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Volume kinetics of glucose 2.5% solution and insulin resistance after abdominal hysterectomy

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Background. We hypothesized that volume kinetics can be used to predict the rate of infusion of glucose 2.5% solution required to yield any predetermined plasma glucose level and degree of plasma dilution during the postoperative period.

Methods. In 15 women, mean age 50 yr (range 37–63), 2 days after an abdominal hysterectomy, a volume kinetic analysis was performed on an i.v. infusion of 12.5 ml kg^{-1} (~900 ml) of glucose 2.5% given over 45 min. The insulin resistance was measured by a glucose clamp, and it was compared with daily bioimpedance analyses, which indicated the hydration of the intra/extra-cellular body fluid spaces.

Results. The clearance of glucose was 0.42 litre min^{-1} (0.60 litre min^{-1} is normal) while the other five parameters in the kinetic model were similar to those obtained in healthy volunteers. Computer simulations indicated that in a 70-kg female, at steady state, the rate of infusion (ml min^{-1}) should be three times the allowed increase in plasma glucose (mmol litre^{-1}). To maintain a predetermined plasma dilution the corresponding rate factor was 160. The glucose uptake during clamping was 3.9 mg kg^{-1} min^{-1} (7.0 is normal), which, during the second day after hysterectomy, correlated with the dehydration of the intracellular space ($r=0.77$; $P<0.002$) and with the protein catabolism as indicated by the urinary excretion of 3-methylhistidine ($r=-0.76$, $P<0.002$).

Conclusion. The anaesthetist can prescribe postoperative administration of glucose 2.5% to reach any desired plasma glucose level and dilution by using the two presented nomograms. Insulin resistance correlated with intracellular dehydration and protein catabolism.

Glucose solutions are commonly given by i.v. infusion in the postoperative period after major surgery. They provide for the basic energy and water needs, but the optimal dosing is difficult to determine as insulin resistance develops as a result of the 'stress' response to trauma.[1 2] Insulin resistance starves the cells of glucose, but it can also dehydrate them as the osmotic strength of intracellular glucose attracts water. One method of studying interactions between metabolic changes and the fluid balance is to apply volume kinetics, which allows simultaneous modelling of the distribution and elimination of glucose and water. The characteristics of this mathematical approach have been described,[3] its linearity validated[4] and the model was recently applied during laparoscopic surgery.[5]

In the present study, volume kinetics were applied to describe the distribution and elimination of the glucose and volume components of glucose 2.5% in the postoperative period after abdominal hysterectomy. The purpose was to use the results from these kinetic analyses, if consistent enough, to create nomograms, which would make it possible for the anaesthetist to predict how fast a glucose solution needs to be infused to reach any predetermined target with respect to plasma glucose and volume expansion. For explorative analyses, the results of volume kinetics were compared with those of a euglycaemic hyperinsulinaemic glucose clamp,[2 3 6 7] fluid balance calculations and changes in cellular hydration as studied by bioimpedance.[8 9]

Materials and methods

Fifteen women aged between 37 and 63 yr (mean 50 yr), and body weight between 58 and 90 kg (mean 70 kg), were studied. They were to undergo elective abdominal hysterectomy for non-cancerous conditions. None of the patients was on any medication although one woman was receiving

thyroxine substitution therapy. One additional patient was excluded on discovery of latent diabetes and hypertension during the study. The protocol was approved by the local Ethics Committe and the informed consent was obtained from all the patients.

The operating time (from incision to the last suture) and the surgical blood loss were recorded. After surgery, and during the follow-up period, each patient was equipped with a patient-controlled analgesic pump containing ketobemidone 1 mg ml^{-1}.

To quantify the degree of surgical stress, serum concentrations of two cytokines, interleukin-6 and vascular endothelial growth factor (VEGF), were measured using Quantikine kits (R&D Systems, Minneapolis, MN, USA) in the morning on the first day after surgery. The coefficient of variation of these measurements was less than 5%.

Glucose clamp

On the first morning after surgery, a euglycaemic hyperinsulinaemic clamp was performed. The glucose infusion rate required to maintain a constant level of plasma glucose (clamp) during infusion of a standardized amount of insulin is a measure of insulin sensitivity.[6 7] The patients fasted overnight and, at 08:00 the i.v. infusion of insulin (Actrapid Novo, Copenhagen, Denmark) was started at a constant rate of 40 mU m^{-2} min^{-1} using an infusion pump. The insulin was added to 500 ml saline into which 20 ml of the patient's own plasma had been added to prevent adsorption by the plastic material of the infusion set. Glucose 20% was administered i.v. at a rate that was adjusted every 5 min depending on the immediately measured blood glucose level (YSI Inc., Yellow Springs, OH, USA), with the aim of maintaining euglycaemia (mean 6 mmol litre^{-1}). Serum insulin and serum C-peptide concentrations were measured every 15 min, using ELISA kits (Mercodia AB, Uppsala, Sweden).

