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Validation of volume kinetic analysis of glucose 2.5% solution given by intravenous infusion

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Background. The distribution and elimination of glucose solutions can be analysed by means of a volume kinetic model, but the ability of the model to predict plasma dilution ('model linearity') has not been evaluated.

Methods. Six male volunteers received four separate infusions of glucose 2.5%: 10 ml kg^{-1} and 15 ml kg^{-1} over 30 min, and 15 ml kg^{-1} and 25 ml kg^{-1} over 60 min. The kinetic model was fitted to measurements of plasma glucose concentration and haemodilution.

Results. The mean volume of distribution for the glucose was 9.2 (SEM 0.4) litres while the infused fluid expanded a central body fluid space (V_1) of 3.1 (0.3) litres. Increasing the amount of infused fluid, but not the infusion rate, resulted in a proportional increase in the area under the curve for plasma glucose and plasma dilution, the only confounder being glycosuria. The bias of computer simulation was slightly increased by rebound hypoglycaemia, which could occur with the highest infusion rates, but the accuracy was almost identical regardless of whether the kinetic parameters from all 24 experiments or from any of the subgroups were used.

Conclusion. The volume kinetic model for glucose 2.5% is linear and can therefore be used for computer simulation as long as marked glycosuria does not occur.

Glucose solutions are administered i.v. for nutritional and fluid balance support following surgery.[1 2] In some countries, glucose is also infused during surgery as a means of supplying 'free water', which remains after the glucose has been metabolized, to replace evaporation losses.[3] Glucose given before surgery reduces the insulin resistance resulting from surgical trauma[4] and these solutions given together with insulin may even improve survival during intensive care after cardiac surgery.[5] The fluid used as a carrier of the glucose constitutes a substantial volume, which should be considered when evaluating the need for plasma volume support. However, the volume effect is difficult to predict as water is carried along when glucose is taken up by the cells.

Glucose is usually supplied as a 5% solution, although 2.5% might be more useful in the surgical patient.[6 7] Recently, a volume kinetic model in which the glucose metabolism is considered was used to analyse the distribution and elimination of these fluids.[8] The proposed model

enabled separation of osmotic-driven translocation of fluid, which is affected by diabetes and postoperative insulin resistance, from dilution-dependent elimination, which also becomes impaired by surgery[9] and blood loss.[10]

In the present study we evaluate whether the kinetic model proposed for glucose solutions is linear, that is, whether the kinetic analysis shows the same result regardless of how fast and how much of the fluid is infused. Linearity is required for the kinetic model to be used to simulate the outcome of experiments not performed. For this purpose, glucose 2.5% was infused at four different rates in six male volunteers. The volumes were differentiated by continuing the infusions for 30 or 60 min.

Materials and methods

After approval by the local ethics committee, six healthy male volunteers aged 24–33 yr (mean 30 yr) and with a body

Table 1 Infusion data for the four series of experiments performed on different occasions in six male volunteers. Data are mean (SEM where applicable). Divide by 0.18 to convert g glucose to mmol glucose

Infusion rate (ml kg^{-1} h^{-1})	15	20	25	30
Infusion time (min)	60	30	60	30
Infused fluid volume (ml kg^{-1})	15	10	25	15
Infused fluid volume (ml)	1151 (97)	760 (64)	1922 (159)	1147 (95)
Infused glucose (g)	28.7 (2.4)	19.0 (1.6)	48.1 (4.0)	28.7 (2.4)

weight of 60–95 kg (mean 77 kg) agreed to participate. None had a family history of diabetes. On four separate occasions, each volunteer received one i.v. infusion of iso-osmotic glucose 2.5% with electrolytes (sodium 70 mmol litre^{-1}, chloride 45 mmol litre^{-1} and acetate 25 mmol litre^{-1}; Rehydrex, Pharmacia, Uppsala, Sweden) via an infusion pump (Flo-Gard 6201, Baxter Healthcare Ltd, Deerfield, IL, USA).

The infusion programme was chosen to disclose differences in kinetics by varying the rate of administration (15, 20, 25 and 30 ml kg^{-1} h^{-1}) and the infusion time (30 and 60 min) while still aiming at avoiding glycosuria (Table 1).

Measurements

After fasting overnight, the volunteers rested comfortably on a bed with an equilibration period of at least 30 min before the experiments started at 8.00 a.m. Before any fluid was administered, one cubital vein on each arm was cannulated. Fluid was infused through one of them. Venous blood was collected from the cannula in the opposite arm every 5 min during the 30-min infusions and every 10 min during the 60-min infusions. After the infusions, venous blood was withdrawn every 10 min up to 90 min and every 15 min thereafter until 120 min after the infusion ended. 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.

