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Neurocognitive Effect of Biased μ-Opioid Receptor Agonist Oliceridine, a Utility Function Analysis and Comparison with Morphine

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Oliceridine is a μ-opioid receptor agonist that, unlike conventional opioids, preferentially 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
- Over clinically relevant concentration ranges, oliceridine has a higher probability of providing analgesia than producing respiratory depression, and morphine has a higher probability of producing respiratory depression than providing analgesia

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 a randomized, double-blind, placebo-controlled, dose-ranging, partial block three-way crossover study of 20 healthy volunteers
- The utility function was the probability of providing analgesia, an increase in hand withdrawal latency of 50% or more, minus the probability of producing a change of at least 25% in neurocognitive function, measured as saccadic peak velocity and body sway

ABSTRACT

Background: Oliceridine (Olinvyk) is a μ-opioid receptor agonist that in contrast to conventional opioids preferentially engages the G-protein–coupled signaling pathway. This study was designed to determine the utility function of oliceridine *versus* morphine based on neurocognitive tests and cold pressor test.

Methods: The study had a randomized, double-blind, placebo-controlled, partial block three-way crossover design. Experiments were performed in 20 male and female volunteers. The subjects received intravenous oliceridine (1 or 3 mg; cohorts of 10 subjects/dose), morphine (5 or 10 mg; cohorts of 10 subjects/dose), or placebo on three separate occasions. Before and after dosing, neurocognitive tests, cold pressor test, and plasma drug concentrations were obtained at regular intervals. Population pharmacokinetic–pharmacodynamic analyses served as the basis for construction of a utility function, which is an objective function of probability of benefit minus probability of harm. Antinociception served as the measure of benefit, and slowing of saccadic peak velocity and increased body sway as the measures of neurocognitive harm.

Results: The oliceridine and morphine C_{50} values, *i.e.*, the effect-site concentrations causing 50% effect, were as follows: antinociception, 13 ± 2 and 23 ± 7 ng/ml; saccadic peak velocity, 90 ± 14 and 54 ± 15 ng/ml; and body sway, 10 ± 2 and 5.6 ± 0.8 ng/ml, respectively. The ratio oliceridine/morphine of the therapeutic indices, C_{50}(benefit)/C_{50}(harm), were 0.34 (95% CI, 0.17 to 0.7; $P < 0.01$) for saccadic peak velocity and 0.33 (0.16 to 0.50; $P < 0.01$) for body sway. The oliceridine utility was positive across the effect-site concentration 5 to 77 ng/ml, indicative of a greater probability of benefit than harm. The morphine utility was not significantly different from 0 from 0 to 100 ng/ml. Over the concentration range 15 to 50 ng/ml, the oliceridine utility was superior to that of morphine ($P < 0.01$). Similar observations were made for body sway.

Conclusions: These data indicate that over the clinical concentration range, oliceridine is an analgesic with a favorable safety profile over morphine when considering analgesia and neurocognitive function.

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- Over clinically relevant concentration ranges, oliceridine had positive utility functions for both saccadic peak velocity (a biomarker of sedation) and body sway, and the morphine utility functions were not different from zero

Although μ–opioid receptor agonists appear to have the same molecular site of action, *i.e.*, the μ–opioid receptor,[1,2] evidence is accumulating that large differences exist among μ–opioids in their efficacy and adverse effects

profile.[3,4] These variations can be attributed to multiple factors, including pharmacokinetics, receptor kinetics, intraneuronal translation pathways, and pharmacodynamics.[3,4] Recently, a new class of opioid was discovered, biased toward G-protein intraneural activation,[5,6] of which the opioid oliceridine (Olinvyk) was approved in the United States for use in adults in the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. We earlier showed in young and older volunteer populations that oliceridine has advantages over morphine with respect to respiratory depression.[7,8] For example, in young volunteers, we demonstrated that the oliceridine utility function is superior to that of morphine.[7] The utility function, U_1, is defined by the probability of benefit (*i.e.,* antinociception) minus the probability of harm (*e.g.,* respiratory depression) or $U_1 = P(B) - P(H)$.[7,9] While oliceridine utility was positive over the clinical concentration range, morphine utility was negative and significantly different from oliceridine.[7] These data indicate that oliceridine has a greater likelihood for pain relief than respiratory depression, while the reverse is true for morphine. This marked difference may be due to a specific postreceptor engagement by oliceridine, which shows preferential (*i.e.,* biased) postreceptor activation of G-protein signaling and reduced β-arrestin recruitment and receptor internalization, unlike morphine.[5,6]

In addition to respiratory depression, opioids induce psychomotor effects such as sedation and motor effects affecting balance, which may also be undesirable. These neurocognitive effects have been associated with the inability to mobilize or a high likelihood of falling, memory loss, and confusion, and in the elderly, delirium and possibly progression of already existing cognitive impairment.[10–15]

This study aimed to compare the neurocognitive impact of oliceridine *versus* morphine using a validated neurocognitive test battery in a population of healthy male and female volunteers.[16] Utility functions were constructed based on pharmacokinetic and pharmacodynamic modeling and derived from two measures of neurocognitive function: saccadic peak velocity and body sway, and antinociception as measured by the cold pressor test. We chose saccadic peak velocity as a surrogate biomarker of sedation and body sway as a surrogate for balance or motor stability.[16–18] The hypothesis is that oliceridine has superior utility compared to morphine in these pharmacodynamic domains. A description of the complete neurocognitive data set will be reported elsewhere.

