Universitair Medisch Centrum Groningen
Afdeling Anesthesiologie

Dosing Anesthetics and analgesics in the Obese patient

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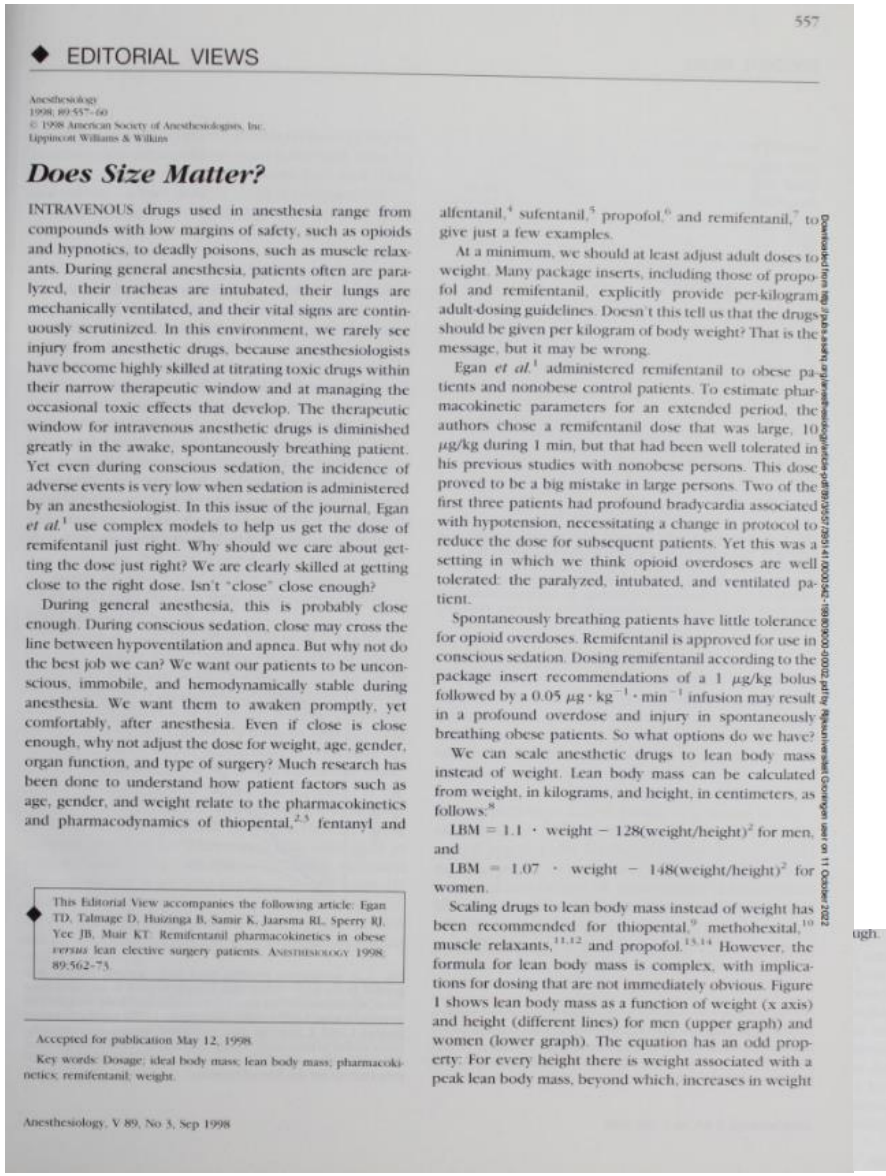
Conflicts of interest

My research group/department received *(over the last 3 years)* research grants and consultancy fees from Masimo (Irvine, CA, USA), Becton Dickinson (Eysins, Switzerland), Fresenius (Bad Homburg, Germany), Dräger (Lübeck, Germany), Paion (Aachen, Germany), Medcaptain Europe (Andelst, The Netherlands). I receive royalties on intellectual property from Demed Medical (Temse, Belgium) and the Ghent University (Gent, Belgium). I am an editorial board member and Director for the British Journal of Anaesthesia, associate editor for Anesthesiology and incoming chair of the Scientific Committee for ESAIC.

Changes in pharmacokinetics : hypnotics and analgesics

- <u>Problems with obesity in anesthesia :</u>
  - Most drugs are given using standard-dosing guidelines without knowledge of their pharmacokinetics
    …. “anesthesiologists are very good in titrating drugs based on their clinical intuition ”. (S.L. Shafer 1998)
  - Pharmacokinetic data are obtained from studies with normal-weight individuals
  - Most dosage recommendations are scaled to TBW
  - Alterations in distribution volume, clearance and protein binding, pharmacodynamics

Does size matter ?



◆ EDITORIAL VIEWS

Anesthesiology
1998; 89:557–60

Does Size Matter?

INTRAVENOUS drugs used in anesthesia range from compounds with low margins of safety, such as opioids and hypnotics, to deadly poisons, such as muscle relaxants. During general anesthesia, patients often are paralyzed, their tracheas are intubated, their lungs are mechanically ventilated, and their vital signs are continuously scrutinized. In this environment, we rarely see injury from anesthetic drugs, because anesthesiologists have become highly skilled at titrating toxic drugs within their narrow therapeutic window and at managing the occasional toxic effects that develop. The therapeutic window for intravenous anesthetic drugs is diminished greatly in the awake, spontaneously breathing patient. Yet even during conscious sedation, the incidence of adverse events is very low when sedation is administered by an anesthesiologist. In this issue of the journal, Egan *et al.*[1] use complex models to help us get the dose of remifentanil just right. Why should we care about getting the dose just right? We are clearly skilled at getting close to the right dose. Isn't "close" close enough?

During general anesthesia, this is probably close enough. During conscious sedation, close may cross the line between hypoventilation and apnea. But why not do the best job we can? We want our patients to be unconscious, immobile, and hemodynamically stable during anesthesia. We want them to awaken promptly, yet comfortably, after anesthesia. Even if close is close enough, why not adjust the dose for weight, age, gender, organ function, and type of surgery? Much research has been done to understand how patient factors such as age, gender, and weight relate to the pharmacokinetics and pharmacodynamics of thiopental,[2,3] fentanyl and alfentanil,[4] sufentanil,[5] propofol,[6] and remifentanil,[7] to give just a few examples.

At a minimum, we should at least adjust adult doses to weight. Many package inserts, including those of propofol and remifentanil, explicitly provide per-kilogram adult-dosing guidelines. Doesn't this tell us that the drugs should be given per kilogram of body weight? That is the message, but it may be wrong.

Egan *et al.*[1] administered remifentanil to obese patients and nonobese control patients. To estimate pharmacokinetic parameters for an extended period, the authors chose a remifentanil dose that was large, 10 μg/kg during 1 min, but that had been well tolerated in his previous studies with nonobese persons. This dose proved to be a big mistake in large persons. Two of the first three patients had profound bradycardia associated with hypotension, necessitating a change in protocol to reduce the dose for subsequent patients. Yet this was a setting in which we think opioid overdoses are well tolerated: the paralyzed, intubated, and ventilated patient.

Spontaneously breathing patients have little tolerance for opioid overdoses. Remifentanil is approved for use in conscious sedation. Dosing remifentanil according to the package insert recommendations of a 1 μg/kg bolus followed by a 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion may result in a profound overdose and injury in spontaneously breathing obese patients. So what options do we have?

We can scale anesthetic drugs to lean body mass instead of weight. Lean body mass can be calculated from weight, in kilograms, and height, in centimeters, as follows:[8]

LBM = 1.1 · weight − 128(weight/height)^2 for men, and

LBM = 1.07 · weight − 148(weight/height)^2 for women.

Scaling drugs to lean body mass instead of weight has been recommended for thiopental,[9] methohexital,[10] muscle relaxants,[11,12] and propofol.[13,14] However, the formula for lean body mass is complex, with implications for dosing that are not immediately obvious. Figure 1 shows lean body mass as a function of weight (x axis) and height (different lines) for men (upper graph) and women (lower graph). The equation has an odd property: For every height there is weight associated with a peak lean body mass, beyond which, increases in weight

◆ This Editorial View accompanies the following article: Egan TD, Talmage D, Huizinga B, Samir K, Jaarsma RL, Sperry RJ, Yee JB, Muir KT: Remifentanil pharmacokinetics in obese *versus* lean elective surgery patients. ANESTHESIOLOGY 1998; 89:562–73.

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Key words: Dosage; ideal body mass; lean body mass; pharmacokinetics; remifentanil; weight.

ugh.

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"TBW is not always right and might lead to overdose"… certainly dangerous in a spontaneous-breathing sedated patient.

"We need to provide the scientific foundation to get the dose just right so we can help prevent the complications that arise when close isn't close enough."

