Population Volume Kinetics in Volunteers: Comment

To the Editor:

I have read the article by Nyberg *et al.*[1] with interest, and would like to comment on their approach to model fluid volume kinetics.

The two-volume model they used is well known to become unstable if the plasma dilution time curve has a flat appearance postinfusion.[2] To prevent this problem, the customary procedure is to equalize the elimination to the urinary excretion. The authors quantified the excreted urine by weighing but did not use this information. Their choice resulted in an unstable model, which is evidenced by a coefficient of variation as large as 123% for the elimination rate constant (k_e). Recent articles using the same population kinetic model report a coefficient of variation for k_e of only 5% to 15%.[3–5]

The key result requires clarification. The study compared the plasma dilution in bled volunteers who did and did not receive isoflurane anesthesia. The Abstract says that the maximum plasma dilution was 35% higher, and that the area under the curve for the plasma dilution was 99% larger, in the group that received isoflurane anesthesia. However, the observed data plotted in figs. 6 and 7, as well as my own simulation based on table 1, show that the plasma dilution was similar between both groups and was even slightly lower among those who received isoflurane.

I still assume that the Abstract is correct because previous studies show that induction of epidural, spinal, or general anesthesia increase the plasma dilution resulting from infused crystalloid fluid. The magnitude of this dilution depends directly on the decrease in arterial pressure.[6–8] The reason is retarded distribution.[8] No excessive dilution occurs if the pressure is unchanged.[6,9] Nyberg *et al.* established arterial access and measured the pressure, but they did not consider the anesthesia-induced hypotension in their model.

Finally, the mean arterial pressure was the strongest predictor of k_e in a population volume kinetic analysis of 78 conscious and anesthetized humans receiving crystalloid fluid,[4] as well as in another cohort of anesthetized patients.[10] This potential covariate does not seem to have been considered either.

Competing Interests

The author declares no competing interests.

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Population Volume Kinetics in Volunteers: Reply

In Reply:

We thank Dr. Hahn for his excellent comments[1] and thorough interest in our study.[2] In this study, we tried to identify important covariates that could be used for designing future volume kinetic studies.

We acknowledge our study limitations. Namely, in the present study, imprecise urine data were obtained *via* bladder ultrasound resulting in an uncertainty in urinary output with regard to timing and volume. Thus, to not introduce bias, urine measurements were not incorporated in the modeling. We appreciate that this drawback potentially resulted in a less stable model with higher interindividual variability. In addition, the design of the study, the study population, and the low number of subjects[3] and observations could also result in higher estimated interindividual variability of the elimination rate constant (k_e) compared with previous studies.

In our study, mean arterial pressure was strongly associated with the subject's state (*e.g.*, being either anesthetized or awake). Including highly associated covariates in a stepwise covariate model building procedure will result in high imprecision and instability in the covariate analysis.[4,5] Therefore, we chose to only include the subject's state as covariate. Additionally, because the subject's state would likely be known before any intervention, this covariate could be easier to apply when designing future studies. Consequently, because the correlation between mean arterial pressure and the subject's state is high, we do not believe that including anesthetized-induced hypotension would improve the model fit but instead would likely dilute the impact of the subject's state covariate.

We have thoroughly reexamined table 1 in the original manuscript[2] and confirm that the estimates from the model building are correct. Thus, the model (represented by table 1)[2] could be used for extrapolation and design of future studies. There is, however, a typographical error in the simulations, switching the central-to-peripheral transfer rate constant to the peripheral-to-central transfer rate constant when simulating the subject's state effect. This error would impact the simulations for the subject's state (anesthetized or awake) in the opposite direction (*i.e.*, resulting in a slightly lower area under the curve and maximum plasma dilution with anesthetized subjects compared with awake subjects). We thank Dr. Hahn for detecting this error.

Competing Interests

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