ANESTHESIOLOGY

Respiratory Effects of Biased Ligand Oliceridine in Older Volunteers: A Pharmacokinetic–Pharmacodynamic Comparison with Morphine

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- After μ-opioid receptor activation, oliceridine selectively engages the G protein–coupled signaling pathway, which is associated with analgesia, and has reduced engagement of the β-arrestin pathway, which is associated with adverse effects such as respiratory depression
- In healthy young males, oliceridine had a higher probability of providing analgesia than producing respiratory depression over the clinically relevant concentration range, while morphine had a higher probability of producing respiratory depression than providing analgesia
- Older and somewhat obese individuals of both sexes may be more vulnerable to opioid-induced respiratory depression than younger individuals

What This Article Tells Us That Is New

- The hypothesis that oliceridine and morphine differ in their pharmacodynamic behavior, measured as effect on ventilation at an extrapolated end-tidal P_{CO_2} of 55 mmHg ($\dot{V}_E55$), was tested in a four-arm, double-blind, randomized crossover study of eighteen 56- to 87-yr-old male and female volunteers
- The effect-site oliceridine concentration causing a 50% depression of $\dot{V}_E55$ was 39% higher than that of morphine
- The onset and offset of the respiratory effect of oliceridine was five times faster than that of morphine

ABSTRACT

Background: Oliceridine is a G protein–biased μ-opioid, a drug class that is associated with less respiratory depression than nonbiased opioids, such as morphine. The authors quantified the respiratory effects of oliceridine and morphine in elderly volunteers. The authors hypothesized that these opioids differ in their pharmacodynamic behavior, measured as effect on ventilation at an extrapolated end-tidal P_{CO_2} at 55 mmHg, $\dot{V}_E55$.

Methods: This four-arm double-blind, randomized, crossover study examined the respiratory effects of intravenous 0.5 or 2 mg oliceridine and 2 or 8 mg morphine in 18 healthy male and female volunteers, aged 55 to 89 yr, on four separate occasions. Participants' *CYP2D6* genotypes were determined, hypercapnic ventilatory responses were obtained, and arterial blood samples were collected before and for 6 h after treatment. A population pharmacokinetic–pharmacodynamic analysis was performed on $\dot{V}_E55$, the primary endpoint; values reported are median ± standard error of the estimate.

Results: Oliceridine at low dose was devoid of significant respiratory effects. High-dose oliceridine and both morphine doses caused a rapid onset of respiratory depression with peak effects occurring at 0.5 to 1 h after opioid dosing. After peak effect, compared with morphine, respiratory depression induced by oliceridine returned faster to baseline. The effect-site concentrations causing a 50% depression of $\dot{V}_E55$ were 29.9 ± 3.5 ng/ml (oliceridine) and 21.5 ± 4.6 ng/ml (morphine), the blood effect-site equilibration half-lives differed by a factor of 5: oliceridine 44.3 ± 6.1 min and morphine 214 ± 27 min. Three poor *CYP2D6* oliceridine metabolizers exhibited a significant difference in oliceridine clearance by about 50%, causing higher oliceridine plasma concentrations after both low- and high-dose oliceridine, compared with the other participants.

Conclusions: Oliceridine and morphine differ in their respiratory pharmacodynamics with a more rapid onset and offset of respiratory depression for oliceridine and a smaller magnitude of respiratory depression over time.

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In-hospital use of opioids is associated with multiple adverse events, prolonged length of stay, and opioid-related readmissions.[1–4] Particularly respiratory depression from potent opioids is associated with not only respiratory depression, but also cardiorespiratory collapse and death.[5] Despite these adverse effects, opioids remain the cornerstone of pharmacotherapy for moderate-to-severe acute pain because of their efficacy.[6] One strategy to mitigate opioid-induced adverse events is the development of safer opioids,[7–11] *e.g.*, opioids that produce less respiratory depression and lead to less addiction or abuse. One example of this strategy is the development of oliceridine that was recently approved by regulatory authorities in the United States for the treatment of postoperative pain.[7,8] It differs from other

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opioids in that it is assumed that, after activation of the μ-opioid receptor, oliceridine is biased toward the G-protein intracellular pathway, which is predominantly associated with analgesia, and shows limited recruitment of the β-arrestin pathway, which is associated with opioid-related adverse events (*e.g.,* respiratory depression and tolerance).[8,9,12] Theoretically, this would suggest that oliceridine has a lower probability of respiratory depression than, for example, morphine, a full μ-opioid receptor agonist without bias toward the G-protein pathway. This was indeed observed in a study that examined the antinociceptive and respiratory effects of oliceridine *versus* morphine and showed a higher probability of antinociception *versus* respiratory depression for oliceridine while the reverse was true for morphine.[13] In that study, healthy young volunteers were studied. In the current study, we tested older and somewhat obese individuals (age range 55 to 90 yr, body mass index up to 34 kg/m^2) because such individuals are an increasing part of our clinical caseload, and opioids in these older individuals possibly may have a higher potency for respiratory depression than in younger individuals. In the current sample of such older individuals, we performed a population pharmacokinetic–pharmacodynamic modeling study on the effect of intravenous oliceridine *versus* morphine on ventilation at an extrapolated end-tidal carbon dioxide concentration of 55 mmHg ($\dot{V}_E$55), the main endpoint of the study. We hypothesized that oliceridine and morphine differ in their pharmacodynamic behavior, measured as effect on ventilation at an extrapolated end-tidal P_{CO_2} of 55 mmHg.

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Materials and Methods

Ethics and Registration

The study was performed at a single site after approval of the protocol by the medical ethics committee of the Leiden University Medical Center, METC Leiden-Den Haag-Delft (under identifier P21.025) and the Central Committee on Research Involving Human Subjects (competent authority) in The Hague, The Netherlands (identifier NL75790.058.21). The study was performed from June 29, 2021, to January 4, 2022, in the Anesthesia and Pain Research Unit of the Department of Anesthesiology at Leiden University Medical Center. The study was registered in the trial register of the Dutch trial registry, currently available at the World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int), under identifier NL9524 on June 2, 2021. The principal investigator of the study was Albert Dahan, M.D., Ph.D. The study was conducted in accordance with current Good Clinical Practice Guidelines and adhered to the principles of the Declaration of Helsinki. Before enrollment, all subjects gave oral and written informed consent. Thereafter, their medical history was obtained, and a physical examination was performed. The whole project was monitored by an independent data input monitor and a data safety monitoring committee.

Participants

Healthy volunteers of either sex were recruited to participate in the study. Inclusion criteria were age 55 yr or older; body mass index in the range 19 to 35 kg/m^2 (inclusive); absence of any significant medical, neurologic, or psychiatric illness as determined by the investigators; and willing and able to sign a written informed consent. The inclusion process was aimed to include an equal number of men and women, include half of the participants with an age of 65 yr or older, and a third of subjects with a body mass index range of 30 to 35 kg/m^2, to represent an average elective surgical population. The main exclusion criteria were intolerance, hypersensitivity, or recent (less than 1 month) exposure to opioids; a positive drug test or breath alcohol test on screening or subsequent study visits; inability to perform the study procedures as tested during screening; cognitive impairment as determined by the short version of the Mini Mental Status Examination (score less than 24); any clinically significant laboratory abnormality; abnormalities on the electrocardiogram including a corrected QT interval greater than 450 ms; alcohol intake of more than 4 units per day; participation in a drug trial in the 30 days before screening; or any other condition that in the opinion of the investigator would complicate or compromise the study or the well-being of the subject.

Study Design

The following study drugs were administered on 4 separate study days, at least 1 week apart in a double-blind,

randomized order: 0.5 mg low-dose oliceridine (Trevena Inc., USA), 2.0 mg high-dose oliceridine, 2.0 mg low-dose morphine hydrochloride (Centrafarm BV, Etten-Leur, The Netherlands), or 8.0 mg high-dose morphine hydrochloride. The study drugs were administered intravenously for over 60 s. The study drugs were prepared by the pharmacy and dispensed to the study team in identical, unmarked, numbered (subject and visit numbers) syringes on the morning of the experiment. Randomization was performed using a computer-generated randomization list; the list was available to the pharmacy and the data safety monitoring committee. Unblinding was only justified in case of drug-related serious adverse events.

