General purpose models for intravenous anesthetics, the next generation for target-controlled infusion and total intravenous anesthesia?

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Purpose of review
There are various pharmacokinetic-dynamic models available, which describe the time course of drug concentration and effect and which can be incorporated into target-controlled infusion (TCI) systems. For anesthesia and sedation, most of these models are derived from narrow patient populations, which restricts applicability for the overall population, including (small) children, elderly, and obese patients. This forces clinicians to select specific models for specific populations.

Recent findings
Recently, general purpose models have been developed for propofol and remifentanil using data from multiple studies and broad, diverse patient groups. General-purpose models might reduce the risks associated with extrapolation, incorrect usage, and unfamiliarity with a specific TCI-model, as they offer less restrictive boundaries (i.e., the patient ''doesn't fit in the selected model'') compared with the earlier, simpler models. Extrapolation of a model can lead to delayed recovery or inadequate anesthesia. If multiple models for the same drug are implemented in the pump, it is possible to select the wrong model for that specific case; this can be overcome with one general purpose model implemented in the pump.

Summary
This article examines the usability of these general-purpose models in relation to the more traditional models.

Keywords
anesthetic drug delivery, general-purpose models, propofol, remifentanil, target-controlled infusion

INTRODUCTION

Total intravenous anesthesia (TIVA) has gained popularity in clinical practice due to the reduction of postoperative nausea and vomiting but also due to an increased awareness of the impact of volatile anesthetics on climate change [1]. With TIVA, anesthesiologists can dose drugs with manual boluses and continuous infusions, but this can be complex, labor-intensive, and time consuming. Target-controlled infusion (TCI) [2▪] is a computer-controlled infusion technique to calculate and administer drug doses and infusion rates to establish and maintain a targeted plasma or effect-site concentration, which can ease the clinical application of TIVA. These systems using internal pharmacokinetic or pharmacokinetic-pharmacodynamic (PK-PD) models.

In current anesthetic clinical practice, TCI is mainly used to dose propofol (Schnider *et al*. [3], Paedfusor *et al*. [4], Marsh *et al*. [5], and Eleveld *et al*. [6]) remifentanil (Minto *et al*. [7], Eleveld *et al*. [8], and Kim *et al*. [9]), sufentanil (Gepts *et al*. [10]) and hypnotics dexmedetomidine (Dyck-model [11] and Hannivoort-Colin [12]). Other models [13] have been developed, but these have not found

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KEY POINTS

- General-purpose models can be used in a broader range of patients, including children, adults, obese, and elderly patients.
- General-purpose models might reduce the risks associated with extrapolation, incorrect usage, and unfamiliarity with a specific TCI-model.
- For clinicians, general-purpose PKPD models applied in TCI reduce the burden to understand the specific limitations of perhaps several population-specific models available and to select the correct model for a given clinical case.
- General-purpose models may require fewer target concentration adjustments after induction during anesthetic maintenance.

widespread application in clinical practice. Some recently developed models [14] are developed and validated [15] on very specialized populations.

This article addresses recent developments in PK-PD models with a specific focus on models for TCI for propofol and remifentanil. It examines the benefits of recently developed general-purpose models in relation to the more traditional approach, which have typically been developed for restricted patient population.

WHEN IS A MODEL APPROPRIATE?

As a TCI system relies on an underlying pharmacokinetic or PK-PD model for accurate calculation of drug dosing, its performance is dependent on the accuracy and applicability of the model. To avoid misuse, a clinician must be aware of the strengths and limitations of the underlying pharmacological model. The majority of existing models were derived from restricted populations such as healthy volunteers, individuals with a normal BMI, a specific sex or age range. However, it seems likely that a clinical patient would differ from these populations. A complete overview of the demographic ranges of commercially available models can be found in a recent publication by Hannivoort *et al.* [2▪].

Some authors have suggested that an optimal approach would be required to develop different models for various clinical situations and apply them as appropriate [16]. The drawback of this approach is that it requires substantial scientific knowledge from users and some models may simply not be available in a clinical setting for the diversity of cases [17].

