latency in the cold pressor test by at least 50%, and respiratory depression ≥ 0.25 is the decrease of the hypercapnic ventilatory response by at least 25%. Values are median ± standard error of the estimate.

Results: The two drugs were equianalgesic with similar potency values (oliceridine: 27.9 ± 4.9 ng/ml; morphine 34.3 ± 9.7 ng/ml; potency ratio, 0.81; 95% CI, 0.39 to 1.56). A 50% reduction of the hypercapnic ventilatory response by morphine occurred at an effect-site concentration of 33.7 ± 4.8 ng/ml, while a 25% reduction by oliceridine occurred at 27.4 ± 3.5 ng/ml (potency ratio, 2.48; 95% CI, 1.65 to 3.72; $P < 0.01$). Over the clinically relevant concentration range of 0 to 35 ng/ml, the oliceridine utility function was positive, indicating that the probability of analgesia exceeds the probability of respiratory depression. In contrast, the morphine function was negative, indicative of a greater probability of respiratory depression than analgesia.

Conclusions: These data indicate a favorable oliceridine safety profile over morphine when considering analgesia and respiratory depression over the clinical concentration range.

(ANESTHESIOLOGY 2020; 133:559–68)

Opioid analgesics, the cornerstone of contemporary treatment of acute moderate to severe pain, come with numerous adverse effects, of which respiratory depression is potentially life-threatening due to disturbance (and at high dose silencing) of respiratory centers in the pons and brainstem after activation of locally expressed μ-opioid receptors.[1] The fact that the number of opioid-related deaths has recently sharply increased is therefore not surprising given the dramatic increase in prescription and illicit opioid use and misuse in the last decade.[2,3] Classical opioid analgesics, such as morphine, oxycodone, and fentanyl, are full agonists at the μ-opioid receptor.[1] After receptor activation, these opioids engage two distinct transduction pathways, the G-protein–coupled signaling pathway and the β-arrestin pathway, with separate pharmacologic effects.[4–6] The

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a visual abstract available in the online version.

Submitted for publication January 9, 2020. Accepted for publication June 2, 2020. Published online first on July 1, 2020. From the Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands (A.D., C.J.v.D., M.N., M.v.V., E.O.), and Trevena Inc., Chesterbrook, Pennsylvania (M.J.F., M.A.D.).

 Anesthesiology 2020; 133:559–68. DOI: 10.1097/ALN.0000000000003441

<zdoi;. DOI: 10.1097/ALN.0000000000003441>

G-protein pathway is primarily involved in analgesia, reward, and liking, whereas the β-arrestin pathway is involved in adverse effects such as respiratory depression and gastrointestinal effects, as well as the attenuation of analgesic effects.[5,6] Considering the high incidence and potentially serious consequences of respiratory toxicity, recent focus has been on the development of a new class of opioids, biased ligands, which are μ-receptor agonists that selectively engage the G-protein–coupled signaling pathway with reduced activation of the β-arrestin pathway.[7,8] Biased ligands may have an advantage over nonbiased, or non-elective μ-opioid receptor agonists as they may be associated with less respiratory depression. The experimental opioid oliceridine (formerly known as TRV130) is a biased ligand that is being developed for treatment of moderate to severe acute pain.[5,6]

Although both opioid benefit and toxicity, such as respiratory depression, arise from the same treatment, it is not straightforward how to consider these contrasting effects simultaneously since these endpoints have different concentration–effect relationships.[9] We have recently developed utility or safety functions of several opioids to capture their contrasting effects into one function.[10–12] The utility function is an economic concept from decision theory and has been used in various scientific areas to describe multiple effects of treatment or behavior integrated into a single number or function.[13–15] The functions we developed are based on population pharmacokinetic–pharmacodynamic analyses of the opioid concentration–effect relationships.

In the current study, we compared the utility of the biased ligand oliceridine and the classical opioid morphine. Analgesia and respiratory data from three recently published studies were reanalyzed.[16–18] The first data set is an experimental study performed in healthy volunteers.[16] The two other data sets are clinical studies in postoperative patients.[17,18] The utility functions were constructed from the experimental study. In an exploratory analysis, we next extrapolated the results of the utility analyses to patients in clinical practice by calculating the utility values at occurrence of respiratory depression events in patients treated with either morphine or oliceridine for postoperative pain. We hypothesize that the utility function of oliceridine is superior to that of morphine and that the results of the utility function analysis can be extrapolated to clinical practice. We postulate that respiratory depression events occur at specific predefined utility values.

Materials and Methods

This study is a reanalysis of three earlier published data sets on comparison between oliceridine and morphine on analgesic efficacy and respiratory depression.[16–18] The aims of the current study are to compare benefit (analgesia) and harm (respiratory depression) of oliceridine and morphine as measured by their respective utility functions. We next extrapolated the results of the utility analysis to patients in clinical practice by calculating the utility values at occurrence of respiratory depression events in patients treated with either morphine or oliceridine for postoperative pain.

Healthy Volunteer Study (Study 1003): Development of Utility Functions

Utility functions were derived from an experimental study performed in healthy male volunteers.[16] All subjects received an intravenous oliceridine bolus dose of 1.5, 3, and 4.5 mg and an intravenous morphine bolus dose of 10 mg on four separate visits. On each occasion, two pharmacodynamic endpoints were obtained, the cold pressor test as a test of analgesia and the ventilatory response to hypercapnia at a fixed increase in inspired carbon dioxide concentration as a test for respiratory depression. The setup is explained in detail elsewhere.[16] In brief, the cold pressor test was performed by submerging one hand in a continuous circulating water bath held at 2.0 ± 0.05°C. The time from immersion to hand withdrawal from the water bath was measured by stopwatch (pain tolerance). Pain intensity was quantified using the 11-point numeric pain rating scale at the time of hand removal. The maximum allowable time of hand immersion was 180 s. Measurements were obtained before dosing (baseline) and at t = 10 and 30 min, and 1, 2, 3, 4, 6, and 8 h after dosing.

The ventilatory response to hypercapnia was obtained from each subject by having them breathe 5% carbon dioxide in 95% oxygen *via* a facemask from a rebreathing gas-mixing system for 5 min at t = 0 (before dosing) and 0.5, 1, 2, 3, and 4 h after dosing. Fifth minute ventilation, respiratory rate, flow rates, and end-tidal carbon dioxide concentration were measured and used in the calculation of the ventilatory response to hypercapnia (minute ventilation/end-tidal carbon dioxide concentration).