The plasma glucose concentration was measured in single samples using the GLU Gluco-quant reagent (Roche Diagnostic Inc., Mannheim, Germany) on a Hitachi 917 (Hitachi Co., Naka, Japan). The blood haemoglobin (Hb) concentration, the red blood cell count (RBC) and the mean corpuscular volume (MCV) were measured in single samples and the baseline in triplicate samples, using a Technicon Advia 120 (Bayer, Tarrytown, NY, USA). Hb was obtained by colorimetry at 546 nm and RBC and MCV were measured by light dispersion at two angles using a helium neon laser. The coefficient of variation, as calculated from the baseline samples, was 1.0% for Hb, 1.2% for RBC and 0.5% for MCV. The serum concentration of insulin was measured using a Mercodia insulin ELISA kit (Mercodia AB, Uppsala, Sweden) with a coefficient of variation of 5% for the baseline level and 4.4% for the higher concentrations in the study.
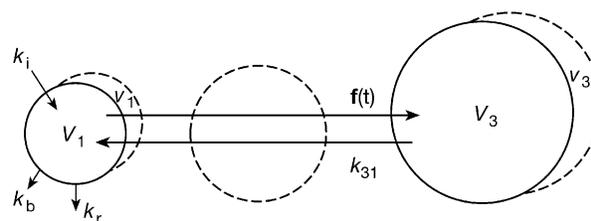

Fig 1 The model used to analyse the volume kinetics when an osmotic gradient acts like a driving force, f(t). Infused fluid is distributed in a volume V_1 and enters, by virtue of osmosis, a distant fluid space V_3. After metabolism, the fluid equilibrates again between V_1 and V_3 at a rate determined by k_{31}. The elimination of fluid is given by basal fluid losses, k_b, and a renal mechanism that operates at a rate given by the product of k_r and the dilution of V_1.

The subjects voided just before the infusions started and, in the recumbent position, whenever necessary during the study. All volunteers also voided at the end of the study. The urine volume and its concentration of glucose, sodium and potassium were measured using a Hitachi 917 System (Hitachi Co., Naka, Japan).

Glucose kinetics and uptake

The WinNonlin Standard 1.5 program (Pharsight Corp., Mountain View, CA, USA) was used to calculate the volume of distribution (V_d), area under the curve (AUC), clearance (CL) and half-life ($T_{1/2}$) of the infused glucose. The input was the glucose concentration above baseline, and the kinetic analysis was ended when the concentration had returned to baseline. Weights inversely proportional to the predicted concentration were applied. When analysing the results statistically using the F-test, the one-compartment open model was consistently justified.[8]

Since glucose 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 that does not equilibrate with venous plasma. The net uptake of glucose into this remote compartment was calculated for each sampling interval as the product of V_d and the incremental change in plasma glucose concentration. During the infusion, the calculation of the incremental net uptake also took account of the amount of glucose added to the system. The equations used for the kinetic analysis and for calculating glucose uptake were given in a previous study.[8]

Volume kinetic models

The distribution and elimination of infused fluid was studied by volume kinetic analysis[8–10] (Fig. 1). An i.v. infusion given at a constant rate (k_i) enters a central body fluid space having the volume (v_1) which 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 V_1 and at a low basal rate (k_b, fixed rate). Osmotic

Table 2 Results of pharmacokinetic analysis of the infused glucose molecules when iso-osmotic glucose 2.5% solution was infused in male volunteers. The first line for each parameter gives the mean (SEM) of all estimates in the respective groups. The second line shows the precision of these estimates, specified as the mean (SEM) of the standard errors associated with them. V_d, volume of distribution; CL, clearance; $T_{1/2}$, half-life; AUC, area under the curve for plasma glucose

