The Drug Titration Paradox: Correlation of More Drug With Less Effect in Clinical Data

Thomas W. Schnider[1,*], Charles F. Minto[2] and Miodrag Filipovic[1]

While analyzing clinical data where an anesthetic was titrated based on an objective measure of drug effect, we observed paradoxically that greater effect was associated with lesser dose. With this study we sought to find a mathematical explanation for this negative correlation between dose and effect, to confirm its existence with additional clinical data, and to explore it further with Monte Carlo simulations. Automatically recorded dosing and effect data from more than 9,000 patients was available for the analysis. The anesthetics propofol and sevoflurane and the catecholamine norepinephrine were titrated to defined effect targets, i.e., the processed electroencephalogram (Bispectral Index, BIS) and the blood pressure. A proportional control titration algorithm was developed for the simulations. We prove by deduction that the average dose–effect relationship during titration to the targeted effect will associate lower doses with greater effects. The finding of negative correlations between propofol and BIS, sevoflurane and BIS, and norepinephrine and mean arterial pressure confirmed the titration paradox. Monte Carlo simulations revealed two additional factors that contribute to the paradox. During stepwise titration toward a target effect, the slope of the dose–effect data for the population will be "reversed," i.e., the correlation between dose and effect *will not be positive*, but will be negative, and will be "horizontal" when the titration is "perfect." The titration paradox must be considered whenever data from clinical titration (flexible dose) studies are interpreted. Such data should not be used naively for the development of dosing guidelines.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ It is generally expected that there is a positive correlation between dose and effect, i.e., increasing dose is associated with increasing effect as described by classical pharmacodynamic models (e.g., Hill E_{max} (maximum effect) model).

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Why is the expected positive slope of the dose–effect relationship paradoxically negative when drugs are titrated to effect?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study is the first to describe the process of stepwise titration of drug dosing based on measured drug effect. It provides an explanation of factors that contribute to the titration paradox, i.e., the finding of a negative correlation between dose and effect.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Data from drug titration studies cannot naively be described with pharmacodynamic models that expect increasing effect with increasing dose. Data from early-phase dose–effect studies where the dose is chosen independently of the observed effect should not be analyzed together with data obtained from clinical titration studies.

It has been well established, based on many high-quality scientific publications, that there is a clear relationship between drug dose and effect—more drug will cause more effect and vice versa. Indeed, the effect of a new drug is usually explored in small numbers of subjects and ultimately modeled with mathematical equations that predict increasing effect with increasing dose (up to some maximum). This *positive correlation* between dose and effect is widely accepted and expected for both the individual and population dose–effect data.

During an initial analysis of automatically recorded data during intravenous anesthesia for surgery, we unexpectedly observed that during the maintenance phase of anesthesia, lower doses of propofol were associated with greater brain effect, i.e., there was a *negative correlation* between dose and effect. Based on this paradoxical

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observation, we developed a hypothesis that the *average* dose–effect relationship obtained during titration of dose to effect will associate lower doses with greater effects. We refer to this *negative correlation* between dose and effect as the "titration paradox." We developed our hypothesis based on the assumption that the sensitivity of patients is different and that the goal of drug titration is to achieve the same therapeutic effect in all patients.

In the context of titration, the term "dose" refers to repetitive dosing, not a single dose. Instead, dose relates to a steady state or pseudo-equilibration among dosing rate, blood drug concentrations, and measured drug effects. In the acute setting of clinical anesthesia, a "titrated dose" often refers to one of several types of infusions. This study, therefore, will examine three types of infusion as a dose in their respective relationships to titration to effect. Norepinephrine is administered by a zero-order infusion rate, sevoflurane is administered as a percent of inhaled gases, and propofol is administered via a continuously adjusting infusion rate designed pharmacokinetically to quickly achieve and maintain a target propofol concentration in blood or in a time-offset effect site.

In this study, we explored our hypothesis in three ways. Firstly, we sought to develop a mathematical proof that the *average* dose–effect relationship during titration to effect will associate lower doses with greater effects. Secondly, we examined a larger set of clinical data for evidence of the titration paradox in the relationships between the dose and brain effect of propofol, the dose and brain effect of sevoflurane and the dose and blood pressure effect of norepinephrine. Thirdly, we performed Monte Carlo simulations to explore other factors that might contribute to the titration paradox.

METHOD

Mathematical proof

With reference to the sigmoid E_{max} pharmacodynamic model,[1] we sought to describe and prove by deduction our hypothesis which is outlined in **Figure 1**, that the average dose–effect relationship during titration to the targeted effect will associate lower doses with greater effects.

Clinical data

The study was conducted at the Kantonsspital St Gallen, a tertiary care hospital in Switzerland. Data from adult patients during anesthesia for all surgical specialties except for cardiac surgery were included. With approval by the local ethics committee (Ethikkommission Ostschweiz, Switzerland (EKOS)) the individual written consent was waived, but a general consent for the use of anonymized data was available. Anesthesia cases, automatically recorded with ten-second resolution of drug dosing and effect data, between May, 2015 and August, 2019, were analyzed. The data were accessed with a data management system developed by LowTeq (LOWTeq GmbH, Cologne, Germany).