Venous blood samples were obtained for measurement of oliceridine and morphine and its metabolite morphine-6-glucuronide in plasma. Samples were obtained at 2, 12, and 30 min and 1, 2, 3, 4, and 8 h after dosing. Oliceridine was quantified in plasma by a validated liquid chromatography–tandem mass spectrometry assay as previously reported.[19] The lower quantitation limit was 0.05 ng/ml. The assay was linear in the range 0.05 to 50 ng/ml, with precision ranging between 1.9 and 7.3% and accuracy between 9.4 and 13.8%, respectively. The morphine and morphine-6-glucuronide assay used was a proprietary third-party assay not previously published. The morphine quantitation range was 0.500 to 100 ng/ml with precision (% coefficient of variation) between 5.0 and 14.2% and accuracy (% bias) between −1 and 2%. The quantitation range for morphine-6-glucuronide was linear between 2.5 and 500 ng/ml, with a lower limit of quantitation of 2.5 ng/ml. Assay precision ranged between 3.7 and 8.7%, and accuracy ranged between −5.0 and −0.9%. Both assays showed acceptable stability under room temperature and freeze–thaw conditions. We here report on the oliceridine and morphine

data. The morphine-6-gludronide data were not considered in the creation of the utility functions as we know that the contribution of morphine-6-glucronide to analgesia in individuals with a normal renal function is rather small.[20]

Pharmacokinetic–Pharmacodynamic Modeling. The pharmacokinetics and pharmacodynamics of oliceridine and morphine were analyzed with NONMEM VII (Icon Plc, USA), a software package for nonlinear mixed effects modeling, using a population approach.[21] All NONMEM files are available from the authors. In stage 1 of the analysis, the pharmacokinetic analysis, the individual empirical Bayesian estimates of the pharmacokinetic parameters were obtained and subsequently applied in stage 2, the pharmacodynamic analysis.

Analgesia and ventilation data were analyzed separately. The optimal pharmacokinetic model was obtained by fitting the oliceridine and morphine plasma concentration to two and three compartment pharmacokinetic models. The number of compartments in the model was determined by the magnitude of the decrease in the minimum objective function value (chi-square test, $P < 0.01$ considered significant). The observed hysteresis between plasma concentration and biophase (the postulated effect compartment) was characterized as a first-order process with rate constant ke0.

For the hand latency withdrawal data, a log-logistic distribution was assumed, and censored data (cutoff times = 180 s) were considered. The predicted latency time is used as the median of the log-logistic distribution,

$$\text{Predicted latency}(t) = \text{latency at baseline} \times \left(1 + \frac{CE(t)}{C100}\right)$$

where the latency at baseline is the latency before any drug administration, CE(t) is the drug concentration in the biophase or postulated effect-site at time t, and C100 is the biophase drug concentration causing the doubling of the withdrawal latency. In the case where the hand withdrawal latency reached the cutoff value, the probability of the censored observation is

$$\log P(\text{withdrawal time} > \text{cutoff}) = \text{survival and survival} = -\log[1 + (\text{observation} / \text{prediction})^{Z}]$$

where Z is a shape factor; otherwise,

$$\log P(\text{withdrawal time} = \text{observation}) = \log(Z) - \log(\text{prediction}) + (Z \times \log(\text{observation} / \text{prediction}) + 2 \times \text{survival})$$

Ventilatory response to hypercapnia-plasma concentration data were modeled with an inhibitory sigmoid maximum effect model with occurrence of apnea at high drug concentrations,

$$\text{Ventilatory response to hypercapnia}(t) = (\text{Ventilatory response to hypercapnia at baseline}) - (\text{Ventilatory response to hypercapnia at baseline}) \times [C_E(t) / Cx]^{\gamma} / [1 + (C_E(t) / Cx)^{\gamma}]$$

where the ventilatory response to hypercapnia at baseline is the response before any drug administration, γ is a shape parameter, and Cx is the biophase drug concentration causing a reduction of the ventilatory response to hypercapnia by factor x. Given the differences in effect size, for oliceridine, x was set at 25% (C25), and for morphine, x was set at 50% (C50). With the C25 for the oliceridine model, the parameter estimation improved, with disappearance of seemingly significant covariances between parameters when using a C50.

To determine whether the models adequately describe the data, plots of the individual predicted *versus* measured data and residuals *versus* time were created and inspected. To allow a visual predictive check of the final pharmacokinetic or pharmacodynamic models, the normalized prediction discrepancies were estimated.[22] To that end, 300 Monte Carlo simulations were performed that were based on the final model considering the distributions of the fixed and random effects. The number of times an observation was greater than the model prediction was counted, and then the normalized prediction discrepancies are given by the counts divided by 300, transformed *via* the inverse normal distribution. Under the null hypothesis that the model is correct, the normalized prediction discrepancies should have a standard normal distribution. It was visually checked that the normalized prediction discrepancies *versus* time showed no trends, heteroscedasticity, or both. Parameter estimates are reported as median ± standard error of the estimate.

Utility Functions. The utility function was defined as the probability of obtaining the desired effect, analgesia, minus the probability of obtaining a side effect, in this study respiratory depression. The threshold for the desired effect was set at a 50% or more increase in hand withdrawal latency relative to the predrug baseline values (analgesia ≥ 0.50); the threshold for respiratory depression was set at a decrease of at least 25% of the ventilatory response to hypercapnia relative to pre-drug baseline levels (respiratory depression ≥ 0.25),

$$\text{Utility} = P(\text{analgesia} \geq 0.50) - P(\text{respiratory depression} \geq 0.25)$$

where P is probability.

The utility was a function of the biophase or postulated effect-site concentrations of oliceridine or morphine. The threshold for respiratory depression was chosen given the obtained data; for analgesia, several thresholds were tested ranging from a 10% to a 200% increase in latencies. We here present the utility data with a threshold of 50%.