Materials and Methods

Ethics and Registration

The ethics committee BEBO (Stichting Beoordeling Ethiek Biomedisch Onderzoek, Assen, The Netherlands) and the national competent authority, the Central Committee on Research Involving Human Subjects (CCMO, The Hague, The Netherlands), approved the protocol. All study procedures were conducted in accordance with the principles of the declaration of Helsinki and Good Clinical Practice guidelines. All subjects provided written informed consent before any assessments. The study was conducted from February 4, 2022, to June 10, 2022, and was registered at the World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int/) on June 2, 2021, under identifier ISRCTN13308001 with Geert Jan Groeneveld as principal investigator.

Subjects

Twenty subjects, both male and female, were enrolled in the study after an initial screening visit. The main inclusion criteria were age (18 to 55 yr, inclusive), body mass index (18 to 32 kg/m², inclusive), absence of a current or history of any medical or psychiatric disease, and use of any illicit or prescribed drugs. Subjects who were identified as poor metabolizers of CYP 450 2D6 substrates through genotyping at screening were excluded (as such phenotypes are associated with poor oliceridine metabolism and consequently high oliceridine concentrations),[8] as were subjects with a known medical condition affecting sensitivity to cold and those who indicated the pain test to be intolerable or achieved pain tolerance at more than 80% of maximum input intensity for the cold pressor pain at screening. The complete list of inclusion and exclusion criteria is given in Supplemental Digital Content 1 (https://links.lww.com/ALN/D300).

Study Design and Treatment

The study was conducted at the Center for Human Drug Research (CHDR) in Leiden, The Netherlands, and had a randomized, double-blind, placebo-controlled, dose-ranging, partial block three-way crossover design. All participants were tested on three separate days and randomly assigned to receive one of five treatments on each study day, excluding any previously received treatment. A total of 20 unique sequences (of 60 possible unique sequences) were used with treatments: placebo (5% dextrose), 1 mg oliceridine, 3 mg oliceridine, 5 mg morphine, or 10 mg morphine.

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All treatments were dissolved in 5% dextrose. The administration of each treatment occurred more than 60 s through an intravenous access line in a volume of 3 ml. Olicerdine was obtained from Trevena Inc. (USA); morphine and 5% dextrose were obtained from the local accredited pharmacy (Leiden University Medical Center). Consequently, each unique treatment was given to 12 subjects, and each drug combination occurred six times, but in different sequences. There were at minimum 7-day washout periods in between the dosing days.

The oliceridine and morphine doses were chosen as they were considered approximately equianalgesic assuming a 1:5 potency ratio oliceridine:morphine of Olinvyk[19] and were anticipated to cause measurable neurocognitive effects with manageable other adverse effects.[7,8] Clinically, oliceridine doses of 1 to 2 mg are given intravenously with additional bolus doses of 1 to 3 mg every 1 to 3 h as needed.[7] According to the label, higher single oliceridine doses are not recommended. The morphine doses were based on clinical use, with 10 mg morphine considered the highest dose manageable in an outpatient study with healthy volunteers.

Randomization and Blinding

After successful screening, each subject was assigned a unique subject number. The treatment assignments were randomized using a computer-generated randomization list created in SAS 9.4. The randomization code was shared exclusively with the pharmacy of the Leiden University Medical Center and remained confidential until the study was completed and the data lock was lifted. Emergency envelopes containing unblinding information were prepared as a precautionary measure to ensure subject safety, but they were not utilized during the study. On dosing days, the pharmacy provided the investigators the appropriate study medication in masked syringes.

Measurements

Venous blood samples of 4 ml each were collected from a large vein in the arm opposite to the arm of drug infusion. The samples were obtained at specific timepoints, including predose and postdose at 5, 10, 15, 30, 60, 90, 120, 180, 240, 300, 360, and 720 min. A window of ±2 min was applied for samples obtained in the first 60 min, and ±5 min for subsequent samples. The collected blood samples were shipped to Labcorp Bioanalytical Services (USA), where the quantitation of oliceridine, morphine, and morphine-6-glucuronide plasma concentrations was performed using validated high-performance liquid chromatography with tandem mass spectrometry bioanalytical assays.[7,8]

Additionally, all subjects underwent repeated neurocognitive testing using the validated NeuroCart test battery.[16] This battery consists of a range of tests that assess central nervous system functioning, which are administered sequentially in a fixed sequence; we have demonstrated previously that the tests do not influence each other and have negligible learning effects. The assessment of antinociception was also conducted using the cold pressor test. The primary endpoint of the study was *a priori* designated as the drug effect on one specific neurocognitive test: saccadic eye movement peak velocity. Secondary endpoints included anterior–posterior body sway and the pain detection tolerance threshold. The current analysis performed at Leiden University Medical Center (by E.O. and A.D.) aimed to construct utility functions using these three endpoints.

During the screening visit, all subjects were familiarized with the saccadic peak velocity test.[16–18] On study days, the test was performed twice predose and postdose (with dosing at t = 0 min) at 30, 60, 120, 180, 240, 300, and 360 min. The eye movement recordings took place in a quiet room with dimmed lighting. Disposable silver–silver chloride electrodes were placed on the subject's forehead and beside the lateral canthi of both eyes for registration of the electro-oculographic signals. The skin resistance was reduced to less than 5 kΩ before measurements to ensure adequate readings. Head movements were restricted using a fixed head support. The subject was requested to track a moving dot displayed on a computer screen. Saccadic eye movements were recorded for stimulus amplitudes of approximately 15° in both directions. Fifteen saccades were recorded, with random interstimulus intervals varying from 3 to 6 s. The average values of saccadic peak velocity from all correctly executed saccades were used as input to the pharmacodynamic model.

