Hot air or full steam ahead? An empirical pharmacokinetic model of potent inhalational agents

Potent inhalational agents were the first drugs used in general anaesthesia, approximately 150 yr ago. Before the introduction of the calibrated vaporizer they were introduced into the breathing system by bolus injection, much like our current practice with most intravenous anaesthetic drugs. Dose size (ml of fluid) and interdose intervals were determined by the clinician’s experience and the observed patient response. The calibrated vaporizer did away with these imprecise methods. It enabled the anaesthetist to precisely and deliberately alter the concentration of anaesthetic released into the fresh gas flow. With a calibrated vaporizer, the anaesthetist needed only a rough idea about the time constants influencing the equilibration between the inspired gas and the anaesthetic effect, and could directly dial in a partial pressure (concentration) and establish the desired ‘depth of anaesthesia’. No fancy mathematics were needed. With the availability of breath-to-breath gas analysers, which have been a mainstay of any modern anaesthesia workstation since the late 1980s, the availability of end-expiratory (alveolar) concentrations did away with the guesswork about most time constants. Alveolar (presumably arterial) partial pressure is one time constant short of the ‘real stuff’, the concentration in the brain. This time constant, called $k_{eq}$, has been determined for isoflurane, sevoflurane (both 0.29 ± 0.04 min$^{-1}$) and desflurane (0.61 ± 0.11 min$^{-1}$) using the 95% spectral edge of the EEG power spectrum as an endpoint.$^1$ The corresponding equilibration half-times amount to 2.4 min for both isoflurane and sevoflurane and 1.1 min for desflurane, implying fast equilibration between arterial and cerebral concentrations. The clinical anaesthetist therefore knows the actual partial pressure at the effect site (concentration) quite well, a situation that can never be achieved for injectable anaesthetics. So why do the pharmacokinetics of volatile anaesthetics volatile anaesthetics at all?

First, we have to be able to characterize the pharmacokinetic behaviour of new volatile agents. Second, the availability of several agents necessitates comparison of their pharmacokinetic properties in order to rationally select the best agent for a certain surgical procedure. Third, since every individual is unique, we need to identify the characteristics (e.g. weight, age and, gender) that predict individual deviation from ‘standard’ pharmacokinetics. Physiological flow- and partition-based models are entirely adequate for the characterization of a new agent and the type of simulation required for rational drug selection.$^{1,2}$ However, physiological models are relatively complex. Additionally, it is impossible to fit all parameters by observing the time course of alveolar ventilation, and the fraction inspired and fraction exhaled, as available from clinical data. Thus, physiological models are not well suited for the analysis of partial pressure versus time curves obtained in a clinical setting. For this task, a parsimonious empirical polyeponential model similar to those used to describe the concentration time course of injectable drugs would be preferable.

In this issue of the British Journal of Anaesthesia, Rietbrock and colleagues describe a methodology for developing parsimonious empirical models from routine clinical data.$^3$ In an accompanying companion manuscript, Wissing and colleagues describe the details of such models for three commonly used inhaled anaesthetics: isoflurane, sevoflurane, and desflurane.$^4$ Application of these models to vast numbers of patients undergoing general anaesthesia with potent volatile anaesthetics will enable researchers to establish databases containing hundreds of observation units and to perform covariate analyses from routine clinical data, the dream of every population pharmacokineticist. Highly useful models can be developed by combining Wissing’s approach with patient covariates (e.g. age, height and weight), and measures of alveolar ventilation, administered concentration, exhaled concentration and the corresponding times. In Wissing’s study of 48 patients, the type of procedure and the patient population were quite homogeneous, resulting in a homogeneous anaesthetic time course. Furthermore, at the end of their observations it appears that 76% of the desflurane, 90% of the isoflurane, and 91% of the sevoflurane remained in the body. These are conspicuously high values compared with accepted values for conventional pharmacokinetic analysis of intravenously administered drugs. Therefore we suspected that the...
model predictions would only be similar to those of a physiological model at and below a duration of administration of 2 h, and suspected that the model might mispredict concentrations during the wash-out after a longer duration of anaesthesia.

We decided to do a little stress testing on our own. We implemented the pharmacokinetic model with the respective parameter sets by Wissing and colleagues for each agent in NONMEM. Then we simulated the uptake behaviour administering 1 MAC inspired and the wash-out behaviour after inhalation of 1 MAC inspired for 1 h, 2 h, 4 h, and 12 h for each volatile anaesthetic. All simulation results were displayed graphically as wash-in/wash-out curves.