The utilities were calculated from the population pharmacokinetic and pharmacodynamic model with the estimated values for the population and their inter-individual variability parameters (ω^2); see Supplemental Digital Content table S1 (http://links.lww.com/ALN/C434; pharmacokinetic parameter estimates) and table 1 (pharmacodynamic parameter estimates). Two × 10,000 simulations (once for antinociception

Table 1. Pharmacodynamic Parameter Estimates

Parameter	Estimate ± Standard Error of the Estimate	ω^2 ± Standard Error of the Estimate	υ^2 ± Standard Error of the Estimate
Hand withdrawal latency			
Oliceridine			
Hand withdrawal latency at baseline (s)	40.1 ± 2.6	0.12 ± 0.03	0.46 ± 0.14
Potency parameter C100 (ng/ml)	27.9 ± 4.9	0.68 ± 0.21	0.22 ± 0.06
Parameter Z	7.1 ± 0.4	—	—
Blood-effect-site equilibration half-life (min)	—		
Morphine			
Hand withdrawal latency at baseline (s)	44.4 ± 3.7	0.17 ± 0.54	
Potency parameter C100 (ng/ml)	34.3 ± 9.7	1.28 ± 0.06	
Parameter Z	9.7 ± 1.0	0.16 ± 0.09	
Blood-effect-site equilibration half-life (h)	0.6 ± 0.2	1.11 ± 0.60	
Ventilatory response to hypercapnia			
Oliceridine			
Ventilatory response to hypercapnia at baseline ($l \cdot min^{-1} \cdot mmHg^{-1}$)	0.40 ± 0.02	0.07 ± 0.03	0.02 ± 0.01
Potency parameter C25 (ng/ml)	27.4 ± 3.5	0.24 ± 0.12	0.21 ± 0.18
Parameter γ	1 (fixed)	0.29 ± 0.25	—
Parameter F	0.62 ± 0.09	—	—
Parameter σ^2	0.125 ± 0.025		
Morphine			
Ventilatory response to hypercapnia at baseline ($l \cdot min^{-1} \cdot mmHg^{-1}$)	0.41 ± 0.02	0.07 ± 0.02	
Parameter C50 (ng/mL)	33.7 ± 4.8	0.27 ± 0.10	
Parameter γ	1 (fixed)	—	
Blood-effect-site equilibration half-life (h)	1.24 ± 0.15	—	
Parameter σ^2	0.014 ± 0.002		

ω^2 and υ^2 are between-subject and between-occasion variances (on the log scale). —, not included in the statistical model. Hand withdrawal latency: C100 is the drug concentration causing a doubling of the withdrawal latency, and parameter Z is a steepness coefficient of the log-logistic distribution. Covariances were present for oliceridine for υ^2 between C100 and baseline hand withdrawal latency: 0.27 ± 0.09; covariances were present for morphine for ω^2 between C100 and baseline hand withdrawal latency: –0.19 ± 0.12, between parameter Z and C100: –0.08 ± 0.05, and between parameter Z and baseline hand withdrawal latency: 0.33 ± 0.17. Ventilatory response to hypercapnia: C25 and C50 are the drug concentrations causing a 25% and 50% reduction of baseline ventilatory response to hypercapnia; γ is a steepness parameter, σ^2 the within-subject proportional error variance. For oliceridine, parameter F relates baseline ventilatory response to hypercapnia to blood-effect-site equilibration half-life by blood-effect-site equilibration half-life = baseline ventilatory response to hypercapnia × F.

and once for the ventilatory response to hypercapnia) were performed using NONMEM's simulation step for oliceridine and once more for morphine. The occurrences of desired and side effects (*i.e.*, analgesia and respiratory depression) were determined and divided by 10,000 to estimate these probabilities (note that these are uncorrelated because no correlations between the ω^2 were identified in the pharmacodynamic analysis). To assess the uncertainty in these measures (probabilities), a Bayesian estimation step with noninformative priors was added after the importance sampling step in all pharmacodynamic analyses. This is a substitute for a bootstrap analysis.[23] The step yielded 10,000 estimates of both the typical model parameters and the interindividual variances (ω^2).

Extrapolation of Utility Functions to Clinical Practice

Clinical Studies. The data from two double-blind randomized clinical studies,[17,18] comparing oliceridine, morphine, and placebo for the treatment of moderate to severe acute pain after either bunionectomy (study 3001) or abdominoplasty (study 3002), were used to extrapolate the findings from the experimental study to clinical practice. In the current analyses, the placebo data were not used. We used the data from the experimental study to create individual utility P(analgesia ≥ 0.50) − P(respiratory depression ≥ 0.25).

Study 3001. Patients (average age, 40 yr) scheduled to undergo an elective unilateral, first metatarsal bunionectomy with osteotomy and internal fixation were enrolled in the study. The surgical procedure was performed under a continuous popliteal sciatic nerve block with oral oxycodone 5 mg every 4 h when the anesthetic was deemed insufficient. The nerve block and oxycodone therapy (if needed) were continued after surgery; the infusion of the local anesthetic was terminated at 3 AM on postoperative day 1. Exclusion criteria included chronic opioid or nonsteroidal anti-inflammatory drug therapy for treatment of pain, diagnosis or suspicion of sleep-disordered breathing, use of centrally acting drugs that could affect the response to opioid medication (*e.g.*, antidepressants, antipsychotics, neuroleptics, adrenergic medication), or parenteral corticosteroid use. Patients were enrolled in the study when they experienced moderate pain (pain score of 4 or greater on an 11-point numerical rating scale ranging from 0, no pain, to 10, most severe pain imaginable)

within 9 h after discontinuation of the sciatic nerve block and oral oxycodone. Details of the experimental design and inclusion/exclusion criteria may be found elsewhere.[17]

The patients included in the current analysis were randomized to receive one of three regimens of oliceridine or one morphine regimen. Oliceridine treatment consisted of a loading dose of 1.5 mg followed after 10 min by patient-controlled analgesia doses of 0.1 mg (0.1 mg regimen), 0.35 mg (0.35 mg regimen) or 0.5 mg (0.5 mg regimen). The patient-controlled analgesia system had a lockout period of 6 min. Patients randomized to the morphine group received a morphine loading dose of 4 mg followed after 10 min by patient-controlled analgesia doses of 1 mg with lockout period of 6 min. Additionally, if needed, the supervising clinician could administer a supplemental intravenous dose of 0.75 mg oliceridine or 2 mg morphine starting 1 h after the initial loading doses at a minimum 1-h interval. If study medication was insufficient (numerical rating score greater than 4), the patients could receive rescue medication (oral etodolac 200 mg) every 6 h when necessary. None of the patients received supplemental oxygen. Study duration was 48 h.

