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Measuring the Size of the Extracellular Fluid Space Using Bromide, Iohexol, and Sodium Dilution

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There is a need to find methods to assess the size of the extracellular fluid (ECF) volume without involving radioactive tracers. For this purpose, we applied 3 methods for measuring the ECF volume in 10 male volunteers (mean age, 34 yr). Steady-state plasma bromide concentration (control) was compared to the results of kinetic analysis of plasma iohexol and to kinetic analysis of the dilution of serum sodium after IV infusion of 1 L of isotonic mannitol. The volume of distribution of these tracers was used to indicate the ECF volume. The results disclosed statistically significant correlations between the results of all 3 methods, although the average sodium dilution showed 0.7 L lower values than iohexol and 1.4 L lower than bromide. All three methods correlated significantly with body weight. The percentage of the body weight indicated by the methods was 18.3% (3.1%) for sodium, 19.6% (1.0%) for iohexol, and 20.5% (1.1%) for bromide. We conclude that sodium dilution may be performed at bedside but iohexol and bromide showed less intersubject variability. Iohexol simultaneously measures the glomerular filtration rate and should be a viable clinical option if the hospital performs routine assessments of kidney function using this tracer.

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There is a need for reasonably simple methods to measure the extracellular fluid (ECF) volume in critically ill patients. Although the ECF volume is maintained remarkably constant in healthy humans (1), marked changes occur in severe trauma, major surgery, and critical illness (2–4). For example, this fluid space is greatly expanded in burn injuries after proper fluid therapy (5). In septic patients, there is often interstitial edema, which may increase the body weight by more than 10% (6).

Methods for measuring the ECF volume that can be easily applied in the clinical environment would offer the possibility of maintaining patients within a predetermined volume range through fluid administration and diuretics. This is not done today because of the shortcomings of the current methods. Several of them use radioactive tracers, which are not readily accepted in clinical medicine. Furthermore, laboratory analyses must be reasonably simple and daily measurements possible. The time needed for each assessment should also be relatively short.

In the present study, we used three methods in volunteers based on the indicator-dilution principle but we used nonradioactive tracers. Our hypothesis was that two new methods, using sodium dilution and iohexol, are simpler to perform than those that use a conventional tracer, bromide, but still yield similar results. The sodium dilution method involves mathematical treatment of concentration-time data on serum sodium after dilution with isotonic mannitol (7). Iohexol is a radiographic contrast medium that is also used to measure the glomerular filtration rate (GFR) (8). Iohexol is excreted from the body more rapidly than bromide and, therefore, concentration-time data must be analyzed using pharmacokinetic processing. The "control" agent, bromide, is an ion whose volume of distribution corresponds to that of chloride (9).

Methods

Ten healthy males, 25 to 59 yr of age (mean age, 34 yr) with a body weight of 67 to 93 kg (mean weight, 80 kg) were studied after the protocol had been approved by the Ethics Committee of Linköping University. Each volunteer gave informed consent and was then subjected to 3 measurements of the ECF space using bromide, iohexol, and sodium dilution. Bromide and

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iohexol dilution were performed simultaneously. Because the sodium dilution method increases ECF, however, it was applied after the other two methods.

The subjects had only a light meal before the experiments. Cannulae were inserted into antecubital veins of both arms and weighed amounts of tracer were injected into one of these veins. Blood samples were drawn from the venous cannula on the opposite arm. A blood sample for measurement of preinfusion concentrations of all 3 indicators of the ECF space was drawn before the experiments started.

Bromide ions reside mainly in the ECF space (9). The serum bromide concentration resulting from injection of known amounts of bromide reaches steady-state after about 1–2 h (10,11). Elimination of bromide through the kidneys is slow. After correction for urinary losses, the volume of distribution (V_d) for the injected bromide indicates the size of the ECF space directly, without any need for kinetic calculations (Appendix).

A bolus injection of 350 mg of sodium bromide (3.4 mmol of bromide) was given IV and the serum bromide concentration was measured at baseline and at 10, 60, 120, 180, and 240 min later. Analyses were performed using mass spectrometry (Sector, HR-ICP-MS or SF-ICP-MS Element, ThermoFinnigan MAT, Bremen, Germany), during which ions are separated according to mass. The amount is indicated by the number of ions that produce electrical pulses when hitting a detector (12). The intra-assay and inter-assay coefficients of variation (CV) were 3% and 5%–10%, respectively.

