Oral oxycodone-induced respiratory depression during normocapnia and hypercapnia: a pharmacokinetic-pharmacodynamic modeling study

Hellinga, M.; Algera, M.H.; Olofsen, E.; Schrier, R. van der; Sarton, E.; Velzen, M. van; ... ; Niesters, M.

Oral Oxycodone-Induced Respiratory Depression During Normocapnia and Hypercapnia: A Pharmacokinetic-Pharmacodynamic Modeling Study

Marieke Hellinga[1], Marijke Hyke Algera[1], Erik Olofsen[1], Rutger van der Schrier[1], Elise Sarton[1], Monique van Velzen[1], Albert Dahan[1,2,*] and Marieke Niesters[1]

The widely prescribed opioid oxycodone may cause lethal respiratory depression. We compared the effects of oxycodone on breathing and antinociception in healthy young volunteers. After pharmacokinetic/pharmacodynamic (PK/PD) modeling, we constructed utility functions to combine the wanted and unwanted end points into a single function. We hypothesized that the function would be predominantly negative over the tested oxycodone concentration range. Twenty-four male and female volunteers received 20 (*n* = 12) or 40 (*n* = 12) mg oral oxycodone immediate-release tablets. Hypercapnic ventilatory responses (visit 1) or responses to 3 nociceptive assays (pain pressure, electrical, and thermal tests; visit 2) were measured at regular intervals for 7 hours. the PK/PD analyses, that included carbon dioxide kinetics, stood at the basis of the utility function: probability of antinociception minus probability of respiratory depression. Oxycodone had rapid onset/offset times (30–40 minutes) with potency values (effect-site concentration causing 50% of effect) ranging from 0.05 to 0.13 ng/mL for respiratory variables obtained at hypercapnia and antinociceptive responses. Ventilation at an extrapolated end-tidal carbon dioxide partial pressure of 55 mmHg, was used for creation of 3 utility functions, one for each of the nociceptive tests. Contrary to expectation, the utility functions were close to zero or positive over the clinical oxycodone concentration range. The similar or better likelihood for antinociception relative to respiratory depression may be related to oxycodone's receptor activation profile or to is high likeability that possibly alters the modulation of nociceptive input. Oxycodone differs from other μ-opioids, such as fentanyl, that have a consistent negative utility.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Consumption of high-dose or potent opioids may cause life-threatening respiratory depression. The contrasting respiratory and analgesic pharmacodynamics of the popular opioid oxycodone is unknown.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ To address oxycodone respiratory and analgesic pharmacodynamics (PDs) in humans, we performed a pharmacokinetic/PD modeling study on these two end points and constructed utility functions that combine the contrasting opioid effects into a single function by calculating probability of analgesia minus probability of respiratory depression as a function of oxycodone concentration.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ We show that oxycodone is a potent respiratory depressant, but its likelihood for antinociception is equal or possibly somewhat greater than that for respiratory depression, causing utility functions that are close to zero or positive.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Utility function analysis can be used in comparative opioid pharmacology to detect the opioid with the least respiratory effects for a certain degree of analgesia.

The μ-opioid receptor agonist oxycodone is a widely used opioid analgesic because of its high effectiveness in relieving pain. Most physicians are aware of the many side effects that all opioids possess, most important likability, which carries the risk for dependence, and respiratory depression with the potential risk of cardiorespiratory collapse and death. Still, different opioids might

[1]Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands; [2]PainLess Foundation, Leiden, The Netherlands.
*Correspondence: Albert Dahan (a.dahan@lumc.nl)

WHO International Clinical Trials Registry Platform https://trialsearch.who.int; identifier NTR7696; date: December 31, 2018.
Received December 16, 2022; accepted January 31, 2023. doi:10.1002/cpt.2863

vary in effectiveness and adverse effects profile, due to differences in pharmacokinetic (PK; including receptor kinetics) and pharmacodynamic (PD) properties.[1] Few studies examined the respiratory effects of oxycodone and there are no modeling studies that compared the analgesic vs. respiratory depressant effects of oxycodone. PK/PD studies that consider both end points will give an indication of the opioid utility in the treatment of pain.[2–7] It enables optimizing the dose that is associated with the likelihood of high efficacy and low toxicity. Additionally, such analyses will allow comparison among opioids and may help in the selection of specific opioids for treatment of pain, rather than relying on intuition and/or trial-and-error when choosing an opioid.[7]

In this study, we evaluated the effect of two oral oxycodone doses (20 and 40 mg immediate-release tablets) on ventilatory control (by measuring the hypercapnic ventilatory response) and three nociceptive assays (pressure pain, electrical pain, and thermal pain) in a group of healthy young male and female volunteers. Respiratory and nociceptive data were analyzed by population PK/PD modeling. In the analysis of respiratory data, we simultaneously analyzed baseline data (prior to the inhalation of carbon dioxide) and the hypercapnic ventilatory response.[3,8] The PK/PD parameter estimates and their variability served as basis of the construction of safety or utility functions, which gives the difference in probability of benefit and probability of harm from opioid treatment.[2–7] We hypothesized that oxycodone has a predominantly negative utility (i.e., that the probability of respiratory depression exceeds the probability of antinociception).

METHODS

Ethics

This study was a single-center, randomized study conducted at the Leiden University Medical Center from January 2019 to October 2020, and was approved by the local institutional review board. The study was registered at the World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int), under identifier NTR7696 (December 31, 2018). Prior to enrollment all subjects were informed on the nature and risks of the study and all signed a consent form indicating that they understood the potential risks involved and indicated their willingness to participate.

Participants

Twenty-four healthy volunteers of either sex, aged 18–33 years, with a body mass index < 30 kg/m^2 were enrolled in the study. Exclusion criteria were any psychiatric, neurologic, or medical condition (current or in the past), a history of illicit drug use, excessive alcohol use (> 21 units/week), known allergies to study medication, participation in another trial in 3 months before enrollment, regular use of any medication (except oral contraceptives in women), pregnancy, or lactation. Upon arrival at the laboratory, the urine drug screen and a urine pregnancy test (female subjects) and an alcohol breath test were performed. Subjects were excluded if any of these tests were positive. An arterial line was placed in the radial artery of the left or right arm for blood sampling. In case a subject dropped out for any reason, he or she was replaced by another subject.

Study design: Treatment

Subjects were randomized to a low or a high dose regimen. In the low-dose regimen, a single oxycodone immediate-release 20 mg capsule was studied, in the high-dose regimen, a single oxycodone immediate-release 40 mg capsule (Mundipharma Pharmaceuticals BV, Hoevelaken, The Netherlands). All subjects were tested twice, on visit 1, ventilation was measured, and on visit 2, nociception was measured. The study drug was ingested with 100 mL non-carbonated water. Oxycodone tablets were ingested after baseline measurements were completed. To minimize the risk of nausea, all subjects received intravenous ondansetron 4 mg before dosing. Throughout the study, monitoring of oxygen saturation (SpO_2), the electrocardiogram, and noninvasive blood pressure was conducted. Between study visits, there was a washout period of at least 1 week.