With structured query language scripts, cases with duration of surgery longer than one hour were selected. Other selection criteria were age > 18 years, body mass index < 35 kg/m^2, muscle relaxation with rocuronium, availability of uninterrupted recordings of propofol and sevoflurane concentrations, and brain effect as measured by the Bispectral Index (BIS) (Covidien, Inc., Mansfield, MA). BIS is a proprietary algorithm for measuring the effects of anesthetics on the brain and calculates a unitless number between 100 (fully awake) and 0 (no cortical electrical activity). From this cohort, cases with norepinephrine infusion during surgery were selected for analysis of the norepinephrine mean arterial blood pressure relationship. The dose–effect data at 30 minutes were considered long enough after skin incision and long enough before the end of surgery for one-hour cases to be considered a maintenance value. Thus, for each individual the values of BIS (BIS30), propofol target effect site concentrations (CeT30), sevoflurane end-tidal concentrations (ET30), norepinephrine infusion rates (NE30), and mean arterial blood pressure (MAP30) 30 minutes after skin incision were used for the analysis.

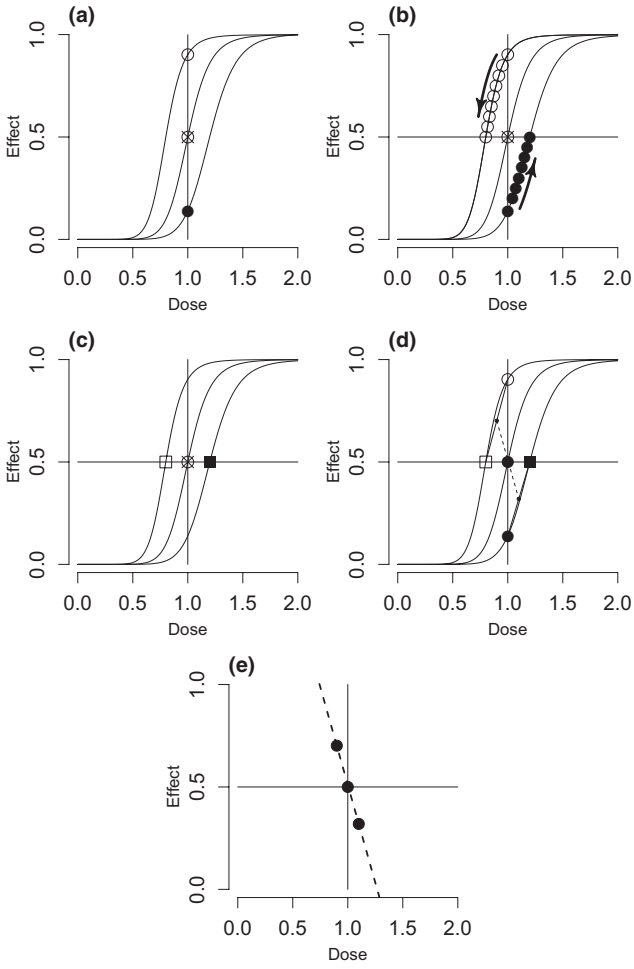

Figure 1 The dose–effect relationship for three cohorts: sensitive, typical, and resistant. (**a**) The effect of the same dose given to the three cohorts. The targeted effect is achieved in the typical cohort (circle cross), is too high in the sensitive cohort (circle), and too low in the resistant cohort (filled circle). (**b**) Gradual titration to same targeted effect by decreasing the dose in the sensitive cohort and increasing the dose in the resistant cohort (with no dose adjustment required in the typical cohort). (**c**) After titration, three different doses achieve the same effect in the three cohorts. (**d**) The average of the first (circles) and final (squares) doses showing the "titration paradox" (dashed line) with lower doses being associated with a greater effect and vice versa. (**e**) The data, as presented to the data analyst, show the titration paradox, i.e., there is a negative correlation between dose and effect.

The conduct of anesthesia (see Supplementary Material S1) was based on an institutional best-practice protocol. With regard to the two investigated drug effect measures, the institutional dosing guidelines request that:

1. Propofol or sevoflurane is titrated to control the hypnotic effect as measured by the BIS. The targeted BIS is 50 (with an acceptable range between 40 and 60). Propofol is titrated using the effect-site TCI model described by Schnider *et al.*[2,3]
2. Norepinephrine is administered by infusion at the discretion of the anesthesiologist to maintain the MAP above 65 mmHg.