	Infusion rate (ml kg^{-1} h^{-1})			
	15	20	25	30
V_d (litre)	8.20 (0.85)	9.24 (0.80)	9.26 (0.69)	10.21 (0.75)
Standard error	0.78 (0.13)	0.72 (0.07)	0.84 (0.13)	0.58 (0.11)
CL (litre min^{-1})	0.66 (0.12)	0.61 (0.08)	0.54 (0.03)	0.56 (0.08)
Standard error	0.03 (0.01)	0.03 (0.01)	0.03 (0.00)	0.03 (0.01)
$T_{1/2}$ (min)	10.9 (3.2)	12.1 (2.5)	12.2 (1.2)	15.9 (5.2)
Standard error	0.8 (0.1)	1.1 (0.2)	1.1 (0.2)	1.2 (0.3)
AUC (mmol litre^{-1} min^{-1})	281 (78)	192 (34)	503 (39)	281 (51)
Standard error	13 (2)	10 (2)	24 (4)	14 (3)
Dose (mmol)	160 (13)	106 (9)	267 (22)	160 (13)

fluid shifts take place between V_1 and a more remote fluid space, V_3, and have the strength f(t). As all infused fluid was isotonic, f(t) is governed in the absence of glycosuria by the net uptake of glucose into the remote compartment and the osmotic pressure of glucose; 3.6 ml water was translocated to v_3 per mmol 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 (50 g litre^{-1} or 278 mmol litre^{-1} being isotonic). In the model, fluid also returns from v_3 to v_1, which occurs at a rate proportional by a constant (k_{31}) to the dilution of V_3. The starting estimate for V_3 in the curve-fitting procedure was 40% of the body weight,[11] but the kinetic output is presented as k_{31}/V_3 (i.e. the slope for the dilution of V_3) as its volume could not be determined with confidence.

The possibility of a body fluid space between V_1 and V_3 being expanded was considered by fitting a three-volume model[8] to the data, but meaningful parameter estimates could not be obtained or the expansion of a third volume was not justified according to the F-test.

Calculations of fluid distribution

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

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

at the time t of the experiment. The dilution of the RBC count was calculated in the same way as for Hb and the mean value of the two was used after correction for changes in cell volume as indicated by MCV. Furthermore, a correction of the dilution was always made for the withdrawn amount of erythrocytes based on the baseline blood volume, as estimated according to a regression formula based on the height and weight of the subjects.[8] A k_b of 0.8 ml min^{-1} was used, which represents the sum of the insensible fluid loss of 0.5 ml min^{-1} and the amount of extracellular fluid withdrawn during blood sampling.[3]

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 plus 0.1 were applied.

Predictive performance measures

Computer simulations were made to assess the linearity of the kinetic systems. The residual error between the measured data points in each experiment and the computer-simulated (predicted) values for the group, based on the best parameter estimates according to Tables 2 and 3, was used to describe how well the kinetic model fitted the data. The results were expressed as the median residual error, which shows whether the measured data points are systematically higher or lower than the predicted ones (i.e. the bias), and the median absolute residual error, which reflects the degree of deviation of measured from predicted data points (i.e. the inaccuracy).

The following equation used V_d and CL to obtain the predicted glucose concentration during the infusion:[12]

$$C = \frac{k_i}{CL}\left(1 - e^{-CL^*t/V_d}\right)$$

After the infusion, it is:

$$C = \frac{k_i}{CL}\left(1 - e^{-CL^*T/V_d}\right)e^{-CL^*(t-T)/V_d}$$

where T is the infusion time. The resulting osmotic strength, f(t), and the dilution of V_1 were simulated using solutions to the differential equations described previously.[8]

Table 3 Volume kinetic parameters and urinary excretion during and after infusion of glucose 2.5% in male volunteers. The first line for each kinetic parameter gives the median (25–75th percentile range) 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 associated with them. V_1=the size of the central body fluid space; k_r=dilution-dependent elimination rate governed only by excess fluid in the system; k_{31}/V_3=the slope of the curve for the elimination of fluid from V_3

	Infusion rate (ml kg^{-1} h^{-1})			
	15	**20**	**25**	**30**
V_1 (litre)	2.37 (0.57)	3.16 (0.63)	3.62 (0.50)	3.40 (0.46)
Standard error	0.68 (0.26)	0.50 (0.14)	0.53 (0.10)	0.47 (0.14)
k_r (ml min^{-1})	100 (69–105)	104 (68–110)	105 (84–199)	125 (121–147)
Standard error	25 (11–51)	25 (14–35)	16 (12–43)	17 (13–23)
k_{31}/V_3 (10^{-3} min^{-1})	10.0 (5.9–13.5)	10.9 (0.6–20.6)	2.8 (1.1–5.1)	2.1 (0.22–15.3)
Standard error	10.8 (4.6–24.1)	10.5 (2.6–24.5)	1.5 (1.3–2.3)	2.4 (1.9–89.4)
Urinary excretion (ml)	748 (90)	460 (113)	1188 (213)	766 (133)
Urine/infused fluid	0.64 (0.03)	0.57 (0.10)	0.60 (0.07)	0.66 (0.09)
Sodium excretion (mmol)	38 (6)	36 (16)	45 (15)	45 (10)

Statistics

The results are expressed as the mean (SEM). Data showing a skewed distribution were given as the median and the 25–75th percentile range. The AUC for the plasma glucose and plasma dilution were calculated by the linear trapezoidal method for as long as the data points exceeded baseline. Differences between and during the experiments were evaluated by repeated-measures ANOVA. Correlations between parameters were studied by simple and multiple linear regression; $P<0.05$ was considered significant.

