Intravenous hydration with a 2.5 % glucose solution in Type II diabetes

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ABSTRACT

Physicians are often unclear about how fast intravenous glucose solutions should be administered to adequately hydrate patients with Type II diabetes while avoiding hyperglycaemia and excessive plasma volume expansion. The aim of the present study was to analyse the disposition of a 2.5 % glucose solution and create a nomogram which could serve as a guide to fluid therapy in these patients. Twelve males (mean body mass index, 29 kg/m²) with Type II diabetes due to insulin resistance, as quantified by an euglycaemic hyperinsulinaemic glucose clamp, received an infusion of iso-osmotic 2.5 % glucose solution with electrolytes (70 mmol/l sodium, 45 mmol/l chloride and 25 mmol/l acetate) at individual rates over 30 and 60 min respectively. Blood glucose and haemoglobin levels were measured repeatedly over 3.5 h to estimate the kinetics of glucose and fluid volume. Mean insulin sensitivity was $4.2 \times 10^{-4}$ dl·kg⁻¹·min⁻¹·(µ-units/ml)⁻¹. The individualized infusion rates reached the predetermined blood glucose level of 12 mmol/l with a mean difference of 0.2 mmol/l. The disposition of glucose was an important factor governing fluid distribution. The volume of distribution of exogenous glucose averaged 19.8 litres, but for the fluid volume it was only 3.7 litres. The clearance was 0.37 litre/min for glucose and 0.10 litre/min for the fluid volume, and the results of the 30-min and 60-min infusions agreed reasonably well. It is concluded that kinetic analysis can be used to guide the infusion time and infusion rate of 2.5 % glucose to reach any predetermined glucose level and volume expansion.

INTRODUCTION

As many as 30–40 % of geriatric patients are undernourished and probably also dehydrated when admitted to hospital, and approx. 50 % of the residents in nursing homes suffer from the same conditions [1,2]. There is a need to supply extracellular volume, but water should also be provided to maintain metabolic balance by hydrating the cells [3–5]. In the clinical setting, safe treatment of patients with water is only made possible by adding glucose to the solution. Glucose-containing fluids are therefore widely used for intravenous fluid balance and nutritional support in both adults and children [6–8]. Hyperglycaemia and glycosuria are important concerns when planning intravenous rehydration with glucose solutions and often lead to overly cautious administration. This issue is particularly delicate when treating the increasing number of patients with Type II diabetes.

Volume kinetics is a mathematical tool that could allow the estimation of the effects of a glucose solution on blood glucose levels and the accompanying fluid shifts in these patients. The aim of the present study was to use this technique to analyse the disposition of a 2.5 % glucose solution in patients with Type II diabetes. Kinetic data would then be used to create nomograms showing how treatment with the 2.5 % glucose solution should be planned to reach any predetermined glucose level and volume expansion.

Key words: glucose metabolism, haemodilution, hydration, pharmacokinetics, Type II diabetes, volume kinetics.

Abbreviations: GIR, glucose infusion rate; Hb, haemoglobin; MCV, mean corpuscular volume; RBC, red blood cell; SI, index of insulin sensitivity.

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Infusions were planned to reach a pre-determined B-glucose of 12 mmol/l based on $V_d$ and $Cl$ from previous studies (dotted line).

The experiments started.

The dotted lines represent our simulated increase in B-glucose curve before the study began.

After 1/3 of the infusions (arrows) the rates were adjusted individually due to differences in $V_d$ and $Cl$ for the glucose molecules. In all cases, more fluid had to be given to reach 12 mmol/l.

**MATERIALS AND METHODS**

Twelve male patients with Type II diabetes gave their informed consent to participate in the study, which had been approved by the Ethics Committee of Human Research in Southern Stockholm.

**Glucose clamp**

A euglycaemic hyperinsulinaemic clamp was performed in each patient to quantify insulin sensitivity [12]. During the 120-min test, insulin (40 m-units $m^2 \cdot min^{-1}$; human Actrapid; NovoNordisk) was infused along with 20% glucose (Fresenius Kabi). The glucose clamp-derived $S_I$ (index of insulin sensitivity) was calculated from the GIR (glucose infusion rate), corrected for body weight, during the final 30 min as follows:

$$S_I = \frac{GIR_{SS}}{G_{SS}} \times I_{SS}$$

where $GIR_{SS}$ is the steady-state GIR (in mg/min), $G_{SS}$ is the steady-state blood glucose concentration (in mg/dl), and $I_{SS}$ is the difference between basal and steady-state plasma insulin levels (in $\mu$-unit/ml).

