Editorial

Anaesthetic induction with propofol: How much? How fast? How slow?

"What determines anesthetic induction dose? It's the Front-End Kinetics, Doctor!"[1]

It has long been realised that linear dosing according to total body weight (TBW) results in overdosing obese patients and under-dosing small children. Injected drug doses calculated on a $mg.kg^{-1}$ body weight basis work well only for patients of normal habitus. As long ago as 1969, in a study of induction doses of thiopentone, Wulfsohn and Joshi[2] concluded that thiopentone was better administered according to lean body mass (LBM) than to TBW. They reasoned that endomorphic somatotypes required less thiopentone than mesomorphs and ectomorphs of the same TBW, because they had less LBM. They pointed out that there is a strong association between LBM, cardiac output and basal metabolic rate, and suggested that the LBM contained the "pharmacologically active mass". Obese patients can perhaps be loosely regarded as ordinary individuals entrapped in a cocoon of fat into which hardly any injected drug is distributed. However the LBM of obese persons also increases as they accumulate fat, mainly due to increased muscle mass, as well as enlargement of other organs and blood volume. The dilemma is that LBM does not increase at the same rate as the increase in fat. Thus, although we know that they need more drug than normal-weight patients, how much more is often uncertain.

In this edition of the Journal, Smith and co-workers report how they addressed this question with regard to propofol, regarding induction of anaesthesia in normal-weight, overweight and obese patients. They scaled the doses according to an equation based on the assumption that as much as 40% of an obese patient's excess body weight is due to an accompanying increase in LBM.[3] Besides noting the number of patients who lost consciousness, they recorded the processed electroencephalogram (EEG) whereby they could assess the maximum depth of hypnosis, as well as document the duration that State Entropy (SE) remained below a threshold of 60. Only two of the 96 subjects did not lose consciousness and additionally, their SE values did not dip below the 60 threshold. Regarding those who lost consciousness, there was a wide scatter of the EEG data: Lowest SE values ranged from 7 to 55 and the duration that SE values were less than 60 ranged from three seconds to 10.7 minutes. Thus some patients experienced an overshoot with regard to depth of hypnosis and duration of effect, while others were unconscious barely for long enough to permit airway management.

The time course of drug concentrations can be mathematically modelled using classic two- or three-compartment mammillary pharmacokinetic models whereby drug is injected into a central compartment from which it is excreted, distributed to peripheral compartments and redistributed. These models have been successfully implemented in target-controlled infusion pumps in routine use. However although these models can achieve and maintain desired blood and even effect-site concentrations with a clinically acceptable degree of accuracy, they are poor at predicting the fate of drugs during the first few minutes after intravenous injection. There are two weaknesses: firstly, the central compartment is regarded as a uniform, well-stirred "black box" that contains not only the blood circulation but also unspecified organs (Figure 1). Secondly, it is assumed that upon injection, drug instantaneously fills the central compartment. Fortunately, even though the model is wrong, it can successfully predict blood and brain drug concentrations when given

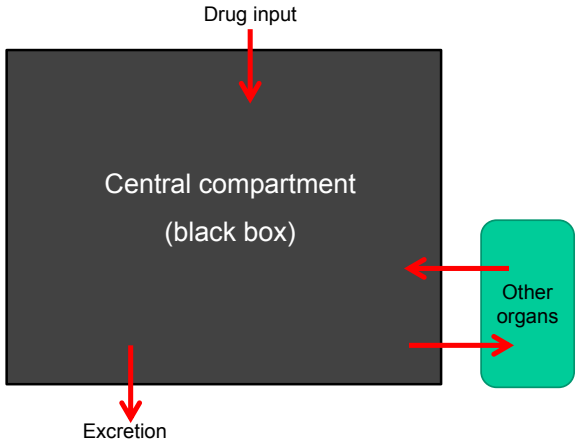

Figure 1. A typical two-compartment mammillary pharmacokinetic model

by infusion. The words of the eminent statistician, George Box echo true: *"Remember that all models are wrong; the practical question is how wrong do they have to be, to not be useful".*[4]

