Benefit *versus* Severe Side Effects of Opioid Analgesia

Novel Utility Functions of Probability of Analgesia and Respiratory Depression

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ABSTRACT

Background: Previous studies integrated opioid benefit and harm into one single function—the utility function—to determine the drug toxicity (respiratory depression) in light of its wanted effect (analgesia). This study further refined the concept of the utility function using the respiratory and analgesic effects of the opioid analgesic alfentanil as example.

Methods: Data from three previous studies in 48 healthy volunteers were combined and reanalyzed using a population pharmacokinetic–pharmacodynamic analysis to create utility probability functions. Four specific conditions were defined: probability of adequate analgesia without severe respiratory depression, probability of adequate analgesia with severe respiratory depression, probability of inadequate analgesia without severe respiratory depression, and probability of inadequate analgesia with severe respiratory depression.

Results: The four conditions were successfully identified with probabilities varying depending on the opioid effect-site concentration. The optimum analgesia probability without serious respiratory depression is reached at an alfentanil effect-site concentration of 68 ng/ml, and exceeds the probability of the most unwanted effect, inadequate analgesia with severe respiratory depression (odds ratio, 4.0). At higher effect-site concentrations the probability of analgesia is reduced and exceeded by the probability of serious respiratory depression.

Conclusions: The utility function was successfully further developed, allowing assessment of specific conditions in terms of wanted and unwanted effects. This approach can be used to compare the toxic effects of drugs relative to their intended effect and may be a useful tool in the development of new compounds to assess their advantage over existing drugs. **(ANESTHESIOLOGY 2018; 128:932-42)**

OPIOID analgesics, especially those opioids that are full agonists at the μ-opioid receptor, have a high likeability, rendering them high-risk drugs of abuse, misuse, and eventually addiction.[1,2] Equally important, μ-opioid receptors are abundantly expressed on brainstem respiratory neurons and activation of these receptors is associated with bradypnea, hypoventilation, and apnea.[3] This is especially true when the opioid is overdosed or used in combination with other centrally acting depressant drugs such as alcohol, benzodiazepines, or other illicit substances.[4] It is currently well understood that the combination of misuse/abuse and respiratory depression is a serious threat, especially to a society in which opioid prescriptions for noncancer-related pain reached epidemic proportions.[5,6] For example, in 2013 in The Netherlands, 1 million individuals (in a population of 17 million) received a prescription for opioid treatment, a doubling since 2004.[7] There are no numbers of opioid deaths in The Netherlands, but in the United States, prescription

What We Already Know about This Topic

- The utility of a drug has been defined as the benefit minus the harm it produces
- The utility function has been used to characterize respiratory depression relative to the analgesic effectiveness of various opioids

What This Article Tells Us That Is New

- The concept of the utility function was further developed for alfentanil by calculating the probabilities of adequate analgesia with or without respiratory depression and the probabilities of inadequate analgesia with or without respiratory depression using data from three studies of 48 patients
- A 50% decrease in minute ventilation was taken as the threshold for severe respiratory depression and both 25% and 50% increases in tolerated electrical current were thresholds for analgesia
- The probabilities of the four conditions varied with alfentanil effect-site concentrations

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opioids have been implicated in 165,000 deaths since 1999.[6] Also in an acute setting such as postoperative care, opioid analgesics are associated with cardiorespiratory arrest and mortality.[3,8–10]

Despite these alarming numbers, opioid analgesics remain the cornerstone of modern medicine in the treatment of moderate to severe acute and chronic pain. The main reason is their high efficacy and current lack of adequate alternatives. Presently, novel opioid drugs are being developed with specific modes of action (*e.g.,* acting at multiple receptor systems that offset respiratory depression, or so-called "biased ligands" that circumvent the opioid respiratory pathway) that possibly have advantages over full μ-opioid receptor agonists with less risk of respiratory depression.[11,12] There are various methods that allow assessment of opioid safety. For example, data obtained from postmarketing studies give some indication of safety in large patient populations. However, such studies are available only after development and registration. We propose the development and use of utility or safety functions to determine opioid toxicity (*e.g.*, respiratory depression but it may be any negative outcome such as sedation and dizziness) in light of opioid benefit (analgesia).[13,14] These utility functions may be created and reviewed early on in development (in phase 1 or 2 trials), and allow an objective and reliable characterization of the opioid benefit and risk to determine an optimal dosing regimen.[14] Additionally, utility functions may be used to compare drugs and establish which drug has a better benefit-risk behavior over the other in specific patient populations.[15]

In this study, we further developed the concept of the utility function by calculating probabilities of benefit and risk and by calculating the probabilities of four distinct conditions: the probability of presence of benefit (adequate analgesia) with or without toxicity (respiratory depression) and the probability of inadequacy of benefit (inadequate analgesia) with or without toxicity (respiratory depression). We calculated these probabilities for the μ-opioid receptor agonist alfentanil by analysis of data derived from three different previously published data sets. Probabilities were calculated as function of concentration and as function of time after a bolus infusion.

Materials and Methods

Study Design

The construction of the alfentanil utility function is based on three different study protocols where the effects of alfentanil on ventilation and/or analgesia were analyzed. Part of the results of these three studies have been published previously.[16–18] In two studies (studies 1 and 2), both alfentanil-induced respiratory depression and antinociception were measured in the same subjects[17,18]; in one study (study 3), only alfentanil-induced antinociception was measured.[16] In studies 1 and 2, breath-to-breath ventilation data were collected at isohypercapnia using the "end-tidal forcing" technique.[17,18] The end-tidal partial pressure of carbon dioxide was increased, producing a ventilation level of 20 ± 2 l/min after which alfentanil was infused; during infusion the end-tidal partial pressure of carbon dioxide was maintained at baseline level. The technique is described elsewhere in detail.[19] In brief, subjects breathed through a face mask attached to a pneumotachograph and pressure transducer system (Hans Rudolph, Inc., USA) and to three mass flow controllers (Bronkhorst High Tech, The Netherlands) for the delivery of oxygen, carbon dioxide, and nitrogen. All three controllers received input using custom made RESREG/ACQ (Leiden University Medical Center, The Netherlands) software. Inhaled and exhaled oxygen and carbon dioxide partial pressures were measured at the mouth using a capnograph (Datex Capnomac, Finland). In studies 1 to 3, antinociception (or analgesia) was measured using an electrical pain model.[16–18] Two electrodes were placed on the skin over the shinbone of the right leg, 2 cm apart and 10 cm above the lateral malleolus. A custom-made computer-interfaced current stimulator (Leiden University Medical Center, The Netherlands) generated a current, which increased with 0.5 mA/s and started at 0 mA. The subject had to indicate on a control box when pain threshold (first pain was observed) and pain tolerance (pain could not be tolerated any further) were reached. Pressing the button for pain tolerance ended the stimulus train.