Iohexol is a tracer that is also distributed throughout the ECF space, but it is excreted more rapidly than bromide by the kidneys. Because a reasonably steady-state is never reached, calculation of V_d must consider the continuous elimination of iohexol, which occurs solely by glomerular filtration. In the present study, the serum iohexol concentration was measured at 0, 5, 10, 15, 30, 60, 90, 120, 150, 180, and 240 min after the IV injection of 10 mL iohexol (Omnipaque® 647 mg iohexol/mL, Nycomed Amersham, Lidingö, Sweden). The analysis was performed using a high-performance liquid chromatography technique on a C^{18} column with ultraviolet detection (13) with intra- and inter-assay CV of 2.3% and 3.1%, respectively.

A two-compartment kinetic model was fitted to the data using the WinNonlin Standard 1.5 program (Pharsight Corp., Mountain View, CA) (8). We expected a distribution phase of approximately 20 min, as suggested by kinetic analysis of molecules having similar size (11,14). The essential parameters in the model (see Appendix) are reported as obtained, except for the total V_d (V_{ss}), which is given after correction by a factor of 0.934 to account for the water content of plasma (1,15). The precision by which these parameters were estimated is shown in the Appendix.

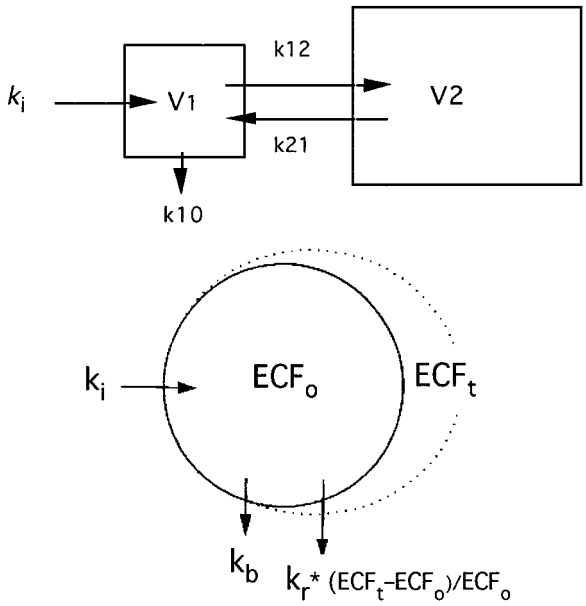

Figure 1. The two-compartment open model used for analyzing the iohexol data (above) and the volume kinetic model used for the sodium dilution (below). In the latter case, the tracer (fluid volume) expands its own volume of distribution.

The ECF volume was also measured by diluting the sodium space. For this purpose, 15 mL/kg of a sodium-free fluid, mannitol 5%, was infused IV over 30 min (mean volume, 1197 mL). The resulting changes in the serum sodium concentration were measured with ion-selective electrodes. Further calculations were performed according to the principles of volume kinetics, consisting of a pharmacokinetic model adapted for infusion fluids that has usually been applied to changes in hemoglobin (Hb) concentration (16).

The distribution of a fluid given by IV infusion can be analyzed using a volume-of-fluid-space kinetic model (Fig. 1, bottom). Fluid given at the rate k_i is distributed in the ECF volume at time t (ECF_t), which the body strives to maintain at the baseline volume, ECF_o. The fluid leaves ECF_t at a basal rate (k_b) and at a controlled rate proportional by a constant (k_r) to the deviation from ECF_o. The situation is described by the differential equation:

$$\frac{dECF}{dt} = k_i - k_b - k_r \frac{ECF_t - ECF_o}{ECF_o}$$

Because the plasma is a part of the ECF, the dilution of the serum sodium concentration in the cubital vein was used to obtain $(ECF_t - ECF_o)/ECF_o$. The data on dilution were corrected for loss of tracer (sodium) during the blood sampling, which was performed at 0, 3, 8, 12, 20, 30 33, 38, 42, 50, 60, 80, 100, and 120 min with an intra-assay and inter-assay CV of 1%. Serum sodium was also corrected for urinary loss of sodium