The glucose uptake (M value) was calculated during 1 h of steady state, usually between the 60 and 120 min of clamping. The normal M is about 7 mg kg^{-1} min^{-1}.[2 6 7]

Volume kinetics

On the second postoperative day, at 08:00, after a light breakfast (consisting of one sandwich and one cup of tea or coffee), the patients were taken from the ward to the laboratory. An i.v. infusion of 12.5 ml kg^{-1} (mean volume 888 ml, glucose load 22 g) of iso-osmotic glucose 2.5% with electrolytes (Na 70, Cl 45 and acetate 25 mmol litre^{-1}; Rehydrex, Pharmacia, Uppsala, Sweden) was given over 45 min via an infusion pump. Venous blood was drawn every 5 min for a 75-min period, and thereafter every 10–15 min for up to 185 min for measuring the concentration of plasma glucose (GLU Gluco-quant reagent, Roche, Mannheim, Germany), blood haemoglobin, the red blood cells count, and the mean corpuscular volume (Hitachi 917, Hitachi Co., Naka, Japan). All indices of the erythrocytes

were measured in duplicate and the mean value was used in the calculations. Serum insulin was measured every 45 min.

The data were used to calculate the kinetics of glucose and of the infused volume load. In brief, plasma glucose over time was analysed according to a one-compartment turnover model, which yielded the volume of distribution (V_d), glucose clearance (*CL*) and endogenous glucose production ($k_{i\ en}$). In the absence of glucosuria, each mmol of glucose eliminated from the system implied that it was taken up by the cells and then, by virtue of osmosis, drew in 3.6 ml of fluid to a peripheral (intracellular) space, V_3.[3 4] The fate of the remaining excess fluid was studied according to volume kinetic principles where it expands a body fluid space of size V_1, from which elimination occurs in the form of insensible fluid losses k_b, which was fixed at 0.5 ml min^{-1}, and a dilution-dependent mechanism for which the rate is proportional by a parameter k_r to the expansion of V_1. Moreover, fluid is returned from the cells, mainly as a result of glucose oxidation, at a rate that is proportional to the fluid uptake in V_3 by a parameter k_{31} (see Appendix). An analysis was also made to test for the possible expansion of an intermediate space, V_2, but this did not yield statistical significance.[3]

The model parameters for the glucose and volume components of glucose 2.5% were calculated in each individual patient using Matlab version 6.5 (Math Works Inc., Natick, MA, USA). The kinetic models used a non-linear least-squares regression routine based on a modified Gauss–Newton method. Corrections were made for iatrogenic dilution caused by the blood sampling, which averaged 7 ml for each sampling procedure. The output parameters consisted of V_d, *CL*, $k_{i\ en}$, V_1, k_r and k_{31} which, along with the uncertainty of the estimates, were expressed as their standard deviations (SD).

Glucosuria was not assessed as our previous studies show that such losses are very small, if at all present, with a short glucose peak of about 11–12 mmol litre^{-1}.[3–5]

Bioimpedance and fluid balance

On four consecutive mornings, starting on the day of surgery, the extracellular fluid (ECF) and intracellular fluid (ICF) volumes were estimated by bioelectrical impedance using a Xitron 4000B Spectrum Analyzer (Xitron Technologies, San Diego, CA, USA).[8 9] Each reported value is the mean of three successive recordings. The preoperative body weight was used as an input variable in all estimations of these physiological body fluid spaces, which were performed by the software delivered with the apparatus.

The total amount of fluid and electrolytes administered during surgery and until 08:00 the next morning (=day of surgery) was measured. Urine was collected from after induction of anaesthesia until 3 successive days for analyses of electrolytes, urea and creatinine. The urinary excretion of 3-methylhistidine (3-MH) on the second postoperative day was measured, using a LC3000 (Viotronic, Mainthal, Germany). This amino acid is found in actin and myosin

in muscle and is used as an index of protein catabolism as 3-MH cannot be re-utilized for protein synthesis.[10][11] Increased precision in quantifying muscular breakdown is obtained on reporting the ratio between the urinary 3-MH and the urinary creatinine concentration.[12]

Statistics

Results are expressed as the mean (SD). Because of skewed distributions, the median (interquartile range) was used where appropriate. Changes were evaluated by repeated-measures ANOVA and linear correlations by simple linear regression. $P<0.05$ was considered significant.

Results

The operating time was 101 (28) min and the blood loss 300 (163–563) ml. On the day after surgery, the serum interleukin-6 concentration was 28 (14) ng litre^{-1} and serum VEGF amounted to 231 (182–363) pg ml^{-1}.

