Fentanyl Utility Function

A Risk–Benefit Composite of Pain Relief and Breathing Responses

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ABSTRACT

Introduction: Integrating opioid risk and benefit into a single function may give a useful single measure of the opioid’s positive and negative effects. An explorative study on the effects of fentanyl on antinociception and respiratory depression was performed to construct fentanyl risk–benefit (utility) functions.

Methods: Twelve volunteers received a 3.5-μg/kg fentanyl intravenous injection on 2 separate study days. On one occasion, ventilation at a clamped increased carbon dioxide concentration was measured and on another the pain tolerance to electrical stimulation. In both sessions, arterial plasma samples were obtained. The data were analyzed with a population pharmacokinetic–pharmacodynamic model. A simulation study was performed, using the model parameter estimates and their variances, in which simulated subjects received 3.5 μg/kg of fentanyl. The resultant distributions were used to calculate the utility functions, defined as the difference between the probability of a wanted effect and the probability of a side effect.

What We Already Know about This Topic

• The behavior of a drug has traditionally been represented by concentration–effect relationships, which are important for understanding steady-state drug behavior
• A utility function provides a composite description of the risks and benefits of a drug in time and concentration domains as the difference between the probability of a wanted effect and the probability of a side effect

What This Article Tells Us That Is New

• During the first half hour after the bolus injection of 3.5 μg/kg fentanyl, the probability of respiratory depression exceeds that of analgesia
• The shape of the utility function depends on the response thresholds chosen and the rate of drug administration
Results: Fentanyl produced significant respiratory depression and analgesia. The pharmacokinetic and pharmacodynamic models adequately described the data. The constructed utility functions were negative at effect-site concentrations of greater than 0.5 ng/ml in the first 90 min after the 3.5 μg/kg bolus infusion.

Conclusions: Utility functions based on fentanyl’s experimental effects on respiration and pain relief were successfully constructed. These functions are useful in multiple effect comparisons among experimental drugs. Further studies are required to assess whether this risk–benefit analysis is valuable in clinical practice.

It is well known that opioids are able to produce life-threatening respiratory depression. A recent editorial brought to attention the sharp increase, since the early 1990s, in unintentional drug overdose and consequently death because of ingestion of prescription painkillers in the United States. As discussed, this is related to a 10-fold increase in the medical use of synthetic opioids, marketing tactics, and the proactive identification of patients with chronic pain. Also in the perioperative setting, opioid-induced respiratory depression is a common observation with regular reports of fatalities. Overall, there is the ongoing need for vigilance when potencies opioids are administered to spontaneously breathing and opioid-naïve patients. Opioid risk (in the acute setting: respiratory depression) is best viewed in context of its beneficial effect, i.e., analgesia. Recently, Katz proposed the construction of a risk–benefit composite for analgesia. The resultant distributions are used to calculate the UF. In the current approach, we calculated the probability of an increase in pain tolerance of 50% or more minus the probability of drug-induced bleeding-related event. In the current study, we constructed a UF for the opioid analgesic fentanyl. This fentanyl UF is constructed based on the results of a population pharmacokinetic–pharmacodynamic study on the effect of fentanyl on respiration and anticoagulation. Next, a simulation study is performed, using the pharmacokinetic–pharmacodynamic parameter estimates and their variances, in which 2X 9,999 simulated subjects received fentanyl. The resultant distributions are used to calculate the UF. In the current approach, we calculated the probability of an increase in pain tolerance of 50% or more minus the probability of respiratory depression of 50% or more.

Materials and Methods

Subjects

After approval of the protocol by the local Human Ethics Committee (Commissie Medische Ethiek, Leiden University Medical Center, Leiden, The Netherlands) and the Central Committee on Research involving Human Subjects (Commissie Mensgebonden Onderzoek, The Hague, The Netherlands) and informed consent was obtained according to the Declaration of Helsinki, 12 men volunteers, aged 18–45 yr, were initially recruited to participate in the study. One subject dropped out and was replaced by a 13th subject. All recruits were subjected to a medical history, physical examination, 12-leads electrocardiogram, and blood screening before inclusion. Only healthy subjects, without a history of alcohol or illicit drug abuse and a body mass index between 20 and 28, were included in the study.

Study Design

All subjects were studied twice with at least 2 weeks interval between sessions (the sequence of sessions was random). On one occasion, the effect of a single intravenous infusion of fentanyl (3.5 μg/kg infusion for more than 90 s) on respiration was tested and on the other occasion, the effects of fentanyl (3.5 μg/kg infusion for more than 90 s) on pain responses to a cutaneous noxious electrical stimulus were tested.

Respiratory Measurements.