The choice of the opioid doses was based on earlier clinical studies. Available oliceridine and morphine comparative data from the literature suggest that oliceridine is 6.7 times more potent than morphine in the cold pressor test and 3.3 times more potent in pupil constriction as derived from a phase 1 study obtained in younger adults (less than 50 yr),[14] and 4 times more potent in decreasing pain intensity as derived from a phase 2 study in 144 postoperative patients (age range 18 to 75 yr).[15] Based on these observations, we consider that the doses used in our study (2 mg and 8 mg morphine and 0.5 and 2 mg oliceridine) are equianalgesic.

Before each visit, participants were asked to fast for at least 8 h. Upon arrival in the research unit, the subjects were screened for the use of illicit substances by using a urine dipstick (Alere Toxicology Plc., Oxfordshire, United Kingdom), and screened for alcohol use with a breath analysis test (AlcoHawk CA-120, USA). Thereafter, the participants received an intravenous catheter in the median cubital vein of the left or right arm and an arterial line in the left or right radial artery. The arterial line was connected to a FloTrac Sensor and HemoSphere (Edwards Lifesciences, USA) for hemodynamic monitoring. Finally, a 3-lead electrocardiogram (Datex Cardiocap, Helsinki, Finland) and a finger probe for pulse oximetry (Masimo Corporation, USA) were placed.

Respiratory Measurements.

After a short period of relaxation, the ventilatory response to hypercapnia was measured by using a modified rebreathing method.[16–18] During respiratory testing, the subjects were semirecumbent and breathed through a face mask positioned over the mouth and nose. The face mask was connected to a pneumotachograph and pressure transducer system (Hans Rudolph Inc., USA) to measure ventilation on a breath-to-breath basis. Inspired and expired carbon dioxide concentrations were measured at the mouth using a Datex Capnomac (Datex, Finland). After a 4-min period of relaxed breathing of room air, the subjects were coached to hyperventilate for 2 to 3 min while breathing a hyperoxic gas mixture (F_{IO_2} = 1), followed by normal breathing for 30 s of the hyperoxic gas mixture, after which rebreathing from a 6-l balloon containing 7% carbon dioxide in 93% oxygen was initiated. The rebreathing period lasted for 3 to 4 min. We obtained eight responses, one before any drug administration, and 30 min, 1, 2, 3, 4, 5, and 6 h after drug infusion. The following breath-to-breath data were collected: minute ventilation, end-tidal oxygen and carbon dioxide concentration, and oxygen saturation.

Blood Sampling and Analysis.

At the following time points, 2 ml blood was drawn from the arterial line for determination of oliceridine or morphine and morphine-6-glucuronide concentrations: 0 (predose) 2, 5, 10, 15, 30, and 45 min, and 1, 1.5, 2, 3, 4, 5, and 6 h (postdose). Plasma samples were shipped to Labcorp Bioanalytical Services LLC, Indianapolis, Indiana, for analysis.

Oliceridine plasma concentrations were quantified using a validated high-performance liquid chromatography with tandem mass spectrometry bioanalytical assay.[7,13] Oliceridine and the internal standard TRV0110813A:2 (tri-deutero ^{13}C-labeled oliceridine) were extracted from human plasma containing K_2EDTA by supported-liquid extraction. The lower limit of quantitation for oliceridine in human plasma was 0.05 ng/ml, with linearity demonstrable up to 50 ng/ml (upper limit of quantitation), using a 50-μl sample volume. Mean coefficient of variation among the various analytical runs ranged from 5.9 to 7.1% with bias ranging from 0.5 to 5.5% and accuracy from 100.5 to 105.5%. Oliceridine metabolites were not measured because none of them are pharmacologically active.

Morphine and morphine-6-glucuronide concentrations were determined by a validated high-performance liquid chromatography with tandem mass spectrometry method, after solid-phase extraction of morphine and internal standard morphine-d3 and morphine-6-glucuronide and internal standard morphine-6β-D-glucuronide-d3 from human plasma containing K_2EDTA. The lower limits of quantitation for morphine and morphine-6-glucuronide in human plasma were both 0.5 ng/ml, with linearity demonstrable up to 250 ng/ml (upper limit of quantitation), using a 50-μl sample volume. For morphine, the mean coefficient of variations among the analytical runs ranged from 5.2 to 7.5% with bias ranging from 0.5 to 3.2% and accuracy from 100.5 to 103.2%. For morphine-6-glucuronide, the mean coefficient of variations ranged from 5.2 to 6.8% with bias ranging from 0.5 to 5.6% and accuracy from 100.5 to 105.6%. The assay has not been published previously, but see Dahan *et al.*[13]

To determine the drug metabolizer status of the participants, one additional blood sample was drawn for determination of the *CYP2D6* genotype. Genotyping was performed by the ISO15189-accredited laboratory of the Leiden University Medical Center Pharmacy and Toxicology Department using the TAG CYP2D6 Kit v3 (Luminex Corporation, Den Bosch, The Netherlands). *CYP2D6*-haplotypes and copy number variants were determined.[19]

Adverse Events

Side effects were evaluated on an 11-point visual analog scale (0 to 10) for the following items: nausea (none to severe), sedation (none to most intense), dizziness (none to most severe), lightheadedness (none to most severe), drug likability (5 was equivocal, under 5 was do not like, over 5 was like). Additionally, we scored occurrence vomiting (yes/no). These items were queried at baseline, t = 45 min, and subsequently at 1-h intervals until t = 345 min after drug administration. Also, adverse effects spontaneously reported by the participant or observed by the investigators were recorded.

Data Analysis

Data analysis was performed in several steps. First, $\dot{V}_E55$ or ventilation at an extrapolated end-tidal P_{CO_2} of 55 mmHg (units l/min) was calculated from the slope of the ventilatory response to hypercapnia. The slope was determined in R (the R-Foundation for Statistical Computing, www.r-project.org) by fitting all ventilation-end-tidal P_{CO_2} data points of the linear part of the ventilatory response to hypercapnia curve to the equation $S = \text{Ventilation}(t)/[\text{end-tidal } P_{CO_2}(t) - B]$, where S is the slope of the ventilatory response to hypercapnia and B the apneic threshold or extrapolated end-tidal P_{CO_2} at zero ventilation; this process was automated in R.[20] Next, the population pharmacokinetic data were analyzed, followed by a population pharmacokinetic–pharmacodynamic analysis using $\dot{V}_E55$, the main endpoint of the study, as pharmacodynamic input to the model.

Pharmacokinetic–Pharmacodynamic Analysis.

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. Although measured in plasma, morphine-6-glucuronide was not included in the analyses, because previous studies indicated a rather low potency of morphine-6-glucuronide on generating respiratory effects in individuals with a normal renal function with a potency ratio of approximately 1:20 for depression of isohypercapnic ventilation and 1:50 for isocapnic hypoxic ventilation.[21] The pharmacokinetic data were analyzed using three-compartment models. The following analysis sequence was applied: initialization using iterative two-stage, parameter estimation using stochastic approximation expectation maximization, objective function evaluation using importance sampling, and a final No U-Turn sampling Bayesian step using noninformative priors to visualize and quantify parameter uncertainty.

The early samples at 2 min after infusion showed considerable variability. Because infusion was done manually for 1 min, it was hypothesized that this could be caused, at least in part, by variability of the infusion duration. Therefore, NONMEM's parameter of the infusion duration (D_1) was set up to be an estimable parameter.

Body weight and, for oliceridine, the metabolizer status based on the genotype of the *CYP2D6* gene, were incorporated as covariates in the pharmacokinetic analyses. The change in NONMEM's objective function value was tested to assess whether weight *via* allometric scaling improved the fit (because this requires no extra parameters, incorporating allometric scaling would be preferable with any decrease in the objective function value). For metabolizer status, the clearance for each nonnormal status was tested for statistically significant difference from the clearance for the normal status (change in objective function value of at least 6.63; $P < 0.01$).