Glucose clamp

Glucose uptake during steady state with the clamp (M value) was 3.9 (1.8) mg kg^{-1} min^{-1} and the corresponding serum insulin level was 365 (69) pmol litre^{-1}. The C-peptide concentration, which is an index of endogenous insulin production, decreased gradually from 0.65 (0.28) to 0.42 (0.22) nmol litre^{-1} during clamping ($P<0.001$).

Volume kinetics

The plasma glucose concentration (baseline 6.1 mmol litre^{-1}) was doubled during the glucose infusion but had returned to baseline after 60 min (Fig. 1A). The infused fluid diluted the plasma by 10%. The dilution was more rapidly normalized than plasma glucose (Fig. 1B). The insulin concentration increased 3-fold (Fig. 1C).

The model parameters obtained by the analyses of the glucose and the volume kinetics are given in Table 1.

Bioimpedance and fluid balance

Bioimpedance indicated that the ECF volume increased during the day of surgery ($P<0.002$), while the ICF volume decreased on the second and third postoperative mornings ($P<0.03$, Fig. 2).

The infused fluid on the day of surgery consisted of 4200 (795) ml of crystalloid fluid, which contained 351 (103) mmol of sodium and 86 (32) g of glucose. Colloid dextran and/or erythrocytes were only given to four patients and averaged 800 ml. One-third of the administered fluid volume was excreted as urine. The ratio of sodium to potassium excretion was doubled over the subsequent postoperative days, and was mostly a result of a reduction of the potassium excretion (Table 2).
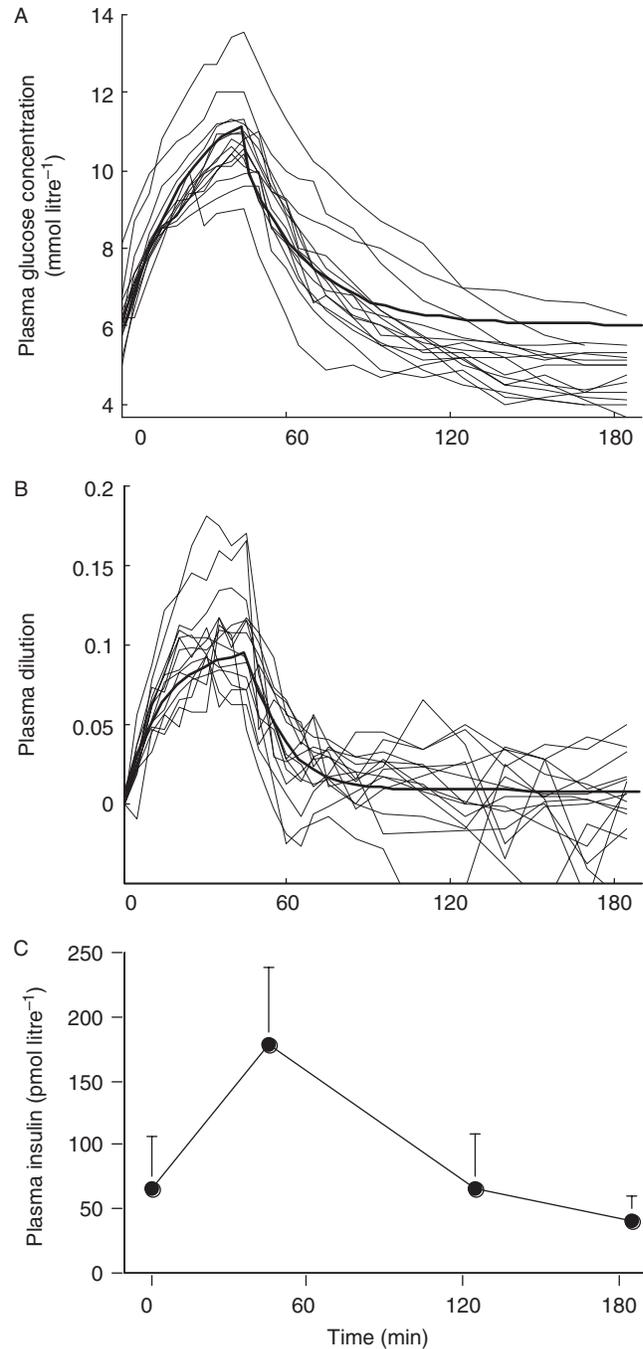

Fig 1 The plasma glucose concentration (A), plasma dilution (B), and the plasma insulin concentration (C) during and after the infusion of about 900 ml of glucose 2.5% with electrolytes over 45 min 2 days after abdominal hysterectomy. In A and B, the thin lines are individual curves while thick lines represent simulations based on the averaged best estimates of the kinetic parameters. C shows the mean and the error bars represent SD.

Intercorrelations

Comparisons between parameters were made based on individual patients. The M value correlated inversely with postoperative protein catabolism (Fig. 3A) and also implied a greater dehydration of the ICF space (Fig. 3B).