During the respiratory studies, subjects breathed through a facemask (fitted over nose and mouth). The airway gas flow was measured by a pneumotachograph (#4813; Hans Rudolph, Kansas City, MO) connected to a pressure transducer, which yields a volume signal. The pneumotachograph was heated (37°C) throughout the study period. This signal was calibrated with a 1-l calibration syringe (Hans Rudolph). The pneumotachograph was connected to a T-piece; one arm of the T-piece received a gas mixture at a flow rate of 45 l/min from a gas mixing system, consisting of three mass-flow controllers (Bronkhorst High-Tec, Veenendaal, The Netherlands) via which the flow of oxygen, nitrogen, and carbon dioxide could be set individually at any desired level. A computer provided control signals to the mass-flow controllers allowing adjustment of the inspired gas mixture to force the end-tidal gas concentrations of oxygen and carbon dioxide to follow a specific pattern in time. Gas concentrations were measured with a gas analyzer (Datex Multicap, Helsinki, Finland); arterial hemoglobin oxygen saturation was measured via a finger probe with a Masimo pulse oximeter (Irvine, CA).

Respiration was measured at a clamped increased end-tidal carbon dioxide tension (PCO2) using the “Dynamic End-Tidal Forcing” technique. In each subject, the end-tidal PCO2 was increased in steps of 2–3 mmHg until ventilation reached a value 20–24 l/min. The end-tidal PCO2 was kept constant at this level throughout the study (baseline end-tidal PCO2 level). This procedure was performed in a “training” session 30–45 min before dosing. The end-tidal
oxygen concentration \((P_{O_2})\) was kept constant at 110 mmHg throughout the study. After a steady state in ventilation was obtained, fentanyl was infused, and continuous breath-to-breath ventilatory measurements were obtained for the next 90 min. Thereafter, 3-min measurements were obtained at 30-min intervals until \(t = 4\) h after the administration and at 1-h intervals until \(t = 6\) h. The following variables were collected on a breath-to-breath basis on a computer disc for further analysis: inspiratory minute ventilation, end-tidal \(P_{CO_2}\), end-tidal \(P_{O_2}\), and oxygen saturation.

**Pain Responses.** Acute pain was induced by an electrical current through two surface electrodes (3M; Red Dot, London, Ontario, Canada) placed on the skin overlaying the left tibial bone (transcutaneous electrical stimulation).

The electrodes were attached to a computer interfaced current stimulator (Leiden University Medical Center). The intensity of the noxious stimulation was increased from 0 mA in steps of 0.5 mA/s. The stimulus train consisted of a square-wave pulse of 0.2-ms duration applied at 10 Hz and had a cutoff of 128 mA. The subjects were instructed to press a control button when they felt pain ("pain threshold") and when no further increase in stimulus intensity was acceptable ("pain tolerance"); this ends the stimulus train. Pain responses were obtained at baseline and at \(t = 10, 25, 40, 55, 70, 90, 110, 130, 160, 190, 220, 250, 310,\) and 370 min after dosing. We analyzed the pain tolerance data for the current report.

**Blood Sampling.** Blood samples (3 ml) were obtained from an arterial line placed in the left or right radial artery (opposite to the arm through which the drug was infused) for determination of the plasma concentrations of fentanyl. Blood samples were obtained at \(t = 2, 5, 10, 15, 30, 60, 90, 150, 210, 270, 330, 390,\) and 480 min after dosing. Plasma was separated within 30-min of blood collection and stored at \(-20°C\) until analysis.

**Analytical Assay for the Determination on Fentanyl in Human Plasma Samples by Liquid Chromatography–Mass Spectrometry.** Fifty microliter of the plasma samples were transferred into reaction vials. Twenty-five microliter of the internal standard (0.1 ng per component) were added. For extraction, 20 µl ammonia solution and 0.5 ml methanol tert-butyl ether were added. The reaction vials were closed and shaken for 15 min. After centrifugation (16,000 rpm), the organic layers were transferred into auto sampler vials and dried under nitrogen. The residues were reconstituted with 100 µl high-performance liquid chromatography starting solvent. Aliquots (5 µl) were injected by a cooled autosampler (approximately 10°C) onto the column of the liquid chromatography–mass spectrometry system. Samples with fentanyl concentration above the calibration range were diluted before the measurement using human blank plasma.

Chromatographic separation was performed using an Agilent 1200 liquid chromatograph (Agilent Technologies Inc., Santa Clara, CA) and a PAL HTC-xt (Axel Semrau GmbH & Co., Sprockhövel, Germany) autosampler. A Varian Pursuit 3 µ C18 30 × 2 (30 × 2 mm²) column (Walnut Creek, CA) and Varian MetaGuard Pursuit 3 µ C18 10 × 2 mm² guard column were used as stationary phases. The analytes were eluted using gradient elution with a mobile phase consisting of formic acid (0.1%) and acetoniitril (containing 0.1% formic acid) at 30°C with a flow rate of 0.7 ml/min (table 1, see Supplemental Digital Content 1, http://links.lww.com/ALN/A953, which is a table listing the applied gradients of solvents A and B from time 0.1 to 5.5 min).

