

Volume kinetics of glucose solutions given by intravenous infusion[†]

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Glucose solutions given by intravenous (i.v.) infusion exert volume effects that are governed by the amount of fluid administered and also by the metabolism of the glucose. To understand better how the body handles glucose solutions, two volume kinetic models were developed in which consideration was given to the osmotic fluid shifts that accompany the metabolism of glucose. These models were fitted to data obtained when 21 volunteers who were given approximately 1 litre of glucose 2.5 or 5% or Ringer's solution (control) over 45 min. The maximum haemodilution was similar for all three fluids, but it decreased more rapidly when glucose had been infused. The volume of distribution for the infused glucose molecules was larger (~12 litres) than for the infused fluid, which amounted to (mean (SEM)) 3.7 (0.3) (glucose 2.5%), 2.8 (0.2) (glucose 5%), and 2.5 (0.2) litres (Ringer). Fluid accumulated in a remote (cellular) body fluid space when glucose had been administered (~0.2 and 0.4 litres, respectively), while expansion of an intermediate fluid space (7.1 (1.3) litres) could be demonstrated in 33% of the Ringer experiments. In conclusion, kinetic models were developed which consider the relationship between the glucose metabolism and the disposition of intravenous fluid. One of them, in which infused fluid expands two instead of three body fluid spaces, was successfully fitted to data on blood glucose and blood haemoglobin obtained during infusions of 2.5 and 5% glucose.

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Glucose solutions are frequently used to hydrate patients with acute disease or after surgery.^{1,2} The volume changes in the body fluid compartments when infusing glucose solutions differ from those seen when infusing balanced electrolyte solutions in that transport of glucose into the cells causes osmotic transport of water. Later, the translocated water equilibrates with the extracellular fluid space as metabolism of glucose eliminates the osmotic pressure of the glucose molecule. This makes the volume effect of infused glucose solutions difficult to predict.

The purpose of the present report was to evaluate whether volume kinetic principles³ can be used to study the disposition of the volume component of glucose solutions given by intravenous (i.v.) infusion. Volume kinetics has previously been used to analyse and simulate the effects of isotonic salt solutions in normo- and hypovolaemic

volunteers^{4–6} and also after surgery⁷ and trauma.⁸ These studies report the size of body volumes that become expanded and the rate at which fluid becomes distributed and eliminated. However, there was a need for a new kinetic model, which considers an additional volume located more peripherally. Successful application of such a model would make it possible to analyse the disposition of solutions that generate osmotic fluid shifts, which is what happens when glucose is taken up to the cells.

Materials and methods

Twenty-one healthy male volunteers, with no family history of diabetes, were included in two separate investigations.

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The first study comprised glucose 2.5% and the second glucose 5% and Ringer's acetate solution. The Local Ethics Committee approved both procedures and the informed consent of all subjects was obtained.

Glucose 2.5%

Twelve subjects aged between 24 and 36 (mean 28) yr of age and with a body weight of 62–113 (mean 79) kg participated. After an overnight fast, the volunteers rested comfortably on a bed for at least 20 min of equilibration before the experiments started at 08:00. Before any fluid was administered, a cubital vein of each arm was cannulated for the purpose of withdrawing (including sampling) blood and for infusing fluid, respectively. The volunteers were given an i.v. infusion of 12.5 ml kg⁻¹ of glucose 2.5% with electrolytes (Na 70, Cl 45 and acetate 25 mmol litre⁻¹; Rehydrex, Pharmacia, Uppsala, Sweden) at a constant rate over 45 min via an infusion pump (Flo-Gard 6201, Baxter Healthcare Ltd, Deerfield, IL, USA). Venous blood was collected every 5 min for 75 min and thereafter every 10 min up to 195 min. The plasma glucose concentration was measured in single samples except for the baseline, which was in duplicate. The blood haemoglobin (Hb_b) concentration, the red blood cell count (RBC), and the mean corpuscular volume (MCV) were measured in duplicate samples, and the baseline in quadruplicate samples. The heart rate and arterial pressure were measured using an automatic device (Propaq 104, Protocol Systems Inc., Beaverton, OR, USA) immediately after each blood sampling procedure. Venous blood was also withdrawn at 0, 45, 125, and 195 min to determine the serum concentrations of sodium, potassium, and insulin.

The subjects voided just before the infusions started and, in the recumbent position, whenever necessary during the study. The urine volume and its concentration of glucose, sodium, and potassium were measured.

Glucose 5% and Ringer's acetate

Nine subjects (mean age 27 yr, range 24–38, and body weight 79 kg, range 59–88) underwent two i.v. infusion experiments on separate days at least 1 week apart. On one of these occasions they received 1000 ml of glucose 5% without electrolytes over 45 min via the infusion pump. The same amount of Ringer's acetate solution (Na 130, K 4, Ca 2, Mg 1, acetate 30, and Cl 110 mmol litre⁻¹) was given on the other occasion (Pharmacia). Blood was sampled every 5 min for 135 min to measure RBC, MCV, and the Hb_b and plasma glucose concentrations. Venous blood was also withdrawn at 0, 45, 75, and 135 min to measure the serum concentrations of sodium, potassium, and insulin. Monitoring of haemodynamics and urine was the same as in the study of glucose 2.5%.

Blood chemistry

The plasma glucose (P-glucose) concentration was measured with the GLU Gluco-quant reagent (Boehringer Mannheim) on a Hitachi 917 (Hitachi Co., Naka, Japan). The Hb_b concentration was measured on a Technicon H2 (Bayer, Tarrytown, NY, USA) using colourimetry at 546 nm. RBC and MCV were measured with the same equipment, but by light dispersion at two angles using a helium neon laser. Before each infusion, one sample was drawn in duplicate or quadruplicate and the mean value was used in the calculations. The coefficients of variation for the samples were 1.2% for plasma glucose, 1.0% for Hb_b, 1.2% for RBC, and 0.5% for MCV. The serum concentration of insulin was determined by radioimmunoassay (Insulin RIA 100, Pharmacia) and the serum concentrations of sodium and potassium using an Ektachem 950IRC System (Johnson & Johnson, Inc., NY, USA).