Study design: Measurements

Respiratory study. On visit 1, the following respiratory variables were obtained on a breath-to-breath basis for analysis: inspired carbon dioxide partial pressure, end-tidal partial carbon dioxide pressure ($P_{ET}CO_2$), and minute ventilation ($\dot{V}_E$). Prior to oxycodone administration and at 1-hour intervals, we obtained the hypercapnic ventilatory response (HCVR) using the dynamic end-tidal forcing technique.[9] A total of eight responses were obtained on each study day. The hypercapnic ventilatory test in this study consisted of an initial 4–6 minutes of breathing of a normoxic gas mixture with end-tidal oxygen partial pressure ($P_{ET}O_2$) of 13.5 kPa (101 mmHg) without any added inspired carbon dioxide. This was followed by 3–4 stepwise increases in $P_{ET}CO_2$: the first was a step in $P_{ET}CO_2$ of 0.6 kPa (4.5 mmHg) above resting $P_{ET}CO_2$; subsequent steps were 1.2 kPa (9 mmHg), 1.8 kPa (13.5 mmHg), and 2.4 kPa (18 mmHg) above resting $P_{ET}CO_2$. Each step lasted 6–8 minutes depending on the ventilatory response. Only when ventilation had reached a steady-state for at least 2 minutes, a next step was initiated or, after the last step, the hypercapnic ventilatory test ended and the subjects breathed room air until the next HCVR. If, during room air breathing, the subject desaturated to SpO_2 values of 90% or lower, the subject was verbally stimulated to breathe until SpO_2 reached values of 94% or higher. Stimulation, desaturation, and the occurrence of apneic episodes were noted, with apnea defined by the loss of respiratory activity for at least 20 seconds.

To obtain the HCVR, the subjects breathed through a face mask placed over the mouth and nose that was connected to a pneumotachograph and pressure transducer system (Hans Rudolph) to measure minute ventilation.[9,10] Oxygen, carbon dioxide, and nitrogen were delivered to the subject through three mass flow controllers (Bronkhorst Nederland BV, Veenendaal, The Netherlands). These mass flow controllers were controlled by a computer running custom-made software (RESREG/ACQ; Leiden University) enabling variations in inspired gas concentrations to achieve the desired $P_{ET}CO_2$ and $P_{ET}O_2$ values, independent of the ventilatory response or venous return.

Nociceptive assays. On visit 2, three nociceptive tests were applied, prior to dosing and at 40-minute intervals after dosing (last test 7 hours after dosing):

A *Pressure pain test*. An algometer (FDN 100/FDN200; Wagner Instruments) was used to deliver pressure to the dorsal skin area (1 cm^2) between the thumb and index finger. A gradually increasing pressure was applied manually and subjects were asked to indicate when the procedure became painful (pressure pain threshold). Prior to dosing, the test was performed 9 times, at least 20 minutes apart; after dosing, the measurements were performed in triplicate and averaged.

B *Electrical pain test*. A custom-made computer interfaced constant current stimulator (Leiden University) was used to deliver transcutaneous electrical stimulation through 2 surface electrodes 1.5 cm apart attached to the skin covering left tibial bone. Initially, the current that evoked a score of 8 on a 10 cm paper visual analog scale (VAS) was determined. The subject was instructed that 0 equaled no pain and 10 cm equaled the most severe pain. The electrical current evoking a VAS score of 8 was used for the remainder of the study. Prior to dosing, the test was repeated until the subject

consistently scored a VAS of 8 ± 0.5 cm. Following dosing, each test was conducted in duplicate and the data were averaged for analysis.

C *Thermal pain*. A 3 × 3 cm thermal probe connected to the Pathway Neurosensory analyzer (Medoc, Israel) delivered a heat pain stimulus to the volar side of the arm. The subject scored the level of pain intensity using a computerized visual analog scale (coVAS), which ranged from 0 (no pain) to 10 cm (most severe pain). Prior to dosing, the temperature evoking a coVAS of 8 ± 0.5 cm was determined by applying a train of stimuli starting at 40°C in steps of ± 0.5°C. The test was repeated until the subject consistently scored a coVAS of 8 ± 0.5°C. That temperature was used in the remainder of the study. Following dosing, each test was conducted in duplicate and the data were averaged for analysis. To overcome sensitization, the thermal probe was moved across three different zones on the arm.

We use the term antinociception because, in our study, painful stimuli were applied in a population that was without any pain symptoms or painful syndromes.

Blood sampling and oxycodone analysis. Blood samples were drawn from the arterial line for measurement of the oxycodone plasma concentrations. A 4 mL blood sample was drawn before dosing and at 1-hour intervals for 7 hours. The samples were analyzed by Ardena Bioanalytical Laboratory (Assen, The Netherlands). Oxycodone concentrations were measured with liquid-chromatography tandem mass spectrometry methods validated over a range of 0.2–200 ng/mL. All samples were measured in one batch. Accuracy of the standards ranged from 99% to 109%, bias from −1.5 to 3%, and coefficient of variation from 3 to 10%.

Sample size and main end points

In this PK/PD modeling study, there was no need for creating a contrast between treatments. We therefore did not perform a formal power analysis but enrolled 24 subjects with 12 subjects per dose, which is in line with the number of subjects in recent PK/PD modeling studies.[2,3,8] The main end point of the study was the extrapolated ventilation at an $P_{ET}CO_2$ of 55 mmHg (7.3 kPa; $\dot{V}_E55$).[9–11] Secondary end points included the effect of oxycodone on the different components of the hypercapnic ventilatory response apart from $\dot{V}_E55$ (see **Figure 1**; parameters independent of CO_2 inhalation: baseline $\dot{V}_E$, baseline end-tidal PCO_2 and the ventilatory recruitment threshold (VRT); parameter dependent on inhaled CO_2: the slope of the HCVR) and the outcome of the 3 nociceptive tests. The data were modeled using a population PK/PD approach and the resulting models were used to construct utility functions.

Pharmacokinetic/pharmacodynamic data analyses

The PKs and PDs of oxycodone were analyzed with NONMEM VII (Icon Plc.), using a population approach.

Pharmacokinetics. The PK data were analyzed using a two-compartmental model. Parameter estimation was done using Stochastic Approximation Expectation Maximization, followed by objective function evaluation using Importance sampling. Rather than using an absorption compartment, we used the zero-order infusion duration for absorption of oxycodone from capsule to blood (D_1).