Body sway was assessed using a body sway meter while subjects had their eyes closed and were wearing comfortable low-heeled shoes.[16–18] The body sway meter, a pot string meter from Celesco (Intertechnology Inc., Canada) permits measurement of body movements in a single plane and provides a measure of postural stability *via* a string attached to the subject's waist. Before starting a measurement, subjects were asked to stand still with their feet approximately 10 cm apart and their hands in a relaxed position alongside their body. All body movements over a 2-min period were integrated and expressed as mm of sway. Measurements were obtained before dosing and at the specific time points after dosing (t = 0 min): 50, 80, 140, 200, 260, 320, and 380 min.

Nociceptive tolerance thresholds were measured using the cold pressor pain test.[7,20,21] During screening, a training session was conducted to exclude subjects who found the pain test intolerable or reached tolerance at more than 80% of the maximum input intensity, with a cutoff time of 120 s. During the test, the subjects placed their nondominant hand into a warm-water bath at 35 ± 0.5°C for 120 s. After 105 s, a blood pressure cuff on the upper arm was inflated to a pressure of 20 mmHg below their resting diastolic blood pressure, limiting compensatory blood flow without causing pain. At 120 s, the subject transferred their hand from the warm-water bath to a cold-water bath of similar size, with circulating water, maintained at a temperature of 1.0 ± 0.5°C. Subjects were instructed to indicate when

they reached their pain tolerance, by moving the slider of an electronic visual analog scale to the rightmost position. Alternatively, if the limit of 120 s was reached, before reaching pain tolerance, the study ended. Either way, when the subjects removed their hand from the water, the blood pressure cuff deflated. Measurements were obtained before dosing and at specific time points after dosing (t = 0 min): 20, 90, 150, 210, 270, 330, and 390 min.

Pharmacokinetic–Pharmacodynamic Data Analysis and Construction of Utility Functions

We used NONMEM 7.5.1 (ICON plc., USA) to describe the population pharmacokinetics and pharmacodynamics of oliceridine and morphine[7]; for specifics, see Supplemental Digital Content (https://links.lww.com/ALN/D301). In brief, the analysis had two stages. In the first stage, the pharmacokinetic data were analyzed using a two compartment PK model, in agreement with earlier modeling studies using venous samples.[7] This resulted in individual empirical Bayesian pharmacokinetic model parameter estimates. These were used in the second stage: the pharmacodynamic analysis. This resulted in baseline parameters and potency parameters, C_{50} values, with their interindividual and interoccasion variances. The observed hysteresis between plasma concentration and effect site was characterized as a first-order process with half-life $t_{1/2}k_{e0}$. The data from the two drugs were analyzed separately, but the analgesia and neurocognitive data were combined. Parameter estimates are reported as median ± standard error of the estimate.

Neurocognitive Effects

Saccadic peak velocity and body sway were analyzed using sigmoid E_{MAX} models. For saccadic peak velocity, a possible maximum effect was assumed to be zero; for body sway, the possible maximal effect was assumed to be infinite. Saccadic peak velocity C_{50} indicates a 50% decrease from baseline, while body sway C_{50} indicates a 50% increase in sway from baseline. Shape parameter γ was fixed to 1 in the analyses.

Cold Pressor Test

Although the analysis of the cold pressor test was published before,[7] we provide a description for the sake of completeness. In the analysis of the hand latency withdrawal data, a log-logistic distribution was assumed, considering the 120-s cutoff times. The predicted latency time was estimated as the median of the log-logistic distribution using the following equation:

$$\text{Predicted latency} (t) = \text{Baseline} \times (1 + 0.5 \times C_E(t)/C_{50})$$

where Baseline is the baseline latency (*i.e.*, before opioid administration), $C_E(t)$ is the drug concentration in the effect site at time t, and C_{50} is the effect-site drug concentration causing 50% increase in withdrawal latency time. In cases in which the hand withdrawal latency reached the cutoff value, the probability of the censored observation was:

logP(withdrawal time > cutoff) = survival and survival = $-\log[1 + (\text{observation/prediction})^Z]$, where Z is a shape factor; otherwise:

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

Goodness of Fit

To assess the adequacy of the data fits, plots of the individual predicted *versus* measured data, population predicted *versus* measured data, and residuals *versus* time were created and inspected. To further evaluate the final pharmacokinetic or pharmacodynamic models, visual predictive checks were conducted by estimation of the normalized prediction discrepancies. We visually confirmed that the normalized prediction discrepancies *versus* time showed no discernable trends, heteroscedasticity, or both.

Utility Functions

We defined the utility function as the probability of the desired effect (analgesia) minus the probability of an adverse effect (in this study, the specified neurocognitive effects).[7,9] The threshold for the desired effect was *a priori* set at a 50% or more increase in hand-withdrawal latency relative to the predrug baseline values (benefit or analgesia greater than or equal to 0.50); the threshold for neurocognitive effects was *a priori* set at a change of at least 25% of the response (saccadic peak velocity or body sway) relative to predrug baseline levels (harm greater than or equal to 0.25). We constructed two utility functions:

U_1 = P(benefit ≥ 0.50) − P(harm ≥ 0.25), and

U_2 = (P benefit AND NOT harm),

where P is the probability.

Utility functions were constructed as a function of the opioid effect-site concentrations and as a function of time after a 1-min infusion of either 3 mg oliceridine or 10 mg morphine.[9] The utilities were calculated from the population pharmacokinetic and pharmacodynamic parameter estimates and their interindividual variability parameters, ω (tables 1 and 2).

Utility probabilities were calculated by counting the number of times either outcome (benefit or harm) occurred with 10,000 simulations and then dividing the counts by 10,000. At each simulation step, individual values for the model parameters were generated by random number generators based on the typical values and interindividual and interoccasion variances. These procedures were run for the two drugs and comparison endpoints separately. Utility functions are presented ± 95% CI.

