Background. Analyses of the distribution and elimination of glucose 2.5% solutions can be used to suggest combinations of infusion rates and infusion times which yield a predetermined plasma glucose level and degree of plasma dilution during surgery.

Methods. Twelve patients aged between 27 and 51 (mean 40) underwent laparoscopic cholecystectomy. An i.v. infusion of 1.4 litres of glucose 2.5% over 60 min was started when surgery began. A volume kinetic model was fitted to measurements of the plasma glucose concentration and the degree of haemodilution. Nomograms were constructed based on the kinetic results.

Results. The volume of distribution for the glucose and infused fluid and the plasma insulin levels were similar to the ones recorded in previous volunteer studies, but 50–70% lower values were obtained for the clearance of glucose (mean 0.21 litres min⁻¹), endogenous glucose production (1.1 mmol min⁻¹) and the elimination rate constant for the infused fluid (median 37 ml min⁻¹). Urinary excretion was markedly depressed and amounted to 9% of the infused fluid volume 4 h after starting surgery. To prevent hyperglycaemia, nomograms suggested that the infusion should be directed towards a ‘target’ glucose concentration and then slowed down in a controlled way. At steady state, the infused fluid maintains a 3.5% plasma dilution for each mmol that plasma glucose remains above baseline.

Conclusion. Metabolic changes warrant careful balancing of infusion rates of glucose 2.5% during laparoscopic cholecystectomy, which is facilitated by a nomogram. Volume expansion from the infused fluid volume should be recognized.
Materials and methods

The kinetics of an i.v. infusion of glucose 2.5% with electrolytes was studied during elective laparoscopic cholecystectomy in 12 patients aged between 27 and 51 yr (mean 40), two males and 10 females, and with a body weight of 58–88 (mean 75) kg. None were on any medication or had a family history of diabetes. The protocol was approved by the Local Ethics Committee and the informed consent of all patients was obtained.

The patients arrived at the hospital at 7 am and received no fluid or food before the surgery started at 8.30 am. All of them were given 2.5–7.5 mg of ketobemidone by i.m. injection for pre-medication about 1 h before entering the operating theatre. A cannula was placed in the cubital vein of each arm for the respective purposes of sampling blood and infusing fluid. The sampled plasma volume was replaced by the equivalent amount of saline 0.9%.

Without infusing any fluid, general anaesthesia was induced with thiopental 5 mg kg$^{-1}$ and maintained with intermittent doses of 0.1 mg of fentanyl every 30 min and continuous administration of a gas mixture containing sevoflurane 1–3% in oxygen and ambient air. Tracheal intubation was facilitated by i.v. injection of 0.5 mg kg$^{-1}$ of rocuronium. Monitoring of the patients included continuous pulse oximetry and electrocardiography.

When the first skin incision was made, an i.v. infusion of iso-osmotic glucose 2.5% with electrolytes (Na$^+$ 70, Cl$^-$ 45 and acetate 25 mmol litre$^{-1}$; Rehydrex, Pharmacia, Uppsala, Sweden) was started. As most patients receive about 1.5 litres of fluid in connection with cholecystectomy at our hospital, we aimed at administering this volume to an 80-kg patient over 60 min, which was done via an infusion pump (Flo-Gard 6201, Baxter Healthcare Ltd, Deerfield, IL, USA). After adjustment for body weight, the actual amount of fluid was 1413 (sd 193) ml, which was infused at a rate of 23.6 (3.2) ml min$^{-1}$. The dose of glucose was 35.3 (4.8) g or 196 (27) mmol. No more fluid was given during the 240-min experiment.

Measurements

Venous blood was collected every 5 min during the first 90 min and every 10 min for up to 240 min. The plasma glucose concentration was measured in single samples with 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 duplicate samples, and the baseline in triplicate samples, using Technicon Advia 120 (Bayer, Tarrytown, NY, USA). Venous blood was also withdrawn every 30 min for measurements of the serum sodium concentration by the Hitachi 917 system (Hitachi Co., Naka, Japan) and every 60 min for plasma insulin using an ELISA kit (Mercodia AB, Uppsala, Sweden). The coefficient of variation for the 800 duplicate samples was 1.3% for Hb, 1.2% for RBC, and 0.2% for MCV, while serial testing yielded 5% for insulin.