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Size descriptors

Size descriptors

- BMI
  - Definition: weight (kg) /height² (m²)
  - Classification:
    - IBW = 22-28
    - Obesity = 29-35
    - Morbid obesity >40 or >35 with comorbidity
    - Super obesity >55

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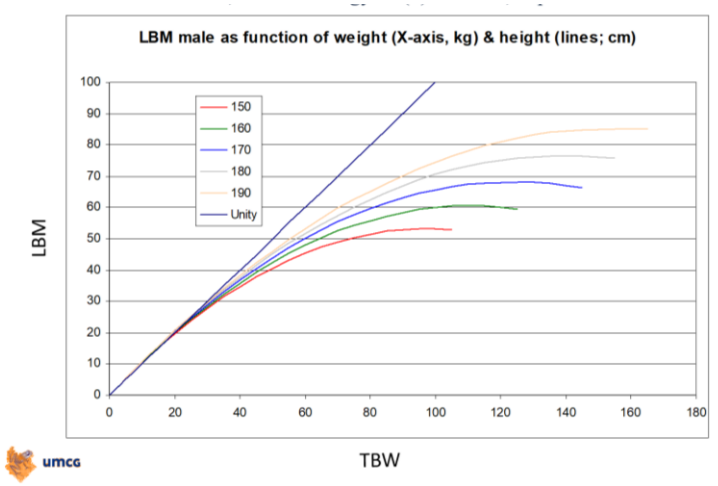
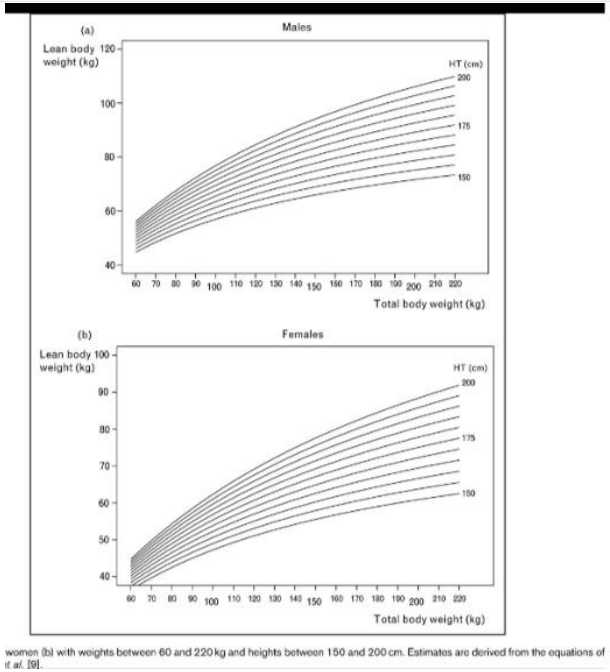
Size descriptors

- <u>LBM or LBW</u>
  - Definition *[James et al]*:
    - men: [1.10 * weight] - [128 * (weight/ height)²]
    - women: [1.07 * weight] - [148 * (weight/ height)²]
  - Definition *[Janmahasatian et al]*:
    - men: 9270 * weight/(6680 + 216 * BMI)
    - women: 9270 * weight/(8780 + 244 * BMI)





women (b) with weights between 60 and 220 kg and heights between 150 and 200 cm. Estimates are derived from the equations of
et al. [9].

Size descriptors

- IBW
  - Definition *[Abernethy et al]*:
    - men: 49.9 + 0.89 * [height (cm) - 152.4]
    - women: 45.4 + 0.89 * [height (cm) - 152.4]
  - Broca Index:
    - men: height (cm) - 100
    - women: height (cm) - 105

Size descriptors

- Fat Free Mass :

Al-Sallami fat free mass calculation :

$$FFM_{males}(kg) = \left(0.88 + \frac{1-0.88}{1+(AGE/13.4)^{-12.7}}\right) \cdot \left(\frac{9270 \cdot WGT}{6680 + 216 \cdot BMI}\right)$$

$$FFM_{females}(kg) = \left(1.11 + \frac{1-1.11}{1+(AGE/7.1)^{-1.1}}\right) \cdot \left(\frac{9270 \cdot WGT}{8780 + 244 \cdot BMI}\right)$$

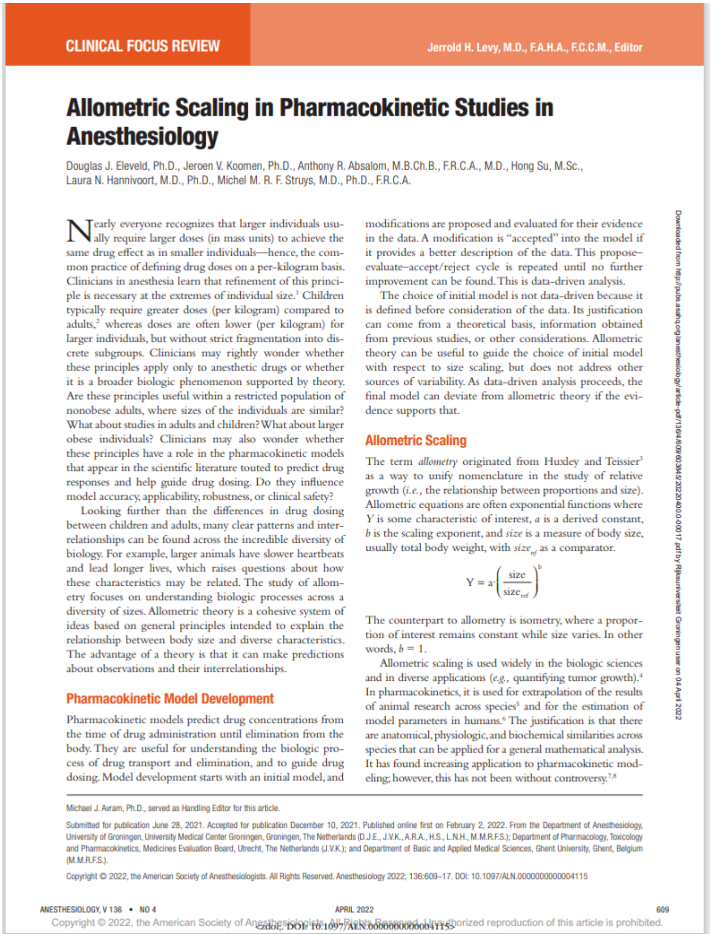
Dubois Equation for Body Surface Area calculation :

$$Surface = 0.20247 \cdot HGT^{0.725} \cdot WGT^{0.425}$$

Size descriptors : allometric scaling

For PK modeling usually:

- Volumes (l) scale linearly with size
- Clearances (l/min) scale to size to the power 0.75



Allometric Scaling in Pharmacokinetic Studies in Anesthesiology

Douglas J. Eleveld, Ph.D., Jeroen V. Koomen, Ph.D., Anthony R. Absalom, M.B.Ch.B., F.R.C.A., M.D., Hong Su, M.Sc., Laura N. Hannivoort, M.D., Ph.D., Michel M. R. F. Struys, M.D., Ph.D., F.R.C.A.

Nearly everyone recognizes that larger individuals usually require larger doses (in mass units) to achieve the same drug effect as in smaller individuals—hence, the common practice of defining drug doses on a per-kilogram basis. Clinicians in anesthesia learn that refinement of this principle is necessary at the extremes of individual size.[1] Children typically require greater doses (per kilogram) compared to adults,[2] whereas doses are often lower (per kilogram) for larger individuals, but without strict fragmentation into discrete subgroups. Clinicians may rightly wonder whether these principles apply only to anesthetic drugs or whether it is a broader biologic phenomenon supported by theory. Are these principles useful within a restricted population of nonobese adults, where sizes of the individuals are similar? What about studies in adults and children? What about larger obese individuals? Clinicians may also wonder whether these principles have a role in the pharmacokinetic models that appear in the scientific literature touted to predict drug responses and help guide drug dosing. Do they influence model accuracy, applicability, robustness, or clinical safety?

Looking further than the differences in drug dosing between children and adults, many clear patterns and interrelationships can be found across the incredible diversity of biology. For example, larger animals have slower heartbeats and lead longer lives, which raises questions about how these characteristics may be related. The study of allometry focuses on understanding biologic processes across a diversity of sizes. Allometric theory is a cohesive system of ideas based on general principles intended to explain the relationship between body size and diverse characteristics. The advantage of a theory is that it can make predictions about observations and their interrelationships.

Pharmacokinetic Model Development

Pharmacokinetic models predict drug concentrations from the time of drug administration until elimination from the body. They are useful for understanding the biologic process of drug transport and elimination, and to guide drug dosing. Model development starts with an initial model, and modifications are proposed and evaluated for their evidence in the data. A modification is "accepted" into the model if it provides a better description of the data. This propose–evaluate–accept/reject cycle is repeated until no further improvement can be found. This is data-driven analysis.

The choice of initial model is not data-driven because it is defined before consideration of the data. Its justification can come from a theoretical basis, information obtained from previous studies, or other considerations. Allometric theory can be useful to guide the choice of initial model with respect to size scaling, but does not address other sources of variability. As data-driven analysis proceeds, the final model can deviate from allometric theory if the evidence supports that.

Allometric Scaling

The term *allometry* originated from Huxley and Teissier[3] as a way to unify nomenclature in the study of relative growth (*i.e.*, the relationship between proportions and size). Allometric equations are often exponential functions where *Y* is some characteristic of interest, *a* is a derived constant, *b* is the scaling exponent, and *size* is a measure of body size, usually total body weight, with $size_{ref}$ as a comparator.

$$Y = a \cdot \left(\frac{size}{size_{ref}}\right)^{b}$$

The counterpart to allometry is isometry, where a proportion of interest remains constant while size varies. In other words, $b = 1$.

Allometric scaling is used widely in the biologic sciences and in diverse applications (*e.g.*, quantifying tumor growth).[4] In pharmacokinetics, it is used for extrapolation of the results of animal research across species[5] and for the estimation of model parameters in humans.[6] The justification is that there are anatomical, physiologic, and biochemical similarities across species that can be applied for a general mathematical analysis. It has found increasing application to pharmacokinetic modeling; however, this has not been without controversy.[7,8]

Michael J. Avram, Ph.D., served as Handling Editor for this article.

