Dosing Anesthetics and analgesics in the Obese patient

Michel MRF Struys, MD, PhD, FRCA

Professor and Chair
Department of Anesthesia
University Medical Center Groningen
Groningen, The Netherlands

Professor, Department of Basic and Applied Medical Sciences
Ghent University, Gent, Belgium
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

• Problems with obesity in anesthesia:

  • 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?

“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.”
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
Size descriptors

• **LBM or LBW**

  • Definition *James et al*:
    • men: \[1.10 \times \text{weight} - [128 \times (\text{weight}/\text{height})^2]\]
    • women: \[1.07 \times \text{weight} - [148 \times (\text{weight}/\text{height})^2]\]

  • Definition *Janmahasatian et al*:
    • men: \[9270 \times \text{weight}/(6680 + 216 \times \text{BMI})\]
    • women: \[9270 \times \text{weight}/(8780 + 244 \times \text{BMI})\]
Size descriptors

• **IBW**

  • Definition *Abernethy et al*:
    • men: $49.9 + 0.89 \times [\text{height (cm)} - 152.4]$  
    • women: $45.4 + 0.89 \times [\text{height (cm)} - 152.4]$

• **Broca Index**:
  • men: $\text{height (cm)} - 100$
  • women: $\text{height (cm)} - 105$
Size descriptors

• Fat Free Mass:

Al-Sallami fat free mass calculation:

\[
\begin{align*}
\text{FFM}_{\text{mimo}} (kg) &= \left( 0.88 + \frac{1 - 0.88}{1 + (\text{AGE} / 13.4)^{1.25}} \right) \left( \frac{9270 \cdot \text{WGT}}{6680 + 216 \cdot \text{BMI}} \right) \\
\text{FFM}_{\text{fmofo}} (kg) &= \left( 1.11 + \frac{1 - 1.11}{1 + (\text{AGE} / 7.1)^{1.1}} \right) \left( \frac{9270 \cdot \text{WGT}}{8780 + 244 \cdot \text{BMI}} \right)
\end{align*}
\]

Dubois Equation for Body Surface Area calculation:

\[
\text{Surface} = 0.20247 \times \text{HGT}^{0.725} \times \text{WGT}^{0.425}
\]
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
Hypnotics and opioids and the obese patient
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

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


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

Luc E.C. De Baeremaeker, MD, DEAA; Stefan Jacobs, MD; Nadia M.M. Den Blauwen, MD; Piet Pattyn, MD, PhD; Luc L.G. Herregods, MD, PhD; Eric P. Mortier, MD, DSc; Michel M.R.F. Struys, MD, PhD

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

-Remifentanil guided by hemodynamic responses.
Volatile anesthetics and the obese patient

Intra-operative results

• Hypertension (% of time) : sevoflurane = desflurane

• Hypotension (% of time)
  • Overall : sevoflurane > desflurane
  • Bolus period : sevoflurane = desflurane

• Hypnotic stability (BIS)
  • Overall : sevoflurane > desflurane
  • Bolus period : 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
Intravenous drugs and the obese patient

• **Midazolam**
  • 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

- **Thiopental**
  - Increased Vd and elimination half-life, but unchanged total clearance values
  - Adequate dosage: 7.5 mg/kg IBW

  [Buckley et al]

  [Buckley et al]
Intravenous drugs and the obese patient

• **Analgesics & opioids**
  
  • **Alfentanil**
    
    • Decreased clearance and prolonged $t_{1/2}$, but unchanged max. plasma concentration and $V_d$ -> LBM
    
    [Bentley et al]
    
    • No effect on clearance, but increased central compartment volume -> TBW
    
    [Maître et al]
Intravenous drugs and the obese patient

- **Analgesics & opioids**
  - **Fentanyl**
    - No difference in beta-elimination half-life ($t_{\frac{1}{2}B}$)
      - [Bentley et al]
  
  Shibutani et al:
  The Shibutani correction for the Cp: Corrected Cp = Cp Shafer * $(1 + \frac{196.4 * e^{-0.025kg-53.66}}{100})$