Table 1 Pharmacokinetic analysis of the infused glucose, and volume kinetic analysis of the accompanying fluid volume when 12.5 ml kg^{-1} of glucose 2.5% was infused over 45 min after hysterectomy. V_d=volume of distribution, CL=clearance, $k_{i\ en}$=endogenous glucose production, V_1=central body fluid space, k_r=elimination rate constant, k_{31}/V_3=slope of the dilution–time curve for V_3. *Given as the median (interquartile range) because of skewed distribution

	Mean (SD)
Glucose kinetics	
V_d (litres)	10.2 (2.7)
SD	0.6 (0.3)
CL (litres min^{-1})	0.42 (0.08)
SD	0.03 (0.01)
$k_{i\ en}$ (mmol min^{-1})	2.24 (0.44)
SD	0.22 (0.04)
Volume kinetics	
V_1 (litres)	2.68 (1.10)
SD	0.43 (0.1)
k_r (ml min^{-1})	131 (40)
SD	20 (11)
k_{31}/V_3 (10^{-3} min^{-1})	10 (8–18)*
SD	8 (4–27)*
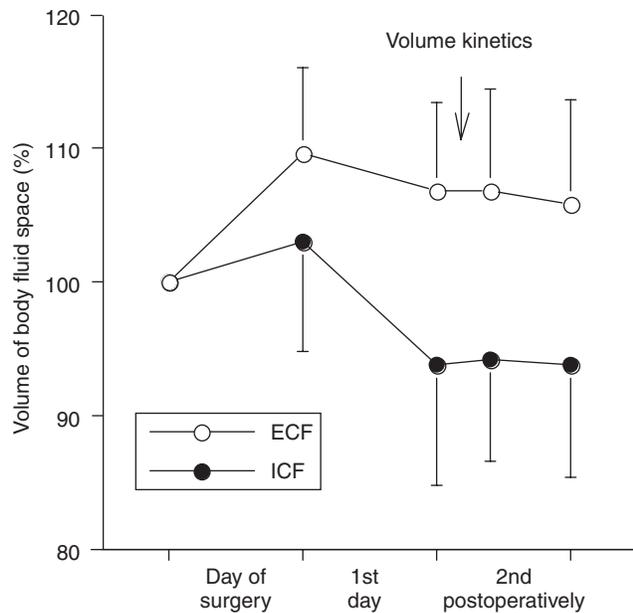
Fig 2 Relative changes in the hydration of the ECF and ICF from before hysterectomy and until the beginning of the third postoperative day as measured by bioimpedance. Each new day begins at 08:00.

Table 2 Composition of urine on 3 days during and after hysterectomy. Mean (SD)

Amount excreted per 24 h	Day of surgery	First postoperative day	Second postoperative day
Urine (ml)	1510 (696)	2047 (846)	2249 (1042)
Sodium (mmol)	124 (51)	84 (61)	128 (57)
Potassium (mmol)	64 (28)	39 (23)	31 (11)
Urea (mmol)	172 (48)	210 (82)	208 (69)
Creatinine (mmol)	6.4 (3.7)	8.1 (4.1)	8.2 (3.8)

The M value did *not* correlate with CL for glucose, but it correlated with CL divided by the serum insulin concentration at the end of infusions (r=0.73, $P<0.001$). As expected, this index of insulin resistance correlated strongly with protein catabolism (Fig. 3C). The latter parameter also correlated with the dehydration of the ICF space, although most clearly when measured on the third postoperative morning (Fig. 3D).

Simulations

The plasma glucose concentration expected to result from infusing glucose 2.5% at various rates is given in Figure 4, which is based on computer simulation using the kinetic parameters in Table 1. A corresponding nomogram for the expected plasma dilution is shown in Figure 5.

These nomograms indicate that the steady-state increase in plasma glucose (Δglucose) and the plasma dilution resulting from i.v. infusion of glucose 2.5% can be extrapolated as follows: infusion rate=3•Δglucose=160•dilution.

A simulation was also done to illustrate differences in plasma glucose and plasma dilution during and after infusion of glucose 2.5% in the postoperative, intraoperative, and laboratory settings (Fig. 6). For this purpose, parameter sets from the present and two previous studies were used.[4][5]

Discussion

Glucose 2.5% with electrolytes is a mixture of glucose 5% and Ringer's acetate and is a valid option for i.v. hydration and basic energy supplementation after surgery. The present study indicates how fast this fluid should be administered to reach a target elevation of plasma glucose (Fig. 4) and also the infusion rate and infusion time required to obtain and maintain any predetermined plasma dilution (Fig. 5). These results might serve as guides for the anaesthetist when prescribing infusion fluids for the postoperative period.

There is a common belief that glucose solution expands the plasma volume only very slightly, but glucose 2.5% and 5% both compare well with Ringer's solution in this respect.[3] For example, increasing plasma glucose by 5 mmol litre^{-1} over 40 min using glucose 2.5% expands the plasma volume by 10%, which is not negligible.