Fentanyl was detected in the multiple reaction monitoring mode using an electrospray ion source on a triple quadrupole mass spectrometer API-5500 QTrap equipped with a Turbo-Ionspray™ Interface (Applied Biosystems, Framingham, MA) operating in positive ionization mode. The MS/MS (tandem mass spectrometry) transitions 337/188 for fentanyl and 342/188 for D₅-fentanyl were monitored for quantitation of the compound.

Using the described chromatography, fentanyl had a retention time of approximately 3.0 min. The calibration range of the bioanalytical assay was 0.005–5.00 ng/ml. Calibration samples were prepared at 0.005, 0.010, 0.050, 0.200, 1.00, 2.00, 3.75, and 5.00 ng fentanyl/ml plasma. The calibration curve was linear in the investigated range. Linear regression and weighting 1/\(y^2\) was applied. The calibration curve was found to be consistently accurate and precise over the calibration range. Quality control samples were prepared at concentrations of 0.015, 2.00, and 5.00 ng fentanyl/ml plasma. The values for the overall accuracy and the overall precision for quality controls assayed during analysis of study samples were 97.2–106.2% and 1.7–9.5%, respectively. The samples were analyzed in six batches with interbatches accuracy of 95.9–104.9% and coefficient of variation of 1.9–6.9% over the calibration range of 0.005–5.0 ng/ml.

**Pharmacokinetic–Pharmacodynamic Analysis**

Multiple compartment models were fitted to the fentanyl pharmacokinetic data. Model selection (the number of compartments) was based on the goodness-of-fit criterion. Only the “best” models will be described here.

To eliminate a possible hysteresis between plasma concentration and effect, an effect compartment was postulated that equilibrates with the plasma compartment with a half-life \(t/2k_{e0}\) (i.e., the blood-effect-site equilibration half-life).

The ventilation data were modeled as:

\[
\text{Effect}(t) = \text{Emax} + [\text{Emin} - \text{Emax}] \cdot \left(\frac{A}{(1 + A)}\right)
\]

\[
A = \left[\frac{C_e(t)}{C_{50}}\right]^{\gamma}
\]

where effect is the effect at time \(t\) (minute ventilation), Emax maximum or predrug effect (baseline ventilation), Emin minimum effect (an Emin of zero indicates that apnea may be reached), \(C_e(t)\) effect-site concentration at time \(t\), and \(C_{50}\) the effect-site or steady-state concentration causing 50% depression of ventilation.
Untranscutaneous electrical pain responses were modeled as:10–12

\[ \text{Pain Response}(t) = \text{Baseline} \cdot [1 + 0.25 \cdot B] \] and
\[ B = \left[ \frac{\text{Ce}(t)}{C_{25}} \right] \]

where pain response(t) is the stimulus intensity at which a pain tolerance response occurs at time t. Baseline the predrug stimulus intensity at which a pain threshold or pain tolerance response occurs, Ce(t) the effect-site concentration at time t, and C_{25} the effect-site or steady-state concentration causing an increase of 25% stimulus intensity for a response. Estimation of C_{25} rather than C_{50} was performed as the 25% increase in stimulus intensity was midpoint of the observed responses.

The pharmacokinetic–pharmacodynamic data were analyzed using the mixed-effects modeling software NONMEM VII (ICON Development Solutions, Ellicott City, MD).13 The pharmacokinetic–pharmacodynamic analysis was performed in two stages. From the first stage (pharmacokinetic analysis), empirical Bayesian estimates of the pharmacokinetic parameters were obtained. In the second stage (pharmacodynamic analysis), the pharmacokinetic parameters were fixed to those obtained in the first stage. An integrated data analysis was performed in NONMEM, i.e., combining all pharmacodynamic data (respiratory and pain data) in one analysis. Model parameters were assumed to be log-normally distributed. Residual error was assumed to have both an additive and a relative error for concentrations and only an additive error for all effect parameters. Covariance between random effects (\( \eta \)) for the pharmacodynamic endpoints were explored using $\text{OMEGA}$ BLOCKS.

The number of compartments in the pharmacokinetic analysis was determined by the magnitude of the decrease in the minimum objective function value (chi-square test; \( P < 0.01 \) was considered significant). In the pharmacokinetic analysis, weight and height were considered as covariates. \( P \) values less than 0.01 were considered significant.

**Visual Predictive Check**

Visual predictive checks were performed to assess the adequacy of the description of both fixed and random effects by simulating data using the models and calculating their 2.5th, 50th, and 97.5th percentile at all sampling times.

