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Target-controlled-infusion models for remifentanil dosing consistent with approved recommendations

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Abstract

Background: Target-controlled infusion (TCI) systems use pharmacokinetic (PK) models to predict the drug infusion rates necessary to achieve a desired target plasma or effect-site concentration. As new PK models are developed and implemented in TCI systems, there can be uncertainty as to which target concentrations are appropriate. Existing dose recommendations can serve as a point of reference to identify target concentrations suitable for clinical applications.
Methods: Simulations of remifentanil TCI were performed using three PK models (Minto, Eleveld, and Kim). We sought to identify models and target concentrations for remifentanil administration in children, adult, older people, and severely obese individuals, consistent with the remifentanil product label. In a typical adult this is an induction dose of 0.5–1 μg kg^{-1} and starting maintenance infusion rate of 0.25 μg kg^{-1} min^{-1}.
Results: For the Minto, Eleveld, and Kim remifentanil models, a plasma target concentration of ~ 4 ng ml^{-1} achieves drug administration consistent with product label recommended initial doses for all groups with minor exceptions. With effect-site targeting in older individuals, a target concentration of ~2 ng ml^{-1} is required for induction and ~4 ng ml^{-1} for starting maintenance to achieve drug dosages close to product label recommendations.
Conclusions: We identified remifentanil TCI target concentrations that resulted in drug administration similar to product label dosing recommendations. This approach did not necessarily identify target concentrations that achieve desired clinical effect, only those that are consistent with the product label recommended doses. We estimate that plasma target concentrations of 3.1–5.3 ng ml^{-1} are suitable for initial dosing.

Keywords: modelling; pharmacokinetics; pharmacology; remifentanil; target-controlled infusion

Editor's key points

- Target-controlled infusion (TCI) systems use pharmacokinetic models to predict drug infusion rates necessary to achieve a desired target plasma or effect-site concentration.
- Simulations of remifentanil TCI were performed using three models (Minto, Eleveld, and Kim) to identify target concentrations for remifentanil administration in children, adults, older people, and severely obese individuals consistent with the product label.
- A plasma target concentration of about 4 ng ml^{-1} results in remifentanil administration consistent with recommended initial doses for all groups with several minor exceptions.
- For older individuals, effect-site target concentrations of 1.8–2 ng ml^{-1} during induction, increased to about 4 ng ml^{-1} for starting maintenance infusions, results in the recommended dosing.

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Target-controlled infusion (TCI) systems[1] rely on pharmacokinetic (PK) models to calculate drug administration rates necessary to achieve a target concentration in a population typical individual, either in the plasma or at a hypothetical effect site.[2] It is not apparent from inspection how the complex model equations would behave during a clinical TCI application. As new PK models are developed and implemented in TCI systems, it is uncertain what target concentrations may be needed because they are not necessarily equivalent for different PK models.

During the registration process for new drugs, manufacturers are required to inform the registration authorities of the range of effective and safe doses, information that is eventually included in the SmPC (summary of product characteristics) or product label sheet in drug packaging. These recommendations can serve as a point of reference to evaluate the doses administered with different PK models and target concentrations. The dose delivered by a TCI system depends on the PK model, patient characteristics that influence the model parameters, and the target concentration chosen. For high target concentrations, overdosing might occur, and for low target concentrations, underdosing might occur. Between these extremes, target concentrations are sought that result in TCI drug administration consistent with doses approved by regulatory authorities. This approach does not identify target concentrations that achieve specific clinical effects, but rather those consistent with the product label recommended doses. The purpose of this study was to identify target concentrations for TCI models that result in remifentanil administration matching approved SmPC recommendations for children, adult, older, and obese subjects.

Methods

Patient demographic data (age, weight, height, and sex) of a large population were obtained from an external study[3] for use as a test population. Relevant ethics authority approval was obtained for the external study. Simulations were performed using NONMEM version 7.4 (ICON Development Solutions, Ellicott City, MD, USA) and analysed using R (version 2.14.1) (R Foundation for Statistical Computing, Vienna, Austria).[4] For the product label, we used the USA Food and Drug Administration (FDA) approved drug label[5] and the European Medicines Agency (EMA) approved SmPC.[6] Where appropriate, interpolation between age groups was performed. Dose recommendations in the severely obese [30% more than the ideal body weight (IBW)] were calculated relative to IBW in accordance with recommendations in the SmPC. IBW was calculated using the equation IBW=22•HGT,[2] where HGT is height in m.

We considered the Minto,[7,8] Eleveld,[9] and Kim[10] remifentanil PK models for both plasma and effect-site targeting modes. The lean body mass calculation in the Minto model shows anomalous behaviour[11] with the potential for predicting inappropriately low doses in obese patients.[12] Some TCI systems set a maximum body weight[13] because of the limitations of the internal lean body mass equations, so we simulated this for the Minto model. The Kim model does not include an estimate of effect-site equilibration constant (k_{e0}) necessary for effect-site targeting so for this model the Minto model k_{e0} was used.

