

## **New Models for Remifentanil, Propofol and Dexmedetomidine.**

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The current infusion models we use for remifentanil, propofol and dexmedetomidine were derived in small numbers of healthy adults. For propofol and remifentanil there have been numerous studies looking at the accuracy of these models when used for TCI, in quite diverse populations and occasional criticism of their accuracy. They function surprisingly well clinically given the quite restricted populations they were derived from. However, a robust model will fulfil the criteria of working well in demographically and geographically diverse populations, representative of the broad range of patients we meet in every day anaesthetic practice. Recently more complete models for propofol and remifentanil that address this need have been created (Table 1).

In the case of propofol, the new model does indeed embrace the full range of ages and weights of patients that we encounter and represents a pooled analysis of 30 studies. The analysis is very sophisticated, but clearly justifies the incorporation of the 18 model parameters it contains. It holds the promise of providing one model for all our patients and should perform better when used for patients that currently do not fit the cohort the March and Schnider models were derived in.

In the case of remifentanil, two studies have been published, one incorporating a broad range of patient ages and the other a broad range of patient weights. There is unfortunately no pooled analysis that incorporates the two, however review of the models reveals little difference in performance.

Dexmedetomidine has not undergone the same rigorous appraisal. However there are stable models available for our typical patients. Recently the new model by Hannivoort was confirmed to be more accurate than the Dyke model in a small study. Detailed PK-PD analysis has also revealed a link between the level of observed sedation and the degree of bradycardia observed, providing an additional check on the amount of drug we should target.

These models hold the promise of improving the accuracy of TCI for a broader range of patients. The caution is that they do not account for PK-PD changes that occur with trauma and disease.

**Table 1**

Number and diversity of volunteers and patients that have contributed data to some Target Controlled Infusion models for propofol, remifentanil and dexmedetomidine (Adapted from Reference 7).

<b>Model</b>	<b>No. of patients</b>	<b>Age range (years)</b>	<b>Weight range (kg)</b>	<b>Number of blood samples</b>	<b>Number of model parameters</b>
<b>Propofol</b>					
Marsh	16	25 - 65	48 - 84	481	7
Schnider	24	25 - 81	44 - 123	1006	11
Eleveld	1033	0.5 - 82	0.68 - 160	15433	18
<b>Remifentanil</b>					
Minto	60	20 - 85	45 - 106	1992	11
Eleveld	131	5 days - 85	2 - 106	2634	12
Kim	229	20 - 85	45 - 215	4455	9
<b>Dexmedetomidine</b>					
Dyck	16	27 - 40	71 - 98	224	7
Hannivoort	18	20 - 70	51-110	408	7

## References

1. Schnider T, Minto C, Gambus P, Andresen C, Goodale D, Shafer S, Youngs E. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998; 88: 1170–82
2. Eleveld DJ, Colin P, Absalom AR, Struys MMRF. A pharmacokinetic-pharmacodynamic model for propofol for broad application in anaesthesia and sedation. *Br J Anaesthesia* 2018; 120:942-59
3. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* 1997; 86: 10–23
4. Eleveld DJ, Proost JH, Vereecke H, Absalom AR, Olofsen E, Vuyk J, Struys MMRF. An allometric model of remifentanil pharmacokinetics and pharmacodynamics. *Anesthesiology* 2017; 126: 1005-18
5. Kim TK, Obara S, Egan TD, Minto CF, La Colla L, Drover DR, Vuyk J, Mertens M; Remifentanil pharmacokinetics in obesity investigators. disposition of remifentanil in obesity: a new pharmacokinetic model incorporating the influence of body mass. *Anesthesiology* 2017; 126: 1019-32
6. Hannivoort LN, Eleveld DJ, Proost JH, Reyntjens KM, Absalom AR, Vereecke HE, Struys MM. Development of an optimized pharmacokinetic model of

dexmedetomidine using target-controlled infusion in healthy volunteers. *Anesthesiology*. 2015;123:357-67

7. Short TG, Campbell D, Egan TD. Increasing the utility of target controlled infusions -one model to rule them all. *Br J Anaesth*. 2018; 120:887-90