Plasma dilution and the rate of infusion of Ringer’s solution

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Summary
Changes in the volume of the fluid space expanded by i.v. infusion of Ringer’s acetate solution have been analysed recently using mathematical models. Data obtained by such analyses allow simulation of the dilution of the plasma volume during infusion of the solution at different rates. To obtain basic kinetic data for such simulations, the plasma dilution–time curves were measured during and after i.v. infusion of Ringer’s solution 25 ml kg⁻¹ over 30 min in 15 healthy male volunteers (mean age 31 yr) and over 30, 45 and 80 min in six females (mean age 32 yr). Based on these experiments, nomograms were constructed from which the rate of infusion of Ringer’s solution and the infusion time required to obtain a defined plasma dilution in both males and females can be estimated together with the infusion rate needed to maintain the dilution at the level reached. (Br. J. Anaesth. 1997; 79: 64–67).

Key words

I.v. volume loading is frequently carried out by anaesthetists. The fluid load is usually given at a high rate to prevent circulatory instability before induction of spinal and extradural anaesthesia. Many anaesthetists also give a fluid load before general anaesthesia. However, the infusion rate required to rapidly expand the blood volume to a predetermined degree is largely unknown.

We have used a recently developed pharmacokinetic model adapted for body fluid spaces¹² to simulate the infusion rates required to effectively obtain and maintain a defined dilution of the plasma volume with Ringer’s solution in healthy males and females. Our purpose was to open up the possibility of optimizing i.v. fluid therapy in clinical practice by setting a predetermined dilution of the plasma volume as the therapeutic goal. Volume expansion is the product of this dilution and baseline plasma volume. The kinetic data required for the simulations were obtained from volunteer experiments in which Ringer’s acetate solution was infused i.v.

Subjects and methods
MALE VOLUNTEERS
We studied 15 healthy men, aged 25–36 yr (mean 31 yr), weighing 65–100 kg (mean 78 kg). The study was approved by the local Ethics Committee and informed consent of all subjects was obtained.

Ringer’s acetate solution 25 ml kg⁻¹ (Pharmacia, Uppsala, Sweden) was given at a constant rate over 30 min via one or several infusion pumps (IVAC 560, San Diego, CA, USA). The ionic content of this solution is (in mmol litre⁻¹): Na⁺ 130, K⁺ 4, Ca²⁺ 2, Mg²⁺ 1, acetate 30 and Cl⁻ 110. Before any fluid was given, a cannula was placed in the cubital vein of each arm for blood sampling and infusion of fluid.

Venous blood was collected every 5 min for 3 h and blood haemoglobin concentration was measured using a Technicon H·2 (Bayer, Tarrytown, NY, USA) with a coefficient of variation of 1.3%. The first sample was obtained in duplicate and the mean value was used in calculations.

FEMALE VOLUNTEERS
Six female volunteers, aged 23–46 yr (mean 32 yr), body weight 50–75 kg (mean 60 kg) received 24 infusions of Ringer’s solution. Under the same basic conditions as in the males, the volunteers were given, in random order and at intervals of at least 1 day, 25 ml kg⁻¹ of this fluid over 30, 45 and 80 min.

Samples for measuring blood haemoglobin concentration on a Coulter Counter STKS (Counter Electronics, Hialeah, Fla., USA) were obtained from the venous cannula not used for infusion, before infusion, every 10 min during infusion and at 0, 5, 10, 15, 20, 25, 30, 60, 80, 100 and 120 min after infusion. The first haemoglobin sample in the series was obtained in duplicate and the mean was used in calculations.