Study 3002. American Society of Anesthesiologists I or II–classified patients (average age, 38 yr) scheduled to undergo elective abdominoplasty under general anesthesia (propofol/fentanyl with or without volatile anesthetics or muscle relaxants) were enrolled in the study. Exclusion criteria included a history of opioid hypersensitivity, diagnosis of sleep apnea, use of chronic opioid therapy, use of any analgesic medication within the 48-h before surgery, use of nonsteroidal anti-inflammatory drugs for more than 2 weeks within the 6 months before surgery, use of centrally acting drugs that could affect the analgesic response, use of oral or parenteral corticosteroids, surgery lasting more than 2.5 h, and occurrence of surgical/anesthetic complications. Further details of the inclusion/exclusion criteria and experimental design are presented elsewhere.[18] In brief, patients included in the current analysis were randomized to receive patient-controlled analgesia demand doses of morphine (1 mg) or oliceridine (0.1, 0.35, or 0.5 mg) in the postoperative period. Initially, all patients received a loading dose (oliceridine 1.5 mg, morphine 4 mg) followed 10 min later by patient-controlled analgesia. After each successful patient-controlled analgesia opioid administration, there was 6-min lockout period. Clinician-administered supplemental doses of oliceridine (0.75 mg) or morphine (2 mg) were allowed as often as needed at 1-h intervals. If treatment with study medication was inadequate, patients could receive rescue medication (etodolac 200 mg) every 6 h when the numerical rating score was 4 or greater. The study duration was 24 h.[18]

Utility Values at Respiratory Depression Events. Drug dosing data of studies 3001 and 3002 were used to calculate the individual patient utility functions over time. For each patient, we calculated utility values and *a priori* postulated that a respiratory event should likely occur when the utility function 0.2 or less. A respiratory event was defined by the occurrence of an arterial hemoglobin-oxygen saturation less than 90%, a respiratory rate of 8 breaths/min or less, or a sedation score of 3 or more as measured on the Moline–Roberts Pharmacologic Sedation Scale.[24]

Results

Healthy Volunteer Study

This study was completed in 29 healthy male volunteers with the characteristics age, 19 to 50 yr, and body mass index, 19 to 32 kg/m^2. Oliceridine displayed a dose-dependent increase in plasma concentration with peak concentrations (mean ± SD) at 8.7 to 11 min after dosing of 56.8 ± 60.6 ng/ml (1.5 mg), 96.6 ± 87.4 ng/ml (3.0 mg), and 145.1 ± 110.5 ng/ml (4.5 mg). For morphine 10 mg, mean peak concentration, observed at 3.5 min, was 209.6 ± 175.9 ng/ml (fig. 1A).

Pharmacokinetic Data Analysis. For both oliceridine and morphine, the final pharmacokinetic models consisted of one central compartment and one peripheral compartment The estimated pharmacokinetic model parameters are given in Supplemental Digital Content, table S1 (http://links.lww.com/ALN/C434). Overall between-subject variance on all parameters was 0.08 ± 0.03 for the oliceridine data and 0.04 ± 0.01 for the morphine data. The individual pharmacokinetic data fits for intravenous oliceridine 1.5, 3, and 4.5 mg and morphine 10 mg are given in Supplemental Digital Content, figure S1A (http://links.lww.com/ALN/C434). Goodness-of-fit plots (individual predicted *vs.* measured data, conditional individual weighted residuals *vs.* time, and normalized prediction discrepancies) are given in Supplemental Digital Content figure S2 (http://links.lww.com/ALN/C434). Inspection of the data fits and all three diagnostic plots indicate that the two-compartment pharmacokinetic models of oliceridine and morphine adequately described the data.

Pharmacodynamic Data Analysis. The baseline hand withdrawal latency (46 ± 6 s, mean ± SD) increased to 94 ± 19 s after 1.5 mg oliceridine, 120 ± 19 s after 3.0 mg oliceridine, and 129 ± 18 s after 4.5 mg oliceridine (fig. 1B) at 10 min after dosing, after which the latencies decreased over time toward baseline values about 2 h after dosing. The lack of a further increase at 4.5 mg is related to the cutoff of 180 s. Peak latency after 10 mg morphine occurred at 30 min and was 89 ± 20 s. Ventilatory response to hypercapnia values at baseline (0.39 ± 0.04 l · min^{-1} · mmHg^{-1}) reduced to 0.32 ± 0.04 (1.5 mg), 0.27 ± 0.03 (3.0 mg), and 0.25 ± 0.02 (4.5 mg) l · min^{-1} · mmHg^{-1} after 30 min, after which the ventilatory response to hypercapnia slowly increased (fig. 1C). After 10 mg morphine, the ventilatory response to hypercapnia reduced to 0.30 ± 0.04 l · min^{-1} · mmHg^{-1} at t = 30 min. In contrast to oliceridine, the return of

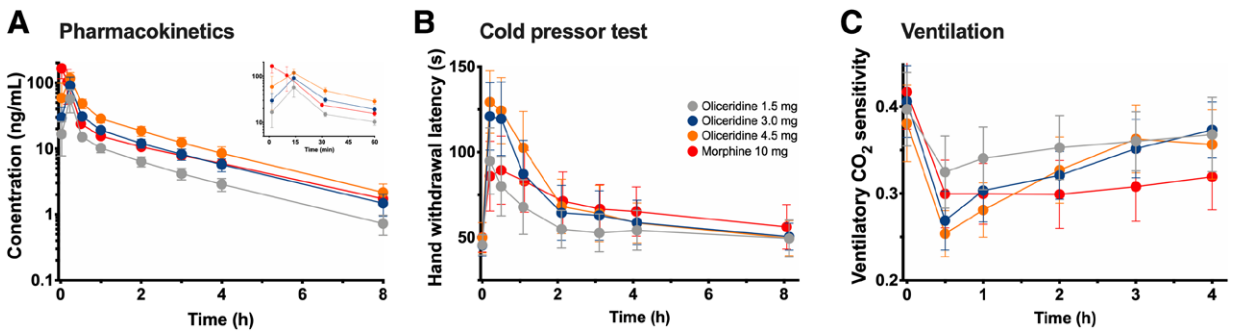

Fig. 1. Pharmacokinetic and pharmacodynamic data after intravenous injection with oliceridine and morphine in healthy volunteers. (*A*) Plasma oliceridine and morphine concentrations. (*B*) Hand withdrawal latencies. (*C*) Ventilatory responses to hypercapnia. Three oliceridine doses were injected, 1.5 mg (*gray symbols*), 3 mg (*blue symbols*), and 4.5 mg (*orange symbols*), and one morphine dose of 10 mg (*red symbols*). Data are mean ± 95% CI.

morphine toward baseline was considerably slower and was not reached during the time of the experiment (fig. 1C).