The heart rate and arterial pressure were measured using an automatic device (Datex-Ohmeda Instrumentation Inc., Box 900, Finland) after each blood sampling procedure.

All patients had an indwelling urinary catheter, which was used to obtain data on the urine volume and the concentrations of glucose and sodium and potassium as measured by the Hitachi 917 system.

Glucose kinetics

The kinetics of glucose were calculated according to principles described in two previous laboratory studies, but here the endogenous production of glucose ($k_{ie\,en}$) was also estimated. The plasma concentration ($C_{ex}$) at any time ($t$) resulting from exogenous administration of glucose at the rate $k_{ex}$ was calculated from the following equation:

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

in which $V_d$ is the volume of distribution and $CL$ the clearance of glucose. The glucose concentration ($C_{en}$) resulting from endogenous production of glucose ($k_{ie\,en}$) is given by:

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

The measured plasma glucose concentration is the sum of $C_{ex}$ and $C_{en}$. Naturally, the endogenous production is...
Table 1 Results of pharmacokinetic analysis of the infused glucose molecules (top) and volume kinetic analysis of the accompanying fluid volume (below) when glucose 2.5% was infused over 1 h during cholecystectomy. \( V_d \) = volume of distribution, \( CL \) = clearance, \( k_{en} \) = endogenous glucose production, \( V_1 \) = size of the central body fluid space, \( k_r \) = elimination-dependent elimination rate governed by excess fluid. The first line for each parameter gives the mean (SD) of all estimates in the respective group. The second line shows the precision of these estimates, specified as the mean (SD) of the standard errors associated with them. *As a result of a skewed distribution, these results are given as the median and interquartile range.

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<td>( V_d ) (litres)</td>
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<td>36.7 (20.3–88.0)</td>
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<td>SD</td>
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Calculations
The model parameters for the glucose and volume components of glucose 2.5% were calculated in each individual patient using Matlab version 6.5.1 (Math Works Inc., Natick, MA, USA). The kinetic models used a non-linear least-squares regression routine based on a modified Gauss-Newton method. Input data obtained at baseline (time 0) and at any later time \( t \) comprised Hb, RBC and MCV and the baseline haematocrit. They were used to calculate the plasma dilution, which also represented the dilution of \( V_1 \):

\[
\frac{V_1 - V_t}{V_1} = 0.5 \left( \frac{Hb_0}{Hb(t) - 1} + \frac{RBC_0}{RBC(t) - 1} \right) \cdot \frac{MCV_o}{MCV(t)}
\]

Corrections were made for iatrogenic dilution caused by the blood sampling, which averaged 7 ml for each sampling procedure. No correction for surgical bleeding was made; this amounted to 120 ml in one patient while no blood loss was recorded in the others. Weights inversely proportional to the predicted dilution plus 0.1 were applied. Output consisted in \( V_1 \) and \( k_r \) along with the uncertainty of these estimates, expressed as their SD.

Nomograms were constructed by simulating the expected plasma glucose and plasma dilution responses to various theoretical infusions of glucose 2.5% based on the numerical solutions to the differential equations describing the kinetic models. The best estimate of the model parameters (Table 1) were inserted into the solutions which had been programmed into the Matlab software.

Intracellular accumulation of fluid was calculated based on sodium and water balance. The equation for this ‘sodium dilution method’ is given elsewhere.

The results are expressed as the mean (SD). Because of skewed distributions, the median (interquartile range) was chosen where appropriate. Differences 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
Glucose kinetics
The plasma glucose concentration tripled during the infusion but returned to baseline during the 3-h follow-up (Fig. 2A). The variability of the concentration–time curves was quite small, and a simulation based on the average kinetic data from all infusions provided a good representation of them (Fig. 2B).