Data analysis: The data were graphically presented as scatterplots with dose on the x-axis as is the convention for dose–response data. To test our hypothesis that, as a consequence of the titration paradox, the *average* dose–effect relationship during titration to effect will associate lower doses with greater effects, we determined the slope of the relationship between drug dose and effect, i.e., the correlations between BIS30 and propofol CeT30, BIS30 and sevoflurane ET30, and between MAP30 and norepinephrine NE30 were quantified with linear regression and graphed together with the 99% confidence interval (CI) using the *R* (R Core Team 2019) functions *lm()* and *confint()*.[4]

We also quantified the clinical relevance of the titration paradox by comparing the empirical cumulative distribution of the propofol dose for the 1,000 subjects with the lowest BIS30 with the 1,000 subjects with the highest BIS30. The confidence intervals for the CeT30 which is related to a BIS30 of 50 were calculated based on the Dvoretzky–Kiefer–Wolfowitz inequality.[5]

Monte Carlo simulations

We programmed a simulation to explore the impact of drug titration on the observed relationship between drug dose and drug effect. The fundamental dose–effect relationship was described using a simplified E_{max} equation, which assumed that the drug effect (E) ranges from zero to one.

$$E = D^{\gamma} / (D^{\gamma} + D_{50}^{\gamma}), \quad (1)$$

where D is the administered dose, D_{50} is the dose causing 50% effect and γ is the slope parameter describing the steepness of the relationship. In the context of this study, we refer to "dose" as any mode of drug input at steady-state conditions, e.g., regular oral dosing achieving a stable effect, a constant infusion at steady-state effect or target concentration-controlled infusion after effect site equilibration. Thus, we assumed that for each dose, D, the resulting effect, E, represented the steady-state relationship. We normalized the potency to $D_{50} = 1$ and we used $\gamma = 2.93$ based on a volunteer study investigating the relationship between propofol and the BIS.[6] To simulate interindividual variability, we used a value of 0.18 for the standard deviation of a lognormal distribution for D_{50} from the same publication.

To simulate a clinical titration scenario, we developed a titration algorithm to calculate the change in the dose (ΔD) at each titration step, based on a proportional controller with two proportional gain terms (β_1 and β_2):

$$\Delta D = \beta_1 * \left(\frac{(E_T - E_i)}{k} \right) + \beta_2 * (D_T - D_i) \quad (2)$$

where E_T is the target effect, E_i is the individual's measured effect, D_T is the initial dose to achieve E_T ($D_T = 1$ and $E_T = 0.5$), D_i is the individual's current dose, and β_1 and β_2 are scalars to adjust the contribution of the two dose terms to the dose titration calculation. The variable k is the first derivative of the Eq. (1) solved at $D = 1$ and $\gamma = 2.93$. Additional explanation of Eq. 2 is provided in Supplementary Material S2.

We performed the following simulations:

1. A population of 5,000 individuals was simulated. A log normally distributed random initial dose of mean 1.0 and standard deviation 0.4 was administered, and the resulting effect in each individual was calculated and plotted.
2. Another population of 5,000 individuals was simulated. Each individual was given a dose equal to their individual D_{50} so as to achieve a target effect = 0.5.
3. A population of 5,000 individuals was simulated. A target effect = 0.5 was specified. An initial identical dose, $D = 1.0$, was administered to each individual. The resulting effect in each individual was calculated. For sequential titration steps, the increase or decrease in dose required to achieve the target effect in each individual was calculated based on our titration algorithm (Eq. 2) with $\beta_1 = 0.5$ and $\beta_2 = 0.0$. This titrated dose was administered and at each titration step, the resulting effect was calculated and plotted for each individual and a linear regression was performed to examine the dose–effect relationship.
4. Same as Simulation 3, but with $\beta_1 = 0.5$ and $\beta_2 = 0.1$.

We added log normal random noise (mean = 0, SD = 0.015) on the individual's D_{50} at each titration step to simulate noise due to, e.g., changing surgical stimulus. The simulations were implemented in the programming language R with the package Shiny.[7] The R source code is available from the authors (T.W.S.) via https://github.com/TWS001/TitrationParadoxR, and the application is accessible online through https://tws001.shinyapps.io/titrationparadox_m/, (user interface optimized for mobile devices) where other simulations can be explored at each step using different parameter values.

RESULTS

Mathematical proof

By deduction we prove that the average dose–effect relationship during titration to the targeted effect will associate lower doses with greater effects:

Given:

$$E = E_0 + (E_{max} - E_0) \left(\frac{\left(\frac{D}{D_{50}}\right)^{\gamma}}{1 + \left(\frac{D}{D_{50}}\right)^{\gamma}} \right) = f_1 (D_{50}, D).$$

Solved for D:

$$D = \sqrt[\gamma]{\frac{(E - E_0) D_{50}^{\gamma}}{(E_{max} - E)}} = f_2 (D_{50}, E).$$

Where:

E = Effect.
E_0 = Baseline effect.
E_{max} = Maximum effect.
γ = Steepness parameter.
D = Dose.
D_{50} = Dose associated with 50% Effect.

f_1 and f_2 are abbreviations of the Hill function and inverse Hill function, respectively, and read as "is function of," e.g., D_{50} and D and E, respectively.

Initial dose

Given:

$\overline{E_T}$ = Target effect.
$\overline{D_{50}}$ = population mean.

We will study a population of three cohorts, defined as:
Cohort 1, "resistant" subjects: $\overline{D_{50,1}}$ = population mean and $\overline{D_{50,1}} \gg \overline{D_{50}}$,

Cohort 2, "typical" subjects, $\overline{D_{50,2}}$ = population mean and $\overline{D_{50,1}} = \overline{D_{50}}$,

Cohort 3, "sensitive" subjects, $\overline{D_{50,3}}$ = population mean and $\overline{D_{50,3}} \ll \overline{D_{50}}$.