Allometric scaling using standard powers of weight (1 for volumes and 0.75 for clearances) was assumed *a priori* and implemented in the pharmacokinetic models.[22] During model evaluation, it was checked that incorporating allometric scaling indeed reduced NONMEM's objective function value and that it decreased the dependence of interindividual variability terms on weight. To quantify the hysteresis between the arterial drug concentration and effect, an effect site is postulated characterized by a first-order process with rate constant ke0 and half-life t½ke0 (= ln2/ke0).

The ventilatory effects of oliceridine and morphine were modeled using an inhibitory sigmoid E_{MAX} model. Ventilation at an extrapolated isohypercapnic level of 55 mmHg ($\dot{V}_E55$) was modeled as follows:

$$\dot{V}_E55\,(t) = \dot{V}_E55 \text{ at baseline} - \dot{V}_E55 \text{ at baseline} \times \left[\frac{C_E(t)^\gamma}{C_{50}^\gamma}\right] \Big/ \left[1+\frac{C_E(t)^\gamma}{C_{50}^\gamma}\right]$$

where baseline is the value before any drug administration, $C_E(t)$ is the effect-site concentration at time t, C_{50} the effect-site concentration causing a 50% depression of $\dot{V}_E55$, and γ a shape parameter, which was fixed to 1 in the analyses. The same estimation steps were followed as was done for the pharmacokinetic analyses. To determine whether the models adequately described the data, goodness-of-fit plots were created and inspected. To allow a visual predictive check of the final pharmacokinetic or pharmacodynamic models, the normalized prediction discrepancies were estimated. Parameter estimates are reported as median ± standard error of the estimate; $P < 0.01$ was considered significant.

No formal sample size analysis was performed. A previous study from our laboratory enrolled 15 subjects and was able to detect a significant difference between two opioids (oxycodone and tapentadol) on $\dot{V}_E55$ in a young healthy population (mean difference 5 l/min, 95% CI –7 to –3 l/min).[23] In the current study, we planned to enroll 18 subjects to consider some variability in the data obtained from an older sample and possible withdrawal of up to 3 subjects.

The time to peak effect after a bolus dose is determined by both the blood-effect-site equilibration half-life and the pharmacokinetics.[24] This composite measure may be

useful for the design of target-controlled infusion systems where the available models from the literature are evaluated. From the estimated parameters for both oliceridine and morphine, we calculated the time to peak effect using the method described in Minto *et al.*[24] implemented in R (the root of the derivative of the effect-site concentration function of time after a unit bolus dose).

Simulations.

We simulated the effect of multiple doses to reach a level of respiration depression of maximal 65% of isohypercapnic baseline ventilation in a typical 70-kg patient. The simulations were performed in R using implementation of the final models and estimated typical population parameters with simulated data obtained at 1-min intervals. After a bolus dose, a subsequent sequence of doses, three to four per hour, mimicking patient-controlled analgesia, was simulated while advancing simulated time considering a lockout time of 6 min. Three runs were done: one for morphine and two for oliceridine with normal and low elimination clearance. The bolus dose was 10 times and 3 times higher than the subsequent repetitive dose (10:1 and 1.5:0.5), for morphine and oliceridine, respectively, as applied clinically.[14,15]

Results

A total of 341 individuals responded to an online mailing for participation in our study. Twenty-two were assessed for eligibility of which 4 were excluded because they did not show up on the first study day (n = 1), they met exclusion criteria (n = 2), or they declined to participate (n = 1). Eighteen subjects (9 men and 9 women) were enrolled in the study and randomly assigned; 17 subjects successfully completed the trial. One male subject withdrew consent after the second visit because of a (transient) painful hematoma that developed at the location of the vascular access line after the subject returned home; his data are included in the analyses. All other subjects completed the study without any serious or unexpected adverse effects. The mean age

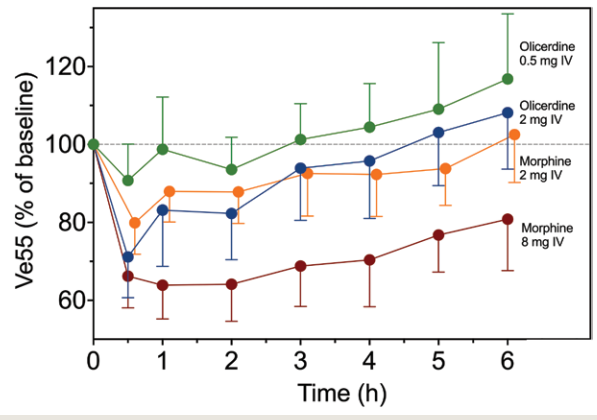

Fig. 1. Ventilation at an extrapolated carbon dioxide partial pressure of 55 mmHg, $\dot{V}_E55$, for the four treatment arms (*green*, 0.5 mg oliceridine; *blue*, 2 mg oliceridine; *orange*, 2 mg morphine; and *red*, 8 mg morphine). Data are averaged percentage of baseline ± 95% CI.

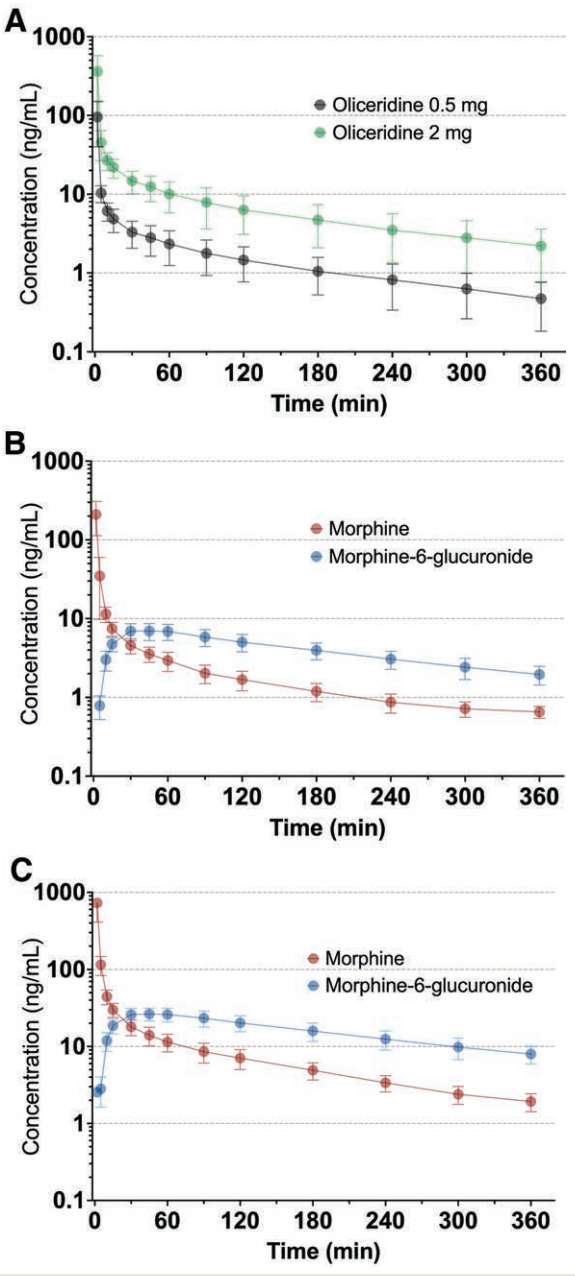

Fig. 2. Mean pharmacokinetic data ± 95% CI after intravenous administration of morphine and oliceridine. (*A*) 0.5 mg oliceridine (*gray symbols*) and 2 mg oliceridine (*green symbols*). (*B*) 2 mg morphine (*red symbols*) and morphine-6-gucuronide (*blue symbols*). (*C*) 8 mg morphine (*red symbols*) and morphine-6-gucuronide (*blue symbols*).

of the participants was 71 yr (range 56 to 87 yr), height 170 cm (155 to 189 cm), and body mass index 26 kg/m^2 (20 to 34 kg/m^2). Five subjects, with age range 69 to 75 yr, had a body mass index greater than 30 kg/m^2 (mean value 33 kg/m^2, with range 32 to 34 kg/m^2); the other subjects (age range 56 to 87 yr) had a mean body mass index of 24 kg/m^2 (20 to 29 kg/m^2).