In females, Ringer’s solution was also infused very rapidly (100 ml min⁻¹ over 15 min). However, these results were not used as the infusions caused symptoms, and therefore could not be used clinically. The results also differed from those at the slower infusion rates, which indicates that a different state exists when Ringer’s solution is infused very rapidly. Details of these experiments are given elsewhere.²

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DATA ANALYSIS

Data on haemoglobin concentrations were analysed according to the one-volume fluid space (VOFS1) model which assumes that the infused fluid is distributed in a single well-stirred body fluid space. Fluid is infused at a constant rate \( k_i \) and enters the body fluid space having the volume \( V \), which changes as a result of fluid leaving the space at a basal rate \( k_b \) and at a controlled rate \( k_c \) proportional to the deviation from the target value \( V \). Based on these assumptions, the following equation describes the volume change of the body fluid space expanded by the infusion:

\[
\frac{dV}{dt} = k_i - k_b - k_c (V - V')/V
\]

During (d) and after (a) infusion, the solution to this differential equation is:

\[
w_d(t) = \left[ (k_i - k_b)/k_c \right] \left( 1 - e^{-k_c t/V} \right), \quad 0 \leq t \leq t_i
\]

\[
w_d(t) = -k_b/k_c \left( 1 - e^{-k_b (t - t_i)}/V \right) + w_d(t_i) e^{-k_b (t - t_i)}/V
\]

where \( w_d(t) \) is the dilution \( (V(t) - V)/V \).

The random search method was chosen for the least-squares fitting procedure to obtain the best estimates of the unknown variables in the model \( (V' \) and \( k_c) \), whereas \( k_b \) (basal fluid loss) was set to 1 ml min\(^{-1}\).

Plasma dilution over time was simulated by setting these variables to the mean values for the respective groups of volunteers studied. For males, \( V \) was 6.61 litre (95% confidence interval 5.34–7.89 litre) and \( k_i \) 148 (95–201) ml min\(^{-1}\). For females, we used 4.09 (3.44–4.74) litre and 111 (79–142) ml min\(^{-1}\), respectively.

Simulations were performed in two steps, using Matlab version 4.2 (Math Works, Notich, MA, USA). The first step studied the infusion rate and infusion time required to obtain a definitive plasma dilution. The purpose of the second step was to maintain the dilution already obtained at a steady-state level (fig. 1). The required infusion rate is then dependent on the mode by which the infusion was given initially.

A two-volume fluid space model (VOFS2) has also been developed. In that model, the rate of volume equilibration between a primary and secondary fluid space is proportional to the difference in the relative deviation from the target value. Fitting the dilution–time curves to both VOFS1 and VOFS2 sometimes indicates that the latter model significantly reduces the mean square error. In particular, this occurs when urinary excretion in response to infusion is small. Only VOFS1 is used here because it is difficult to know, in the clinical setting, for which patient VOFS2 is statistically justified. However, we undertook simulations also with VOFS2 in order to evaluate the magnitude of the error inflicted by the fact that some infusions are described better by the two-volume model.

Results

The nomograms for men and women are shown in figures 2 and 3, respectively. In both cases, the first part of the fluid loading phase, when plasma dilution increased, was obtained from the left half of the nomogram. When the appropriate dilution is found, we trace the horizontal to the right half of the figure (along the same infusion rate line) to the line corresponding to the infusion time used. Thereafter, the steady-state infusion rate is given by the vertical correlation.

Consider that a male patient receives an infusion of Ringer’s solution at a rate of 30 ml min\(^{-1}\) for 30 min (900 ml), after which a steady-state dilution is desired. The left nomogram indicates that dilution of plasma volume is close to 10%. The infusion rate that leads to a steady state is 15 ml min\(^{-1}\) and is given in the right half of the nomogram.

An example of how dilution of plasma volume by 15% can be found and maintained is shown in figure 1.

The nomograms were based on the VOFS1 model despite the fact that VOFS2 was statistically justified in 10 of the 15 experiments in males and in eight of the 24 experiments in females. In males, however, the times required to reach any target dilution when VOFS2 was applied differed by only ±2 min from those indicated by our nomogram. This difference was somewhat greater in females. With VOFS2, a plasma dilution of 5–15% was reached 2–5 min faster than that indicated by our nomogram. At the extreme, this difference amounted to 7–15 min when
a low infusion rate was used to obtain a dilution of 20–25%.