Design of Study 1. (A Study on the Influence of Respiratory Stimulant GAL021 on Alfentanil-induced Respiratory Depression and Antinociception)[17]. Subjects were dosed twice on separate visits, once with GAL021 and once with placebo; only the placebo data are included in the current analysis. Alfentanil was administered using a stepped drug infusion design. After reaching isohypercapnic steady-state ventilation, an initial intravenous infusion of 1.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 6 min was given (loading dose), followed by a continuous infusion of 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 104 min. This was done to achieve a 25 to 30% decrease in ventilation. If the reduction in ventilation was less than 25%, a second dose of 1.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was given and the subsequent continuous infusion was increased to 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$. If the loading dose caused ventilation to decrease by more than 30%, the continuous infusion was reduced to 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Next (110 min after the start of infusion), another loading dose of 1.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$ alfentanil was given for 6 min, followed by a continuous infusion, which was twice the earlier infusion dose. After another 30 min, the alfentanil infusion ended. Total infusion time was 140 to 146 min. Arterial blood samples were taken a t = 0 (baseline), 1, 2, 4, 8, 19, 31, 47, 80, 112, 116, 120, 129, 141, 170, 200, and 250 min; t = 0 is start of alfentanil infusion.

Design of Study 2. (A Study on the Influence of Respiratory Stimulant Doxapram on Alfentanil-induced Respiratory Depression and Antinociception)[18]. All subjects were dosed twice on separate visits, once with doxapram and once with placebo; only the placebo data are included in the current analysis. The study protocol was in accordance

with study 1, except for differences in infusion regimen and sample times. In this protocol, the loading dose was 8 μg · kg^{-1} · min^{-1} for 2 min, followed by a maintenance infusion of 0.6 μg · kg^{-1} · min^{-1} for 98 min. Hereafter, the loading dose was repeated and maintenance infusion was increased to 0.9 μg · kg^{-1} · min^{-1} for 30 min. Total infusion time was 132 min. Arterial blood samples were taken at t = 0 (baseline), 1, 2, 4, 5, 7, 8, 10, 19, 31, 40, 47, 59, 80, 88, 99, 101, 102, 104, 105, 107, 110, 119, 131, 140, 155, and 170 min.

Design of Study 3. (A Pharmacokinetic–Pharmacodynamic Modeling Study on Alfentanil-induced Antinociception)[16]. All subjects were dosed twice on separate visits, once with alfentanil and once with placebo; only the alfentanil data are included in the current analysis. Subjects received a target-controlled infusion of alfentanil with plasma concentration targets of 50 ng/ml for 10 min, followed by 100 ng/ml for another 10 min and 150 ng/ml for a final 10 min. Antinociception was measured during and for 270 min after infusion. Arterial blood samples were obtained at t = 0 (baseline), 3, 5, 9, 13, 15, 19, 23, 25, 29, 31, 33, 35, 38, 43, 53, 60, 75, 90, 120, 150, 180, 240, and 300 min.

Pharmacokinetic–Pharmacodynamic Analysis

The population pharmacokinetics and pharmacodynamics of alfentanil were determined in two stages using NONMEM version 7.3.0 (software for nonlinear mixed-effects modeling; ICON plc, USA).[20] In the first stage, the pharmacokinetics data were analyzed with a three-compartment model based on previous analyses.[16–18] To eliminate a possible hysteresis between alfentanil plasma concentration and effect site, an effect compartment was postulated with blood effect-site equilibration half-life $t_{½}k_{e0}$. In the second stage, population pharmacodynamics model parameters were determined with fixed individual pharmacokinetics model parameters as determined in the first stage.

Ventilation data were modeled by[13,17]:

$$V(t) = V_B \left[1 + \left(C_E(t) / C_{50,V}\right)^{\gamma_V}\right]^{-1} \quad (1)$$

where the V(t) is the ventilation at time t, V_B baseline ventilation, $C_E(t)$ is the effect-site concentration at time t, $C_{50,V}$ the effect-site concentration producing a 50% decrease in ventilation, and Υ_V the shape or Hill parameter for ventilation.

Transcutaneous electrical pain responses were modeled by[13,16]:

$$P(t) = P_B \left[1 + 0.5 \bullet \left(C_E(t) / C_{50,A}\right)^{\gamma_A}\right] \quad (2)$$

where the P(t) is the pain stimulus intensity at which a pain tolerance response occurs at time t, P_B is the predrug or baseline stimulus intensity at which pain tolerance response occurs, $C_E(t)$ is the effect-site concentration at time t, $C_{50,A}$ the effect-site concentration producing a 50% increase in stimulus intensity, and Υ_A the shape or Hill parameter for analgesia.

Model parameters were assumed to be log-normally distributed. Residual error was assumed to contain an additive and a relative error for concentration and an additive error for effect parameters.

Utility Functions

The utility functions (U) were calculated as previously described.[13] In brief, 1,000 pharmacodynamic profiles as functions of concentration, $U(C_E)$, and time, U(t), were simulated according to the medians and interindividual variabilities (ω^2) as listed in table 1. The number of times severe respiratory depression and adequate analgesia occurred were divided by N to obtain estimates of the probabilities of their occurrence. A 50% reduction in minute ventilation was taken as a threshold for severe respiratory depression, *i.e.*, P(R > 0.5), and both a 25% and a 50% increase in tolerated electrical current were taken as threshold for analgesia, *i.e.*, P(A > 0.25) and P(A > 0.5), respectively. The utilities U1 were defined as:

Table 1. Pharmacokinetic and Pharmacodynamic Parameter Estimates

Parameter	Estimate ± SEE	ω^2 ± SEE	ν^2 ± SEE
Pharmacokinetic parameter estimates			
V_1 (l)	5.73 ± 0.82	0.08 ± 0.03	0.04 ± 0.02
V_2 (l)	3.02 ± 1.41	0.58 ± 0.42	0.03 ± 0.02
V_3 (l)	12.1 ± 0.56	0.05 ± 0.02	*
CL (l/min)	0.29 ± 0.01	0.11 ± 0.04	0.01 ± 0.004
Q_2 (l/min)	1.55 ± 0.18	*	0.08 ± 0.03
Q_3 (l/min)	0.43 ± 0.05	0.04 ± 0.02	*
σ_1	2.85 ± 0.85		
σ_2	0.14 ± 0.01		
Pharmacodynamic parameter estimates			
Ventilation			
V_B	19.5 ± 1.18	0.0719 ± 0.0237	
$C_{50,V}$ (ng/ml)	81.6 ± 20.5	0.896 ± 0.305	
Υ_V	1 (fixed)	0.746 ± 0.616	
$t_{1/2}k_0V$ (min)	3.99 ± 1.63	*	
σ_V	2.26 ± 0.189		
Analgesia			
P_B	16.0 ± 1.12	0.176 ± 0.0589	
$C_{50,P}$ (ng/ml)	97.9 ± 19.4	1.08 ± 0.428	
Υ_P	1 (fixed)	0.193 ± 0.079	
$t_{1/2}k_0P$ (min)	11.7 ± 5.22	0.219 ± 0.155	
σ_P	3.60 ± 0.655		

*Not estimable.