Table 1. Kinetic Parameters Calculated When Estimating the Size of the Extracellular Fluid Space

Bromide	
V_d at 10 min (L)	14.01 ± 2.46
60 min	16.44 ± 1.69
120 min	18.64 ± 3.70
180 min	17.09 ± 2.20
240 min	16.72 ± 2.22
Mean 180–240 min	16.91 ± 2.10
Iohexol	
V_1 (L)	10.5 ± 2.2
k_{10} (10^{-3} min^{-1})	12.5 ± 2.8
k_{12} (10^{-3} min^{-1})	21.8 ± 18.4
k_{21} (10^{-3} min^{-1})	32.4 ± 11.9
V_{SS} (L)*	15.8 ± 2.0
Clearance (mL/min)	128 ± 14

* Corrected by 0.934 to account for the water content of plasma.
$n = 10$.

by assuming that the rate of sodium loss at each point in time was proportional to the uncorrected dilution of the serum sodium level, as suggested by previous work with electrolyte-free fluids (17). (See Appendix for details). Hence, only one measurement of the sodium excretion was made.

Two approaches were used in the subsequent kinetic analyses. In the first approach, both ECF_o and k_r were estimated simultaneously. In the second approach, k_r was obtained as the urinary excretion divided by the area under the dilution-time curve and, hence, only ECF_o was estimated. In both cases, k_b was set to 0.5 mL/min to account for basal fluid loss of approximately 700 mL per 24 h (insensible water loss and diuresis) (16).

To estimate the model parameters, the solution to the differential equation describing the volume kinetic model (Appendix) was applied to the data on dilution by using a nonlinear least-squares regression routine programmed in Matlab version 4.2 (Math Works Inc., Natick, MA), which was repeated until no parameter changed by more than 0.001 (0.1%) in each iteration. More complex models were also applied but did not markedly improve the curve fit (16,18).

The results are presented as the mean (SD) and as box plots. Comparisons between the groups were made using repeated-measures analysis of variance, simple linear regression analysis (where r = correlation coefficient), and Bland-Altman plots. $P < 0.05$ was considered significant.

Results

The volume of distribution (V_d) for bromide was 16.4 (1.7) L based on the serum concentration measured at 60 min. From 120 min onward, V_d for bromide became 5%–10% larger (Table 1). The V_{ss} for iohexol was 15.8 (2.0) L (Fig. 2).

Mannitol was infused after the bromide and iohexol measurements had been completed. The ECF_o expanded by this fluid was 13.7 (3.4) L when the curve-fitting procedure estimated both ECF_o and k_r. When k_r was determined by the urinary excretion, which amounted to 719 (221) mL with a sodium concentration of 63 (27) mmol/L, the corresponding volume was 14.9 (3.5) L (Fig. 2). The results of the two methods of calculating ECF_o were very similar but the one based on the measured urinary excretion, which rests on fewer assumptions, was used in further comparisons.

There were no statistically significant differences among the results of the 3 methods (analysis of variance). Instead, the V_d for the three techniques correlated well, the $r = 0.84$ for sodium dilution versus iohexol, $r = 0.88$ for bromide (at 60 min) versus iohexol, and $r = 0.64$ for bromide versus sodium (Fig. 3 a-c, left). Bland-Altman plots for the agreement among the techniques showed that sodium dilution yielded a 0.7 L lower mean value than iohexol, whereas bromide was 0.7 L higher than iohexol. Finally, sodium was 1.4 L lower than bromide (Fig. 3 a-c, right).

The V_d increased with body weight for bromide ($r = 0.84$, $P < 0.01$), for iohexol ($r = 0.94$, $P < 0.001$), and for the sodium dilution ($r = 0.68$, $P < 0.05$). The V_d was 18.3% (3.1%) of the body weight when measured by sodium dilution, 19.6% (1.0%) when obtained using iohexol, and 20.5% (1.1%) when obtained using bromide (Fig. 4).