The volume of distribution for glucose \( V_d \) averaged 9.14 litres, the clearance \( CL \) 0.21 litres min\(^{-1}\) and the

Table 2 Results of pharmacokinetic analysis of the infused glucose molecules (top) and volume kinetic analysis of the accompanying fluid volume (below) when glucose 2.5% was infused over 1 h during cholecystectomy. \( V_d \) = volume of distribution, \( CL \) = clearance, \( k_{en} \) = endogenous glucose production, \( V_1 \) = size of the central body fluid space, \( k_r \) = elimination-dependent elimination rate governed by excess fluid. The first line for each parameter gives the mean (SD) of all estimates in the respective group. The second line shows the precision of these estimates, specified as the mean (SD) of the standard errors associated with them. *As a result of a skewed distribution, these results are given as the median and interquartile range.

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487
endogenous glucose production 1.1 mmol min⁻¹ (Table 1, top). In the entire group of 12 patients, the CL for glucose correlated with the endogenous glucose production (r=0.77; P<0.004; Fig. 3A), but not to the baseline plasma glucose level, which was 5.1 (0.7) mmol litre⁻¹.

There was a 5-fold increase in the plasma insulin concentration during surgery (Fig. 3B) and the concentration was also high at 120 min, although a marked decrease in the plasma glucose level had already occurred at that time.

**Volume kinetics**

The plasma dilution increased gradually during the infusion, too, and decreased to a quasi-steady state 30 min later (Fig. 4A). The dilution–time curves showed more variability than the glucose concentration, although the kinetic analysis yielded an acceptable average curve during surgery (Fig. 4B).

The analyses were stopped at the termination of anaesthesia, however, as awakening was often associated with marked haemoconcentration (Fig. 4C) and, in other cases, a transient but abrupt increase of the haemodilution (curves not shown). Therefore, the time period used for this curve-fitting procedure was limited to 85 (67–106) min while the plasma glucose analysis was based on all data up to 240 min as waking up apparently did not affect this curve.

The size of the expanded central body fluid space (V₁) averaged 3.89 litres and the elimination rate constant (kₑ) was 36.7 ml min⁻¹ (Table 1, bottom).

**Haemodynamic variables and urine**

The systolic and diastolic arterial pressures decreased during induction of anaesthesia (P<0.001) but increased when surgery and the glucose infusion started (P<0.01). Thereafter, the arterial pressures and the heart rate remained fairly constant until the end of anaesthesia 85 min later (Fig. 5).

The urinary excretion amounted to 48 (38–77) ml at 120 min, while being 127 (105–185) ml for the entire 240-min
study period. These volumes corresponded only to, respectively, 3.2 (2.7–6.0) and 9.1 (7.0–13.9)% of the infused volume.

The total urinary excretion of sodium was 12.1 (7.1±18.3) mmol, which is 12.8 (6.4±18.2)% of the administered amount of sodium. Minimal glycosuria occurred in most patients, amounting to 0.4 (0.1–6.4) mmol, which should be compared with the average amount of infused glucose of 196 mmol.

Serum sodium decreased from 139.3 (2.2) mmol litre⁻¹ at baseline to 136.1 (1.9) mmol litre⁻¹ at 90 min (P<0.001) but the concentration was then restored partly. The sodium dilution method indicated an intracellular accumulation of 433 (151) ml of fluid at 120 min and 312 (222–353) ml at 240 min (P<0.001 vs baseline).

Simulations

The plasma glucose concentration expected to result from infusing glucose 2.5% at various rates is given in the form of

![Nomogram showing the relationship between infusion rate and infusion time required to increase plasma glucose concentration (A) and the infusion rate required thereafter to maintain a steady-state glucose concentration (B) during laparoscopic cholecystectomy in a patient weighing 75 kg. The isobars show the predicted glucose level. The computer simulations for the graph were performed using the average kinetic parameters from Table 1. Please note the different scales for rate on the vertical axes.](489)