Primary Endpoint: Opioid Effect on $\dot{V}_E$55

The effect of oliceridine and morphine on mean isohypercapnic ventilation, $\dot{V}_E$55, are given in figure 1. The dynamic patterns observed after the opioid infusions were different for the two opioids. High-dose oliceridine and high- and low-dose morphine showed a rapid drop in $\dot{V}_E$55, an indication of rapid onset of respiratory depression, *i.e.,* within 30 min of administration. High-dose oliceridine and low-dose morphine returned toward baseline within 3 h, and high-dose morphine lagged behind, and a slow return toward baseline (more than 6 h) was observed. Low-dose oliceridine did not produce any significant respiratory depression. In contrast to $\dot{V}_E$55 after high-dose morphine, $\dot{V}_E$55 after low- and high-dose oliceridine infusion had mean values greater than pre-drug baseline values from t = 4 h on.

Population Pharmacokinetic Analyses

The average plasma concentrations of oliceridine, morphine, and morphine-6-glucuronide are given in figure 2. Goodness-of-fit plots (individual and population predicted *versus* measured data, conditional weighted residuals *versus* time, and normalized prediction discrepancy errors *versus* time) are given in figure 3; the population predicted pharmacokinetic outcomes and measured plasma concentrations of each individual of the four treatment arms are given in figure 4. Inspection of the data fits and goodness-of-fit plots indicate that the three-compartment models adequately described the data of both opioids. The estimated pharmacokinetic model parameter estimates are given in table 1. For all 4 treatment arms, the infusion rate parameter (D_1) was not significantly different from 1, but its variability was significantly different from 0. Fixing it to zero had a marked effect on the remaining variability parameters and also on the population estimates. Therefore, including variability on D_1 likely reduced the bias on all parameter estimates. The decrease in NONMEM's objective function value was 141 and 139 points for morphine and oliceridine, respectively. Weight had an effect on the pharmacokinetic parameters *via* allometric scaling, indicated by a decrease in objective function value of 43 and 24 points for morphine and oliceridine, respectively.

With respect to the *CYP2D6* genotype, 10 subjects were classified as normal oliceridine metabolizers (2 functional alleles), 4 as intermediate metabolizer (heterozygous with one functional allele), 3 as poor metabolizer (with two alleles lacking activity due to *4/*4, *3/*4, and *4/*4 with

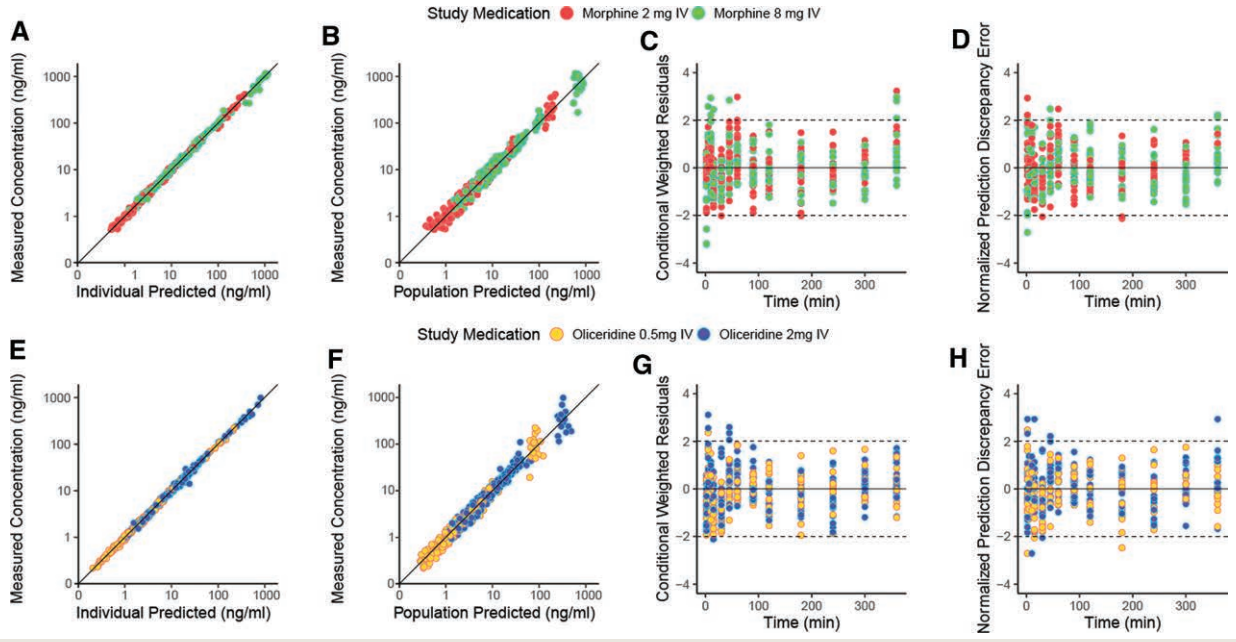

Fig. 3. Goodness-of-fit plots of the pharmacokinetic data analyses for morphine (*A* to *D*) and oliceridine (*E* to *H*). (*A* and *E*) Measured concentration *versus* individual predicted concentration. (*B* and *F*) Measured concentration *versus* population predicted concentration. (*C* and *G*) Conditional weighted residuals *versus* time. (*D* and *H*) Normalized prediction discrepancy error *versus* time. *Dotted lines* represent the upper and lower limits of the 95% CI. *Red symbols*, 2 mg morphine; *green symbols*, 8 mg morphine; *blue symbols*, 0.5 mg oliceridine; *yellow symbols*, 2 mg oliceridine.

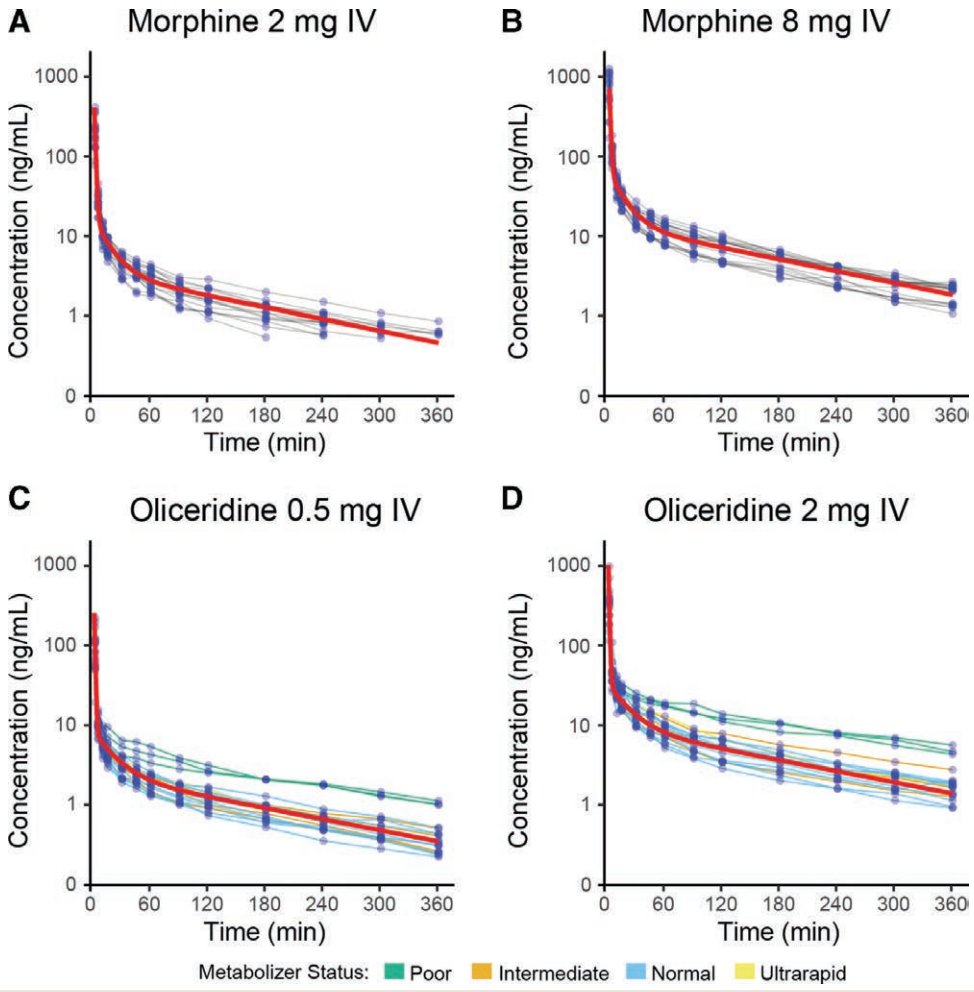

Fig. 4. The population pharmacokinetic model outcome (*red lines*) and the observed pharmacokinetic data points of each individual *versus* time for 2 mg morphine (*A*), 8 mg morphine (*B*), 0.5 mg oliceridine (*C*), and 2 mg oliceridine (*D*). For oliceridine the status of the *CYP2D6* genotype is given: poor metabolizer (*green*), intermediate metabolizer (*dark yellow*), normal metabolizer (*blue*), and ultrarapid metabolizer (*yellow*).