For each individual, simulations were performed to calculate 'TCI induction dose' and 'TCI starting maintenance infusion rate' as shown schematically in Fig 1 for the Minto model targeting 4 ng ml^{-1} for a 35-yr-old, 70 kg, 170 cm tall female. The remifentanil product label states that the induction dose should be administered over 30–60 s; to accommodate this slower administration in our simulations, we calculated TCI induction dose as the total dose over the first 45 s, consisting of the loading dose (dose at time 0) plus the cumulative infusion over the first 45 s.

After the induction dose, the product label recommends a maintenance infusion of 0.25 μg kg^{-1} min^{-1} for adults. Adjustments to infusion rate should be considered every 2–5 min, allowing assessment of initial drug effects before adjusting to the patient and clinical conditions to reach the desired μ-opioid effect, that is dose individualisation or titration-to-effect. We calculated the TCI starting maintenance infusion rate as the average (non-zero) infusion rate from 45 s to 3 min to simulate the clinical practice of waiting 3 min after induction before maintenance infusion rates or target concentrations are adjusted.

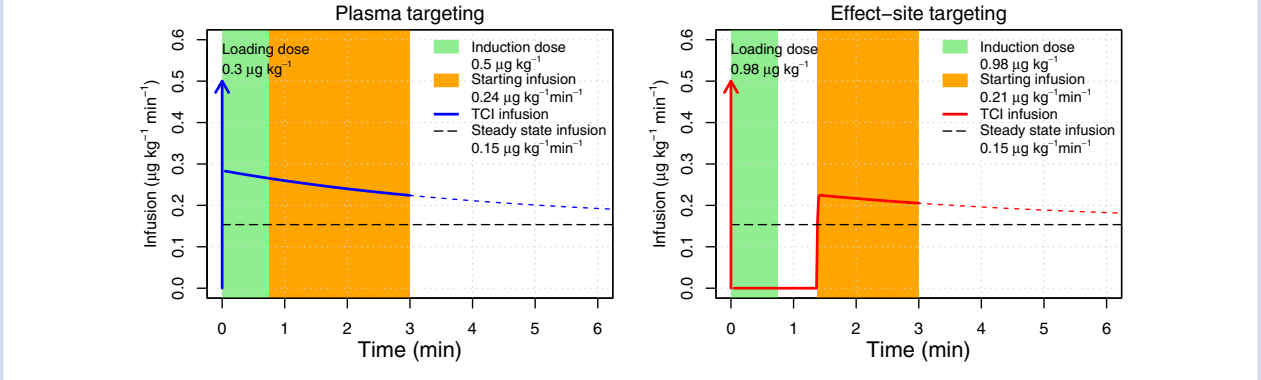

Fig 1. Simulation of target-controlled infusion (TCI) for the Minto model targeting 4 ng ml^{-1} for a 35-yr-old, 70 kg, 170 cm tall female. The induction dose was the total dose administered in the first 45 s (shaded green). This is the initial loading dose (given at time 0) plus the infused dose over the first 45 s. The starting maintenance infusion rate was the average non-zero infusion rate from 45 s to 3 min (shaded orange).

Table 1 Remifentanil administration recommendations for anaesthesia from the product insert. Source is the US FDA approved drug label and the EMA approved SmPC, unless otherwise specified. *Source is interpolated between neonates and adults.

	Induction (μg kg^{-1})	Starting maintenance infusion rate (μg kg^{-1} min^{-1})	Individualised infusion rate (μg kg^{-1} min^{-1})
Neonates (0–2 months)	1	0.4±30%	
Children (2 months–12 yr)	1	0.325±30%*	0.05–1.3
Adults (12–65 yr)	0.5–1	0.25±30%	0.05–2
Older individuals (>65 yr)	50% reduced from adults	25% reduced from adults	Same as adults
Severely obese adults (weight >30% over ideal)	Same as adults but scaled to ideal body weight	Same as adults but scaled to ideal body weight	Same as adults

The recommended maintenance dosing range from the remifentanil product label is 0.05–2 μg kg^{-1} min^{-1} in adults and 0.05–1.3 μg kg^{-1} min^{-1} in children. This very wide range likely indicates the desire of the regulatory authorities to allow for individualised dose rates. To determine the lower bound for target concentrations, we considered the target concentration that results in the lowest steady-state infusion rate across the population (typically in older individuals), which matches the lower bound of the recommended individualised maintenance infusion rate (0.05 μg kg^{-1} min^{-1}). For the upper bound, we considered the target concentration that results in the highest starting maintenance infusion rate (in young adults or young children, depending on the model), which matches the corresponding upper bound for the recommended individualised maintenance infusion rate range. For each model and all individuals, a target concentration of 4 ng ml^{-1} was simulated and the TCI induction dose, starting maintenance infusion rate, and steady-state infusion rate were calculated. These results were extrapolated to target concentrations of 2, 6, and 8 ng ml^{-1} because current remifentanil PK models are linear in target concentration response to dose.