The hand withdrawal latency and ventilatory response to hypercapnia data were adequately fitted by the pharmacodynamic model (see Supplemental Digital Content, figs. S3, S4, S5, and S6 for the individual data fits and goodness-of-fit plots, http://links.lww.com/ALN/C434). The antinociceptive pharmacodynamic model was able to take the censored data (*i.e.*, the hand latency boundary of 180 s) into consideration (Supplemental Digital Content, fig. S3, http://links.lww.com/ALN/C434). Pharmacodynamic model parameter estimates are given in table 1. The two drugs were equianalgesic with C100 values (the biophase or steady-state plasma concentration causing a doubling of the hand withdrawal latency) of 27.9 ± 4.9 (median ± standard error of the estimate) ng/ml for oliceridine and 34.3 ± 9.7 ng/ml for morphine (potency ratio, 0.81; 95% CI, 0.39 to 1.56). However, morphine had a 2.48-fold greater respiratory potency (95% CI, 1.65 to 3.72) compared to oliceridine with a reduction by morphine of the ventilatory response to hypercapnia by 50% at 33.7 ± 4.8 ng/ml against a ventilatory response to hypercapnia reduction by oliceridine of 25% at 27.4 ± 3.5 ng/ml. Hysteresis between plasma concentration and effect was quantified by the blood-effect-site equilibration half-life (table 1). For the cold pressor test, the value of the blood-effect-site equilibration half-life for oliceridine was not quantifiable given the chosen sampling times, suggesting that the equilibrium between plasma and effect-site concentration was almost instantaneous. In contrast, morphine had a blood-effect-site equilibration half-life for antinociception of 0.6 ± 0.2 h. In the respiratory assay, the oliceridine value of the blood-effect-site equilibration half-life (0.25 h) was shorter than that of morphine (1.2 ± 0.2 h) and was dependent on the baseline ventilatory response to hypercapnia value (table 1).

Utility Functions. The utility function shows a marked difference between oliceridine and morphine (fig. 2). The function for oliceridine is positive (fig. 2, *blue line*), which indicates that oliceridine has a higher probability of analgesia than respiratory depression. At high concentrations (greater than 30 ng/ml), the probabilities of the two endpoints are not different. In contrast, the morphine utility (fig. 2, *orange line*) is predominantly negative, which indicates a higher probability of respiratory depression than analgesia. At the low concentration end (0 to 7.5 ng/ml), the probabilities of analgesia and respiratory depression do not differ.

Extrapolation of Utility Analysis to Studies 3001 and 3002

In clinical studies 3001 and 3002, patients undergoing bunionectomy (3001) under sciatic nerve block and abdominoplasty (3002) under general anesthesia were treated using intravenous patient-controlled analgesia with either oliceridine (n = 309 patients, at demand doses of 0.1, 0.35, or 0.5 mg) or with morphine (n = 159 patients). For each patient, the utility function was calculated over time and utility values at a respiratory depression event were noted (fig. 3). We *a priori* defined utility value limits below which we expected a respiratory event to occur, *i.e.*, at a utility value of 0.2 or less. A total number of 96 respiratory events was observed, 60 times during oliceridine administration (combined over all three dose regimens) and 36 times during the single morphine treatment regimen. The measured utility values indicate that the majority of events (83/96, 86%) occurred at utility values of 0.2 or less (oliceridine 47/60, morphine 36/36; fig. 3C).

Discussion

Respiratory depression is a major complication of opioid therapy, since it is potentially life-threatening. The use of prescription and illicit opioids is associated with a high number of fatalities due to respiratory depression.[2,3] Also, in perioperative care, patients on opioids experience adverse respiratory events in high numbers,[25] often not fatal, but

preventable fatalities do occur.[1,26] Opioid analgesia and side effects frequently coincide, and the benefit of treatment relies heavily on the occurrence and severity of adverse events. We developed a utility function that combines various endpoints into a single function allowing objective and precise comparisons among opioid analgesics.[9–12] Here we report on the comparison of a novel opioid, oliceridine, and morphine. Oliceridine is the first opioid of a new class, so-called biased ligands, that are biased toward the G-protein–coupled transduction pathway with a lesser effect on the β-arrestin pathway, and consequently may produce less respiratory depression.[5,6] Oliceridine is intended to be used to treat acute moderate to severe pain.[17,18] The question remains whether oliceridine has a superior utility relative to morphine in terms of analgesia and respiratory depression.

Our analyses were performed in several steps. First, we performed a pharmacokinetic–pharmacodynamic analysis of the concentration-effect data derived from a volunteer study.[16] The antinociceptive assay was the cold pressor test, a sensitive test of opioid analgesic effects,[27] while the ventilatory response to hypercapnia, an equally sensitive measure of opioid-induced respiratory depression,[28] was used to quantify the opioid effect on respiration. From the pharmacokinetic–pharmacodynamic data, we constructed the utility function that gives the difference between the probabilities of analgesia and respiratory depression. This function incorporates the contrasting opioid effects into one function, and consequently it may be used to compare opioid utilities. We also used this function to predict whether a respiratory depression event in clinical practice is likely to occur for a given probability of analgesia. For example, we expect such events when the probability of respiratory depression exceeds that of analgesia (fig. 3). To determine whether the utility functions differed significantly, we determined concentration ranges at which their 95% CI did not overlap (fig. 2). The utilities differed significantly over the range of 12 to 35 ng/ml (which is the clinical concentration range for both drugs),[19,29] with positive values for oliceridine and negative values for morphine.