$C_{50,P}$ = the effect-site concentration causing a 50% increase in stimulus intensity; $C_{50,V}$ = effect-site concentration causing 50% reduction of ventilation; CL = clearance of compartment V_1; P_B = baseline pain tolerance; Q_2 and Q_3 = intercompartmental clearances between compartments V_2 and V_1 and V_3 and V_1; SEE = standard error of the estimate; V_1, V_2, V_3 = volume of compartments 1, 2, and 3; ω^2 = variance of the model parameter across the population; σ_1 = SD of absolute residual variability; σ_2 = SD of relative variability; σ_V = SD of the absolute residual variability for ventilation; σ_P = SD of the absolute residual variability for analgesia; $t_{1/2}k_0V$ = the blood effect-site equilibration half-life for ventilation; ν^2 = variance of between-occasion variability; V_B = baseline ventilation; Υ_P = a shape parameter for analgesia; Υ_V = a shape parameter for ventilation.

$$U1(A > 0.25) = P(A > 0.25) - P(R > 0.5) \quad (3)$$

and

$$U1(A > 0.5) = P(A > 0.5) - P(R > 0.5) \quad (4)$$

A disadvantage of this definition is that the U_1 cannot be interpreted as a probability, because its values range between –1 and 1. The utility may be positive although the probability of adequate analgesia is small. We therefore calculated utility U2 giving the probability of adequate analgesia without severe respiratory depression (a desirable condition), with the probability of adequate analgesia defined as P(A > 0.25) or P(A > 0.5):

$$U2(A > 0.25) = P(A > 0.25 \text{ AND } R \leq 0.5) \quad (5)$$

and

$$U2(A > 0.5) = P(A > 0.5 \text{ AND } R \leq 0.5) \quad (6)$$

Finally, we defined the utility U3 that gives the probability of severe respiratory depression and inadequate analgesia (the least desirable condition) for P(A ≤ 0.25) and P(A ≤ 0.5):

$$U3(A \leq 0.25) = P(R > 0.5 \text{ AND } A \leq 0.25) \quad (7)$$

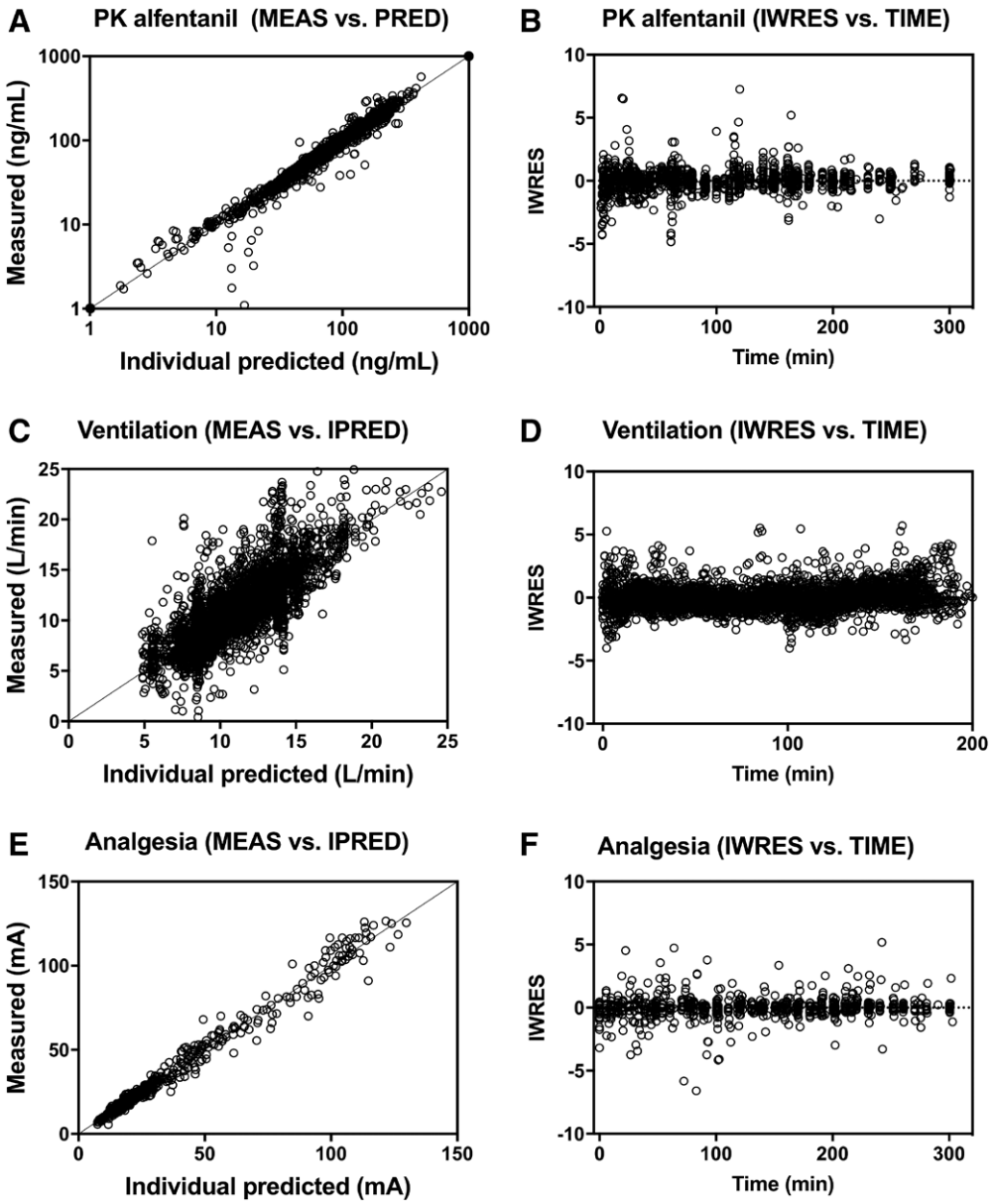

Fig. 1. Goodness-of-fit plots of the pharmacokinetic and pharmacodynamic analysis. (*A*) Alfentanil concentration: measured values (MEAS) *versus* individual predicted values (IPRED). (*B*) Alfentanil concentration: individual weighted residuals (IWRES) *versus* time. (*C*) Ventilation: measured *versus* individual predicted values. (*D*) Ventilation: IWRES *versus* time. (*E*) Analgesia: measured *versus* individual predicted values. (*F*) Analgesia: IWRES *versus* time.

and

$$U3(A \le 0.5) = P(R > 0.5 \text{ AND } A \le 0.5) \quad (8)$$

To assess the uncertainty in these measures, the above procedure was repeated for 1,000 bootstrap-derived replicated estimates of the model parameters (medians and expected value η covariances). Because the full bootstrap is not feasible with respect to computer time, we used the simplified nonparametric bootstrap method as implemented in NONMEM.[21] In short, rather than sampling from individual data to create bootstrap data sets and fitting each data set, the simplified bootstrap samples from the empirical Bayesian estimates of the interindividual variability terms (η) from the fit of the original data. This yields estimates of the interindividual variability in the model parameters for each simplified bootstrap iteration, so that the uncertainty in the interindividual variability estimates—and hence the uncertainty in the utility functions—can be assessed. Pharmacokinetic–pharmacodynamic profiles were calculated in the software environment R, rather than in NONMEM to gain speed (with analytical expressions for concentrations after a bolus dose).