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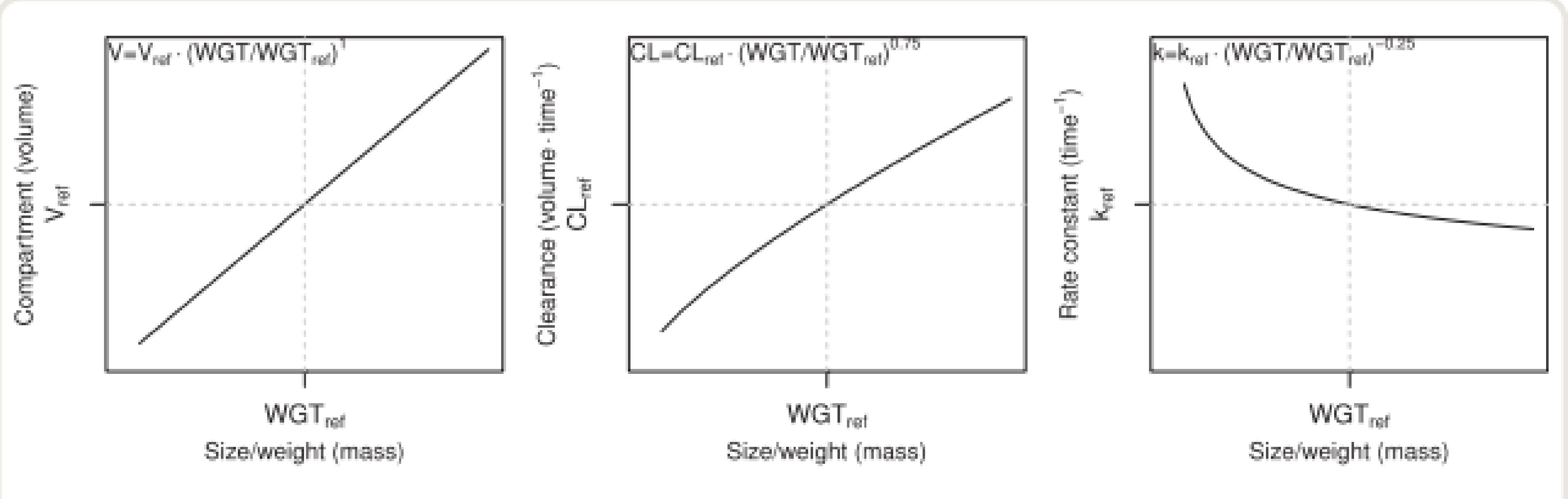
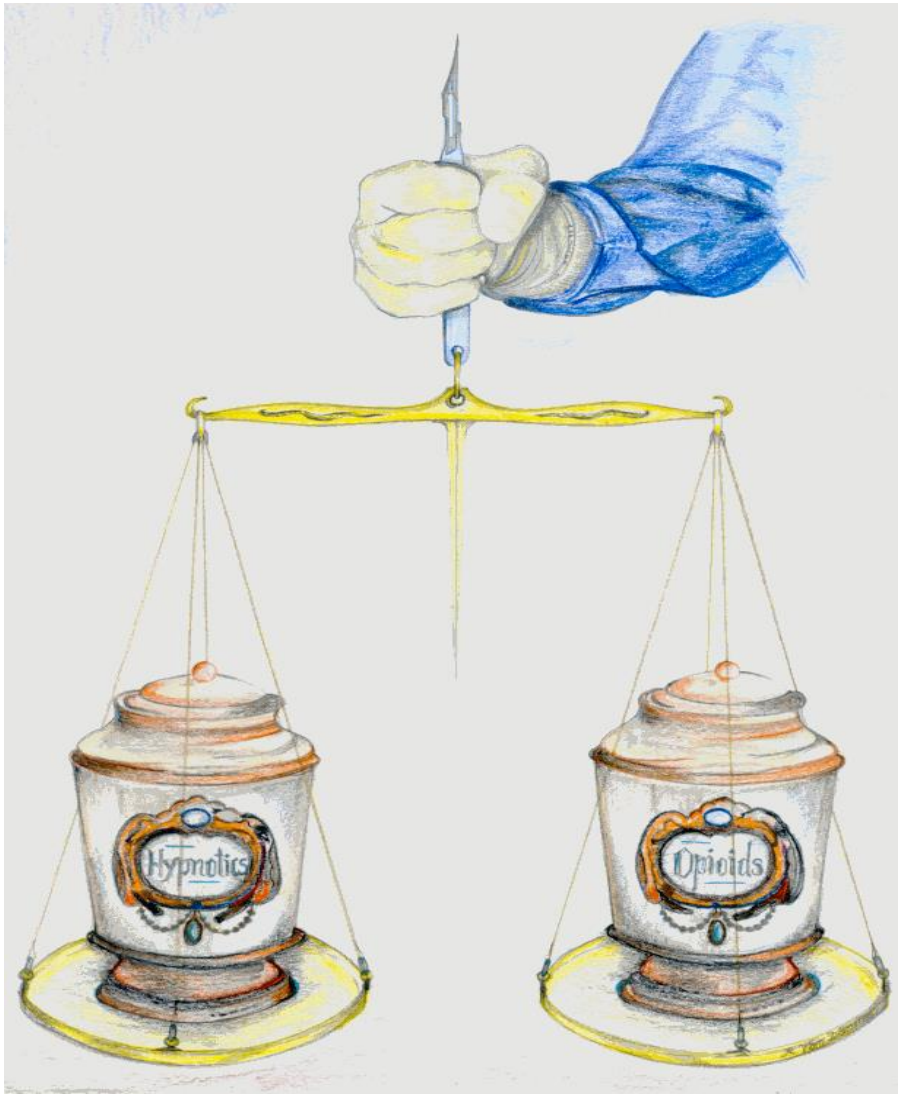


Fig. 1. Example allometric scaling equations. CL, drug clearance; k, rate constant; V, compartmental volume; WGT, body weight. Subscript *ref* indicates a reference value that functions as a comparator.

Hypnotics and opioids and the obese patient



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Volatile anesthetics and the obese patient

- Advantages compared with IV anesthetics
  - MAC (analgesic effect) and MAC-awake (absence of memory) correlate with the end-tidal concentrations of the anesthetics
  - End-tidal concentration ~ age and temperature, but weight correction is not necessary
  - Permanent monitoring of end-tidal concentration possible
  - Stable ratio between arterial partial pressure and end-tidal partial pressure
  - Optimization in inhaled drug administration by using “inhalation bolus technique” and closed-circuit anesthesia systems

Volatile anesthetics and the obese patient

British Journal of Anaesthesia **91** (**5**): 638–50 (2003)
DOI: 10.1093/bja/aeg236

BJA

Optimization of desflurane administration in morbidly obese patients: a comparison with sevoflurane using an 'inhalation bolus' technique

L. E. C. De Baerdemaeker[1]*, M. M. R. F. Struys[1], S. Jacobs[1], N. M. M. Den Blauwen[1], G. R. P. J. Bossuyt[1], P. Pattyn[2] and E. P. Mortier[1]

Obesity Surgery, **16**, 728-733

Postoperative Results after Desflurane or Sevoflurane Combined with Remifentanil in Morbidly Obese Patients

Luc E.C. De Baerdemaeker, MD, DEAA[1]; Stefan Jacobs, MD[1]; Nadia M.M. Den Blauwen, MD[1]; Piet Pattyn, MD, PhD[2]; Luc L.G. Herregods, MD, PhD[3]; Eric P. Mortier, MD, DSc[4]; Michel M.R.F. Struys, MD, PhD[5]

-BIS guided sevo or des with the use of "inhalation bolus technique"

-Remifentanil guided by hemodynamic responses.

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Volatile anesthetics and the obese patient

Intra-operative results

- Hypertension (% of time) : sevoflurane = desflurane
- Hypotension (% of time)
  - Overall : sevoflurane > desflurane
  - Bolusperiod : sevoflurane = desflurane
- Hypnotic stability (BIS)
  - Overall : sevoflurane > desflurane
  - Bolusperiod : desflurane more overshoot than sevoflurane
- Immediate recovery : desflurane faster than sevoflurane (2 min !)
- Recovery :
  - sedation score : sevo=des
  - Aldrete score = sevo = des
  - Oxygen saturation : sevo = des
  - VAS pain scores : sevo = des
  - PONV : at 30 and 60 min : sevo = des
    at 120 min : sevo < des

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Intravenous drugs and the obese patient

- <u>Midazolam</u>
  - Linear increased Vd and elimination half-life, but unchanged total clearance values *[Greenblatt et al]*
  - Continuous infusion ~ IBW *[Reves et al]*

Intravenous drugs and the obese patient

- <u>Thiopental</u>
  - Increased Vd and elimination half-life, but unchanged total clearance values
    [Buckley et al]
  - Adequate dosage: 7.5 mg/kg IBW *[Buckley et al]*

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Intravenous drugs and the obese patient

- <u>Analgesics & opioids</u>
  - Alfentanil
    - Decreased clearance and prolonged t ½ ß, but unchanged max. plasma concentration and Vd
      -> LBM

      [Bentley et al]
    - No effect on clearance, but increased central compartment volume -> TBW

      [Maître et al]

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Intravenous drugs and the obese patient

- Analgesics & opioids
  - Fentanyl
    - No difference in beta-elimination half-life (t ½ ß)
      [Bentley et al]

      Shibutani et al :

      The Shibutani correction for the Cp : Corrected Cp = Cp Shafer * (1 + (196.4 * e -0.025kg – 53.66)/100)
  - Fentanyl, alfentanil and remifentanil
    - Dosage ~ corrected BW
    - Decreased arterial pressures after induction, but in all groups within acceptable limits
      [Salihoglu et al]

Intravenous drugs and the obese patient

- Analgesics & opioids
  - Sufentanil
    - Prolonged t ½ ß and increased Vd
    - Loading dose ~ TBW
      [Schwartz et al]
    - Maintenance dose must be prudently reduced
    - Pharmacokinetic set of *Gepts et al* -> accurately prediction of sufentanil plasma concentrations in morbidly obese patients, but BMI > 40 -> overestimation of sufentanil plasma concentration *[Slepchenko et al]*
    - TCI using *Gepts* model -> no weight correction necessary but no obese patients in study population!