The first dose in all cohorts will be:

$$D_{\text{initial}} = f_2\left(\overline{D_{50}}, E_T\right) = \sqrt[\gamma]{\frac{\left(E - E_0\right)\overline{D_{50}}^{\gamma}}{\left(E_{\max} - E\right)}}$$

The effect in cohort i will be

$$E_{\text{initial},i} = f_1\left(\overline{D_{50,i}}, D_{\text{initial}}\right).$$

The initial doses and effects thus demonstrate:

$$D_{\text{initial},1} = D_{\text{initial},2} = D_{\text{initial},3}$$
$$E_{\text{initial},1} < E_{\text{initial},2} < E_{\text{initial},3}$$

Final dose

Given: A series of gradual dose adjustments reaches the correct dose to achieve the target effect in each cohort.

The final dose is given by

$$D_{f,i} = f_2\left(\overline{D_{50,i}}, E_T\right) = \sqrt[\gamma]{\frac{\left(E - E_0\right)\overline{D_{50,i}}^{\gamma}}{\left(E_{\max} - E\right)}}$$

Because the dose is titrated to achieve the same effect:

$$D_{\text{final},1} > D_{\text{final},2} > D_{\text{final},3}$$
$$E_{\text{final},1} = E_{\text{final},2} = E_{\text{final},3}$$

Average dose and response

$$D_{\text{average},1} > D_{\text{average},2} > D_{\text{average},3}$$
$$E_{\text{average},1} < E_{\text{average},2} < E_{\text{average},3}$$

Thus, the *average* dose vs. effect relationship during titration to effect will associate lower doses with greater effects.

Clinical titration data

From the automatically recorded anesthesia cases, the data set was complete and fulfilled the selection criterion for 9,372 cases with total intravenous anesthesia, 1,007 cases with sevoflurane anesthesia, and 3,916 cases with norepinephrine. The demographic data are summarized in Table 1. Of the 9,372 cases with intravenous anesthesia, 4,584 cases were used previously for an analysis of the variability of propofol target concentration during anesthesia.[8]

Figure 2 shows the raw data and the linear regression analysis. The slope of the BIS30 to CeT30 relationship was 4.33 BIS units ml μg^{-1} ($P < 0.001$; 99% CI, 3.99–4.68) (**Figure 2a**); for BIS30 to ET30 relationship 3.09 BIS units $\%^{-1}$ ($P < 0.001$; 99% CI, 1.32–4.86) (**Figure 2b**); and for the NE30 to MAP30 relationship − 1.25 mmHg min μg^{-1} ($P < 0.001$; 99% CI, −1.48 to 1.08) (**Figure 2c**). Note that the BIS scale ranges from 100 (no effect) to 0 (maximal effect), so that the positive slope of the linear regression indicates that lower doses are associated with greater effects.

Table 1 Demographic data

	Propofol (9,372)	Sevoflurane (1,007)	Norepinephrine (3,916)
Weight (kg)	75	79	75
Height (cm)	170	171	168
Age	59	61	69
M	5362	681	2342
F	4010	326	1574

The demographic data of the patients in the propofol CeT30 vs. BIS30 analysis, the sevoflurane ET30 vs. BIS30 analysis, and the norepinephrine NE30 vs. blood pressure MAP30 analysis.
BIS30, Bispectral Index at 30 minutes; CeT30, propofol target effect site concentrations at 30 minutes; ET30, sevoflurane end-tidal concentrations at 30 minutes; F, female; M, male; MAP30, mean arterial blood pressure at 30 minutes; NE30, norepinephrine infusion rates at 30 minutes.

Figure 3 shows the empirical cumulative distribution of the 1,000 subjects with lowest BIS30 with the 1,000 subjects with highest BIS30. The median of the 1,000 lowest BIS30 was 34 and the CeT30 1.9 μg/ml (99% CI, 1.84–1.94). The median of the highest BIS30 was 58 and the CeT30 2.5 μg/ml (99% CI, 2.47–2.63).

Monte Carlo simulations

Figure 4 shows the results for the simulations. **Figure 4a** shows the resulting effect when a normally distributed random dose was administered to 5,000 simulated individuals (Simulation 1). **Figure 4b** shows the resulting effect when given a dose equal to the individual D_{50} was administered to 5,000 simulated individuals (Simulation 2). **Figure 4c and d** show the progression of the titration from step 1 to step 5 for $\beta_1 = 0.5$ and $\beta_2 = 0.0$ (Simulation 3). After 5 steps, 99% of the simulated subjects had an effect between 0.45 and 0.53. The coefficient of variation of the effect for the population was 2.89%. **Figure 4e and f** show the progression of the titration from step 1 to step 5 for $\beta_1 = 0.5$ and $\beta_2 = 0.1$ (Simulation 4). After 5 steps, 99% of the simulated subjects had an effect between 0.41 and 0.56. The coefficient of variation of the effect for the population was 5.53%.