Obviously, drug is never instantaneously distributed into a "well-stirred" central compartment. Following rapid injection, a chain of physiological and anatomical factors, from the site of entry to the cerebral circulation, determine the time course of arterial concentrations and ultimately the effect site concentrations.[5] Firstly, drug is mixed in the venous flow before entering the pulmonary circulation, through which it must undergo a first-pass before entering the systemic circulation. The lungs delay the passage of drugs and may even remove some.[6-8] The systemic circulation then distributes drug to various organs (including the targeted organ) through which it is also subjected to a first-pass process. Thereafter a portion is returned to the venous flow and recirculated. Figure 2 illustrates how a lot more takes place within the "black box".

The fate of drugs soon after rapid intravenous administration is called

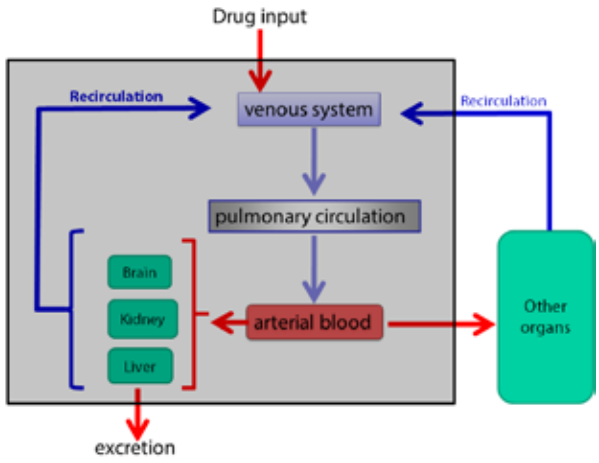

Figure 2. A recirculatory pharmacokinetic model for drugs injected rapidly into the venous circulation

"front-end" kinetics" a term that was coined in an editorial by Krejcie and Avram,[1] commenting on studies of chronically instrumented sheep by Upton and co-workers.[9] The course of events is akin to the measurement of cardiac output by dye- or thermo-dilution, whereby the area under the arterial concentration-time curve is inversely related to the cardiac output. Various studies have indicated that cardiac output has a particularly important influence on blood drug concentrations.[10] As cardiac output increases, peak arterial concentrations decrease in response to a bolus dose and the area under the arterial concentration-time curve decreases, leading to decreased effects on the targeted organ. Distribution of arterial blood flow to the brain also plays an important role in determining the extent of drug effect; the greater the cerebral blood flow, the higher the peak brain concentrations and the greater the effects.[11]

Hybrid mathematical models that incorporate circulatory physiology into compartmental models (including lung first-pass kinetics and recirculation phenomena) have been shown to satisfactorily predict the early time course of propofol concentrations in the circulation and the brain.[12] These models have been expanded to include cerebral blood flow and dynamics. They are able to simulate the complex effects that circulatory changes exert on the pharmacokinetics and pharmacodynamics of propofol in sheep,[9,11-14] as well as in humans.[12] The simplest model consists of two compartments, the lungs (V_{lung}), which receives the total cardiac output and the rest of the body (V_{body}) from which clearance occurs.[15] The mathematics associated with this model are complex, however they have been programmed into a spreadsheet, to provide a useful tool for teaching front-end kinetics (kindly supplied by Prof. Richard Upton[15]). The examples that follow, simulate the time courses of concentrations of an hypothetical lipid-soluble drug with properties similar to thiopentone or propofol.

Example 1

The influence of cardiac output on arterial drug concentrations.

In Figure 3, 100 mg is administered during one minute to three identical "patients" whose cardiac outputs differ from low (2.5 L.min^{-1}) to normal (5 L.min^{-1}) to high (10 L.min^{-1}). A dotted line indicates an hypothetical threshold for loss of consciousness. The graph illustrates the following.