Sufentanil : Gepts model (Gepts et al. Anesthesiology 1995;83:1194-1204)

V1 = 14.3L

k10 = 0.0645/min

k12 = 0.1086/min

k13 = 0.0229/min

k21 = 0.0245/min

k31 = 0.0013/min

k41determined by tPeak = 5.6min (Shafer et al.: Anesthesiology 1991;74:53-63)

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Intravenous drugs and the obese patient

- <u>Analgesics & opioids</u>
  - remifentanil
    - Maintenance dose ~ age and LBM
      [Minto et al]
    - Maintenance dose ~ LBM
      [Egan et al]

Anesthesiology
1998; 89:562–73

Remifentanil Pharmacokinetics in Obese versus Lean Patients

Talmage D. Egan, M.D., Bernou Huizinga, M.D.,† Samir K. Gupta, Ph.D.,‡ Rudy L. Jaarsma, M.D.,†, Richard J. Sperry, M.D., Ph.D.,§ James B. Yee, M.D., Ph.D.,‖ Keith T. Muir, Ph.D.¶*

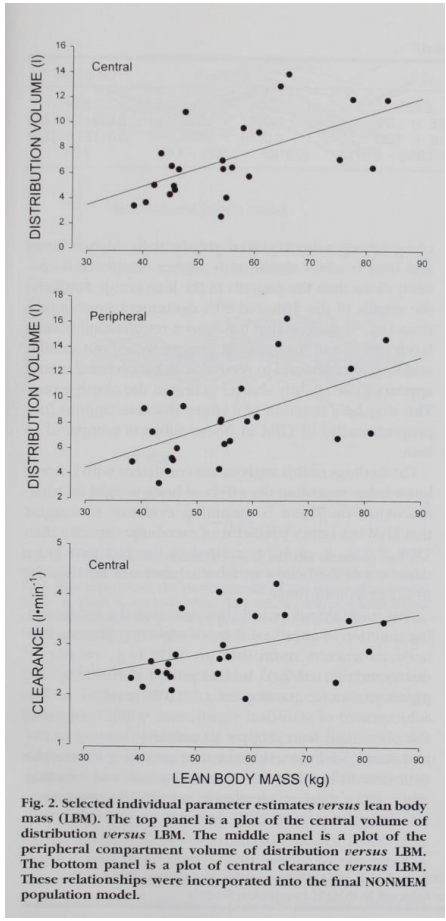

Fig. 2. Selected individual parameter estimates *versus* lean body mass (LBM). The top panel is a plot of the central volume of distribution *versus* LBM. The middle panel is a plot of the peripheral compartment volume of distribution *versus* LBM. The bottom panel is a plot of central clearance *versus* LBM. These relationships were incorporated into the final NONMEM population model.

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Intravenous drugs and the obese patient

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Table 1. Patient Demographic Features

Patient Number	Dose (μg)	TBW (kg)	LBM (kg)	Height (cm)	Gender	Age (yr)	ASA
Obese group							
1	1,236	124	54	170	F	32	2
2	840	84	48	157	F	36	2
3	968	97	45	154	F	36	2
5	900	118	55	170	F	49	2
6	1,020	136	81	180	M	54	2
7	780	105	56	170	F	33	1
8	800	107	58	173	F	36	3
9	720	95	54	168	F	30	2
12	920	123	54	170	F	29	2
14	900	120	77	178	M	32	1
16	1,050	140	84	183	M	44	2
17	820	110	75	178	M	47	1
Average	913	113	62	171		38	2
SD	141	17	14	9		8	1
Lean group							
4	450	61	46	168	F	32	2
10	450	60	46	173	F	45	1
11	460	60	40	150	F	36	1
13	470	63	46	165	F	35	1
15	600	82	66	183	M	33	2
18	630	78	64	185	M	44	2
19	550	70	59	180	M	53	2
20	415	55	42	163	F	36	2
21	340	49	38	159	F	34	2
22	550	77	61	173	M	43	2
23	425	57	43	165	F	30	2
24	435	57	45	173	F	38	2
Average	481	64	50	170		38	2
SD	84	10	10	10		7	0

TBW = total body weight; LBM = lean body mass.

Intravenous drugs and the obese patient

- <u>Propofol</u>
  - Induction dose ~ IBW
    [Gepts et al, Kirby et al, Redfern et al]
  - Plasma propofol concentration at the end of surgery after a fixed rate infusion ~ TBW

    [Hirota et al]
  - No accumulation in morbidly obese patients if dosage for maintenance of anesthesia ~ corrected BW *[Servin et al]*
    - corrected body weight = IBW + (0.4 * excess weight)

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Anesthesiology
78:657–665, 1993

J. B. Lippincott Company, Philadelphia

Propofol Infusion for Maintenance of Anesthesia in Morbidly Obese Patients Receiving Nitrous Oxide

A Clinical and Pharmacokinetic Study

Frédérique Servin, M.D., Robert Farinotti, Ph.D.,† Jean-Pierre Haberer, M.D.,‡ Jean-Marie Desmonts, M.D.§*

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Frédérique Servin, M.D., Robert Farinotti, Ph.D.,† Jean-Pierre Haberer, M.D.,‡ Jean-Marie Desmonts, M.D.§*

Anesthesia was induced and maintained using a stepwise infusion regimen of propofol 21 $mg \cdot kg^{-1} \cdot h^{-1}$ for 5 min, 12 $mg \cdot kg^{-1} \cdot h^{-1}$ for 10 min, and 6 $mg \cdot kg^{-1} \cdot h^{-1}$ for the remainder of the procedure. The weight used for the calculation of the infusion rate was established using an empirical formula (corrected weight = ideal weight + [0.4 × excess weight]) because, in these patients, the dosages calculated on an actual weight basis were so high that the absence of deleterious hemodynamic effects could not be assured.

Table 1. Clinical Characteristics of the Patients

Patients	Surgical Procedure	Age (yr)	Sex	Weight (kg)	Ideal Body Weight (kg)	Plasma Albumin Concentration (g/L)	Plasma Creatinine Concentration (μM)	Hemoglobin Concentration (g/100 ml)
Obese								
1	Hip replacement	55	F	108	55.5	40	81	15
2	Cholecystectomy	37	F	160	62.0	37	90	14
3	Cholecystectomy	30	F	97	52.5	38	93	13.5
4	Cholecystectomy	66	M	130	72.5	38	100	16.2
5	Wound dehiscence	66	F	105	55.0	37	91	13.4
6	Wound dehiscence	53	M	107	62.7	38	119	13.7
7	Lipoma resection	25	F	100	55.0	47	57	14
8	Wound dehiscence	45	F	117	53.5	44	71	14.3
Mean ± SD		47.1 ± 15.6	6F/2M	115.5 ± 20.8	58.6 ± 6.8	39.9 ± 3.7	87.8 ± 18.7	14.3 ± 0.93
Control*								
1	Femoral pseudarthrosis repair	24	M	60	66.5	40	75	11.9
2	Femoral pseudarthrosis repair	34	M	55	63.5	42	74	14.1
3	Pulmonary resection	42	M	54	65.0	33	93	16.3
4	Pleurectomy	54	F	55	56.5	40	65	12.7
5	Colectomy	55	M	70	66.5	46	107	16.6
6	Hysterectomy	52	F	85	61.0	38	57	14.9
7	Wound dehiscence	56	M	70	65.0	36	48	13.8
8	Selective vagotomy	33	M	61	66.5	31	81	14.4
9	Cholecystectomy	39	M	96	75.5	38	85	15.2
10	Ileal resection	30	F	50	55.0	36	55	12
Mean ± SD		41.9 ± 11.7	3F/7M	65.6 ± 14.9†	64.1 ± 5.8	38.0 ± 4.3	74.0 ± 18.3	14.2 ± 1.6

* Patients included in the concurrent study.[5]

† $P \leq 0.001$.

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Target-controlled infusion and the obese patient

- <u>Propofol : In Europe we have TCI ? Can we use it in obese patients ?</u>

  - Pharmacokinetical models predict a set concentration in one of the pharmacokinetical compartments

  - These models have been implemented into TCI devices to rapid achievement and maintenance of the desired predicted concentration in a specific compartment

    …. We learned a lot on PKPD in obese patients ! (propofol as an example)

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target-controlled infusion (TCI)

- A computer-assisted drug infusion

SYRINGE PUMP

- Aim is to achieve user-defined ‘target’ concentration at the plasma or “effect-site”

PKPD MODEL

- On start-up user must
  - Select the drug and elect pharmacokinetic-dynamic model
  - Input patient characteristics (weight, height, age, gender, ...)
- System implements required infusion rates to reach and maintain target concentration

TCI ALGORITHM

- User can increase or decrease target concentration

Propofol US Smpc (FDA)

INDICATION	DOSAGE AND ADMINISTRATION
Induction of General Anesthesia:	**Healthy Adults Less Than 55 Years of Age:** 40 mg every 10 seconds until induction onset (2 mg/kg to 2.5 mg/kg). **Elderly, Debilitated, or ASA-PS III or IV Patients:** 20 mg every 10 seconds until induction onset (1 mg/kg to 1.5 mg/kg). **Cardiac Anesthesia:** 20 mg every 10 seconds until induction onset (0.5 mg/kg to 1.5 mg/kg). **Neurosurgical Patients:** 20 mg every 10 seconds until induction onset (1 mg/kg to 2 mg/kg). **Pediatric Patients - healthy, from 3 years to 16 years of age:** 2.5 mg/kg to 3.5 mg/kg administered over 20 seconds to 30 seconds. (see **PRECAUTIONS, *Pediatric Use*** and **CLINICAL PHARMACOLOGY, Pediatrics**)
Maintenance of General Anesthesia:	**Infusion** **Healthy Adults Less Than 55 Years of Age:** 100 mcg/kg/min to 200 mcg/kg/min (6 mg/kg/h to 12 mg/kg/h). **Elderly, Debilitated, ASA-PS III or IV Patients:** 50 mcg/kg/min to 100 mcg/kg/min (3 mg/kg/h to 6 mg/kg/h). **Cardiac Anesthesia:** Most patients require: Primary DIPRIVAN with Secondary Opioid – 100 mcg/kg/min to 150 mcg/kg/min. Low-Dose DIPRIVAN with Primary Opioid – 50mcg/kg/min to 100 mcg/kg/min. (see **DOSAGE AND ADMINISTRATION**, Table 4) **Neurosurgical Patients:** 100 mcg/kg/min to 200 mcg/kg/min (6 mg/kg/h to 12 mg/kg/h). **Pediatric Patients - healthy, from 2 months of age to 16 years of age:** 125 mcg/kg/min to 300 mcg/kg/min (7.5 mg/kg/h to 18 mg/kg/h). Following the first half hour of maintenance, if clinical signs of light anesthesia are not present, the infusion rate should be decreased. (see **PRECAUTIONS, *Pediatric Use*** and **CLINICAL PHARMACOLOGY, Pediatrics**)
Maintenance of General Anesthesia:	**Intermittent Bolus** **Healthy Adults Less Than 55 Years of Age:** Increments of 20 mg to 50 mg as needed.
Initiation of MAC Sedation:	**Healthy Adults Less Than 55 Years of Age:** Slow infusion or slow injection techniques are recommended to avoid apnea or hypotension. Most patients require an infusion of 100 mcg/kg/min to 150 mcg/kg/min (6 mg/kg/h to 9 mg/kg/h) for 3 minutes to 5 minutes or a slow i to 5 minutes followed immediately by a maintenance infusion. **Elderly, Debilitated, Neurosurgical, or ASA-PS III or IV Patients:** Most patients require dosages similar to healthy adults. Rapid boluses are to be avoided (see **WARNINGS**).