The kinetics of glucose 2.5% solution in the postoperative period is quite similar to that found in laboratory experiments, while it is much more affected during surgery. How different clinical situations compare can be highlighted in simulation experiments designed to predict the response to a fluid infusion with respect to plasma glucose, plasma dilution, volume expansion, and cellular hydration (Fig. 6). Estimates of the kinetic parameters can also be compared directly. In general, altered physiological conditions change the parameters expressing *rates* but only to a lesser degree those denoting *volume*.

The CL was between 0.55 and 0.70 litre min^{-1} in the laboratory[3][4] and 0.20 litre min^{-1} during laparoscopy;[5] in
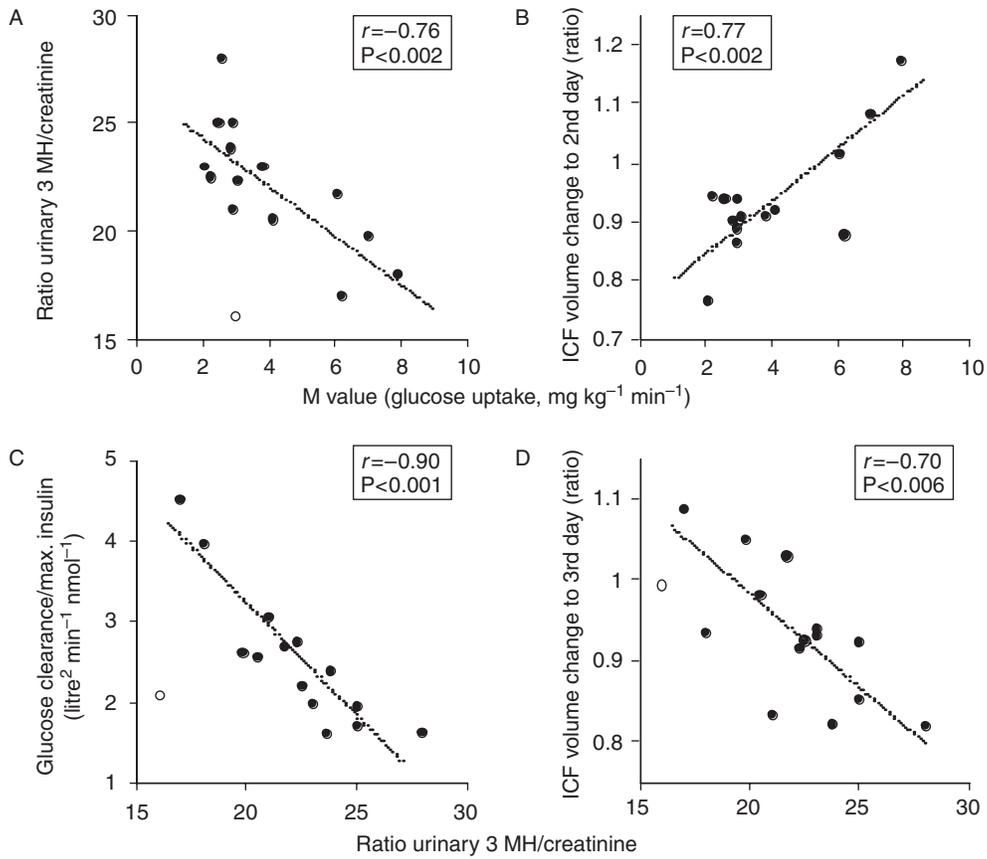
Fig 3 Intercorrelations between the M value obtained during glucose clamping (subplots A and B), the protein catabolism as indicated by the urinary excretion of 3-MH (A, C, and D), and the change in ICF volume as measured by bioimpedance on the second (B) and third (D) postoperative mornings. Also shown is the ratio of glucose clearance to plasma insulin at the end of the infusion, which was subjected to kinetic analysis (C). Each point represents one patient. One outlier (open circle) was excluded from the linear regression analysis as the collection of urine was probably incomplete.
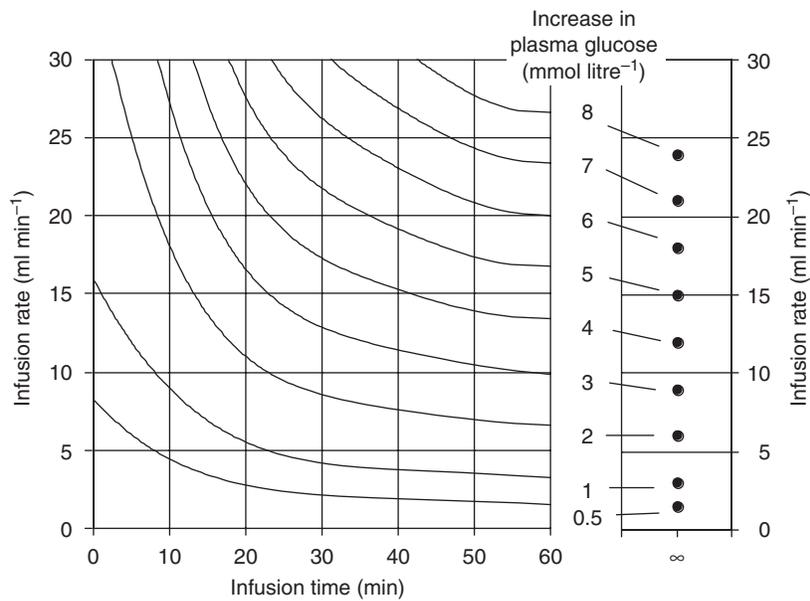