Table 1. Pharmacokinetic Parameter Estimates

Parameter	Estimate ± SEE (%RSE)	ω ± SEE (%RSE) [%CV]	Lower, Upper Values
Oliceridine			
V_1, l	65.9 ± 2.9 (4)	0.15 ± 0.03 (20) [40]	60.0, 71.6
k_{10}, h^{-1}	0.68 ± 0.03 (4)	*	0.63, 9.74
k_{12}, h^{-1}	0.29 ± 0.05 (20)	0.38 ± 0.10 (30) [68]	0.20, 0.42
k_{21}, h^{-1}	0.78 ± 0.07 (9)		0.65, 0.93
σ	0.16 ± 0.01 (5)		0.15, 0.18
V_2, l†	23.9 ± 2.8 (10)		18.5, 29.8
CL_1, l/h†	44.9 ± 2.3 (5)		40.3, 49.3
CL_2, l/h†	18.8 ± 3.2 (20)		13.3, 26.3
Morphine			
V_1, l	38.0 ± 3.4 (9)	‡	31.2, 45.5
k_{10}, h^{-1}	3.2 ± 0.2 (9)		2.7, 3.7
k_{12}, h^{-1}	9.1 ± 0.7 (7)		7.8, 10.4
k_{21}, h^{-1}	1.8 ± 0.1 (4)		1.7, 2.0
σ	0.17 ± 0.01 (5)		0.16, 0.19
V_2, l†	186 ± 10 (5)		169, 205
CL_1, l/h†	119 ± 5 (5)		110, 131
CL_2, l/h†	342 ± 19 (5)		308, 381

When parameters are ommitted, they were not estimable.

*The Interoccasion variability for oliceridine k_{10} is 0.14 ± 0.03 with RSE of 20%, CV of 39%, lower value of 0.09, and upper value of 0.22. †Derived from the one sampling importance resampling step, performed after the importance sampling step using NONMEM and the "table_resample" utility (see the Supplemental Digital Content, https://links.lww.com/ALN/D301). ‡The interoccasion variability for morphine V_1 is 0.12 ± 0.03 with RSE of 30%, CV of 36%, lower value of 0.07, and upper value of 0.19.

CL_1, clearance from compartment 1; CL_2, intercompartmental clearance between compartments 1 and 2; CV, coefficient of variation for interindividual or interoccasion variability, which is calculated as $\sqrt{[\exp(\omega^2) - 1]} \times 100$; k_{10}, elimination rate constant; k_{12}, rate constant in between compartments 1 and 2; k_{21}, rate constant in between compartments 2 and 1; RSE, relative standard error; SEE, standard error of the estimate; V_1, volume of compartment 1; V_2, volume of compartment 2; σ is additive residual error variance; ω, interindividual variability.

Results

Participants

A total of 73 participants were screened, 23 of whom were randomized (10 females, 13 males). Nineteen (8 females, 11 males) completed all three study visits as planned per protocol. Two of the initially enrolled participants did not complete all planned visits (one was discontinued after the first visit due to symptomatic COVID-19 disease, and the other withdrew consent after the second visit) and were replaced. One replacement participant withdrew consent after one visit and a second replacement was scheduled. The other replacement withdrew consent after two visits and was not replaced. No participants withdrew consent due to adverse events; no serious adverse events were reported during the study. Characteristics of the randomized population are given in table 3. The full analysis of all data derived from the NeuroCart test battery will be reported elsewhere.

Pharmacokinetic Analyses

The last samples (t = 720 min) of all subjects were excluded from the analyses as they had unexpectedly high values relative to the other samples. The individual pharmacokinetic data and mean plasma concentrations for low- and high-dose oliceridine and morphine are given in supplemental figure 1, A to D (https://links.lww.com/ALN/D302). The pharmacokinetic models were parameterized with volumes (V_1) and rate constants, as these were the best in terms of objective function and standard errors of the variability parameters. This may be due to fewer covariances between the parameters compared to the parameterization with volumes and clearances. Additionally, we derived V_2 and clearances from the one sampling importance resampling step as explained in the Supplemental Digital Content.[22] All pharmacokinetics parameter estimates are given in table 1. The population model output is plotted in supplemental figure 1A (oliceridine; https://links.lww.com/ALN/D302) and supplemental figure 1C (morphine; https://links.lww.com/ALN/D302) for low- and high-dose drug administration. Inspection of the individual data fits and goodness–of–fit plots (supplemental figure 1, E to L; https://links.lww.com/ALN/D302) indicate that the pharmacokinetic models adequately describe the data.

Pharmacodynamic Analyses

Data from one subject (ID 16) were excluded from the pharmacodynamic analyses, as this subject was unresponsive with respect to drug effect in the cold pressor test and had rather unexpected small baseline cold pressor test latency values. Supplemental figures 2 to 4 (https://links.lww.com/ALN/D302) present the pharmacodynamic responses and data analyses. Both opioids exhibit a dose-response relationship for all three endpoints. The adequacy of the data fits was determined by examining individuals fits (data not shown) and the goodness–of–fit plots (supplemental figures 2 to 4; https://links.lww.com/ALN/D302).