*3 = 2549delA and *4 = 100C>T, 1661G>T, 1846G>A, 2850C>T, or 4180G>C) and 1 as ultrarapid metabolizer (more than two functional alleles).[25] A significant difference in clearance (CL_1) by about 50% was observed in the three poor oliceridine metabolizers. This caused higher plasma concentrations in these three subjects after both low- and high-dose oliceridine compared with the other participants (fig. 4, C and D).

Pharmacodynamic Analyses

The population predicted pharmacodynamic outcomes and measured pharmacodynamic data points ($\dot{V}_E$55) of each individual of the four treatment arms are illustrated in figure 5, and goodness-of-fit plots are given in figure 6. Inspection of the data fits and goodness-of-fit plots indicate that the pharmacodynamic model adequately described the data of both opioids. The estimated pharmacodynamic model parameter estimates are given in table 2. Two relevant observations are that oliceridine displays a 39% higher C_{50} value than morphine, and the two drugs differ by a factor of 5 in their onset/offset times (t½ke0) with oliceridine being 5 times more rapid than morphine in the transition from plasma to effect site. The time to peak effect was 10.5 min and 56.0 min for oliceridine and morphine, respectively. For both drugs, parameter γ was not significantly different from 1 and therefore fixed to 1.

Simulations

Results of the simulation study are given in figure 7. They show the effect of multiple dosing aimed at a steady state in effect to maximal depression of 65% of baseline isohypercapnic ventilation. Irrespective of genotype (oliceridine), the differences in pharmacokinetic and pharmacodynamic properties result in less variation in the effect-site concentrations

Table 1. Pharmacokinetic Parameter Estimates

	Parameter ± SEE	Between-Subject Variability ω^2 ± SEE	Interoccasion Variability ν^2 ± SEE
Oliceridine			
V_1, l/70 kg	1.1 ± 0.1		0.07 ± 0.03
V_2, l/70 kg	5.6 ± 0.5		
V_3, l/70 kg	45.3 ± 1.8		0.01 ± 0.01
CL_1, l/h at 70 kg	33.1 ± 1.5	0.02 ± 0.01	0.006 ± 0.003
CL_2, l/h at 70 kg	22.8 ± 2.3	0.04 ± 0.02	0.02 ± 0.01
CL_3, l/h at 70 kg	27.6 ± 2.0	0.05 ± 0.03	
D_1, min	1		0.83 ± 0.43
CL_1^{PM}, l/h at 70 kg	17.8 ± 1.5		
σ^2	0.009 ± 0.001		
Morphine			
V_1, l/70 kg	3.3 ± 0.3	0.05 ± 0.02	
V_2, l/70 kg	7.1 ± 0.6		
V_3, l/70 kg	90.2 ± 3.7	0.02 ± 0.01	
CL_1, l/h at 70 kg	80.1 ± 2.3	0.016 ± 0.004	
CL_2, l/h at 70 kg	35.8 ± 2.3		
CL_3, l/h at 70 kg	51.4 ± 2.4		
D_1, min	1.0	1.1 ± 0.5	
σ^2	0.012 ± 0.001		

CL_1, the clearance from compartment 1 with CL_1^{PM} is CL_1 of the oliceridine poor metabolizer, CL_2 and CL_3, the intercompartmental clearances between compartments 1 and 2 and 1 and 3, respectively; D_1, the infusion duration; ω^2, intersubject variability; SEE, standard error of the estimate; σ^2, measure of residual variability; V_1, V_2, and V_3, the volumes of compartments 1, 2 and 3, respectively.

for morphine (difference between peaks and valleys 1 ng/ml) *versus* oliceridine (5 ng/ml) and variation in ventilation for morphine (difference between peaks and valleys 2% of baseline) *versus* oliceridine (7%). For morphine, in a 24-h period, the total drug dose given is 27 mg, which is made up of an initial bolus dose of 10 mg followed by 17 1-mg doses. For oliceridine in normal and poor metabolizers, the initial bolus dose was 1.5 mg followed by 20 doses of 0.5 mg in normal metabolizers (total dose given 11.5 mg) and 11 doses of 0.5 mg in poor metabolizers (total dose 7 mg). This indicates that less oliceridine was needed in poor than in normal metabolizers to induce a similar level of respiratory depression.

Adverse Effects

All reported and observed adverse effects are given in table 3. At low dose and high dose, the total number of events was similar between opioids. Most frequently reported events were dizziness, lightheadedness, somnolence, and horizontal vertigo after oliceridine administration, and nausea, lightheadedness, dizziness, and somnolence following morphine (all occurring on at least 8 visits). The queried adverse events are given in figure 8. It shows the more protracted occurrence of events after morphine than oliceridine.

Discussion

We studied oliceridine and morphine and measured isohypercapnic ventilation at an end-tidal P_{CO_2} of 55 mmHg as a biomarker of drug effect in a sample of moderately overweight older men and women. Our main observations were as follows: (1) there was a 30% difference in respiratory potency between oliceridine and morphine with a 50% reduction of $\dot{V}_E 55$ (C_{50}) observed at 29.9 ± 3.5 ng/ml oliceridine and 21.1 ± 4.6 ng/ml morphine; (2) oliceridine had a 5-times faster onset and offset of respiratory effect than morphine (blood-effect-site equilibration half-life, t½ke0, 44 ± 6 min for oliceridine *versus* 214 ± 27 min for morphine); and (3) oliceridine metabolism was dependent on the *CYP2D6* enzyme genotype. Simulations revealed that about 40% less oliceridine is needed to achieve the same level of respiratory depression in poor metabolizers compared with normal metabolizers over 24 h.

The study was conducted in older subjects as opposed to the more typically young and healthy study population. Previously, we studied healthy young volunteers (18 to 30 yr) to determine the respiratory effects of a range of opioids, including morphine, morphine-6-glucuronide, oxycodone, fentanyl, and buprenorphine.[20,21,23,26] Although these studies are of interest from a pharmacologic perspective, the current study sample is clinically more relevant, because patients aged 55 yr and older comprise the vast majority of patients in anesthetic practice. The differences in estimated model parameters indicate that, on bolus dose administration, oliceridine produces respiratory depression more rapidly than morphine, but the oliceridine effect wears off more quickly. In clinical practice, often higher opioid doses are administered than in our experimental study. This may be necessary, for example, to achieve rapid pain relief. Because we did not obtain pain data in our study (see next