The calculated TCI induction dose and starting maintenance infusion rates for the test population were compared with the recommended induction dose and starting maintenance infusion rate for anaesthesia in combination with propofol or inhalation anaesthetics from the remifentanil product label. We accepted modest underdosing (typical dose >50% of the lower bound) for TCI induction dose as adequate. Remifentanil has a rapid equilibration with a time to peak effect of 1–2 min[14]; thus, moderate initial underdosing only exists for a short time during TCI before steady-state is approached. We considered maintenance infusion rates as adequate if they were within 30% of the recommended value. All models were tested over the whole population, which means that the Minto and Kim models were tested outside of their intended population, that is in children.

Results

For each method, TCI simulations of 1033 individuals were performed. The age range was from 27 weeks post-menstrual age to 88 yr, and the weight range was 0.68–160 kg. The remifentanil administration guidelines are summarised in Table 1.

The results of simulations of the Minto, Eleveld, and Kim models are shown in Figs 2–4, respectively. Calculated steady-state infusion rates are shown in Fig 5. The recommended induction dose range mentioned in Table 1 is shaded green, and the recommended starting maintenance infusion rate is indicated in orange. Grey-shaded areas indicate age ranges outside of that used for model development.

Minto model

Simulations using the Minto model are shown in Fig 2. A plasma target concentration of 4 ng ml^{-1} in adult and older patients results in induction doses (Fig 2a) and starting maintenance infusion rates (Fig 2b) close to recommendations, and also in severely obese individuals (Fig 2c and d).

With effect-site targeting there does not appear to be a single target for all individuals consistent with recommendations. With a target concentration of 4 ng ml^{-1}, induction dose approaches the upper limit of 1 μg kg^{-1} for adults, and exceeds recommendations in older individuals (Fig 2e) and severely obese (Fig 2g). For the same target concentration of 4 ng ml^{-1}, starting maintenance infusion rates are close to recommendations for adults and older individuals (Fig 2f) and severely obese individuals (Fig 2h). Target concentrations close to 2 ng ml^{-1} are needed in older individuals during induction, but target concentrations of about 4 ng ml^{-1} are needed for starting maintenance infusions to be close to product label recommendations.

Figure 5 shows that steady-state infusion rates at a target concentration of 2 ng ml^{-1} result in infusion rates in older individuals close to 0.05 μg kg^{-1} min^{-1}, the lower limit for individualised maintenance infusion rates. The starting maintenance infusion rate for a target concentration of 4 ng ml^{-1} in a 12-yr-old child is about 0.4 μg kg^{-1} min^{-1} (Fig 2b), and the upper limit to individualised maintenance infusion rates in children is 1.3 μg kg^{-1} min^{-1}, which is about 3.25 times as large. Thus the estimated upper limit plasma target concentration for individualised maintenance infusion rates is (4×3.25=) about 13 ng ml^{-1}.

In summary, for the Minto model a plasma target concentration of about 4 ng ml^{-1} results in induction doses and starting maintenance infusion rates close to recommendations for adults and older individuals. For individualised (i.e. titrated-to-effect) maintenance infusions, a plasma target concentration range between about 2 and 13 ng ml^{-1} is consistent with product label recommendations. In children, TCI induction doses and starting maintenance infusion rates increased steeply with decreasing age for both plasma and effect-site targeting.

Eleveld model

Simulations using the Eleveld model are shown in Fig 3. A plasma target concentration of 4 ng ml^{-1} in adults and older