The estimated parameter values are given in table 2. For the potency parameter C_{50}, a single between-subject variability parameter, ω, was included in the statistical model for all three endpoints, while an additional ω was added for the cold pressor morphine C_{50}. Compared to morphine, oliceridine C_{50} values were greater for both neurocognitive endpoints but not for the cold pressor test, indicative of a lower potency for developing adverse effects but greater potency for analgesia. In addition, the hysteresis parameter $t_{1/2}k_{e0}$ differed between the two drugs with a more rapid onset/offset for oliceridine compared to morphine, irrespective of the measured endpoint. In the cold pressor test, oliceridine displayed an almost instantaneous response ($t_{1/2}k_{e0}$, 0.07 ± 0.03 h), suggestive of a rapid equilibration between plasma concentration and effect site. Morphine $t_{1/2}k_{e0}$ ranges (1 to 3h) indicate the rather slow passage of this opioid across the blood-brain barrier. When comparing the C_{50} values across endpoints, oliceridine showed similar potency values for body sway and the cold pressor test (*i.e.*, equipotency), while peak saccadic velocity was approximately one tenth as potent compared to the other two endpoints.

Table 2. Pharmacodynamic Parameter Estimates

Parameter	Estimate ± SEE (%RSE)	ω ± SEE (%RSE) [%CV]	Lower, Upper Values
Oliceridine			
Saccadic peak velocity			
Baseline, °/s	453 ± 8.5 (2)	0.08 ± 0.01 (20) [30]	435, 466
C_{50}, ng/ml	90 ± 14 (20)	0.46 ± 0.12 (20) [76]*	66, 116
$t_{\frac{1}{2}}k_{e0}$ (h)	0.7 ± 0.1 (20)	0.56 ± 0.19 (30) [86]	0.4, 0.9
σ	21 ± 1 (6)		19, 23
Body sway			
Baseline (mm)	174 ± 19 (10)		137, 221
C_{50} (ng/ml)	10 ± 2 (20)	0.46 ± 0.12 (20) [76]	7, 16
$t_{\frac{1}{2}}k_{e0}$ (h)	1.1 ± 0.2 (20)		0.7, 1.4
σ	64 ± 4 (6)		58, 73
Cold pressor test			
Baseline (s)	29 ± 4 (10)	0.60 ± 0.09 (20) [90]	21, 37
C_{50} (ng/ml)	13 ± 2 (10)	0.46 ± 0.12 (20) [76]*	10, 17
$t_{\frac{1}{2}}k_{e0}$ (h)	0.07 ± 0.03 (40)		0.03, 0.13
Z	9.15 ± 0.62 (7)		8.1, 10.3
Morphine			
Saccadic peak velocity			
Baseline (°/s)	459 ± 11 (2)	0.10 ± 0.10 (20) [32]	439, 480
C_{50} (ng/ml)	54 ± 15 (30)	0.41 ± 0.13 (30) [71]†	30, 85
$t_{\frac{1}{2}}k_{e0}$ (h)	3.4 ± 1.0 (30)		2.0, 5.5
σ	21.9 ± 1.3 (6)		20, 25
Body sway			
Baseline (mm)	229 ± 28 (10)	0.44 ± 0.09 (20) [75]	176, 287
C_{50} (ng/ml)	5.6 ± 0.8 (10)	0.41 ± 0.13 (30) [71]†	4, 8
$t_{\frac{1}{2}}k_{e0}$ (h)	2.7 ± 2.5 (90)	1.81 ± 0.332 (20) [230]	0.3, 9.8
σ	132 ± 11 (8)		115, 154
Cold pressor test			
Baseline (s)	32 ± 4 (10)	0.52 ± 0.08 (20) [82]	24, 41
C_{50} (ng/ml)	23 ± 7 (30)	0.41 ± 0.13 (30) [71]†‡	13, 40
$t_{\frac{1}{2}}k_{e0}$ (h)	1.0 ± 0.2 (20)		0.6, 1.6
Z	8.9 ± 0.70 (8)		7.6, 10.3

When parameters were ommitted, theyr were not estimable.

*The interoccasion variability for oliceridine $t_{\frac{1}{2}}k_{e0}$ (body sway) is 0.52 ± 0.08 with RSE of 20% and CV of 82%. For oliceridine, one ω was included in the statistical model for C_{50} of all three endpoints. †Similarly, for morphine, one ω was included in the statistical model for C_{50} of all three endpoints. ‡One additional ω was added for morphine C_{50} (cold pressor test), which was 0.91 ± 0.31 with RSE of 30% and CV of 120%.

CV, coefficient of variation for interindividual or interoccasion variability, calculated as $\sqrt{[\exp(\omega^2) - 1]} \times 100$; C_{50}, potency parameter (*i.e.*, the effect-site drug concentration causing a 50% effect); RSE, relative standard error; SEE, standard error of the estimate; $t_{\frac{1}{2}}k_{e0}$, the blood-effect-site equilibration half-life; Z, steepness coefficient of the log-logistic distribution; σ, residual noise component; ω is interindividual variability.

For morphine, the highest potency was observed for body sway, followed by cold pressor test (factor 4) and finally peak saccadic velocity (factor 10).

Therapeutic Indices

Adverse effects relative to cold pressor test were analyzed by comparing therapeutic indices as follows: $[C_{50}$(cold pressor test)/C_{50}(saccadic peak velocity) oliceridine]/$[C_{50}$(cold pressor test)/C_{50}(saccadic peak velocity) morphine] = 0.34 with 95% CI, 0.17 to 0.71. For body sway, this ratio was 0.33 (0.16 to 0.50). Both indicate the favorable behavior of oliceridine compared to morphine as based on these therapeutic indices.

Utility Functions

The utility functions are given in figure 1 for U_1 = P(B) − P(H) with their 95% CI. All four curves indicate that the oliceridine utilities were superior to those of morphine.

