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Clinical Investigation

CLINICAL INVESTIGATION

The drug titration paradox: more drug does not correlate with more effect in individual clinical data

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Abstract

Background: A fundamental concept in pharmacology is that increasing dose increases drug effect. This is the basis of anaesthetic titration: the dose is increased when increased drug effect is desired and decreased when reduced drug effect is desired. In the setting of titration, the correlation of doses and observed drug effects can be negative, for example increasing dose reduces drug effect. We have termed this the drug titration paradox. We hypothesised that this could be explained, at least in part, by intrasubject variability. If the drug titration paradox is simply an artifact of pooling population data, then a mixed-effects analysis that accounts for interindividual variability in drug sensitivity should 'flip' the observed correlation, such that increasing dose increases drug effect.

Methods: We tested whether a mixed-effects analysis could correctly reveal the underlying pharmacology using previously published data obtained during automatic feedback control of mean arterial pressure (MAP) with alfentanil (effect site concentration, Ce_{Alf}) during surgery. The relationship between MAP and Ce_{Alf} was explored with linear regression and a linear mixed-effects model.

Results: A linear mixed-effects model did not identify the correct underlying pharmacology because of the presence of the titration paradox in the individual data.

Conclusions: The relationship between drug dose and drug effect must be determined under carefully controlled experimental conditions. In routine care, where the effect is profoundly influenced by varying clinical conditions and drugs are titrated to achieve the desired effect, it is nearly impossible to draw meaningful conclusions about the relationship between dose and effect.

Keywords: alfentanil; drug titration paradox; feedback control; pharmacodynamics; pharmacokinetics; titration

Editor's key points

- Correlation between drug doses delivered and drug effects can be negative, which the authors have termed the drug titration paradox.
- This study used previously published data obtained during automatic feedback control of mean arterial pressure with alfentanil during surgery to analyse the relationship with linear regression and a linear mixed effects model.
- The drug titration paradox was confirmed in individual data. The authors suggest that changing level of surgical stimulus is the most likely confounding factor accounting for the paradoxical relationship.
- When an effect is profoundly influenced by varying clinical conditions and drugs are titrated to achieve the desired effect, it is challenging to draw meaningful conclusions about the relationship between dose and effect.

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A fundamental concept in pharmacology is that increasing dose increases drug effect.[1–3] This is the basis of anaesthetic titration: dose is increased when increased drug effect is desired, and decreased when reduced drug effect is desired. In the setting of titration, correlation of observed doses and drug effects can be negative, for example increasing dose is correlated with reducing drug effect, which we have termed the drug titration paradox.[4] We demonstrated in a population of patients that increased propofol and sevoflurane doses were associated with higher bispectral index (BIS), the opposite of the pharmacological expectation.[4] We also showed that increased norepinephrine was associated with reduced blood pressure, again the opposite of the pharmacological expectation.

To understand the drug titration paradox, it is important to understand the implications of the titrated dose being *dependent upon the effect*. Interpatient differences in sensitivity to the drug mean that dose will be decreased in patients whose measured effect is greater than the desired effect. Similarly, dose will be increased in patients whose measured effect is less than desired. One reason that this occurs is because those who are most sensitive will have the greatest effect and will require less drug than the typical patient, and those who are most resistant will have the least effect and will require more. Ultimately, with 'perfect titration' all patients will have precisely the same effect, but different doses, with the result that there will be *no correlation* between dose and effect. Of course, 'perfect titration' is unlikely if the desired effect includes a range of acceptable values (e.g. BIS 40–60), if there is some limitation on the range of acceptable doses (e.g. strict dosage guidelines), or if there is another confounding factor influencing the drug effect.

If the drug titration paradox is simply an artifact of pooling population data, Shafer and Stanski[5] and our group[4] hypothesised that a mixed-effects model will be able to identify the underlying *positive* correlation between dose and effect in an individual even though the pooled population data shows a *negative* correlation owing to the drug titration paradox. We tested whether a mixed-effects analysis could correctly reveal the underlying pharmacology using previously published data[6] obtained during automatic feedback control of MAP with alfentanil (Ce_{Alf}) during surgery.