Results

In the analysis we included pharmacokinetic data sets from 48 subjects, ventilation pharmacodynamic data from 19 subjects, and analgesia data from 32 subjects. All subjects were Caucasian with a mean age (range) of 23.7 (19 to 31) yr, mean weight of 78.8 (70.5 to 99.8) kg, and mean body mass index of 24.0 (20.2 to 29.5) kg/m^2.

Pharmacokinetic Analysis

The PK model consisted of three compartments: one central compartment (V_1) and two peripheral compartments (V_2 and V_3). The pharmacokinetic parameters estimates are shown in table 1. Two error terms were incorporated in the model, an additive (σ_1) and a relative (σ_2). Goodness-of-fit plots are shown in figure 1, panels *A* and *B*. Inspection of the data demonstrates that the model adequately describes the data. There is a small misfit in the alfentanil pharmacokinetic data in the lower concentration ranges as described previously (data from study 1).[17]

Pharmacodynamic Analysis

The goodness-of-fit plots, shown in figure 1, panels *C* to *F*, show that the pharmacodynamic models adequately describe the ventilation and analgesia data. Pharmacodynamic parameter estimates are given in table 1. The blood effect-site equilibration half-life of alfentanil-induced ventilatory depression was relatively small (estimate = 3.99 ± 1.6 min); the $C_{50,V}$ or potency parameter estimate = 81.6 ± 20.5 ng/ml. Compared to ventilation, the blood effect-site equilibration half-life for analgesic effect was greater by a factor of 3 ($t_{1/2}k_0$ for analgesia

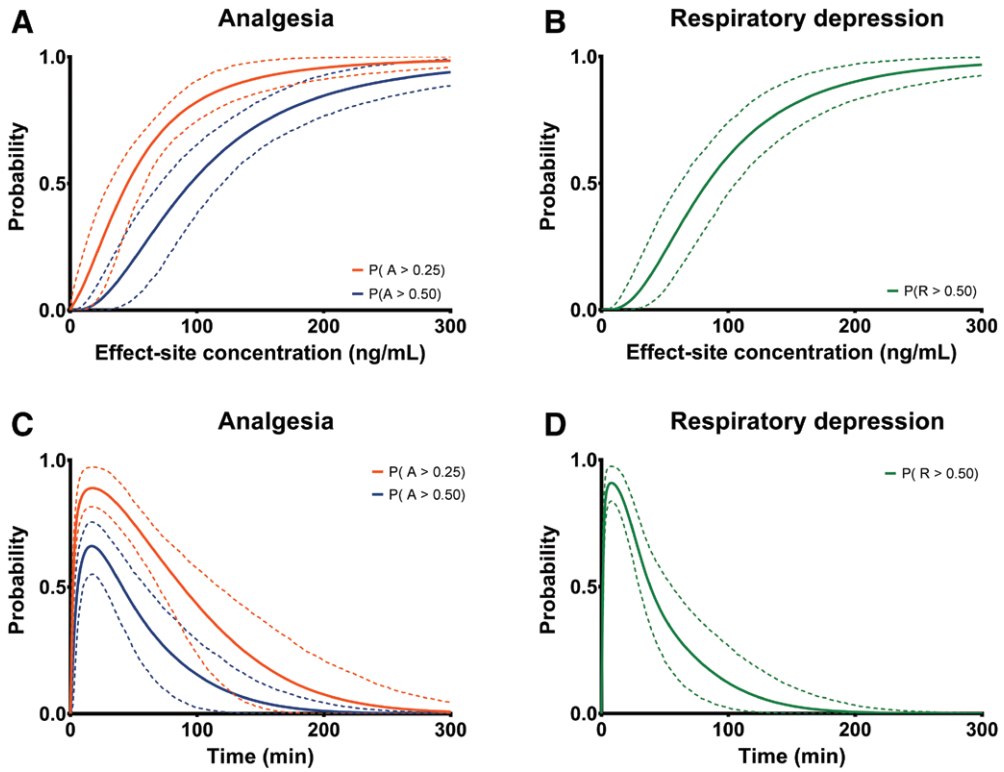

Fig. 2. Probability of analgesia and respiratory depression. (*A*) Probability of analgesia *versus* effect-site concentration for P(A(C_E) > 0.25) (*orange lines*) and P(A(C_E) > 0.5) (*blue lines*). (*B*) Probability of respiratory depression *versus* effect-site concentration for P(R(C_E) > 0.5). (*C*) Probability of analgesia *versus* time after a bolus infusion of 50 μg alfentanil for P(A(t) > 0.25) (*orange lines*) and P(A(t) > 0.5) (*blue lines*). (*D*) Probability of respiratory depression *versus* time after a bolus infusion of 50 μg alfentanil for P(R(t) > 0.5). The *broken lines* are the 95% CIs.

= 11.7 ± 5.2 min), while potency parameter $C_{50,A}$ was of the same order of magnitude (C_{50} for analgesia = 97.9 ± 19.4 ng/ml).

Utility Functions

The sigmoidal relationships between effect probability and effect-site concentrations are given in figure 2A for $P(A(C_E) > 0.25)$ and $P(A(C_E) > 0.5)$ and for $P(R(C_E) > 0.5)$ in figure 2B. The relationships are given plus or minus the 95% CIs. The probability of effect in the time domain after a bolus administration of 50 μg/kg alfentanil is given in figure 2C for $P(A(t) > 0.25)$ and $P(A(t) > 0.5)$ and in figure 2D for $P(R(t) > 0.5)$. As expected, the probabilities of at least 25% analgesia exceed that of at least 50% analgesia in both concentration and time domains. Directly after the bolus infusion (fig. 2, C and D), the probability of analgesia greater than 25% and respiratory depression greater than 50% both approach 1. Due the rapidly decreasing effect-site concentration, the probabilities drop toward zero, albeit at a greater speed for respiratory depression than for analgesia ($P(A(t) > 0.25)$: not different from zero at t > 200 min; $P(R > 0.5)$: not different from zero at t > 130 min).

U1. The calculated utility functions ± 95% CIs as function of effect-site concentration are shown in figure 3, A and B, for $P(A(C_E) > 0.25) - P(R(C_E) > 0.5)$ and $P(A(C_E) > 0.5) - P(R(C_E) > 0.5)$. The utility function $P(A(C_E) > 0.25) - P(R(C_E) > 0.5)$ is positive over the effect-site concentration range of 0 to 300 ng/ml, but only significantly different from zero from 26 to 158 ng/ml (fig. 3A). This indicates that over the effect-site concentration ranges from 26 to 168 ng/ml $P(A > 0.25) > P(R > 0.5)$. The maximum effect ($U1(C_E) = 0.31$; 95% CI, 0.08 to 0.52) occurred at an effect-site concentration of 52 ng/ml. The utility function $P(A(C_E) > 0.5) - P(R(C_E) > 0.5)$ was not different from zero over the effect-site concentration range of 0 to 300 ng/ml (fig. 3B), indicative of a balance between the probability for analgesia and respiratory depression, *i.e.*, $P(A(C_E) > 0.5) = P(R(C_E) > 0.5)$.