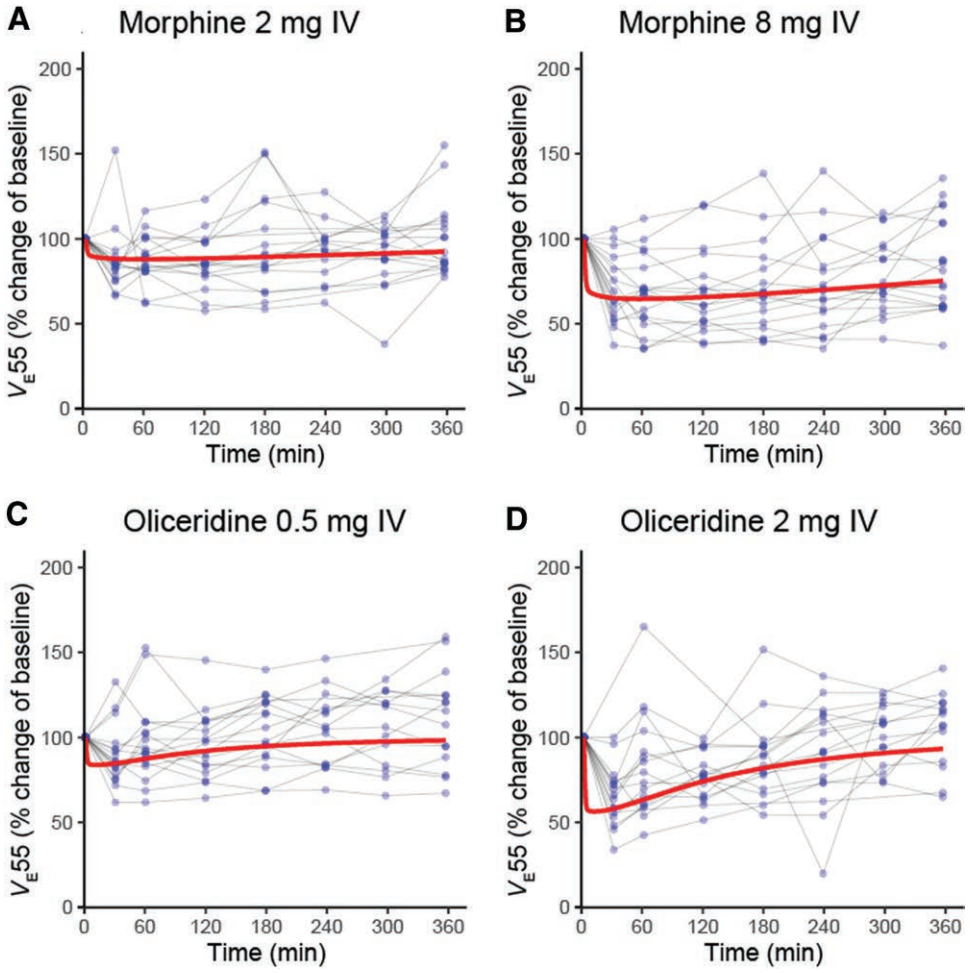

Fig. 5. The population pharmacodynamic model outcome (*red lines*) and the measured pharmacodynamic data points points ($\dot{V}_E$55) of each individual *versus* time for 2 mg morphine (*A*), 8 mg morphine (*B*), 0.5 mg oliceridine (*C*), and 2 mg oliceridine (*D*). Data are averaged percentage of baseline ± 95% CI.

paragraph), we remain uninformed how the ventilatory effects that we observed relate to the antinociceptive effects. This requires further study.

Previously, Dahan *et al.*[13] analyzed respiratory and antinociceptive oliceridine and morphine data in a younger cohort of healthy male volunteers (19 to 50 yr) to construct utility functions or therapeutic indices of the two opioids. They showed superiority for oliceridine compared with morphine in the utility U = P(A) – P(R), where P(A) is the probability for analgesia and P(R) is the probability for respiratory depression. In the current study, we had planned to construct similar utility functions and therefore measured antinociceptive responses (cold pressor and electrical pain tests, data not shown) in our subjects. However, we experienced early on that the older subjects had difficulty scoring the applied noxious stimuli. They consistently were insensitive to the intense cold-water stimuli (1.5°C) and we did not detect a dose- or time-dependent effect in the electrical pain assay. We therefore discarded the antinociceptive data obtained in the study. We demonstrated earlier that volunteers (mean age 37 yr, body mass index under 30 kg/m^2) were not able to reliably score thermal or electrical stimuli after opioid administration.[27] This may be even worse in the elderly because the nociceptive fibers in the skin are affected by the normal aging process and there is also evidence for functional alterations in pain-processing regions in the brain of elderly individuals.[28,29] Additionally, we showed that a sample of predominantly women with morbid obesity (mean age 43 yr, body mass index range 43 kg/m^2) were hypoalgesic to noxious stimuli and had difficulty grading thermal and electrical stimuli.[30] All of these factors could have impacted the pain measurement in our current study.

It was not possible to compare the respiratory safety of oliceridine and morphine in the older subjects of the present study because of our inability to construct utility

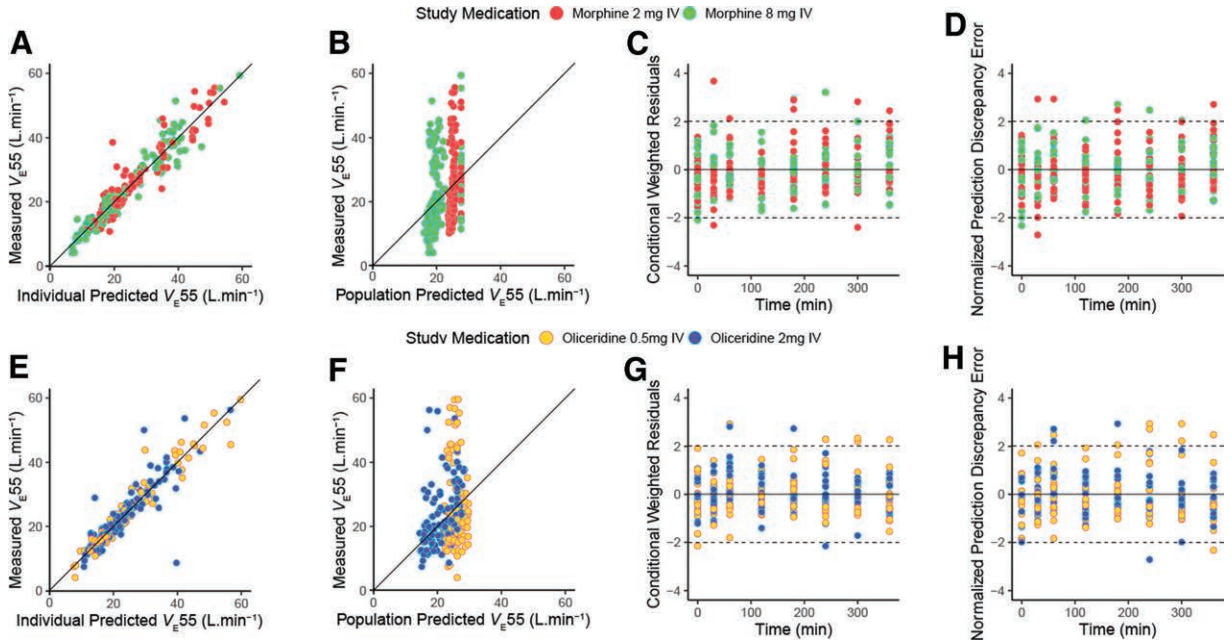

Fig. 6. Goodness-of-fit plots of the pharmacodynamic data analyses for morphine (*A* to *D*) and oliceridine (*E* to *H*). (*A* and *E*) Measured concentration *versus* individual predicted concentration. (*B* and *F*) Measured concentration *versus* population predicted concentration. (*C* and *G*) Conditional weighted residuals *versus* time. (*D* and *H*) Normalized prediction discrepancy error *versus* time. *Dotted lines* represent the upper and lower limits of the 95% CI. *Top panels*: *red symbols*, 2 mg morphine; *green symbols*, 8 mg morphine. *Bottom panels*: *yellow symbols*, 0.5 mg oliceridine; *blue symbols*, 2 mg oliceridine.