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Reference ID: 4089428

Maintenance of MAC Sedation:	**Healthy Adults Less Than 55 Years of Age:** A variable rate infusion technique is preferable over an intermittent bolus technique. Most patients require an infusion of 25 mcg/kg/min to 75 mcg/kg/min (1.5 mg/kg/h to 4.5 mg/kg/h) or incremental bolus doses of 10 m **In Elderly, Debilitated, Neurosurgical, or ASA-PS III or IV Patients:** Most patients require 80% of the usual adult dose. A rapid (single or repeated) bolus dose should not be used (see **WARNINGS**).
Initiation and Maintenance of ICU Sedation in Intubated, Mechanically Ventilated	
	Adult Patients - Because of the residual effects of previous anesthetic or sedative agents, in most patients the initial infusion should be 5 mcg/kg/min (0.3 mg/kg/h) for at least 5 minutes. Subsequent increments of 5mcg/kg/min to mcg/kg/min (0.3mg/kg/k to 0.6 mg/kg/h) over 5 minutes to 10 minutes may be u desired clinical effect is achieved. Maintenance rates of 5 mcg/kg/min to 50 mcg/kg/min (0.3 mg/kg/h to 3 mg/kg/h) or higher may be required. Adminis exceed 4 mg/kg/hour unless the benefits outweigh the risks (see **WARNINGS**). **Evaluation of clinical effect and assessment of CNS function should be carried out daily throughout maintenance to determine the minimum dose of DIPRIVAN required for sedation.** **The tubing and any unused DIPRIVAN drug product should be discarded after 12 hours because DIPRIVAN contains no preservatives and is capable of supporting growth of microorganisms (see WARNINGS and DOSAGE AND ADMINISTRATION).**

Administration with Lidocaine

If lidocaine is to be administered to minimize pain on injection of DIPRIVAN, it is recommended that it be administered prior to DIPRIVAN administration or that it be added to DIPRIVAN immediately before administration and in quantities not exceeding 20 mg lidocaine/200 mg DIPRIVAN.

Compatibility and Stability

DIPRIVAN should not be mixed with other therapeutic agents prior to administration.

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Reference ID: 4089428

Propofol TCI models

Propofol : Marsh model (Marsh et al. BJA 1991;67:41-48)

Vc = 0.228 * weight (L*kg)

k10 = 0.119/min

k12 = 0.112/min

k13 = 0.0419/min

k21 = 0.055/min

k31 = 0.0033/min

k41 = 0.26/min (extracted from not related data by Schüttler et al).

Propofol : Schnider model

V1 = 4.27 L

V2 = 18.9 L-0.391*(age-53)

V3 = 238 L

Cl1 = 1.89 + 0.0456*(weight-77) - 0.0681*(lbm-59) + 0.0264*(height-177)

Cl2 = 1.29-0.024*(age-53)

Cl3 = 0.836

k41 determined by tPeak=1.6min or ke0 = 0.456/min

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inf	Age (yr)	Weight (kg)	Height (cm)	Gender
25	34	46.3	158	F
25	31	123	196	M
25	62	79.4	170	M
25	65	79.4	182	M
25	77	74.8	183	M
25	70	62.6	175	M
50	30	64.4	170	M
50	27	74.8	188	M
50	46	93.4	182	M
50	41	90.7	178	F
50	72	88.4	183	M
50	75	64.4	168	F
100	29	95.2	188	M
100	26	88.4	178	M
100	55	44.7	168	F
100	51	79.8	175	F
100	81	74.8	178	M
100	72	70.3	170	F
200	31	91.2	180	F
200	25	63.5	158	F
200	62	86.2	180	M
200	38	88.4	173	F
200	74	70.3	160	F
200	75	44.4	155	F

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Propofol TCI models

British Journal of Anaesthesia **103** (**1**): 26–37 (2009)
doi:10.1093/bja/aep143 Advance Access publication June 10, 2009

BJA

Pharmacokinetic models for propofol—defining and illuminating the devil in the detail

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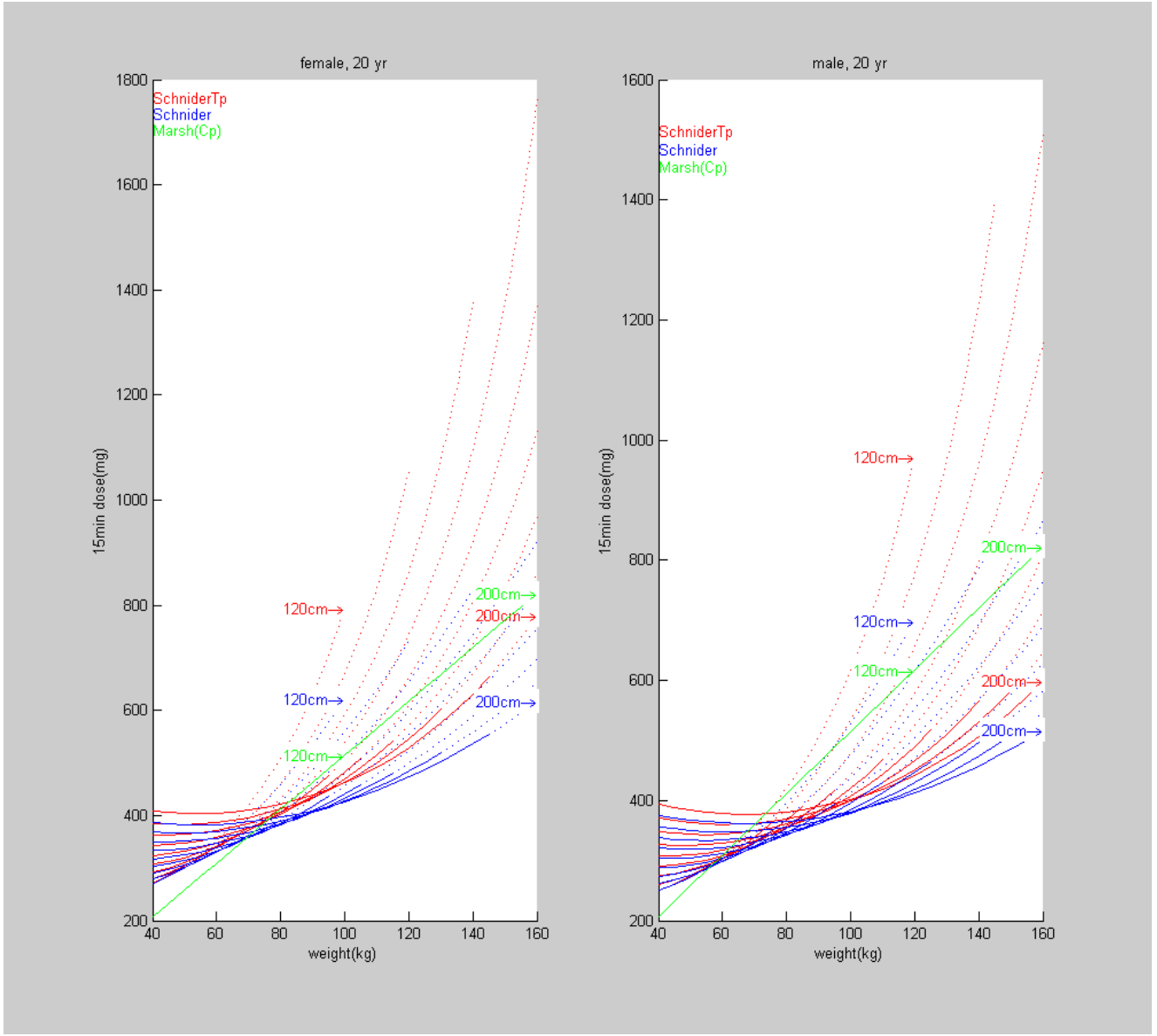

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General purpose propofol PK-PD model

BJA

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doi: 10.1016/j.bja.2018.01.018
Advance Access Publication Date: 12 March 2018
Clinical Practice

Pharmacokinetic–pharmacodynamic model for propofol for broad application in anaesthesia and sedation

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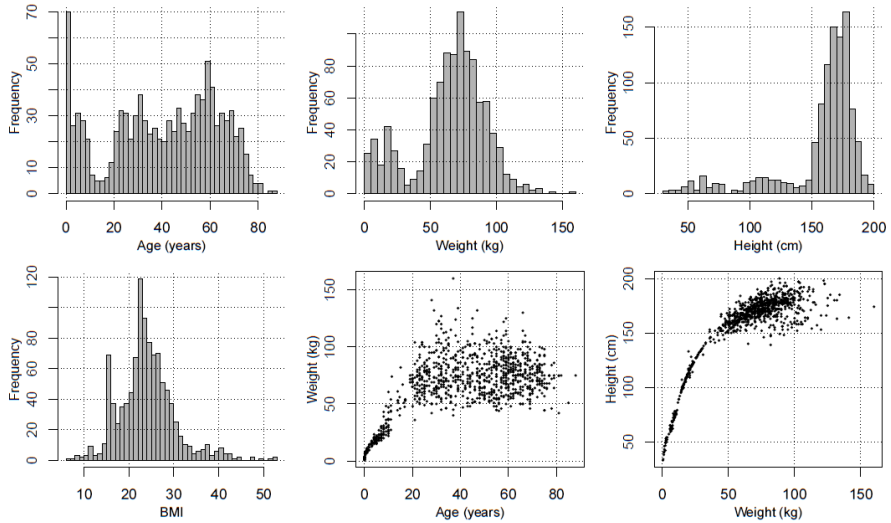
[1]Department of Anesthesiology, University Medical Center Groningen, Groningen, The Netherlands, [2]Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium and [3]Department of Anesthesia and Peri-operative Medicine, Ghent University, Ghent, Belgium



PK :11530 arterial, 3903 venous samples from 1033 individuals over an age range of 27 weeks PMA to 88 years, and a weight range was 0.68 kg to 160 kg.

