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Kinetics of Isotonic and Hypertonic Plasma Volume Expanders

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Background: **Major differences in plasma volume expansion between infusion fluids are fairly well known, but there is a lack of methods that express their dynamic properties. Therefore, a closer description enabled by kinetic modeling is presented.**

Methods: **Ten healthy male volunteers received, on different occasions, a constant-rate intravenous infusion over 30 min consisting of 25 ml/kg of 0.9% saline, lactated Ringer's solution, acetated Ringer's solution, 5 ml/kg of 7.5% saline, or 3 ml/kg of 7.5% saline in 6% dextran. One-, two-, and three-volume kinetic models were fitted to the dilution of the total venous hemoglobin concentration over 240 min. Osmotic fluid shifts were considered when hypertonic fluid was infused.**

Results: **All fluids induced plasma dilution, which decreased exponentially after the infusions. The ratio of the area under the dilution-time curve and the infused fluid volume showed the following average plasma-dilution dose-effect (efficiency), using 0.9% saline as the reference (= 1): lactated Ringer's solution, 0.88; acetated Ringer's solution, 0.91; hypertonic saline, 3.97; and hypertonic saline in dextran, 7.22 ("area approach"). Another comparison, based on kinetic analysis and simulation, showed that the strength of the respective fluids to dilute the plasma by 20% within 30 min was 0.94, 0.97, 4.44, and 6.15 ("target dilution approach"). Between-subject variability was approximately half as high for the latter approach.**

Conclusions: **The relative efficiency of crystalloid infusion fluids differs depending on whether the entire dilution-time profile or only the maximum dilution is compared. Kinetic analysis and simulation is a useful tool for the study of such differences.**

THE administration of intravenous volume support is common practice during surgery and is indispensable in the management of many medical conditions.[1] However, fluids differ in volume-supportive effect because of a variable content of salt and colloid, which influences the distribution and elimination of the infused volume.[1–3] Commonly used crystalloid fluids include 0.9% saline, lactated Ringer's solution, and acetated Ringer's solution. Normal saline is often replaced by Ringer's solution to avoid hyperchloremic acidosis,[4] but the lactate or acetate used as buffer may alter the volume-supportive effect because of intrinsic vasodilating properties.[5,6] Among the hypertonic fluids, 7.5% is recommended for resuscitation by the US Army,[7] and 7.5% saline with dextran is registered for prehospital use in the European Union.[8]

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The aim of this study was to compare these five infusion fluids with respect to their ability to become enriched in, and thereby to dilute, venous plasma. For this purpose, serial measurements of the blood hemoglobin concentration and erythrocyte count were converted into dilution-time data. One approach was to calculate the area under the dilution-time curve, a method often used to summarize concentration-time data in pharmacokinetics. Another analytical approach is based on volume kinetic compartmental modeling, which was adapted in this study to account for the osmotically driven transcellular flow of fluid when hypertonic fluids are infused.[9] The compartmental modeling enables comparisons of volume expansion by computer simulation.[10,11]

Materials and Methods

Ten healthy male volunteers, aged 24–44 yr (mean, 32 yr) and with a mean body weight of 81 kg (range, 72–95 kg), participated in 50 intravenous infusion experiments. The study was approved by the appropriate Ethics Committee, and the informed consent of the participants was obtained.

Procedure

Each volunteer received, in random order and at least 1 week apart, a 30-min infusion of the following fluids: 25 ml/kg of 0.9% saline, Ringer's acetate solution (Baxter Medical AB, Kistor, Sweden; ionic content in mEq/K; Na^+,130; K^+, 4; Ca^{2+}, 2; Cl^-,110; acetate, 130; pH, 6.5; and osmolality, 273 mOsm/l), Ringer's lactate solution (Baxter Healthcare LTD., Deerfield, IL; ionic content; Na^+,130; K^+, 4; Ca^{2+}, 2.7; Cl^-, 109; lactate, 28; pH, 6.5; and osmolality 273 mOsm/l), 5 ml/kg of 7.5% saline, and 3 ml/kg of 7.5% saline in 6% dextran. The volunteers had a light breakfast consisting of one glass of water or milk and one sandwich 2 h before the infusion, which began at approximately 9.00 AM. They voided and were weighed just before the infusion started. During the study, the subjects rested comfortably on a bed covered with blankets. Cannulas were inserted into the antecubital veins in both arms. One was used for infusion and the opposite for blood sampling. A recumbent equilibration period of 30 min was allowed before the first blood sample was drawn in duplicate for an accurate baseline determination and calculation of the coefficient of variation (1.1% for blood hemoglobin and 1.3% for the erythrocyte count and mean corpuscular volume). When an infusion had started, venous blood (3 ml) was drawn every 5 min for 2 h and every 10 min during the subse-

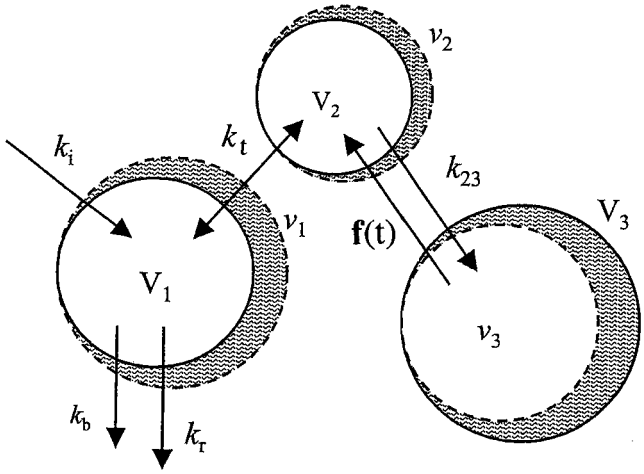

Fig. 1. The three-volume model used for analyzing the kinetics of infusion fluids.

quent 2 h, amounting to 37 samples and 74 ml of blood. The blood hemoglobin concentration (Hb), erythrocyte count, and the mean corpuscular volume were measured on a Technicon H2 (Bayer, Tarrytown, NY), which determines hemoglobin by colorimetry at 546 nm and uses an electrical impedance passage method for the other two variables.

Heart rate and blood pressure were recorded immediately after each blood sample was drawn, using a noninvasive automatic device (Propaq 104, Protocol Systems Inc., Beaverton, OR). To ascertain a stable preexperimental fluid status, the bioelectrical impedance (Xitron 4000B Spectrum Analyzer, Xitron Technologies Inc. San Diego, CA) was measured before starting each session.[12] The sizes of the extracellular and intracellular spaces were calculated using the software supplied with the apparatus. The mean of three consecutive measurements was used to detect differences in fluid status between sessions.