Table 2. Pharmacodynamic Parameter Estimates

	Parameter ± SEE	Between-subject Variability ω^2 ± SEE	Interoccasion Variability ν^2 ± SEE
Oliceridine $\dot{V}_E$55			
Baseline, l/min	28.3 ± 3.3	0.21 ± 0.10	0.07 ± 0.03
t½ke0, min	44.3 ± 6.1		
C_{50}, ng/ml	29.9 ± 3.5		
σ^2	15.1 ± 5.7	1.95 ± 0.82	
Morphine $\dot{V}_E$55			
Baseline, l/min	27.8 ± 3.1	0.20 ± 0.08	0.05 ± 0.02
t½ke0, min	214 ± 27		
C_{50}, ng/ml	21.5 ± 4.6	0.49 ± 0.28	1.81 ± 0.55
σ^2	6.7 ± 1.7		

C_{50}, effect-site concentration causing 50% respiratory depression; SEE, standard error of the estimate; ω^2, intersubject variability; σ^2, a measure of residual variability; t½ke0, blood to effect-site equilibration half-life; $\dot{V}_E$55, extrapolated ventilation at an end-tidal P_{CO_2} of 55 mmHg.

functions. This is particularly so because respiratory depression is related to drug dose and plasma concentration, speed of drug infusion, timing of measurement and underlying pain, which are considered in the utility function. Similarly, a comparison with our previous study in younger volunteers should be made with caution given the many differences in protocol, such as inclusion of only male subjects, venous sampling, and a different respiratory test in the earlier study.[13] Despite these differences, a comparison of respiratory potency ratios (C_{50} oliceridine)/(C_{50} morphine) remains meaningful. The ratio equaled 1.4 in the current study and was 1.6 in the cohort of younger men.[13] This shows that the potency ratio is maintained over the age ranges studied (19 to 50 yr and 56 to 87 yr). Further, the estimated blood-effect site equilibration half-lives are in the same range as observed in earlier morphine and oliceridine

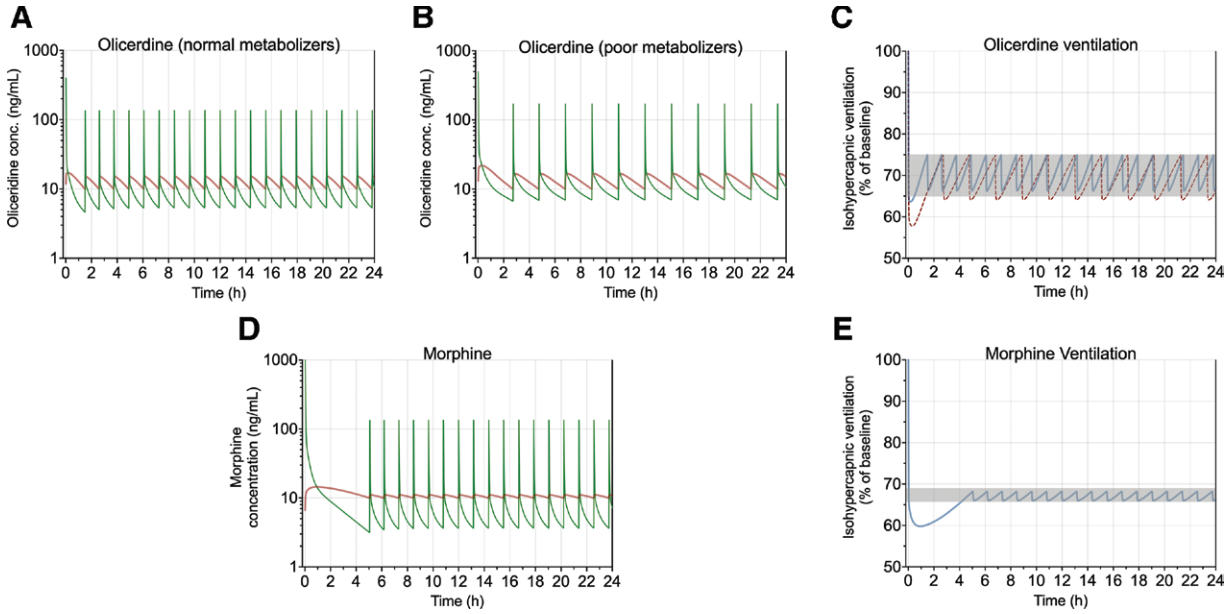

Fig. 7. Simulation study of the effect of multiple doses of oliceridine and morphine, mimicking patient-controlled analgesia and aimed at a maximum level of respiratory depression of 65% of baseline ventilation. (*A*) Oliceridine pharmacokinetics in normal metabolizers. (*B*) Oliceridine pharmacokinetics in poor metabolizers. (*C*) Ventilation in normal (*blue line*) and poor oliceridine metabolizers (*red broken line*). The *gray area* indicates the ventilation variability. (*D*) Morphine pharmacokinetics. (*E*) Ventilation following morphine. (*A*, *B*, and *D*) *Green lines* depict plasma concentration; *red lines* effect-site concentrations. (*C* and *E*) *Gray areas* depict the ventilation variability.

Table 3. Adverse Effects

	Oliceridine 0.5 mg	Oliceridine 2 mg	Morphine 2 mg	Morphine 8 mg
Apnea*				1
Bradycardia			1	3
Dizziness	4	12	4	7
Drowsiness	1	1	1	2
Flushing		3	1	2
Headache	3	6	4	4
Hoarseness				1
Lightheadedness	5	8	3	8
Myalgia shoulders				1
Nausea (without vomiting)		6	2	10
Nausea and vomiting		1	2	5
Numbness shoulders			1	
Paresthesia extremities		1	1	3
Paresthesia whole body		1		
Pruritis at injection site		1	2	1
Rigidity of the thorax				1
Shivering			1	
Slurred speech		2		1
Somnolence	4	7	2	6
Syncope	1		1	1
Vertigo (horizontal)	2	6		3
Vertigo (vertical)		4		2
Total	20	59	26	62

Data are n (subjects).

*Cessation of breathing for at least 30 s.