PD : 28639 BIS observations from 122 individuals over an age range of 3 to 74 years and a weight range of 15 to 141 kg.

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General purpose propofol PK-PD model

Table 1 Details of the component datasets.

Dataset	N	Sampling	Age (years)	Weight (kg)	Additional drugs	Publication	Source
Bailey et al.	30	Arterial	44–79	50–122	Alfentanil	Bailey JM, Mora CT, Shafer SL. Pharmacokinetics of propofol in adult patients undergoing coronary revascularization. Anesthesiology: The Journal of the American Society of Anesthesiologists. 1996 Jun 1;84(6):1288–97.	Open-TCI
Billard 1998 Propofol	51	Venous	29–69	40–89	Alfentanil	SFAR abstract 1998, poster R279	Open-TCI
Coetzee Validation	30	Arterial	21–58	42–83	Sufentanil	Coetzee JF, Glen JB, Boshoff L. Pharmacokinetic model selection for target controlled infusions of propofol assessment of three parameter sets. Anesthesiology: The Journal of the American Society of Anesthesiologists. 1995 Jun 1;82(6):1328–45.	Open-TCI
Doufas Induction Speed	18	Arterial	20–43	51–83		Doufas AG, Bakhshandeh M, Bjorksten AR, Shafer SL, Sessler DI. Induction speed is not a determinant of propofol pharmacodynamics. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2004 Nov 1;101(5):1112–21.	Open-TCI
Doufas DeRamp	10	Arterial	26–44	45–83		Doufas AG, Morioka N, Mahgoub AN, Bjorksten AR, Shafer SL, Sessler DI. Automated responsiveness monitor to titrate propofol sedation. Anesthesia & Analgesia. 2009 Sep 1;109(3):778–86.	Open-TCI
Doufas Fixed Reduction	10	Arterial	21–44	57–82		See Doufas DeRamp	Open-TCI
Doufas Redhead	29	Arterial	19–39	50–99		Doufas AG, Orhan-Sungur M, Komatsu R, Lauber R, Akca O, Shafer SL, Sessler DI. Bispectral index dynamics during propofol hypnosis is similar in red-haired and dark-haired subjects. Anesthesia & Analgesia. 2013 Feb 1;116(2):319–26.	Open-TCI
Dyck et al.	59	Arterial	23–82	57–114		See Coetzee Validation	Open-TCI
Gepts et al.	16	Arterial	25–65	48–84	Locoregional	Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate intravenous infusions in humans. Anesthesia and analgesia. 1987 Dec;66(12):1256–63.	Open-TCI
Kataria et al.	53	Venous	3–11	15–60	Fentanyl	Kataria BK, Ved SA, Nicodemus HF, Hoy GR, Lea D, Dubois MY, Mandema JW, Shafer SL. The pharmacokinetics of propofol in children using three different data analysis approaches. Anesthesiology. 1994 Jan;80(1):104–22.	Open-TCI
Schnider et al.	24	Arterial	25–81	44–123		Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology: The Journal of the American Society of Anesthesiologists. 1998 May 1;88(5):1170–82.	Open-TCI
Servin et al, (obese)	8	Arterial	25–66	97–160	N20fentanyl	Servin F, Farinotti R, Haberer JP, Desmonts JM. Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide. A clinical and pharmacokinetic study. Anesthesiology. 1993 Apr;78(4):657–65.	Open-TCI
Servin et al, (alcoholic)	30	Venous	19–72	51–97	Alfentanil	Servin FS, Bougeois B, Gomeni R, Mentré F, Farinotti R, Desmonts JM. Pharmacokinetics of propofol administered by target-controlled infusion to alcoholic patients. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2003 Sep 1;99(3):576–85.	Open-TCI
Struys et al.	10	Arterial	22–48	51–86		Struys MM, Coppens MJ, De Neve N, Mortier EP, Doufas AG, Van Bocxlaer JF, Shafer SL. Influence of administration rate on propofol plasma–effect site equilibration. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2007 Sep 1;107(3):386–96.	Open-TCI
Coppens et al.	28	Venous, BIS	3–11	15–54		Coppens MJ, Eleveld DJ, Proost JH, Marks LA, Van Bocxlaer JF, Vereecke H, Absalom AR, Struys MM. An evaluation of using population pharmacokinetic models to estimate pharmacodynamic parameters for propofol and bispectral index in children. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2011 Jul 1;115(1):83–93.	(MMRF Struys)
Marsh et al.	37	Venous	2–17	12–54	Regional	Marsh BM, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. BJA: British Journal of Anaesthesia. 1991 Jul 1;67(1):41–8.	(M White)
Cortinez et al. (children)	41	Arterial	0–2	5–11	Sevoflurane	Sepulveda P, Cortinez LI, Saez C, Penna A, Solari S, Guerra I, Absalom AR. Performance evaluation of paediatric propofol pharmacokinetic models in healthy young children. British journal of anaesthesia. 2011 Oct 1;107(4):593–600.	(I Cortinez)
Cortinez et al. (obese)	19	Arterial	28–56	82–134	Remifentanil	Cortinez LI, Anderson BJ, Penna A, Olivares L, Munoz HR, Holford NH, Struys MM, Sepulveda P. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. British journal of anaesthesia. 2010 Oct 1;105(4):448–56.	(I Cortinez)
Servin et al. (cirrhosis)	9	Arterial	24–56	50–96	Opioids	Servin F, Cockshott ID, Farinotti R, Haberer JP, Winckler C, Desmonts JM. Pharmacokinetics of propofol infusions in patients with cirrhosis. British Journal of Anaesthesia. 1990 Aug 1;65(2):177–83.	(I Glen)
Swinhoe et al.	41	Arterial	21–79	36–104	Alfentanil	Swinhoe CF, Peacock JE, Glen JB, Reilly CS. Evaluation of the predictive performance of a 'Diprifusor'TCI system. Anaesthesia. 1998 Apr 1;53(s1):61–7.	(I Glen)
White et al.	107	Venous	17–88	42–100	Alfentanil	White M, Kenny GN, Schraag S. Use of target controlled infusion to derive age and gender covariates for propofol clearance. Clinical pharmacokinetics. 2008 Feb 1;47(2):119–27.	(M White)
Sahinovic et al.	40	Arterial, BIS	23–74	51–114		Sahinovic MM, Beese U, Heeremans EH, Kalmar A, van Amsterdam K, Steenbakkers RJ, Kuiper H, Spanjersberg R, Groen RJ, Struys MM, Absalom AR. Bispectral index values and propofol concentrations at loss and return of consciousness in patients with frontal brain tumours and control patients. British journal of anaesthesia. 2014 Jan 1;112(1):110–7.	(M.Sahinovic)
Colin et al.	20	Arterial, BIS	20–50	50–106		Colin P, Eleveld DJ, van den Berg JP, Vereecke HE, Struys MM, Schelling G, Apfel CC, Hornuss C. Propofol breath monitoring as a potential tool to improve the prediction of intraoperative plasma concentrations. Clinical pharmacokinetics. 2016 Jul 1;55(7):849–59.	(C. Hornuss)
Index of Consciousness	15	Arterial, BIS	23–66	50–95		ISAP abstract 17 at https://www.isaponline.org/events/past-annual-meetings/2013-annual-meeting/2013-annual-meeting-abstracts	(MMRF Struys)
Cortinez et al. (obese)	20	Arterial, BIS	21–53	77–141	Remifentanil	Cortínez LI, De la Fuente N, Eleveld DJ, Oliveros A, Crovari F, Sepulveda P, Ibacache M, Solari S. Performance of propofol target-controlled infusion models in the obese: pharmacokinetic and pharmacodynamic analysis. Anesthesia & Analgesia. 2014 Aug 1;119(2):302–10.	(I Cortinez)
Allegaert et al.	25	Arterial	0–0.07	0.68–4	Opioids	Allegaert K, Peeters MY, Verbesselt R, Tibboel D, Naulaers G, De Hoon JN, Knibbe CA. Inter-individual variability in propofol pharmacokinetics in preterm and term neonates. British journal of anaesthesia. 2007 Dec 1;99(6):864–70.	(K Allegaert)
Blussé van Oud-Alblas	14	Arterial	10–20	37–82	Remifentanil		(H.J. Blussé van Oud-Alblas)
Przbylowski (cancer)	23	Arterial	51–75	44–125	Some remifentanil	Przybyłowski K, Tyczka J, Szczesny D, Bienert A, Wiczling P, Kut K, Plenzler E, Kaliszan R, Grześkowiak E. Pharmacokinetics and pharmacodynamics of propofol in cancer patients undergoing major lung surgery. Journal of pharmacokinetics and pharmacodynamics. 2015 Apr 1;42(2):111–22.	(P Wiczling)
Kuizenga and colleagues (neural inertia)	72	Arterial	20–70	48–104	Some opoids	Kuizenga MH, Colin PJ, Reyntjens KM, Touw DJ, Nalbat H, Knotnerus FH, Vereecke HE, Struys MM. Test of neural inertia in humans during general anaesthesia. British Journal of Anaesthesia. 2017 Dec 13.	(MMRF Struys)
van den Berg and colleagues (adaptive TCI)	120	Arterial	44–75	46–114	Opoids	van den Berg JP, Eleveld DJ, De Smet T, van den Heerik AV, van Amsterdam K, Lichtenbelt BJ, Scheeren TW, Absalom AR, Struys MM. Influence of Bayesian optimization on the performance of propofol target-controlled infusion. British Journal of Anaesthesia. 2017 Nov 1;119(5):918–27.	(MMRF Struys)

Table 1 Continued

Author name in brackets indicates personal communication.
Source: Open-TCI=http://www.opentci.org/ (downloaded on 11/13/2013).