Volume Kinetic Models

In the overarching three-volume model for kinetic analysis of the distribution and elimination of infused fluid, an intravenous infusion, given at a constant rate (k_i), enters a central body fluid space having the volume (v_1). Fluid leaves v_1 by two mechanisms: one rate proportional by a constant k_r to the deviation of v_1 from the baseline volume V_1 (this may be regarded as dilution-dependent urinary excretion), and at a basal rate (k_b, perspiration and baseline diuresis, a fixed rate). The net fluid exchange between v_1 and a peripheral fluid space, v_2, occurs at a rate proportional to the relative difference in deviation from the target values (V_1 and V_2) by a constant (k_t). In case the infused fluid is hypertonic, the infusion is accompanied by an osmotic shift of fluid, **f**(t), to v_2 from a more remote space, v_3. At all times, fluid may diffuse in the opposite direction, from v_2 to v_3, and this flow is governed by a constant k_{23} (fig. 1). Hence, the net fluid shift reverses after the infusion is ended. The differential equations describing the volume changes in V_1, V_2, and V_3 and their matrix solutions are shown in the Appendix.

The expansion of V_2 was reported if a F test indicated that adding another exponent to the equation describing the dilution-time curve resulted in a statistically significant reduction of the mean square error (MSQ), which is a measure of the average difference between model-predicted and the measured data points.[13] If V_2 was not statistically justified in the analysis of the two hypertonic fluids, fluid was assumed to be translocated directly from v_3 to v_1, and the flow back to v_3 was then governed by a constant k_{13}.

Osmotic Fluid Shift

For isotonic and nearly isotonic fluid, **f**(t) was set to 0, whereas for hypertonic fluid, **f**(t) was > 0. The latter case implied that water is being translocated from v_3 to v_2 at a rate governed by the osmotic load. This transfer of water during each 5-min period was calculated based on the law of isoosmolality in the body fluids with guidance from standard textbooks in physiology. An osmotic shift is known to occur across the cell membrane and exchanges water from the intracellular to the extracellular fluid space, which amounts to 40% and 20% of the body weight (BW), respectively.[9] Using the baseline osmolality, which was 291 ± 8 mOsm/l (mean ± SD) in the present study, the translocated volume **f**(t), which can only accumulate in expandable body fluid spaces of the kind identified by volume kinetics, was obtained from:

$$\frac{\text{BW*0.2*291 + infused osmoles}}{\text{BW*0.2 + }\mathbf{f}(t)\text{ + infused volume}} = \frac{\text{BW*0.4*291}}{\text{BW*0.4 - }\mathbf{f}(t)}$$

Applying the calculated osmolality of 2,458 for the two hypertonic fluids, this equation indicates that the first infused milliliter translocated 4.9 ml of water. The osmotic force became progressively reduced for each subsequent amount of infused fluid because the osmolality of all body fluids gradually increased. Therefore, **f**(t) was entered as linear function in the analysis process where **f**(t) at each point in time was governed by the total amount of infused fluid.

Calculation of Model Parameters

The dilution of venous plasma was used to quantitate the water load as the infused fluid remains outside the erythrocytes. The blood hemoglobin concentration and the baseline hematocrit were used as follows to obtain the dilution of V at time (t):

$$\frac{v(t) - V}{V} = \frac{\dfrac{\text{baseline Hb}}{\text{Hb}(t)} - 1}{1 - \text{baseline hematocrit}}$$

The dilution of the erythrocyte concentration was calcu-

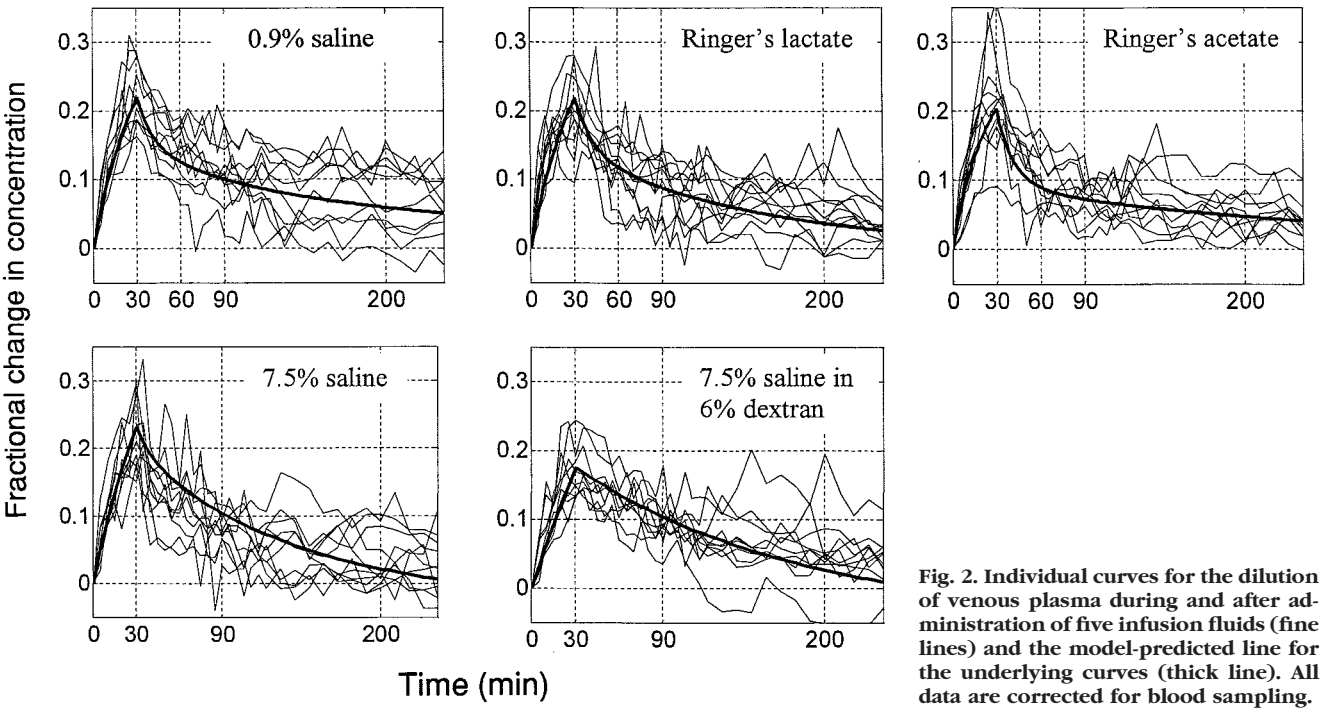

Fig. 2. Individual curves for the dilution of venous plasma during and after administration of five infusion fluids (fine lines) and the model-predicted line for the underlying curves (thick line). All data are corrected for blood sampling.