Fig 4 Nomogram showing the relationship between infusion rate and the infusion time required to increase the plasma glucose concentration (left) and the infusion rate required thereafter to maintain a steady-state glucose concentration (right) during the postoperative follow-up after hysterectomy (body weight 70 kg). The computer simulations for the graph were performed using the kinetic parameters from Table 2.
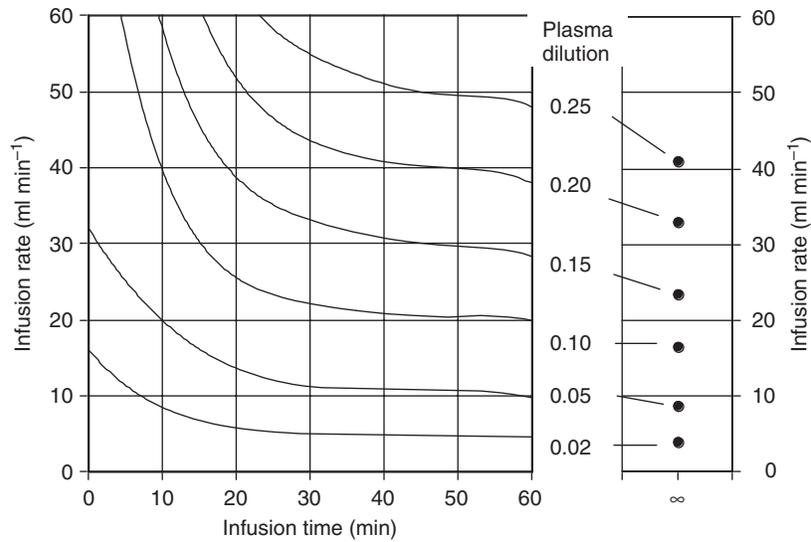
Fig 5 Nomogram showing the relationship between infusion rate and the infusion time required to dilute the plasma to a predetermined degree (left) and the infusion rate required thereafter to maintain a steady-state dilution (right) during the postoperative follow-up after hysterectomy (body weight 70 kg). The steady-state rate is given for a 30-min infusion but should be increased by 5% for the shortest infusion rate (10 min) and reduced by 5% for the longest one (60 min).
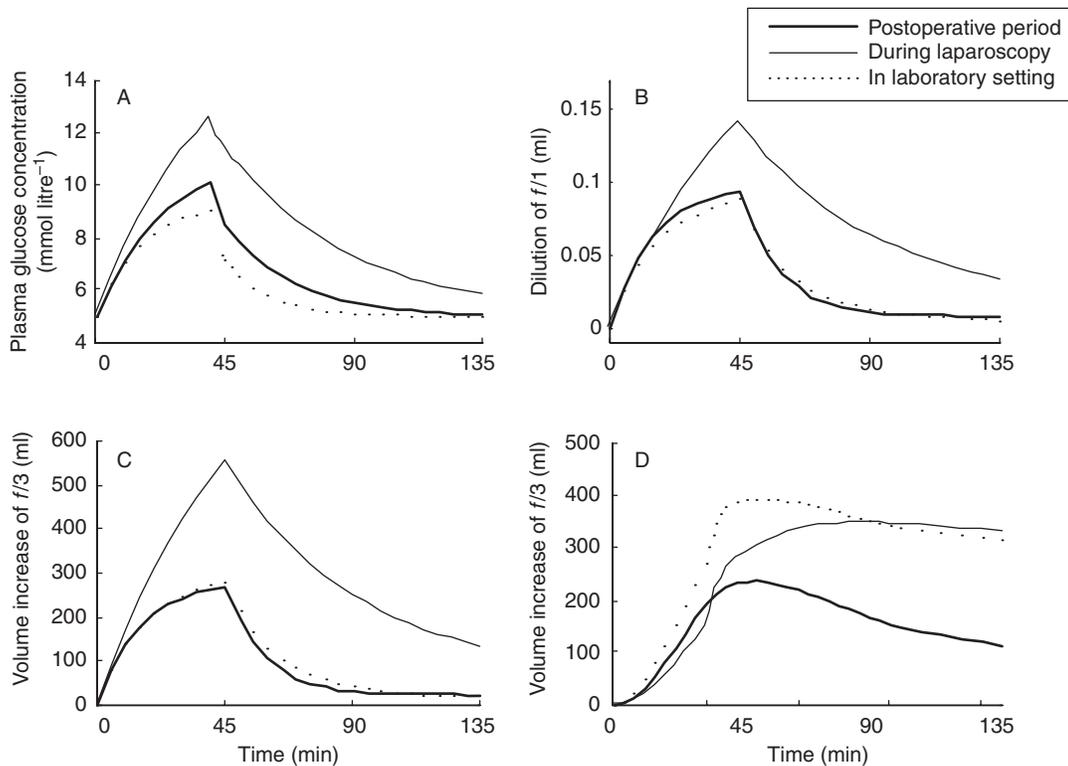
Fig 6 Computer simulations of the plasma glucose concentration (A), plasma dilution (B), and the volume expansion of the central (C) and peripheral (D) body fluid spaces during and after infusion of 12.5 ml kg^{-1} of 2.5% glucose solution in the postoperative period, during laparoscopy and in the laboratory setting. Parameter estimates from the present and two previous studies[4][5] were used.