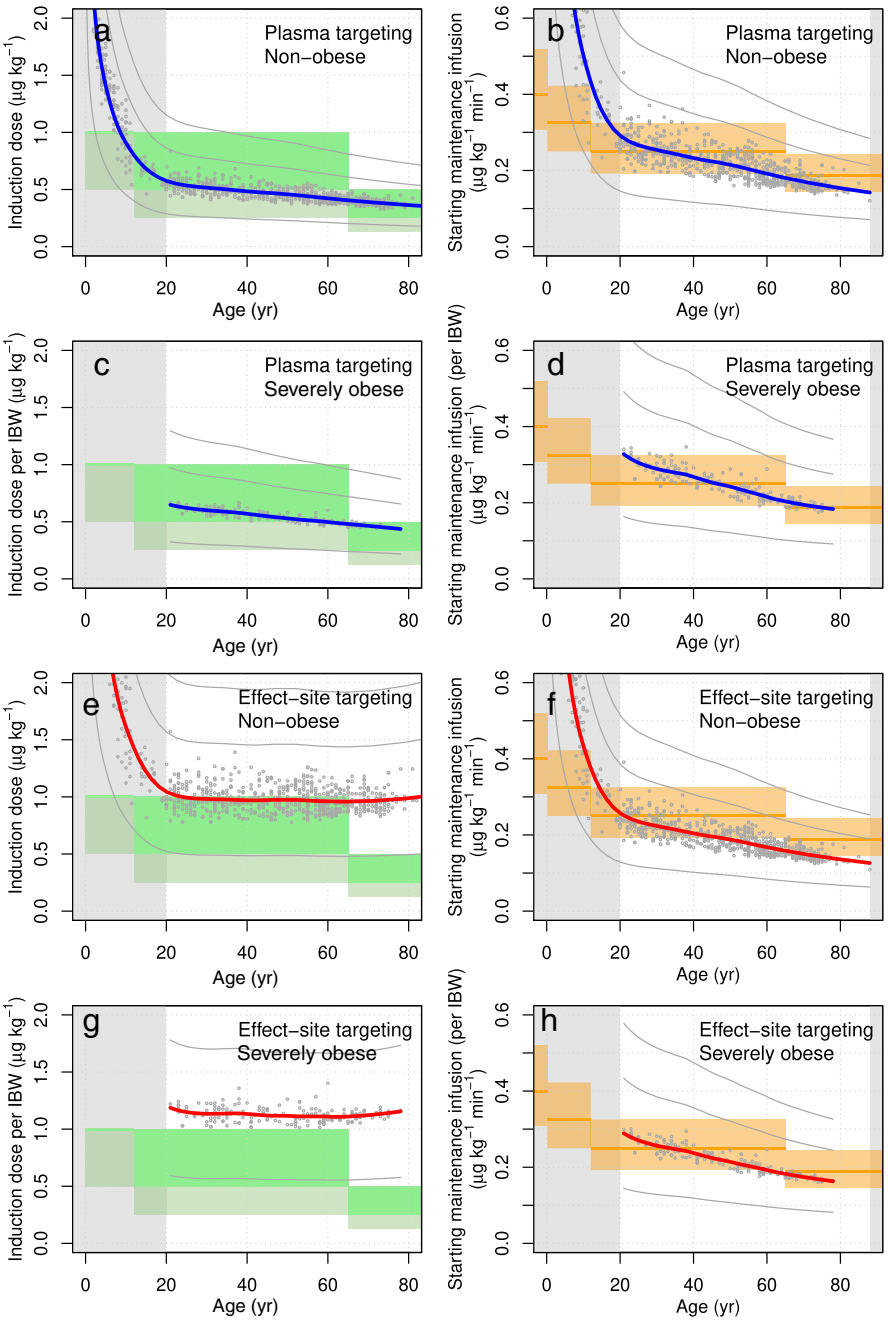

Fig 2. Remifentanil administration for target-controlled infusion using the Minto model. Smoothed lines are shown for targeting 2, 4, 6, and 8 ng ml^{-1}. Data points and thick lines are shown for 4 ng ml^{-1} (plasma, blue; effect site, red). Green shaded areas indicate the induction dose recommendations and light green areas the range of moderate acceptable underdosing. The orange line indicates the recommended starting maintenance infusion rate and the light orange area indicates 30% deviation. IBW, ideal body weight.

individuals results in induction doses (Fig 3a) and starting maintenance infusion rates (Fig 3b) close to recommendations, and in severely obese individuals (Fig 3c and d) with some minor exceptions. For young children (<2 yr), the starting maintenance infusion rates are about 45% greater than recommended, and for younger (<30 yr) severely obese individuals it is about 40% greater.

With effect-site targeting there does not appear to be a single target for all individuals consistent with recommendations. With a target concentration of 4 ng ml^{-1}, induction dose