The utility in the time domain, given for a bolus dose of 50 μg/kg (figs. 3, C and D), is biphasic for both $P(A(t) > 0.25)$ and $P(A(t) > 0.5)$. For $P(A(t) > 0.25) - P(R(t) > 0.5)$, the function is negative from t = 2 to 6 min (peak effect, –0.25; 95% CI, –0.043 to –0.08, at t = 2 min) followed by values significantly greater than zero from t = 22 to 124 min (fig. 3C). Thereafter, the function is not different from zero, indicative of similar probabilities for analgesia and respiratory depression. For $P(A(t) > 0.5) - P(R(t) > 0.5)$ the function is negative from t = 1 to 21 min (peak effect, –0.54; 95% CI, –0.74 to –0.36, at t = 2 min), after which the function is not different from zero (fig. 3D).

U2. The desirable outcome of opioid treatment of pain is analgesia with limited respiratory depression. We give the utility functions $P(A(C_E) > 0.25$ and $R(C_E) \leq 0.5)$ and

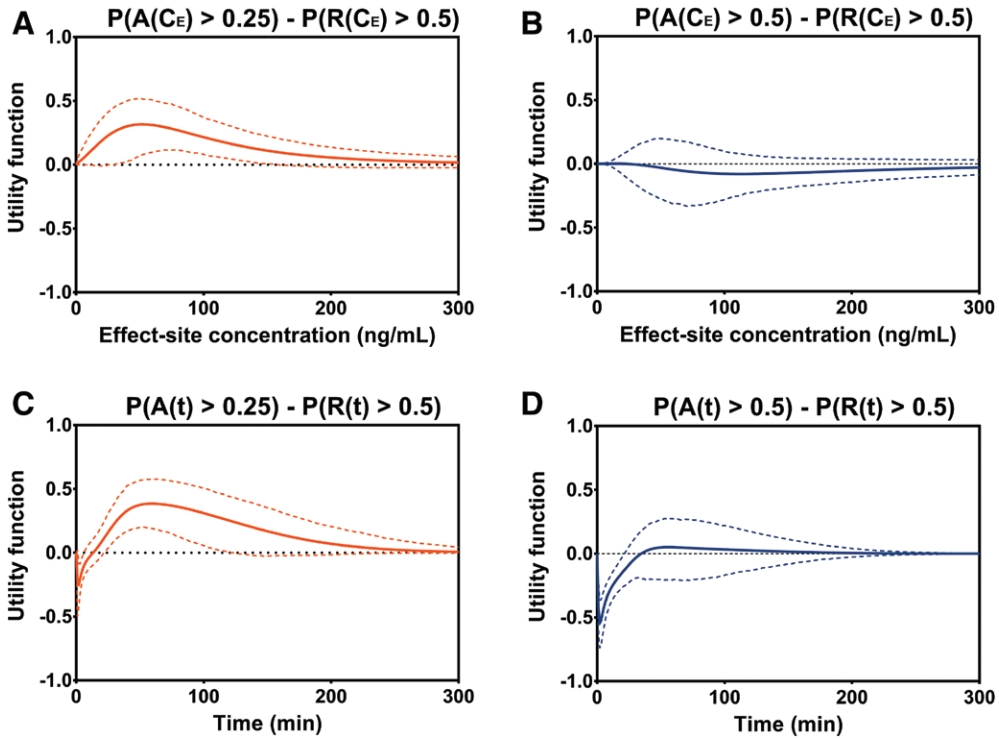

Fig. 3. Utility functions. (*A*) Probability of at least 25% analgesia minus the probability of at least 50% respiratory depression *versus* effect-site concentration. (*B*) Probability of at least 50% analgesia minus the probability of at least 50% respiratory depression *versus* effect-site concentration. (*C*) Probability of at least 25% analgesia minus the probability of at least 50% respiratory depression *versus* time after a bolus infusion of 50 μg alfentanil. (*D*) Probability of at least 50% analgesia minus the probability of at least 50% respiratory depression *versus* time after a bolus infusion of 50 μg alfentanil. The *continuous lines* represent the utility function, the *broken lines* the 95% CIs.

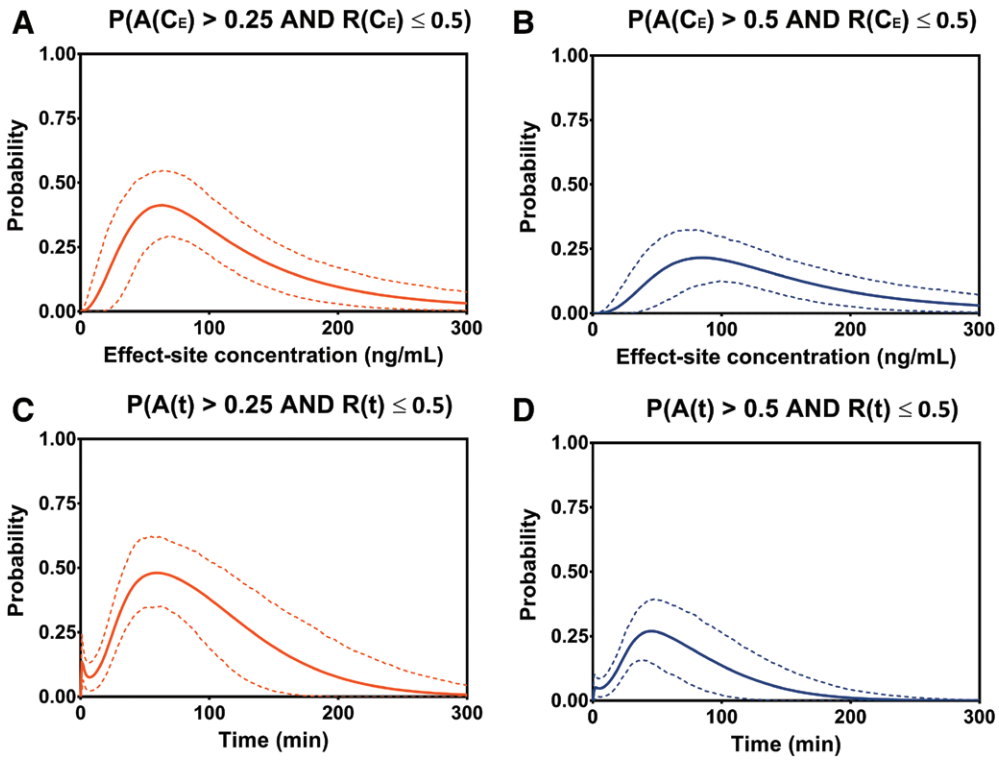

Fig. 4. (*A*) Probability of at least 25% analgesia and no more than 50% respiratory depression *versus* effect-site concentration. (*B*) Probability of at least 50% analgesia and no more than 50% respiratory depression *versus* effect-site concentration. (*C*) Probability of at least 25% analgesia and no more than 50% respiratory depression *versus* time after a bolus infusion of 50 μg alfentanil. (*D*) Probability of at least 50% analgesia and no more than 50% respiratory depression *versus* time after a bolus infusion of 50 μg alfentanil. The *continuous lines* are the probabilities, the *broken lines* the 95% CIs.