DISCUSSION

In this study, we provide evidence to support our titration paradox hypothesis in three ways. Firstly, we describe and prove by deduction that the *average* dose–effect relationship during titration to effect will associate lower doses with greater effect (**Figure 1**). Secondly, we found confirmatory evidence of the titration paradox in our clinical titration data of automatically recorded clinical anesthesia cases, where drugs were titrated according to institutional protocols. Specifically, a greater brain effect was associated with a lower dose for both propofol and sevoflurane, and a greater blood pressure was associated with a lower dose of norepinephrine (Figures 2 and 3). Thirdly, based on Monte Carlo simulations, we identified two other factors that contribute to the titration paradox (**Figure 4**).

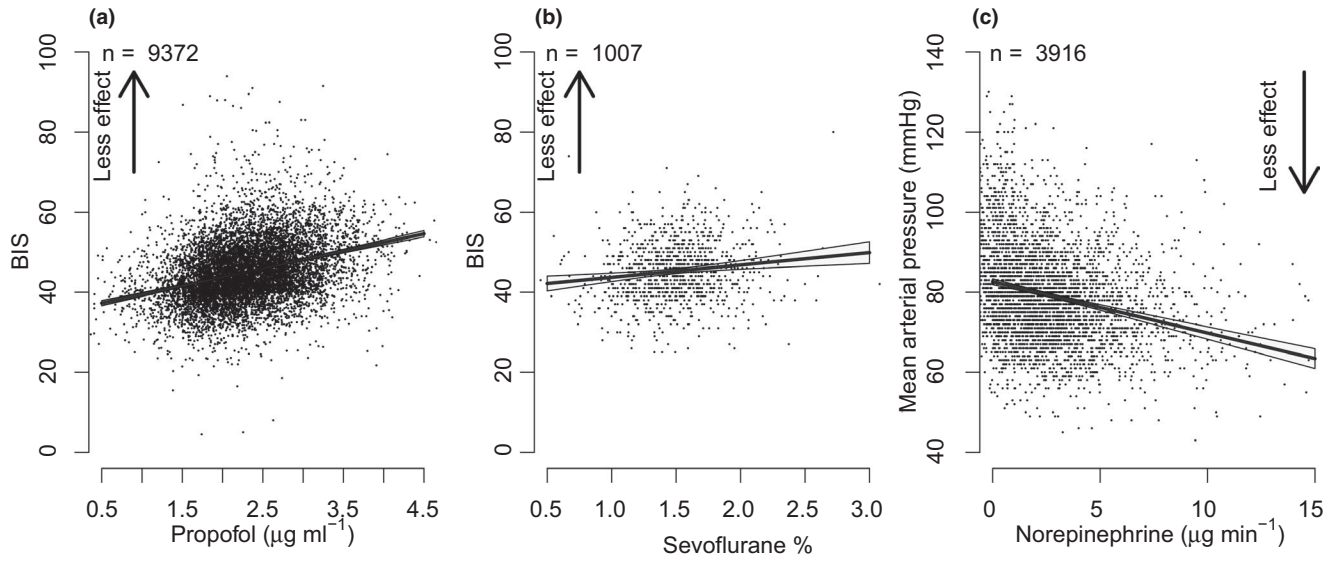

Figure 2 The raw clinical data used for the linear regression analysis for (**a**) propofol CeT30 and (**b**) sevoflurane ET30 titration to BIS30 and (**c**) norepinephrine NE30 titration to MAP30. The data points are "jittered" to avoid overlapping data points. The linear regression line is plotted together with its 99% CI. All regression lines show the titration paradox, i.e., decreasing drug effect with increasing drug dose. BIS, Bispectral Index; BIS30, Bispectral Index at 30 minutes; CeT30, propofol target effect site concentrations at 30 minutes; CI, confidence interval; ET30, sevoflurane end-tidal concentrations at 30 minutes; MAP30, mean arterial blood pressure at 30 minutes; min, minutes; NE30, norepinephrine infusion rates at 30 minutes.

Our proof has shown that, in the context of a sigmoid E_{max} model, the *average* dose–effect relationship during titration to effect will associate lower doses with greater effects. In developing this proof, it also became clear that during the process of gradual titration of drug dose toward a targeted drug effect, there will always be a *negative correlation* between dose and effect. This negative correlation will gradually decrease as the targeted effect is approached, until ultimately—after "perfect" titration—there will be "zero" correlation between dose and effect, i.e., the effect will be the same in all individuals. Thus, the corollary to our proof is that when drug dose is titrated to a targeted effect, *there will not be a positive correlation* between dose and effect as expected from the underlying sigmoid E_{max} model. We conclude that a negative or zero (i.e., "horizontal") correlation is the expected finding.