Results

Glucose kinetics

The plasma glucose concentration increased markedly in response to the infusions (Fig. 2). Kinetic analysis of the concentration–time curves showed an overall V_d for glucose of 9.23 (0.39) litre, a CL of 0.59 (0.04) litre min^{-1} and a half-life of 12.8 (1.6) min (Table 2). The AUC vs the amount of administered glucose was the only statistically significant relationship between the infusion parameters and these kinetic parameters (Fig. 3).

Slight glycosuria (1–5% of the infused amount) was observed during five experiments, while excretion of 8.5% was observed in one patient and 10.5% in another patient. Glycosuria did not influence the kinetics of glucose as indicated by V_d and CL.

Fluid kinetics, area approach

The AUC of the dilution–time profile increased with the volume of infused glucose solution (Fig. 4A). The AUC response to infused fluid tended to change for higher infusion rates, but this relationship was not statistically significant (Fig. 4B). This lack of linearity could be accounted for by glycosuria, which reduced the AUC ($r=-0.51$, $P<0.01$).
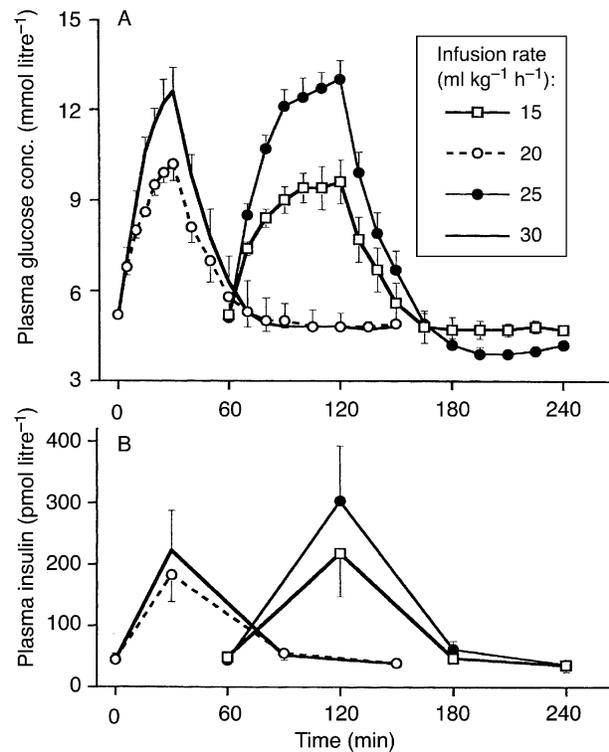

Fig 2 The plasma glucose (A) and insulin (B) concentrations during and after infusions of glucose 2.5% at 15, 20, 25 and 30 ml kg^{-1} h^{-1}. Data are mean (SEM).

Fluid kinetics, compartment analysis

In all 24 experiments, V_1 amounted to 3.14 (0.26) litres, k_r to 104 (9) ml min^{-1} and the ratio k_{31}/V_3 to 5.5 (0.8–12.8) min^{-1}. Separate data for the four series of experiments and the corresponding curve fits and residual plots are shown in Table 3 and Fig. 5, respectively.