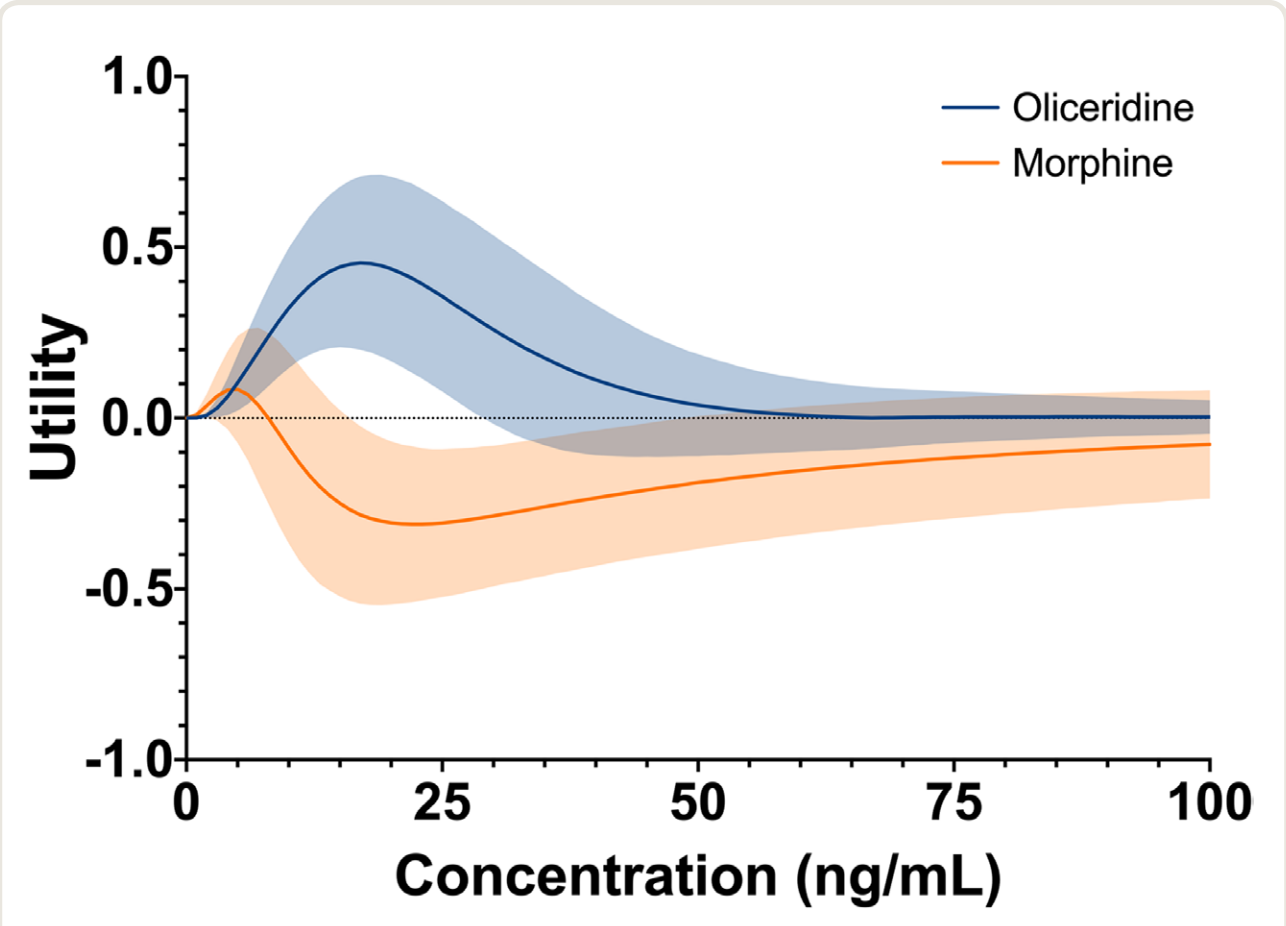

Fig. 2. Utility functions constructed from the pharmacokinetic and pharmacodynamic analysis of the volunteer data. Utility = the difference in probability of analgesia and probability of respiratory depression. The utility functions are a function of the biophase oliceridine or morphine concentration. In *blue*, the oliceridine utility function (*blue continuous line* is the mean with blue 95% CI band). In *orange*, the morphine utility function (*continuous lines* are the mean with orange 95% CI band).

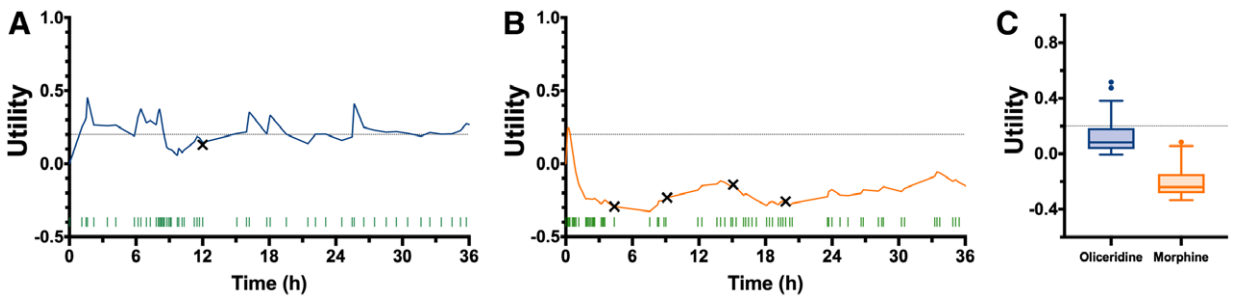

Fig. 3. (*A and B*) Utility values in two postoperative patients treated with oliceridine (*A*) or morphine (*B*). The *green lines* denote dosing events with a patient controlled intravenous infusion system. The *X*'s mark the occurrence of a respiratory depression event. All events occur at utility values of 0.2 or less. (*C*) *Box plots* of utility values at a respiratory depression events in patients treated with oliceridine or morphine after surgery for bunionectomy under peripheral nerve block or abdominoplasty under general anesthesia. There were 96 respiratory depression events; 86% of these events occurred at utility values of 0.2 or less (oliceridine 47 out of a total of 60 events, morphine 36/36).

Above the concentration of 35 ng/ml, the two drugs behave similarly, with utility values not significantly different between opioids (fig. 2). Overall, these data indicate a superior utility of oliceridine over morphine in terms of its safety profile and consequently a clinical benefit of oliceridine over morphine in the clinical concentration range.