A limitation of population-based models is that there will always be some residual error due to inter-individual variability. This results in a difference between the population-based estimate and the plasma (or effect-site) concentration in the individual [18]. The accuracy of a model is most often expressed in terms of the Varvel criteria [19], which compare the prediction of drug concentration to observed values. It is generally accepted that a median absolute prediction error (also known as MDAPE or predictive precision) should not exceed 30% for plasma concentrations [20]. Further individualization of population-based models, for example Bayesian optimization, has shown to reduce population-based errors but only with a limited effect [18,21]. Although the residual error defines the accuracy of a pharmacokinetic model to predict drug concentrations, it may have only a limited impact for TCI in clinical practice. Clinicians perform titration-to-effect and define target concentrations as adequate or inadequate and not as accurate or inaccurate. Thus, they may not be aware of bias in the pharmacokinetic predictions because it has little influence on their clinical tasks. Despite some bias in the performance, these TCI systems are very good at establishing a steady-state drug level, which is helpful to the clinician by achieving the desired drug effect. Given a tradeoff between ease-of-use and predictive accuracy, a model that has practical benefits may weigh up against a slight decrease in the prediction ability.

The broad diversity across patients can cause mismatch between the clinical case and the PK-PD model, especially when the patient characteristics are outside the range of covariates used in the model (i.e., outside the range of body weight used to build the model). If this occurs, clinicians may choose to extrapolate or adjust the patient characteristics input into the TCI device in order to improve the patient ''fit to the model'' and accommodate the use of a TCI system that may be available. Although performance may be suboptimal, it may still be suitable if the alternative is manual calculation and adjustment using manually administered drug boluses and continuous infusions. Extrapolation can lead to uncertainty of the correct dose and potentially to underdosing or overdosing, with a risk of inadequate anesthesia or delayed recovery.

GENERAL-PURPOSE MODEL

Improved scientific knowledge and availability of databases such as the ''opentci.com network'' has lead to the development of general-purpose or ''second generation'' models [22]. These models take the relationship between the patient characteristics (age, weight, BMI, sex, and so on) from broad populations into account to predict the time course of drug concentrations for a greater diversity of

patients. The relationships between the patient covariates and the pharmacokinetics and PK-PD model parameters may be simple associations. However, model development is increasingly focused on mechanistic explanations. For example, glomerular filtration rate is known to decrease with advancing age, and it is reasonable to assume that elimination clearance for renally cleared drugs shows similar behavior. Other than these mechanistic drivers no theoretical models of ageing exist. In contrast, theoretical explanations for the relationship between pharmacokinetic and body size have been increasingly applied in pharmacokinetic and PK-PD model development [23] by applying allometric scaling theory. This is based on the work of West-Brown-Enquist [24] and is widely applied in other branches of the biological sciences and is well known in drug development for extrapolation between species. For clinical anesthesia, allometric scaling provides a theory (cohesive system of ideas based on general principles) for long-standing observations that larger, heavier individuals require greater drug doses (in mass units) for comparable drug concentrations and effects, but lower doses when expressed per-kg bodyweight. Although allometric scaling is now often used by PK-model builders, some have criticized empiric application of the concept [25].

For clinicians, general-purpose TCI models reduce the burden to understand the specific limitations of perhaps several population-specific models available and to select the correct model for a given clinical case. This reduces or eliminates the need for extrapolation or adjustment of patient characteristics (i.e., the need to modify the body weight, height or sex to fit the patient into the model) simplifies clinical decision making, and reduces the risk of error. Importantly, these benefits are obtained without any additional effort from the clinicians themselves because they are obtained by efforts expended during the model development process. Furthermore, clinical training requirements can be simplified because they do not have to take into account the arbitrary boundaries in age, weight, BMI, and so on, which are imposed by multiple TCI models. This likely results in fewer TCI target concentrations adjustments after induction while entering anesthetic maintenance. At the same time, there may be complex relationships between an individual's patient drug sensitivity and an appropriate clinical target concentration due to the titration-paradox [26▪▪].

PROPOFOL

To administer propofol, several commercial models are available, most of them developed for a specific group of patients, for example adults or children. Table 1 shows some of the commercially available models with their boundaries [3–10,27]. A detailed comparison between the models was recently described by Vandemoortele *et al.* [28]. They concluded that general-purpose models have the potential to increase the clinical acceptance of TCI, as there are less restrictions in their use compared with other models.