lated in the same way as for hemoglobin, and the mean of the two was used after correction for changes in cell volume, as indicated by the mean corpuscular volume. A correction was also made for the losses of erythrocytes in connection with the blood sampling procedure based on the baseline blood volume, as estimated according to a regression formula using the height and weight of the subjects.[14]

The kinetics of the fluid infused intravenously was modeled separately for each subject, using Matlab version 5.3 (Math Works Inc., Notich, MA), whereby a nonlinear least-squares regression routine based on a modified Gauss-Newton method was repeated until no parameter changed by more than 0.001 (0.1%) in each iteration. The output of the kinetic analysis consisted in the lowest possible MSQ and the corresponding best estimate and the SEM for each parameter in the model. The parameter k_b was set to 0.5 ml/min and used to correct for the insensible fluid loss of 10 ml · kg^{-1} · day^{-1}.[15] No correction was made for the withdrawn plasma because an equal volume of 0.9% NaCl was injected after each blood sampling.

The size of V_3 could not be estimated with confidence by the curve-fitting procedure. In the kinetic program, V_3 was set to the same size as the expected size of the intracellular fluid space, which is about 40% of the body weight.[9] In the tables, however, we present the rate k_{23}/V_3, which describes the slope of the curve for the accumulation of fluid in V_3, independently of the size of V_3. In addition, k_r and k_{23} could not be determined when $\mathbf{f}(t)$ was > 0 because they operated during the same period. For the hypertonic fluids, therefore, k_r was determined as the total urinary excretion during the experiment divided by the area under the dilution-time curve, assuming that half of the basal fluid loss (k_b) consisted of dilution-independent urinary excretion.[16] The area under the curve was calculated by the linear trapezoidal method over the entire 240-min observation period, without extrapolation to zero.

Simulations

Method. Predictions of the expected dilution response in V and V_1 were based on the numerical solutions to the differential equations describing the kinetic models used. The solutions to the models in which $\mathbf{f}(t) = 0$ have been given in a previous publication,[3] whereas those for $\mathbf{f}(t) > 0$ are shown in the Appendix. The best estimate of the model parameters were inserted into the solutions that had been programmed into the Matlab software. A time-stepping method was then used to yield the dilution-time curve.

Efficiency. For each experiment, the "efficiency" of the plasma expanders was obtained as the area under the curve divided by the actually infused fluid volume (area approach). The efficiency was also obtained from simulations based on the volume kinetic parameters and then was taken as the computer-predicted fluid volume required to reach a dilution of 20% at the end of a 30-min infusion (target dilution approach). Numerical presentation of this predicted fluid requirement is usually expressed relative to the volume of 0.9% saline needed to reach the same goal in the same person.

Pooling of Curves. The kinetics of each experiment was described by one set of parameters. Graphical pre-

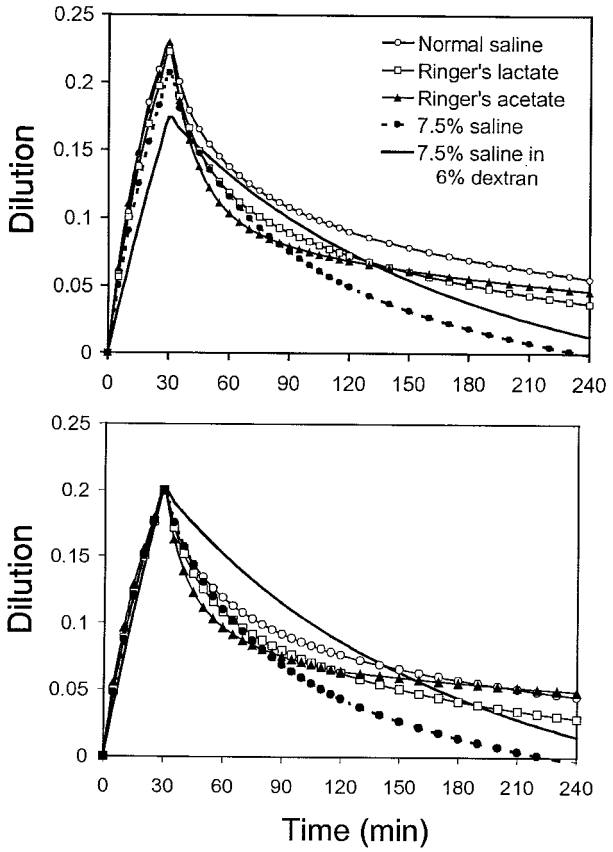

Fig. 3. Model-predicted dilution-time curves for five infusion fluids. Each curve is the mean of ten simulated curves that all represent a single infusion experiment (top). Dilution for the same infusion fluids when the infusion rate was modified to yield a precise dilution of 0.2 at the end of the 30-min infusion (bottom).

sentation of the expected overall dilution response to infusion of a fluid was obtained from the mean of all 10 simulated dilution-time curves from the respective series of 10 experiments, each based on the appropriate one-, two-, or three-volume model as indicated by the F test (figs. 2 and 3).

Statistics

Data are presented as the mean ± SD or, when there was a skewed distribution, the median and the 25th and 75th percentiles. Statistical comparisons of dilution were based on measured and simulated data at 30, 60, 90, and 200 min of the experiments using one-way analysis of variance (ANOVA), followed by the Newman–Keuls test. The same methods were used to compare the area under the dilution-time curves and also the fluid volumes required to yield a predetermined dilution. $P < 0.05$ was considered significant.

Results

Area Approach

The dilution of the plasma increased gradually during all infusions and decreased exponentially after they were ended (fig. 2). The dilution response to the fluids varied depending on their tonicity; the ratio of the area under the curve of the dilution-time profiles to the infused fluid volume was almost twice as high for 7.5% saline in dextran (84.8 ml^{-1}) as for 7.5% saline (45.3 ml^{-1}), whereas 0.9% saline and the two Ringer's solutions had an average ratio of 12.0 ml^{-1} (table 1). The relative volume effects, measured as the area under the dilution curve of the infused fluids during the 240-min study period were, using 0.9% saline as a reference (= 1): lactated Ringer's solution, 0.88 ± 0.25; acetated Ringer's solution, 0.91 ± 0.46; hypertonic saline, 3.97 ± 1.97; and hypertonic saline in dextran, 7.22 ± 4.48 (mean ± SD).