Discussion

Our aim was to compare volume kinetics and iohexol with a conventional method for measuring the ECF space in volunteers. None of the methods involved radioisotopes. Bromide dilution has been used as a standard procedure, but slow elimination makes daily measurements questionable. The more rapid elimination of the tracer used in the iohexol and volume kinetic techniques makes daily repetition of these techniques more feasible (5). Kinetic analysis must then be applied to obtain a valid result, but this has become less problematic with the availability of personal computers.

We chose isotonic mannitol solution for the volume kinetic technique, as it is well tolerated and does not contain any sodium ions. The infusion implied administration of nearly pure water, which diluted the ECF space. The resulting dilution of the serum sodium concentration is the result of both the water V_d and the equilibration of sodium ions throughout the ECF space. Previous work using volume kinetics has been focused on the distribution of the infused fluid volume, which can be obtained by applying the kinetic models to the blood Hb, plasma albumin, or blood

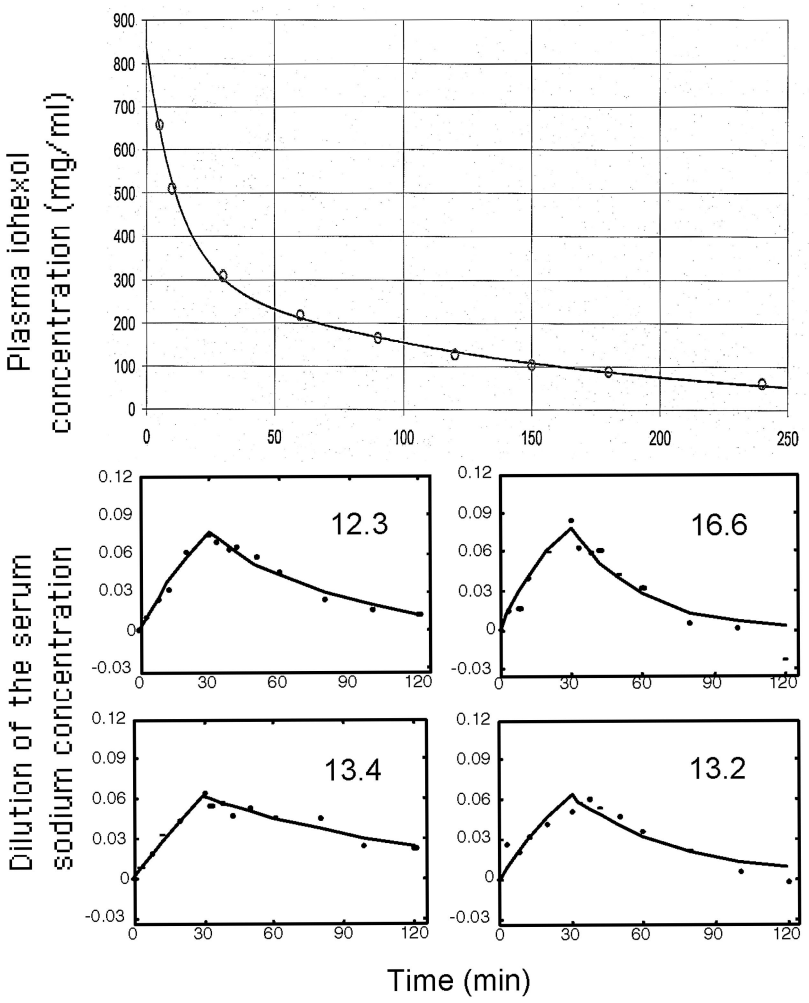

Figure 2. One representative curve showing iohexol elimination (above) and four curves showing the dilution of the serum sodium level on infusion of mannitol (below). In the latter cases, the size of the expanded body fluid space (V) in L is shown for each subplot. All points are measured data and the line represents the optimal curve fit obtained by kinetic analysis.

water concentrations (16). Thus, the method seems quite practicable in the clinical setting using standard laboratory methods, provided that the patients can tolerate volume expansion. A good curve fit was obtained using a one-volume model, the simplest of the models developed.