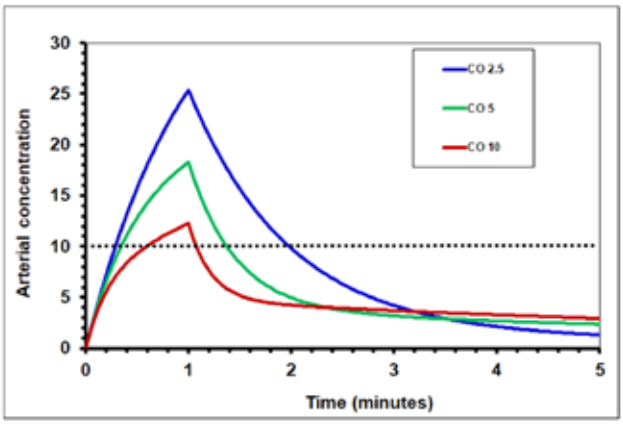

Figure 3. Graphs illustrating how cardiac output influences early arterial drug concentration profiles following rapid intravenous infusion

Simulation demonstrating the the influence of various cardiac outputs on arterial drug concentrations after injection of an hypothetical anaesthetic induction agent 100 mg during one minute.
Patient parameters: Clearance = 2 L.min^{-1}; Volumes of distribution, Vlung = 2.5 L; Vbody = 15 L.
The dotted line depicts a threshold arterial concentation at which loss of consciousness occurs.
CO = cardiac output (L.min^{-1}).

Comparing the high cardiac output patient with the normal patient:

- The onset of hypnosis is delayed slightly.
- The peak concentration is decreased.
- The duration of hypnotic effect is reduced.

The opposite occurs in the patient with the low cardiac output:

- The onset of hypnosis occurs a little earlier.
- The peak concentration is increased, implying possible haemodynamic effects.[16]
- The duration of hypnosis is greatly increased due to the drug concentration overshoot.

Example 2

The rate of injection influences arterial drug concentrations.

In Figure 4, 100 mg is administered at different rates to identical "patients" with the same "normal" cardiac output of 5 L.min^{-1}; i.e. during 30, 60,120 and 180 seconds. These graphs illustrate the following:

The rapid injection (20 seconds) produces:

- A short onset time
- A high peak arterial concentration that is rapidly achieved (an overshoot), again leading to possible haemodynamic side effects.
- A short duration of hypnosis

A slower rate of injection (60 seconds) results in:

- A slightly longer onset time
- A lower peak arterial concentration that is achieved later
- Little difference in the duration of hypnosis

A more prolonged rate of injection (120 seconds) ensues in:

- A prolonged onset time

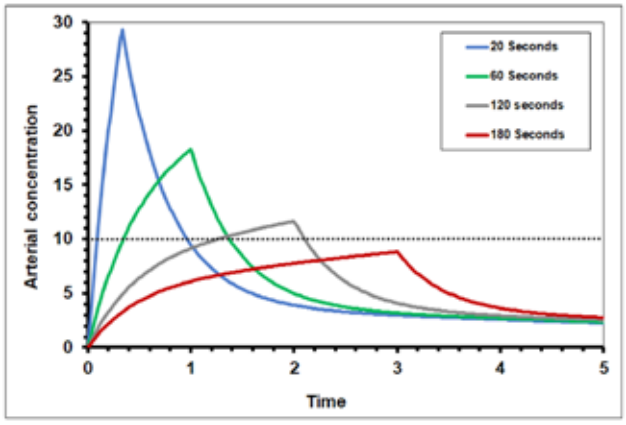

Figure 4. Graphs illustrating how varying the rate of injection influences arterial drug concentrations

Simulation demonstrating arterial drug concentrations resulting from injection of an hypothetical anaesthetic induction agent 100 mg at various rates. Patient parameters: CO = 5 L.min^{-1}; Clearance 2 L.min^{-1}; Volumes of distribution: Vlung = 2.5 L; Vbody = 15 L.
The dotted line depicts an hypothetical arterial concentration at which consciousness is lost

- A low peak concentration that is achieved much later
- A short duration of effect

Of course a point is reached when the rate of injection (180 seconds) is too slow for the arterial concentrations to reach hypnotic levels.