**Utility Function**

The utility of drug effect, U, was defined as the probability of obtaining the desired effect minus the probability of obtaining a side effect.6,14 If we define the desired effect as a 50% or more increase in current tolerated relative to the predrug baseline current and the side effect as a decrease in minute ventilation of 50% or more from the carbon dioxide-increased predrug baseline level, and the probability of obtaining these as \( P(A \geq 0.5) \) and \( P(R \geq 0.5) \), respectively, then \( U = P(A \geq 0.5) - P(R \geq 0.5) \). The utility of fentanyl's effect was calculated as function of effect-site concentration \( (U_1) \) and of time \( (U_2) \) after administration of 3.5 \( \mu g/kg \):

\[ U_1(C_e) = P(A(C_e) \geq 0.5) - P(R(C_e) \geq 0.5) \] (3)

and

\[ U_2(t) = P(A(t) \geq 0.5) - P(R(t) \geq 0.5) \] (4)

where \( P \) is probability, A analgesia, and R respiratory depression.

The UF was calculated from the population pharmacokinetic and pharmacodynamic model with established values for the population and their interindividual variability parameters (\( \omega^2 \)). To this end, \( 2 \times 9,999 \) simulations were performed using NONMEM’s simulation step (with \( \text{SUBPROBLEMS} = 9,999 \)). The occurrence of desired and side effects were counted and divided by 9,999 to estimate probabilities (note that these are uncorrelated because no correlations between the \( \omega^2 \) were identified in the pharmacodynamic analysis).

\( U \) values range from –1 to +1; \( U \) more than 0 indicate that the chance for a desired effect exceeds the chance for an unwanted effect (here respiratory depression), whereas \( U \) less than 0 indicates that the chance for the unwanted effect exceeds the chance for analgesia. \( U \) values between –0.2 and 0.2 are small effects, \( U \) values between –0.2 and –0.4 and 0.2 and 0.4 are moderate effects, and \( U \) values less than –0.4 and more than 0.4 are large effects. Small effects indicate absence of selectivity of action (i.e., no clinically relevant greater chance for analgesia than for respiratory depression and vice versa).

Sensitivity analyses were performed to assess the effect of changes in context (numerical response thresholds in \( P(A) \) and \( P(R) \)) and effect of changes in pain parameter estimates \( t/2k_{s0} \) and \( C_{50} \) on the form of the UFs.

**Results**

One subject dropped out and was replaced by another. The pharmacodynamic data of the dropout were incomplete and therefore discarded. His pharmacokinetic data were used in the population analysis. Consequently, the number of subjects was 13 for the pharmacokinetic data and 12 for the pharmacodynamic data. In one subject, just one set of pharmacokinetic data were available due to failure of arterial line insertion on one occasion. No unexpected or major side effects occurred during the studies. All subjects (\( n = 13 \)) were white men with a mean age of 22.1 yr (range 19–27 yr), height 186 cm (176–200 cm), weight 80.5 kg (64–111 kg), and body mass index of 23.2 kg/m² (21–28 kg/m²). Mean fentanyl plasma concentrations, respiration, and pain responses are shown in figure 1.

**Pharmacokinetic Analysis**

The mean plasma fentanyl concentrations are given in figure 1A. The variability in fentanyl concentrations obtained
in the two distinct study occasions was small as observed in figure 1A. The final pharmacokinetic model consisted of a three-compartment model with one central (V₁) and two peripheral compartments (V₂ and V₃). The pharmacokinetic parameter estimates are given in table 1. Covariate weight (WT in kg) had a significant effect on parameters V₁, V₂, CL₁, and CL₂ with the volumes scaled by (WT/70) and the clearances scaled by (WT/70)⁰.⁷⁵ (P < 0.01). No effect of WT

Table 1. Pharmacokinetic Model Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical Value</th>
<th>SEE (%)</th>
<th>ω²</th>
<th>SEE</th>
<th>η-Shrinkage, %†</th>
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<tr>
<td>V₁, l</td>
<td>8.867</td>
<td>0.652 (7)</td>
<td>0.065*</td>
<td>0.021 (32)</td>
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<td>V₂, l</td>
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<td>V₃, l</td>
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<td>0.011 (41)</td>
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<td>CL₁, l/h</td>
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<td>0.0538 (7)</td>
<td>0.027</td>
<td>0.016 (59)</td>
<td>4</td>
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<td>CL₂, l/h</td>
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<td>0.322 (8)</td>
<td>0.065*</td>
<td>0.021 (32)</td>
<td>1</td>
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<td>CL₃, l/h</td>
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<td>0.157 (8)</td>
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<tr>
<td>IOV on CL₁</td>
<td>0.004</td>
<td>0.002 (50)</td>
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<tr>
<td>σ²</td>
<td>0.109</td>
<td>0.005 (5)</td>
<td>8†</td>
<td></td>
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</table>

SEE in the column to the left (in brackets the SEE as %).
* One η was used for V₁, CL₁, and CL₂. † η-Shrinkage of empirical Bayesian estimates to the population values. ‡ ε-Shrinkage of model output to the observations.