- **Fentanyl, alfentanil and remifentanil**
  - Dosage ~ corrected BW
  - Decreased arterial pressures after induction, but in all groups within acceptable limits
    - [Salihoglu et al]
• **Analgesics & opioids**
  • Sufentanil
    • Prolonged t½ β and increased Vd
    • Loading dose ~ TBW
      \[\text{[Schwartz et al]}\]
    • 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 \[\text{[Slepchenko et al]}\]
  • TCI using *Gepts* model -> no weight correction necessary but no obese patients in study population!
Intravenous drugs and the obese patient

• Analgesics & opioids
  • remifentanil
    • Maintenance dose ~ age and LBM
      [Minto et al]
  • Maintenance dose ~ LBM
    [Egan et al]
• Analgesics & opioids
  • remifentanil
    • Maintenance dose ~ age and LBM
      [Minto et al]
  • Maintenance dose ~ LBM
    [Egan et al]
Propofol

**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)
Intravenous drugs and the obese patient

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

Anesthesia was induced and maintained using a step-wise infusion regimen of propofol 21 mg·kg⁻¹·h⁻¹ for 5 min, 12 mg·kg⁻¹·h⁻¹ for 10 min, and 6 mg·kg⁻¹·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

<table>
<thead>
<tr>
<th>Patients</th>
<th>Surgical Procedure</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Ideal Body Weight (kg)</th>
<th>Plasma Albumin Concentration (g/L)</th>
<th>Plasma Creatinine Concentration (μmol)</th>
<th>Hemoglobin (g/100 mL)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese</td>
<td>Hip replacement</td>
<td>55</td>
<td>F</td>
<td>108</td>
<td>55.5</td>
<td>40</td>
<td>91</td>
<td>15</td>
<td>47.1 ± 15.6 155.5 ± 20.8 58.6 ± 6.8 39.9 ± 3.7 87.7 ± 18.7 14.3 ± 0.93</td>
</tr>
<tr>
<td>1</td>
<td>Cholecystectomy</td>
<td>37</td>
<td>F</td>
<td>160</td>
<td>62.0</td>
<td>37</td>
<td>90</td>
<td>14</td>
<td>47.1 ± 15.6 155.5 ± 20.8 58.6 ± 6.8 39.9 ± 3.7 87.7 ± 18.7 14.3 ± 0.93</td>
</tr>
<tr>
<td>2</td>
<td>Cholecystectomy</td>
<td>30</td>
<td>F</td>
<td>97</td>
<td>52.5</td>
<td>38</td>
<td>93</td>
<td>13.5</td>
<td>47.1 ± 15.6 155.5 ± 20.8 58.6 ± 6.8 39.9 ± 3.7 87.7 ± 18.7 14.3 ± 0.93</td>
</tr>
<tr>
<td>3</td>
<td>Cholecystectomy</td>
<td>66</td>
<td>M</td>
<td>130</td>
<td>72.5</td>
<td>39</td>
<td>100</td>
<td>16.2</td>
<td>47.1 ± 15.6 155.5 ± 20.8 58.6 ± 6.8 39.9 ± 3.7 87.7 ± 18.7 14.3 ± 0.93</td>
</tr>
<tr>
<td>4</td>
<td>Wound dehiscence</td>
<td>66</td>
<td>F</td>
<td>105</td>
<td>55.0</td>
<td>37</td>
<td>91</td>
<td>13.4</td>
<td>47.1 ± 15.6 155.5 ± 20.8 58.6 ± 6.8 39.9 ± 3.7 87.7 ± 18.7 14.3 ± 0.93</td>
</tr>
<tr>
<td>5</td>
<td>Wound dehiscence</td>
<td>53</td>
<td>M</td>
<td>107</td>
<td>62.7</td>
<td>38</td>
<td>119</td>
<td>13.7</td>
<td>47.1 ± 15.6 155.5 ± 20.8 58.6 ± 6.8 39.9 ± 3.7 87.7 ± 18.7 14.3 ± 0.93</td>
</tr>
<tr>
<td>6</td>
<td>Lipoma resection</td>
<td>25</td>
<td>F</td>
<td>100</td>
<td>55.0</td>
<td>47</td>
<td>57</td>
<td>14</td>
<td>47.1 ± 15.6 155.5 ± 20.8 58.6 ± 6.8 39.9 ± 3.7 87.7 ± 18.7 14.3 ± 0.93</td>
</tr>
<tr>
<td>7</td>
<td>Wound dehiscence</td>
<td>45</td>
<td>F</td>
<td>117</td>
<td>53.5</td>
<td>44</td>
<td>71</td>
<td>14.3</td>
<td>47.1 ± 15.6 155.5 ± 20.8 58.6 ± 6.8 39.9 ± 3.7 87.7 ± 18.7 14.3 ± 0.93</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Control