Discussion

The current model for analysis and simulation of the distribution and elimination of glucose solution has been used in two previous volunteer studies. The first one included the mathematical framework and compared the kinetics of glucose 2.5%, glucose 5%, and Ringer’s solution. The second study showed that both the exogenous glucose and the infused fluid volume exhibit model linearity, that is, the kinetic analysis shows the same result for commonly used infusion rates and volumes. An evaluation of the kinetics of glucose 2.5% during surgery is
Another study shows that glucose uptake was reduced by 20% the day after this operation while the figure was 62% greater if we compare real data. Only 9% of the fluid infused was excreted as urine after 4 h while the figure was 62% under non-surgical conditions. Thus, the renal elimination of fluid was in fact reduced twice as much by the surgery as indicated by the kinetic analysis. To examine how much fluid is present in the kinetic system, one can multiply the size of $V_1$ by the dilution at any time and estimate the excess volume in $V_3$ in the same way. At 120 min, 175 ml of excess fluid was present in $V_1$ and almost 500 ml in $V_3$, the latter a logical continuation of previous efforts. The results obtained during laparoscopic cholecystectomy show similarities to but also many differences from those obtained in the laboratory setting.

The volume of distribution ($V_d$) for the administered glucose molecules of 9.1 litres does not differ from that in the previous studies, but the clearance ($CL$) for glucose was only one-third of that obtained under laboratory conditions. The difference in the rate of elimination may also be illustrated by comparing half-lives, which is given by $V_d \times CL$. In $2/CL$. The half-life for glucose was 30 min during cholecystectomy while ranging between 11 and 16 min in the previous five series of glucose infusions in volunteers. The slow elimination of glucose made the patients prone to develop hyperglycaemia. Plasma glucose reached a peak of 16 mmol litres$^{-1}$, but this was followed by only minor glycosuria. Computer simulation indicates that the same infusion would increase plasma glucose to 10 mmol litre$^{-1}$ in a healthy volunteer. The low $CL$ should prevent rebound hypoglycaemia, however, which is a potential problem when a brisk glucose infusion is stopped abruptly.

The low $CL$ for glucose cannot be explained by insulin deficiency as the plasma concentrations of this hormone were very similar to the levels measured in the volunteer studies in which $CL$ was three times higher. Therefore, insulin resistance was undoubtedly present although laparoscopic cholecystectomy is only a moderately stressful operation. Another study shows that glucose uptake was reduced by 20% the day after this operation while the present results were obtained during the surgical procedure. Regardless of trauma, however, insulin resistance develops when fasting is long enough to markedly reduce glycogen stores. The insulin resistance can be abolished by infusing large amounts of glucose before surgery or glucose with insulin during surgery. In the present study, a relative deficit in the glucose supply is indicated by the endogenous glucose production, which was low (1.1 mmol min$^{-1}$) compared with that in volunteers subjected to similar glucose infusions in whom we calculated the same rate in retrospect (mean 2.6 mmol min$^{-1}$). In both studies, the endogenous glucose production correlated closely with $CL$ for glucose (Fig. 3A). This implies that the endogenous glucose production increased with larger amounts of glucose being transported into the cells. This correlation could be expected as $CL$ varied much more than the baseline glucose level. All subjects were in the fasting state, however, which makes anaesthesia and surgical trauma the most apparent factors that differed between the patients and the volunteers. The patients were 10 yr older than the volunteers and mostly women, but this difference is less likely to account for the difference in $CL$ as the body weights were the same in the groups (75 and 77 kg).

The dilution–time curves showed a higher degree of inter-subject variability than for plasma glucose. A prompt plasma dilution occurred in response to the first fraction of the volume load, which might be explained by the vasodilatation resulting from the induction of anaesthesia, which allows more fluid to fill the vascular system. Although no fluid was infused, a plasma dilution of 5% was associated with the induction (data not shown), but this might not have fully accounted for the vasodilatation. Moreover, the surgical technique involves i.p. insufflation of carbon dioxide, which could have affected the early plasma dilution response to glucose 2.5% by modifying the cardiovascular regulatory centres.