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General purpose propofol PK-PD model

$$f_{aging}(x) = exp(x \cdot (AGE - AGE_{ref}))$$

$$f_{sigmoid}(x, E50, \lambda) = x^{\lambda} / (x^{\lambda} + E50^{\lambda})$$

$$f_{central}(x) = f_{sigmoid}(x, \Theta_{12}, 1)$$

$$f_{CLmaturation} = f_{sigmoid}(PMA, \Theta_8, \Theta_9)$$

$$f_{Q3maturation} = f_{sigmoid}(AGE + 40\,weeks, \Theta_{14}, 1)$$

$$f_{opiates}(x) = \begin{cases} 1, & absence\,of\ opiates \\ \exp(x \cdot AGE), & precence\,of\ opiates \end{cases}$$

$$V1_{arterial}(l) = \Theta_1 \cdot \frac{f_{central}(WGT)}{f_{central}(WGT_{ref})} \cdot exp(\eta 1)$$

$$V1_{venous}(l) = V1_{arterial} \cdot (1 + \Theta_{17} \cdot (1 - f_{central}(WGT)))$$

$$V2(l) = \Theta_2 \cdot \frac{WGT}{WGT_{ref}} \cdot f_{aging}(\Theta_{10}) \cdot exp(\eta 2)$$

$$V3(l) = \Theta_3 \cdot \frac{f_{Al-Sallami}}{f_{Al-Sallami,ref}} \cdot f_{opiates}(\Theta_{13}) \cdot exp(\eta 3)$$

$$CL(l \cdot \min^{-1}) = \begin{cases} \Theta_4, & male \\ \Theta_{15}, & female \end{cases} \cdot \left(\frac{WGT}{WGT_{ref}}\right)^{0.75} \cdot \frac{f_{CLmaturation}}{f_{CLmaturation,ref}} \cdot f_{opiates}(\Theta_{11}) \cdot exp(\eta 4)$$

$$Q2_{arterial}(l \cdot \min^{-1}) = \Theta_5 \cdot (V2/V2_{ref})^{0.75} \cdot (1 + \Theta_{16} \cdot (1 - f_{Q3maturation})) \cdot exp(\eta 5)$$

$$Q2_{venous}(l \cdot \min^{-1}) = Q2_{arterial} \cdot \Theta_{18}$$

$$Q3(l \cdot \min^{-1}) = \Theta_6 \cdot (V3/V3_{ref})^{0.75} \cdot \frac{f_{Q3maturation}}{f_{Q3maturation,ref}} \cdot exp(\eta 6)$$

$$\ln(C_{observed}) = \ln(C_{predicted}) + \Theta_7 \cdot \varepsilon \cdot exp(\eta 7)$$

$$Ce50(mg \cdot l^{-1}) = \Theta_1 \cdot f_{aging}(\Theta_7) \cdot \exp(\eta 1)$$

$$ke0(\min^{-1}) = \begin{cases} \Theta_2, & arterial\,PK \\ \Theta_8, & venous\,PK \end{cases} \cdot \left(\frac{WGT}{70}\right)^{-0.25} \cdot \exp(\eta 2)$$

$$BIS_{baseline} = \Theta_3$$

$$\gamma = \begin{cases} \Theta_4, & for\,Ce \le Ce50 \\ \Theta_9, & for\,Ce > Ce50 \end{cases}$$

$$BIS = BIS_{baseline} \cdot \left(1 - \frac{Ce50^{\gamma}}{Ce50^{\gamma} + Ce^{\gamma}}\right) + \Theta_5 \cdot \varepsilon \cdot \exp(\eta 3)$$

$$BIS_{delay}(s) = 15 + \exp(\Theta_6 \cdot AGE)$$

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General purpose propofol PK-PD model (only arterial model)

$V1 = 6.28 * (Fcentral(weight) / Fcentral_{ref})$

$V2 = 25.5 * Fsize * Fage(-0.0156)$

$V3 = 273 * (FFM / FFMref) * Fopiates(-0.0138)$

$Cl1 = Fsexcl * Fsize^{**}0.75 * (Fmatcl / Fmatcl_{ref}) * Fopiates(-0.00286)$

$Cl2 = 1.75 * (V2 / V2ref)^{**}0.75 * (1 + 1.3 * (1 – Fmatq3))$

$Cl3 = 1.11 * (V3 / V3ref)^{**}0.75 * (Fmatq3 / Fmatq3_{ref})$

$ke0 = 0.146 * Fsize^{**} - 0.25$

$E50 = 3.08 * Fage (-0.00635)$

Fsize = weight / 70

Fage(x) = exp(-x*(age - 35))

Fsigmoid(x, e50, gamma) = x**gamma / (x**gamma + e50**gamma)

Fcentral = Fsigmoid (weight, 33.6, 1)

Fopiates(x) = absence: 1, presence: exp(x*age)

Fmatcl = Fsigmoid (post-menstrual age, 42.3 weeks, 9.06)

Fsexcl = male: 1.79, female: 2.10

Fmatq3 = Fsigmoid (age + 40 weeks, 68.3 weeks, 1)

FFM(weight, height, sex) = Al-Sallami equation (Al-Sallami HS, et al. Prediction of fat-free mass in children. Clin Pharmacokin 2015;54:1169-78)

Subscript ref are calculated for a 70 kg, 35 year, 170 cm, male, full term (40 weeks)

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General purpose propofol PK-PD model (only arterial model)

V1 = 6.28 * (Fcentral(weight) / $Fcentral_{ref}$)

V2 = 25.5 * Fsize * Fage(-0.0156)

V3 = 273 * (FFM / FFMref) * Fopiates(-0.0138)

Cl1 = Fsexcl * Fsize**0.75 * (Fmatcl / $Fmatcl_{ref}$) * Fopiates(-0.00286)

Cl2 = 1.75 * (V2 / V2ref)**0.75 * (1 + 1.3 * (1 – Fmatq3))

Cl3 = 1.11 * (V3 / V3ref)**0.75 * (Fmatq3 / $Fmatq3_{ref}$)

ke0 = 0.146 * Fsize** - 0.25

E50 = 3.08 * Fage (-0.00635)

Fsize = weight / 70

Fage(x) = exp(-x*(age - 35))

Fsigmoid(x, e50, gamma) = x**gamma / (x**gamma + e50**gamma)

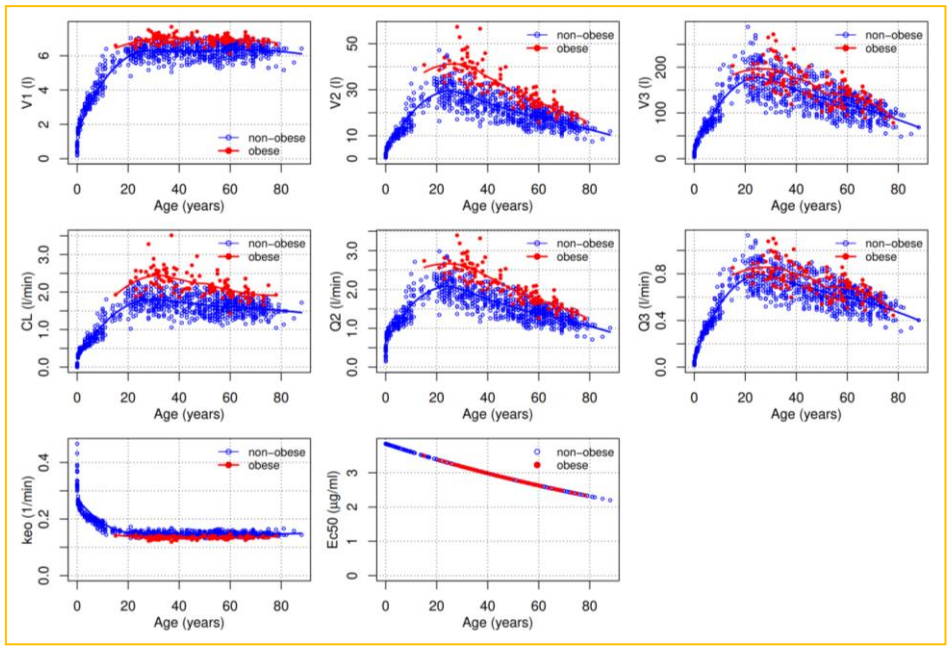
Fcentral = Fsigmoid (weight, 33.6, 1)