CL₁ = elimination clearance; CL₂ and CL₃ = the clearances between compartment 1 and compartments 2 and 3, respectively; IOV = interoccasion variability; SEE = standard error of the estimate; V₁, V₂, and V₃ = the volumes of compartments 1, 2, and 3; σ² = the variance of the residual (relative) error; ω² = the intersubject variability (in the log-domain).
was observed for $V_3$ and $CL_3$. Covariate height had no effect on any of the model parameters. Goodness-of-fit plots (measured vs. individual predicted concentrations and individual weighted residuals vs. time) are given in figure 2. Examples of data fits are given in figures 3 and 4. The goodness-of-fit plots and inspection of the individual data fits indicate that the pharmacokinetic model adequately describes the pharmacokinetic data.

**Pharmacodynamic Analysis**

Mean ventilatory and pain responses are given in figure 1. The peak increase in pain tolerance averaged to 21.9 mA, which (apart from one outlier of 91 mA) was normally distributed (range 5.5–33.5 mA; $n = 11$). Similar response variabilities have been observed in other studies on opioid analgesic efficacy using this same pain model.10–12

Best, median, and worst pharmacodynamic data fits (and corresponding pharmacokinetic fits; the pharmacokinetic fits include the data from both occasions) for the three endpoints are given in figures 3 and 4. The goodness-of-fit plots are given in figure 2, C–F. These plots and inspection of the individual data fits indicate that the pharmacodynamic models adequately describe the pharmacodynamic data. Model parameter values are given in table 2. The ventilation $Emin$ value was not significantly different from 0 l/min ($P > 0.05$) which indicates that at a sufficiently high fentanyl dose apnea will occur. A critical ventilation level (arbitrarily defined as <4 l/min or 20% of baseline) is attained at steady-state plasma fentanyl concentrations of 4 ng/ml or greater. Potency estimates for respiratory depression and pain responses were 1.0 ng/ml ($C_{50}$) and 0.9 ng/ml ($C_{25}$), respectively ($P < 0.01$). The intraindividual variabilities ($\eta$s) were not correlated indicating that the parameter values ($t_{1/2}k_{ed}$, $C_{50}$, and $\gamma$) of the three endpoints were uncorrelated. Peak respiratory depression among subjects ranged from 7 to 12 min after the start of the 90 s infusion.

In figure 1 (Supplemental Digital Content 1, http://links.lww.com/ALN/A953), the results of the visual predictive checks for pharmacokinetic and pharmacodynamic data are shown. The figure gives the median predicted values (continuous lines) and 95% intervals (dashed lines) for the fentanyl plasma concentrations, ventilation, pain threshold, and pain tolerance.

**Utility Function**

The calculated UFs are shown in figure 5, A and B. In the concentration domain ($U_1$, Equation 3), the utility is positive for low fentanyl effect-site or steady-state concentrations (<0.7 ng/ml; fig. 5B). At high concentrations, the function is negative indicating that the chance for respiratory depression of 50% or greater exceeds the chance for analgesia (increase in pain tolerance by 50% or more). At a concentration of 1.74 ng/ml, the UF was most negative ($U_1 = -0.23$) with a chance for analgesia and respiratory depression of 60 and 83%, respectively.

In the time domain ($U_2$, Equation 4; fig. 5A), the UF after a fentanyl dose of 3.5 $\mu$g/kg is initially negative due to the high fentanyl concentrations from the bolus infusion ($t = 6.6$ min the value of $U_2 = -0.44$ with changes for analgesia and respiratory depression of 21 and 65%). With decreasing concentrations, the function becomes positive at $t$ more than 100 min. This corresponds with plasma fentanyl concentrations less than 0.6 ng/ml. At $t = 240$ min, the value of $U = 0.06$ with changes for analgesia and respiratory depression of 10 and 4%, respectively.

**Sensitivity Analyses**

Effect of Variations in $P(A)$ and $P(R)$ Response Thresholds. The results of the sensitivity analyses are given in figures 6, A and B. Figure 6A shows the results of the
analyses in the concentration domain, whereas figure 6B gives the analyses in the time domain. Each set of lines with identical colors represents a set of fixed probabilities for respiratory depression, whereas within these sets the probability for analgesia increases from top to bottom. For analgesia, the probability for greater analgesic effects (for example P(A >75%) or an increase in pain tolerance of at least 75%) occurs at the lower end of the set as the greater opioid concentrations that are required to reach such analgesic levels coincide with a greater probability for respiratory depression. For respiratory depression, going from P(R > 75%) to P(R > 25%), the probability for respiratory depression increases irrespective of the P(A) thresholds. For example, the probability of respiratory depression of at least 25%, P(R > 25%), exceeds that observed for the other effect threshold values, and consequently the function P(A) – P(R) is more negative than the other functions.