For comparison, we repeated all simulations with GasMan, a commercially available simulation program written by James Philip, MD. GasMan is based on a physiological model of uptake and distribution of volatile anaesthetics. Since this program does not allow data export to a spreadsheet for entire wash-out curves, we could only compare single-point GasMan predictions with the wash-in/wash-out curves mentioned above. Since the wash-in and wash-out behaviours of potent volatile anaesthetics differ considerably, these points were chosen on the basis of reaching a certain concentration predicted by GasMan rather than using fixed times regardless of agent.

For wash-in, we compared the end-expiratory (alveolar) concentrations at 0.3, 0.5 and 0.9 MAC in the alveolar space. For wash-out, we compared end expiratory concentrations at the time of termination of administration (1 h, 2 h, 4 h, and 12 h), at 0.5 and 0.33 MAC alveolar concentrations and 0.5, 0.33, 0.2 MAC concentrations in the so-called vessel-rich group (VRG). This was done to get comparisons at clinically relevant concentration time points. The VRG resembles the effect site most closely in the physiological model implemented in GasMan. A MAC value of 0.2 in the VRG is somewhat lower than MAC awake and should correspond to extubation in almost all patients. Comparisons at lower concentrations were deliberately omitted since they have little clinical relevance. The wash-in predictions are displayed in Figure 1, graph A. Graphs B, C, D, and E show the wash-out behaviour after administration of anaesthetic vapour for 1, 2, 4, and 12 h, respectively.

Before to accepting GasMan as the gold standard for this comparison, we had to test the predictions of GasMan against the empirical model under conditions resembling those of the study. Models should predict correctly at or below actual sampling times under conditions used for their development. Discrepancies here would have invalidated the entire approach. In our opinion, as can be seen in Figure 1, graphs A, B, and C, there is sufficient agreement between GasMan and the parsimonious model to accept the testing conditions. With the exception of the earliest assessment (fractional expired of 0.33 MAC), the predictions of wash-in behaviour match the models well. The poor early prediction is probably the result of the inability of Wissing’s model to distinguish between the alveolar, arterial and vessel-rich compartments, which are lumped together into a virtual central compartment and, because of the absolute magnitude of error (1–2 min), are not critical. A similar error can also be seen in the early part of the 1 h and 2 h wash-out curves, and the explanation is probably the same.

We then examined the behaviour of the model for different anaesthetic conditions other than those in the

![Figure 1](image-url)

**Figure 1** Wash-in and wash-out of isoflurane, sevoflurane and desflurane as predicted by a physiological model (GasMan) and by the empirical polyexponential model reported by Wissing and colleagues. The symbols refer to predictions made by GasMan (○ isoflurane, ■ sevoflurane, ▲ desflurane); the curves are derived from pharmacokinetic simulations based on the parameter sets reported by Wissing (– isoflurane, --- sevoflurane, --- desflurane). (a) Wash-in more than 6 h. (b) Wash-out after breathing 1 MAC for 1 h. (c) Wash-out after breathing 1 MAC for 2 h. (d) Wash-out after breathing 1 MAC for 4 h. (e) Wash-out after breathing 1 MAC for 12 h.
original study. When comparing predictions after longer administration times, the correlation works surprisingly well for sevoflurane and desflurane, but breaks down for isoflurane. Wissing’s model predicts that patients would have a hard time to ever awaken from isoflurane anaesthesia of ≥4 h. How can we explain this peculiarity? Fundamentally, pharmacokinetics should not be extrapolated beyond the domain of the original research. This is particularly true for drugs with significant accumulation in fat, where short studies may mistake uptake into fat for systemic elimination, thereby underestimating the terminal elimination half-life. If one wants to predict pharmacokinetics for <4 h of anaesthetic administration, then the pharmacokinetics should be based upon ≥4 h of data.

In summary, the manuscript of Wissing and colleagues introduces a pharmacokinetic model of volatile anaesthetics that may be highly useful for covariate analysis and population pharmacokinetics. We are looking forward to seeing this model used in follow-up studies to refine the parameter sets with anaesthetics of longer duration. Additionally, we are looking forward to seeing these models used in population analyses to characterize mean pharmacokinetics, important patient covariates, and population-based simulations.

T. Bouillon
S. L. Shafer

1 Resident, Department of Anesthesiology and Critical Care Medicine, University of Bonn, Bonn, Germany
2 Staff Anaesthetist, Palo Alto VA Health Care System, Associate Professor of Anesthesia, Stanford University School of Medicine, Stanford, California, USA

References
5 Dean JM. GasMan. MD Comput 1986; 3(3): 537