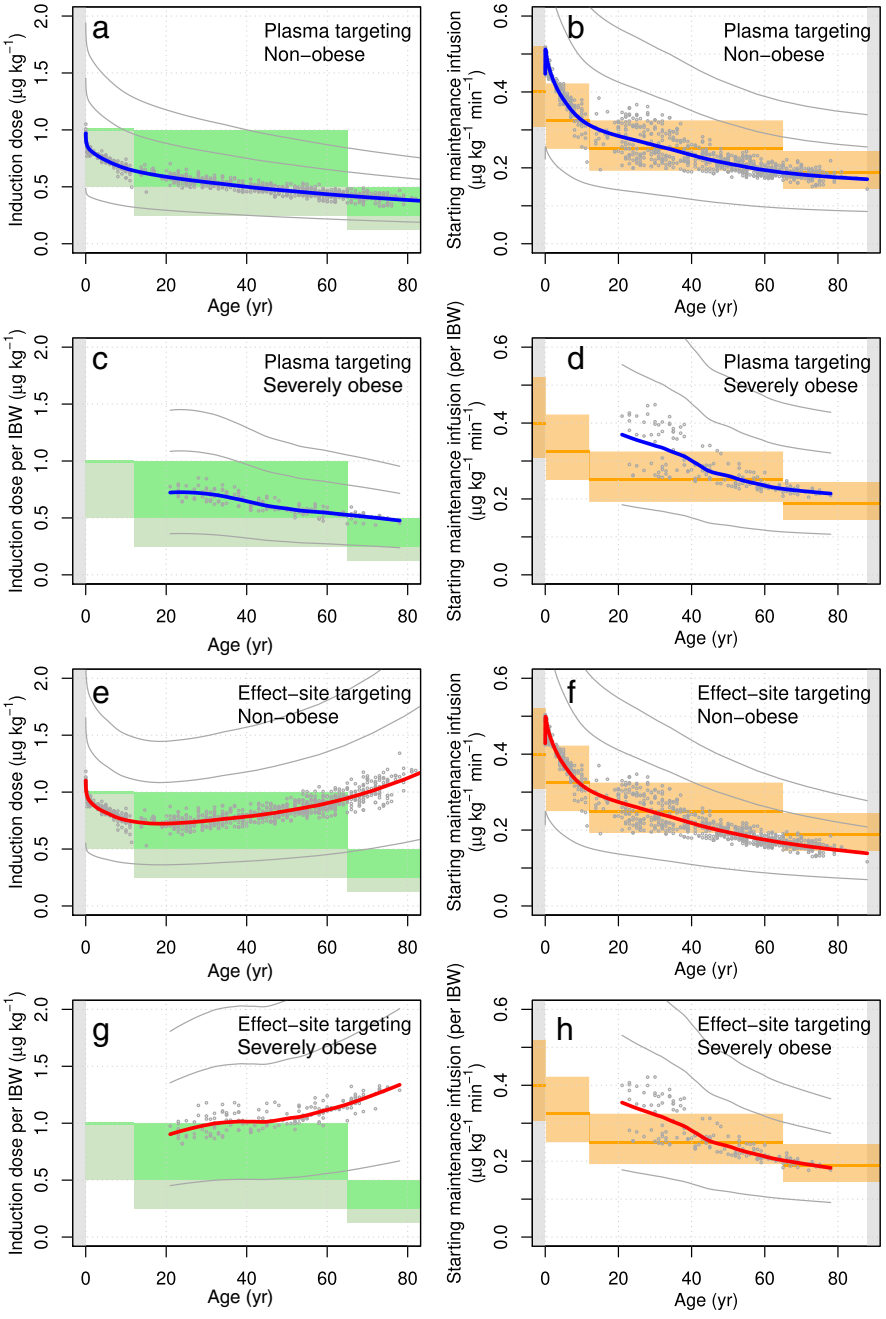

Fig 3. Remifentanil administration for target-controlled infusion using the Eleveld model. Smoothed lines are shown for targeting 2, 4, 6, and 8 ng ml^{-1}. Data points and thick lines are shown for 4 ng ml^{-1} (plasma, blue; effect site, red). Green-shaded areas indicate the induction dose recommendations and light green areas the range of moderate acceptable underdosing. The orange line indicates the recommended starting maintenance infusion rate and the light orange area indicates 30% deviation. IBW, ideal body weight.

exceeds recommendations in older individuals (Fig 3e) and in older (>40 yr) severely obese individuals (Fig 3g). For the same target concentration of 4 ng ml^{-1}, starting maintenance infusion rates are close to recommendations for adults and older individuals (Fig 3f) and older (>30 yr) severely obese individuals (Fig 3h). Target concentrations <2 ng ml^{-1} are warranted in older individuals during induction, but target concentrations of about 4 ng ml^{-1} are needed for starting maintenance infusions, for dosing to be close to product label recommendations.

Figure 5 shows that steady-state infusion rates targeting 2 ng ml^{-1} result in infusion rates in older individuals close to