For saccadic peak velocity (fig. 1A), the largest probability value for U_1 as a function of effect-site concentration was 0.63 (95% CI, 0.44 to 0.83), at an oliceridine concentration of 21 ng/ml, which we consider a large effect. The equivalent value for morphine was 0.09 (−0.11 to 0.26) at a morphine concentration of 8 ng/ml. While oliceridine had a positive probability U_1 over the concentration range of 5 to 77 ng/ml (otherwise not significantly different from 0), morphine probability U_1 was not significantly different from 0 over the plasma concentration range 0 to 100 ng/ml. Based on the 95% CI ranges,[23] the two curves differed significantly from 15 to 50 ng/ml. Similar observations were made for body sway (fig. 1B), with significant differences in probability between opioids over the concentration range of 12 to 87 ng/ml. In addition, for U_2 = P(B AND NOT H), indicative of the probability of occurrence of antinociception without any neurocognitive harm, oliceridine was superior to morphine

(fig. 2). For saccadic peak velocity, the peak probability U_2 was 0.63 (0.45 to 0.83) at an oliceridine concentration of 20 ng/ml and 0.20 (0.05 to 0.49) at a morphine concentration of 15 ng/ml with significant differences in probabilities between the two opioids from 18 to 30 ng/ml. For body sway, equivalent values were 0.44 (0.25 to 0.74) at an oliceridine concentration of 17 ng/ml, 0.09

(0.01 to 0.21) at a morphine concentration of 14 ng/ml, and significantly different over the concentration range of 16 to 52 ng/ml.

For the utility functions as a function of time after 3 mg intravenous oliceridine or 10 mg intravenous morphine administration, we refer to figure 1, C and D, for U_1 and figure 2, C and D, for U_2. Significant differences between the two opioids were observed for saccadic peak velocity from t = 2 to t = 30 min (U_1) and from t = 2 to t = 43 min (U_2), with both in favor of oliceridine, and for body sway from t = 2 to t = 62 min (U_1) and from t = 2 to t = 60 min (U_2), with both in favor of oliceridine.

Discussion

There is a wide variety of opioids available for clinical use,[3,4] with large differences in their pharmacologic properties such as pharmacokinetics, receptor kinetics, and pharmacodynamics. Concerning the latter, this relates to their intended effects, such as pain relief, as well as to the diverse range of adverse effects that opioids produce. For example, opioids vary in the degree of likability and consequently in their potential for abuse, the extent of respiratory depression, and possibly the level of neurocognitive defects.[3,4,11,13] All adverse effects require careful consideration when selecting
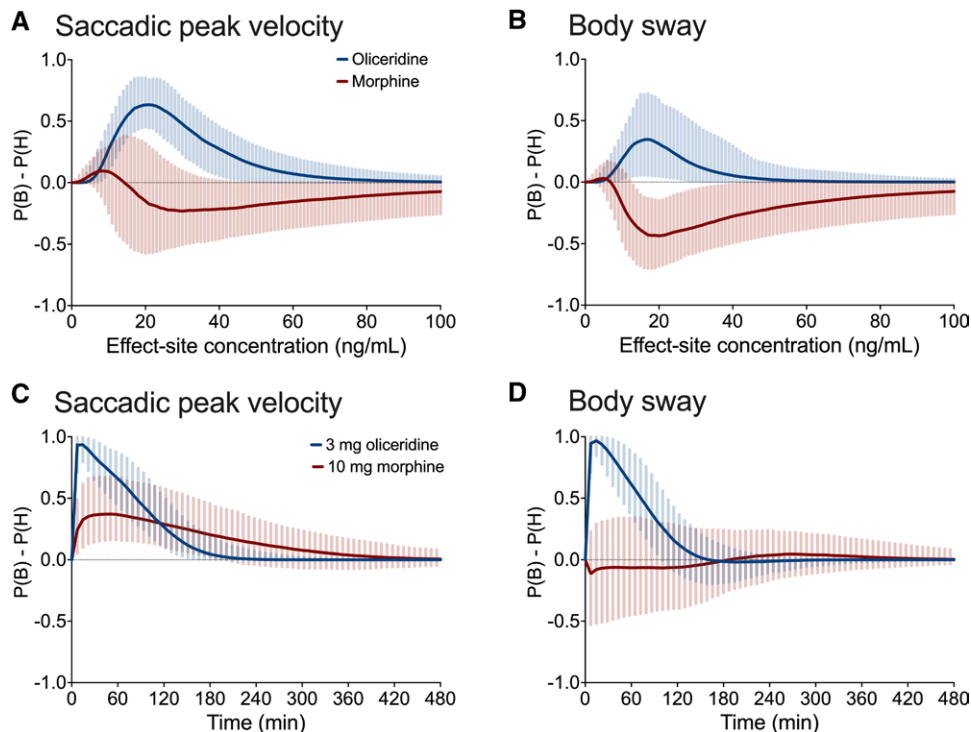
Table 3. Subject Demographics

Characteristic	Randomized Population (n = 23)
Sex	
Female	10
Male	13
Race	
Native American	1
African American	1
Other	2
White	19
Age, yr*	32 ± 12 (19 to 53)
Weight, kg*	73 ± 13 (55 to 105)
Body mass index, kg/m²*	23 ± 3 (20 to 28)

*Mean ± SD (range).