**Effect of Variations in (Pain Model) Parameter Estimates**

$\frac{1}{2}k_{el}$ and $C_{50}$. The results are given in figure 7 and show that an increase in analgesic potency and, although to a lesser extent, a smaller value for $\frac{1}{2}k_{el}$ causes an upward shift of the UF. The reverse is true in case of a lesser analgesic potency and a slower analgesic onset/offset.

**Discussion**

The risk of opioid toxicity is best considered in the context of the opioid’s benefit (i.e., analgesia). Integrating opioid risk and benefit into a single function is useful as it allows multiple effect (wanted effect and side effect) comparisons among opioids. For example, Katz showed in 946 patients with chronic lower back pain that the risk–benefit composite (defined as the proportion of days where the patient is an opioid responder [i.e., experiencing ≥30% pain relief] with no or just moderate adverse events) is significantly greater for the opioid tapentadol than for oxycodone (30 vs. 25%).†† This may help in the choice of opioid treatment for that specific patient population. In the current study, we assessed the risk–benefit composite of fentanyl in an acute administration paradigm by construction of a UF as previously described by Cullberg, etc. i.e., the difference between the probability of a wanted effect (antinociception, a positive effect)
minus the probability of a side effect (respiratory depression, a negative effect).

The UF is context sensitive. The context is the chosen probability for effect and side effect. We chose $P(A \geq 0.5) - P(R \geq 0.5)$ which is the probability for an increase in pain tolerance of at least 50% or more minus the probability for 50% respiratory depression or more. We choose 50% as it compares with other 50% response values used in anesthesia such as minimum alveolar concentration (which gives the anesthetic concentration causing a response in 50% of patient) and $C_{50}$ (which is the drug concentration causing 50% effect). Evidently, other probabilities will result in UFs that deviate in shape from the current functions. A sensitivity analysis using different numerical response thresholds in $P(A)$ and $P(R)$ does indeed show that the UF is context sensitive (fig. 6). The response threshold of $P(A \geq 0.5) - P(R \geq 0.5)$ is well positioned in the middle of the observed functions and reflects the “mid”-response comparable with the minimum alveolar concentration or $C_{50}$. How these results may be interpreted in a clinical setting and which of the response thresholds is most appropriate requires further studies.

The UFs were constructed from $2 \times 9,999$ simulations using the pharmacokinetic–pharmacodynamic parameter estimates. The sometimes-large variance of some parameters is therefore taken into account in the UF. We determined the utility as function of effect-site or steady-state concentration ($U_1$, Equation 3) and time ($U_2$, Equation 4) after a 3.5-$\mu$g/kg fentanyl injection. After the injection, $U_2$ values are negative for the first 90 min with large negative values ($< -0.4$) from $t = 2$ to 17 min (fig. 5A). At $t$ more than 90 min, when plasma fentanyl concentrations were less than 0.6 ng/ml, $U_2$ becomes positive, but the positive values are small. The $U_1$ (concentration) function shows a variation of 0.25, a rather modest variation ranging from +0.05 to −0.20, but still predominantly negative (fig. 5B). Overall, the UFs also show what clinically is apparent: (1) after a high fentanyl bolus dose, the probability of respiratory depression (relative to analgesia) is highest in the first hour after the injection, with a diminishing (but certainly not vanishing) probability of respiratory depression at later times. (2) Although we did not perform a dose–response study, we

![Fig. 4. Effect of fentanyl on pain tolerance. Best, median, and worst fits (as determined by the coefficient of determination, $R^2$) are given, together with the corresponding pharmacokinetic data fits. (A and D) Subject id 004, best pharmacodynamic fit; (B and E) subject id 012, median pharmacodynamic fit; and (C and F) subject id 011, worst pharmacodynamic fit. Because fentanyl was given on two occasions, both pharmacokinetic fits are given if available (A–C; subject id004 has pharmacokinetics data from just one occasion).](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/930990/)
may infer from our analysis that at low doses of fentanyl (up to 50 μg) the probability for analgesia exceeds that of respiratory depression.