Methods

According to the drug titration paradox, we expect to see a negative correlation between dose and effect in the population (i.e. we expect that those patients with the highest average MAP will have the highest average alfentanil target concentrations and those with the lowest average MAP will have the lowest average alfentanil target concentrations; Fig 1a). However, within individual MAP data, we hypothesise a positive correlation between dose and effect (i.e. we hypothesise that increasing an individual's alfentanil concentration will increasingly attenuate individual haemodynamic responses to the surgical stimulus and thus lower MAP [Fig 1b], and that a mixed-effects model will be able to identify the underlying positive correlation between dose and effect [Fig 1c]).

The study was conducted in patients between January and March 2001 with approval by the local ethics committee (Ethics committee of the Canton of Bern, Switzerland). The feedback control algorithm and the clinical performance of the controller used for this clinical study have been described.[6,7] Some of the relevant details are summarised below.

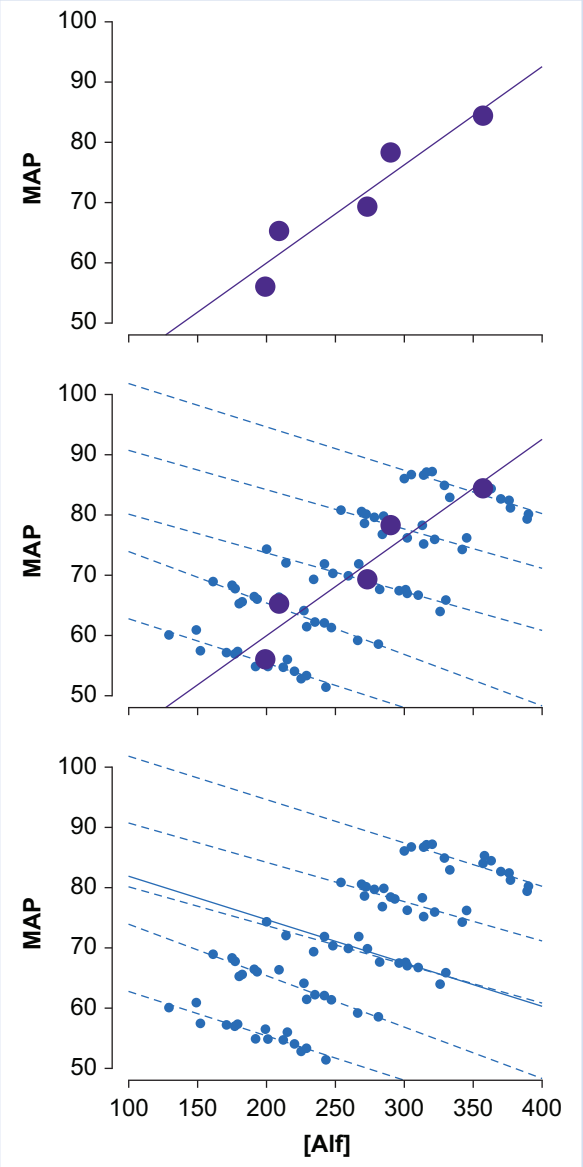

Fig 1. A simulation of the use of alfentanil to attenuate the MAP response to surgical stimulation in five patients to illustrate the study hypothesis. Top panel: the titration paradox, a *negative correlation* (more drug, less effect) between average dose and average effect (purple dots). Middle panel: the superimposed *positive correlation* (more drug, more effect) between dose and effect for the individual data (blue dots and blue dashed lines), that we expect if as alfentanil (Alf) concentration increases MAP decreases slightly. Bottom panel: underlying *positive correlation* between dose and effect is identified by a linear mixed effects model (solid blue line).

Patients

Eleven patients scheduled for elective neurosurgical procedures gave their informed consent to participate in the study. The five female and six male patients were between 38 and 57 yr old (mean age, 47 yr), and had a mean height and weight of 173 cm and 76 kg, respectively. The duration of the surgical procedures and of the automatic control period was 55–130

min (mean, 86 min). Five patients had cervical disc surgery, four had lumbar disc surgery, and one had plastic surgical reconstruction of a skull defect. In addition to standard monitoring, arterial pressure was measured invasively. Isoflurane was manually controlled with a target BIS of 55 (5), and alfentanil was administered by automatic feedback control of MAP. Rocuronium was used for paralysis.