Glucose kinetics

The volume of distribution for the glucose load (V_d) was used as the scaling factor between the P-glucose concentration and the amount of glucose that readily equilibrated with venous plasma. There is abundant evidence that the intracellular glucose belongs to another pool. First, the intracellular concentration of glucose is much lower than the extracellular concentration.⁹ Second, glucose is rapidly phosphorylated when translocated into, for example, muscle cells.¹⁰ Third, and probably most important, glucose requires an active transport mechanism to penetrate the cell membrane.⁹

To obtain V_d , the time–concentration profile of P-glucose for each glucose solution experiment was analysed according to a mono-exponential washout equation in which the plasma concentration (C) at any time (t) after a bolus injection of glucose is expressed as:

$$C = (C_0 - C_{\text{baseline}})e^{-k \cdot t} \quad (1)$$

where k is the elimination rate constant, C_0 is the concentration when the elimination function is extrapolated back to $t=0$, and is the mean of the duplicate determinations of P-glucose just before the infusion started. During a constant-rate infusion, the equation used for the curve-fitting procedure was:¹¹

$$C = (C_0 - C_{\text{baseline}}) (1 - e^{-k \cdot t}) / (kT) \quad (2)$$

where T is the infusion time. After infusion, it was:

$$C = (C_0 - C_{\text{baseline}}) [(e^{k \cdot t} - 1) / (kT)]e^{-k \cdot t} \quad (3)$$

This model was fitted to the data using the Model-PK non-linear regression program for PC (McPherson Scientific, Rosanna, Australia). Weights inversely proportional to the predicted concentrations were applied. Further calculations included the area under the curve (AUC), which was

obtained by the linear trapezoid method for the concentration–time profile of glucose in plasma. The clearance for the glucose load was obtained as the infused dose of glucose divided by the AUC and, in turn, the volume of distribution (V_d) as the clearance divided by k . The half-life ($T_{1/2}$) was obtained as the natural logarithm of 2 divided by k .

The following F test indicated whether it was statistically justified to fit the data to an equation that contained one more exponent ($n+1$) than the simpler equation (n):¹²

$$F = [(SSQ_n - SSQ_{n+1}) / SSQ_{n+1}] \times [df_{n+1} / (df_n - df_{n+1})] \quad (4)$$

where df is the degrees of freedom and SSQ is the sum of squares for the difference between the measured dilution of the plasma and the optimal curve fit. A high F value makes it more likely that the curve is best described by the more complicated model, and significance testing is done by consulting a standard statistical table.

According to Equation 4, the one-compartment open model was consistently justified for analysing the kinetics of the infused glucose load. As glucose is a small molecule, which easily diffuses across the plasma membrane¹³ but requires active transport to enter the cells, a decreasing amount of glucose in V_d corresponds to the uptake of glucose into a peripheral compartment, which does not equilibrate with venous plasma. Hence, the net uptake of glucose into this remote compartment was calculated for each interval between the earlier (time 1) and the later (time 2) sampling point. During infusion, it was obtained as:

$$\text{Uptake of glucose} = \text{infused glucose} - V_d (\text{P-glucose}_2 - \text{P-glucose}_1) \quad (5)$$

After infusion, it was:

$$\text{Uptake of glucose} = V_d (\text{P-glucose}_1 - \text{P-glucose}_2) \quad (6)$$

Volume kinetic models

In the model for kinetic analysis of the distribution and elimination of infused fluids (Fig. 1, upper), an i.v. infusion is given at a constant rate (k_i) and enters a central body fluid space having the volume (v_1). The volume (v_1) strives to be maintained at the baseline volume V_1 by allowing fluid to leave the space at a controlled rate proportional by a constant k_r to the deviation of v_1 from the target volume V_1 (this may be considered as dilution-dependent urinary excretion) and at a basal rate (k_b , perspiration and baseline diuresis, fixed rate). The net rate of fluid exchange between v_1 and v_2 is considered to occur at a rate proportional to the relative difference in deviation from the target values (V_1 and V_2) by a constant (k_t).

Osmotic shifts of fluid, if present, take place between V_2 and a more remote fluid space, V_3 , and has the strength $f(t)$.

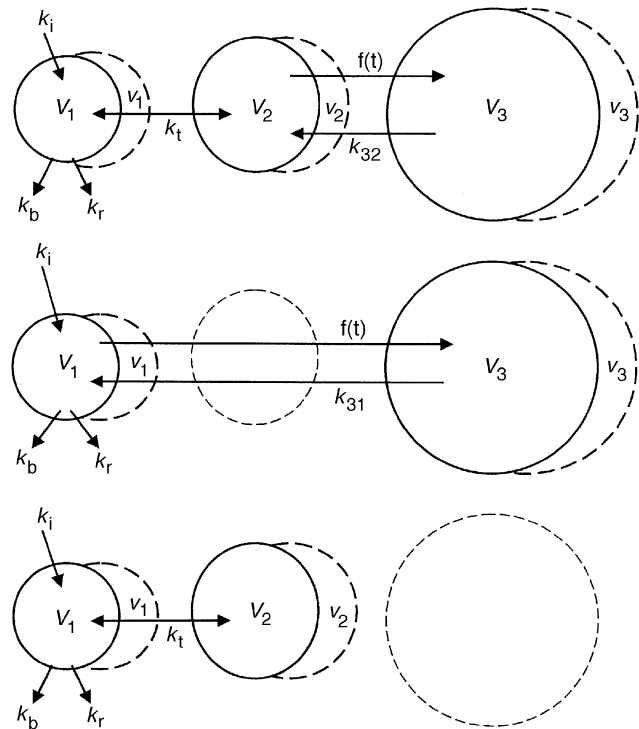


Fig 1 The model used to analyse the volume kinetics when an osmotic gradient acts like a driving force, $f(t)$, in the distribution of infused fluid (top). When glucose 2.5 and 5% were infused, expansion of V_2 did not become statistically significant, and water then entered V_3 in proportion to the insulin-dependent uptake of glucose to the cells (middle). Ringer's solution does not induce any marked osmotic fluid shift and, therefore, expands only one or two body fluid spaces, which communicate freely at a rate governed by a constant k_t (bottom). The elimination of fluid is given by basal fluid losses, k_b , and a renal mechanism which operates at a rate given by the product of k_r and the dilution of V_1 .