<table>
<thead>
<tr>
<th>Patients</th>
<th>Surgical Procedure</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Ideal Body Weight (kg)</th>
<th>Plasma Albumin Concentration (g/L)</th>
<th>Plasma Creatinine Concentration (μmol)</th>
<th>Hemoglobin (g/100 mL)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Femoral pseudarthrosis repair</td>
<td>24</td>
<td>M</td>
<td>60</td>
<td>66.5</td>
<td>40</td>
<td>75</td>
<td>11.9</td>
<td>41.9 ± 11.7 65.6 ± 14.9 64.1 ± 5.8 38.6 ± 4.3 74.9 ± 18.3 14.2 ± 1.8</td>
</tr>
<tr>
<td>2</td>
<td>Femoral pseudarthrosis repair</td>
<td>34</td>
<td>M</td>
<td>55</td>
<td>63.5</td>
<td>42</td>
<td>74</td>
<td>14.1</td>
<td>41.9 ± 11.7 65.6 ± 14.9 64.1 ± 5.8 38.6 ± 4.3 74.9 ± 18.3 14.2 ± 1.8</td>
</tr>
<tr>
<td>3</td>
<td>Pulmonary resection</td>
<td>42</td>
<td>M</td>
<td>54</td>
<td>65.0</td>
<td>33</td>
<td>93</td>
<td>16.3</td>
<td>41.9 ± 11.7 65.6 ± 14.9 64.1 ± 5.8 38.6 ± 4.3 74.9 ± 18.3 14.2 ± 1.8</td>
</tr>
<tr>
<td>4</td>
<td>Pneumonectomy</td>
<td>54</td>
<td>F</td>
<td>55</td>
<td>56.5</td>
<td>40</td>
<td>65</td>
<td>12.7</td>
<td>41.9 ± 11.7 65.6 ± 14.9 64.1 ± 5.8 38.6 ± 4.3 74.9 ± 18.3 14.2 ± 1.8</td>
</tr>
<tr>
<td>5</td>
<td>Colectomy</td>
<td>55</td>
<td>M</td>
<td>70</td>
<td>66.5</td>
<td>46</td>
<td>107</td>
<td>16.6</td>
<td>41.9 ± 11.7 65.6 ± 14.9 64.1 ± 5.8 38.6 ± 4.3 74.9 ± 18.3 14.2 ± 1.8</td>
</tr>
<tr>
<td>6</td>
<td>Hysterectomy</td>
<td>52</td>
<td>F</td>
<td>85</td>
<td>61.0</td>
<td>38</td>
<td>57</td>
<td>14.9</td>
<td>41.9 ± 11.7 65.6 ± 14.9 64.1 ± 5.8 38.6 ± 4.3 74.9 ± 18.3 14.2 ± 1.8</td>
</tr>
<tr>
<td>7</td>
<td>Wound dehiscence</td>
<td>56</td>
<td>M</td>
<td>70</td>
<td>65.0</td>
<td>36</td>
<td>48</td>
<td>13.8</td>
<td>41.9 ± 11.7 65.6 ± 14.9 64.1 ± 5.8 38.6 ± 4.3 74.9 ± 18.3 14.2 ± 1.8</td>
</tr>
<tr>
<td>8</td>
<td>Selective vagotomy</td>
<td>33</td>
<td>M</td>
<td>61</td>
<td>66.5</td>
<td>31</td>
<td>81</td>
<td>14.4</td>
<td>41.9 ± 11.7 65.6 ± 14.9 64.1 ± 5.8 38.6 ± 4.3 74.9 ± 18.3 14.2 ± 1.8</td>
</tr>
<tr>
<td>9</td>
<td>Cholecystectomy</td>
<td>39</td>
<td>M</td>
<td>96</td>
<td>75.5</td>
<td>38</td>
<td>85</td>
<td>15.2</td>
<td>41.9 ± 11.7 65.6 ± 14.9 64.1 ± 5.8 38.6 ± 4.3 74.9 ± 18.3 14.2 ± 1.8</td>
</tr>
<tr>
<td>10</td>
<td>Ileal resection</td>
<td>30</td>
<td>F</td>
<td>50</td>
<td>55.0</td>
<td>36</td>
<td>55</td>
<td>12</td>
<td>41.9 ± 11.7 65.6 ± 14.9 64.1 ± 5.8 38.6 ± 4.3 74.9 ± 18.3 14.2 ± 1.8</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Patients included in the concurrent study.
† P = 0.001.
Target-controlled infusion and the obese patient