The ECF space was 6%–13% smaller (depending on the kinetic model used) with volume kinetics as compared with iohexol. The latter is a small hydrophilic solute with properties similar to those of inulin or Cr-EDTA. The reasons why the volume kinetic model indicates a smaller space are not clear. However, the method rests on measuring as precisely as possible a decrease in serum sodium of only 6–10 mmol/L. Moreover, the result should be corrected for the urinary excretion of both sodium ions and water, which could be more precisely quantified over time than we did.

Besides the potential bias involved in how the measurements were performed, one must also consider that fluid and sodium might not equilibrate as perfectly in the ECF space as is commonly believed. At the tissue level, the interstitium is complex and inhomogeneous. There is a framework of collagen, with a gel phase of glycosaminoglycans, plasma proteins, and a crystalloid solution. The macromolecules are held to be mutually exclusive, i.e., not all of the interstitial space is available to proteins. The hydraulic conductive properties of the tissues are affected by overhydration or fluid depletion. With regard to fluid plasma-to-lymph passage times in different tissues, there are considerable variations in path length, linear velocity, and V_d (19). The volume expansion attained by the infusion of mannitol solution must involve readjustments in all or some of these variables, and the possibility remains that the fluid distributes inhomogeneously, within "preferential fluid spaces."

The volume kinetic model as used here also reflects the capacity of the ECF space to equilibrate the sodium concentration. The process of equilibration might be

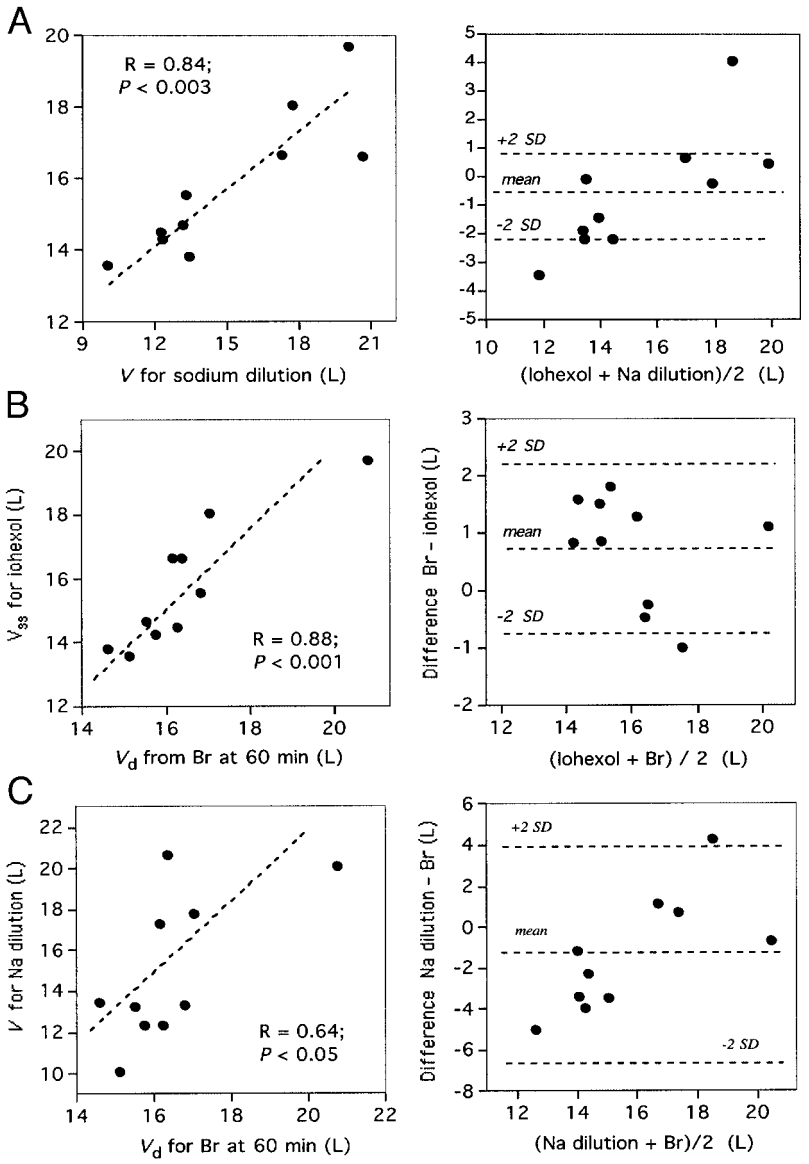

Figure 3. Linear regression plots (left) and Bland-Altman plots (right) showing the agreement between the iohexol, bromide and sodium dilution methods of measuring the extracellular fluid (ECF) volume.