$P(A(C_E) > 0.5$ and $R(C_E) \leq 0.5)$ in figure 4. In the concentration domain, the probability of at least 25% analgesia, but less than 50% respiratory depression reaches a maximum of 0.41 (95% CI, 0.29 to 0.55) at an effect-site concentration of 68 ng/ml (fig. 4A), while for at least 50% analgesia and less than 50% respiratory depression the maximum of 0.21 (95% CI, 0.12 to 0.31) is reached at an effect-site concentration of 93 ng/ml (fig. 4B). The utilities in the time domain (after a bolus of 50 μg/kg alfentanil) are given in fig. 4, C and D.

U3. The least desirable outcome of opioid therapy is a severe respiratory depression, $P(R > 0.5)$ with inadequate analgesia, $P(A(C_E) \leq 0.25)$ or $P(A(C_E) < 0.5)$. We give the utility functions $P(R(C_E) > 0.5$ and $A(C_E) \leq 0.25)$ and $P(R(C_E) > 0.5$ and $A(C_E) \leq 0.5)$ in figure 5. In the concentration domain the probability of at least 50% respiratory depression with no more than 25% analgesia (fig. 5A) is small with a peak at an effect-site concentration of 69 ng/ml (probability 0.13; 95% CI, 0.7 to 0.21). The probability of at least 50% respiratory depression with no more than 50% analgesia (fig. 5B) is greater, the greatest probability (0.29; 95% CI, 0.20 to 0.41) was observed at an effect-site concentration of 98 ng/ml. The utilities in the time domain (after a bolus of 50 μg/kg alfentanil) are given in figure 5, C and D.

Utility Surface

In figure 6A–D, we plotted the continuum of probabilities of presence or absence of alfentanil analgesia in combination with presence or absence of serious respiratory depression (*i.e.*, the utility surface). In panels *A* and *B* of figure 6, we plotted the probabilities against effect-site concentration; in panel *C* and *D* the probabilities against time after a 50 μg/kg alfentanil bolus infusion (or 3.5 mg for a 70 kg patient) at time t = 0.

The utility surface analysis results in multiple conditions presented by colored surfaces and iso-utility lines (panels *B* and *D*); the iso-utility lines are the curves of the utility functions defined by U2 and U3 (compare with curves in figs. 4 and 5), while the surfaces are defined by A and R with A++ at least 50% analgesia, A+ at least 25% analgesia, A– less than 25% analgesia, R+ at least 50% respiratory depression, and R– less than 50% respiratory depression. This results in the following conditions:

Green surface: analgesia without respiratory depression (A++R– and A+R–);
Red surface: no analgesia with respiratory depression (A–R+);
Yellow surface: no analgesia and no respiratory depression (A–R–); and
Orange surface: analgesia with respiratory depression (A++R+ and A+R+).

The smooth transitions between colors are transients in between the given states.

It is clear from figures 4 and 6 (panels *A* and *B*) that the optimum analgesia probability without serious respiratory

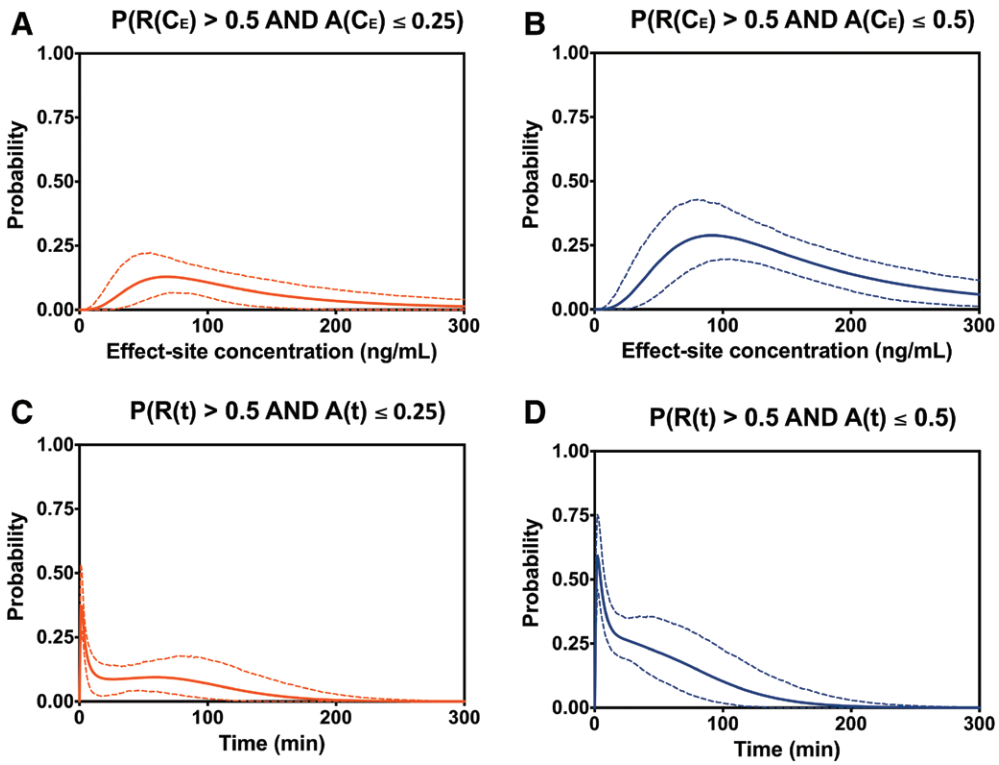

Fig. 5. (*A*) Probability of at least 50% respiratory depression and no more than 25% analgesia *versus* effect-site concentration. (*B*) Probability of at least 50% respiratory depression and no more than 50% analgesia *versus* effect-site concentration. (*C*) Probability of at least 50% respiratory depression and no more than 25% analgesia *versus* time after a bolus infusion of 50 μg alfentanil. (*D*) Probability of at least 50% respiratory depression and no more than 50% analgesia *versus* time after a bolus infusion of 50 μg alfentanil. The *continuous lines* are the probabilities, the *broken lines* the 95% CIs.

depression (green surface in fig. 6) is reached at an effect-site concentration of 60 ng/ml; thereafter, the probability of analgesia is reduced and eventually exceeded by the probability of serious respiratory depression (orange surface). Figure 6, C and D, shows that after a single injection (50 μg/kg), maximum analgesia with serious respiratory depression (orange surface) peaks at 10 min, an optimum in analgesia probability without serious respiratory peaks at 60 min, after which both analgesia and respiratory depression dissipate.