Example 3

Effect of increasing body size only, without increasing cardiac output or clearance.

Figure 5 illustrates the hypothetical situation whereby the size of the body compartment is doubled. The graph is self explanatory: the

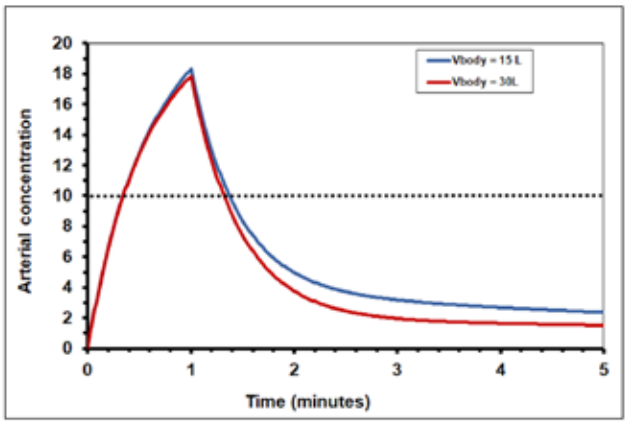

Figure 5. Effect of doubling the peripheral volume of distribution while keeping the cardiac output constant

Dose: 100 mg administered during 60 s.
Patient parameters: CO = 5 L.min^{-1}; Clearance 2 L.min^{-1}; Volumes of distribution: Vlung = 2.5 L; Vbody 15 L & 30 L

concentration-time profiles are virtually identical.

Example 4

Effect of increasing drug clearance only, without increasing cardiac output or the volume of distribution.

Figure 6 illustrates the hypothetical situation whereby the clearance is doubled. Again, the concentration-time profiles are virtually identical. Examples 3 and 4 illustrate that during the first minutes following

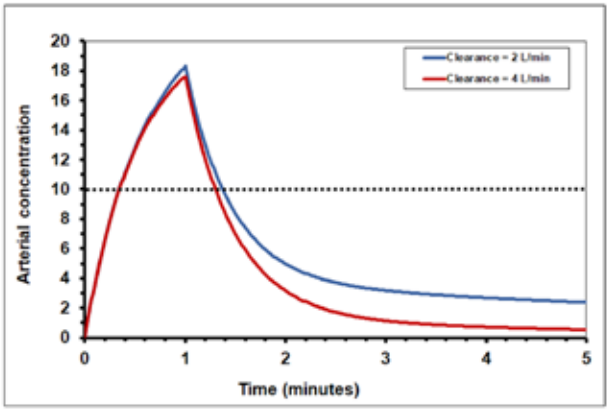

Figure 6. Effect of doubling the clearance while keeping the cardiac output constant

Dose: 100 mg administered during 60 s.
Patient parameters: CO = 5 L.min^{-1}; Volumes of distribution: Vlung = 2.5 L; Vbody 15 L; Clearance 2 L.min^{-1} & 4 L.min^{-1}

intravenous injection, variation of body size and clearance ***per se*** do not exert much influence on the arterial concentration-time profile.

Example 5

Influence of both increased body size and cardiac output on arterial drug concentrations: application of Forbes & Welle's dose adjustment equation.[3]

The somewhat unintuitive finding in Example 3 leads to the hypothesis that adjusting the induction dose for obese patients should rather be based on the known fact that obesity is accompanied by increased resting cardiac outputs.[17] De Simone and co-workers derived an allometric equation to predict cardiac output from TBW.[18]

*Cardiac output (L.min^{-1})=235*TBW^0.71*

Figure 7 illustrates injection of our hypothetical induction agent, 100 mg during one minute, to two patients, weighing 75 kg and 150 kg, each 1.75 m tall. The obese patient is assigned an increased cardiac output from the normal 5 L.min^{-1} to 8.2 L.min^{-1}, calculated using the above equation and the volume of distribution is increased from 15 L to 30 L. The result is as expected: the arterial drug concentration profile of the obese patient is generally lower and smaller. We may now investigate whether the dosing weight adjustment equation of Forbes & Welle[3] is actually compensating for the obese patient's increased resting cardiac output.