Pharmacodynamics: The hypercapnic ventilatory response. For ventilation, we performed a PK/PD analysis incorporating carbon dioxide PKs. To that end, we analyzed the complete curve of the HCVR including data obtained prior to adding inspired carbon dioxide to the gas inhaled gas mixture (**Figure 1**). The response was defined by the following parameters: $P_{ET}CO_2$ prior to any carbon dioxide inhalation (baseline $P_{ET}CO_2$), ventilation prior to any carbon dioxide inhalation (baseline $\dot{V}_E$), PCO_2 at the VRT, and the gain or slope of the HCVR (Slope). From the HCVR curve, we calculated $\dot{V}_E55$ at each hypercapnic response obtained over time. We defined the blood to effect-site equilibration half-time ($t_{½}\,k_{e0}$) to describe the hysteresis between blood concentration and effect, C_{50} or the effect-site concentration causing a 50% decline in effect, and $\dot{V}_E55$.

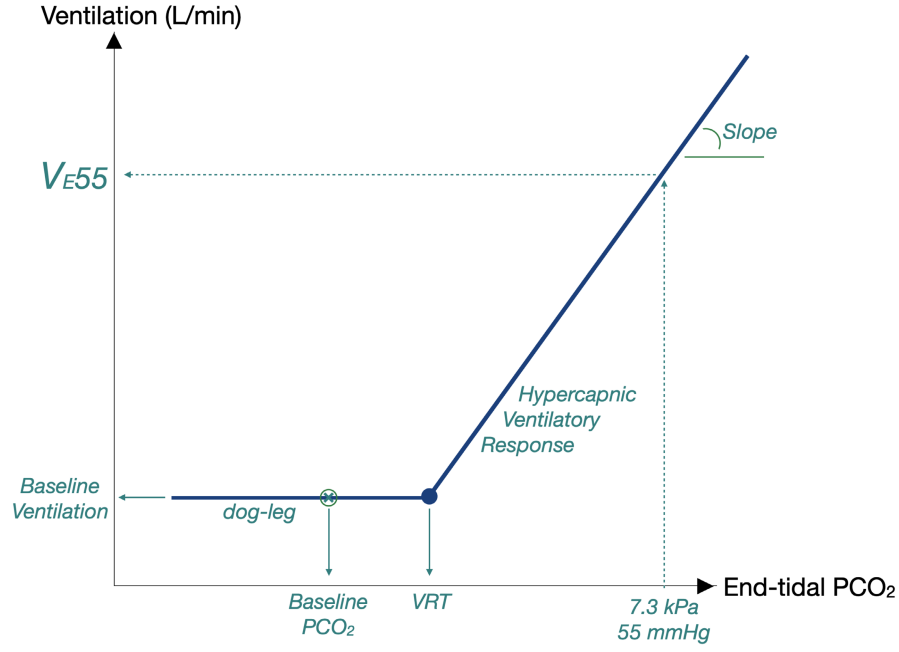

Figure 1 The ventilatory response to hypercapnia and the different components used in the data analysis. The dog-leg refers to the horizontal part of the curve, where PCO_2 has little or no effect on ventilation (also called "the wakefulness drive to breathe"), the ventilatory recruitment threshold (VRT) is the PCO_2 point at which CO_2 sensitivity sets. The gray circles symbolize end-tidal PCO_2 ($P_{ET}CO_2$) – ventilation ($\dot{V}_E$) measurements, the blue the fitted hypercapnic ventilatory response (HCVR) curve with a sensitivity defined by the value of the Slope. Baseline ventilation (baseline $\dot{V}_E$), baseline $P_{ET}CO_2$ and $\dot{V}_E$ at an extrapolated $P_{ET}CO_2$ of 55 mmHg (7.3 kPa) are shown as well.

Carbon dioxide pharmacokinetics.[8,12] The relationship between carbon dioxide content (C) and its partial pressure (P) was assumed to be linear, so that $P = \lambda_0 \times C$, where $\lambda_0 = 0.863$ mmHg/(mL CO_2 in 100 mL blood). The following mass balance equations were used for the lungs and body (approximating the body by one compartment):

$$V_{ALV} \bullet \frac{d\left(\text{arterial } P_{CO_2}\right)}{dt} = \left(\dot{V}_E - \dot{V}_D\right) \bullet \left(\text{inspired } P_{CO_2} - \text{arterial } P_{CO_2}\right) + \lambda_1 \bullet \dot{Q} \bullet \left(\text{venous } P_{CO_2} - \text{arterial } P_{CO_2}\right),$$

and

$$V_{TS} \bullet \frac{d\left(\text{venous } P_{CO_2}\right)}{dt} = \dot{Q} \bullet \left(\text{venous } P_{CO_2} - \text{arterial } P_{CO_2}\right) + \lambda_2 \bullet \dot{V}_{CO_2},$$

where V_{ALV} is the alveolar volume, arterial carbon dioxide pressure is assumed to equal alveolar pressure, $\dot{V}_E$ minute ventilation, $\dot{V}_D$ dead space ventilation, $\dot{Q}$ cardiac output, V_{TS} the apparent tissue volume, $\dot{V}_{CO_2}$ the carbon dioxide production, $\lambda_1 = k \times P_{BW}/\lambda_0/100 \approx 10$ and $\lambda_2 = 100 \times \lambda_0$, where k = the volume conversion factor from standard temperature and pressure, dry to body temperature, and air saturated with water, and P_{BW} is the barometric pressure minus the pressure of air saturated with water. V_{ALV} was fixed to 3 L and $\dot{V}_D$ to 1.8 L/min.

Minute volume was assumed to depend on the effect-site or brain tissue carbon dioxide PCO_2 as:

$$\tau \bullet \frac{\text{brain tissue } P_{CO_2}}{dt} = \text{arterial } P_{CO_2} - \text{brain tissue } P_{CO_2}$$

$$\dot{V}_E = \text{baseline } \dot{V}_E + \text{Slope} \bullet H \bullet \left(\text{brain tissue } P_{CO_2} - \text{VRT}\right)$$

$$H(x) = \delta \bullet \log\left[1 + \exp\left(\frac{x}{\delta}\right)\right],$$

where τ is a time constant and H is the so-called "hinge" function (see https://statmodeling.stat.columbia.edu/2017/05/19/continuous-hinge-function-bayesian-modeling/) with δ fixed to 0.1; V_{TS}, $\dot{Q}$ and τ were parameters to be estimated. The parameters baseline $\dot{V}_E$, baseline PCO_2, VRT, and Slope were estimated for each of the respiratory responses separately, assuming only an inter-run variability; all the separate estimates of the parameters of the HCVR curve constitute the PD data for the next step. These steps were not combined to avoid extraordinary estimation run times. From the parameters of the HCVR curves, the $\dot{V}_E55$ was calculated as a measure of respiratory depression.

Pharmacodynamics: Antinociception. Antinociceptive responses were analyzed with sigmoid maximum effect (E_{max}) models with parameters baseline (measurement before drug administration), C_{50} (the reduction in VAS by 50% for electrical and thermal pain), and C_{100} (the increase in pain pressure threshold by a factor 2 for the pressure pain assay) and γ, a shape parameter.