As all infused fluids were isotonic, the net transfer of water from v_2 to v_3 occurred at a rate governed directly by the osmotic pressure of glucose; 3.6 ml of water was translocated to v_3 per millimole of glucose taken up by V_3 . As water must accompany glucose in order to maintain equal osmolality inside and outside V_3 , the factor 3.6 was obtained from the osmolality of glucose when being in an isotonic solution; 1 litre contains 50 g of glucose, which is equal to 278 mmol, and each mmol is then capable of bringing along 1000 ml/278 mmol=3.6 ml of water. In the model, fluid also returns from v_3 to v_2 , which occurs at a rate proportional by a constant (k_{32}) to the dilution of V_3 .

Furthermore, V_2 was only reported if it was statistically justified by comparing a bi-exponential and tri-exponential curve by means of the F test (Equation 4). If V_2 was not statistically justified, the constant governing the diffusion of fluid from V_3 to V_1 was called k_{31} (Fig. 1, middle).

In order for the kinetic program to calculate the net balance of fluid between V_1 and V_3 (Fig. 1, lower), it required a starting estimate for V_3 . This was set at 40% of the body weight.⁴ The accumulation and elimination (k_{31}) of

Table 1 Results of pharmacokinetic analysis of the infused glucose molecules (top) and volume kinetic analysis of the accompanying fluid volume (below) when approximately 1 litre of iso-osmotic glucose 2.5% (left column) or glucose 5% (right column) solution was infused over 45 min in male volunteers. The first line for each parameter gives the mean (SEM) of all estimates in the respective group. The second line shows the precision of these estimates, specified as the mean (SEM) of the standard errors (SE) associated with them. ^aBecause of skewed distribution, these results are given as the median and 25th and 75th percentiles

	Glucose 2.5% (n=12)	Glucose 5% (n=9)
<i>Glucose kinetics</i>		
C ₀ (mmol litre ⁻¹)	11.8 (0.6)	24.4 (0.9)
SE	0.7 (0.1)	1.3 (0.1)
k (10 ⁻³ min ⁻¹)	61 (5)	49 (5)
SE	4 (1)	3 (1)
V _d (litre)	12.3 (0.9)	11.5 (0.4)
T _{1/2} (min)	12.1 (1.3)	15.7 (2.2)
Clearance (ml min ⁻¹)	0.72 (0.05)	0.54 (0.04)
Sum of squares	0.48 (0.13)	1.46 (0.43)
<i>Volume kinetics</i>		
V ₁ (litre)	3.68 (0.31)	2.70 (0.22)
SE	0.47 (0.07)	0.24 (0.03)
k _r (ml min ⁻¹)	66 (51,134) ^a	32 (16)
SE	16 (12,32) ^a	7 (1)
k ₃₁ /V ₃ (ml min ⁻¹)	2.1 (0.1,5.2) ^a	2.6 (1.8,3.0) ^a
SE	1.6 (1.4,4.9) ^a	0.7 (0.4,0.9) ^a
Sum of squares	0.075 (0.010)	0.100 (0.026)

fluid in V₃ could then be calculated and was presented as k₃₁/V₃ (Table 1), that is slope for the dilution of V₃.

f(t) was set to zero in the infusions of Ringer's acetate as the changes in blood glucose were very small. Here, both a one-volume and a two-volume model were fitted to the data on dilution (Fig. 1, lower), and the *F* test was again used to select the optimal one for presentation. The mathematical details involving *f(t)*=0 have been given in previous work^{3,5} while those for *f(t)*>0 are given in the Appendix.

Calculations

Volume kinetics

The dilution of the plasma in the cubital vein was used to quantitate the water load. As the sampled plasma is a part of *V*, we obtain:

$$(v(t) - V) / V = [\text{baseline Hb}_b / \text{Hb}_b(t) - 1] / (1 - \text{baseline haematocrit}) \quad (7)$$

at any time (*t*). The dilution of the RBC count was calculated in the same way as for Hb_b and the mean value of the two was used, after correction for changes in cell volume as indicated by MCV. Furthermore, a correction was always 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 based on the height and weight of subjects.¹⁴ A k_b of 0.8 ml min⁻¹ was used, which represents the sum of the insensible fluid loss of 10 ml kg⁻¹ day⁻¹ (0.5 ml min⁻¹)¹⁵ and the

withdrawn amount of extracellular fluid during blood sampling.

The model parameters were calculated on a computer using Matlab version 4.2 (Math Works Inc., Natick, MA, USA), in which a non-linear least-squares regression routine based on a modified Gauss–Newton method was used. Weights inversely proportional to the predicted dilution+0.1 were applied. The factor 0.1 was added to the denominator to avoid division by zero at baseline.

Sodium dilution method

The diffusion of fluid into the intracellular space was also estimated from a comparison between the distribution volume corresponding to the dilution of the serum sodium level and the actual amount of infused fluid and the urinary excretion of water and sodium.^{16,17} More details about the calculations are given in the Appendix.

Statistics

The results are expressed as the mean and the standard error of the mean (SEM). Differences between the experiments were evaluated by analysis of variance (ANOVA). Correlations between parameters were studied by simple and multiple linear regression; *P*<0.05 was considered significant.