- Propofol: In Europe we have TCI? Can we use it in obese patients?

- 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)
target-controlled infusion (TCI)

- A computer-assisted drug infusion

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

- 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

- User can increase or decrease target concentration

**SYRINGE PUMP**

**PKPD MODEL**

**TCI ALGORITHM**
## Propofol US Smpc (FDA)

### Indication and Dosage and Administration

#### Induction of General Anesthesia:
- **Healthy Adults Less Than 55 Years of Age:**
  - 40 mg every 15 seconds until induction occurs (2 mg/kg to 2.5 mg/kg).
- **Elderly, Delirious, or ASA-PS III or IV Patients:**
  - 20 mg every 15 seconds until induction occurs (1 mg/kg to 1.5 mg/kg).

#### Maintenance of General Anesthesia:
- **Induction**
  - **Healthy Adults Less Than 55 Years of Age:**
    - 100 mcg/kg/min to 200 mcg/kg/min (6 mcg/kg/h to 12 mcg/kg/h).
  - **Elderly, Delirious, ASA-PS III or IV Patients:**
    - 50 mcg/kg/min to 100 mcg/kg/min (3 mcg/kg/h to 6 mcg/kg/h).
- **Maintenance**
  - **Healthy Adults Less Than 55 Years of Age:**
    - Follow the induction dosage regimen and adjust to maintain anesthesia.
  - **Elderly, Delirious, or ASA-PS III or IV Patients:**
    - maintain at the induction rate or as recommended by the attending physician.

#### 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:**
  - 15 mg every 15 seconds until MAC sedation occurs (1 mg/kg to 1.5 mg/kg).
- **Elderly, Delirious, Neurosurgical, or ASA-PS III or IV Patients:**
  - Most patients require dosages similar to healthy adults. Final dosages are to be assessed (see WARNINGS).

### 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 mcg/kg/h to 4.5 mcg/kg/h) or incremental bolus doses of 10 mg every 5 minutes. In Elderly, Delirious, Neurosurgical, or ASA-PS III or IV Patients:
    - Most patients require 80% of the usual adult dose. A rapid initial or supplemental bolus dose should not be used (see WARNINGS).

### Initiation and Maintenance of ICU Sedation in Intubated, Mechanically Ventilated Patients
- **Adult Patients:**
  - The incidence of adverse effects with propofol is generally less in adults than in children. The desired clinical effect is achieved. Maintenance rates of 5 mcg/kg/min to 50 mcg/kg/min (0.3 mcg/kg/h to 3 mcg/kg/h) or higher may be required. Administer additional 5 mcg/kg/min unless the benefits outweigh the risks (see WARNINGS).