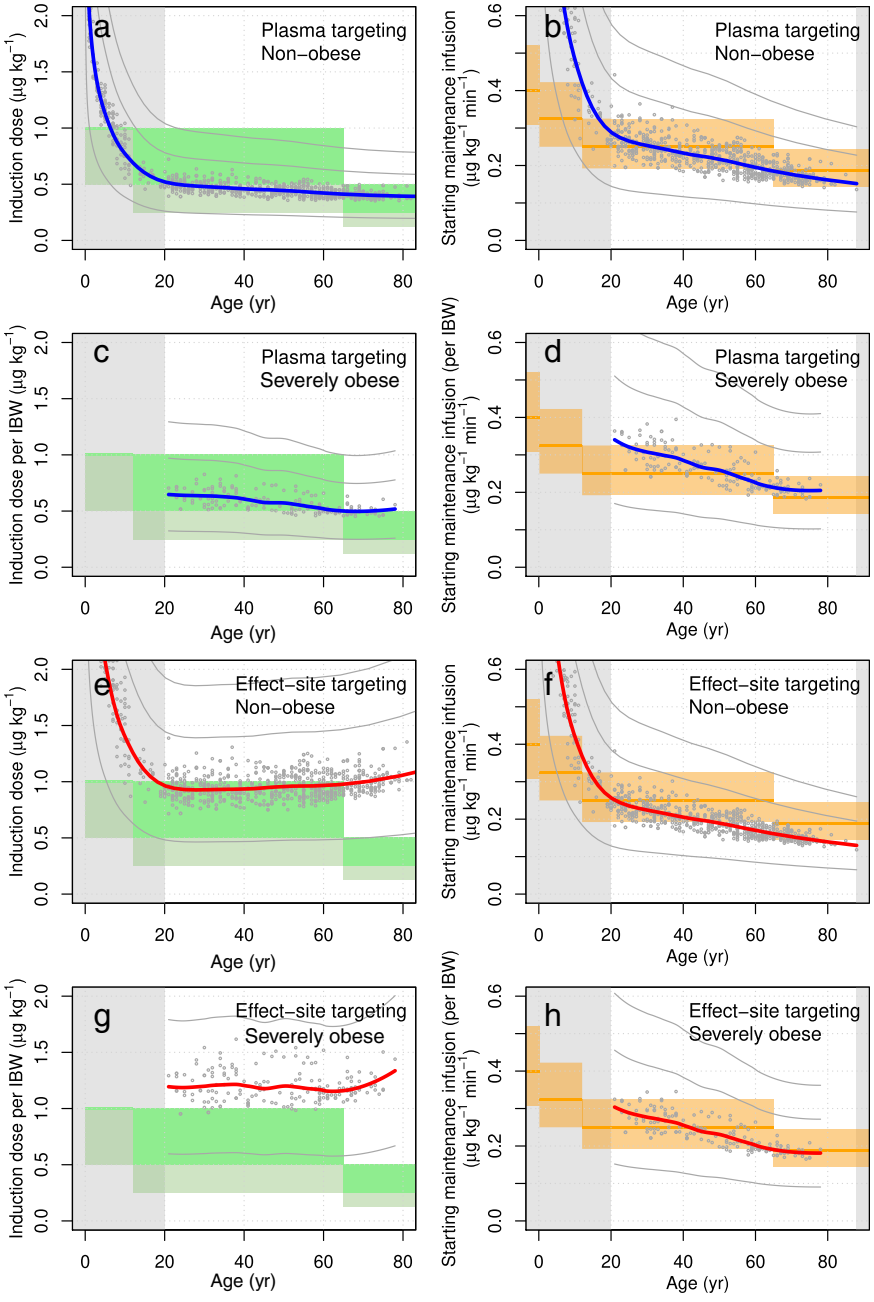

Fig 4. Remifentanil administration for target-controlled infusion using the Kim model. Smoothed lines are shown for targeting 2, 4, 6, and 8 ng ml^{-1}. Data points and thick lines are shown for 4 ng ml^{-1} (plasma, blue; effect site, red). Green shaded areas indicate the induction dose recommendations and light green areas the range of moderate acceptable underdosing. The orange line indicates the recommended starting maintenance infusion rate and the light orange area indicates 30% deviation. IBW, ideal body weight.

0.05 µg kg^{-1} min^{-1}, the lower limit for individualised maintenance infusion rates. The starting maintenance infusion rate for a plasma target concentration of 4 ng ml^{-1} in a 2-yr-old child is about 0.45 µg kg^{-1} min^{-1} (Fig 3b), and the upper limit to individualised maintenance infusion rates in children is 1.3 µg kg^{-1} min^{-1}, which is about 2.9 times as large. Thus the upper limit estimated plasma target concentration for individualised maintenance infusion rates is (4×2.9=) about 11.5 ng ml^{-1}.

In summary, for the Eleveld model a plasma target concentration of about 4 ng ml^{-1} results in induction doses and starting maintenance infusion rates close to recommendations for adults and older individuals. For individualised (i.e.

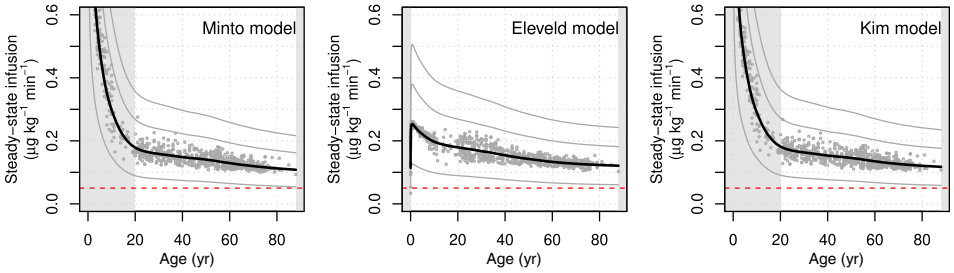

Fig 5. Steady-state infusion rate *vs* age for the Minto, Eleveld, and Kim models. Smoothed lines are shown for targeting 2, 4, 6, and 8 ng ml^{-1}. Data points and thick lines are shown for 4 ng ml^{-1} (plasma, blue; effect site, red).

titrated-to-effect) maintenance infusions, a plasma target concentration range between about 2 and 11 μg kg^{-1} min^{-1} is consistent with product label recommendations.