Results

The Hb_b concentration decreased progressively during the glucose infusions but returned to baseline approximately 45 min after they were completed. Ringer's solution was, however, followed by a more persistent reduction in Hb_b (Fig. 2, top).

The plasma glucose and serum insulin concentrations increased in response to glucose 2.5 and 5%, whereas a slight reduction of them occurred during the infusion of Ringer's solution (Fig. 2, middle and lower). Glucose 5% induced mild hypoglycaemia; the mean plasma glucose level from 60 min after the infusion ended and onwards was below the normal range (3.6 mmol litre⁻¹) in six of nine infusions of glucose 5% (lowest 2.7 mmol litre⁻¹). In contrast, hypoglycaemia did not occur after any of the other infusion experiments (*P*<0.01 vs glucose 2.5%).

Plots of the dilution of venous plasma, with a correction for blood sampling, showed that dilution resulting from the three solutions had a similar time course (Fig. 3). Some of the volunteers receiving glucose showed a negative dilution at the end of the experiment.

Glucose kinetics

The volume of distribution for the administered glucose molecules was 12.3 and 11.5 litres, respectively, when glucose 2.5 and 5% were infused (Table 1, upper). The corresponding half-lives for the glucose loads were 12.1 and 15.7 min (non-significant differences). The AUC for plasma

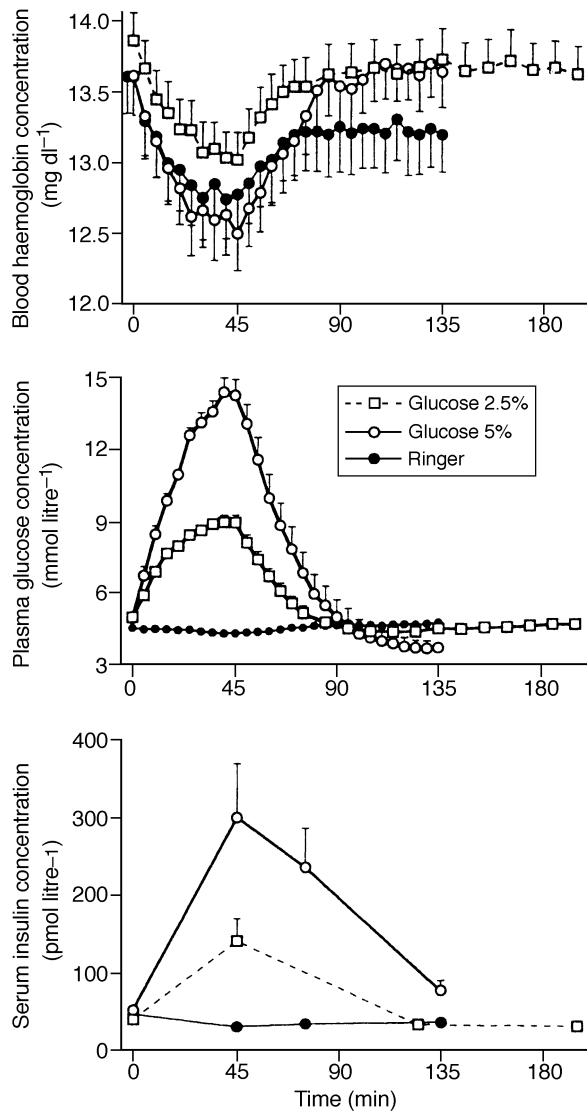


Fig 2 The blood haemoglobin (top), plasma glucose (middle) and serum insulin (bottom) concentrations during and after a 45-min i.v. infusion of approximately 1 litre of glucose 2.5%, glucose 5%, and Ringer's acetate solution in healthy male volunteers.

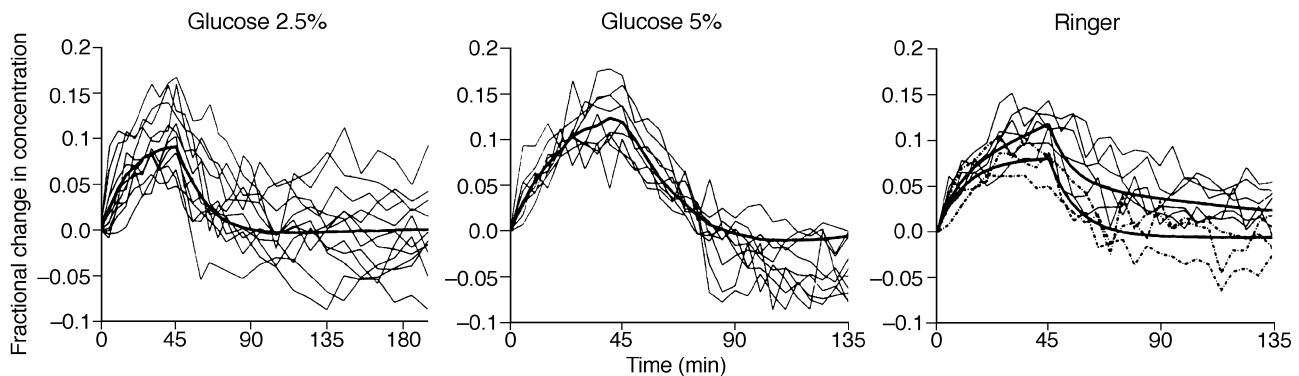


Fig 3 Dilution-time curves for individual volunteer experiments (fine lines) and a simulated curve based on the mean values for the parameter estimates obtained in the volume kinetic analysis of these experiments (thick lines). Two modelled curves are shown for Ringer's acetate (right figure) as the two-volume model was statistically justified in six of the nine experiments (upper thick line) and the one-volume model in the others (lower thick line), the latter being based on experiments illustrated by irregular fine lines.

glucose correlated strongest with the serum insulin concentration measured at 125–135 min ($r=0.82$, $P<0.001$).