### 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.
Propofol TCI models

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

\[ V_c = 0.228 \times \text{weight (L*kg)} \]
\[ k_{10} = 0.119/\text{min} \]
\[ k_{12} = 0.112/\text{min} \]
\[ k_{13} = 0.0419/\text{min} \]
\[ k_{21} = 0.055/\text{min} \]
\[ k_{31} = 0.0033/\text{min} \]
\[ k_{41} = 0.26/\text{min} \quad \text{(extracted from not related data by Schüttler et al).} \]

**Propofol : Schnider model**

\[ V_1 = 4.27 \text{ L} \]
\[ V_2 = 18.9 \text{ L} - 0.391 \times (\text{age-53}) \]
\[ V_3 = 238 \text{ L} \]
\[ C_{l1} = 1.89 + 0.0456 \times (\text{weight-77}) - 0.0681 \times (\text{lbm-59}) + 0.0264 \times (\text{height-177}) \]
\[ C_{l2} = 1.29 - 0.024 \times (\text{age-53}) \]
\[ C_{l3} = 0.836 \]
\[ k_{41} \text{ determined by } t_{\text{Peak}}=1.6\text{min or } k_{e0} = 0.456/\text{min} \]
**Propofol TCI models**

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

\[ V_c = 0.228 \times \text{weight (L*kg)} \]

\[ k_{10} = 0.119/\text{min} \]

\[ k_{12} = 0.112/\text{min} \]

\[ k_{13} = 0.0419/\text{min} \]

\[ k_{21} = 0.055/\text{min} \]

\[ k_{31} = 0.0033/\text{min} \]

\[ k_{41} = 0.26/\text{min} \] (extracted from not related data by Schüttler et al).

**Propofol : Schnider model**

\[ V_1 = 4.27 \text{ L} \]

\[ V_2 = 18.9 \text{ L} - 0.391 \times (\text{age} - 53) \]

\[ V_3 = 238 \text{ L} \]

\[ Cl_1 = 1.89 + 0.0456 \times (\text{weight} - 77) - 0.0681 \times (\text{lbm} - 59) + 0.0264 \times (\text{height} - 177) \]

\[ Cl_2 = 1.29 - 0.024 \times (\text{age} - 53) \]

\[ Cl_3 = 0.836 \]

\[ k_{41} \] determined by \[ t_{\text{Peak}} = 1.6/\text{min} \] or \[ k_{e0} = 0.456/\text{min} \]

<table>
<thead>
<tr>
<th>inf</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>34</td>
<td>46.3</td>
<td>158</td>
<td>F</td>
</tr>
<tr>
<td>25</td>
<td>31</td>
<td>123</td>
<td>196</td>
<td>M</td>
</tr>
<tr>
<td>25</td>
<td>62</td>
<td>79.4</td>
<td>170</td>
<td>M</td>
</tr>
<tr>
<td>25</td>
<td>65</td>
<td>79.4</td>
<td>182</td>
<td>M</td>
</tr>
<tr>
<td>25</td>
<td>77</td>
<td>74.8</td>
<td>183</td>
<td>M</td>
</tr>
<tr>
<td>25</td>
<td>70</td>
<td>62.6</td>
<td>175</td>
<td>M</td>
</tr>
<tr>
<td>50</td>
<td>30</td>
<td>64.4</td>
<td>170</td>
<td>M</td>
</tr>
<tr>
<td>50</td>
<td>27</td>
<td>74.8</td>
<td>188</td>
<td>M</td>
</tr>
<tr>
<td>50</td>
<td>46</td>
<td>93.4</td>
<td>182</td>
<td>M</td>
</tr>
<tr>
<td>50</td>
<td>41</td>
<td>90.7</td>
<td>178</td>
<td>F</td>
</tr>
<tr>
<td>50</td>
<td>72</td>
<td>88.4</td>
<td>183</td>
<td>M</td>
</tr>
<tr>
<td>50</td>
<td>75</td>
<td>64.4</td>
<td>168</td>
<td>F</td>
</tr>
<tr>
<td>100</td>
<td>29</td>
<td>95.2</td>
<td>188</td>
<td>M</td>
</tr>
<tr>
<td>100</td>
<td>28</td>
<td>88.4</td>
<td>178</td>
<td>M</td>
</tr>
<tr>
<td>100</td>
<td>55</td>
<td>44.7</td>
<td>168</td>
<td>F</td>
</tr>
<tr>
<td>100</td>
<td>51</td>
<td>79.8</td>
<td>175</td>
<td>F</td>
</tr>
<tr>
<td>100</td>
<td>81</td>
<td>74.8</td>
<td>178</td>
<td>M</td>
</tr>
<tr>
<td>100</td>
<td>72</td>
<td>70.3</td>
<td>170</td>
<td>F</td>
</tr>
<tr>
<td>200</td>
<td>31</td>
<td>91.2</td>
<td>180</td>
<td>F</td>
</tr>
<tr>
<td>200</td>
<td>25</td>
<td>63.5</td>
<td>158</td>
<td>F</td>
</tr>
<tr>
<td>200</td>
<td>62</td>
<td>86.2</td>
<td>180</td>
<td>M</td>
</tr>
<tr>
<td>200</td>
<td>38</td>
<td>88.4</td>
<td>173</td>
<td>F</td>
</tr>
<tr>
<td>200</td>
<td>74</td>
<td>70.3</td>
<td>160</td>
<td>M</td>
</tr>
<tr>
<td>200</td>
<td>75</td>
<td>44.4</td>
<td>155</td>
<td>F</td>
</tr>
</tbody>
</table>
Pharmacokinetic models for propofol—defining and illuminating the devil in the detail