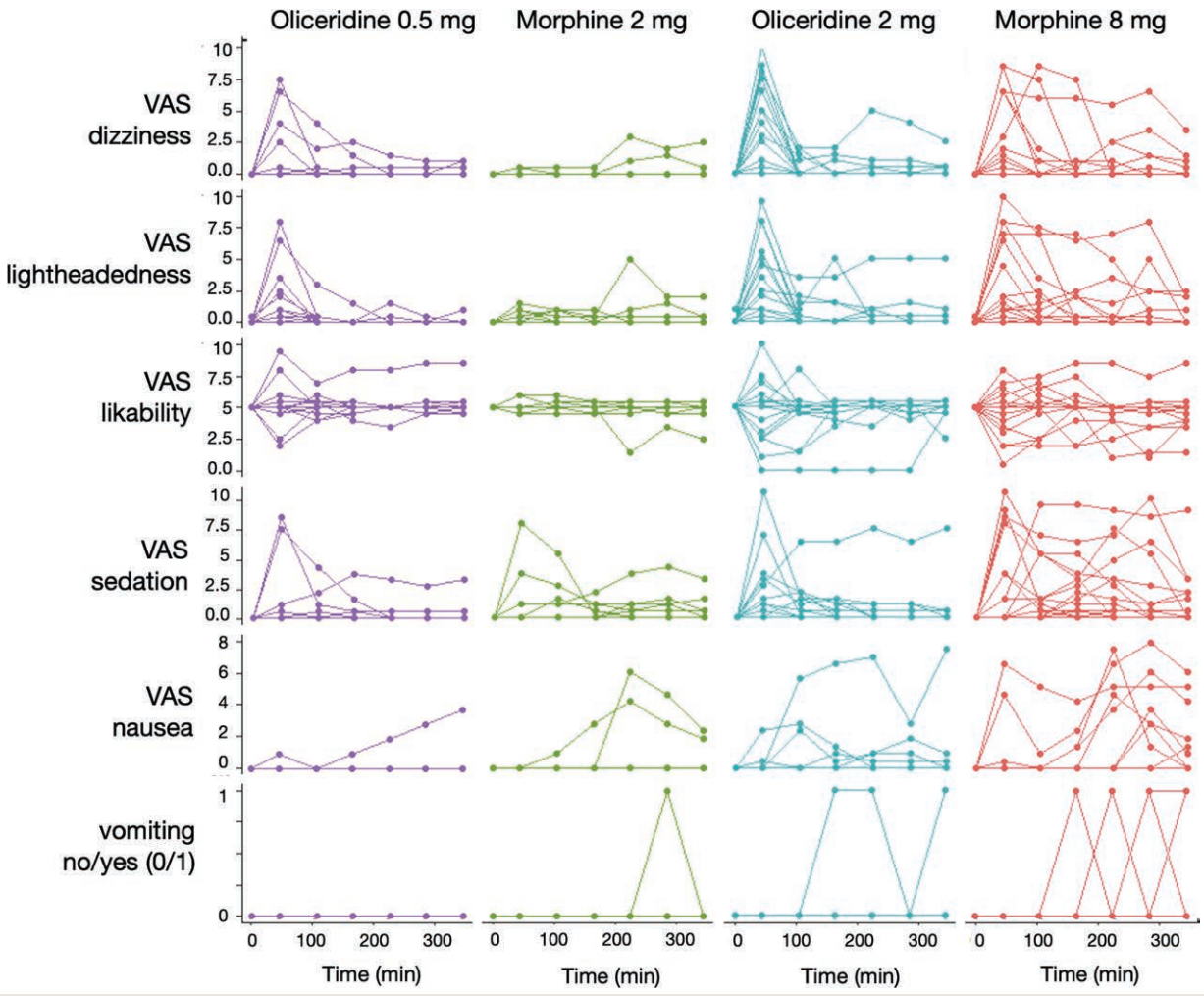

Fig. 8. Adverse events, queried on a visual analog scale for dizziness, lightheadedness, drug likability, sedation, nausea, and vomiting. For drug likability, the score ranges from 0 = I do not like this drug to 10 = I do like this drug, with 5 an equivocal score = I do like/I do not like. VAS, visual analog scale.

respiratory studies.[13,21,31,32] Additional studies in preferably acute pain patients, comparing multiple age cohorts, on pain relief and respiration are needed for definite conclusions.

The pharmacokinetic profile of oliceridine was altered in three poor metabolizers related to the *CYP2D6* genotype. All three had a significantly lower clearance (CL_1) with higher plasma oliceridine concentrations than the other *CYP2D6* genotypes. Similar observations were reported earlier.[33] In reviewing the pharmacokinetic data, we also need to consider the effects of age and body mass index. Among other physiologic changes, at an increasing age, glomerular filtration rate is reduced and there is a shift in the distribution of fat and muscle mass.[34,35] The latter may account for the decreased morphine compartmental volumes compared with volumes reported in younger volunteers with mean age 26 yr.[36] Similar observations were made for remifentanil showing reduced compartmental volumes with increasing age.[37] Our oliceridine pharmacokinetic parameter estimates agree with the pooled analysis of seven oliceridine data sets in acute pain patients of which more than half had an age range of 40 to 65 yr.[7] For morphine, a possible age-related reduction in renal function may cause accumulation of morphine-6-glucuronide, morphine's active metabolite, and subsequently enhance respiratory depression.[38] In our sample, all subjects had a glomerular filtration rate greater than 60 ml/min and a normal liver function.

The morphine and oliceridine C_{50} values (table 2) are lower than previously reported in several studies in younger volunteers.[32] For example, we earlier observed a C_{50} for morphine respiratory effect of about 45 ng/ml in young volunteers in their twenties.[39] Although we did not perform a direct comparison among different age cohorts, these observations point toward an increase in respiratory potency with increasing age for the two tested opioids. Our findings are consistent with earlier studies showing enhanced desired and undesired opioid effect with increasing age.[37,40–42] For potent synthetic opioids,

the age effect is well documented. For example, Scott *et al.*[43] found that the fentanyl dose requirements to produce a similar electroencephalographic effect decreases by 50% at an increasing age (from 20 to 89 yr) in male patients. Similar observations were made for remifentanil.[37] Cepeda *et al.*[42] showed that the risk for postoperative respiratory depression rises with increasing age in 8,855 surgical patients receiving an opioid (fentanyl, meperidine, or morphine) for postoperative pain. Compared with younger patients (16 to 45 yr), those aged 61 to 70 yr, 71 to 80 yr, and 81 yr and older had, respectively, a 2.8, 5.4, and 8.7 times higher risk for the development of respiratory depression. The physiologic basis of the increased opioid respiratory sensitivity with age remains unknown but may be related to an age-dependent imbalance between excitatory and inhibitory neuronal pathways within the respiratory networks of the brainstem after opioid receptor activation.[44] Possibly excitatory pathways are less active in the elderly, leading to increased sensitivity of the ventilatory control system to opioids.

$\dot{V}_E55$ *versus* Slope of the Hypercapnic Ventilatory Response

We measured the non–steady-state ventilatory response to carbon dioxide according to Read,[16] Rebuck,[17] and Florian *et al.*[18] Rather than using the slope of the response curve as our primary endpoint, we used ventilation at an end-tidal P_{CO_2} of 55 mmHg ($\dot{V}_E55$) calculated from the slope (S) and the x-axis intercept (B) as follows: $\dot{V}_E55 = [S \times (55 - B)]$; S and B are estimated from the regression of the breath-to-breath P_{CO_2} ventilation data. As is apparent from the formula, $\dot{V}_E55$ considers the slope and the position of the hypercapnic response curve. Opioids are known to decrease the slope and shift the response curve to the right, both of which are signs of respiratory depression. We and others earlier used $\dot{V}_E55$ to reliably express opioid effects on ventilatory control.[18,20,23] We chose a rebreathing rather than a steady-state technique to quantify the opioid effect on the hypercapnic ventilatory response to enable rapid and frequent testing over time. The steady-state technique is more cumbersome and takes 30 to 40 min to complete.[20] We previously argued that, in contrast to the steady-state technique, the rebreathing technique causes a reduction of the response slope due to a decrease in the differences between end-tidal (and arterial) P_{CO_2} and the CO_2 content in the rebreathing balloon (7%) after opioid administration.[45,46] However, the opioid-induced rise in end-tidal P_{CO_2} is due to the opioid respiratory effect, and, consequently, the reduced slope is a sign of respiratory depression that becomes apparent because of methodologic issues. A reduced slope is often not observed using a nonrebreathing steady-state technique.[47,48] Interestingly, opioids cause a rightward shift of the steady-state hypercapnic response curve, but the effect of opioids on $\dot{V}_E55$ seems independent of the method used to measure the hypercapnic ventilatory response.[48]

In conclusion, our population pharmacokinetic–pharmacodynamic analysis, performed in older individuals, shows that oliceridine has a more rapid onset/offset of respiratory depression, as defined by parameter $t½k_{e0}$, combined with a 30% lesser potency for respiratory depression, as defined by parameter C_{50}, than morphine.

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Competing Interests

T. Nicklas, C. Michalsky, and Dr. Demitrack are or were (Dr. Fossler) employees of Trevena Inc., Chesterbrook, Pennsylvania, at the time of performance of the study. Dr. Fossler is currently employed at Cytel Inc., Cambridge, Massachusetts, a consulting firm for the pharmaceutical industry. The Anesthesia & Pain Research Unit of the Department of Anesthesiology, Leiden University Medical Center (Leiden, The Netherlands) received/receives funding from AMO Pharma Ltd. (Leeds, United Kingdom), Bedrocan BV (Groningen, The Netherlands), Grünenthal GmbH (Stolberg, Germany), and Medtronic (Minneapolis, Minnesota), and MSD Nederland BV (Haarlem, The Netherlands). Dr. Dahan received consultancy and/or speaker fees from Enalare Therapeutics Inc. (Princeton, New Jersey), Grünenthal BV (Breukelen, The Netherlands), Medasense Biometrics Ltd. (Ramat Gan, Israel), Trevena Inc., MSD Nederland BV, LTS Lohmann Therapie Systeme AG (Andernach, Germany), and awards and/or grants from the U.S. Food and Drug Administration (Silver Spring, Maryland) and from the Netherlands Organisation for Health Research and Development (ZonMW, The Hague, The Netherlands). Dr. Sarton received support from the Federation Medical Specialists (Utrecht, The Netherlands) for updating national guidelines.

Reproducible Science

Full protocol available at: a.dahan@lumc.nl. Raw data available at: a.dahan@lumc.nl.

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