Feedback control of MAP with alfentanil

The feedback control algorithm was designed to maintain MAP as closely as possible to a reference value by adjusting the predicted effect site concentration of alfentanil (Ce_{Alf}). The initial controller reference values were set at 70 mm Hg for MAP, and 100–400 ng ml^{-1} for Ce_{Alf} as lower and upper limits, respectively. The anaesthesiologist could adjust these values for each patient as deemed clinically appropriate. The decision to constrain Ce_{Alf} within a clinically acceptable range was included as a trade-off between strict adherence to the MAP control goal and other clinical goals (i.e. to prevent the potential for Ce_{Alf} being too low, which could lead to a sudden increase in MAP because of unexpected noxious stimulation, or too high, which could interfere with recovery from anaesthesia). All data were recorded automatically.

Data analysis

The Ce_{Alf} and MAP data were recorded in 10 s intervals, and subsequently averaged over 1 min. All available recorded data points between skin incision and skin closure entered the analysis, which was performed with the statistical software R (R Project, Version 4.1.0[8]).

Firstly, to confirm the presence of the drug titration paradox, the median of each individual's MAP was plotted against their median Ce_{Alf}, and a linear regression was performed. Secondly, all individual MAP and Ce_{Alf} data were plotted together with the linear regression for each individual. Thirdly, the relationship between MAP and Ce_{Alf} was explored with a linear mixed-effects model (LME).[9] The 95% confidence intervals (CIs) were estimated for the fit of the average data and for the LME fit with the respective R functions *confint*() and *intervals*().

Results

Data from all 11 patients comprising the feedback-control study population were used for the investigation. The top left graph of Fig 2 shows the linear regression for each patient's median MAP *vs* median Ce_{Alf} data. The regression slope was 0.108 (95% CI, 0.0646–0.153), which confirmed the presence of the drug titration paradox. Figure 2 also shows linear regressions for the individual MAP *vs* Ce_{Alf} data. The individual linear regressions in nine of the 11 patients showed decreasing effect (increasing MAP) with increasing Ce_{Alf}, whereas two patients (2 and 8) showed increasing effect (decreasing MAP) with increasing Ce_{Alf}. However, the 95% CI of the slope of the individual linear regressions in all 11 patients included 0.

Figure 3 shows the MAP *vs* Ce_{Alf} LME fit of the data. The slope of the LME fit was 0.0511 (95% CI, 0.0144–0.0878). Higher drug concentration did not correlate with more effect.

Discussion

This study provides evidence of the presence of the drug titration paradox in previously published data obtained during automatic feedback control of MAP with alfentanil in 11 patients undergoing elective neurosurgical procedures. We found a *negative correlation* (increasing MAP with increasing Ce_{Alf}) in 9 of 11 patients' concentration–effect data. Consequently, a LME model did not identify an underlying *positive correlation* between concentration and effect because the underlying correlation was not positive.

In the case of *population* dose–response data, we have shown[1] that a difference in patient sensitivity was the likely confounding factor accounting for the drug titration paradox. As Schamberg and Brown[10] have pointed out, the drug titration paradox is a form of Simpson's paradox.[11] In the current study, the finding of a drug titration paradox in the *individual* dose–response data of the majority of the patients implies another confounding variable. Such paradoxes can be resolved when the appropriate causal relationships and confounding factors are identified.[12]

In considering the causal relationship between dose and effect in our study, we note that the relationship is indirect (i.e. the drug does not directly cause the measured effect). In the absence of a noxious stimulus, we expect a high dose of alfentanil to cause some decrease in MAP. In the context of this study, the intended effect of alfentanil (and indeed the purpose of the closed loop controller) is to attenuate the hypertensive response to noxious surgical stimuli. Therefore, the measured effect does not solely depend upon Ce_{Alf}, but also upon the *intensity* of the noxious stimulus.[13] We also note that if the closed-loop controller worked perfectly, and all subjects had exactly the target MAP throughout their operation, there would be no apparent correlation between MAP and Ce_{Alf}. We should not then conclude that alfentanil had no effect on MAP, nor that the measurement of MAP was not useful, because it did not reflect changes in alfentanil dosing.

We can rearrange the relationship between Ce_{Alf}, MAP, and noxious stimulus such that the noxious stimulus can be considered as the 'dose' of the noxious stimulus, the increase in MAP as the 'effect', and alfentanil as the 'antagonist', which 'shifts the dose–response curve to the right'. This concept underlies the hierarchical model for the opioid–hypnotic interaction proposed by Bouillon and colleagues,[14] in which the noxious stimulus is first attenuated by the opioid, and the attenuated signal then projects to the cortex, where hypnotics act to modulate the probability of response. They proposed that the potency of opioids in attenuating the noxious stimulus decreases with increasing stimulus intensity. Applied to our study, this means that the Ce_{Alf} preventing an increase in MAP that results from a mild noxious stimulus would be insufficient to prevent an increase in MAP that results from a strong noxious stimulus, which is consistent with clinical experience. The relationship between these three factors is complex, but could theoretically be described by a response surface[15,16] with one axis for Ce_{Alf}, a second for MAP, and a third representing intensity of the noxious stimulus.