A. R. Absalom1, V. Manf2, T. De Smet2 and M. M. R. F. Straus3

1University Division of Anaesthesia, Addenbrookes Hospital, Cambridge CB2 0QW, UK. 2Royal Hospital for Sick Children, Duarte Street, Glasgow G3 8SR, UK. 3VUBA Hospital, Molukkenstraat 140, B-9040, Tonger, Belgium.

*Department of Anaesthesia, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GE Groningen, The Netherlands

*Corresponding author. E-mail: r.a.absalom@viro.ox.ac.uk

Propofol TCI models
General purpose propofol PK-PD model

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

D. J. Eleveld\textsuperscript{1,4}, P. Colin\textsuperscript{1,2}, A. R. Absalom\textsuperscript{1} and M. M. R. F. Struys\textsuperscript{1,3}

\textsuperscript{1}Department of Anaesthesiology, University Medical Center Groningen, Groningen, The Netherlands, \textsuperscript{2}Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium and \textsuperscript{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.
General purpose propofol PK-PD model

Table 1 Details of the component datasets.

<table>
<thead>
<tr>
<th>Dataset</th>
<th>N Sampling</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Additional drugs</th>
<th>Publication</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durasfa Fixed Reduction</td>
<td>10</td>
<td>Aranetil</td>
<td>21–44</td>
<td>57–82</td>
<td>Open-TCI</td>
<td>See Durasfa Delaunay</td>
</tr>
<tr>
<td>Durasfa Variable</td>
<td>29</td>
<td>Aranetil</td>
<td>19–99</td>
<td>90–99</td>
<td>See Durasfa Delaunay</td>
<td></td>
</tr>
<tr>
<td>Bussom van Oud-Aalbers</td>
<td>14</td>
<td>Aranetil</td>
<td>20–107</td>
<td>37–82</td>
<td>Open-TCI</td>
<td>Bussom van Oud-Aalbers</td>
</tr>
<tr>
<td>Poryckie (jaheo)</td>
<td>23</td>
<td>Aranetil</td>
<td>51–75</td>
<td>44–123</td>
<td>Open-TCI</td>
<td>Poryckie JA, Bussom van Oud-Aalbers</td>
</tr>
</tbody>
</table>

Table 1 Continued.