Discussion

In the treatment of pain and nociceptive responses we aim to provide optimal analgesic effect with preferably no (or very little) side effects. Still, the most common group of drugs used in pain medicine and anesthesia to relief moderate to severe pain and blunt nociceptive responses (*i.e.*, the opioid analgesics) produces a myriad of side effects. Since "benefit" (analgesia) and "harm" (side effects) coincide, but often with dose or concentration-effect relationships that are distinct (*i.e.*, not parallel), it is often difficult to reliably combine multiple endpoints into one number or function.[14] Sheiner and Melmon introduced a concept derived from economic decision theory that allows combining of different endpoints into one number, the utility, which they defined as the benefit of a drug minus the harm it produces.[22] They applied their concept to describe the benefit and harm of antihypertensive therapy. The concept was later used by Cullberg *et al.* to define the outcome of antithrombin therapy.[23] In earlier studies, we applied the concept of the utility function to characterize a serious and potentially lethal opioid side effect, respiratory depression, relative to the obtained analgesic efficacy. We tested various opioids including fentanyl, oxycodone, and the relatively new opioids, tapentadol and cebranopadol.[11,13,15,24] Our main aim was to create a set of utility functions that allows comparisons among drugs. We argued that a drug with positive utilities over the clinical concentration range (*i.e.*, with a higher probability for analgesia than respiratory depression) is preferable over a drug with a negative utility (*i.e.*, with a higher probability for respiratory depression than analgesia). In their editorial, Kharasch and Rosow argued that while the benefit-risk measure that we developed (*i.e.*, the utility function) "appears to be precise and reproducible [and] also seems to be an excellent method for combining high-quality estimates of population pharmacokinetic–pharmacodynamic modeling," it requires refinement and validation that it predicts relevant clinical outcomes.[14] In the current study we further developed the utility function. We estimate 95% confidence limits around the function based on bootstrap sampling of the nonparametric distribution of the model parameters. Furthermore, we calculate the probabilities of a series of distinct conditions: the probability of adequate analgesia with or without

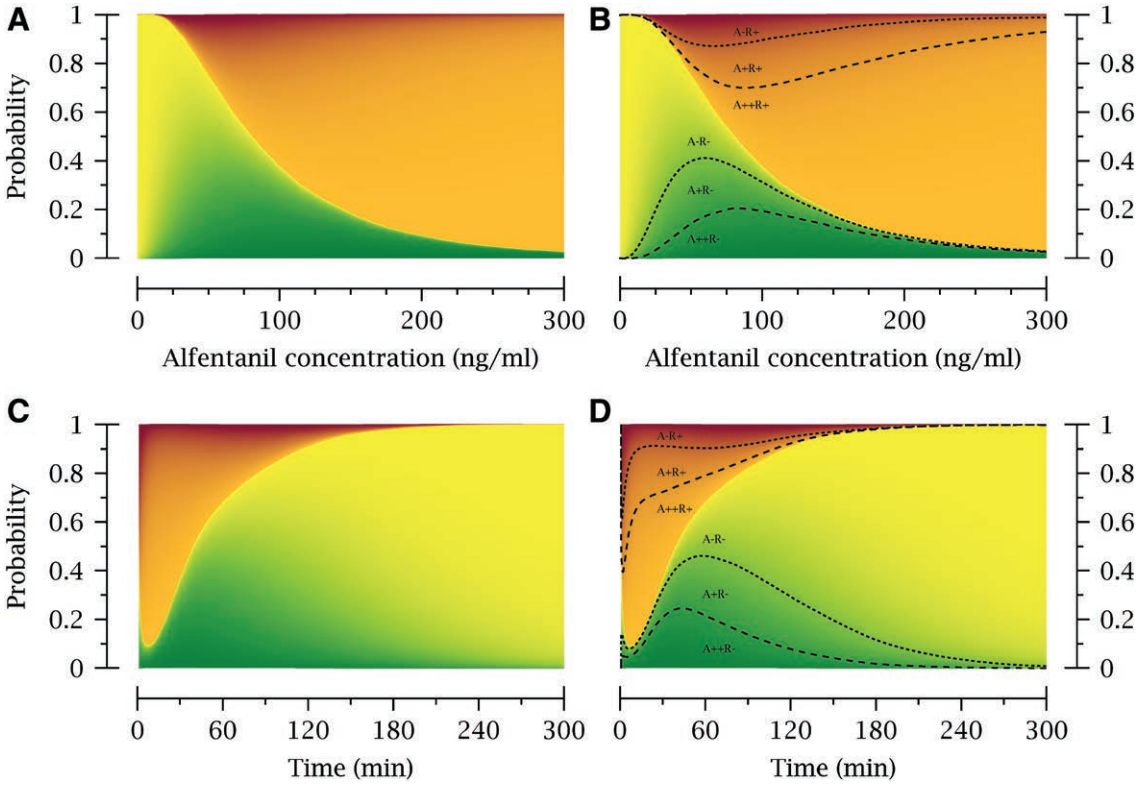

Fig. 6. Alfentanil response surface: continuum of probabilities of alfentanil-induced analgesia and respiratory depression. (*A* and *B*) Probability *versus* alfentanil effect-site concentration. (*C* and *D*) Probability *versus* time after a 50 μg/kg alfentanil bolus at time t = 0. The *color shading* from green to yellow and red to orange represents the context dependency of the utility functions on the postulated threshold for analgesia. The *lines* in panels *B* and *D* are the curves of utility functions U2 and U3 (compare with figs. 4 and 5). The surfaces are defined by A and R with A++ at least 50% analgesia, A+ at least 25% analgesia, A– less than 25% analgesia, R+ at least 50% respiratory depression, and R– less than 50% respiratory depression.

severe respiratory depression (A++R–, A+R–, A++R+, and A+R+; figs. 6 and 7), and the probability of inadequate analgesia with or without severe respiratory depression (A–R+, A–R–, figs. 6 and 7). We argue that the use of these adapted utility functions is preferable above a utility function that is the result of the subtraction of one probability from the other, that is constrained in magnitude between values –1 to +1 and that gives no indication of the probability of distinct outcomes, such as desired (A++R–) and undesired outcomes (A–R+) and all possibilities in between.

In the current study, we applied the adapted utility functions to the μ-opioid analgesic alfentanil. We combined the results of three previous pharmacokinetic–pharmacodynamic analyses into one analysis. The analyses were performed in multiple steps. A population pharmacokinetic analysis led to individual pharmacokinetic parameters estimates that were inputted into the pharmacodynamic models of analgesia and respiratory depression. We subsequently calculated the probabilities of P(A > 0.25), P(A > 0.5), and P(R > 0.5) in both concentration and time domains (fig. 2) by performing 1,000 simulations for both endpoints. Subsequently, the original (U1) and adapted utility functions (U2 and U3) were determined (figs. 3–5). As stated previously, the utility function is context sensitive, in which the context is the numerical response threshold.[13] For example, for P(A) we applied two thresholds: A > 0.25 and A > 0.5; the difference in thresholds reflects the difference in analgesic effect (*i.e.*, a 25% and 50% increase in tolerated electrical current). We regard the 25% threshold as the clinically more realistic endpoint for chronic pain therapy (the effect-site concentration producing a 25% increase in stimulus intensity is in the range of concentrations observed in postoperative pain therapy),[25] while the 50% threshold may be more relevant in anesthesia practice.[26] Further studies will need to confirm whether our extrapolation of experimental data to clinical data is valid.