The calculated uptake of glucose into V_3 increased progressively during the infusions, but it had returned to baseline 90 min after they were completed (Fig. 4). The calculated uptake of glucose for each time interval was then entered as the driving force for fluid uptake (3.6 ml mmol^{-1} glucose) into V_3 in the subsequent kinetic analysis.

Volume kinetics

In the case of glucose infusions, the two-volume kinetic model yielded relatively good curve fits, which were not improved by assuming that the infused fluid also expanded an intermediate body fluid space. The curve fits were relatively good also for the subjects who were given glucose 2.5% and who showed the highest inter-subject variability, as evidenced by Figure 5 and also by the modest standard errors for the parameter estimates (Table 1, lower). The three-volume model was either not statistically significant or the program did not converge to yield meaningful estimates. Therefore, the two-volume model was chosen for presentation.

The mean size of V_1 was 3.68 litres for the infusions of glucose 2.5% and 2.70 litres for glucose 5% (ANOVA, $P=0.03$). The elimination rate constant k_r differed more between the glucose experiments, the estimates being 77 and 32 ml min^{-1} , respectively ($P<0.07$; Table 1, lower). The estimates of k_{31}/V_3 varied more between the volunteers than the other parameters, and one volunteer who became haemoconcentrated after glucose 2.5% even showed a clearly negative k_{31}/V_3 (third patient in the top row of Fig. 5). There was no significant difference between the groups with respect to k_{31}/V_3 .

The two-volume model was statistically justified in six of the experiments with Ringer's acetate solution. The sizes of V_1 and V_2 were 2.39 and 7.12 litres, respectively (Table 2). The remaining three volunteers, who handled Ringer's solution according to the one-volume model, had rates of

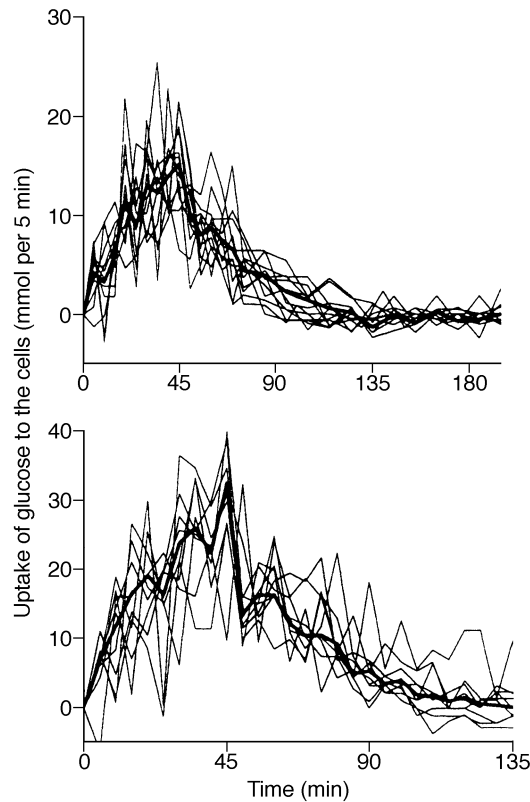


Fig 4 Calculated uptake of glucose into the cells during and after infusion of glucose 2.5% (upper) and glucose 5% (lower) for individual volunteer experiments (fine lines) and as the mean for the group (thick line).

fluid elimination, expressed as k_t/V_1 , nearly three times higher than the others (0.092 vs 0.032 min^{-1} ; $P < 0.03$).

Comparisons between the infusions

Plots based on the average parameter estimates were used to describe the body's handling of the infused fluids. The maximum dilution of V_1 was similar for all infusions, but it decreased more rapidly when glucose had been infused (Fig. 6, top). The trend was the same when the dilution-time curves were converted into volume-time plots by multiplying the function $(v_1(t) - V_1)/V_1$ by the estimate of V_1 to obtain $v_1(t) - V_1$ (Fig. 6, middle). The modelled volume change in the most remote fluid space, which was V_3 for glucose and V_2 for Ringer's, was most pronounced and long lasting for glucose 5% (Fig. 6, bottom).

Haemodynamics, sodium dilution, and urinary excretion

There were no significant changes in systolic and diastolic arterial pressure during the experiments. The heart rate increased significantly from 90 min and onwards during the experiments with glucose 5% (66.9 (2.7) vs 62.9 (2.4) beats

min^{-1} during infusion, $P < 0.001$). No corresponding change occurred after administration of glucose 2.5% (62.2 (1.3) vs 63.7 (1.4) beats min^{-1} during infusion).

The calculations of fluid shifts, based on the dilution of the serum sodium concentration, indicated the existence of a slight cellular accumulation of fluid at the end of the experiments with glucose 5% (Table 3). This fluid induced a smaller urinary loss of sodium and potassium than the other ones, while the volume of urine was larger in response to both glucose solutions than to Ringer's acetate.

Three of the volunteers who received glucose 5% had traces of glucose in their urine. The excreted glucose amounted to 5, 5, and 10 mmol (total amount infused 278 mmol). No glucose could be recovered from the urine when the other solutions were infused.

Discussion

Glucose solutions are not used as volume expanders, but they certainly exert volume effects in the body. The present study shows that the volume effect during infusion of isotonic glucose 2.5 and 5% solutions, as indicated by the acute haemodilution, is very close to that recorded for Ringer's solution. Further studies on the dilution-time curves were made by applying volume kinetic models to the data. In contrast to Ringer's solution, the kinetics of the glucose solutions needed to be analysed by taking into account the body's handling of a glucose load and the effects on water distribution exerted by the osmotic pressure of infused glucose. These results indicate that glucose solution expands a quite small functional body fluid space. The size of V_1 was close to the expected size of the plasma volume and, for many subjects given glucose 5% in sterile water, it was even smaller. Furthermore, we found no evidence that the infused fluid expanded a body fluid space between V_1 and V_3 , as is often the case with Ringer's solution.⁴⁻⁶ Consequently, no results are reported according to the three-volume model. The fluid that entered V_3 must have travelled through such a body fluid space (V_2) but apparently without expanding it to any significant degree. This might be the case in volume kinetics provided that the inflow and outflow of fluid to V_2 are roughly in balance.