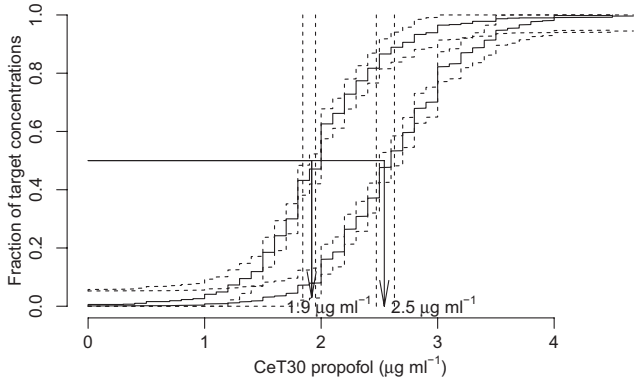

Figure 3 The empirical cumulative distribution (black lines) and the 99% confidence intervals (dashed lines) of the target effect-site concentrations of the 1,000 subjects with lowest BIS30 (i.e., greatest effect, median BIS30 = 34) and the 1,000 subjects with highest BIS30 (i.e., least effect, median BIS30 = 58). BIS30, Bispectral Index at 30 minutes; CeT30, propofol target effect site concentrations at 30 minutes.

For all three investigated dose–effect relationships the correlation was negative, i.e., lower doses were associated with greater effects. Visual inspection of **Figure 2** reveals a substantial variability of the effect. One could argue that this variability is due to inadequate titration. It is important to note that patients either at the upper or lower end of the target effect range already received paradoxically much higher or lower than expected doses. This is visualized with **Figure 3**, which shows this clinically relevant impact of the titration paradox. The 1,000 patients with the greatest propofol effect received a one-fourth lower dose (i.e., the target effect site concentration) than the 1,000 patients with the least effect. It is well known that other drugs used during anesthesia affect both the electroencephalogram and the blood pressure. Based on the protocol for delivery of anesthesia, the electroencephalogram effect was increased and decreased by adjusting the dose of either propofol or sevoflurane. It could be that some of the variability seen in the norepinephrine vs. MAP data is due to the fact that intraoperatively opiates were administered also when blood pressure increased in response to noxious stimulation. Nevertheless, the signal due to norepinephrine administration was still strong enough in our data to show the titration paradox. Although all three of our investigated examples of dose-to-effect relationships are from the same clinical setting (i.e., anesthesia), we believe that the general principle of our observation is applicable in any medical specialty where the drug is titrated to a target effect.

For the analysis of our clinical data, we only used one data point per patient. This was in part for investigator convenience due to the difficulties and time required to graphically display and analyze such "big data." Nevertheless, preliminary analyses of our clinical titration data with other metrics, such