Predictive performance measures

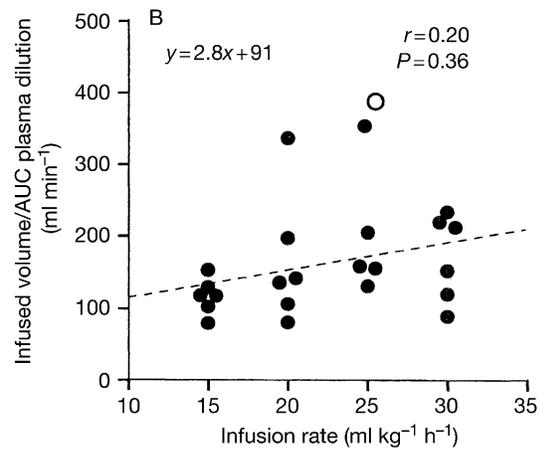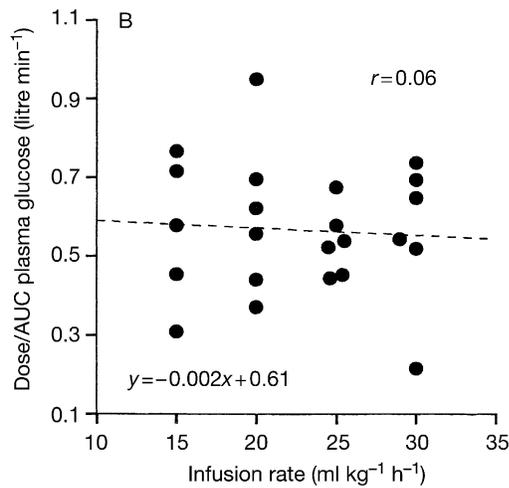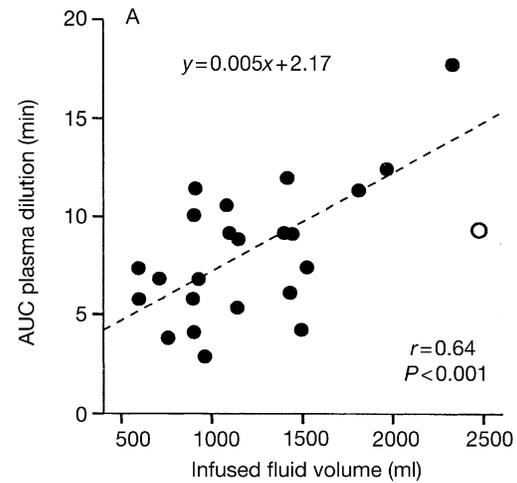The ability of the glucose parameters (Table 2) and volume kinetic parameters (Table 3) to predict the dilution–time
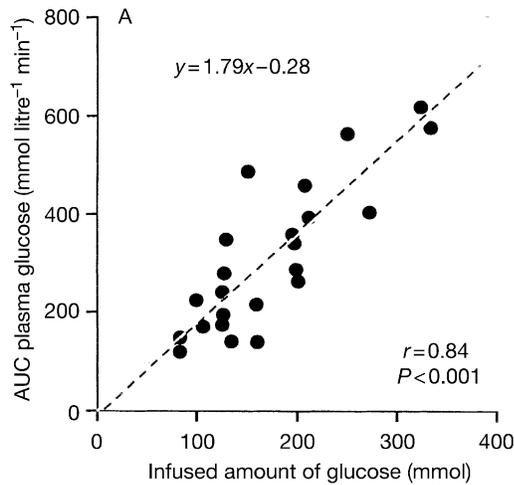
Fig 3 Increase in the area under the curve (AUC) for plasma glucose concentrations for larger amounts of infused glucose 2.5% (A) and the relationship between the ratio of these two parameters (i.e. the clearance) and the rate of infusion (B). Each point represents one experiment.

Fig 4 Increase in the area under the curve (AUC) for the dilution of venous plasma for increasing amounts of infused glucose 2.5% (A) and the relationship between the ratio of these two parameters and the rate of infusion (B). The open circle, which represents the experiment with the most pronounced glycosuria, was not included in the linear regression analyses. Glycosuria was detected in all three outliers in (B).

curves was evaluated by calculating the residual errors between measured and predicted data.

For all 24 experiments, the median residual error was −0.009 (SEM 0.005) dilution units. Most of this error could be attributed to the inability of the glucose simulation program to predict concentrations below baseline; the dilution of V_1 was therefore slightly overestimated during the late stages of the experiments. This error was reduced to −0.003 (0.006) on considering only the data obtained during infusion and 30 min after infusion.

The overall median absolute residual error was 0.026 (0.003), which did not change on exclusion of the late stages of the experiments. This error was less than 0.01 dilution units higher when any dilution–time curve was simulated using the average parameter estimates for all 24 experiments, compared with when it was based on its own series of six infusions. These actual differences for the four series of experiments averaged +0.004, −0.003, −0.006 and +0.005 (Table 4).

Urinary excretion and haemodynamics

The proportion of the infused fluid that was excreted varied very little in the four series of experiments, the overall mean being 62% (Table 3).

As expected, the renal clearance of the infused fluid (urine volume divided by the AUC for dilution) correlated with the elimination rate constant (k_r) yielded by the compartment analysis (Fig. 6A).