Utility functions

For a detailed explanation of the step-by-step construction of the utility functions, see refs. 2-7. In brief, we performed 10,000 simulations for respiratory effect ($\dot{V}_E55$) and 10,000 for each of the 3 antinociceptive nociceptive responses using the typical PK/PD parameter estimates and their interindividual variances (ω^2) using NONMEM's simulation step. The occurrences of respiratory depression and antinociception were determined and divided by 10,000 to estimate these probabilities, as defined by specific thresholds with threshold for respiratory depression, a reduction in $\dot{V}_E55$ by at least 50% (respiratory depression ≥ 50%), and threshold for analgesia a change in antinociception by at least 25% (analgesia ≥ 25%). We then calculated the utility function (U) defined by:

$$U = \left[P\left(\text{analgesia}_x \geq 25\,\%\right) - P\left(\text{respiratory depression} \geq 50\,\%\right)\right]$$

with x one of the three antinociceptive outcomes and P probability. The utility functions are given as functions of the effect-site oxycodone concentration.

RESULTS

Twenty-four subjects (12 men and 12 women) indicated their interest in the study and all were enrolled and completed the study (see **Figure S1** for the consort flow diagram). Mean age of the subjects was 23 years (range 19–33 years) with body mass index 23.4 kg/m^2 (19.1–28.7 kg/m^2) and weight 74 kg (57–103 kg). In between respiratory and analgesic testing, 50% of subjects had at least one apneic episode (20 mg oxycodone 5 subjects and 40 mg oxycodone 7 subjects) causing desaturations SpO_2 < 92% in 4 (20 mg) and 7 subjects (40 mg). These subjects were stimulated to breathe and did not require supplemental oxygen.

Pharmacokinetics

Peak blood plasma concentrations for oxycodone 20 and 40 mg were 50 ± 15 ng/mL and 79 ± 27 ng/mL, respectively (see **Figure 2a**). PK parameter estimates were (see also **Figure S2** for interindividual and interoccasion variabilities): volume of compartment 1 = 37 ± 3 L, volume of compartment 2 = 411 ± 33 L, clearance = 76 ± 7 L/h, intercompartmental clearance = 510 ± 37 L/h, oxycodone absorption time from intake to blood (D_1) = 0.95 ± 0.01 hour, and residual error (σ^2) = 0.022 ± 0.002 (all values are typical value ± standard error of the estimate). Mean concentrations, individual data, population predicted data, and goodness of fit plots (individual predicted vs. measured, population predicted vs. measured, conditional weighted residuals vs. time, and normalized prediction discrepancy error vs. time) are given in **Figure 2**. These latter plots show that the two-compartment model adequately describes the PK data.

The hypercapnic ventilatory response

An example of data analysis of the HCVR of a single subject at baseline (before drug administration) is given in **Figure 3**. It shows inspired and end-tidal PCO_2 and predicted $P_{ET}CO_2$ and estimated effect site PCO_2 (**Figure 3a**), $\dot{V}_E$ vs. time and predicted $\dot{V}_E$ (**Figure 3b**), and the HCVR with measured data and predicted response curve (red line). Population parameter estimates are given in **Table 1**. The individual $\dot{V}_E55$ data and population predicted $\dot{V}_E$ 55 data for the 2 oxycodone doses together with the goodness of fit

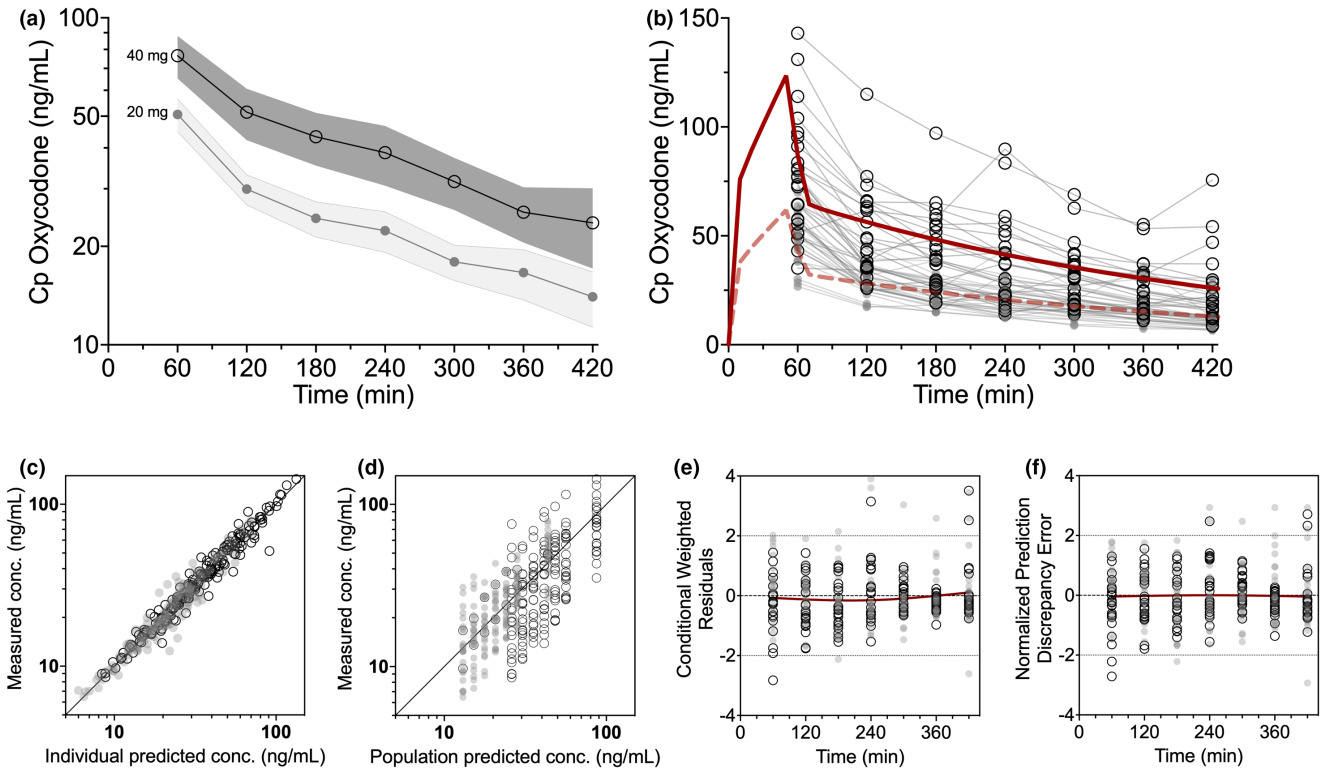

Figure 2 Pharmacokinetic data. (**a**) Mean plasma oxycodone concentrations ±95% confidence interval following low dose oxycodone intake (20 mg) and high dose intake (40 mg). (**b**) Individual measured plasma concentrations and population predicted values. 20 mg oxycodone: gray symbols and broken red line; 40 mg oxycodone: open symbols and continuous red line. (**c–f**) Goodness of fit plots of the pharmacokinetic data analyses: measured concentrations vs. individual predicted concentrations (**c**), measured concentrations vs. population predicted concentrations (**d**), conditional weighted residuals vs. time (**e**) and normalized prediction discrepancy errors vs. time (**f**). Gray symbols points: 20 mg oxycodone, open symbols: 40 mg oxycodone. Red lines are smoothed curves through the complete data sets.