Recently, the Eleveld-model, a general-purpose model for propofol, became available and has been prospectively validated in clinical practice [29▪]. The Eleveld propofol model is unique in that it is applicable to administer propofol in children, adults, elderly, and obese. In its validation study, patients from 3 to 90 years, weights from 12.8 to 152 kg, heights from 95 to 192 cm, and a wide BMI range (14–46.8 kg/m^2) were tested and the single model performed adequately for all populations. The predictive precision was lower than 30% in all groups, and it was not inferior in its predictive performance

Table 1. Overview of TCI models and their boundaries

Model	Age range (years)	Weight range (kg)	Height range (cm)	Number of individuals
Propofol				
Marsh *et al.* [5]	2–17	12–54	ND	37
Schnider *et al.* [3,27]	26–81	44–123	155–196	24
Peadfusor *et al.* [4]	2–13	ND	ND	ND
Eleveld *et al.* [6]	0–88	0.68–160	33–200	1033
Remifentanil				
Minto *et al.* [7]	20–85	48–108 ≈	156–192≈	65
Eleveld *et al.* [9]	0–85	2.5–106	49–193	131
Kim-Obara-Egan *et al.* [10]	20–85	45–215	150–196	229

ND, not described.
[a]General purpose models, ≈approximately based on [7].