<table>
<thead>
<tr>
<th>Dataset</th>
<th>N Sampling</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Additional drugs</th>
<th>Publication</th>
<th>Source</th>
</tr>
</thead>
</table>

Author names in brackets indicates personal communication. Source: Open-TCI (http://www.opentci.org) (downloaded on 11/19/2018).
$f_{aging}(x) = \exp(x \cdot [\text{AGE} \cdot \text{AGE}_{ref}])$

$f_{sigmoid}(x, E50, \lambda) = \frac{1}{1 + \exp(-\lambda(x - E50))}$

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

$f_{CLmaturati} = f_{sigmoid}(\text{PMA}, \Theta_{2}, \Theta_{3})$

$f_{Q3maturati} = f_{sigmoid}(\text{AGE} + 40 \text{ weeks}, \Theta_{4}, 1)$

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

$V_{1, \text{arterial}}(l) = \Theta_{3} \cdot \frac{f_{central}(\text{WGT})}{f_{central}(\text{WGT}_{ref})} \cdot \exp(\eta 1)$

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

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

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

$CL(l \cdot \text{min}^{-1}) = \begin{cases} \Theta_{4}, & \text{male} \\ \Theta_{13}, & \text{female} \end{cases} \left( \frac{\text{WGT}}{\text{WGT}_{ref}} \right)^{0.75} \cdot f_{CLmaturati} \cdot f_{opiates}(\Theta_{14}) \cdot \exp(\eta 4)$

$Q_{2, \text{arterial}}(l \cdot \text{min}^{-1}) = \Theta_{3} \cdot \left( V_{2, \text{ref}} \right)^{0.75} \cdot (1 + \Theta_{16} \cdot (1 - f_{Q3maturati})) \cdot \exp(\eta 5)$

$Q_{2, \text{venous}}(l \cdot \text{min}^{-1}) = Q_{2, \text{arterial}} \cdot \Theta_{18}$

$Q3(l \cdot \text{min}^{-1}) = \Theta_{6} \cdot \left( V_{3, \text{ref}} \right)^{0.75} \cdot f_{Q3maturati} \cdot \exp(\eta 6)$

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

$\text{Ce50 (mg \cdot l^{-1})} = \Theta_{1} \cdot f_{aging}(\Theta_{7}) \cdot \exp(\eta 1)$

$ke0 (\text{min}^{-1}) = \begin{cases} \Theta_{2}, & \text{arterial PK} \\ \Theta_{5}, & \text{venous PK} \end{cases} \left( \frac{\text{WGT}}{70} \right)^{-0.25} \cdot \exp(\eta 2)$

$BIS_{\text{baseline}} = \Theta_{3}$

$\gamma = \begin{cases} \Theta_{4}, & \text{for } Ce \leq \text{Ce50} \\ \Theta_{5}, & \text{for } Ce > \text{Ce50} \end{cases}$

$BIS = BIS_{\text{baseline}} \cdot \left( \frac{1 - \frac{\text{Ce50}'}{\text{Ce50}'} - Ce'}{\text{Ce50}'} \right) + \Theta_{5} \cdot \epsilon \cdot \exp(\eta 3)$

$BIS_{\text{delay}} (s) = 15 + \exp(\Theta_{6} \cdot \text{AGE})$
General purpose propofol PK-PD model (only arterial model)

\begin{align*}
V1 & = 6.28 \times \frac{\text{Fcentral(weight)}}{\text{Fcentral}_{\text{ref}}} \\
V2 & = 25.5 \times \text{Fsize} \times \text{Fage(-0.0156)} \\
V3 & = 273 \times \frac{\text{FFM}}{\text{FFM}_{\text{ref}}} \times \text{Fopiates(-0.0138)} \\
C11 & = \text{Fsexcl} \times \text{Fsize}^{0.75} \times \frac{\text{Fmatcl}}{\text{Fmatcl}_{\text{ref}}} \times \text{Fopiates(-0.00286)} \\
C12 & = 1.75 \times \frac{\text{V2}}{\text{V2}_{\text{ref}}}^{0.75} \times (1 + 1.3 \times (1 - \text{Fmatq3})) \\
C13 & = 1.11 \times \frac{\text{V3}}{\text{V3}_{\text{ref}}}^{0.75} \times \frac{\text{Fmatq3}}{\text{Fmatq3}_{\text{ref}}} \\
\text{ke0} & = 0.146 \times \text{Fsize}^{0.75} - 0.25 \\
\text{E50} & = 3.08 \times \text{Fage} (-0.00635)
\end{align*}