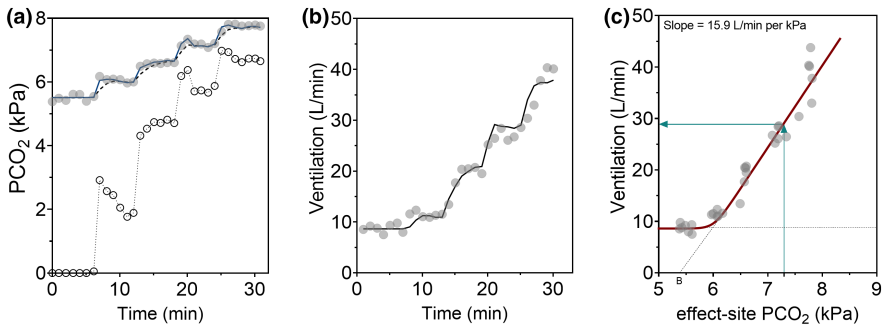

Figure 3 The ventilatory response to hypercapnia of a single subject prior to intake of 20 mg oxycodone (baseline response). (**a**) Inspired (open circles), end-tidal PCO_2 (closed gray circles), predicted end-tidal PCO_2 (continuous line), and estimated effect site PCO_2 (broken line). (**b**) Ventilation vs. time (closed gray circles) and predicted ventilation (continuous line). (**c**) The hypercapnic ventilatory response (closed gray circles, measured ventilation vs. effect-site PCO_2), and the predicted response curve (red continuous line). The green arrows indicate the determination of $\dot{V}_E55$ or ventilation at and extrapolated PCO_2 of 55 mmHg.

plots are given in **Figure 4**. These figures show that the PD model adequately describes the data. Parameter $\dot{V}_E55$ was most sensitive to the effects of oxycodone (C_{50} 0.05 ng/mL, $t½k_{e0}$ 0.7 hour), followed by parameter Slope (C_{50} 0.13 ng/mL, $t½k_{e0}$ 0.7 hour) and parameters that are independent of the inspired carbon dioxide challenge (baseline $\dot{V}_E$, baseline PCO_2 and VRT, analyzed together with C_{50} 0.33 ng/mL, $t½k_{e0}$ 1.9 hour). This indicates that $\dot{V}_E55$ and Slope are relatively faster affected by oral oxycodone, but also return faster to baseline than CO_2-independent parameters. V_{TS}, $\dot{Q}$, and τ ranged from 8–12 L, 3–5 L, and 2–3 minutes, respectively, between the 2 oxycodone doses.

Antinociceptive responses

The individual data obtained from the three nociceptive assays and population predicted data for the two oxycodone doses are given in **Figure S3**, and the goodness of fit plots in **Figure S4**.

Table 1 Pharmacodynamic parameter estimates

	Estimate ± SEE	ω^2 ± SEE
Baseline $\dot{V}_E$ (L/min)	8.0 ± 0.2	0.106 ± 0.006
Baseline $P_{ET}CO_2$ (kPa)	5.3 ± 0.11	0.009 ± 0.003
Baseline VRT (kPa)	5.8 ± 0.1	0.007 ± 0.002
Slope at baseline (L/min/kPa)	16.6 ± 1.5	0.120 ± 0.0 = 49
$\dot{V}_E$55 at baseline (L/min)	32.3 ± 2.8	0.168 ± 0.055
$t½k_{e0}$ {baseline $\dot{V}_E/P_{ET}CO_2$/ VRT} (h)	1.9 ± 0.3	–
C_{50}{baseline $\dot{V}_E/P_{ET}CO_2$/ VRT} (ng/mL)	0.33 ± 0.05	0.12 ± 0.07
$t½k_{e0}$ Slope (h)	0.7 ± 0.2	–
C_{50} Slope (ng/mL)	0.13 ± 0.06	0.749 ± 0.432
$t½k_{e0}$ $\dot{V}_E$55 (h)	0.7 ± 0.1	–
C_{50} $\dot{V}_E$55 (ng/mL)	0.05 ± 0.01	0.248 ± 0.092
Within-subject variability		
σ^2 $\dot{V}_E$ at baseline	0.206 ± 0.024	
σ^2 $P_{ET}CO_2$ at baseline	0.114 ± 0.013	
σ^2 VRT	0.089 ± 0.010	
σ^2 Slope	17.2 ± 2.0	
σ^2 $\dot{V}_E$55	14.8 ± 1.7	

σ^2, measure of residual variability; Baseline, indicates parameter values prior to any oxycodone administration; SEE, standard error of the estimate; Slope, the slope of the hypercapnic ventilatory response; $t½k_{e0}$, the blood to effect-site equilibration half-time; $\dot{V}_E$, minute ventilation; VRT, carbon dioxide partial pressure at the ventilatory recruitment threshold; ω^2, inter-subject variability. The {} indicates that the parameter estimate relates to the combined parameter values within the parentheses.

These analyses show that the nociceptive PD models adequately describe the data. Parameter estimates are given in **Table 2**. Oxycodone had a similar effect on the 3 nociceptive assays, with potency parameters in the same order of magnitude and onset/off-set times ($t½k_{e0}$) about 30 minutes.

Utility functions

The utility functions, *P*(analgesia ≥ 25%) – *P*(respiratory depression ≥ 50%), for the three nociceptive assays and $\dot{V}_E$55 are given in **Figure 5**. The best performance was observed for pressure pain with peak utility value of 0.42 at 0.04 ng/mL, followed by electrical pain with a peak utility value of 0.16 at 0.02 ng/mL. The thermal pain U remained close to zero over the effect-site concentration range tested (0–1 ng/mL).