When pharmacodynamic data are analysed, a fundamental assumption is usually that the system is static (there is no change in the parameters of the pharmacodynamic model over time). This assumption maybe wrong in some clinical situations. For example in the hierarchical model described by Bouillon and colleagues,[14] both the ability of the opioid and the hypnotic to attenuate the response was shifted rightward with increasing stimulus (i.e. the potency decreases). Also, in the Bayesian-based, patient-individualised, model-based, adaptive control method for BIS-guided propofol infusion described by De Smet and colleagues,[17] there was a clear change in

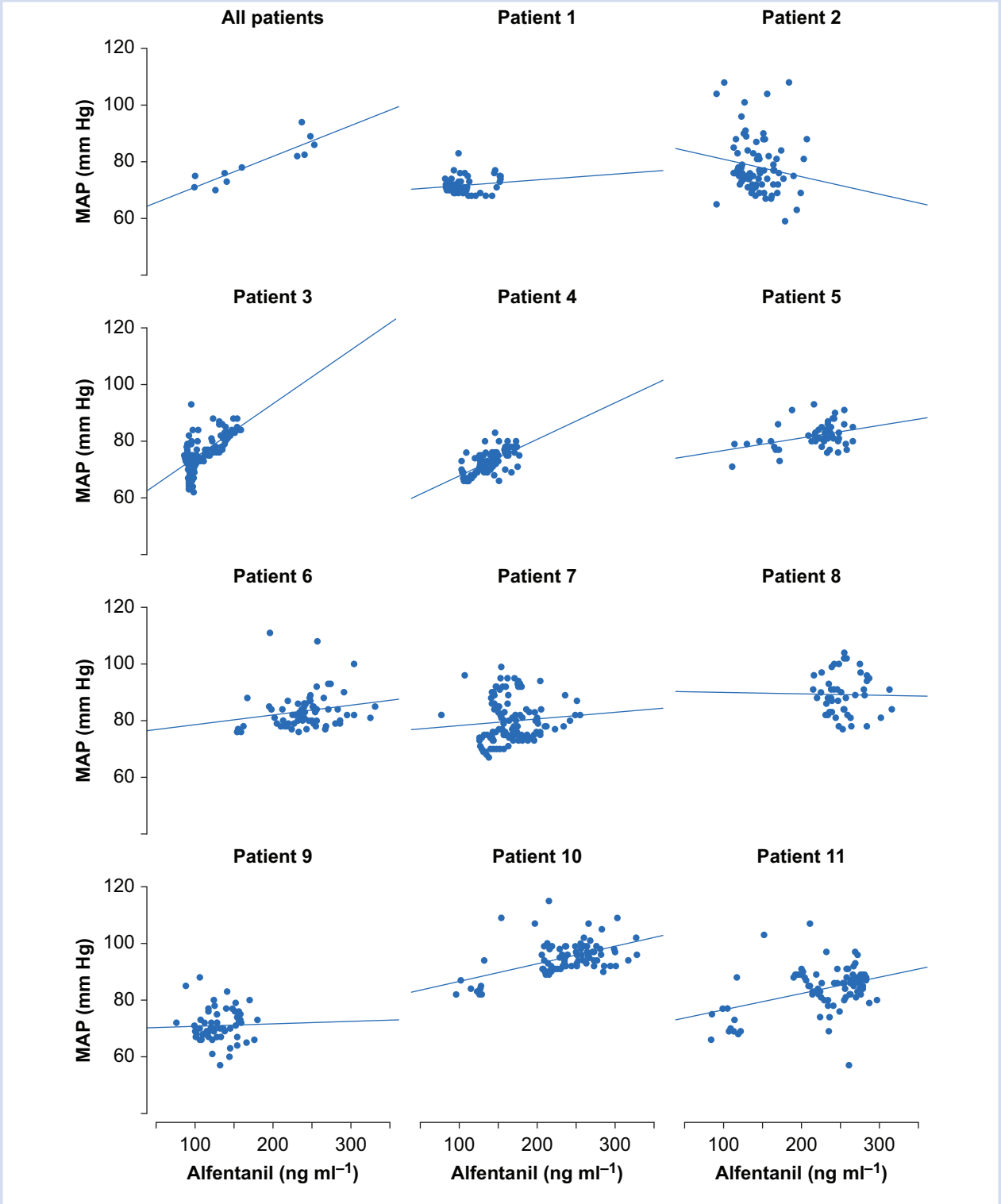

Fig 2. Linear regression of median MAP *vs* median Ce_{Alf} data for all patients (top left graph) and individual linear regressions for all MAP *vs* Ce_{Alf} data for patients 1 to 11 (remaining graphs). The top left graph shows the titration paradox. Patients 2 and 8 show increasing effect (decreasing MAP) with increasing Ce_{Alf} (*positive correlation* between dose and effect). The remaining patients show decreasing effect (increasing MAP) with increasing Ce_{Alf} (*negative correlation* between dose and effect). The 95% CI of the slope of the individual linear regressions in all 11 patients included zero.