The kinetic analysis further indicates that some of the infused fluid remained in the cells at the very end of the experiments when glucose 5% had been given. This view receives support from the sodium-based calculations of the net fluid over the cell membrane.^{15 16} The fact that 25 mmol of sodium was lost by urinary excretion, while no sodium was infused, might account for some of the cell accumulation of fluid. Furthermore, a fraction of the glucose might have been stored as glycogen, a process augmented by high insulin concentrations, before being metabolized into carbon dioxide and water. The fluid remaining in the cells might serve to explain why the total measured urinary excretion was smaller in response to glucose 5% than to

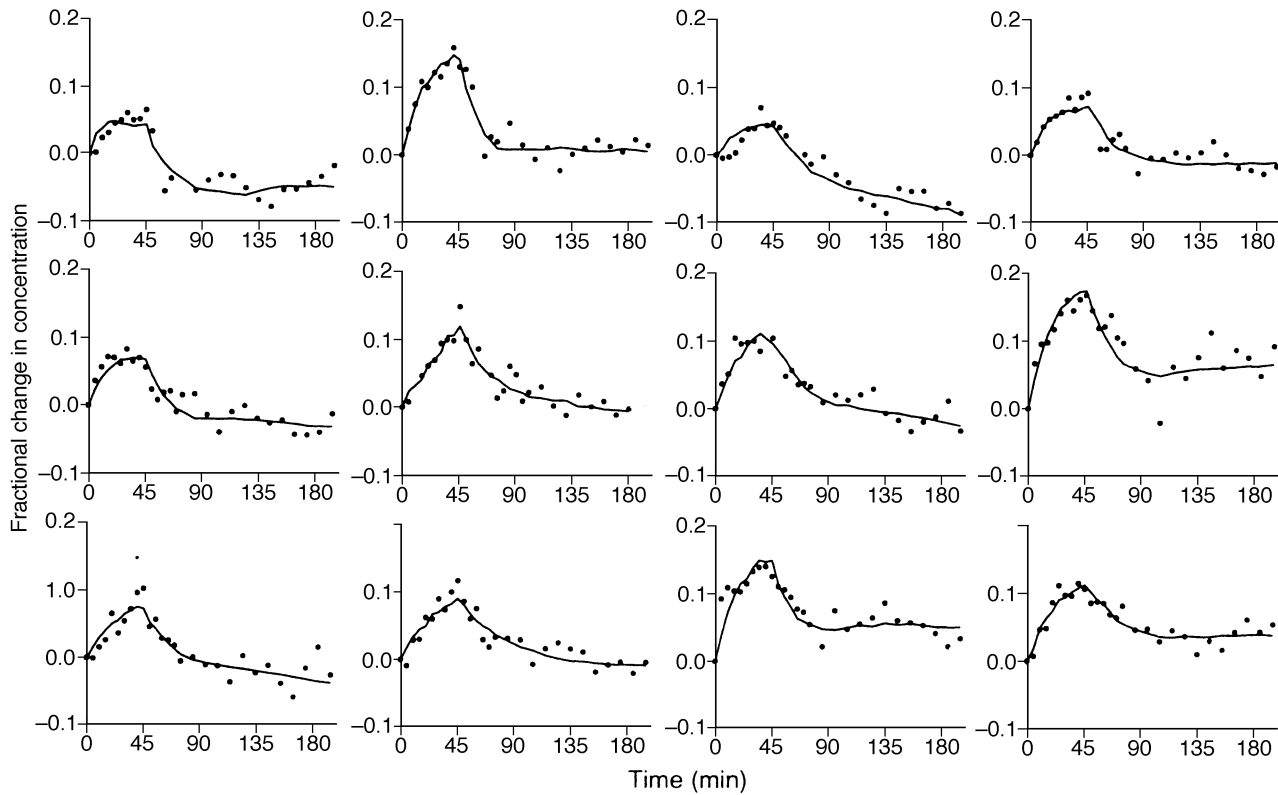


Fig 5 The fractional dilution of venous plasma in 12 experiments when 12.5 ml kg^{-1} of glucose 2.5% was given by i.v. infusion to male volunteers over 45 min (dots) and the curve fits resulting from the subsequent volume kinetic analysis (fine lines).

glucose 2.5%. The urinary excretion after infusion of Ringer's acetate was, however, only half as large as after the glucose infusions.

In our volunteers, the strong insulin response even promoted slight hypoglycaemia and hypovolaemia and probably also physical stress, as the heart rate increased only at the end of the experiments with glucose 5%. These adverse effects suggest that a lower infusion rate of glucose 5% should be recommended than the one we used in the present study. A similar post-infusion 'rebound hypoglycaemia' has been reported after sudden withdrawal of total parenteral nutrition,¹ and also in newborns after glucose solution has been given at a high rate to their mothers just before delivery by Caesarean section.^{19 20}

The slight glucosuria that occurred in some of the experiments with glucose 5% might have reduced k_{31} , as the kinetic models handle such events as if the infused glucose enters the cells while the accompanying fluid never returns to V_1 . Simulations showed that the impact of the glucosuria was small, however; the 'lost' glucose only constituted 3.6% of the infused amount in the most pronounced case. Another uncertainty is how precise the kinetic models are when the dilution is negative. In such cases, we set the dilution-dependent elimination of fluid to zero, although dilution-dependent mechanisms for the generation of urine probably operate with a delay and do not 'shut off' as soon