DISCUSSION

The main finding of the PK/PD analyses of the respiratory and antinociceptive behavior of oxycodone is that, whereas oxycodone is a potent respiratory depressant, its likelihood for antinociception is equal or possibly somewhat greater than that for respiratory depression. This causes utility functions that are close to zero or positive over the concentration range tested. As a result, we reject the hypothesis that oxycodone's utility function is negative.[11]

In contrast to prior PK/PD studies, we considered the complete HCVR, including baseline data and the length of the dogleg, in our analysis (**Figure 1**). The analyses revealed that baseline variables were less responsive to oxycodone than the gain or slope of the hypercapnic ventilatory response (C_{50} values 0.33 vs. 0.13 ng/mL), whereas $\dot{V}_E$55 was most sensitive (C_{50} = 0.05 ng/mL). In other words, the oxycodone potency varies depending on whatever component of ventilatory control is evaluated (potency $\dot{V}_E$55, Slope, baseline variables = 1.0, 0.4, 0.2). This is not surprising because baseline data interact in such a way that when oxycodone decreases baseline ventilation, the subsequent increase in baseline PCO_2 will raise ventilation. A new steady-state develops, in which baseline ventilation is just minimally altered compared to its pre-drug value. Hence, studies that just consider baseline data will estimate high values for C_{50}. For example, Mildh *et al.*[13] estimated C_{50}-values for fentanyl of 5 ng/mL, whereas analysis of isohypercapnic ventilation results in a lower C_{50} (1 ng/mL),[2] one-fifth of the potency of that observed by Mildh *et al*. The finding that baseline respiration is less sensitive to oxycodone did not prevent the occurrence of apnea and desaturations, observed in half of the subjects. This shows that the ventilatory control system remains vulnerable following oxycodone intake, despite a maintained level of baseline ventilation. Onset/offset times for Slope and $\dot{V}_E$55 were 40 minutes, whereas CO_2-indpendent variables responded more slowly, 1.9 hours, probably related to the counteracting effects of baseline ventilation and baseline PCO_2 as discussed above.

Although several studies showed the respiratory depressant effects of oxycodone,[9–11] earlier PK/PD studies explored various non-respiratory end points, but comparison with our results is difficult because of differences in administration modes, sample sites, PD models, and study populations.[14–19] In common with our findings, these PK/PD studies showed rapid effects occurring following oxycodone administration, with onset delays of 10–20 minutes.

We constructed the utility function *U* = *P*(analgesia) – *P*(respiratory depression), which combines the contrasting opioid effects into a single function. We included two end points, respiratory depression and antinociception, but also other end points may be chosen and in fact utilities constructed from more than two end points are possible. A major advantage of the utility function is that in comparative pharmacology, it allows identification of opioids with superior utilities. When comparing utilities, it is imperative to compare utilities derived from similar metrics (e.g., isohypercapnic ventilation and pressure pain threshold), in comparable populations. To be certain of similar conditions, we routinely conduct our studies in similar and well-defined populations, using sensitive nociceptive assays.

When comparing utilities among μ-opioids (considering similarities in outcomes and study populations), the performance of oxycodone was superior to that of fentanyl but inferior to that of two other, unfamiliar μ-opioids, cebranopadol and R-dihydroetorphine.[2,3,5] In all of these studies, isohypercapnic ventilation and electrical pain were used as input to the utility functions. Whereas we evaluated additional μ-opioids, such as oliceridine (Olinvyk) and morphine,[6] the end points in these studies were dissimilar to those used in the current study, but within study comparison remains possible: the oliceridine utility was positive, and that of morphine negative. It is worthwhile to briefly discuss the likely explanations for the differences among the utility of the various μ-opioids. These differences are evidently related to differences in the

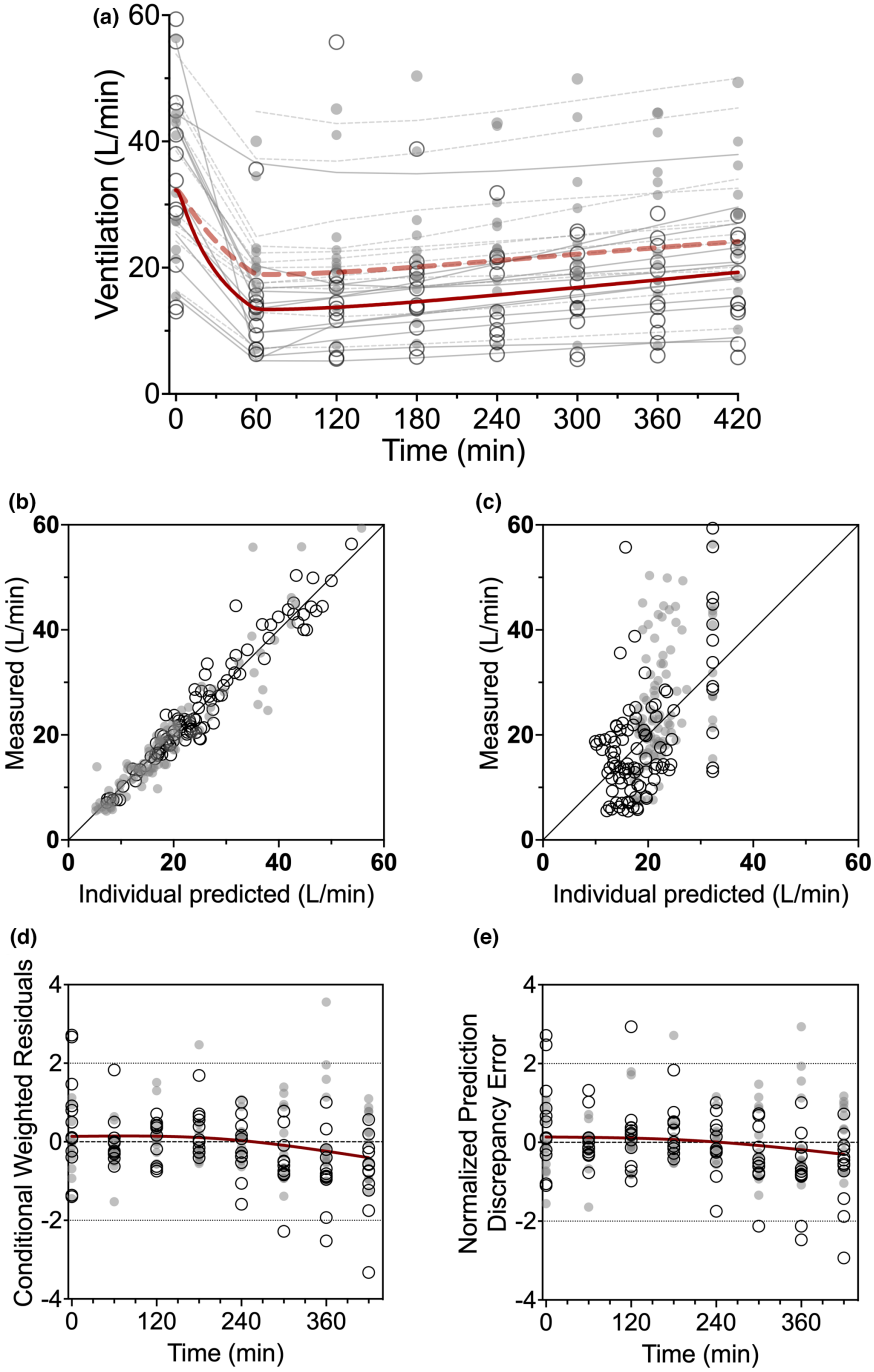

Figure 4 (**a**) Individual measured $\dot{V}_E55$ values, individual data fits and population predicted $\dot{V}_E55$ values. 20 mg oxycodone: gray symbols (measured data), gray broken lines (individual data fits) and broken red line (population predicted); 40 mg oxycodone: open symbols (measured data), gray continuous lines (individual data fits) and dark red line (population predicted). (**b–e**) Goodness of fit plots of the pharmacodynamic data analyses: measured concentrations vs. individual predicted concentrations (**b**), measured concentrations vs. population predicted concentrations (**c**), conditional weighted residuals vs. time (**d**) and normalized prediction discrepancy errors vs. time (**e**). Red lines are smoothed curves through the complete data sets.

