Simplified Estimation of the Volume of Distribution at Peak Effect for Remifentanil

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Pharmacokinetic mammillary models is described as a central compartment distributing a medications to peripheral compartments and is characterized by volumes of distributions of the compartments as well as their associated clearances. In addition, the volume of distribution at peak effect (V_{dpe}) [1], is a theoretical volume that relates the pharmacodynamics of the model after a bolus:

Loading dose = $C_{epe} * V_{dpe}$

Where C_{epe} is the plasma concentration of the drug at peak effect.

For a given patient, the ratio V_{dpe} to the volume of distribution of the central compartment (V_1) is constant and equal to the ratio between the initial plasma concentration (C_0) after a bolus to C_{epe}. This ratio can be determined through simulation by directly calculating C_0/C_{epe} or through non-trivial arithmetic computations.

We propose an alternative approach to determining the ratio through parameter estimation which we apply to Minto's remifentanil model [2]. This approach results in a simple method to calculate the ratio and thus V_{dpe}.

Methods: Using Matlab (R2016b), the C_{epe} along with the C_0 was determined for simulated patient between the ages of 20 and 80 in increments of 5 years, weights of 40 and 120 kg in increments of 5, heights of 120 and 220 cm in increments of 10 cm, as well as both genders. Patients with lean body mass (LBM) below 20 kg were excluded from further analysis. Age, weight, height, gender, LBM, volumes of distribution (V_1, V_2 and V_3), clearances (Cl_1, Cl_2, Cl_3), ke0 and the ratio C_0/C_{epe} were tabulated. Using R (version 3.3.2), a linear model was fit as a function of the ratio in an incremental fashion; the model performances were assessed using both Akaike information criterion (AIC) and Bayesian information criterion (BIC).

Results: 4862 patients were simulated of which 247 were excluded due to a low LBM. The distribution of the calculated ratio is shown in Figure 1. The ratio, as a function of V_1 is shown in Figure 2. Table 1 shows a series of fitted model as well as the calculated AIC and BIC. The optimal model is determined as:

$$\text{Ratio} = 1.35 + 8.9/V_1 - 0.669/Cl_1 - 4.28/(V_1*Cl_1) - 0.154/Cl_2 + 2.24/V_2 - 1.22/\text{LBM} + 0.411/\text{ke0}$$

Figure 3 shows the predicted ratio against the residual errors for the last model

Conclusion: By calculating the ratio with the above equation, one can effectively approximate the V_{dpe} with minimal computational power. The application of this estimate is demonstrated in an accompanying abstract. Whether this method can be extrapolated to other pharmacokinetic models has yet to be determined.

References

1. Flood P et al. Stoeting's Pharmacology & Physiology in Anesthetic Practice, 5th ed, Wolters Kluwer Health, p 31-32
2. Minto CF et al. Anesthesiology 1997: 86(1):10-23.
3. R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/

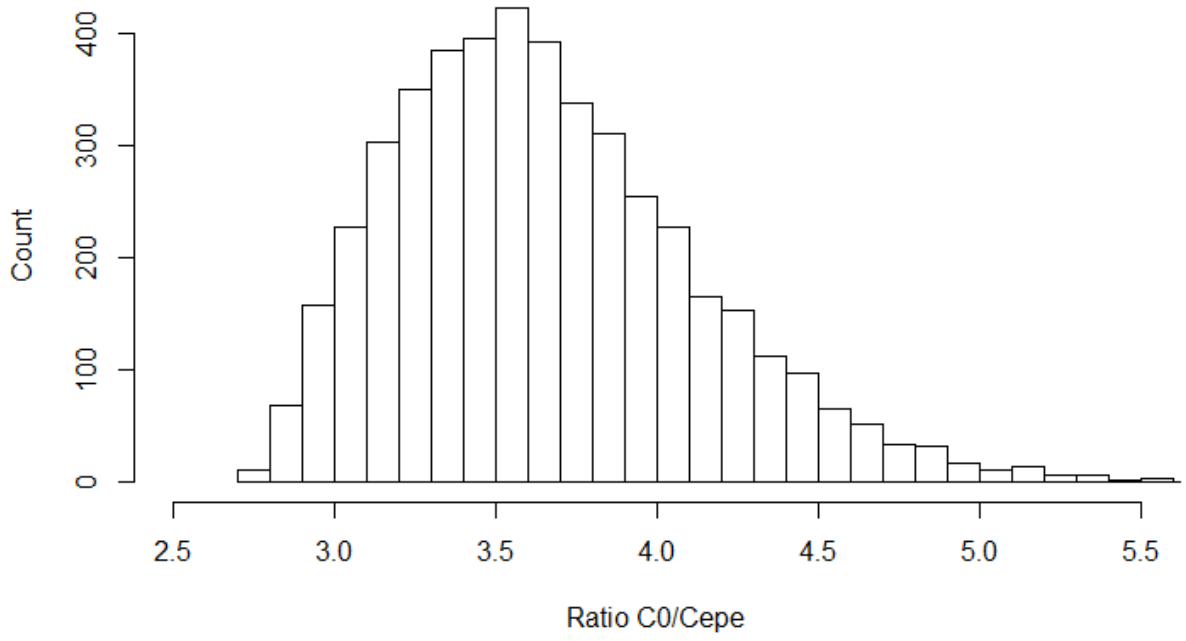

Figure 1: Distribution of the calculated ratio of the initial plasma concentration (C_0) to the plasma concentration of the drug at peak effect (C_{epe}) is shown for all simulated patients.