Kim model

Simulations using the Kim model targeting 4 ng ml^{-1} are shown in Fig 4. They are similar to those found with the Minto model. A plasma target concentration of 4 ng ml^{-1} in adult and older individuals results in induction doses (Fig 4a) and starting maintenance infusion rates (Fig 4b) close to recommendations, as also in severely obese individuals (Fig 4c and d).

With effect-site targeting there does not appear to be a single target for all individuals consistent with recommendations. With a target concentration of 4 ng ml^{-1}, induction dose approaches the upper limit of 1 μg kg^{-1} for recommendations for adults, and exceeds recommendations in older individuals (Fig 4e) and severely obese individuals (Fig 4g). For the same target concentration of 4 ng ml^{-1}, starting maintenance infusion rates are close to recommendations for adults and older individuals (Fig 4f) and severely obese (Fig 4h). Target concentrations close to 2 ng ml^{-1} are needed in older individuals during induction, but target concentrations of about 4 ng ml^{-1} are needed for starting maintenance infusions for dosing to be close to product label recommendations.

Figure 5 shows that steady-state infusion rates targeting 2 ng ml^{-1} result in infusion rates in older individuals close to 0.05 μg kg^{-1} min^{-1}, the lower limit for individualised maintenance infusion rates. The starting maintenance infusion rate for a plasma target concentration of 4 ng ml^{-1} in a 12-yr-old child is about 0.4 μg kg^{-1} min^{-1} (Fig 4b), and the upper limit of individualised maintenance infusion rates in children is 1.3 μg kg^{-1} min^{-1}, which is about 3.25 times as large. Thus the upper limit estimated plasma target concentration for individualised maintenance infusion rates is (4×3.25=) about 13 ng ml^{-1}.

In summary, for the Kim model a plasma target concentration of about 4 ng ml^{-1} results in induction doses and starting maintenance infusion rates close to recommendations for adults and older patients. For individualised (i.e. titrated-to-effect) maintenance infusions, a plasma target concentration range of about 2–13 ng ml^{-1} is consistent with product label recommendations. In children, TCI induction doses and starting maintenance infusion rates increased steeply with decreasing age for both plasma and effect-site targeting.

Discussion

For the Minto, Eleveld, and Kim remifentanil models, a plasma target concentration of about 4 ng ml^{-1} achieves drug administration in the first 3 min of TCI (induction doses and starting maintenance infusion rates) close to product label recommended doses for children (Eleveld only), adults, older individuals, and the severely obese with some minor exceptions (Eleveld, children <2 yr: infusion rate about 45% too high; severely obese <30 yr: infusion rate is about 40% too high). After the initial phase of TCI, clinicians individualise drug dosing to the individual drug requirements on a moment-by-moment basis. For this titration-to-effect, we found that plasma target concentrations of 2–13 ng ml^{-1} (Minto, Kim) or 2–11 ng ml^{-1} (Eleveld) are consistent with product label recommendations. We do not claim that this target concentration achieves appropriate clinical effect in all cases, only that it is broadly consistent with the dosing recommendations in the product label.

Patients differ in their drug sensitivities, physical condition (e.g. healthy or frail), comorbidities, and the types of medical procedures which vary with respect to noxious stimulation and necessary μ-opioid drug effect, and these can vary over time as well. These may not be detailed in the Dosage and Administration section of the product label, and none of these are covariates included in the PK model such that clinicians must compensate for these variabilities in another manner. If we assume that (1) these qualities introduce about 30% variability in remifentanil drug requirements, and (2) drug requirements match the dose in the product label, then our results suggest that a plasma target concentrations in the range of 3.1–5.3 ng ml^{-1} would be appropriate for the initial phase of remifentanil TCI with the Minto, Eleveld, and Kim models.

For equal target concentrations, effect-site targeting always results in greater induction doses than plasma targeting, whereas starting maintenance infusion rates only show minor changes. For the models considered, effect-site target concentrations in older individuals should be about 1.8–2 ng ml^{-1} for induction and about 4 ng ml^{-1} for starting maintenance infusions for dosing similar to recommendations. The adjustment should occur after induction and before the start of maintenance infusions, which is between about 45 s after start of induction and the time to peak drug effect. This is a potential source of user error for clinicians using effect-site

targeting who wish to administer product label recommended doses. This adjustment is not necessary when plasma targeting is used.