building blocks of the utility function, whereas from a mechanistic point of view, differences may be related to factors such as (i) full vs. partial μ-opioid receptor agonism, (ii) co-activation of κ-, *δ*-, and/or nociceptin-opioid receptors, and (iii) differential intracellular signal transduction pathway activation. To summarize:

1. Buprenorphine is an opioid with μ-opioid receptor partial agonism for respiratory depression but not for analgesia, at least not over the clinical concentration range.[20] We previously constructed the buprenorphine utility function using rat data, which was overtly positive, but never reproduced, such an analysis with human data.[21] We do anticipate, however, a similar positive function in humans as well.

Table 2 Antinociceptive pharmacokinetic/pharmacodynamic parameter estimates

Parameter	Estimate ± SEE	ω^2 ± SEE
	Electrical pain	
Visual analogue scale at baseline (cm)	8.1 ± 0.1	0 ± 0
$t½k_{e0}$ (h)	0.52 ± 0.12	0.61 ± 0.40
C_{50} (ng/mL)	0.10 ± 0.02	0.38 ± 0.17
γ	1.8 ± 0.3	0.41 ± 0.19
σ^2	0.33 ± 0.03	
	Thermal pain	
Visual analogue scale at baseline (cm)	8.1 ± 0.1	0 ± 0
$t½k_{e0}$ (h)	0.53 ± 0.10	0.32 ± 0.20
C_{50} (ng/mL)	0.08 ± 0.01	0.19 ± 0.10
γ	3.0 ± 0.6	0.33 ± 0.17
σ^2	4.0 ± 0.4	
	Pressure pain threshold	
Baseline pressure (N)	56 ± 4	0.09 ± 0.02
$t½k_{e0}$ (h)	0.51 ± 0.07	0.27 ± 0.12
C_{100} (ng/mL)	0.08 ± 0.01	0.11 ± 0.05
γ	1.5 ± 0.1	0 ± 0
σ^2	38 ± 4	

Baseline is the pain parameter prior to drug administration; C_{50}, the reduction in VAS by 50% for electrical and thermal pain; C_{100}, the increase in pain pressure threshold by a factor 2 for the pressure pain assay; γ, a shape parameter; $t½k_{e0}$, the blood to effect-site equilibration half-time; ω^2, inter-subject variability; σ^2, a measure of residual variability; SEE, standard error of the estimate

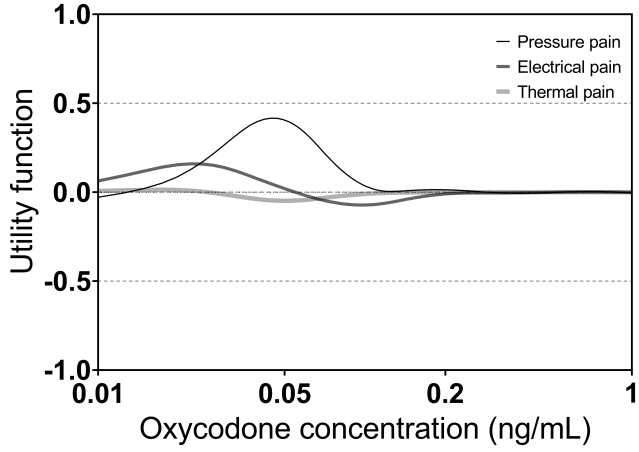

Figure 5 Utility functions, P(analgesia ≥25%) – P(respiratory depression ≥50%), of the three nociceptive assays as function of effect-site oxycodone concentration.

2. R-dihydroetorphine is a full agonist with high affinity for μ-, κ-, and δ-opioid receptors and low affinity for the nociceptin receptor.[5] Its positive utility function may be related to the respiratory protective effect exerted by κ- and δ-opioid receptor activation.[22,23] The full μ-opioid receptor agonist cebranopadol has a positive utility that may be related to its agonistic activity at the nociception-receptor, counteracting part of the respiratory depression from the μ-opioid agonism.[3]
3. Full μ-opioid receptor agonists like fentanyl and oxycodone engage two distinct intracellular transduction pathways, the G-protein–coupled signaling pathway and the β-arrestin pathway, with separate pharmacologic effects.[24] The former pathway is responsible for analgesia and reward, the latter for respiratory depression. Oliceridine is a so-called biased ligand that has a bias toward the G-protein pathway,[25] and is consequently associated with a positive utility function.[6]

The question that remains is why the full μ-opioid agonist oxycodone behaves so differently from fentanyl, which has a negative utility.[2] The evident differences in PKs and PDs play an important role, but there are animal data that suggest that oxycodone has dominant κ-agonistic activity,[26] although this is disputed.[27] Kappa-opioid receptor activation may cause respiratory protection and a shift in utility toward positive values.

Another issue is the concept of likability. Oxycodone is highly likeable, much more than other clinically used opioids.[28] We speculate that high likeability improves the patient's ability to suppress nociceptive stimuli. This may work similarly to the strategies in cognitive behavioral therapy, such as relaxation, stress management, pain avoidance learning, and pain extinction to subdue pain.[29,30] If so, the antinociceptive responses observed in this study will be greater than those observed for opioids with less likeability (and consequently will affect the utility). Irrespective, the combination of an opioid with high probability of respiratory depression is potentially perilous because it increases the likelihood of opioid-induced toxicity and eventually cardiorespiratory collapse.[28]

In conclusion, we conducted a population PK/PD study on the respiratory and antinociceptive effects of oral oxycodone and constructed utility functions and found that these functions were either close to zero or positive (for pressure pain threshold) in contrast to our *a priori* expectations of predominantly negative oxycodone utilities. Whether such differences are related to the κ-agonistic activity of oxycodone or to its likeability requires further study. Utility function analysis can be used in comparative opioid pharmacology and opioid development to detect the opioid with the least respiratory effects for a certain degree of analgesia.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

FUNDING

Support was provided from institutional and/or departmental sources and from Grünenthal GmbH, Aachen, Germany.

CONFLICT OF INTEREST

A.D. received consultancy and/or speaker fees from Grünenthal BV (The Netherlands), funding from the Dutch Research Council (NWO) in the framework of the NWA-ORC Call for research project TAPTOE, Tackling and preventing the opioid epidemic (NWA.1160.18.300), and from the US Food and Drug Administration. All other authors declared no competing interest for this work.