complex and may require some time, as poorly perfused areas of the body are reached with smaller amounts of infused fluid than are well-perfused areas. Therefore, organ aspects need to be considered. In animal studies and in humans, plasma volume expansion with crystalloid fluid induces a differential loss of water and small solutes from the circulation (20). Moreover, the infused solution does not distribute according to organ weight and presumed ECF space, and there seems to be a preponderance of skin and viscera and an underexpansion of skeletal muscle (21). Such incongruencies in distribution, and the fact that the sodium technique reflects two processes instead of one, may explain the slightly lower value for the ECF space indicated by this approach.

Small hydrophilic solutes, cleared exclusively by glomerular filtration, can be used to determine the GFR. Examples of such exogenous substances are inulin, Cr-EDTA, and some radiograph contrast media, such as iohexol. One reason is that it can easily be assayed in plasma or urine by high-performance liquid chromatography or radiograph fluorescence methods, and another is that simplified approaches, such as GFR assessments from one or a few plasma samples, have become available (22). Iohexol has a very low extrarenal clearance, as determined in anephric pigs (23) and in anuric patients (24); it is not handled by the renal tubules or bound to plasma proteins, and it does not influence the GFR. Although inulin and CrEDTA are established tracers for measuring ECF volume, iohexol has only recently been used for this purpose (5).

In view of the kinetic properties of iohexol, it would be an excellent tracer for the ECF volume.

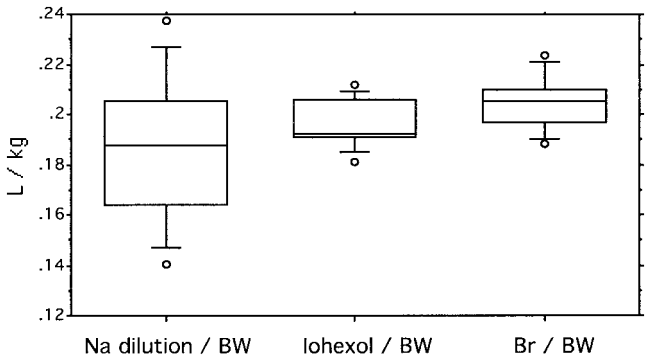

Figure 4. The distribution of the extracellular fluid (ECF) volume divided by body weight (BW) for the three methods, sodium dilution, iohexol, and bromide. The box plots show the 25th, 50th, and 75th percentiles (box), the 10th and 90th percentiles (error bars), and outliers (single points).

Pharmacokinetic models, including up to three compartments, have been validated (25). Our data yielded good curve fits using a two-compartment model. The appearance of the distribution (α) phase varied greatly among the volunteers, resulting in the high SD for k_{12} and k_{21} shown in Table 1. Poor delineation of the α phase leads to uncertainty in the parameter estimation process, which is reflected by the standard deviations presented in the Appendix. However, the computer program used for pharmacokinetic analysis separately specifies the uncertainty inherent in the estimation of each parameter in each volunteer. The uncertainty (SD) for V_{ss} averaged 1.0 L (6%), which shows that, overall, the individual V_{ss} was still estimated with acceptable precision. Kinetic analysis of the concentration-time profile of iohexol also offers a state-of-the-art determination of GFR. In the set of kinetic parameters shown in Table 1, the size of the ECF space is given by $V_{ss,}$ and GFR is represented by the clearance. The rapid elimination of iohexol is captured by the half-life, which is obtained as the logarithm for 2 (0.693) divided by k_{10}. This averaged 58 minutes in our study.