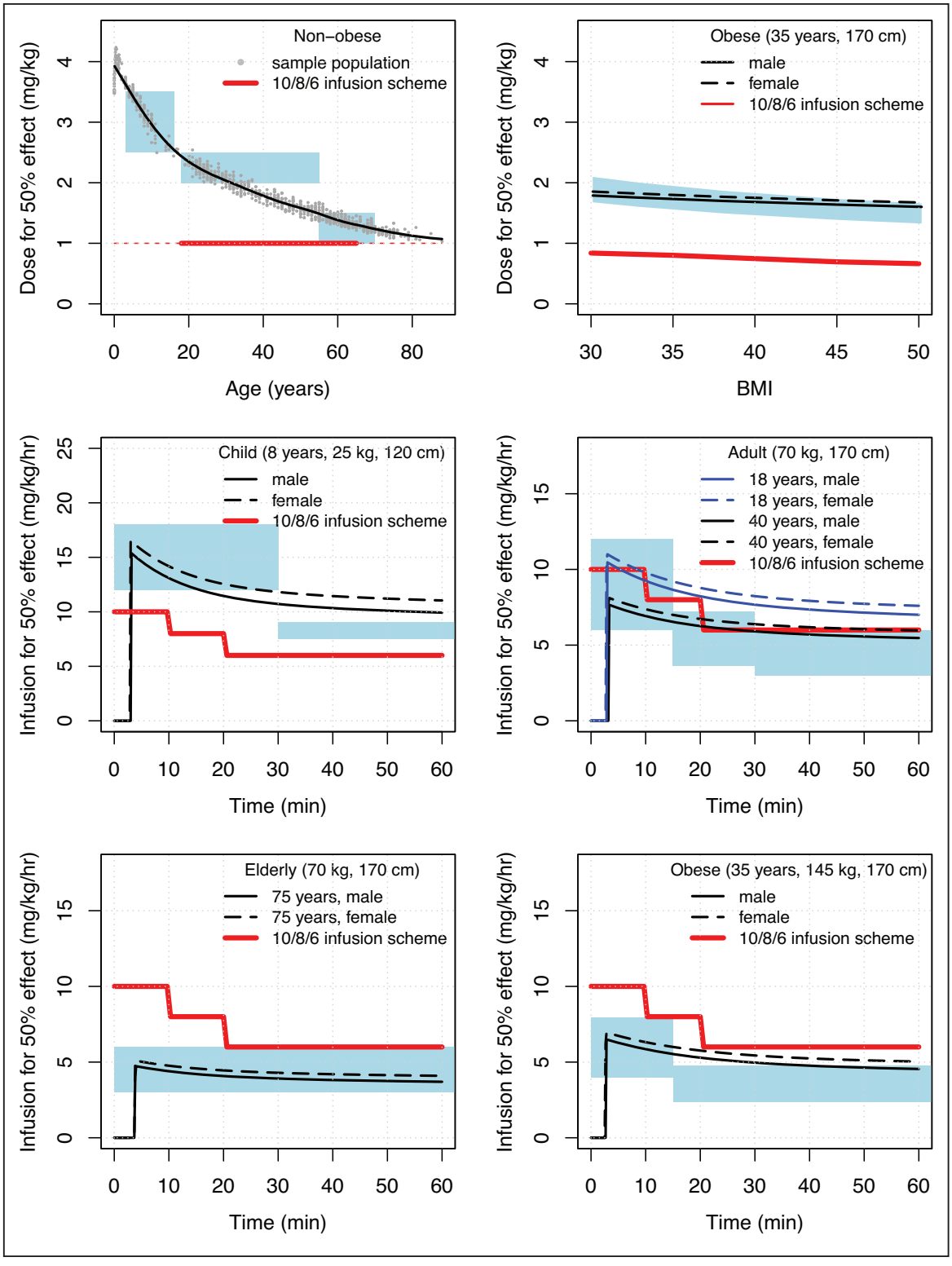

FIGURE 1. Dose recommendations from the product label (blue shaded areas), the 10/8/6 infusion rule (combined with a 1 mg/kg bolus for induction, red lines), both adjusted using Servins-rule for obese individuals, compared with TCI drug administration using Eleveld propofol PK-PD model targeting 50% drug effect. With the Eleveld model, the initial bolus doses and maintenance infusion rates for children, adults, elderly, and obese individuals match recommendations, whereas the 10/8/6 rule results in lower than recommended dosing in children, lower than recommended induction doses in the obese, and higher than recommended maintenance infusion rates for the elderly and obese.

compared with other models. Some models may have better precision, but it is not clear whether this outweighs the benefit of the applicability of all groups (children, obese and the elderly) as none of the other models were applicable over all of the patient groups.

Figure 1 shows dose recommendations from the product label, the ''10/8/6 infusion rule,'' both adjusted using Servins-rule for obese individuals, compared with TCI drug administration using Eleveld propofol PK-PD model targeting 50% drug effect. With the general-purpose Eleveld model, the initial bolus doses and maintenance infusion rates for children, adults, elderly patients, and obese individuals match recommendations, whereas the ''10/8/6 rule'' results in lower than recommended dosing in children, lower than recommended induction doses in the obese, and higher than recommended maintenance infusion rates for the elderly and obese. Simulations of the general-purpose model are useful for clinicians without access to TCI, as it can be inferred that application of the 10/8/6 rule is likely to result in insufficient propofol drug effect in children. Evidence for this are existing recommendations for greater dosing in children [30]. It can similarly be inferred that the ''10/8/6 rule'' is likely to stabilize to excess drug effect in the elderly and to a lesser extent in obese individuals.

Anesthesiologists should be aware that TCI systems using different pharmacokinetic and PK-PD models will result in different drug dosing, even if the same target concentration is used. For example, clinicians familiar with the Schnider model (effect-site mode) or the Marsh model in (plasma mode) may have found that increased target concentrations may be useful to increase initial doses and obtain a quicker loss of consciousness. However, this technique should not be used with the Eleveld model; otherwise, induction doses may exceed recommendations. Similarly, effect-site target concentrations during maintenance of anesthesia are likely to be different across models. The Eleveld model uses an age-specific effect-site concentration needed for a target Bispectral Index (BIS). At induction, using this target concentration results in prediction of decrease BIS from 94 to 47, and this was replicated in the validation study. The age-specific target concentration is detailed in previous work [29▪]. After induction with the Eleveld model using this target concentration, it is often unnecessary to adjust the target concentration [26▪▪], which is a benefit for the workload reduction of the clinician. A very large study of TCI using the Schnider propofol model found that there does seem to be systematic changes in target concentration necessary between induction and maintenance [31].

REMIFENTANIL

For remifentanil, the Minto model is widely applied in diverse clinical situations, but it was developed on a specific population of healthy volunteers. The model does not incorporate allometric size scaling and should not be extrapolated for use in children. For obese individuals, the Minto model internal lean-body-mass calculation shows paradoxical behavior [27] and some authors have suggested inputting a critical weight and fictitious height into the TCI system to address this issue [9]; however, this is obviously not an optimal solution.

To address the limitations of the Minto model, Kim not only developed a remifentanil model from the same dataset Minto used but also included data from obese individuals. This approach makes the Kim model suitable (without requiring adjustments) in an obese population. The Kim Kim-Obara-Egan is suitable for elderly patients as well as the obese (it incorporated advanced age as a covariate effect just like the Minto model). Eleveld *et al.* [8] also considered the same dataset as Minto but included data from children and applied allometric size scaling. An interesting aspect of the Eleveld remifentanil model is that when its use is extrapolated to obese individuals, the resulting dosing is similar to that of the Kim model [32▪]. This suggests that the allometric size scaling incorporated in the Eleveld model allows for reasonable extrapolation from the adult and children development population [23] to obese individuals.

CONCLUSION

For anesthesiologists and clinicians, the primary benefit of a general-purpose model suitable for broad, diverse populations is that it reduces the burden to the clinician to understand the limitations of several pharmacokinetic and PD models with respect to restrictions of age, weight, BMI, and sex. This simplifies the correct application of TCI to diverse clinical cases as well as some of the training necessary for use of TCI. The risks associated with extrapolation and unfamiliarity are also reduced. General-purpose models may require fewer target concentration adjustments after induction during anesthetic maintenance.

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