The UFs we constructed are based on specific pharmacodynamic endpoints commonly used in our laboratory when studying opioid effect and therefore allow comparison among opioids. Ventilation was measured with the dynamic end-tidal forcing technique in which the end-tidal PCO₂ is clamped at a fixed increased level such that predrug baseline ventilation increased to 20–24 l/min.7–10,15–17

**Table 2.** Fentanyl Pharmacodynamic Model Parameters

<table>
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<tr>
<th></th>
<th>Typical Value</th>
<th>SEE (%)</th>
<th>ω²</th>
<th>SEE (%)</th>
<th>η-Shrinkage, %†</th>
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<td><strong>Ventilation</strong></td>
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</tr>
<tr>
<td>t½kₑ₀, min</td>
<td>17.10</td>
<td>3.44 (20)</td>
<td>0.49</td>
<td>0.12 (24)</td>
<td>−2</td>
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<td>Emax, l/min</td>
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<td>0.02</td>
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<td>1</td>
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<td>Emin, l/min</td>
<td>0 (fixed)</td>
<td>*</td>
<td>0 (fixed)</td>
<td>*</td>
<td>−</td>
</tr>
<tr>
<td>C₅₀, ng/ml</td>
<td>1.02</td>
<td>0.18 (18)</td>
<td>0.31</td>
<td>0.07 (23)</td>
<td>−2</td>
</tr>
<tr>
<td>γ</td>
<td>1 (fixed)</td>
<td>*</td>
<td>0.41</td>
<td>0.26 (63)</td>
<td>*</td>
</tr>
<tr>
<td>Σ²</td>
<td>3.71</td>
<td>0.59 (16)</td>
<td></td>
<td></td>
<td>1‡</td>
</tr>
<tr>
<td><strong>Pain relief response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t½kₑ₀, min</td>
<td>41.6</td>
<td>9.27 (22)</td>
<td>0.15</td>
<td>0.07 (47)</td>
<td>20</td>
</tr>
<tr>
<td>Baseline tolerance, mA</td>
<td>26.0</td>
<td>2.87 (7)</td>
<td>0.14</td>
<td>0.04 (29)</td>
<td>−5</td>
</tr>
<tr>
<td>C₂₅, ng/ml</td>
<td>0.91</td>
<td>0.29 (32)</td>
<td>0.85</td>
<td>0.35 (41)</td>
<td>16</td>
</tr>
<tr>
<td>γ</td>
<td>1.59</td>
<td>0.05 (3)</td>
<td>0 (fixed)</td>
<td>*</td>
<td>−</td>
</tr>
<tr>
<td>Σ²</td>
<td>10.9</td>
<td>3.84 (35)</td>
<td></td>
<td></td>
<td>8‡</td>
</tr>
</tbody>
</table>

SEE in the column to the left (in brackets the SEE as %). — Not included in the statistical model.
*Not estimable. †η-Shrinkage of empirical Bayesian estimates to the population values. ‡ε-Shrinkage of model output to the observations.
C₅₀ and C₂₅ = potency parameters or steady-state concentrations at which 50 or 25% of the effect occurred; Emax = baseline ventilation level; Emin = the minimum ventilation level; SEE = standard error of the estimate; t½kₑ₀ = the blood effect-site equilibration constant; σ² = the variance of the residual error; γ = a shape parameter; ω² = the intersubject variability (in the log-domain).

**Fig. 5.** Utility functions (P(A ≥ 50%) – P(R ≥ 50%)) for respiratory responses and pain relief in the time (A; after a 3.5 μg/kg fentanyl injection) and concentration domains (B), where P(A ≥ 50%) is the probability for an increase in pain tolerance of 50% or greater and P(R ≥ 50%) is the probability for respiratory depression of 50% or greater. P(A) > P(R) indicates that the probability for positive effects (analgesia) exceeds the probability for negative effects (respiratory depression); P(R) > (P(A) indicates that the probability for negative effects (respiratory depression) exceeds the probability for positive effects (analgesia). P(A ≥ 50%) is the probability for a 50% or more increase in current tolerated relative to the predrug baseline current. P(R ≥ 50%) is the probability for a decrease in minute ventilation of 50% or more from the carbon dioxide-increased predrug baseline level.
Fentanyl Utility Function

approach has various advantages including the assessment of respiratory effect at constant carbon dioxide stimulation. Under “nonclamped” conditions (1) the arterial carbon dioxide level changes over time after the administration of an opioid resulting in confounding variations in the stimulation of peripheral and central chemoreceptors,18 and (2) the speed of opioid injection influences the time profile of respiratory depression.18 The estimated model parameters of the respiratory effects of fentanyl (C_{50} = 1 ng/ml, t_{1/2}k_{e0} = 17 min) are in close agreement with earlier observations in healthy volunteers.3,19 In the current study, C_{50} is the fentanyl concentration at the effect site (or the steady-state plasma concentration) causing 50% depression in ventilation under conditions of a clamped and increased end-tidal carbon dioxide concentration. Under nonclamped conditions, the estimated C_{50} value will result in an increase in arterial PCO_{2} by 30–40% combined with a reduction in ventilation by 30–40%.