There are several reasons why bromide is an imperfect tracer for measurements of the ECF space. It is enriched in the skin, red cells, connective tissue, and secretory organs. The intracellular distribution is 20%–25% and, as illustrated in the present study, its V_d increases with time. In rats, equilibrium occurs at 28–32 hours, reflecting delayed distribution into the connective tissue, skeleton, transcellular water, and central nervous system (8). The V_d for bromide is probably best calculated using kinetic resolution of the time-concentration curve, as it is for the other two methods, but this is not routine. The changing distribution of the tracer and its time course are not well documented in pathological conditions but may be altered. Such deviations would be difficult to trace on the basis of plasma concentration data alone. In our experiments, V_d for bromide increased by up to 10% from 2 hours onward, compared with the 60-minute value. We chose to focus on the V_d obtained at 60 minutes, as there is little decay in plasma concentration after that time in healthy subjects (11). Given the imperfections of the bromide method, our data will serve mostly as an approximation of the ECF volume and a background for the measurements with the other methods.

The study has some limitations. The number of subjects included was quite small. Although volunteers were studied, the methods are intended for use in intensive care patients. Therefore, the present work must be followed by other studies that test the clinical utility of the methods in critically ill patients. Although a reasonable steady state in fluid balance must be maintained during the measurement period, we believe that tracers with a fairly rapid elimination rate have a better chance to guide the clinician because they allow repeated use. The complexity of elimination and distribution of tracers can usually be resolved by pharmacokinetic analysis of the data. A drawback is that adequate separation of the parameters in the kinetic model requires that a series of samples from body fluids be taken. To measure the steady-state dilution of a tracer such as bromide, lower sampling intensity is required. Finally, although venous samples were used for all measurements, arterial blood would have better delineated the distribution phase of the iohexol kinetics and perhaps also revealed a distribution phase for the sodium dilution (14). The use of arterial sampling would modify the estimates of the V_d.

In conclusion, the three methods used in this study gave slightly different estimates of the ECF volume. The bromide method rests on insecure theoretical foundations and measured a larger space than the others. The iohexol method is appealing because it yields both the size of the ECF volume and the GFR. Moreover, the analytical equipment necessary for this tracer is increasingly available. The volume kinetic approach is also applied to a nonsteady-state situation but showed slightly lower values than iohexol.

Appendix

Bromide

The extracellular fluid (ECF) volume indicated by bromide ions (Br) is equivalent to the distribution volume (V_d) of this ion at time t after injection of a bolus dose injected at $t = 0$. The calculation is corrected for the minor urinary losses of Br, measured when the volunteers voided spontaneously at 122 ± 35 min (mean ± SD) of the study:

$$V_d = \frac{\text{Dose} - (\text{urine volume} \cdot \text{urinary Br conc.})}{(\text{Serum Br}_t - \text{Serum Br}_o)\ \text{conc.}} \cdot 0.9 \cdot 0.95 \cdot 0.934$$

where 0.9 is the correction factor for intracellular bromide, 0.95 corrects for the Donnan effect, and 0.934 is the correction for the water content of plasma (1,15).

Iohexol Kinetics

The disposition of iohexol followed a bi-exponential equation in which the concentration *C* at time *t* after a bolus dose is described by (20):

$$C_t = Ae^{-\alpha t} + Be^{-\beta t}$$

where α and β correspond to the initial and terminal slopes, respectively, and *A* and *B* represent the intercepts on the y-axis with $t = 0$. This equation corresponds to the parameters in the kinetic model (Fig. 1, top), as follows (18):

$$V_1 = \frac{\text{Dose}}{A + B};\ k_{21} = \frac{A\beta + B\alpha}{A + B};\ k_{10} = \frac{\alpha\beta}{k_{21}};$$

$$k_{12} = \alpha + \beta - k_{10} - k_{21};\ V_2 = \frac{V_1 k_{12}}{k_{21}}$$

The ECF space corresponded to the total V_d of iohexol at steady-state, V_{ss}, which is the sum of V_1 and V_2.