Fig. 1. Utility P(B) – P(H). Shown are the oliceridine (*blue lines*) and morphine (*red lines*) utility functions ± 95% CI for U_1 = P(B) – P(H), where B = benefit (pain relief from cold pressor test), and H = harm as function of effect-site concentration (C_E) or time *t*. (*A*) $U_1(C_E)$, where H = saccadic peak velocity. (*B*) $U_1(C_E)$, where H = body sway. (*C*) $U_1(t)$, where H = saccadic peak velocity, after 3 mg oliceridine or 10 mg morphine. (*D*) $U_1(t)$, where H = body sway, after 3 mg oliceridine or 10 mg morphine.
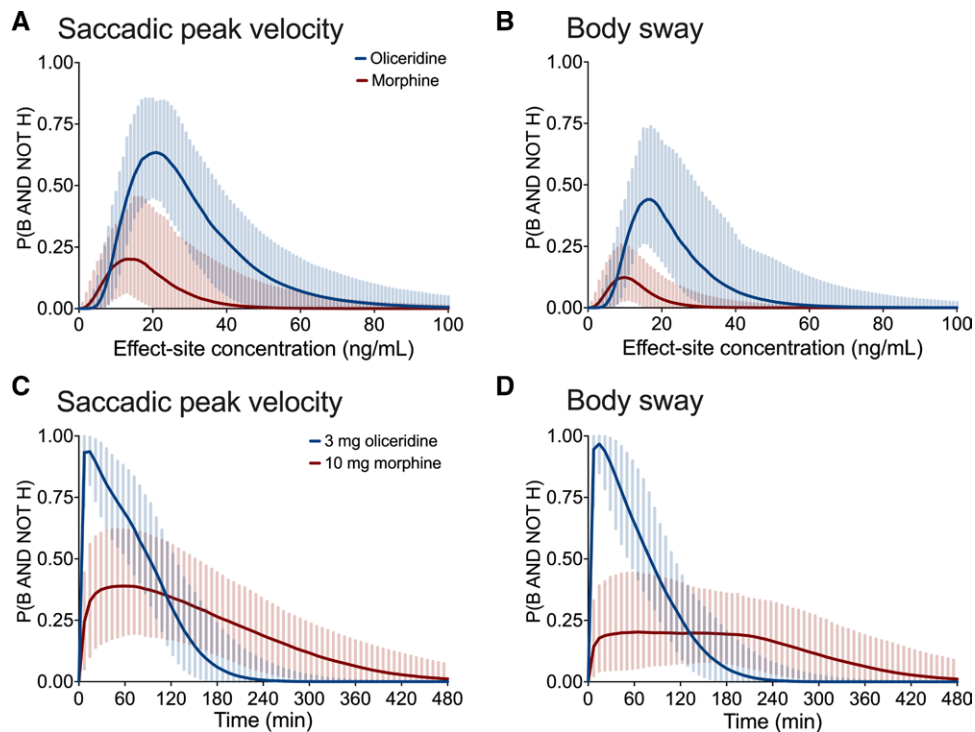
Fig. 2. Utility P(B AND NOT H). Shown are the oliceridine (*blue lines*) and morphine (*red lines*) utility functions ± 95% CI for U_2 = P(B AND NOT H), where B = benefit (pain relief from cold pressor test), and H = harm as function of effect-site concentration (C_E) or time *t*. (*A*) $U_2(C_E)$, where H = saccadic peak velocity. (*B*) $U_2(C_E)$, where H = body sway. (*C*) $U_2(t)$, where H = saccadic peak velocity, after 3 mg oliceridine or 10 mg morphine. (*D*) $U_2(t)$, where H = body sway, after 3 mg oliceridine or 10 mg morphine.

an opioid for clinical use. The difficulty lies in determining the most appropriate opioid for specific objectives, such as managing postoperative pain.

Neurocognitive Tests

In our current study, our primary aim was to compare the negative impact on neurocognitive functions caused by oliceridine and morphine. To that end, we used two measurements from the NeuroCart neurocognitive test battery,[16] which provides objective neurophysiologic and subjective evaluations (such as memory and mood) of neurocognition. Specifically, our focus was on two objective measures of central nervous system function, *i.e.,* saccadic peak velocity and body sway, which we consider pertinent to the postoperative period. Previous studies on the effects of the benzodiazepines on saccadic peak velocity revealed significant linear relationships between drug concentration and effect, although considerable interindividual differences were observed in the magnitude of the concentration–response slope.[17,24] After administration of temazepam, no correlations were observed between the slopes of the concentration–effect curves for subjective scores of alertness and saccadic peak velocity,[17] while after diazepam, peak saccadic velocity changes correlated with decreases in plasma

cortisol levels.[24] These findings suggest that saccadic peak velocity serves as a reliable and objective measure to track the level of sedation. Brain areas involved in the saccadic peak velocity include the superior colliculus, substantia nigra, and amygdala.[16] We consider body sway a measure of balance, motor stability, and postural control, with the cerebellum and brainstem implicated in this measure.[16,25]

Oliceridine *versus* Morphine

Our pharmacodynamic analyses showed that the oliceridine and morphine C_{50} values for saccadic peak velocity were greater than those for antinociception: oliceridine, 90 ± 14 ng/ml (saccadic peak velocity) *versus* 12 ± 2 ng/ml (antinociception); and morphine, 54 ± 15 ng/ml (saccadic peak velocity) *versus* 23 ± 7 ng/ml (antinociception; table 1). Since both opioids are used to manage pain, a combined analysis giving their utility is needed to understand efficacy and safety of these treatments. Here, we present two such analyses. First, we calculated the oliceridine/morphine therapeutic index ratio, which strongly favored oliceridine for both neurocognitive endpoints (ratio values, 0.33 to 0.34; *P* < 0.01). The therapeutic index represents the ratio at which 50% effect is achieved and does not consider other parts of the concentration–effect curves.[26] As desired and adverse

effects often originate from different brain areas, their concentration–effect relationships may diverge significantly.[26] To address this concern, we calculated the difference in predicted probabilities for benefit and harm across a wide concentration range (U_1). Ultimately, a therapeutic index must align with the utility, as they did in our study, but the utility is more broadly applicable. It offers the utility across a range of concentrations and allows assessment of a variety of functions, such as P(B AND NOT H), which indicates the probability of desired effect without any accompanying harm.[27] In summary, our results indicate that oliceridine is a relatively more potent analgesic than morphine (as based on comparison of C_{50} values) and exhibits a reduced adverse effect profile on neurocognition compared to morphine.