The dilution-time profiles were similar during infusion of the isotonic and the slightly hypotonic fluids, but the dilution during the subsequent hour was less pronounced with acetated Ringer's solution than with the other solutions (table 2). The urinary excretion was significantly higher with the two Ringer's solutions than with each of the hypertonic solutions, but only the latter ones resulted in a larger excretion than the infused volume (table 1).

Target Dilution Approach

The volume kinetic analysis showed that the two-volume model was statistically appropriate in most of the experiments with 0.9% saline and the two Ringer's solutions (table 3). The size of the central body fluid space (V_1) was 4.0 l (range, 3.5–5.4 l), and the peripheral fluid space (V_2) averaged 8.3 l (range, 5.7–12.1 l). The two-volume model was usually also appropriate for the hypertonic fluids (table 4).

To overcome random fluctuations in the measurement of dilution, computer simulations were made using individual kinetic parameters and the doses used in the study. These simulated dilution-time curves differed significantly only at 200 min, where 0.9% saline and acetated Ringer's solution were > 7.5% saline ($P < 0.05$; fig. 3, top). Normal saline and the Ringer's solutions left a 5% residual dilution at 240 min, which was not the case for the hypertonic fluids.

A further comparison of the efficiency of the infused fluids was made by multiplying the infusion rate in each volunteer by a factor to yield a precise dilution of 20% at the end of the infusion. We needed to use the following factors to reach this goal (mean): 0.87 for normal saline, 0.85 for lactated Ringer's solution 0.92 for acetated Ringer's solution, 0.27 for hypertonic saline, and 0.16 for hypertonic saline in dextran (fig. 3, bottom). With the adjusted infusion rates, the dilution varied only slightly during the infusions but much more after them (fig. 4).

The fluid volumes required to dilute the plasma by 20% differed markedly between the fluids (table 5). The relative volume effect of the infused fluids was, when using 0.9% saline as a reference (= 1): 0.94 ± 0.14 for lactated Ringer's solution, 0.97 ± 0.28 for acetated Ringer's so-

Table 1. Dose, Area under the Curve, and Urinary Excretion

	(1) Normal Saline	(2) Ringer's Lactate	(3) Ringer's Acetate	(4) 7.5% Saline	(5) 7.5% Saline in Dextran	ANOVA $P < 0.05$
n	10	10	10	10	10	—
Dose (ml)						
Median	2,000	2,000	2,000	400	240	—
25th–75th	(1,900–2,137)	(1,900–2,137)	(1,900–2,137)	(380–428)	(228–256)	
Area (10^3)						
Median	25.8	21.0	20.4	18.6	19.1	—
25th–75th	(18.4–33.7)	(15.4–27.9)	(15.3–24.0)	(11.4–23.0)	(21.1–27.4)	
Area, Dose (ml^{-1})						
Median	14.0	11.2	10.8	45.3	84.8	1–3 < 4 < 5
25th–75th	(9.6–16.5)	(7.6–13.6)	(6.9–12.7)	(25.7–60.6)	(74.8–88.7)	
Urine (ml)						
Median	800	1,188	1,012	720	650	4 < 3 and 5 < 2,3
25th–75th	(525–1,050)	(1,106–1,338)	(862–1,231)	(625–850)	(500–800)	
Urine, Dose						
Median	0.43	0.60	0.50	1.85	2.73	1–3 < 4,5
25th–75th	(0.30–0.47)	(0.52–0.62)	(0.45–0.57)	(1.61–2.20)	(2.15–3.15)	

Data were obtained for five infusion fluids given to 10 male volunteers. "25th and 75th" are percentiles for the distribution of data.
ANOVA = analysis of variance.

lution, 4.44 ± 1.08 for hypertonic saline, and 6.15 ± 1.12 for hypertonic saline in dextran.

Area versus *Target Dilution Approach*

As indicated previously, the area method usually indicated a slightly lower relative efficiency of the fluids in diluting the plasma than the target dilution method did; the mean value was 94% for lactated Ringer's solution, 93% for acetated Ringer's solution, 89% for hypertonic saline, but 117% for hypertonic saline in dextran. The differences between the methods were not statistically significant.

Hemodynamics, Bioimpedance, Adverse Effects

All infusion fluids except normal saline significantly increased the systolic arterial pressure when tested group-wise (ANOVA; $P < 0.02$). The systolic pressure during infusions of all these fluids increased from 120 ± 9 mmHg at baseline to 128 ± 13 mmHg at 30 min. No fluid significantly changed the diastolic pressure. Only 7.5% saline increased the heart rate, from 67 ± 7 to 78 ± 9 beats/min ($P < 0.001$).

The size of the extracellular fluid space before the infusions started, as measured by bioimpedance, varied little in the five series of experiments, the lowest group

Table 2. Plasma Dilution after a 30-min Infusion of Three Isotonic or Nearly Isotonic Fluids

Dilution (%)	(1) Normal Saline	(2) Ringer's Lactate	(3) Ringer's Acetate	ANOVA $P<0.01$
At 30 min				
Median	23.2	21.5	21.9	—
25th–75th	(19.2–28.4)	(20.0–24.6)	(17.5–26.0)	—
At 60 min				
Median	14.1	14.3	10.3	1 > 3
25th–75th	(12.0–17.4)	(8.4–15.5)	(8.6–12.7)	
At 90 min				
Median	10.5	11.3	7.6	1 > 3
25th–75th	(9.9–14.4)	(4.4–12.7)	(5.1–10.9)	
At 200 min				
Median	6.4	4.2	4.8	1 > 2
25th–75th	(3.4–10.7)	(2.6–6.9)	(3.6–7.1)	

Measured dilution of the plasma at various times after starting a 30-min intravenous infusion of normal saline, Ringer's lactate, and Ringer's acetate in 10 volunteers. "25th and 75th" are percentiles for the distribution of data.
ANOVA = analysis of variance.