The sodium excretion was similar in the groups, the total excretion being 41 (6) mmol (differences were not significant, Table 3). This implies that sodium retention was greater when larger amounts of fluid were infused, a relationship that was only disturbed by glycosuria (Fig. 6B). Multiple linear regression analysis confirmed that both the infused fluid volume ($P<0.001$) and glycosuria (inverse
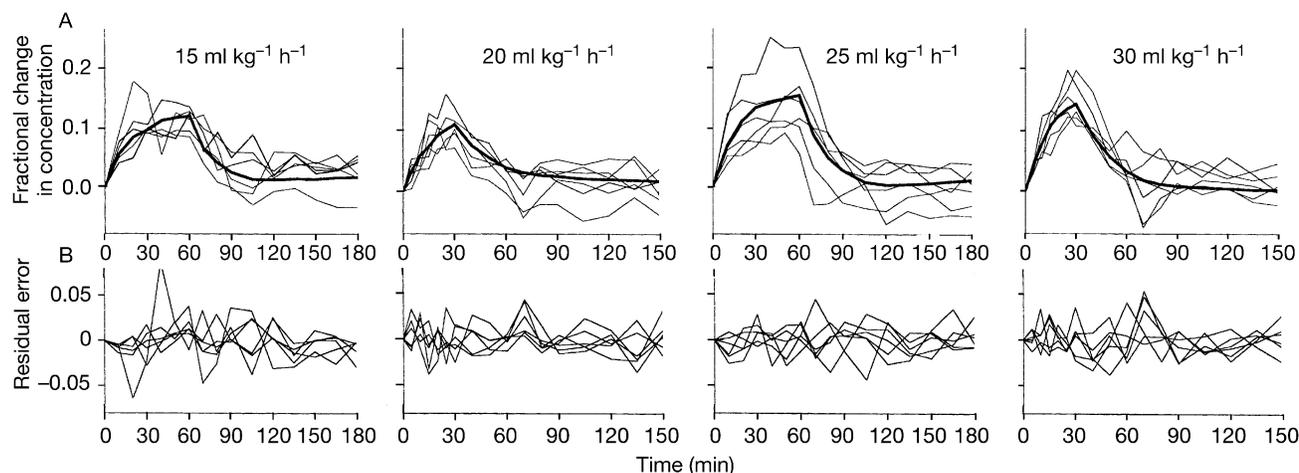
Fig 5 (A) Dilution–time curves for individual experiments in which glucose 2.5% was infused at 15, 20, 25 and 30 ml kg^{-1} h^{-1} in six healthy volunteers (fine lines) and the model-predicted curve-fit based on the mean glucose uptake for each time interval and the average volume kinetic parameter values shown in Table 3 (thick lines). (B) The residual errors for each individual curve fit.

correlation, $P<0.005$) served as independent predictors of sodium retention.

The potassium excretion averaged 19 (2) mmol and differed little between the groups. The highest excretion (66 mmol) occurred in the experiment associated with the most pronounced glycosuria.

The systolic and arterial pressures increased slightly during the experiments, from 123 (2) and 72 (1) mm Hg, respectively, at baseline to 127 (2) (not significant) and 76 (2) mm Hg ($P<0.001$) at 180 min. The heart rate increased from 62 (2) to 64 (2) beats min^{-1} ($P<0.001$).

Discussion

The fluid used as a carrier of glucose exhibits complex kinetics. The normal physiological mechanisms operating to eliminate a fluid overload, involving the action of stretch receptors and hormones, apparently operate alongside osmotically driven distribution, which is strongly dependent on the uptake of infused glucose into the cells. The present study illustrates how these mechanisms interact with each other. For this purpose, glucose 2.5% was infused relatively quickly in volunteers and data on the glucose concentration and the plasma dilution were fitted to a volume kinetic model adapted for glucose solutions.

The kinetic analysis consists of two parts. First, the amount of fluid translocated to the cells by virtue of glucose uptake is estimated using V_d as the calibration factor between the plasma glucose concentration and the amount of glucose that readily equilibrates with the plasma, which mirrors the amount of glucose that has *not* been taken up by the cells. Secondly, a volume kinetic analysis of the remaining fluid is made. An estimate of the size of the central body fluid space expanded by infused fluid (V_1), which is a central concept in volume kinetic theory,[9 10] is made possible by the fact that the dilution of the blood with

Table 4 Predictive performance measures. The median residual error and the median absolute residual error in predicting a dilution–time curve from the best estimates of V_d and CL (Table 2) and V_1, k_r and k_{31}/V_3 (Table 3) for any single series of six experiments or for all 24 experiments. The sign of the residual differences is considered in the first error but not in the second one. Calculations were made using the two-stage approach, the reported data being the mean (SEM) of the median residual error of each experiment. Data represent the plasma dilutions ($\times 10^{-3}$) and are without dimensions