In the case of the obese patient:

Adjusted body mass for dosing=IBM+(0.4(TBW-IBM))=104.5 kg*

where *IBM* = ideal body mass which is calculated as follows:

IBM=24.2 height ^2=74.1 kg*

(Assuming an ideal BMI of 24.2 kg/m^2)

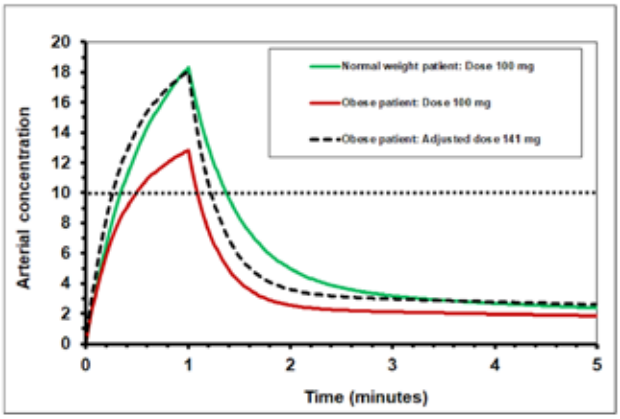

Figure 7. Application of the adjusted dosing weight equation of Forbes & Welle to an obese patient.

Simulation of the concentration-time courses after injecting 100 mg of the hypothetical induction agent during one minute into a normal-weight patient and into an obese patient. The stippled plot depicts the result after an adjusted dose of 141 mg
Normal weight patient: TBW 75 kg; Height 1.75 m; Cardiac output 5 L.min^{-1}; Clearance 2 L.min^{-1}; Vlung 2.5 L; Vbody 15 L.
Obese patient: TBW 150 kg; Height 1.75 m; Cardiac output 8.2 L.min^{-1}; Clearance 2 L.min^{-1}; Vlung 2.5 L; Vbody 30 L.

The standard dose to the normal weight patient was 1.3 mg.kg^{-1}. Applying this dose to the adjusted body mass of 104.5 kg results in a dose of 141 mg to be administered to the obese patient. The resulting stippled plot in Figure 7 is almost identical to the drug concentration-

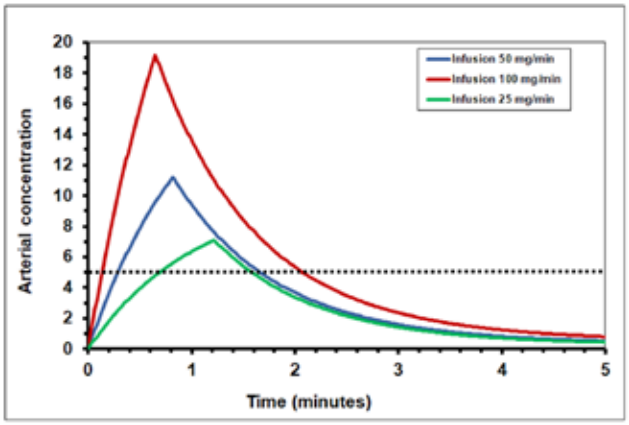

Figure 8. Simulation of induction of anaesthesia in a patient with a low cardiac output and increased sensitivity to the hypnotic effects of the hypothetical anaesthetic drug: titration to loss of consciousness by means of different infusion rates

Patient parameters: CO = 2.5 L.min^{-1}; Volumes of distribution: Vlung = 2.5 L; Vbody 15 L; Clearance 2 L.min^{-1}.
Drug is administered at a constant infusion rate until loss of consciousness. It is assumed that the time taken for drug concentration to equilibrate between the arterial blood and the effect site is 30 seconds. The slower infusion rates result in longer times to loss of consciousness and lower peak concentrations. The dotted line depicts the effect-site concentration at which loss of consciousness occurs.

time profile of a dose of 100 mg administered to the normal-weight patient. We may perhaps hypothesize that the adjusted dosing mass is really adjusting for the increased cardiac outputs of obese patients.