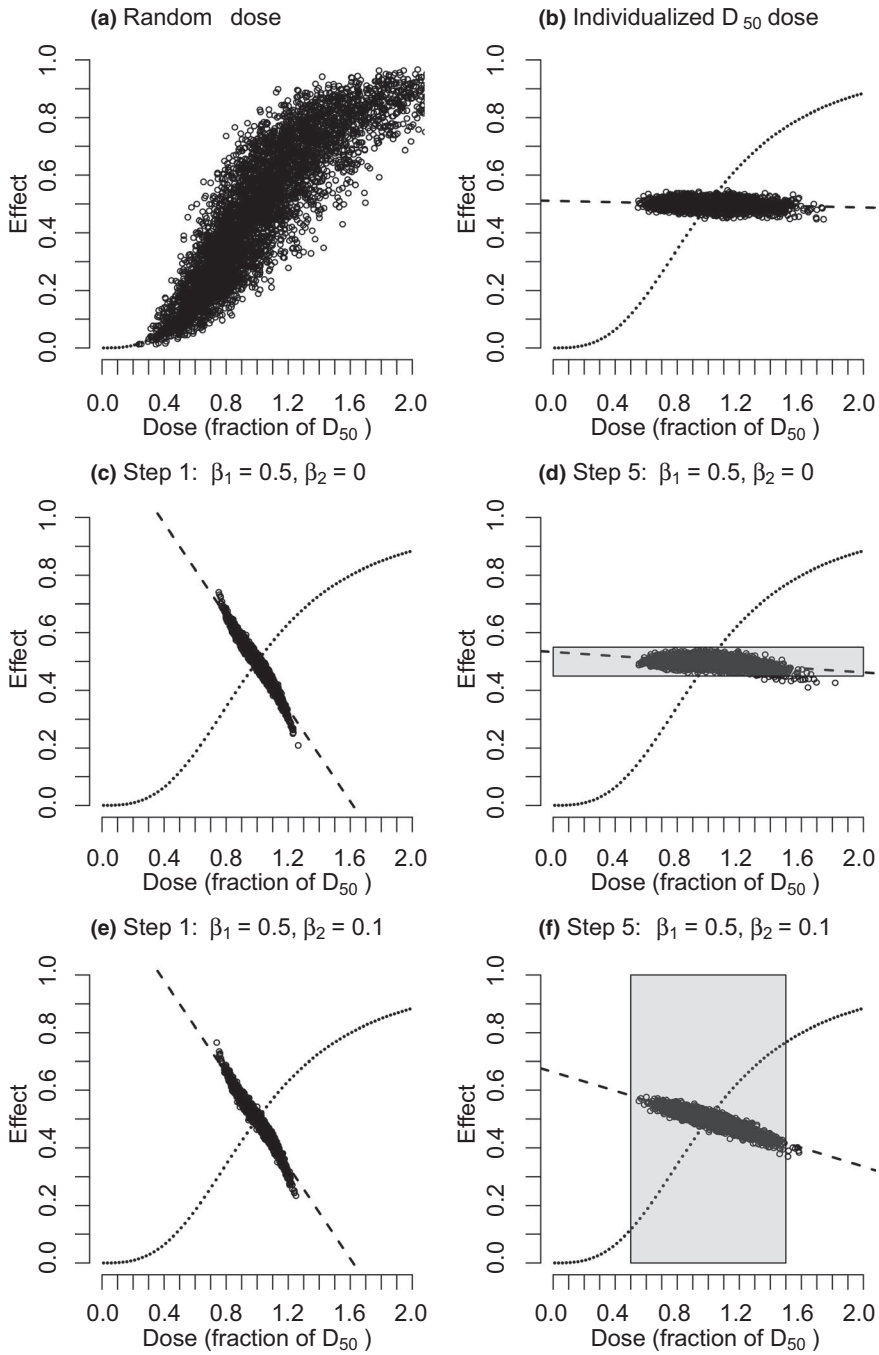

Figure 4 The results of the Monte Carlo simulations. (**a**) Simulation 1: Random dose. (**b**) Simulation 2: Individualized D_{50} dose. (**c** & **d**) Simulation 3: steps 1 and 5 using $\beta_1 = 0.5$ and $\beta_2 = 0.0$. (**e** & **f**) Simulation 4: steps 1 and 5 using $\beta_1 = 0.5$ and $\beta_2 = 0.1$. The dotted line represents the Hill equation. The dashed line is a linear regression through the simulated dose–effect data. The shaded regions provide examples for **d** an acceptable effect range and **f** an acceptable dose range. The titration paradox will be greater for a wider acceptable effect range and a narrower acceptable dose range. D_{50}, the dose causing 50% effect.

as area under the drug input and effect curves, or by using data from the complete duration of surgery at regular intervals (not shown), were all consistent with the results obtained by using the 30 minutes values (**Figure 2**). We used the 30 minutes values to represent the maintenance phase of anesthesia for surgery lasting longer than 60 minutes. During the maintenance phase, we assumed that CeT30 was in equilibrium with the plasma and the effect site concentration. Therefore, our analysis focused on the static nonlinear relationship between concentration and effect, i.e., our approach took care of the potentially confounding effect of pharmacokinetics on the result.

We are unaware of previous reports of the titration paradox based on similarly large clinical data sets. However, others have previously observed a negative correlation between dose and effect, which has been referred to as a "reversed" dose–response relationship in "flexible-dose" clinical trials. For example, Lipkovic

et al. have noted that in flexible-dose clinical trials, the dose–effect relationships may be "obscured and even reversed."[9] Xu *et al*. have noted that titrating dose can lead to selection bias, because subjects who do not respond to a low dose are likely to be given a higher dose (if tolerable), whereas subjects who respond to a low dose are likely to stay on the low dose.[10] They noted that a "reversed dose–response relationship" may be observed if selection bias is not corrected. Thus, the titration paradox is not explained with reference to some underlying biological or pharmacological process, rather it is due to the selection bias inherent to clinical titration because patients who need less (for achieving the target effect) will stay on this low dose, whereas only patients who need more will receive more.

Simulations 1 and 2 contrast the effect after a random initial dose (**Figure 4a**) with that of a "perfectly" targeted dose (**Figure 4b**). With a random dose, some sensitive individuals will get low doses and some high doses, and some resistant individuals will get low doses and some high doses. Thus, each point in **Figure 4a** represents the effect achieved from a random dose in each individual, and so represents one data point on the individual's own sigmoid E_{max} curve. This random spread of data points across many sigmoid E_{max} dose–effect curves reveals the underlying shape of the dose–effect relationship. Such random dosing could occur clinically, if the effect measure under consideration was not used to guide dose titration. Another circumstance that would reveal the underlying sigmoid E_{max} relationship is when multiple data points are collected for each individual while they are deliberately exposed to a wide range of doses (e.g., from no effect to maximum effect), as is done in dose escalation studies, and as we have done in high-resolution pharmacokinetic/pharmacodynamic studies during drug development.[2,3,11,12] In contrast, **Figure 4b** shows the end result from titration to a targeted effect—the population effect data all lie on a horizontal line equal to the targeted effect. These simulations support the corollary of our proof, that when dose is titrated to achieve a specific effect, if the titration is "perfect," the final population dose–effect data *will not* reflect the underlying shape of the sigmoid E_{max} curve, and there will not be a positive correlation between dose and effect.