Discussion

The purpose of carrying out fluid loading with Ringer’s solution is to increase plasma volume by haemodilution. A defined fluid load is usually given over a specific time without an end-point being specified. We suggest that dilution of blood would be a suitable end-point as the volume expansion effect of the fluid is believed to be an important therapeutic goal. We have outlined the possibilities and limitations of this practice in an experimental situation. The nomograms we have constructed allow estimation of the infusion rate and time required to both obtain and maintain a defined dilution of plasma volume. They show how alternative fluid regimens can be found, all of which lead to the same defined dilution of plasma volume.

Although the nomograms quantify what the anaesthetist intuitively knows and does, the computer simulations made us realize that marked haemodilution is difficult to obtain in healthy awake humans. For example, the infusion rate must be at least 50 ml min$^{-1}$ in a young man to yield a plasma dilution of 20%, which corresponds to an increase in blood volume of approximately 10%. Even at this high rate, the infusion has to continue for 40 min (and requires 2000 ml of fluid) to yield the desired dilution. In contrast, an infusion rate below 40 ml min$^{-1}$ is not capable of diluting plasma volume by 20%, regardless of how long the infusion is continued. When fluid is infused at a high rate, it does not matter if the simulation is based on VOFS1 or VOFS2.

The difficulty in achieving pronounced haemodilution can be explained in part by rapid elimination of fluid. In the volume kinetic model, urinary excretion is proportional to plasma dilution, an assumption which receives support from the overall good agreement between measured urine volume
and model-predicted urinary excretion. Furthermore, compliance of the vascular system for volume expansion may prevent excessive haemodilution. When the rate of infusion of Ringer’s solution is increased to 100 ml min\(^{-1}\), haemodilution no longer increases. At this point, compliance is probably lower in the circulation than in the interstitial fluid space, and further infused fluid accumulates there. In our model, such accumulation of fluid is noted as an increase in the expandable fluid space (\(V\)). One should note, however, that haemodilution increases further if the patient’s vascular status is changed, such as by extradural anaesthesia or blood loss. Therefore, the use of the nomograms derived in this study should be restricted to volume loading carried out before anaesthesia is induced. Furthermore, the volume kinetic data should not be extended to infusion rates higher than those used here.

The amount of fluid required for carrying out a fluid load can be estimated readily from the nomograms. Such calculations show that a fast infusion is more effective than a slow one. Imagine we wish to increase plasma volume by 10%, which corresponds to an increase in blood volume of 5%. In males, this can be achieved by infusing Ringer’s solution at a rate of either 50 ml min\(^{-1}\) for 15 min (750 ml) or 25 ml min\(^{-1}\) for 45 min (1125 ml). The second infusion regimen requires 50% more fluid than the first despite the fact that the same dilution is obtained.

Nomograms were constructed for males and females separately as there seems to be sex-related differences in volume kinetics. Body weight and elimination rate constant (\(k_r\)) for Ringer’s solution were 30% higher in males than in females and the size of the expandable fluid space (\(V\)) was 60% higher. These differences explain why marked dilution requires much higher infusion rates in men. Modest degrees of dilution, however, can be obtained by almost the same infusion rates as in women. The right parts of the nomograms (“maintain” dilution) are also similar for males and females, but one must remember that most infusion rates result in more pronounced dilution of plasma volume when Ringer’s acetate is given to females.

The difference in \(V\) between the sexes can probably be explained by the larger body weight and greater percentage of water in the extracellular space, which amounts to 200 ml kg\(^{-1}\) of body weight in men compared with 150 ml kg\(^{-1}\) in females. It is important to note, however, that our nomograms are not based on the size of the extracellular space but on the body fluid space that is actually expanded by Ringer’s solution (\(V\)). This fluid space is different from the volume in which the same fluid is distributed and usually amounts to about twice the plasma volume. The concept of an expandable fluid space is relevant to emergency medicine, trauma care, anaesthesia and surgery, as \(V\) indicates hydration of the body resulting from i.v. fluid therapy.

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**References**