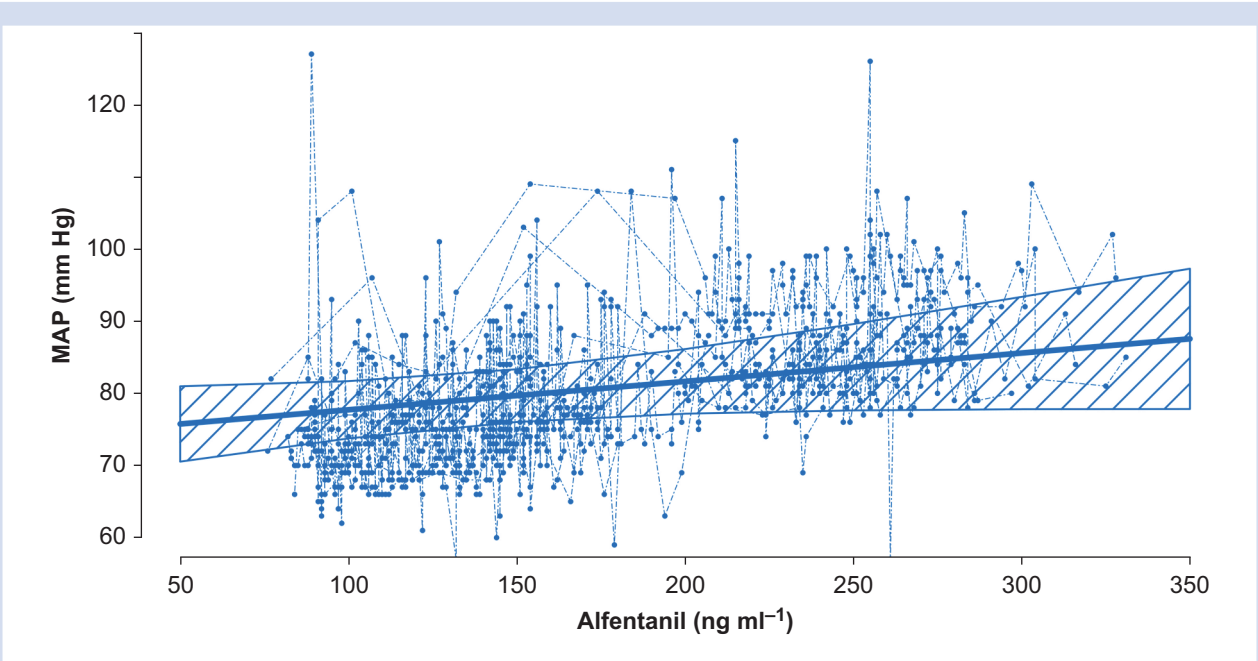

Fig 3. Plot of the individual data for the 11 patients. The dashed line connects the data points of each individual. The solid blue line represents the linear mixed effects model fit and the hatched area the 95% confidence interval. The parameters (standard error [SE]) for the regression are given by: MAP=71.5 (3.06)+0.0511 (0.0187)×Ce_{Alf}. The correlation of the fixed effects (slope and intercept): −0.843. The standard deviation of the random effects; intercept: 9.19, slope: 0.0566, with correlation −0.822. The standard deviation of residuals: 6.17. Increasing Ce_{Alf} is not correlated with more effect (decreasing MAP).

estimated potency of propofol over time (the other parameters of the pharmacodynamic model were assumed to be constant over time). Based upon these insights, Fig 4 illustrates our understanding of how an apparent change in drug potency caused by changes in intensity of a noxious stimulus could cause a drug titration paradox in individual data.

