**Supplementary Digital Content 1**

**KINETICS OF RINGER´S SOLUTION IN DEHYDRATION AND HEMORRHAGE**

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Kinetic base model

Differential equations to the kinetic model are:

 d*v*c /dt = *R*o – *k*10 (*v*c – *V*c) – *k*12 (*v*c – *V*c) + *k*21 (*v*t – *V*t) (Eqn. 1)

 d*v*t /dt = *k*12 (*v*c – *V*c) – *k*21 (*v*t – *V*t) (Eqn. 2)

where symbols in capital letters denote baseline values. Eqn. 1 and 2 are illustrated schematically in Fig. 1A. Fluid is infused at the rate *R*o into the plasma, *V*c, which then is expanded to *v*c. Fluid is distributed to an extravascular space, *V*t, which is then expanded to *v*t, at a rate proportional with a constant *k*12 to the plasma volume expansion, which is written *v*c – *V*c. The flow back from the extra- to the intravascular space is proportional by a rate constant *k*21 to the expansion of the extravascular space, which is written *v*t – *V*t  [7, 8]. Elimination of fluid occurs by urinary excretion, which flow is proportional by a rate constant *k*10 to the expansion of the intravascular space.

The Hb-derived fractional plasma dilution was used to indicate the volume expansion of *V*c resulting from the infusion. Hence:

 (*v*c – *V*c) / *V*c = [(Hb / hb) – 1)] / (1 – Hematocrit) (Eqn. 3)

The relationships between urinary excretion, *k*10, and the half-life of the infused fluid (T1/2) were obtained as follows (AUC = area under the curve):

 *k*10 =urinary excretion / AUC for (*v*c–*V*c) (Eqn. 4)

 T1/2 = ln 2 / *k*10 (Eqn. 5)

Covariate effects

Modification of the fixed parameters (*V*c, *k*12, *k*21, and *k*10) by considering individual-specific covariates improves the ability of the kinetic model to predict the measured plasma dilution and urinary excretion (cf. Fig. B-C, and Fig. E-F).

The decision to include a covariate was based on a reduction in the log likelihood (-2 LL) for the curve-fit of > 3.8 points, which represents *P*< 0.05, and on significance according to the Phoenix software. The confidence interval for the covariate should also be statistically significant (not include 1.0) and the coefficient of variation (i.e., the inter-individual variability) should be < 50%. The First Order Conditional Estimation search routine of Lindstrom-Bates (FOCE LB) and the additive model for the within-subject variability were used in all runs, as preliminary testing with other search routines (FOCE ELS, Laplacian) did not further reduce -2 LL.

The statistical significance for the covariates in Table 2 was *P*< 0.001, except for the effect of hemorrhage on *k*10 and MAP on *k*12 (*P*< 0.01). Finally, the transformation of the diagonal to the full block model, which also considers correlations between the random effects, improved the curve fit by *P*< 0.01.

Because hemorrhage and dehydration could be zero, the linear covariate model was used to describe the influences of hemorrhage and dehydration on the fixed kinetic parameters. Taking the best estimates for covariates from Table 2, the rate constant *k*21 in an individual patient (ind) is expressed as follows:

 *k*21 ind  = tv *k*21 (1 + 1.34 (Hypovolemia ind – mean Hypovolemia) (1 + 1.10 (Dehydration ind – mean Dehydration))

where tv is the "typical value" of *k*21 (i.e., when covariates attain the mean values for all experiments). The mean hemorrhage for all experiments was 0.20 L, dehydration was 0.50 L, MAP was 81.7 mmHg, and the mean infusion rate was 50 mL/min.

A power model best described the influence of MAP on *k*12 and of the rate of the Ringer infusion *V*c. Hence, *V*c in an individual patient (ind) is expressed as follows:

*V*c ind  = tv *V*c (infusion rate ind /mean Infusion rate) 0.21 (1 – 0.32 (Hemorrhage ind – mean Hemorrhage))

Simulations

Computer simulations using MATLAB R2013b (Math Works, Inc., Natick, MA) were used to illustrate the influence of the key covariates on the distribution of fluid between plasma (*V*c) and the extravascular fluid space (*V*t). The best estimates of the model parameters and their covariates (if any) were entered into the solutions (solved by optODE) of Eqn. 1 and Eqn. 2.