Table 3. Volume Kinetic Analysis of Three Isotonic or Nearly Isotonic Infusion Fluids

	(1) Normal Saline	(2) Lactated Ringer's Solution	(3) Acetated Ringer's Solution
One-volume Model			
n	3	4	1
V (l)	8.2 (7.3–9.0)	8.1 (4.5–9.2)	9.7
SE	0.5 (0.4–0.5)	0.7 (0.6–0.7)	0.6
k_r (ml/min)	86 (84–249)	68 (65–154)	220
SE	5 (4–12)	8 (7–12)	12
MSQ (10^{-3})	11 (9–15)	26 (20–33)	11
Two-volume Model			
n	7	6	9
V_1 (l)	4.0 (3.4–6.3)	3.8 (3.2–5.5)	4.1 (3.8–4.8)
SE	0.7 (0.5–1.6)	0.7 (0.5–1.2)	0.5 (0.3–0.6)
V_2 (l)	6.9 (5.8–11.0)	5.8 (5.5–6.6)	12.5 (9.6–14.5)
SE	0.9 (0.8–1.6)	1.2 (0.6–1.8)	2.0 (1.6–3.3)
k_t (ml/min)	168 (124–426)	164 (143–251)	208 (166–385)
SE	34 (27–157)	56 (37–81)	34 (17–39)
k_r (ml/min)	27 (24–55)	65 (36–97)	44 (38–66)
SE	5 (3–33)	8 (3–12)	12 (8–27)
MSQ (10^{-3})	15 (11–20)	18 (7–29)	9 (8–17)

Volume kinetic parameters for normal saline, Ringer's lactate and Ringer's acetate when given by IV infusion to 10 male volunteers. The first line for each variable gives the best estimate and the second (indented) line its standard error (SE). The data on each line gives the median for the group followed by the 25th and 75th percentiles in parenthesis. No statistics was performed.
V = volume; MSQ = mean square error; k_r = elimination rate constant.

Table 4. Volume Kinetic Analysis of Two Hypertonic Fluids

	(4) 7.5% Saline	(5) 7.5% Saline in Dextran
Two-volume Model		
n	6	10
V (l)	10.4 (9.3–11.8)	7.1 (6.5–7.9)
SE	0.8 (0.6–0.9)	0.4 (0.3–0.5)
k_{13}/V_3 (10^{-3} min^{-1})	11.9 (6.1–20.7)	3.6 (2.5–5.2)
SE	1.4 (0.8–2.7)	0.5 (0.5–0.6)
k_r (ml/min)	71 (50–90)	31 (25–38)
MSQ (10^{-3})	27 (20–34)	12 (8–25)
Three-volume Model		
n	4	—
V_1 (l)	0.83 (0.71–1.00)	—
SE	0.18 (0.13–0.25)	—
V_2 (l)	8.2 (7.1–8.8)	—
SE	0.7 (0.7–0.8)	—
k_t (ml/min)	60 (50–74)	—
SE	31 (18–54)	—
k_{23}/V_3 (10^{-3} min^{-1})	4.3 (3.3–5.4)	—
SE	1.2 (1.1–1.5)	—
k_r (ml/min)	25 (21–27)	—
MSQ (10^{-3})	16 (15–24)	—

Selection between a two-volume (top) and a three-volume (bottom) model was made by an *F* test. The first line for each variable gives the best estimate and the second (indented) line its standard error (SE). The data on each line gives the median for the group followed by the 25th and 75th percentiles in parenthesis.

MSQ = mean square error.

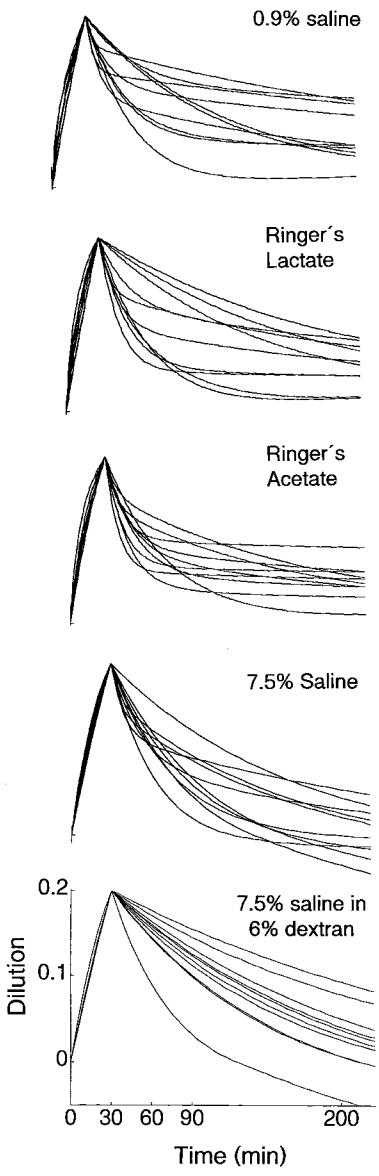

Fig. 4. Marked postinfusion variation in dilution when the infusion rate for each experiment was modified to yield a precise dilution of 0.2 at the end of a 30-min infusion. Each thin line represents one infusion experiment.

mean being 20.0 ± 1.8 l and the highest 20.2 ± 2.0 l. Similarly, the total body water varied between 37.7 ± 4.8 l and 38.4 ± 4.1 l.

No adverse events occurred when 0.9% saline and the two Ringer's solutions were infused. One subject was excluded because he got a headache during the infusion of hypertonic saline, which prompted discontinuation of the experiment.

Another volunteer was excluded from the study because of pain in the arm in which hypertonic saline was infused. Three other volunteers reported mild-to-moderate pain in the infusion arm when the hypertonic fluids were administered, and two developed thrombophlebitis. The hypertonic fluids induced thirst in all volunteers, which subsided after the infusions were ended. The serum sodium concentration increased ($P < 0.001$) to a similar degree with both hypertonic fluids; for hypertonic saline, the concentration increased from 141 ± 1 to 150 ± 1 mEq/l, and during infusion of hypertonic saline in dextran serum sodium changed from 139 ± 4 to 148 ± 2 mEq/l.

Discussion

The efficiency of five infusion fluids as plasma volume expanders was analyzed by their area under the dilution-time curves and also by volume kinetics, which is a tool for studying the distribution and elimination characteristics of infusion fluids. Volunteers were given three isotonic or nearly isotonic fluids, all of which are used in various parts of the world, and two hypertonic solutions. As expected, the first solutions were far less effective in diluting the plasma than the latter ones, but certain differences within these two groups could be disclosed. For example, the area approach showed that lactated and acetated Ringer's solutions were approximately 10% less effective than normal saline during the 240-min observation period. This finding can probably be accounted for by a slightly larger urinary excretion and also by the lower sodium content of the Ringer's solutions compared with 0.9% saline (table 1). The efficiency showed a high intersubject variability, however.