	Median residual error ($\times 10^{-3}$)	Median absolute residual error ($\times 10^{-3}$)
15 ml kg^{-1} h^{-1} experiments by using:		
15 ml kg^{-1} h^{-1} kinetics	4 (8)	22 (2)
20 ml kg^{-1} h^{-1} kinetics	6 (8)	23 (4)
25 ml kg^{-1} h^{-1} kinetics	21 (7)	28 (4)
30 ml kg^{-1} h^{-1} kinetics	27 (8)	33 (5)
Average kinetics	17 (8)	26 (4)
20 ml kg^{-1} h^{-1} experiments by using:		
15 ml kg^{-1} h^{-1} kinetics	−23 (8)	25 (7)
20 ml kg^{-1} h^{-1} kinetics	−18 (8)	24 (6)
25 ml kg^{-1} h^{-1} kinetics	−10 (8)	21 (5)
30 ml kg^{-1} h^{-1} kinetics	−5 (8)	18 (5)
Average kinetics	−7 (4)	21 (5)
25 ml kg^{-1} h^{-1} experiments by using:		
15 ml kg^{-1} h^{-1} kinetics	−40 (13)	45 (10)
20 ml kg^{-1} h^{-1} kinetics	−35 (13)	45 (11)
25 ml kg^{-1} h^{-1} kinetics	−16 (14)	32 (8)
30 ml kg^{-1} h^{-1} kinetics	−1 (15)	32 (5)
Average kinetics	−26 (14)	25 (8)
30 ml kg^{-1} h^{-1} experiments by using:		
15 ml kg^{-1} h^{-1} kinetics	−33 (8)	35 (6)
20 ml kg^{-1} h^{-1} kinetics	−26 (7)	31 (5)
25 ml kg^{-1} h^{-1} kinetics	−13 (7)	24 (3)
30 ml kg^{-1} h^{-1} kinetics	−5 (6)	20 (3)
Average kinetics	−21 (8)	25 (4)

respect to a large macromolecule such as Hb which does not penetrate vessel walls is a measure of the distribution of the infused fluid volume, and not of the macromolecule. In contrast, the concentration of small molecules, such as glucose which easily diffuse across vessel walls is a measure
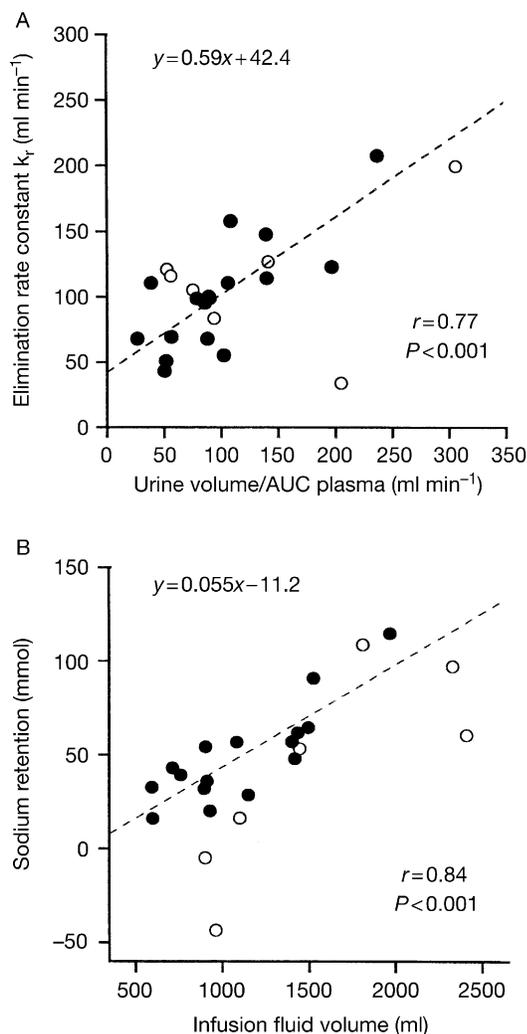
Fig 6 (A) Renal clearance of the infused fluid, obtained as the excreted urine volume divided by the area under the curve (AUC) for plasma dilution, *vs* the elimination rate constant (k_r) yielded by the curve-fitting procedure. (B) Infused volume of glucose 2.5% *vs* sodium retention (i.e. the difference between infused and excreted amounts of sodium). Each point represents one experiment. The regression equations were based on the experiments with glycosuria of less than 1 mmol (closed circles); only those with glycosuria exceeding 1 mmol are marked (open circles).

of the distribution of the molecules and not of the fluid volume.