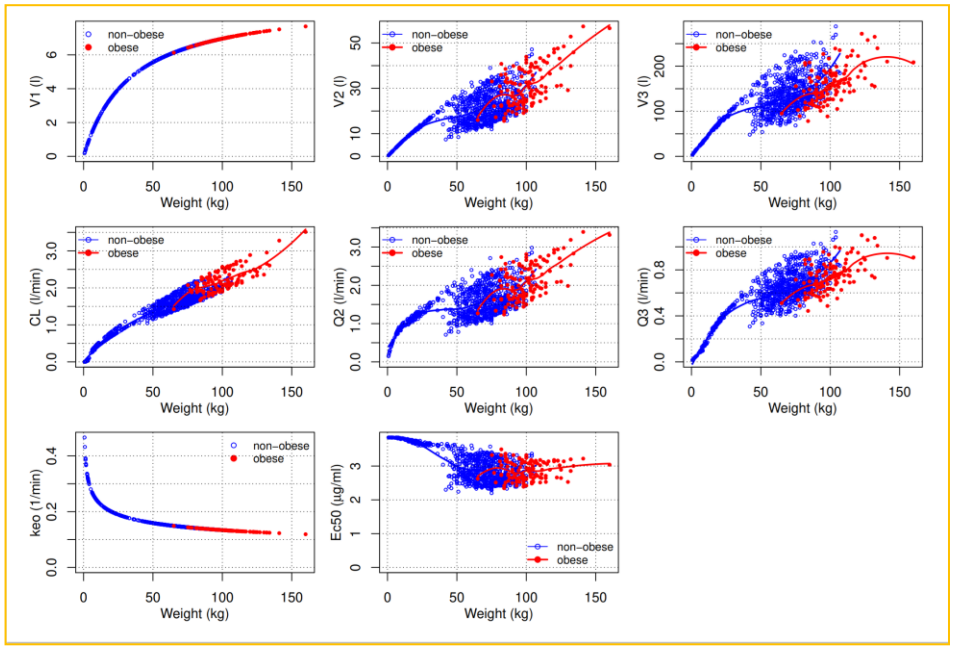
Fopiates(x) = absence: 1, presence: exp(x*age)

Fmatcl = Fsigmoid (post-menstrual age, 42.3 weeks, 9.06)

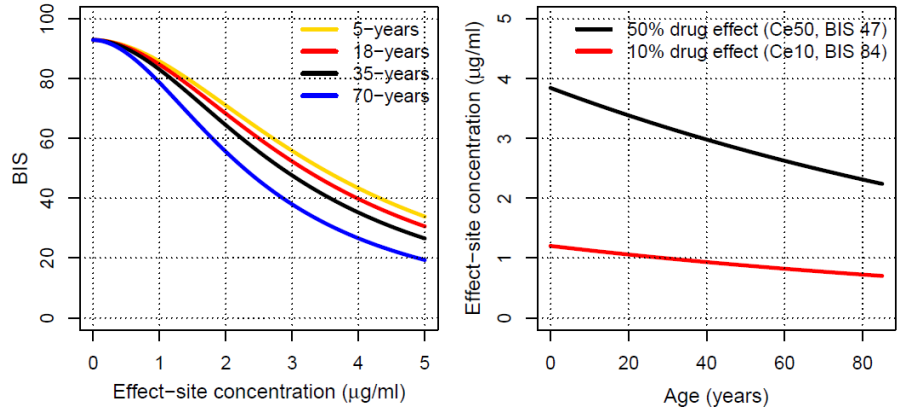
Fsexcl = male: 1.79, female: 2.10

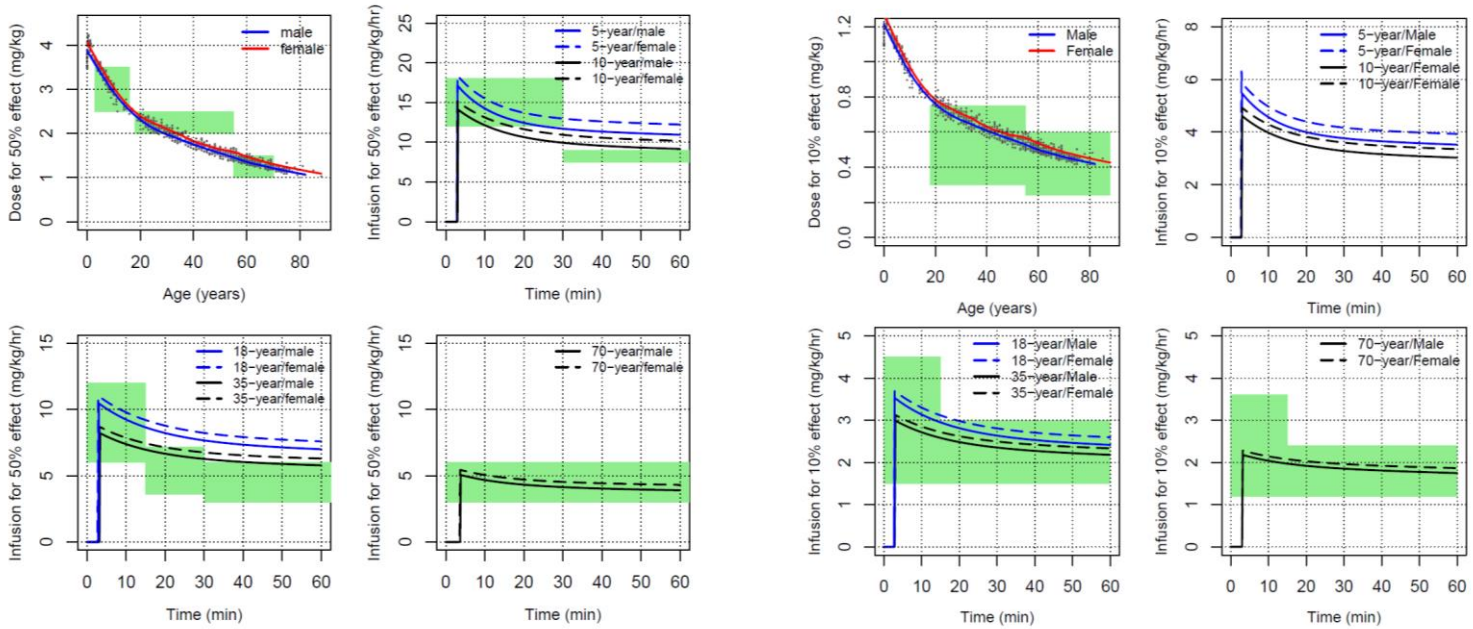
Fmatq3 = Fsigmoid (age + 40 weeks, 68.3 weeks, 1)





General purpose propofol PK-PD model





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General purpose propofol PK-PD model

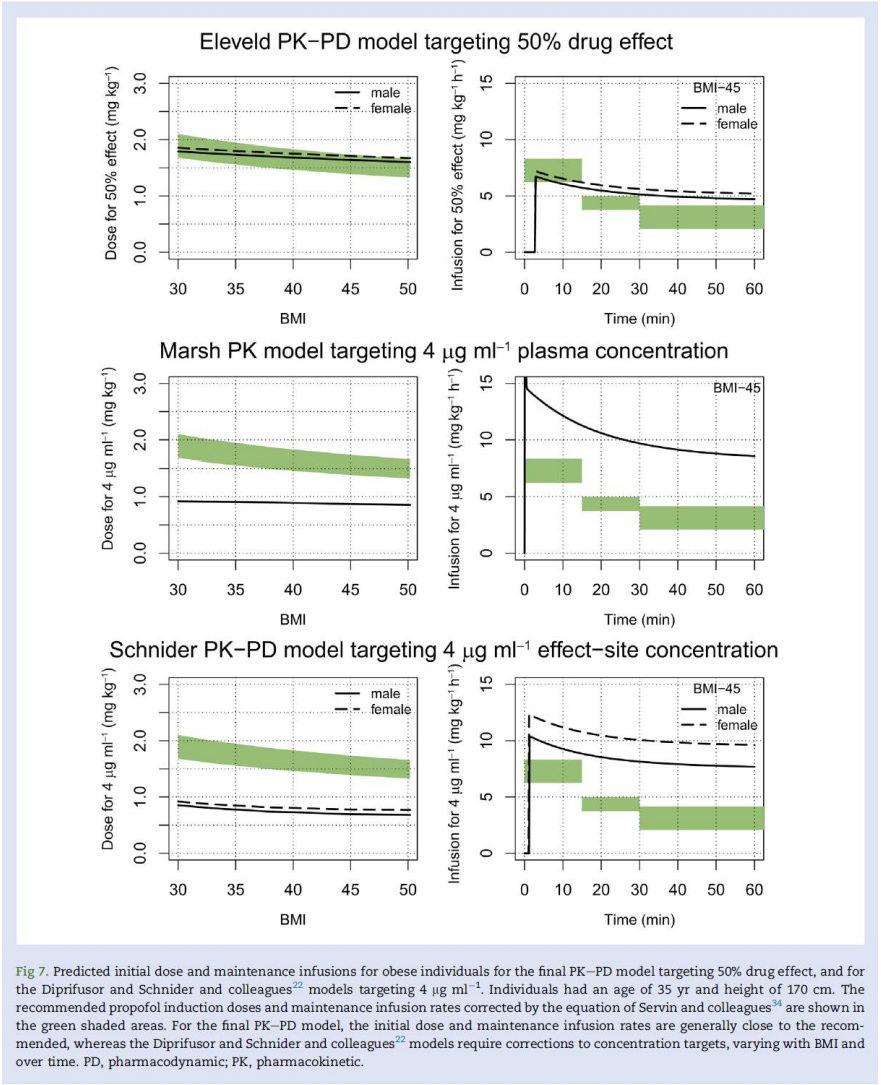

Fig 7. Predicted initial dose and maintenance infusions for obese individuals for the final PK–PD model targeting 50% drug effect, and for the Diprifusor and Schnider and colleagues[22] models targeting 4 μg ml^{-1}. Individuals had an age of 35 yr and height of 170 cm. The recommended propofol induction doses and maintenance infusion rates corrected by the equation of Servin and colleagues[34] are shown in the green shaded areas. For the final PK–PD model, the initial dose and maintenance infusion rates are generally close to the recommended, whereas the Diprifusor and Schnider and colleagues[22] models require corrections to concentration targets, varying with BMI and over time. PD, pharmacodynamic; PK, pharmacokinetic.

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Take home message

- Hypnotics/analgesics should not be administered in obese patients using standard-dosing guidelines without knowledge of their pharmacokinetics in this population.
- Pharmacokinetic/dynamic data should obtained from studies with normal-weight and obese individuals
- Aside “size”, other demographic covariates should be considered

Take home message

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