Our study has several significant limitations. Perhaps most importantly, the number of patients is small and the causal relationship between Ce_{Alf} and MAP is indirect and complex. Another limitation is that changes in MAP is not specific to changes in noxious stimulation intensity and can be affected by other covariates, such as blood loss, heart failure, arrhythmias, and drugs (e.g. volatile anaesthetics, propofol, β blockers, vasodilators), for example. An initial exploratory analysis of the relationship between isoflurane and MAP confirmed that manual control of isoflurane was not a confounding factor. However, these limitations might be partly overcome by the fact that automated administration of alfentanil by the feedback controller,[18–20] together with high resolution automated recording of dose and effect in neurosurgical operations involving a large range of intensities of noxious stimuli, has provided data with enough discriminatory power to identify the correlation of more drug with less effect in individual data. Our data did not support the hypothesis that a mixed-effects model would be able to identify the underlying *positive correlation* between dose and effect for the relationship between Ce_{Alf} and MAP in the individual data. However, we suspect that there will be other data sets that will support the hypothesis, provided that there are no other confounding factors. For example Goulooze and colleagues[21] investigated finerenone, a drug used to delay the progression of kidney disease and reduce the risk of cardiovascular events in patients with chronic kidney disease and type 2 diabetes mellitus. Among its many effects, finerenone blocks the renal mineralocorticoid receptor, which leads to reduced resorption of sodium and consequently reduced excretion of potassium and higher plasma potassium levels. They reported a drug titration paradox for finerenone, in which *higher* finerenone doses were associated with *lower* potassium levels and *lower* incidence of hyperkalaemia based on serum potassium-guided dose titration.

The absence of the drug titration paradox in pooled population data from a drug titration study strongly suggests that titration was suboptimal to that specific effect. For example the presence of a drug titration paradox between a volatile anaesthetic agent and MAP, but not between a volatile anaesthetic and BIS, would suggest that the volatile agent was titrated mostly according to MAP (and not BIS). However, we suggest that the presence of a drug titration paradox in individual data strongly suggests a confounding factor. We believe that this study adds further support to the concept that for some drugs, change in noxious stimulus intensity during surgery is a confounding factor that perturbs the dose–effect relationship in an individual.

In summary, we confirmed the presence of the drug titration paradox in previously published data obtained during automatic feedback control of MAP with alfentanil during neurosurgical anaesthesia. We also identified the titration paradox in the individual data and suggest that changing levels of surgical stimulus is the most likely confounding factor that accounts for this paradoxical result. It was therefore not possible to identify an underlying *positive correlation* between dose and effect in the individual data with a mixed-effects model. We show how a confounding factor, such as changing level of noxious stimulus, could result in a non-static