**Infusion of 2.5% glucose**

Patients participated on two separate occasions during which they received one 30-min infusion and one 60-min infusion of iso-osmotic 2.5% glucose with electrolytes (70 mmol/l sodium, 45 mmol/l chloride and 25 mmol/l acetate; Rehydrex; Fresenius Kabi) via an infusion pump (Figure 1).

After fasting overnight, the patients rested on a bed for 30 min before the experiments started at 08.30 hours.
Neither insulin nor any other medication was taken for 18 h before the experiment started, and none of the patients received insulin during the experiment. Venous blood was collected every 5–10 min for up to 3.5 h. Heart rate and arterial blood pressure were monitored using an automatic device (Propaq 104; Protocol Systems). The glucose concentration in whole blood was measured in single samples using 2300 STAT PLUS (YSY). Hb (haemoglobin), Hct (haematocrit), RBC (red blood cell) count and MCV (mean corpuscular volume) were analysed on a Technicon Advia 120 (Bayer). The baseline sample was drawn in triplicate and the mean value was used in subsequent calculations. Plasma insulin and C-peptide levels were measured by ELISA (Mercodia). Urine volume and its concentration of glucose and sodium were measured on a Hitachi Modular system before, after and repeatedly during the whole time course of the experiments which lasted 180 min and 210 min respectively.

**Glucose kinetics and uptake**

The pharmacokinetics of the exogenous glucose load was analysed using a one-compartment turnover model [9–11]. Here, the plasma concentration \( C_{ex} \) at any time \( t \) resulting from infusing glucose at the rate \( k_{ie} \) is calculated from the following differential equation:

\[
\frac{dC_{ex}}{dt} = \frac{k_{ie} V_d}{V_d} - CL \times C_{ex}(t)
\]

where \( V_d \) is the volume of distribution and \( CL \) is the clearance of glucose. The concentration resulting from endogenous production of glucose \( C_{en} \) was simplified as:

\[
C_{en} = k_{ie}/CL.
\]

The measured blood glucose concentration is the sum of \( C_{ex} \) and \( C_{en} \). Endogenous production is responsible for the baseline concentration in these fasting patients. Fitting these equations to the glucose data yielded the optimal estimates of \( V_d \) and \( CL \).

**Volume kinetic model**

The distribution and elimination of the infused fluid was studied using volume kinetics [9,10]. The following differential equations, in which distribution of fluid occurs between an expandable central body fluid space \( V_1 \) and a peripheral fluid space \( V_3 \), were fitted to repeated measurements of the plasma dilution:

\[
\begin{align*}
\frac{dv_1}{dt} &= k_i - k_e - k_{v1} \frac{v_1 - V_1}{V_1} - f(t) + k_{v3} \frac{v_3 - V_3}{V_3} \\
\frac{dv_3}{dt} &= f(t) - k_{31} \frac{v_3 - V_3}{V_3}
\end{align*}
\]

During volume expansion, the baseline volumes \( V_1 \) and \( V_3 \) are expanded to \( v_1 \) and \( v_3 \) respectively. The size of \( V_3 \) corresponds to the intracellular fluid volume, which is taken to be 40% of the body weight [13]. Fluid can also increase the volume of an intermediate fluid space between \( V_1 \) and \( V_3 \), but this expansion has never been justified statistically [9–11].

Translocation of fluid from \( V_1 \) to \( V_3 \) occurs by virtue of osmosis, \( f(t) \), which is governed by the glucose uptake into the cells (Figure 2). The factor \( f \) is 3.6 ml of fluid/mmol glucose, as 50 g of glucose (278 mmol) per litre is isotonic. Elimination of fluid from \( V_1 \) is governed by the dilution of \( V_1 \), the strength of which is expressed by the parameter \( k_i \) (in practice, renal clearance). Baseline fluid losses from evaporation were set to 0.5 ml/min and an additional 0.3 ml/min was deducted to account for the sampling of plasma [14].

Fluid also returns from \( V_3 \) to \( V_1 \) at a rate proportional to a constant \( k_{31} \) to the dilution of \( V_3 \). The kinetic output
is presented as $k_{31}/V_3$ (i.e. the slope of the dilution of $V_3$) to make the output independent of the assumption that $V_3$ was preset to 40% of the body weight.

For a review of the glucose and volume kinetic models used, see [15].

**Computer calculations**

The model parameters for the exogenous glucose ($V_d$, CL and $k_{in}$) and fluid ($V_1$, $k$, and $k_{31}/V_3$) were calculated on a computer using Matlab version 6.5 (Math Works), in which a non-linear least-squares regression routine based on a modified Gauss–Newton method was used.