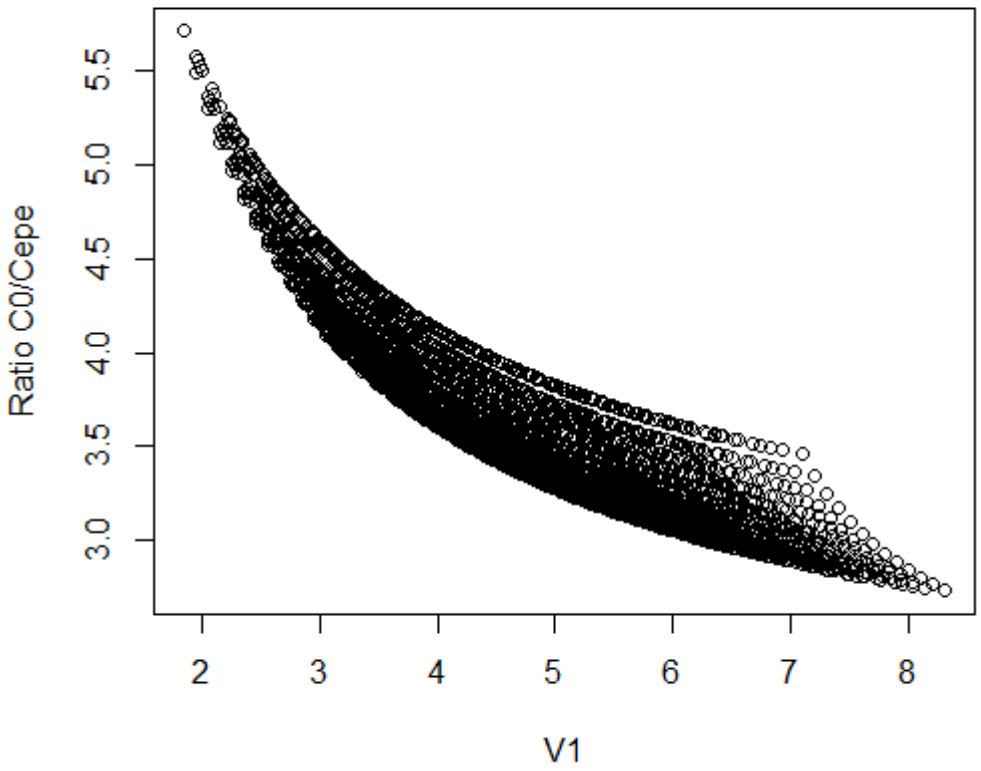

Figure 2: Calculated ratio as a function of V_1 for all simulated patients

		AIC	BIC
Model 1:	$1/Cl_1$	-9983.8	-9964.4
Model 2:	Model 1 + $1/V_1$	-15318	-15344
Model 3:	Model 2 + $1/(V1*Cl_1)$	-15453	-15421
Model 4:	Model 3 + $1/Cl_2$	-26943	-26905
Model 5:	Model 4 + $1/V_2$	-31313	-31268
Model 6:	Model 5 + 1/LBM	-53299	-53248
Model 7:	Model 6 + 1/ke0	-56001	-55943

Table 1: Performance of fitted models to estimate the calculated ratio as determined by AIC and BIC

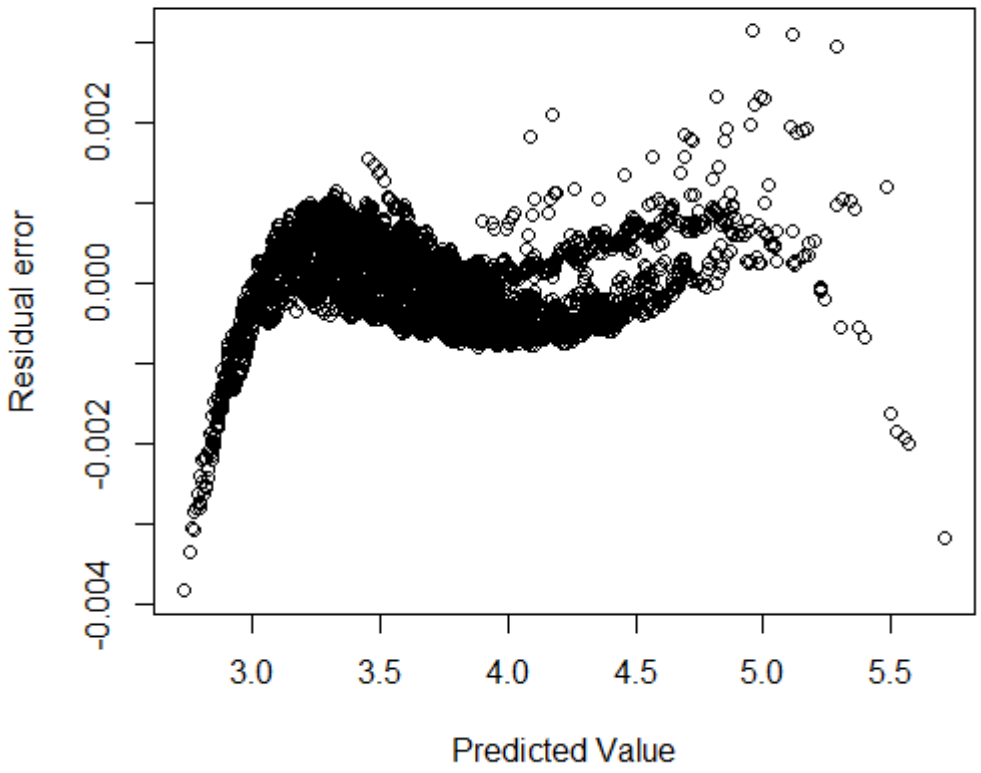

Figure 3: Scatter plot for the predicted ratio of the final model against each estimate's residual error