\begin{align*}
\text{Fsize} & = \frac{\text{weight}}{70} \\
\text{Fage}(x) & = \exp(-x \times (\text{age - 35})) \\
\text{Fsigmoid}(x, e50, \gamma) & = \frac{x^{\gamma}}{x^{\gamma} + e50^{\gamma}} \\
\text{Fcentral} & = \text{Fsigmoid}(\text{weight}, 33.6, 1) \\
\text{Fopiates}(x) & = \text{absence}: 1, \text{presence}: \exp(x \times \text{age}) \\
\text{Fmatcl} & = \text{Fsigmoid}(\text{post-menstrual age}, 42.3 \text{ weeks}, 9.06) \\
\text{Fsexcl} & = \text{male}: 1.79, \text{female}: 2.10 \\
\text{Fmatq3} & = \text{Fsigmoid}(\text{age} + 40 \text{ weeks}, 68.3 \text{ weeks}, 1)
\end{align*}


Subscript \text{ref} are calculated for a 70 kg, 35 year, 170 cm, male, full term (40 weeks)
General purpose propofol PK-PD model (only arterial model)

\[ V_1 = 6.28 \times (\text{Fcentral}(\text{weight}) / \text{Fcentral}_{\text{ref}}) \]
\[ V_2 = 25.5 \times \text{Fsize} \times \text{Fage}(-0.0156) \]
\[ V_3 = 273 \times (\text{FFM} / \text{FFM}_{\text{ref}}) \times \text{Fopiates}(-0.0138) \]
\[ \text{CI}_1 = \text{Fsexcl} \times \text{Fsize}^{0.75} \times (\text{Fmatcl} / \text{Fmatcl}_{\text{ref}}) \times \text{Fopiates}(-0.00286) \]
\[ \text{CI}_2 = 1.75 \times (V_2 / V_{2\text{ref}})^{0.75} \times (1 + 1.3 \times (1 - \text{Fmatq3})) \]
\[ \text{CI}_3 = 1.11 \times (V_3 / V_{3\text{ref}})^{0.75} \times (\text{Fmatq3} / \text{Fmatq3}_{\text{ref}}) \]
\[ \text{ke}_0 = 0.146 \times \text{Fsize}^{0.25} \]
\[ E_{50} = 3.08 \times \text{Fage}(-0.00635) \]

\[ \text{Fsize} = \text{weight} / 70 \]
\[ \text{Fage}(x) = \exp(-x \times (\text{age} - 35)) \]
\[ \text{Fsigmoid}(x, e_{50}, \gamma) = x^{\gamma} / (x^{\gamma} + e_{50}^{\gamma}) \]
\[ \text{Fcentral} = \text{Fsigmoid} (\text{weight}, 33.6, 1) \]
\[ \text{Fopiates}(x) = \text{absence}: 1, \text{presence}: \exp(x \times \text{age}) \]
\[ \text{Fmatcl} = \text{Fsigmoid} (\text{post-menstrual age}, 42.3 \text{ weeks}, 9.06) \]
\[ \text{Fsexcl} = \text{male}: 1.79, \text{female}: 2.10 \]
\[ \text{Fmatq3} = \text{Fsigmoid} (\text{age} + 40 \text{ weeks}, 68.3 \text{ weeks}, 1) \]
General purpose propofol PK-PD model
General purpose propofol PK-PD model

![Eleveld PK–PD model targeting 50% drug effect](image1)

![Marsh PK model targeting 4 µg ml⁻¹ plasma concentration](image2)

![Schnider PK–PD model targeting 4 µg ml⁻¹ effect–site concentration](image3)

![Fig 7](image4)

Predicted initial dose and maintenance infusion values for obese individuals for the final PK–PD model targeting 50% drug effect, and for the Diphetaur and Schnider and colleagues’ 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 Serra and colleagues’ 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 Diphetaur and Schnider and colleagues’ models require corrections to concentration targets, varying with BMI and over time. PD, pharmacokinetic; PR, pharmacodynamic.
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

Size matters.