the present study during the postoperative period, we found its value to be 0.42 litre min^{-1} (Table 1). These rates correspond to half-lives for infused glucose of 12, 30, and 16 min, respectively. Therefore, suitable rates of glucose administration are in-between those proposed during surgery and for healthy individuals. However, the endogenous glucose production at baseline was identical to that obtained in healthy volunteers if expressed per kg

body weight. The reduction of this rate by 50% during laparoscopy[5] would probably result in hypoglycaemia if not counteracted by insulin resistance.

With regard to volume kinetics, the size of the expandable central body fluid space (V_1) was slightly decreased, as compared with the surgical setting, but still within the limits of previous laboratory results.[4] The clearance constant for infused fluid (k_r) was normalized to about 130 ml min^{-1} from being reduced by as much as two-thirds during laparoscopy.[5] Finally, the slope k_{31}/V_3, which denotes the rate of removal of excess water from the cells, was normal (Table 1).

The volume of distribution for glucose 2.5% solution might be anticipated to be equal to the ECF space, which is often taken as 20% of the body weight. However, both V_d for glucose and V_1 for the fluid volume have consistently reached much lower values in our volume kinetic studies. The V_d reported here is 30–40% smaller than the expected size of the ECF volume, but this can be explained by the existence of an interstitial pool, which exchanges glucose very slowly with plasma.[13] Previous authors have suggested that the ECF space should be multiplied by a 'pool fraction' of 0.65 to obtain the V_d for glucose that is of clinical interest.[14] This is important when extrapolating the plasma glucose response to an exogenous glucose bolus.

Why the water of an isotonic fluid has such a small extracellular distribution (2.7 litre) is more difficult to explain, but can probably be attributed to the long time (20–25 min) required to distribute Ringer's solution between a central (V_1) and a peripheral (V_2) extracellular body fluid space.[15] With a high k_r and half-life for glucose of only 16 min, the infused volume is either rapidly excreted or brought into the cells (V_3) along with the glucose. The distribution does not occur fast enough to expand a V_2.

All these comparisons and predictions are based on kinetic analyses of individual curves showing the plasma glucose and the haemoglobin-derived plasma dilution over time. As can be seen from Figure 1B, infused glucose and fluid were both effectively cleared from plasma. One may note that the simulated curve in Figure 1A did not capture the decrease of the plasma glucose below baseline during the third hour, while this 'rebound hypoglycaemia' is incorporated in further calculations of volume kinetics.

This study also comprised a measurement of insulin resistance ('M value') using a hyperinsulinaemic euglycaemic clamp. Our average M of 3.9 represents a decrease from the expected 'normal' value of 7 mg kg^{-1} min^{-1},[67] although an assessment of the degree of individual change would require that another glucose clamp was performed before surgery.[2] We had expected that the CL for glucose would correlate with the M value, but this was not the case. The M value apparently cannot be used directly as a guide to how fast a glucose solution should be infused without leading to hyperglycaemia. On the other hand, the finding that CL divided by the peak insulin concentration correlated with the M value might be tested as a 'minimal model' to estimate

insulin resistance. Additional evaluation is certainly needed and also an account of the dose of administered glucose, as peak insulin, but not CL, is dose-dependent.[4]

Insulin resistance had several interesting implications for the postoperative period. First, bioimpedance indicated that surgery dehydrated the intracellular space from the second postoperative day onwards, and the degree of dehydration correlated with the insulin resistance (Fig. 3B). A similar dehydration by 10% was described by Stillström and colleagues,[16] who also found that Ringer's solution causes more ICF loss than glucose 2.5%. This result is consistent with the fact that water accompanies the uptake of glucose into the cell, as modelled in the volume kinetic analysis. Furthermore, 3-MH excretion, which was used as an index of protein catabolism, was higher in patients with pronounced intracellular dehydration (Fig. 3D).