Table 2 Volume kinetic data for i.v. infusions of 12.5 ml kg^{-1} of Ringer's solution over 45 min in nine male volunteers. The results are reported according to whether the one-volume or the two-volume model was statistically justified. The data are the means (SEM). The first line for each parameter gives the estimate and the second line shows the standard error (SE) associated with this estimate

Parameter	Estimate
<i>One-volume model</i>	
n	3
V (litre)	2.84 (0.16)
SE	0.81 (0.29)
k_t (ml min^{-1})	282 (39)
SE	35 (13)
Sum of squares (10^{-3})	0.092 (0.032)
<i>Two-volume model</i>	
n	6
V_1 (litre)	2.39 (0.26)
SE	0.53 (0.12)
V_2 (litre)	7.12 (1.25)
SE	1.38 (0.27)
k_1 (ml min^{-1})	173 (27)
SE	48 (11)
k_t (ml min^{-1})	62 (16)
SE	16 (3)
Sum of squares (10^{-3})	0.031 (0.004)

as zero dilution is reached. Hence, the measured urinary excretion during the period of hypovolaemia sometimes exceeded the volume indicated by k_b alone.

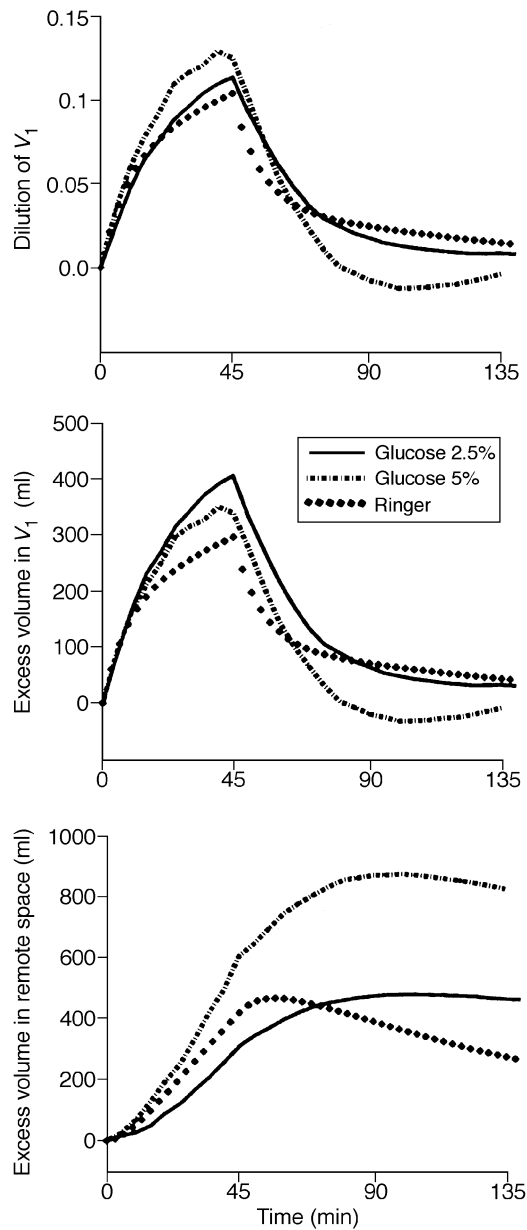


Fig 6 Simulations of the dilution of V_1 (top), the volume change of V_1 (middle), and the volume change of the most remote body fluid space, V_2 or V_3 (bottom), when about 1 litre of glucose 2.5%, glucose 5%, and Ringer's acetate solution are infused at a constant rate over 45 min. The curves were based on the mean values obtained in the volume kinetic analyses shown in Tables 1 and 2. For Ringer's acetate, however, the simulated curve is the weighted mean for the three experiments analysed by the one-volume model and the six analysed by the two-volume model, that is dilution $(t) = (3 \times \text{one-volume curve } (t) + 6 \times \text{two-volume curve } (t))/9$.

The derived volume kinetic models may be used to understand the relationship between the disposition of fluid given i.v. and the glucose metabolism. We hope that there will be a useful asset in studies of fluid balance during and after surgery, such as when evaluating the effects of surgery-induced insulin resistance on the disposition of infused fluid. When both the glucose kinetics and the

Table 3 Calculated accumulation of fluid in the cells at the end of each experiment and the measured urinary excretion of fluid, sodium, and potassium (mean (SEM)). ^aThe change in intracellular fluid (ΔICF) volume was indicated by the serum sodium method

	Glucose 2.5%	Glucose 5%	Ringer's acetate	ANOVA
ΔICF (ml) ^a	60 (70)	218 (86)	-100 (40)	$P < 0.01$
Urine volume (ml)	1022 (145)	841 (118)	472 (96)	$P < 0.01$
Urinary sodium (mmol)	63 (11)	25 (3)	51 (11)	$P < 0.04$
Urinary potassium (mmol)	26 (3)	9 (2)	15 (2)	$P < 0.001$

volume kinetics have been analysed, a simulation program can predict, for example, the effect of a reduction in the glucose clearance on the disposition of infused fluid. Such programs have been constructed. Before they are used, however, more volunteer experiments are needed to outline how much k_r and k_{31} normally change at different infusion rates and glucose concentrations, as these parameters varied much more than the size of V_1 in the present study. The volume kinetic parameters have previously been found to be quite similar when Ringer's acetate is given at different infusion rates.^{4 18}

The kinetic models derived here are also valid for other fluids, which induce a fluid shift to or from V_3 as a result of osmotic forces, such as hypertonic saline with and without dextran added. Their usefulness is not changed by the fact that glucose and hypertonic solutions shift fluid in opposite directions. In the case of hypertonic saline, calculating $f(t)$ is easy as it can be deduced directly from the infused amount of sodium.

In conclusion, kinetic models showing the relationships between the disposition of infused fluid and the glucose metabolism were developed and successfully applied to data from volunteers. Glucose 2.5 and 5% expanded a functional body fluid space of similar size as the plasma volume when account had been taken of the fluid shifts associated with the metabolism of glucose.