Example 6

Titration of to the point of loss of consciousness:

Patients who may have low cardiac outputs and additionally, a low threshold concentration for loss of consciousness (e.g. hypovolaemia; elderly, frail patients) present a challenge to anaesthetists who prudently induce anaesthesia by slow intravenous injection. The following simulation demonstrates the dose-sparing effect of such an approach. Figure 8 depicts induction of such a patient by three different constant-rate infusions until the point of loss of consciousness. It is assumed for the hypothetical drug that there is a 30 second delay for transfer from the arterial circulation to the effect site and that the threshold for loss of consciousness is five concentration units. The most rapid infusion (100 mg.min^{-1}) requires the highest dose and produces a rapid loss of consciousness at a cost of a large overshoot. The slower infusion rates progressively prolong the times to loss of consciousness with accompanying smaller doses (Table 1).

Table 1: Results of titration to effect by three different infusion rates

Infusion rate (mg.min^{-1})	Time to loss of consciousness (min)	Total dose (mg)	Peak concentration (concentration units)
100	0.65	65	19
50	0.82	41	11
25	1.22	30.5	7

It should be noted that not all obese patients have healthy hearts and increased cardiac outputs. Certain morbidly obese patients have comorbidities including obesity cardiopathy[17] that predispose to left ventricular dysfunction as well as pulmonary hypertension and cardiac failure. Ill-considered application of the adjusted dosing weight equation of Forbes and Welle[3] may result in unexpected adverse effects.

These simulations have several weaknesses. Firstly, the model does not predict cerebral blood flow and effect site concentrations as has been done with regard to both sheep[11,19-23] and humans.[12] Secondly, it would have been useful to specifically simulate the kinetics of propofol, the drug that is most commonly employed for anaesthetic induction, as has been demonstrated by Upton and Ludbrook[9,12,19-22]. Nevertheless, this simplified recirculatory model, simulating injection of drug somewhat similar to propofol, adequately demonstrates the basic principles of front-end kinetics that are in accordance with more sophisticated models. The model is also consistent with previous studies that call attention to the influence of cardiac output and the speed of injection on induction of anaesthesia,[10,16,24-28]

JF Coetzee

Department of Anaesthesiology and Critical Care, Faculty of Medicine and Health Sciences,Stellenbosch University