The succession in which these relationships develop may provide a clue to how they operate. The insulin clamp was applied on the first postoperative day when intracellular dehydration had not yet developed. This suggests that insulin resistance develops first and dehydration later. The next correlation that between dehydration and protein catabolism, is consistent with a theory by Häussinger, which holds that protein catabolism is triggered by cellular dehydration.[17 18] A possible chain of events is that insulin resistance leads to intracellular dehydration, which leads to protein catabolism.

The interleukin-6 response suggests that abdominal hysterectomy inflicts a moderately severe trauma in the patients. The rise in this serum concentration is proportional to the degree of surgical trauma.[19] In the first postoperative morning after abdominal hysterectomy, we obtained levels midway between those obtained after laparoscopic and open cholecystectomy.[2 20] The cytokine VEGF was measured because it greatly increases vascular permeability[21] and is up-regulated in response to factors involved in the inflammatory cascade, such as hypoxia, endothelin-1, and interleukin-1, while nitric oxide acts as an inhibitor.[22] However, the serum concentration of VEGF was not elevated. It is plausible that the measured alterations in cellular hydration and insulin resistance reported by us would be more pronounced with a more severe trauma response to the surgery.[23]

Limitations of this study include the circumstance that the endogenous glucose production was estimated by a turn-over kinetic model. This assumes that CL for glucose is unchanged down to a plasma glucose level of zero, which assumption has not been tested. Radioactive tracers show that endogenous glucose production 2 h after an abdominal hysterectomy is 40% lower than that reported by us for the second postoperative day,[24] although this rate agrees quite well with our findings during surgery.[5] Moreover, fluid intake and feeding could only be monitored on the day of surgery until the clamp was performed. The data on urinary output collected later can therefore only be used to indicate an expected normal recovery (Table 2) and we can only

assume that the intake of meat, which would affect the index of protein catabolism, was small during the first postoperative day. The bioimpedance calculations could also have been slightly different using body weights measured daily. The patient with the smallest 3-MH excretion in the study was excluded from the linear regression analysis in Figure 3, where she appears as an outlier, as we suspect that the urinary collection was incomplete. This exclusion hardly changed the slopes of these relationships, but Figure 3 should still merely be regarded as explorative extensions of the present study, and further evaluation is clearly needed.

In conclusion, the kinetics of glucose 2.5% solution are essentially normal 2 days after hysterectomy with the exception of a reduced glucose clearance. Infusion therapy can be planned using nomograms, which outline the expected plasma glucose and dilution of this fluid. The study also reported intercorrelations between postoperative insulin resistance, cellular dehydration and an index of protein catabolism.

Appendix

Key mathematics

Glucose. The body's handling of exogenous glucose is first analysed by conventional pharmacokinetics. Here, the plasma concentration (C_{ex}) at any time (t) during and after administration of glucose at the rate $k_{i\,ex}$ is determined by:

$$\frac{dC_{ex}}{dt} = \frac{k_{i\,ex}}{V_d} - \frac{CL}{V_d} * C_{ex}(t)$$

The concentration resulting from endogenous production of glucose (C_{en}) is given by:

$$C_{en} = \frac{k_{i\,en}}{CL}$$

The measured plasma glucose concentration is the sum of C_{ex} and C_{en}. The endogenous production is responsible for the baseline glucose concentration and best represents this rate just before the glucose infusion begins.

Fluid volume. The expansion of the central (v_1) and the peripheral (v_3) body fluid spaces during infusion of 2.5% glucose solution is given by:

$$\begin{cases} \dfrac{dv_1}{dt} = k_i - k_b - k_r \dfrac{v_1 - V_1}{V_1} - f(t) + k_{31} \dfrac{v_3 - V_3}{V_3}, & v_1(0) = V_1 \\[2ex] \dfrac{dv_3}{dt} = f(t) - k_{31} \dfrac{v_3 - V_3}{V_3}, & v_3(0) = V_3 \end{cases}$$

The main input variable is the plasma dilution, which is represented by $(v_1 - V_1)/V_1$ in this system of differential equations. $f(t)$ denotes the osmotic uptake of fluid associated with glucose transport into the cells, which is obtained for each time interval during each experiment as the product of V_d and the change in plasma glucose concentration, taking account of any exogenous administration of glucose. Detailed explanations of how the calculations were carried out along with the solutions to the differential equations are given in previous work.[3–5]

Simulations. The best estimate of the model parameters (Table 1) was inserted into the mathematical solutions to the differential equations shown above, which had been programmed into the Matlab software. A time-stepping method was then used to predict the glucose concentration and the plasma dilution over time.

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