The nociceptive model used by us is transcutaneous electrical stimulation. This model is used frequently in pain research because it allows repetitive testing without confounders such as sensitization or adaptation.10–12,20 The opioid response to electrical stimulation is slower than expected from other endpoints including respiratory depression and changes in electroencephalographic parameters.11,19–22 The slower response has been observed for other opioids as well and is further discussed by Olofsen et al.11 It is most probably related to slow neuronal dynamics and activation of short-term potentiation at central sites involved in the processing of electrical pain.11 Irrespective, the fentanyl potency value (C_{25} 0.9 ng/ml; extrapolated C_{50} 1.4 ng/ml) is well within the expected clinical concentration range and corresponds with the concentration causing a 40% reduction in isoflurane minimum alveolar concentration and potent analgesia in clinical settings.23 To get an indication of the importance of variations in t_{1/2}k_{e0} and potency on the shape of the UFs, we performed an additional set of simulations (fig. 7) with variations in the analgesia model parameters. Variation in C_{25} was the more dominant factor with larger changes in the shape of the UF compared with changes in t_{1/2}k_{e0}. At a lower analgesic potency, the UF becomes more negative, both in time and concentration domains. A smaller value for t_{1/2}k_{e0} (i.e., a more rapid onset/offset of effect) results in an upward shift of the UF (fig. 7A). Variations in t_{1/2}k_{e0} have no effect on the steady-state UF (fig. 7B).

The UF in drug research is still experimental and our study is exploratory. It may already be argued that the UF may be useful for comparing the safety profile of specific drugs and for choosing a specific opioid dose with an optimal UF. Traditionally, the behavior of opioids is presented in terms of effect-site or steady-state concentration-effect relationships. These relationships are useful as they give a population prediction of steady-state effect and allow comparison among effects and drugs. In figure 8, we plotted the fentanyl concentration–effect relationship and show the very different behavior of fentanyl on pain relief and analgesia. The curves are not parallel and are not similarly shaped. The effect on respiration sets in at already low steady-state fentanyl concentrations, whereas analgesia requires greater fentanyl concentrations. This explains the predominantly negative UF observed for fentanyl as constructed in the concentration domain. The advantage of UFs is that it takes into account the interindividual

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**Fig. 6.** Sensitivity analysis of the effect of different numerical response thresholds in P(A) and P(R) on the shape of the utility functions. Each set of lines with identical colors represents a set of fixed probabilities for respiratory depression, whereas within these sets the probability for analgesia increases from top to bottom. (A) Utility functions in the concentration domain. (B) Utility functions in the time domain. P(A) = probability for analgesia; P(R) = probability for respiratory depression.
variability in the measured responses and dynamics of the response and integrates two (opposing) endpoints of treatment. Apart from respiratory depression (as negative endpoint), other endpoints may be used in the construction of UFs, including sedation, dizziness, nausea/vomiting, and psychomimetic side effects.

In conclusion, we have performed an explorative study on the construction of UFs in which the probability for respiratory depression is subtracted from the probability for analgesia as part of a risk–benefit analysis of opioid effect. The shape of the UF is dependent on the context, i.e., the numerical response thresholds for P(A) and P(R) as well as the administration history (i.e., the change in effect-site concentration over time). In the current study, probabilities for P(A) and P(R) of 50% or more were used that reflect an increase in pain tolerance of at least 50% and respiratory depression of at least 50%. These functions may be useful in the comparison of the safety profile among drugs relative to their analgesic efficacy, and consequently may become an important tool in drug development. Further studies are required to compare our experimental data with clinical observations and assess whether the UF is a valuable additional tool in drug selection.

Fig. 7. Influence of variations in blood-effect-site equilibration half-life, $t_{1/2ke0}$ (A and B), and potency parameter, $C_{25}$ (C and D), on the shape of the utility functions (UFs). Continuous lines are the data estimated from the current study (UF in time domain are constructed for a 3.5 μg/kg of fentanyl injection). (A and B) Dashed line is the UF with analgesia’s $t_{1/2ke0} \times 2$, the dotted line is the UF with analgesia’s $t_{1/2ke0} \times 0.5$ (note that in the concentration domain, changes in $t_{1/2ke0}$ do not affect the shape of the UF). (C and D) - - - are the UFs with a lower potency for analgesia ($C_{25} \times 2$), o-o- are the UFs with a higher potency for analgesia ($C_{25} \times 0.5$). P(A) = probability for analgesia; P(R) = probability for respiratory depression.
Fig. 8. Fentanyl effect-site or steady-state concentration-effect relationships for pain relief (pain tolerance in blue) and respiratory depression (in red). Effect (y-axis) represents the tolerated current (pain tolerance) as percentage of baseline current (baseline value is 100% or 26 mA; table 2), and ventilation as percentage of baseline ventilation (baseline value is 100% or 19.9 l/min; table 2).

References