Appendix

Volume kinetics

When glucose is infused, uptake of glucose into the cells (V_3) is followed by a fluid shift in proportion to the change in osmolality across the cell membrane, $f(t)$. In cases where an intermediate body fluid space between V_1 and V_3 is not statistically significant, the differential equations showing the changes in volumes v_1 and v_3 , respectively, are:

$$\begin{cases} \frac{dv_1}{dt} = k_i - k_b - k_r \frac{v_1 - V_1}{V_1} - f(t) + k_{31} \frac{v_3 - V_3}{V_3}, & v_1(0) = V_1 \\ \frac{dv_3}{dt} = f(t) - k_{31} \frac{v_3 - V_3}{V_3}, & v_3(0) = V_3 \end{cases} \quad (8)$$

Introduce

$$w_1 = \frac{v_1 - V_1}{V_1}, \quad w_2 = \frac{v_3 - V_3}{V_3}$$

and we obtain:

$$\begin{cases} \frac{dw_1}{dt} = \frac{k_i - k_b}{V_1} - \frac{k_r}{V_1} w_1 - \frac{1}{V_1} f(t) + \frac{k_{31}}{V_1} w_2 \\ \frac{dw_2}{dt} = \frac{1}{V_3} f(t) - \frac{k_{31}}{V_3} w_2 \end{cases} \quad (9)$$

These differential equations cover the volume kinetics model in the following three cases, infusion ($k_i > 0$), no infusion ($k_i = 0$), and $w_1 < 0$, in which case $k_r = 0$. The initial values of the process are $w_1(0) = 0$ and $w_2(0) = 0$. At time $t = T_1$, the infusion stops, and the solution then has the values $w_1(T_1) = w_{1T1}$ and $w_2(T_1) = w_{2T1}$. We continue with these values as initial values and $k_i = 0$. If, at time $t = T_2$, $w_1(T_2) = 0$ and $dw_1/dt(T_2) < 0$, we set $k_r = 0$ and continue the solution of (2) with the initial values $w_1(T_2) = 0$, $w_2(T_2) = w_{2T2}$.

Introduce vector and matrix notation:

$$\bar{w} \begin{pmatrix} w_1 \\ w_2 \end{pmatrix}, \quad A = \begin{pmatrix} -(k_r/V_1) & (k_{31}/V_1) \\ 0 & (k_{31}/V_3) \end{pmatrix},$$

$$\bar{a}(t) = \begin{pmatrix} (k_i - k_b)/V_1 - (f(t)/V_1) \\ (f(t)/V_3) \end{pmatrix} \quad (10)$$

The differential equations in Equation 9 can be written as:

$$\frac{d\bar{w}}{dt} = A\bar{w} + \bar{a}(t) \quad (11)$$

The solution of this linear system of differential equations is:

$$\bar{w}(t) = e^{A(t-T)}\bar{w}(T) + \int_T^t e^{A(t-s)}\bar{a}(s) ds \quad (12)$$

where e^{At} is the exponential matrix, T is the initial time, and $\bar{w}(T)$ 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

$$\bar{w}_{k+1} = e^{A\Delta t}\bar{w}_k + (e^{A\Delta t} - I)A^{-1}\bar{a}_k, \quad k = 0, 1, \dots, N-1 \quad (13)$$

where $\Delta t = t_{k+1} - t_k$, $\bar{w}_0 = \bar{w}(T)$ and provided that A is non-singular. In cases where $k_r = 0$, however, A is singular

and the recursion formula (Equation 13) cannot be used. Instead, we use

$$\bar{w}_{k+1} = e^{A\Delta t}\bar{w}_k + [\Delta t(I + \alpha A) - \alpha^2(1 - e^{-\Delta t/\alpha})A]\bar{a}_k \quad (14)$$

where $\alpha = V_3/k_{31}$.

The *three-volume model* is described by Equation 9 with

$$\bar{w} = \begin{pmatrix} w_1 \\ w_2 \\ w_3 \end{pmatrix},$$

$$A = \begin{pmatrix} (-k_r/V_1) - (k_t/V_1) & (k_t/V_1) & 0 \\ (k_2/V_2) & -(k_t/V_2) & (k_{32}/V_2) \\ 0 & 0 & (-k_{32}/V_3) \end{pmatrix},$$

$$\bar{a}(t) = \begin{pmatrix} (k_i - k_b)/V_1 \\ (-f(t)/V_2) \\ (f(t)/V_3) \end{pmatrix} \quad (15)$$

The solution is given by Equation 12, and after approximating $\bar{a}(t)$ with piecewise constant values as in the two-volume model, the numerical solution is obtained from Equation 13; the matrix A is non-singular also in the special case $k_r = 0$.

Sodium dilution method

As sodium ions (Na) are distributed throughout the extracellular fluid (ECF) space, the serum sodium concentration at any time (t) during or after i.v. infusion of fluid (S-Na_t) equals the amount of Na in the ECF volume divided by the current ECF volume. This relationship can be expressed as:

$$S - Na_t = \frac{\text{Added Na} + (S - Na_0 \times ECF_0 - Na_{\text{loss}})}{(ECF_0 + \text{infused volume} - \text{urine volume} - \Delta ICF)} \quad (16)$$

where $S - Na_0$ and ECF_0 are the serum sodium concentration and ECF volume at baseline, respectively, Na_{loss} is the natriuresis (in mmol), and ΔICF is the change in the water content of the intracellular fluid compartment. As ECF_0 corresponds to 20% of the body weight,⁸ ΔICF could be calculated by rearranging Equation 16:

$$\Delta ICF = ECF_0 + (\text{infused} - \text{urine})\text{volume} - \frac{\text{Added Na} + (S - Na_0 \times ECF_0 - Na_{\text{loss}})}{S - Na_t} \quad (17)$$

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