Table 5. Simulation to a Maximum Dilution of 20% during a 30-min Intravenous Infusion

	(1) Normal Saline	(2) Ringer's Lactate	(3) Ringer's Acetate	(4) 7.5% Saline	(5) 7.5% Saline in Dextran	ANOVA $P<0.05$
n	10	10	10	10	10	—
Dose for 20% dilution						
Mean (ml)	1778	2067	1809	428	363	—
SD	391	799	379	154	137	—
Dilution, 60 min (%)						
Mean	11.9	10.8	9.2	11.0	15.2	5 > 1–4
SD	2.9	3.9	2.3	2.2	2.4	
Dilution, 90 min (%)						
Mean	9.2	8.0	6.9	6.9	14.4	5 < 2,3
SD	3.5	4.0	2.3	2.9	6.6	
Dilution, 200 min (%)						
Mean	5.3	3.7	4.2	2.2	5.0	—
SD	3.2	2.5	2.1	3.1	4.1	—

Computer simulation of the dose required of five different fluids to reach a final dilution of 20% when infused at a constant rate over 30 min. The postinfusion dilution at three points in time are also shown. Data are mean ± SD.

ANOVA = analysis of variance.

Further comparisons of the dilution-time profiles of the fluids were made by means of volume kinetic analysis, which allowed a more precise comparison of their efficiency by simulating to a predetermined dilution (target dilution approach). Because all fluids differ in dynamics, volume kinetics can be used to contrast selected characteristics of the fluids by equilibrating one specific characteristic of them. The target dilution approach described the differences between the fluids with a smaller intersubject variability than the area method, which can be understood as the dilution varied less during the actual infusion than later during the experiment. Further, the average differences in efficiency between the fluids were not identical to those obtained by the area approach. For example, at the end of a simulated 30-min infusion, to a target dilution of 20%, the efficiency of 0.9% saline and the two Ringer's solutions was more similar than indicated by the area approach.

Hypertonic saline exerted an average plasma dilution effect that was 4.4 times greater than that of normal saline, which is less than would be expected from the 8.3 times difference in osmolality between the infused fluid and the body fluids. When infusing hypertonic saline, however, one part of the sodium chloride load apparently redistributes water, whereas the other part serves to increase the osmolality of the extracellular fluid.[17]

The addition of dextran to hypertonic saline was originally carried out to prolong the plasma volume expansion,[18] but dextran increased the volume effect of hypertonic saline by more than 50%, although the duration of the effect was only slightly prolonged. The reason for the greater volume expansion is probably the predominantly intravascular distribution of dextran, whereas hypertonic saline *per se* is distributed in a much larger volume.

The hypertonic fluids differ from the isotonic solutions also in their dehydrating effect, which is probably caused by natriuresis induced by the sodium load.[19] Hence, the urinary excretion was 1.8 times larger than the infused fluid volume of hypertonic saline, whereas it was 2.7 times larger when hypertonic saline with dextran was given.

The kinetic method used for analyzing the dilution-time profiles in venous plasma was developed in the late 1990s to better characterize the disposition of infusion fluids.[3,10,11] The body fluid space expanded by the infused fluid (V) is a central concept in volume kinetics and can be estimated because the dilution of the blood with respect to such macromolecules as hemoglobin, which do not penetrate vascular vessel walls, is a measure of the distribution of the infused fluid volume and not of the macromolecule. The fitting of the kinetic model to the data also yields the rate of elimination and sometimes the distribution of fluid into a peripheral body fluid space. In the present study, this approach was used to compare the efficiency of the fluids by adjusting the infusion rates and also to illustrate the variability of the dilution-time profiles after the infusions ended.

Several modifications of the kinetic model were introduced here. All group-wise simulations are based on a single summarized (pooled) dilution-time curve representing all experiments with each fluid, which makes them independent of the number of experiments reported according to the one- and two-volume models (isotonic fluid) and two- or three-volume model (hypertonic fluid). The model has also been developed to account for the specific fluid shifts induced by an osmotic load, which the original one- and two-volume model first presented cannot handle correctly. The powerful volume effect of the hypertonic fluids can be understood from an osmotically driven translocation of

fluid from cells to noncells. The model now considers the flow of fluid to and from a distant body fluid space, V_3, although the size of V_3 could not be estimated with confidence. Further, two mechanisms involved in the removal of a hypertonic fluid volume are separated. Fluid is eliminated by a dilution-dependent mechanism, k_r, which essentially represents renal excretion, but also by another mechanism, k_{23}, through which fluid returns to V_3, the strength of which probably reflects the degree of natriuresis.

For both hypertonic fluids, the return of fluid to V_3 was more important than the urinary excretion in removing fluid from central parts of the body. This can be concluded by comparing the urinary excretion and the sum of the infused fluid volume and the translocated amount, which was approximately 4.7 times the infused, while considering that the baseline volume of V_1 had been essentially restored at the end of the study period. The kinetics of hypertonic saline has previously been analyzed by assuming that $\mathbf{f}(t) = 0$, which results in unrealistically small values for V and k_r.[3] The present approach reflects the forces governing the fluid distribution in the body more accurately.

Hypertonic saline is known to restore a lowered arterial pressure and may have a positive inotropic effect. Clinical trials show that the same physiologic responses can be elicited by infusing only one tenth as much 7.5% saline in 6% dextran as lactated Ringer's solution.[20–22] Other comparative studies on the efficiency of volume support using isotonic and hypertonic fluids are usually based on hypovolemic shock in animals. Kramer *et al.*[23] found that 7.5% saline in 6% dextran is six times more effective than lactated Ringer's solution in restoring cardiac output in adult sheep subjected to severe hemorrhage, which is approximately 30% more than the relation we found in healthy volunteers.

Lactated and acetated Ringer's solutions were both studied because the latter is marketed in Scandinavia. Acetate is used as a buffer because it is, just like lactate, easily degraded to bicarbonate. A difference is that lactate is metabolized only in the liver and kidney, whereas acetate is degraded in all body cells, which is proposed to be beneficial in situations of lactic acidosis and a hypokinetic circulation.[24] Acetate, which is a vasodilator,[5,6,25] may redistribute blood to the splanchnic bed[26] and impairs cardiac function during hemodialysis.[27,28] The handling of infused acetated Ringer's solution may therefore differ from that of lactated Ringer's solution and 0.9% saline, although it was not clear to us whether differences in vasodilation could be disclosed at the doses used here.

The present study used noncompartmental and compartmental expressions to illustrate the efficiency of an infusion fluid. The first one includes the relationships between the area under the dilution-time profile, the infused fluid volume, and the urinary excretion. Such expressions rest on few assumptions. More assumptions are involved when fitting a compartmental model, such as those used in volume kinetics, to the data. Most of these assumptions are given directly by the model. The benefit of using the kinetic model is that by using various simulations, a better understanding is gained, and, in addition, differences in the handling of fluid can be attributed to a specific mechanism. For example, the increased dilution after infusing acetated Ringer's solution in hypovolemic volunteers was found to be a result of a reduced rate of elimination (k_r) and not a result of an increased volume of distribution, which could also reduce the dilution response.[11] Further, the size of the body fluid spaces expanded by the infused fluid can be estimated.