The results of our analyses are summarized in the utility surface of figure 6, which combines multiple conditions into one graph: analgesia without respiratory depression (green surface), respiratory depression without analgesia (red surface), neither respiratory depression nor analgesia (yellow surface), and analgesia combined with respiratory depression (orange surface). If we compare the two extremes (red *vs.* green surfaces), it is obvious that the probability of the desired effect (green surface) exceeds the probability of the most unwanted effect (red surface). At an effect-site concentration of 68 ng/ml the probabilities differ significantly (odds ratio, 4.0; fig. 6, A and B); similarly, 1 h after a bolus dose of 50 μg/kg, the probabilities differ (odds ratio 4.0; fig. 6, C and D).

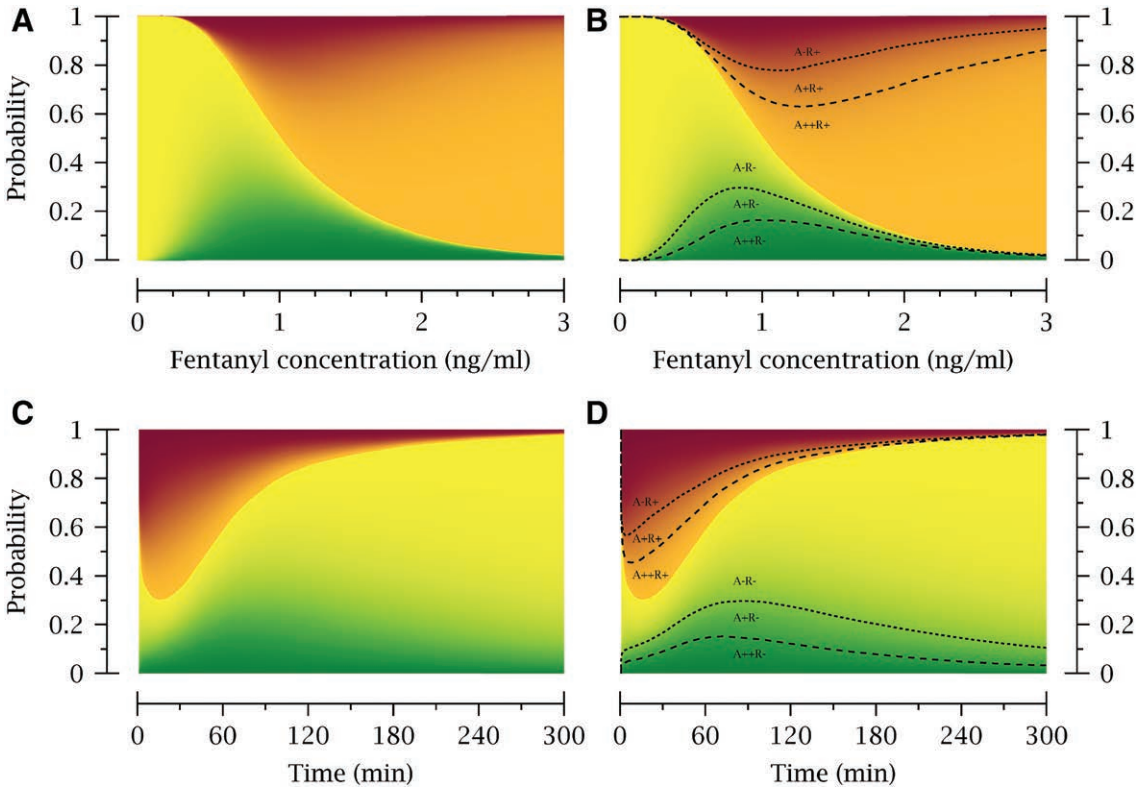

Fig. 7. Fentanyl response surface: continuum of probabilities of fentanyl-induced analgesia and respiratory depression. (*A* and *B*) Probability *versus* alfentanil effect-site concentration. (*C* and *D*) Probability *versus* time after a 50 μg/kg alfentanil bolus at time t = 0. The *color shading* from green to yellow and red to orange represents the context dependency of the utility functions on the postulated threshold for analgesia. The *lines* in panels *B* and *D* are the curves of utility functions U2 and U3. The surfaces are defined by A and R with A++ at least 50% analgesia, A+ at least 25% analgesia, A– less than 25% analgesia, R+ at least 50% respiratory depression, and R– less than 50% respiratory depression.

It is important to realize that while the probabilities of the most desired condition (adequate analgesia without respiratory depression) and the least desired condition (inadequate analgesia with respiratory depression) are both maximal at about the same effect-site concentration, their probabilities are different. The probability of the most desired condition is much higher than the probability of the least desired condition, which would be expected of a clinically useful drug. Even if the probabilities were about the same, or reversed, the utility function would retain its utility as classifying the drug under investigation as a drug with lower clinical utility. The concentrations where the probabilities of the conditions are maximal depend on the thresholds chosen, as can be seen in figure 6, and the potencies for the desired and side effects. The point is that the clinical utility of drugs may be compared, under the condition that the chosen thresholds are the same.

We consider the utility function suitable for a comparison among drugs. As an example, we compared the utility surfaces of alfentanil and fentanyl. Both are fenylpiperidine μ-opioid analgesics and are used as intravenous anesthetics. In figure 7, we plotted the fentanyl utility surface based on our previous population pharmacokinetic–pharmacodynamic analysis.[13] Figure 7, A and B (utility *vs.* fentanyl C_E), may be compared to figure 6, A and B (utility *vs.* alfentanil C_E). These response surfaces of the two opioids are similar and imply that fentanyl is more potent by a factor of 70 to 80 (in terms of effect-site concentration). This potency difference derived from the utility surface is similar to the potency ratio of 75 observed for the effect-site concentration that caused one-half of the electroencephalogram-slowing (6.9 ng/ml for fentanyl and 520 ng/ml for alfentanil).[26] These similarities give further validity to our approach. The surface similarity indicates that for the same probability of analgesia, a similar probability of respiratory depression is observed for these two opioids. While we believe that the comparison between these two opioids is valid (both drugs were tested in a similar population of healthy volunteers using identical experimental set-ups), we realize that our data are derived from young volunteers without pain or comorbidities, and further studies should address the utility of opioid treatment in patients. For example, our approach is suitable to compare the utility of analgesic medication between patient subpopulations, such as patients with and without sleep apnea syndrome, patients with and without chronic pain, opioid-naive patients *versus* chronic opioid users. Additionally, our approach enables construction of utility functions of drug efficacy *versus* slowly emerging complications of long-term drug therapy, such as development

of tolerance, hyperalgesia, cognitive dysfunction, or the late occurrence of tissue damage.

In conclusion, we further refined the utility function as (surrogate) measure of opioid benefit *versus* harm. We defined four distinct states of analgesia and respiratory depression that reflect four clinical conditions that are either desirable (analgesia without respiratory depression) or highly undesirable (respiratory depression without analgesia), and two intermediate (undesirable) states (neither analgesia nor respiratory depression and analgesia combined with respiratory depression). Our utility function may be used to compare the respiratory effects of analgesics and may be a useful tool in the development of novel (opioid) analgesics.

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Competing Interests

The authors declare no competing interests.

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