Data from two clinical trials on the comparison of efficacy of oliceridine and morphine in the treatment of postoperative pain were used to determine whether respiratory depression events would occur at predefined utility values. In patients treated with oliceridine and morphine, there were 60 and 36 respiratory events, respectively. Respiratory depression events occurred at utility values of 0.2 or less in 86% of events (fig. 3). One may argue that the threshold for analgesia of 50% (obtained from experimental pain) is too low when considering postoperative pain related to tissue injury. We additionally calculated utility values at a more stringent value of 0.75, *i.e.,* P(analgesia ≥ 0.75), with respiratory depression events occurring at utility values of 0.2 or less in 94% of cases. Choosing the exact threshold values for (prediction of) respiratory depression events in clinical practice is challenging and the choice of thresholds has not been settled as of yet. Still, our current analysis does show an adequate association between occurrence of a respiratory depression event and utility value. Consequently, we argue that opioids with utility values greater than 0.2 over a large clinical concentration range will have fewer respiratory events than opioids with utility values of 0.2 or less. In this respect, the experimental and clinical analyses show that oliceridine has a superior utility than morphine at utility values greater than 0.2. It may be argued that rather than using the utility function to predict respiratory depression events, P(respiratory depression) may be useful. However, this specific probability does not consider the effect of appropriate pain relief. P(respiratory depression) may be used to predict respiratory depression events when not in pain, for example in recreational opioid users.

This study has some methodologic issues that deserve comment. (1) We constructed the utility functions from a volunteer study and used experimental endpoints that are considered precise and simultaneously are well-accepted surrogate measures of analgesia and respiratory depression. Our approach allowed the comparison of two opioids using standardized endpoints in a healthy population without confounding factors that might influence the study outcome, such as variations in pain perception, underlying disease, comedication, age effects, or other unknown factors. (2) We extrapolated the pharmacokinetic data from the volunteer study to construct the utility functions in patients receiving plastic surgery. The pharmacokinetic analysis of experimental study 1003 that we performed resulted in similar parameter estimates compared to an earlier analysis of grouped data from volunteers and patients (including studies 1003 and 3001).[19] Additionally, the patients from clinical trials 3001 and 3002 were relatively healthy (American Society of Anesthesiologists class I or II) and within the same age range and body weight as the volunteers of the experimental study 1003. (3) Our analgesia and respiratory depression thresholds are arbitrary. Possibly, more stringent thresholds, *e.g.*, P(analgesia ≥ 1.0) or P(respiratory depression ≥ 0.75), better reflect the effects of opioids in clinical practice. However, we chose to use thresholds that were within the quantitative range of pharmacodynamic observations in the experimental study (fig. 1, B and C). Still, even at higher threshold values, the superiority of oliceridine over morphine persisted (data not shown), which suggests that the analysis is not overly sensitive to the chosen thresholds. (4) The two clinical trials that were used to validate our assumptions differed significantly in anesthesia technique and amount of tissue damage and consequently in nociception, with greater nociception in postoperative patients after abdominoplasty surgery. This was reflected by a better fit of utility values with respect to respiratory depression events in the bunionectomy study

than the abdominoplasty study (data not shown). We combined both data sets as we reasoned that postoperative pain relief should be similarly optimal, irrespective of tissue damage and anesthesia technique. (5) Residual levels of anesthesia or use of comedication may have affected respiratory depression events. We assume that these confounders did not differ between treatment arms. Still, these confounders as well as many other, often poorly understood, factors may have caused respiratory depression events to occur at utility values above or below the predefined threshold value of 0.2. (6) Our observation that respiratory depression events occurred at utility values of 0.2 or less in 86% of events is reassuring, but ideally, the utility function should be constructed from analgesic drug concentration effect data obtained in postsurgical patients. This is a challenging but necessary task, so that the concept of the utility function acquires a definite place in clinical pharmacology. Therefore, currently, the utility function is best considered a novel pharmacologic paradigm that enables determination of simultaneous intended and adverse behaviors of therapeutics (determined in experimental studies under well-defined and standardized conditions), and allows the comparison of utilities among such treatments in terms of probability of benefit and harm. (7) The pharmacokinetic and pharmacodynamic parameter estimates and associated analyses were based on venous sampling and may not be compared to studies that used arterial sampling. Finally, (8) the subjects in the experimental study were all male. We know that the opioid effect in men and women may differ, which is true for both the respiratory and analgesic effects of morphine.[30,31] Future studies should include both sexes, allowing comparison between men and women.

Despite these limitations, these clinical utilities are a useful way to compare two drugs within a given class, and are useful in showing clinical meaningful differences between two medications. The utility functions demonstrate that oliceridine better separates analgesia from respiratory depression than morphine, within the clinically relevant concentration range. Prediction of respiratory depression events based on the utility function should currently be considered exploratory, and further studies are needed to confirm our approach and results.

Research Support

Trevena Inc. (Chesterbrook, Pennsylvania) provided the data for the analyses.

Competing Interests

Drs. Fossler and Demitrack are employees of Trevena Inc. (Chesterbrook, Pennsylvania) Dr. Dahan received consultancy fees from Trevena. The Anesthesia and Pain research unit received/receives funding from MSD Nederland BV (Haarlem, The Netherlands), Grünenthal GmbH (Aachen, Germany), Bedrocan BV (Veendam, The Netherlands), and Medasense (Ramat Gan, Israel), all unrelated to the current project. Dr. Dahan also received consultancy fees from MSD Nederland BV, Medasense, and LTS Lohmann (Andernach, Germany), all unrelated to the current project.

Correspondence

Address correspondence to Dr. Dahan: Department of Anesthesiology, Leiden University Medical Center, H05-022, P.O. Box 9600, 2300 RC Leiden, The Netherlands. a.dahan@lumc.nl.