In the present study, comparisons between the fluids were complicated by the need for several model variants. However, a central body fluid space (V_1) having a volume of approximately 4 l could be detected in most experiments with the isotonic and nearly isotonic fluids. The size of the peripheral body fluid space (V_2) was usually between 6 and 7 l, which is consistent with previous work,[3,11,29] whereas acetated Ringer's solution showed a larger V_2. This peripheral body fluid space was not statistically significant in 8 of the 30 experiments, which occurred when the rate of elimination is rapid.[29] The hypertonic fluids expanded a total body fluid space of 7–10 l. The fact that the occasional V_1 is smaller than the expected size of the plasma volume is probably because preferential enrichment of fluid in the well-perfused vascular beds, where the transit time for plasma is short. A previous study proposes that long transit times are further prolonged by vasodilation during spinal anesthesia,[30] which promotes excessive enrichment of infused fluid in a small central compartment, and hypertonic fluids also have vasodilating properties.[31]

Other monitoring in the present study included hemodynamic changes, which were slight, although most of the fluids consistently increased the systolic arterial pressure. The bioimpedance analyses showed that the baseline state of hydration of the volunteers was similar in the five series of infusions. An unexpected finding was the high incidence of pain on infusion of the hypertonic fluids, although the fluids clearly entered the bloodstream. Most reports on hypertonic fluids involve their use for fluid resuscitation in trauma, where a blurred sensorium probably limits the patients' complaints about pain on infusion.[8] The pain may be an unpleasant surprise, however, if clinicians make use of such hypertonic fluids in awake patients, such as in surgical procedures performed with regional anesthesia. Hydration with 3% saline before inducing spinal anesthesia apparently does not elicit pain.[32]

In conclusion, we suggest that the area under the curve of the plasma dilution-time profile (area approach) and computer simulation of the fluid volume required to

reach a predetermined dilution (target dilution approach) are useful tools for describing the efficiency of plasma volume expanders. Using 0.9% saline as the standard solution, there were similar relationships between fluids, but the between-subject variability using the target dilution method was approximately half as high as for the area method.

Appendix

In the simplest volume kinetic model, the osmotic shift $\mathbf{f}(t) = 0$, and V_2 is not statistically significant by the F test.[13] The volume change of the single expandable body fluid space is then indicated by the dilution of the venous plasma according to equation 1:

$$\frac{dv}{dt} = k_i - k_b - k_r \frac{(v - V)}{V} \quad (1)$$

The existence of V_2 is said to be statistically justified if the lowest possible average difference between the model-predicted and measured data points (mean square error, MSQ) is significantly reduced by fitting the solution to equation 2 to the measured data points instead of the solution to equation 1. If the osmotic shift is still $\mathbf{f}(t) = 0$, the situation in the central body fluid space, V_1, and the peripheral body fluid space, V_2, are as follows:

$$\frac{dv_1}{dt} = k_i - k_b - k_r \frac{(v_1 - V_1)}{V_1} - k_t \left[\frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2}\right] \quad (2)$$

$$\frac{dv_2}{dt} = k_t \left[\frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2}\right] \quad (3)$$

Solutions to these differential equations have been published in previous work.[3,10]

When hypertonic sodium is infused, $\mathbf{f}(t) > 0$, and water is translocated to v_2 from a remote body fluid space, v_3, at a rate governed by the osmotic load (see Osmotic Fluid Shift in Materials and Methods). In case V_2 is not statistically justified by the F test, the following differential equations show the changes in the volume of v_1 and v_2, respectively:

$$\frac{dv_1}{dt} = k_i - k_b - k_r \frac{(v_1 - V_1)}{V_1} + f(t) - k_{13} \frac{(V_3 - v_3)}{V_3} \quad (4)$$

$$\frac{dv_3}{dt} = k_{13} \frac{(V_3 - v_3)}{V_3} - f(t) \quad (5)$$

The volume change of v_3 is expressed differently from v_1 since this fluid space contracts instead of becoming expanded. Introduce $w_1 = \frac{v_1 - V_1}{V_1}$, $w_2 = \frac{V_3 - v_3}{V_3}$ and we obtain:

$$\frac{dw_1}{dt} = \frac{k_i - k_b}{V_1} - \frac{k_r}{V_1} w_1 + \frac{1}{V_1} f(t) - \frac{k_{13}}{V_1} w_2 \quad (6)$$

$$\frac{dw_2}{dt} = \frac{1}{V_3} f(t) - \frac{k_{13}}{V_3} w_2 \quad (7)$$

Introduce vector and matrix notation:

$$\bar{w} = \begin{pmatrix} w_1 \\ w_2 \end{pmatrix}, \; A = \begin{pmatrix} -\frac{k_r}{V_1} & -\frac{k_{13}}{V_1} \\ 0 & -\frac{k_{13}}{V_3} \end{pmatrix}, \; \bar{a}(t) = \begin{pmatrix} \frac{(k_i - k_b)}{V_1} + \frac{f(t)}{V_1} \\ \frac{f(t)}{V_3} \end{pmatrix} \quad (8)$$

The differential equations in equation 8 can be written as:

$$\frac{d\bar{w}}{dt} = A\bar{w} + \bar{a}(t) \quad (9)$$

The solution of this linear system of differential equations is:

$$\bar{w}(t) = e^{A(t-T)}\bar{w}(T) + \int_T^t e^{A(t-s)}\bar{a}(s)ds \quad (10)$$

where e^{At} is the exponential matrix, T is the initial time, and $\bar{w}(T)$ is the corresponding initial value. The integral can be evaluated if $\bar{a}(t)$ is approximated by a constant $\bar{a}_k$ in the time interval $[t_k, t_{k+1}]$. The numerical solution $\bar{w}_{k+1}$ *at* $t = t_{k+1}$ is then computed recursively from

$$\bar{w}_{k+1} = e^{A\Delta t}\bar{w}_k + (e^{A\Delta t} - I)A^{-1}\bar{a}_k, \; k = 0, 1, \ldots, N-1 \quad (11)$$

where $\Delta t = t_{k+1} - t_k$, $\bar{w}_0 = \bar{w}(T)$.