The awakening from anaesthesia disturbed the dilution–time curve, which made it necessary for the kinetic analysis to involve the period of anaesthesia alone. As compared with laboratory conditions, the size of the body fluid space expanded by the infused fluid ($V_1$) was 10–20% larger while the elimination rate constant ($k_e$) was only between one-half and one-third as high. This means that, in addition to the reduced distribution of fluid to $V_3$ resulting from insulin resistance, the rate of elimination of fluid from the kinetic system was also decreased in a way similar to the elimination of Ringer’s solution during anaesthesia and trauma surgery. As $k_e$ corresponds to $CL$ in conventional kinetics, the $CL$ for glucose and fluid appeared to be reduced to the same degree during laparoscopy.

The decrease in the rate of elimination of fluid is even greater if we compare real data. Only 9% of the fluid infused was excreted as urine after 4 h while the figure was 62% under non-surgical conditions. Thus, the renal elimination of fluid was in fact reduced twice as much by the surgery as indicated by the kinetic analysis. To examine how much fluid is present in the kinetic system, one can multiply the size of $V_1$ by the dilution at any time and estimate the excess volume in $V_3$ in the same way. At 120 min, 175 ml of excess fluid was present in $V_1$ and almost 500 ml in $V_3$, the latter
figure corresponding quite well to the intracellular accumulation of fluid of 443 ml estimated by the sodium dilution method. With a urinary excretion of only 48 ml at this time, the amount of ‘missing’ fluid is as large as 700 ml. This discrepancy has not been encountered in our volunteer experiments.11 12

Excessive evaporation from the airways during general anaesthesia might account for part of this volume, but there are two other possible explanations for the ‘missing’ fluid. The first is that the glucose solution occupied the fluid space between V₁ and V₃, which has been considered but not supported by the mathematical analysis. Computer simulations show that this space (V₂) is likely to be expanded when CL and kₑ are very low. In this study, the shape of the dilution–time curve typical for the presence of an intermediate body fluid space expanded by fluid was not present, but the relatively high variability of the curves and the fact that the curve-fitting was based on data from only 2 h make it impossible to rule out such a possibility. The second explanation relates to the finding that isoflurane anaesthesia creates a similar discrepancy between model-predicted elimination and renal excretion when saline 0.9% is infused in sheep.22 The effect is not a result of the mechanical ventilation but to the isoflurane itself.23 In the present study, anaesthesia was maintained with sevoflurane, which might cause the same ‘third-spacing’ effect as isoflurane. Where the fluid resides is not known but, in any event, it does not readily equilibrate with V₁.

The results of the kinetic analyses were illustrated by nomograms, which may be useful in clinical practice. They show that infusing glucose 2.5% at a constant rate throughout laparoscopic cholecystectomy is not optimal therapy. To prevent hyperglycaemia and progressive volume expansion, the infusion rate should be high at the beginning of surgery and then slowed down. In the nomogram for glucose, the anaesthetist can choose an acceptable increase in plasma glucose during and immediately after laparoscopy (Fig. 6). After having selected an acceptable ‘target’ rise in plasma glucose in the left part of the nomogram, any combination of infusion rates or infusion times can be used to hit the isobar showing the acceptable increase. Once this ‘target’ is reached, the task is then to infuse enough glucose 2.5% to maintain the plasma concentration. This is done by following the isobar to the right and turning down the infusion rate to the value obtained in that part of the figure.

The nomogram for plasma dilution is based on the same principle as the one for plasma glucose, the only difference being that the steady-state level varied slightly, about 6% between a 10- and a 60-min infusion, because of variable amounts of fluid returning from V₃ after metabolism of the glucose. The volume effect of glucose 2.5% is not negligible and should be considered when administering the fluid (Fig. 7). For example, an increase of plasma glucose by 2 mmol litre⁻¹ to slightly above the normal range, can apparently be maintained by supplying glucose 2.5% at a rate of 3 ml min⁻¹ (180 ml h⁻¹). The infused fluid volume then dilutes the plasma by 7%, which corresponds to a plasma volume increase of about 250 ml in a normal-sized patient.

In conclusion, kinetic analysis of glucose 2.5% solution during laparoscopic cholecystectomy showed low values for endogenous glucose production and for the clearance of glucose and infused fluid volume. This results in an altered disposition of the fluid.

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