References

1. Krejcie TC, Avram MJ. What determines anesthetic induction dose? It's the front-end kinetics, doctor! Anesth Analg. 1999;89(3):541-4.
2. Wulfsohn NL, Joshi CW. Thiopentone dosage based on lean body mass. Br J Anaesth. Jun 1969;41(6):516-21.
3. Forbes GB, Welle SL. Lean body mass in obesity. Int J Obes. 1983;7(2):99-107.
4. Box GEP, Draper NR. Empirical Model-Building and Response Surfaces: John Wiley Inc.; 1987.
5. Ludbrook GL, Upton RN. Determinants of drug onset. Curr Opin Anaesthesiol. 2002;15(4):409-14.
6. Dawidowicz AL, Fornal E, Mardarowicz M, Fijalkowska A. The role of human lungs in the biotransformation of propofol. Anesthesiology. 2000;93(4):992-7.
7. He YL, Ueyama H, Tashiro C, Mashimo T, Yoshiya I. Pulmonary disposition of propofol in surgical patients. Anesthesiology. 2000;93(4):986-91.
8. Kuipers JA, Boer F, Olieman W, Burm AG, Bovill JG. First-pass lung uptake and pulmonary clearance of propofol: assessment with a recirculatory indocyanine green pharmacokinetic model. Anesthesiology. 1999;91(6):1780-7.
9. Upton RN, Ludbrook GL, Grant C, Martinez AM. Cardiac output is a determinant of the initial concentrations of propofol after short-infusion administration. Anesth Analg. 1999;89(3):545-52.
10. Adachi YU, Watanabe K, Higuchi H, Satoh T. The determinants of propofol induction of anesthesia dose. Anesth Analg. 2001;92(3):656-61.
11. Upton RN, Ludbrook GL, Grant C, Doolette DJ. The effect of altered cerebral blood flow on the cerebral kinetics of thiopental and propofol in sheep. Anesthesiology. 2000;93(4):1085-94.
12. Upton RN, Ludbrook G. A physiologically based, recirculatory model of the kinetics and dynamics of propofol in man. Anesthesiology. 2005;103(2):344-52.
13. Upton RN, Ludbrook GL. A physiological model of induction of anaesthesia with propofol in sheep. 1. Structure and estimation of variables. Br J Anaesth. Oct 1997;79(4):497-504.
14. Upton RN, Ludbrook GL. A model of the kinetics and dynamics of induction of anaesthesia in sheep: variable estimation for thiopental and comparison with propofol. Br J Anaesth. Jun 1999;82(6):890-9.
15. Upton RN. The two-compartment recirculatory pharmacokinetic model--an introduction to recirculatory pharmacokinetic concepts. Br J Anaesth. Apr 2004;92(4):475-84.
16. Zheng D, Upton RN, Martinez AM, Grant C, Ludbrook GL. The influence of the bolus injection rate of propofol on its cardiovascular effects and peak blood concentrations in sheep. Anesth Analg. May 1998;86(5):1109-15.
17. Alpert MA, Karthikeyan K, Abdullah O, Ghadban R. Obesity and Cardiac Remodeling in Adults: Mechanisms and Clinical Implications. Progress in cardiovascular diseases. Jul - Aug 2018;61(2):114-23.
18. de Simone G, Devereux RB, Daniels SR, Mureddu G, Roman MJ, Kimball TR, et al. Stroke volume and cardiac output in normotensive children and adults. Assessment of relations with body size and impact of overweight. Circulation. 1 Apr 1997;95(7):1837-43.
19. Ludbrook GL, Upton RN. A physiological model of induction of anaesthesia with propofol in sheep. 2. Model analysis and implications for dose requirements. Br J Anaesth. 1997;79(4):505-13.
20. Ludbrook GL, Upton RN, Grant C, Gray EC. Brain and blood concentrations of propofol after rapid intravenous injection in sheep,

and their relationships to cerebral effects. Anaesth Intensive Care. Aug 1996;24(4):445-52.
21. Ludbrook GL, Upton RN, Grant C, Martinez A. The effect of rate of administration on brain concentrations of propofol in sheep. Anesth Analg. Jun 1998;86(6):1301-6.
22. Ludbrook GL, Upton RN, Grant C, Martinez A. A compartmental analysis of the pharmacokinetics of propofol in sheep. J Pharmacokinet Biopharm. Jun 1999;27(3):329-38.
23. Upton RN, Ludbrook GL, Grant C. The cerebral and systemic kinetics of thiopentone and propofol in halothane anaesthetized sheep. Anaesth Intensive Care. 2001;29(2):117-23.
24. Goodman NW, Black AM. Rate of injection of propofol for induction of anesthesia. Anesth Analg. 1992;74(6):938-9.
25. Ingrande J, Brodsky JB, Lemmens HJ. Lean body weight scalar for the anesthetic induction dose of propofol in morbidly obese subjects. Anesth Analg. Jul 2011;113(1):57-62.
26. Peacock JE, Lewis RP, Reilly CS, Nimmo WS. Effect of different rates of infusion of propofol for induction of anaesthesia in elderly patients. Br J Anaesth. Sep 1990;65(3):346-52.
27. Peacock JE, Spiers SP, McLauchlan GA, Edmondson WC, Berthoud M, Reilly CS. Infusion of propofol to identify smallest effective doses for induction of anaesthesia in young and elderly patients. Br J Anaesth. Oct 1992;69(4):363-7.
28. Stokes DN, Hutton P. Rate-dependent induction phenomena with propofol: implications for the relative potency of intravenous anesthetics. Anesth Analg. 1991;72(5):578-83.