AUTHOR CONTRIBUTIONS

M.H., M.H.A., E.O., R.v.d.S., E.S., M.v.V., A.D., and M.N. wrote the manuscript. A.D., M.N., E.O., and R.v.S. designed the research. M.H.,

M.H.A., E.S., R.v.d.S., and M.v.V. performed the research. E.O., M.N., and A.D. analyzed the data.

1. Drewes, A.M. *et al*. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. *Br. J. Clin. Pharmacol.* **75**, 60–78 (2012).
2. Boom, M. *et al*. Fentanyl utility function: a risk-benefit composite of pain relief and breathing responses. *Anesthesiology* **119**, 663–664 (2013).
3. Dahan, A. *et al*. Respiratory effects of the nociceptin/orphanin FQ peptide and opioid receptor agonist, cebranopadol, in healthy human volunteers. *Anesthesiology* **126**, 697–707 (2017).
4. Roozekrans, M. *et al*. Benefit vs. severe side effects of opioid analgesia: novel utility functions of probability of analgesia and respiratory depression. *Anesthesiology* **128**, 932–942 (2018).
5. Olofsen, E. *et al*. Analgesic and respiratory depressant effects of R-dihydroetorphine: a pharmacokinetic-pharmacodynamic analysis in healthy male volunteers. *Anesthesiology* **131**, 1327–1339 (2019).
6. Dahan, A. *et al*. Benefit and risk evaluation of biased μ-receptor agonist oliceridine vs. morphine. *Anesthesiology* **133**, 559–568 (2020).
7. van Dam, J. *et al*. Opioid utility function: methods and implications. *Ann. Pall. Med.* **9**, 528–536 (2020).
8. Olofsen, E. *et al*. Modeling the non-steady-state respiratory effects of remifentanil in awake and propofol sedated healthy volunteers. *Anesthesiology* **212**, 1382–1395 (2010).
9. van der Schrier, R. *et al*. Influence of ethanol on oxycodone-induced respiratory depression: a dose-escalating study in young and elderly volunteers. *Anesthesiology* **126**, 534–542 (2017).
10. Florian, J. *et al*. Effect of paroxetine or quetiapine combined with oxycodone *vs* oxycodone alone on ventilation during hypercapnia: a randomized clinical trial. *JAMA* **328**, 140514 (2022).
11. van der Schrier, R. *et al*. An experimental study on the comparison of the respiratory effects of tapentadol and oxycodone in healthy volunteers. *Br. J. Anaesth.* **119**, 1169–1177 (2017).
12. van der Schier, R. *et al*. Carbon dioxide tolerability and toxicity in rat and man: a translational study. *Front. Toxicol.* **4**, 1001709 (2022).
13. Mildh, L.H., Scheinin, H. & Kirvelä, O.A. The concentration-effect relationship of the respiratory depressant effects of alfentanil and fentanyl. *Anesth. Analg.* **93**, 939–946 (2011).
14. Lalovic, B., Kharasch, E., Hoffer, C., Risler, L., Liu-Chen, L.Y. & Shen, D.D. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. *Clin. Pharmacol. Ther.* **79**, 461–479 (2006).
15. Staahl, C. *et al*. Pharmacokinetic-pharmacodynamic modeling of morphine and oxycodone .Concentrations and analgesic effect in multimodal experimental pain models. *J. Clin. Pharmacol.* **48**, 619–631 (2008).
16. Xu, X.S., Etropolski, M., Upmalis, D., Okamoto, A., Lin, R. & Nandy, P. Pharmacokinetic and pharmacodynamic modeling of opioid-induced gastrointestinal side effects in patients receiving tapentadol IR and oxycodone IR. *Pharm. Res.* **29**, 2555–2264 (2012).
17. Labedo, L. *et al*. Population pharmacokinetic/pharmacodynamic modeling of liquid and controlled-release formulations of oxycodone in healthy volunteers. *Basic Clin. Pharmacol. Toxicol.* **126**, 263–276 (2020).
18. Dari, A., Buller, S., Gautrois, M., Stahlberg, H.J., Rengelshausen, J. & Freijer, J. Oxycodone effect on pupil constriction in recreational opioid users: a pharmacokinetic/pharmacodynamic meta-analysis approach. *Clin. Pharm.* **60**, 785–794 (2021).
19. Lalovic, B.B., Shireman, L., Shen, D.D. & Cherrier, M.M. Model-based analysis of the influence of alcohol use and age on pharmacokinetics-pharmacodynamics of oral oxycodone in middle-age and older community-dwelling adults. *J. Clin. Pharmacol.* **62**, 1177–1190 (2022).
20. Dahan, A. *et al*. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br. J. Anaesth.* **96**, 627–632 (2006).
21. Yassen, A., Olofsen, E., Dahan, A. & Danhof, M. Pharmacokinetic-pharmacodynamic modeling of the efficacy and safety of buprenorphine in rats. *Pharm. Res.* **25**, 183–193 (2008).
22. Yi, S.P. *et al*. The opioid receptor triple agonist DPI-125 produces analgesia with less respiratory depression and reduced abuse liability. *Acta Pharmacol. Sin.* **38**, 977–989 (2017).
23. Dosaka-Akita, K., Tortella, F.C., Holaday, J.W. & Long, J.B. The kappa opioid agonist U-50,488H antagonizes respiratory effects of mu opioid receptor agonists in conscious rats. *J. Pharmacol. Exp. Ther.* **264**, 631–637 (1993).
24. Manglik, A. *et al*. Structure-based discovery of opioid analgesics with reduced side effects. *Nature* **537**, 185–190 (2016).
25. Stahl, E.L. & Bohn, L.M. Low intrinsic efficacy alone cannot explain the improved side effect profiles of new opioid agonists. *Biochemistry* **61**, 1923–1935 (2022).
26. Ross, F.B. & Smith, M.T. The intrinsic antinociceptive effects of oxycodone appear to be kappa-opioid receptor mediated. *Pain* **73**, 151–157 (1997).
27. Ollkola, K.T., Kontinen, V.K., Saari, T.I. & Kalso, E.A. Does the pharmacology of oxycodone justify its increasing use as an analgesic? *TIPS* **34**, 206–214 (2013).
28. Remillard, D., Kaye, A.D. & McAnally, H. Oxycodone's unparalleled addictive potential: is it time for a moratorium? *Curr. Pain Headache Rep.* **23**, 15 (2019).
29. Icenhour, A. *et al*. Neural circuitry underlying effects of context on human pain-related fear extinction in a renewal paradigm. *Hum. Brain Mapp.* **36**, 3179–3193 (2015).
30. Jepma, M., Roy, M., Ramlakhan, K., van Velzen, M. & Dahan, A. Different brain systems support learning from received and avoided pain during human pain-avoidance learning. *eLife* **11**, e71749 (2022).