Comparison with the Literature

Our current results agree well with earlier analyses performed by us.[7,8] For example, we analyzed data from a study that compared antinociceptive (cold pressor test) and respiratory (isohypercapnic ventilation) responses from 30 healthy volunteers who had similar characteristics to those enrolled in the current study, after receiving intravenous oliceridine doses (1.5, 3, and 4.5 mg) and morphine (10 mg).[7] U_1 utility functions as functions of drug concentrations were constructed. The results were consistent with our current observations (fig. 1, A and B). However, in the current study, we noticed greater variability in the morphine U_1 for both neurocognitive endpoints and in the oliceridine U_1 for body sway. In a separate study,[8] we determined the C_{50} for respiratory depression from oliceridine and morphine in an elderly population ranging from 55 to 89 yr old. We observed an oliceridine/morphine ratio of 0.70, which corresponds well to values observed in this study for peak saccadic velocity (0.60) and body sway (0.56). Combined, these earlier and current data strongly suggest that the likelihood of benefit after oliceridine treatment outweighs that of harm when considering pain relief, as well as neurocognitive and respiratory effects. The opposite is true for morphine.

Mechanism

While our study was not designed to uncover underlying mechanisms, it is worth discussing potential reasons for the observed differences in drug effect.

(1) *Difference in bias toward the β-arrestin protein pathway.* Morphine and oliceridine are both μ-opioid receptor agonists, but, unlike morphine, oliceridine possesses a bias toward G-protein signaling with reduced β-arrestin recruitment and receptor internalization.[5,6] The G-protein system is predominantly (but not exclusively) associated with analgesia, and the β-arrestin system is associated with opioid-related adverse events.[28] Although involvement of the β-arrestin protein in effects of opioids on neurocognitive function is theoretically possible, we found no evidence in the literature of such effects in young and healthy individuals. Furthermore, while β-arrestin expression is reduced in the aging brain, and β-arrestin gene overexpression is detected in age-related neurodegenerative disorders, these long-term changes do not reflect the acute effects induced by the two opioids in our study.[29,30] Therefore, no conclusions can be drawn regarding the potential positive or negative effect of β-arrestin activity on opioid-induced neurocognitive defects.

(2) *Toll-like receptor 4 (TLR4).* Apart from their effects on opioid receptors, opioids can interact with other receptors or neurotransmitter systems, leading to diverse physiologic effects. One such off-target interaction is with TLR4.[14,31–33] Opioids, particularly morphine, may cause the release of proinflammatory mediators from microglia cells through the activation of TLR4 expressed on these cells. Morphine-induced neuroinflammation is associated with effects that oppose the opioid system, such as hyperalgesia and tolerance, and possibly even cause opioid-induced respiratory depression.[14,31,33] Additionally, neurocognitive defects may arise from neuroinflammation and TLR4 activation.[14,33] Morphine, but not oliceridine, increases spinal expression of TLR4 in rats after surgery,[34] suggesting that oliceridine may induce less neuroinflammation and subsequently fewer neurocognitive defects.

It is important to note that the specific mechanisms underlying the observed differences require further research and investigation to gain a comprehensive understanding of the contrasting effects between oliceridine and morphine.

Study Limitations

We acknowledge that our analyses are on just two of the eight neurocognitive tests performed in this study.[16] We *a priori* carefully selected the most relevant endpoints for our purposes, aiming to obtain indications of drug effect on neurocognition specifically relevant to the postoperative period. The two tests we analyzed, saccadic peak velocity (the primary endpoint of the study) as an index of sedation and body sway as an index of balance motor stability, provided similar results in terms of divergence between oliceridine and morphine on neurocognition. A final limitation may be that since tests were performed repetitively; one test may have influenced the other test, although we did not observe any indication for that in previous studies with the same tests.[35] In addition, as all neurocognitive tests (except the first postdose saccadic eye movement) were performed at least 30 min after the pain tests, such influences (if present) were assumed to be minimal.

Conclusions

Our analyses indicate that the biased ligand oliceridine has a superior utility on neurocognitive outcomes compared

to morphine. This was true for peak saccadic velocity and body sway. The current findings agree with earlier data on respiratory depression and highlight the potential advantages of oliceridine over morphine in terms of safety and neurocognitive effects. Further research is warranted to delve deeper into the underlying mechanisms and validate our conclusions.

Research Support

Competing Interests

Dr. Demitrack and Ms. Kim are employees of Trevena Inc. (Chesterbrook, Pennsylvania). Dr. Dahan received funding from the Dutch Research Council (The Hague, The Netherlands) in the framework of the Nederlandse Wetenschapsagenda- onderzoek op routes door consortia (NWA-ORC) Call for research project TAPTOE, Tackling and Preventing the Opioid Epidemic (NWA.1160.18.300) and awards and grants from the U.S. Food and Drug Administration (Silver Spring, Maryland). Dr. Dahan received consultancy fees from Trevena Inc. and Enalare Therapeutics Inc. (Princeton, New Jersey) and holds Enalare stock options. The other authors declare no competing interests.

Reproducible Science

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

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Supplemental Digital Content

Supplemental document 1. Inclusion and exclusion criteria, https://links.lww.com/ALN/D300.
Supplemental document 2. Methods and utility functions, https://links.lww.com/ALN/D301.
Supplemental document 3. Supplemental figures 1 to 4, https://links.lww.com/ALN/D302.

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