References

1. Dahan A, Aarts L, Smith TW: Incidence, reversal, and prevention of opioid-induced respiratory depression. Anesthesiology 2010; 112:226–38
2. Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS: Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. Science 2018; 361:eaau1184
3. Bedene A, Lijfering WM, Niesters M, van Velzen M, Rosendaal FR, Bouvy ML, Dahan A, van Dorp ELA: Opioid prescription patterns and risk factors associated with opioid use in the Netherlands. JAMA Netw Open 2019; 2:e1910223
4. Huang W, Manglik A, Venkatakrishnan AJ, Laeremans T, Feinberg EN, Sanborn AL, Kato HE, Livingston KE, Thorsen TS, Kling RC, Granier S, Gmeiner P, Husbands SM, Traynor JR, Weis WI, Steyaert J, Dror RO, Kobilka BK: Structural insights into μ-opioid receptor activation. Nature 2015; 524:315–21
5. Violin JD, Lefkowitz RJ: Beta-arrestin-biased ligands at seven-transmembrane receptors. Trends Pharmacol Sci 2007; 28:416–22
6. Siuda ER, Carr R 3rd, Rominger DH, Violin JD: Biased mu-opioid receptor ligands: A promising new generation of pain therapeutics. Curr Opin Pharmacol 2017; 32:77–84
7. Manglik A, Lin H, Aryal DK, McCorvy JD, Dengler D, Corder G, Levit A, Kling RC, Bernat V, Hübner H, Huang XP, Sassano MF, Giguère PM, Löber S, Da Duan, Scherrer G, Kobilka BK, Gmeiner P, Roth BL, Shoichet BK: Structure-based discovery of opioid analgesics with reduced side effects. Nature 2016; 537:185–90
8. Schmid CL, Kennedy NM, Ross NC, Lovell KM, Yue Z, Morgenweck J, Cameron MD, Bannister TD, Bohn LM: Bias factor and therapeutic window correlate to predict safer opioid analgesics. Cell 2017; 171:1165–1175.e13
9. Kharasch ED, Rosow CE: Assessing the utility of the utility function. Anesthesiology 2013; 119:504–6
10. Boom M, Olofsen E, Neukirchen M, Fussen R, Hay J, Groeneveld GJ, Aarts L, Sarton E, Dahan A: Fentanyl utility function: A risk-benefit composite of pain

relief and breathing responses. Anesthesiology 2013; 119:663–74
11. Roozekrans M, van der Schrier R, Aarts L, Sarton E, van Velzen M, Niesters M, Dahan A, Olofsen E: Benefit *versus* severe side effects of opioid analgesia: Novel utility functions of probability of analgesia and respiratory depression. Anesthesiology 2018; 128:932–42
12. van Dam CJ, Algera MH, Olofsen E, Aarts L, Smith T, van Velzen M, Sarton E, Niesters M, Dahan A: Opioid utility function: Methods and implications. Ann Palliat Med 2020; 9:528–36
13. Sheiner LB, Melmon KL: The utility function of antihypertensive therapy. Ann N Y Acad Sci 1978; 304:112–27
14. Cullberg M, Eriksson UG, Wåhlander K, Eriksson H, Schulman S, Karlsson MO: Pharmacokinetics of ximelagatran and relationship to clinical response in acute deep vein thrombosis. Clin Pharmacol Ther 2005; 77:279–90
15. Habibi I, Cheong R, Lipniacki T, Levchenko A, Emamian ES, Abdi A: Computation and measurement of cell decision making errors using single cell data. PLoS Comput Biol 2017; 13:e1005436
16. Soergel DG, Subach RA, Burnham N, Lark MW, James IE, Sadler BM, Skobieranda F, Violin JD, Webster LR: Biased agonism of the μ-opioid receptor by TRV130 increases analgesia and reduces on-target adverse effects *versus* morphine: A randomized, double-blind, placebo-controlled, crossover study in healthy volunteers. Pain 2014; 155:1829–35
17. Viscusi ER, Skobieranda F, Soergel DG, Cook E, Burt DA, Singla N: APOLLO-1: A randomized placebo and active-controlled phase III study investigating oliceridine (TRV130), a G protein-biased ligand at the μ-opioid receptor, for management of moderate-to-severe acute pain following bunionectomy. J Pain Res 2019; 12:927–43
18. Singla NK, Skobieranda F, Soergel DG, Salamea M, Burt DA, Demitrack MA, Viscusi ER: APOLLO-2: A randomized, placebo and active-controlled phase III study investigating oliceridine (TRV130), a G protein-biased ligand at the μ-opioid receptor, for management of moderate to severe acute pain following abdominoplasty. Pain Pract 2019; 19:715–31
19. Fossler MJ, Sadler BM, Farrell C, Burt DA, Pitsiu M, Skobieranda F, Soergel DG: Oliceridine (TRV130), a novel G protein-biased ligand at the μ-opioid receptor, demonstrates a predictable relationship between plasma concentrations and pain relief. I: Development of a pharmacokinetic/pharmacodynamic model. J Clin Pharmacol 2018; 58:750–61
20. Romberg R, Olofsen E, Sarton E, den Hartigh J, Taschner PE, Dahan A: Pharmacokinetic-pharmacodynamic modeling of morphine-6-glucuronide-induced analgesia in healthy volunteers: Absence of sex differences. Anesthesiology 2004; 100:120–33
21. NONMEM Users Guide (1989-2017). Edited by Beal SL, Sheiner LB, Boeckmann AJ, Bauer RJ. Gaitersburg, MD, ICON plc
22. Comets E, Brendel K, Mentre F: Model evaluation in nonlinear mixed effect models, with application to pharmacokinetics. J Soc Franc Stat 2010; 151:106e27
23. Bauer RJ: NONMEM tutorial Part II: Estimation methods and advanced examples. CPT Pharmacomet Syst Pharmacol 2019; 8:538–56
24. Moline B, Roberts M, Houser J: Validity and inter-rater reliability of the Moline-Roberts Pharmacologic Sedation Scale. Clin Nurse Spec 2012; 26:140–8
25. Khanna A, Buhre W, Saager L, Di Stefano P, Weingarten T, Dahan A, Brazzi L, Overdyk F: Derivation and validation of a novel opioid-induced respiratory depression risk prediction tool. Crit Care Med 2019; 47(S1):18
26. Overdyk F, Dahan A, Roozekrans M, van der Schrier R, Aarts L, Niesters M: Opioid-induced respiratory depression in the acute care setting: A compendium of case reports. Pain Manag 2014; 4:317–25
27. 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
28. van der Schrier R, Roozekrans M, Olofsen E, Aarts L, van Velzen M, de Jong M, Dahan A, Niesters M: Influence of ethanol on oxycodone-induced respiratory depression: A dose-escalating study in young and elderly individuals. Anesthesiology 2017; 126:534–42
29. Sam WJ, MacKey SC, Lötsch J, Drover DR: Morphine and its metabolites after patient-controlled analgesia: Considerations for respiratory depression. J Clin Anesth 2011; 23:102–6
30. Niesters M, Dahan A, Kest B, Zacny J, Stijnen T, Aarts L, Sarton E: Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies. Pain 2010; 151:61–8
31. Dahan A, Sarton E, Teppema L, Olievier C: Sex-related differences in the influence of morphine on ventilatory control in humans. Anesthesiology 1998; 88:903–13