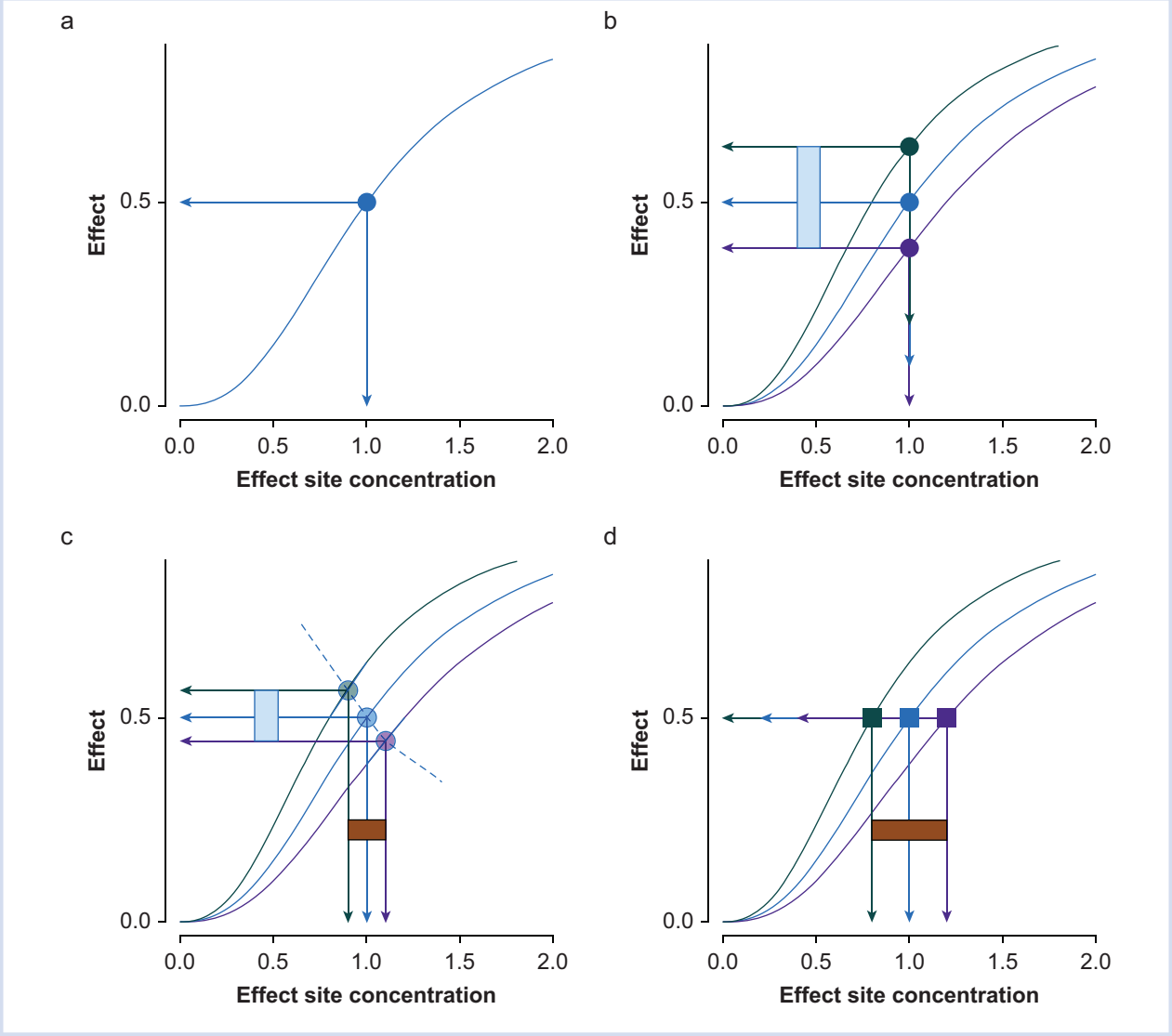

Fig 4. The titration paradox for individual data. (a) The effect–site (Ce) *vs* effect relationship in one individual for a drug with a direct relationship between concentration and effect, characterised by a sigmoid Emax model, when the relationship is static (stable over time), for example the Ce resulting in 50% maximal effect (blue dot) is unaffected by noxious stimulus. (b) Range of effects (light blue bar) for the same Ce when the Ce–effect relationship is not static, for example at three levels of noxious stimulus where increasing stimulus shifts the curve to the right; low stimulus (green) has greater effect, typical stimulus (blue) has typical effect, high stimulus (purple) has lesser effect. (c) Partial titration of Ce at three levels of noxious stimulus showing a *negative correlation* between effect and Ce (dashed line); low (green), typical (blue), high (purple). (d) 'Perfect titration' of Ce for three levels of noxious stimulus showing *no correlation* between effect and a range of titrated Ce (brown bar). All effects are the same for different Ce and different levels of stimulus; low (green), typical (blue), high (purple). Each curve represents a different slice through a response surface for each level of noxious stimulus.

pharmacodynamic system that consequently causes a drug titration paradox in the individual dose–response data. This is analogous to how differences in individual sensitivity result in the drug titration paradox in a population. The drug titration paradox has potentially important implications for anaesthesia clinical pharmacology studies both in terms of how previous studies are re-interpreted and how future studies are designed.[6,22] The relationship between drug dose and drug effect must be determined under carefully controlled experimental conditions. In routine care, where the effect is profoundly influenced by varying clinical conditions and drugs are titrated to achieve the desired effect, it is nearly impossible to draw meaningful conclusions about the relationship between dose and effect.

Authors' contributions

Drafting of the manuscript: TS, CM
Data acquisition: TS, ML
Research design: TS, CM, TDE
Data analysis: TS, CM
Review and approval of the final manuscript: CM, ML, TDE

Declarations of interest

TDE is a member of the associate editorial board of the *British Journal of Anaesthesia*. The other authors declare that they have no conflicts of interest.

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