The clearance (*CL*) is given by the dose divided by the area under the curve (*AUC*) for the entire concentration-time profile. If the latter is unknown, it can be deduced from the equation describing this profile. Hence,

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta}$$

Sodium Dilution

The dilution of the serum sodium (SNa) concentration was used to estimate the dilution of the ECF space. In its simplest from, this relationship can be written as:

$$\frac{ECF_t - ECF_o}{ECF_o} = \frac{SNa_o}{SNa_t} - 1$$

where SNa_o is the serum sodium concentration at baseline (t = 0). Although further calculations *per se* do not require the assumption of the existence of the ECF space, the correction of dilution for sodium loss does, and ECF_o was then initially set to 20% of the body weight. Assuming that the number of sodium ions is constant in the ECF space except for losses that can be measured, we obtain:

$$ECF_o * SNa_o = Na\ amount_o$$

$$Na\ amount_t = Na\ amount_o - \text{urinary Na loss}_{(t-to)} - SNa_o * \text{sampled plasma volume}$$

$$ECF_t = \frac{Na\ amount_t}{SNa_t}$$

The relative expansion of the ECF volume yields the same result as the raw sodium dilution quoted above, but it becomes slightly shifted downward when sodium is lost.

In this study, the urinary excretion of sodium and water was not measured for each blood sample but only as the total amount during the experiment. To mimic the real situation, where more sodium and water are excreted depending on the ECF dilution (19), the losses were graded by calculating a parameter k_{Na} that describes the tendency to excrete sodium for any specific degree of ECF dilution:

$$k_{Na} = \frac{\sum \text{Excreted Na}}{AUC \text{ for } \dfrac{(ECF_t - ECF_o)}{ECF_o}}$$

This parameter, k_{Na}, multiplied by the ECF dilution and the time (*t*), then yields the cumulative sodium loss up to any time (*t*). Hence, by rearrangement:

$$\text{Excreted Na}_{(t-to)} = k_{\text{Na}} \cdot AUC_{(t-to)} \text{ for } \frac{(ECF_t - ECF_o)}{ECF_o}$$

The disposition of the infused fluid that dilutes the serum sodium concentration is described by the following differential equation (Fig. 1, bottom), in which the dilution is corrected according to the calculations of the expansion of the ECF space (16):

$$\frac{d\,ECF}{dt} = k_i - k_b - k_r \frac{ECF_t - ECF_o}{ECF_o}$$

where k_i is the infusion rate of mannitol 5%, k_b is an evaporation factor which is set to 0.5 mL/min, and k_r is a dilution-dependent elimination rate constant (16). During (d) infusion, this differential equation has the following solution:

$$w_d(t) = \frac{k_i - k_b}{k_r}(1 - e^{-kr\,t/ECF_o})$$

and after (a) infusion

$$w_a(t) = \frac{-k_b}{k_r}(1 - e^{-k_r(t-t_1)/ECF_o}) + w_d(t_1)e^{-k_r(t\,-\,t_1)/ECF_o}$$

where $w(t)$ is the dilution $(ECF_t - ECF_o)/ECF_o$ and t_1 is the infusion time.

On considering that approximately half of the basal fluid losses were represented by urine excretion, the parameter k_r was calculated as the renal clearance for infused fluid, assuming that half of the basal fluid losses appeared as urine:

$$k_r = \frac{\sum \text{urine volume } (T) - 0.5 * k_b * T}{AUC \text{ for } \frac{ECF_t - ECF_o}{ECF_o}}$$

where T is the total time of the experiment. The kinetic model was first fitted to measured data on SNa with a correction for sodium losses as described above. The computer repeated the analysis 4 times, using progressively more precise estimates of ECF_o as input, until the final ECF_o was taken as the size of the ECF.

Uncertainty of the Calculations

The kinetic equations used to calculate the ECF volume with the iohexol and sodium methods have no definitive solutions. Therefore, the parameters are estimated with some uncertainty, which can be quantified as an SD. The following list shows the uncertainty of pertinent estimates, described as the mean value for all 10 volunteers.

For iohexol:

$$V_1 = 0.4 \text{ L}; k_{10} = 0.8 \cdot 10^{-3} \text{ min}^{-1};$$

$$k_{12} = 4.8 \cdot 10^{-3} \text{ min}^{-1};$$

$$k_{21} = 8.7 \cdot 10^{-3} \text{ min}^{-1};$$

$$V_{ss} = 1.0 \text{ L}$$

For the sodium method:

$$V = 0.9 \text{ L}$$

These data of uncertainty serve as an adjunct to the evaluation of how the best estimates of each parameter vary between the volunteers, which is shown in Table 1.

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