Author's response to reviews

Title: Mathematical Method to Build an Empirical Model for Inhaled Anesthetic Agent Wash-In.

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Author's response to reviews: see over
Reviewer #2
Major compulsory revisions
8% desflurane: I believe there are circumstances where 8% may not be sufficient. Some patients are quite tolerant, and the published average MAC value of 6%, of course, only deals with 50% of the population. Further, the use of induction agents with a short blood:brain equilibrium half time (e.g., thiopentone) can potentially risk a shortfall in anaesthesia depth. However, for the purposes of this initial analysis, and in recognition that later work may explore other concentrations, 8% is a reasonable choice. If the authors are considering other concentrations in later work this might be briefly raised in the Discussion.

The manuscript states that the model should not be extrapolated beyond the restraints within which was developed. We agree that some patients might need concentrations outside the range modeled. The following comment has been added to the discussion section (new paragraph): "Other limitations may exist. ... Also, the model is limited to a maximum end-expired concentration of 8% - higher concentrations might be needed in some patients, but this comes at a risk of irritating the airway."

Patient numbers: Whilst formal Power analysis is not always required for studies, I imagine that approximate numbers per group in Part 2 were based, for example, on experience from Part 1. If so, this should be mentioned specifically.

We agree power analysis is not required in this study.

Wash in time: This has been effectively addressed.

Circuit details: This has been effectively addressed

Ventilation rate: It is correct that standardization of ventilation has allowed other sources which impact on the model to be identified. However, spontaneous ventilation seems likely to be a relevant variable in clinical practice. This would be well dealt with by a comment in the new text in the Discussion which mentions other factors which might be important.

We agree spontaneous ventilation will complicate the issue, were it not for the sole fact that it makes getting reliable end-expired measurements very difficult when some degree of hypoventilation is present right after intravenous induction. This, by the way, is an issue for modern automated closed-loop end-tidal feedback system as well, e.g., the Zeus anesthesia machine (Dräger, Lübeck, Germany). The following paragraph has been added to the Discussion section (new paragraph): “Other limitations exist. The wash-in model may not be applicable when spontaneous ventilation is allowed immediately following intravenous induction of anesthesia, because the irregular and inconsistent breathing at that time does not allow the acquisition of reliable end-expired concentrations. This also is an issue for modern anesthesia machines that use automated closed-loop end-tidal feedback administration of inhaled agents.”

Population variability: This has been addressed effectively.

Pharmacodynamics: The risk of airway irritation and rate of change of concentrations is
a real issue with desflurane with an unprotected airway. This has led to dissemination of
guidelines on aspects such as vaporiser dial settings at induction. This, to some degree,
overlaps the current work. Hence, although this study involved a protected airway, and,
as the authors point out, it is usually an obvious issue (at least to the experienced
anaesthetist), I believe it should at least rate some mention.

We agree. We believe limiting the rate of rise to a maximum of 8 % after 5 min addresses
this issue. The following has been added to the Discussion section (new paragraph):
“Also, the model is limited to a maximum end-expired concentration of 8% - higher
concentrations might be needed in some patients, but this comes at a risk of
irritating the airway.”

Minor essential revisions
These have largely been addressed.
Legend to Figure 4: This comment relates in fact to the legend for Figure 3.
This has been corrected.
There is also a missing ‘closed bracket’

Discretionary revisions
The author responses are fine.