The three-volume model is described by equation 9 with

$$\bar{w} = \begin{pmatrix} w_1 \\ w_2 \\ w_3 \end{pmatrix}, \; A = \begin{pmatrix} \frac{-k_r}{V_1} - \frac{k_t}{V_1} & \frac{k_t}{V_1} & 0 \\ \frac{k_t}{V_2} & -\frac{k_t}{V_2} & -\frac{k_{23}}{V_2} \\ 0 & 0 & -\frac{k_{23}}{V_3} \end{pmatrix}, \; \bar{a}(t) = \begin{pmatrix} \frac{(k_i - k_b)}{V_1} \\ \frac{f(t)}{V_2} \\ \frac{f(t)}{V_3} \end{pmatrix} \quad (12)$$

The form of the solution is given by equation 10, and after approximating $\bar{a}(t)$ with piece-wise constant values as in the two-volume model, the numerical solution is obtained from equation 11.

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References

1. Haljamäe H: Plasma volume support, Balliere's Clinical Anesthesiology. London, Balliére Tindall, 1997
2. American College of Surgeons, Committee on Trauma: Advanced Trauma Life Support Program for Physicians (Instructor Manual). Chicago, American College of Surgeons, 1984, pp 189–91 and 201–3
3. Svensén C, Hahn RG: Volume kinetics of Ringer solution, dextran 70 and hypertonic saline in male volunteers. ANESTHESIOLOGY 1997; 87:204–12
4. Scheingraber S, Rehm M, Sehrmisch C, Finsterer U: Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. ANESTHESIOLOGY 1999; 90:1265–70
5. Chen YL, Wolin MS, Messina EJ: Evidence for cGMP mediation of skeletal muscle arteriolar dilation to lactate. J Appl Physiol 1996; 81:349–54
6. Saracoca MA, Mulinari RA, Bessa AM, Ferreira Filho SRT, Riberio AB, Ramos OL: Comparison of the hemodynamic effects of sodium acetate in euvolemic dogs and in dogs submitted to hemorrhagic shock. Brazil J Med Biol Res 1986; 19:455–8
7. Committee on Fluid Resuscitation for Combat Casualties: Executive summary, Fluid Resuscitation. Edited by Pope A, French G, Longnecker DE. Washington, DC, National Academy Press, 1999, pp 1–7
8. Kramer GC, Wade CE, Prough DS: Hypertonic saline dextran: Efficacy and regulatory approval. Acta Anaesthesiol Scand 1998; 42:141–4
9. Guyton AC, Hall JE: The body fluid compartments: Extracellular and intracellular fluids; interstitial fluid and edema, Textbook of Medical Physiology, 9th edition. Philadelphia, WB Saunders, 1996, 297–313
10. Ståhle L, Nilsson A, Hahn RG: Modelling the kinetics of changes in volume of body fluid spaces. Br J Anaesth 1997; 78:138–43
11. Drobin D, Hahn RG: Volume kinetics of Ringer's solution in hypovolemic volunteers. ANESTHESIOLOGY 1999; 90:81–91
12. de Lorenzo, Andreoli A, Matthie J, Withers P: Predicting body cell mass with bioimpedance by using theoretical methods. J Appl Physiol 1997; 82: 1542–58
13. Boxenbaum HG, Riegelman S, Elashoff RM: Statistical estimations in pharmacokinetics. J Pharmacokin Biopharm 1974; 2:123–48
14. Nadler SB, Hidalgo JU, Bloch T: Prediction of blood volume in normal human adults. Surgery 1962; 51:224–32
15. Cox P: Insensible water loss and its assessment in adult patients: A review. Acta Anaesthesiol Scand 1987; 31:771–6

16. Hahn RG, Drobin D: Urinary excretion as an input variable in volume kinetic analysis of Ringer's acetate. Br J Anaesth 1998; 80:183–8
17. Hahn RG, Nilsson A, Hjelmqvist H, Zhang W, Rundgren M: Renal function during intravenous infusion of irrigating fluids in the sheep. Acta Anaesthesiol Scand 1996; 40:671–8
18. Smith GJ, Kramer GC, Perron P, Nakayama S, Gunther RA, Holcroft JW: A comparison of several hypertonic solutions for resuscitation of bled sheep. J Surg Res 1985; 39:517–28
19. Eklund J, Hallberg D: Renal elimination of free osmoles during induced saline hyperosmolality in dogs. Acta Chir Scand 1970; 136:541–6
20. Velasco IT, Pontieri V, Rocha e Silva M Jr, Lopes OU: Hyperosmotic NaCl and severe hemorrhagic shock. Am J Physiol 1980; 239:H664–73
21. de Felippe J Jr, Timoner J, Velasco IT, Lopes OU, Rocha e Silva M Jr: Treatment of refractory hypovolemic shock by 7.5% sodium chloride injections. Lancet 1980; 2:1002–4
22. Dubick MA, Bruttig SP: Hypertonic saline dextran: A development update. Army Med Dep J 1996; 8:16–20
23. Kramer GC, Perron PR, Lindsey C, Ho HS, Gunther RA, Boyle WA, Holcroft JW: Small-volume resuscitation with hypertonic saline dextran solution. Surgery 1986; 100:239–47
24. Kveim M, Nesbakken R: Utilization of exogenous acetate during canine hemorrhagic shock. Scand J Clin Lab Invest 1979; 39:653–8
25. Nutting CW, Islam S, Ye M, Batlle DC, Daugirdas JT: The vasorelaxant effects of acetate: Role of adenosine, glycolysis, lyotropism, and pH_i and Ca_i^{2+}. Kidney Int 1992; 41:166–74
26. Buyer DR, Krahmer RL, Lau AH, Wang H-C, Ferguson JL, Daugirdas JT: Regional blood flow redistribution due to acetate. J Am Soc Nephrol 1993; 4:91–7
27. Aizawa Y, Ohmori T, Imai K, Nara Y, Matsouka M, Hirasawa Y: Depressant action of acetate upon the human cardiovascular system. Clin Nephrol 1977; 8:477–80
28. Wizemann V, Soetanto R, Thormann J, Lübbecke F, Kramer WE: Effects of acetate on left ventricular function in hemodialysis patients. Nephron 1993; 64:101–5
29. Svensén C, Drobin D, Olsson, J, Hahn RG: Stability of the interstitial matrix after crystalloid fluid loading studied by volume kinetic analysis. Br J Anaesth 1999; 82:496–502
30. Hahn RG, Resby M: Volume kinetics of Ringer solution and 3% dextran 70 during induction of spinal anaesthesia for Caesarean section. Can J Anaesth 1998; 45:443–51
31. Rocha e Silva M: Hypertonic saline resuscitation. Medicina 1998; 58:393–402
32. Baraka A, Taha S, Ghabach M, Sibaii A, Nader A, Matta M: Hypertonic saline prehydration in patients undergoing transurethral resection of the prostate under spinal anaesthesia. Br J Anaesth 1994; 72:227–8