The results confirm previous findings that the net removal of glucose from plasma occurs quite quickly in healthy volunteers.[8] The plasma had been cleared of excess glucose 30 min after the infusions ended. The infused water had also been cleared, although the volume of urine measured 90 min later shows that the osmotic fluid shift still retained 38% of the infused fluid in the body. Predictions based on the kinetic data suggested that the excess fluid in V_3 was between 0.20 and 0.25 litres at the end of the experiments (figure not shown), which is consistent with the measured urinary excretion provided that we also consider insensible

fluid losses. The cellular volume thus seems to remain expanded for a much longer time than V_1.

The kinetic analysis indicated that the infused glucose is distributed in a volume three times larger than that of the infused fluid. No expansion of a body fluid space between the small V_1 and the remote body fluid space V_3 could be supported by adding one more exponent to the equation for the dilution–time curve. The lack of a V_2 can probably be explained by the rapid uptake of glucose, which occurred at a rate similar to the expected time course for distribution of fluid between V_1 and V_2.[10 13] Furthermore, the close correlation between k_r derived from the urinary excretion and k_r estimated by the curve-fitting procedure (Fig. 6A) supports the theory that fluid was indeed removed from V_1 only by urinary excretion or by uptake into V_3. In pharmacokinetics, this argument would correspond to the view that a drug is fully eliminated by urinary excretion if the renal *CL* corresponds closely to the total body *CL*.

The evaluation of model linearity also consisted of two parts. The first one confirmed that the AUC for glucose increased in proportion to the dose and that *CL* was virtually the same regardless of the infusion rate (Fig. 3). As concerns the fluid volume, glycosuria reduced the AUC for the plasma dilution and thereby distorted the comparisons (Fig. 4). However, on removing the cases involving glycosuria, the linearity was almost as good for the fluid volume as for the glucose.

The second part of the evaluation of linearity was based on predictive performance measures. This is an alternative to comparing the kinetic parameters for the four groups studied. Kinetic parameters usually show some degree of intercorrelation, and it might be difficult to judge whether the slightly higher V_d and lower *CL* we observed for higher infusion rates of glucose (Table 2) have any practical meaning, or whether they cancel out when the parameters are used for simulation. The approach used here to assess predictive performance was inspired by a study on infusion pumps,[14] although we report absolute instead of relative errors as a long period of late dilution close to baseline is needed for the estimation of k_{31}/V_3.

The results show that the errors associated with simulation were usually quite small. However, the dilution was usually slightly overestimated during the later stages of the experiments when glucose 2.5% was infused rapidly, mostly because the kinetic model could not take account of dilution below baseline. This limited capacity to deal with 'rebound hypoglycaemia' must be kept in mind when simulating an abrupt stop of glucose administration liberal enough to raise the plasma glucose level close to the renal threshold (>12 mmol litre^{-1}). The inaccuracy of simulating by computer, expressed as the median absolute residual error, averaged 0.026 dilution units but, more importantly, it was practically the same when the kinetic parameters used for simulation were based on all 24 infusions, as compared with when they were derived from any of the four subgroups. Hence, using

the parameter estimates from the pooled series of infusions did not increase the inaccuracy of the simulations.

Slight glycosuria occurred in several volunteers despite the lack of a family history of diabetes. Glycosuria may occur in healthy patients who receive glucose infusions[2] and might be difficult to prevent completely.[15] As could be expected, however, it mostly occurred in the two groups with the highest infusion rates.[6] Glycosuria did not affect the parameters describing glucose kinetics as glucose was cleared from plasma as fast as the fluid volume. The AUC for plasma dilution was reduced, however, which can, from a kinetic point of view, be attributed to less fluid being returned from V_3 to V_1 after metabolism of the glucose. This probably explains why the estimates of k_{31}/V_3 were lower when glucose was infused at the two highest rates. Computer simulations indicated that k_{31}/V_3 governed a slight upward shift of the dilution–time profile of V_1 after infusion but otherwise had a quite limited impact on the curve. Variations in glucose kinetics also seemed to have a relatively small influence on V_1, which was clearly most affected by k_r (figures not shown).

In conclusion, by using an area method and comparing residual errors after simulation, we found linearity for glucose 2.5% when infused at different volumes and rates. Glycosuria and rebound hypoglycaemia appeared to be confounders, however.

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