TCI systems are often described as administering doses consistent with the product label.[15–17] Our work verifies this statement for specific models, targets, and populations. This may be helpful from a regulatory perspective because it clarifies the relationship between TCI models and target concentrations and the safe and effective doses described in the product label. Product labels can also be (necessarily) vague with respect to dynamic, non-steady-state conditions, so TCI dosing should not be expected to conform exactly to the product label. In the future, TCI-based administration should be considered a part of new drug development and product labelling to maximise clarity for clinicians.

The Minto model is available in commercial TCI systems. Our results are consistent with other recommendations to target 2–6 ng ml^{-1}.[18] Although some recommendations[19] suggest higher doses for adults (<50 yr) of 5–8 ng ml^{-1}, reduced targets are recommended in older individuals (>50 yr) of 3–6 ng ml^{-1}, with the suggestion to use plasma targeting in older less robust individuals to reduce the induction bolus dose. Our approach does not necessarily provide new information for the Minto model, for which target concentration recommendations already exist, but it does provide target concentration recommendations for the Eleveld and Kim models.

For the Minto and Kim models, the youngest individual used in model development was 20 yr old. These models were not intended for use in children, which may explain the steep relationship between age and dosing for children. These models were developed without use of allometric scaling,[20,21] so there was no assumed relationship between body size and drug volumes and clearances, and thus there are no corrections for the small body sizes found in children. Based on our results, it is not surprising that TCI infusion pumps set a lower limit of age of 12 yr for the Minto model,[13] and this limitation seems appropriate for the Kim model as well.

Our approach can be performed during model development to differentiate the qualities of models and act as an adjunct to the observed-data driven model development process. Many PK studies are performed on groups with limited weight and age ranges, and the recorded data are subsequently not informative for weight scaling or age corrections. Our approach can be used to inform model selection as to the most useful structures and scaling, even if the models cannot be differentiated based on their fit to a particular dataset. This approach was used in the development of a PK–pharmacodynamic (PD) model for propofol[3] to choose an appropriate effect-site equilibration rate constant k_{e0} for young children even though no PD data were available from that group. The k_{e0} model structure chosen was judged to result in drug administration more closely matching recommendations from the propofol product label.

Taking a different perspective than our approach of evaluating model and target concentration combinations in terms of dose (i.e. in the dose domain),[22] one could also evaluate TCI models in terms of drug effects (i.e. in the effect domain).[22] Large databases from hospital information systems would be a good source for this information. This would provide a better evaluation of clinical utility and a more granular view of the necessary clinical dosing; however, it is more complex and costly than the approach we use here.

A limitation of our approach is that approved product labels are not always informative, with some labels lacking dose–response evaluations.[23] Similarly, it is also not useful for new drugs where an approved product label does not exist. Another limitation of our method is that there is no objective measure of the degree of agreement between TCI drug administration and dose recommendations. A universal measure seems unlikely given that various qualities have differing importance across drugs and clinical situations. In addition, drug recommendations often describe discrete changes between groups whereas clinical experience supports gradual changes. For the current investigation, we subjectively identified the deficiencies in the models relevant to remifentanil administration. However, others might come to different conclusions, especially if other drugs and clinical applications are considered.

We conclude that for the Minto, Eleveld, and Kim remifentanil models, a plasma target concentration of about 4 ng ml^{-1} results in drug administration consistent with SmPC recommended initial doses for all applicable groups with some minor exceptions. When effect-site targeting is used in older individuals, target concentrations of 1.8–2 ng ml^{-1} are needed during induction, increased to about 4 ng ml^{-1} for starting maintenance infusions, in order for initial drug administration to be close to recommendations. Our approach does not necessarily identify target concentrations that achieve the appropriate clinical effect, only that are consistent with the product label recommended doses.

Authors' contributions

Study design: DJE, PC, ARA, MMRFS
Data analysis: DJE
Drafting of the manuscript: DJE, PC, ARA, MMRFS
Approval of the final version of the manuscript: DJE, PC, ARA, MMRFS.

Declarations of interest

DJE is an associate editor for *Anesthesiology Journal*. PC declares no conflict of interest. ARA has performed paid consultancy work for Janssen Pharma, The Medicines Company and Ever Pharma (payment to institution). He is an editorial board member and editor of the *British Journal of Anaesthesia*. He was not involved in the editorial process of this publication. MMRFS and his research group/department received (over the past 3 yr) research grants and consultancy fees from The Medicines Company (Parsippany, NJ, USA), Masimo (Irvine, CA, USA), Fresenius (Bad Homburg, Germany), Dräger (Lübeck, Germany), Paion (Aachen, Germany), and Medtronic (Dublin, Ireland). He receives royalties on intellectual property from Demed Medical (Temse, Belgium) and the Ghent University (Gent, Belgium). He is an editorial board member and director of the *British Journal of Anaesthesia* and associate editor for *Anesthesiology*. He was not involved in the editorial process of this publication.

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