These simulations also suggested two other factors that could contribute to less than "perfect" titration, both of which seem plausible from a clinical perspective. The first factor relates to an acceptable target range. This is illustrated by Simulation 3 (**Figure 4c and d**). If the clinically acceptable target range for the effect was between 0.45 to 0.55, **Figure 4d** would be considered adequate, because > 99% of the effect measures are within this range. For those with too much effect (i.e., effect > 0.55), the dose was only titrated downward until the effect was just < 0.55 (rather than until $E = 0.5$). Whereas, for those with too little effect (i.e., effect < 0.45), the dose was only titrated upward until the BIS was just > 0.45 (rather than until $E = 0.5$). We also note that a drug with a narrow acceptable effect range will require a wider dose range than one with a wide acceptable effect range, given the same interindividual variability in the dose–effect relationship. The second factor relates to an acceptable dose range. This is illustrated by Simulation 4 (**Figure 4e and f**). A clinician familiar with the acceptable dose range of a drug could hesitate to dose outside of that acceptable range. So, as the dose is reduced in an attempt to reduce the effect in a sensitive patient, there could be a lower limit below which they are hesitant to dose and a higher limit above which they are hesitant to dose. This behavior is also a feature of automatic feedback control algorithms, which often explicitly constrain the drug input in order to prevent unreasonably low or high drug input.[13]

As with our clinical data, we simplified the dose–effect relationship for our simulations by ignoring the complexities of modeling the effect-site pharmacokinetics. We simulated the effect caused by single dose as if it resulted in a steady-state concentration and steady-state effect. We have also ignored interindividual pharmacokinetic variability and measurement error. However, by adding random variability to the individual D_{50} values at each step of the titration, we were still able to explore the impact of random "noise" on the dose–effect relationship.

Our finding emphasizes that the association between dose and effect is fundamentally different when the dose is a consequence of an observed, i.e., measured effect. This process of effect-guided drug administration is called "titration" and is also referred to in the literature as a "flexible-dose" regimen. Although it seems the logical approach to drug dosing, Schuck *et al*. found that in the US Food and Drug Administration (FDA) new drug approvals from 2013 to 2017[14] only 22% included more than one dosing regimen in the drug label and that only 39% of all drugs approved for conditions that were considered amenable to effect-guided titration had such information in the label. Chen has outlined many of the factors contributing to the challenge of implementing within-patient drug titration to effect.[15] Compared with many other medical specialties, anesthesiologists are fortunate to use drugs with *relatively* rapid onset and offset of effect, that are *relatively* easy to titrate using pharmacokinetic model–driven infusion pumps, with clinical effects that are *relatively* easily measured, with *relatively* wide safety margins between therapeutic and toxic effects during anesthesia, and with dose–effect relationships being *relatively* stable over time. Although titration, particularly of anesthetics to an observed effect has a long tradition, the titration paradox has not been described previously.

Whitlock *et al*.[16] proposed that a "high correlation coefficient would be observed between a DOA (depth of anesthesia) index and the anesthetic concentration in the brain." This DOA index performance criterion was previously proposed as relevant by a group of experts.[17] They stated that "A strong correlation between a DOA index and anesthetic drug concentration, and/or between a DOA index and deepening sedation, provides construct validity for DOA monitoring." Although this makes intuitive sense, our study strongly suggests that it will be true only if the analyzed data are not obtained during clinical titration to a specific effect target. It could be inferred from our results that in studies investigating and comparing the impact of monitors of drug effect, absence of the titration paradox is evidence that the monitor has not been used adequately for dose selection. However, in previous large studies, which have used BIS-guided titration of anesthetic drugs in thousands of patients, the correlation between drug dose and drug effect was not reported.[18–20]

While it is tempting to use all available clinical data to improve the understanding of the dose–effect relationship,[21] it is important to understand the impact of the titration paradox on that relationship. Clearly, a naïve attempt to fit a sigmoid E_{max} model to dose–effect data showing negative or zero correlation is not appropriate. However, it is possible that if multiple data points per patient are available, a mixed-effects model could describe the underlying sigmoid dose–effect relationship by taking into account the selection bias, and by allowing the individual to vary in their dose–response parameters. Xu *et al*. have used computer simulations to evaluate the potential for dynamic linear mixed-effects models to evaluate dose–effect data in controlled randomized clinical trials using flexible-dose designs.[10] They found that, given certain conditions, dynamic linear mixed-effects may be an unbiased and efficient modeling method to identify the underlying dose–effect relationship.

In summary, we have presented a hypothesis to explain the paradoxical negative correlation between dose and effect when drugs are titrated to effect. We have shown supporting evidence for this titration paradox by mathematical proof, by clinical data for three different drugs, and by Monte Carlo simulations of the simplified dose–effect relationship using a simple proportional control algorithm. Of note, our simulations have shown that, *during* stepwise titration toward a target effect, the slope of the dose–effect data for the population will be "reversed," i.e., the correlation between dose and effect *will not be positive* (as expected for the sigmoid E_{max} model), but will be negative. Also, when the titration is "perfect" the slope will be horizontal, i.e., the effect will be the same in all individuals. *Our* simulations have also shown that this titration paradox will be more pronounced when there is a wider acceptable effect range and when there is a limitation on the dose range. We believe that it is essential to understand the implications of the titration paradox in any specialty when analyzing and interpreting dose–effect data obtained during dose titration (flexible dose) studies.

SUPPORTING INFORMATION

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

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

T.W.S. and C.F.M. wrote the manuscript. T.W.S., C.F.M., and M.F. designed and performed the research. T.W.S. analyzed the data.

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