The dilution of the plasma in the cubital vein (equivalent to $V_1$), which served as input data in the curve-fitting process, was calculated based on the blood chemistry obtained at baseline (time 0) and at any later time ($t$). The principle is to convert haemodilution into plasma dilution based on the average of the HB and RBC count dilutions, as these are measured by different laboratory methods (photometry and laser beam dispersion respectively).

$$\frac{(V_1 - V_t)}{V_1} = 0.5 \left( \frac{HB_0/Hb(t) - 1}{1 - Hct_0} + \frac{RBC_0/RBC(t) - 1}{1 - Hct_0} \right)$$

Before use, this expression was corrected for ‘iatrogenic’ dilution resulting from sampling and also by the ratio $MCV_3/MCV_1$ to account for changes in RBC sizes [16].

Nomograms were made by simulating the glucose and dilution responses to various dose ranges [5,11]. The volume expansion of $V_1$ was obtained as the product of the size of $V_1$ and the dilution at any time ($t$). Intracellular accumulation of fluid was obtained as the volume increase of $V_3$ and also from the sodium balance. The latter approach implies that any discrepancy in serum sodium response to known additions and losses of sodium and water over time is due to a fluid shift between the intra- and extra-cellular fluid space [9,16].

**Reaching a pre-determined glucose level**

The individual infusion rates of 2.5% glucose were planned to reach a blood glucose level of 12 mmol/l at the end of the infusion in order to avoid overshooting renal tubular transport capacity (Figure 1). This was done by measuring the baseline glucose concentration, which was entered into the computer simulation program based on the single-compartment model for glucose kinetics described above. The simulations used were $V_d = 10$ litres and $CL = 0.3$ litres/min, which reduction of $CL$ is suggested by previous work to account for insulin resistance [11]. Blood glucose was measured at the bedside again after one-third of the infusion time, and the rate was then corrected to reach 12 mmol/l more precisely at the end of the infusion.

**Statistics**

Results are means (S.D.). Data showing a skewed distribution are presented as medians (25th–75th percentile range). Differences between the two series of experiments were evaluated by a paired Student $t$ test, where the $\chi^2$ test was used for categorical data. $P < 0.05$ was considered significant.

**RESULTS**

**Subjects**

The group of 12 patients studied were aged 63 (8) years, had a body weight of 94 (17) kg and a body mass index of 29.0 (3.9) kg/m². Their glycaemic control was achieved by diet only (two patients), diet plus oral hypoglycaemic drugs (one patient with metformin and one patient with metformin and sulphonurone) or insulin plus oral hypoglycaemic drugs (five patients with insulin and metformin, one patient with insulin and a combination of metformin and sulphonurone). Furthermore, two patients had insulin as the only treatment. HbA1c (glycated Hb) was 6.4 (1.1)% and the creatinine clearance was 114(41) ml/min.

**Glucose clamp**

All 12 patients had insulin resistance as evidenced by an euglycaemic hyperinsulinaemic clamp. Before the clamp, blood glucose was 6.4 (0.7) mmol/l, plasma insulin was 182 (84) pmol/l, C-peptide was 597 (93) pmol/l and glucagon was 12.6 (1.3) pmol/l. At steady state, the glucose level was 6.4 (0.7) mmol/l, insulin was 574 (71) pmol/l, C-peptide was 542 (13) pmol/l and glucagon 4.4 (0.9) pmol/l. During the final 30 min of the 2-h clamp, GIR was 3.4 (1.5) mg · kg⁻¹ · min⁻¹ of body weight · min⁻¹ and $S_I$ was 4.2 (2.9) × 10⁻⁴ dl · kg⁻¹ · min⁻¹ · (µ·units/ml)⁻¹, which is consistent with insulin resistance.

**Glucose kinetics**

In the experiments with the 2.5% glucose solution, baseline values of blood glucose were 7.5 (1.6) mmol/l for the 30-min infusion and 7.1 (1.5) mmol/l for the 60-min infusion. As expected, the infusions markedly raised blood glucose, C-peptide and plasma insulin concentrations (Figure 4). Kinetic analysis of the glucose concentration–time curves showed an overall $V_d$ for glucose of 19.8 (5.1) litres, a CL of 0.37 (0.12) litre/min and an endogenous glucose production of 2.6 (0.9) mmol/min. These parameters were estimated with an uncertainty (S.D.) of 4.6, 7.8 and 9.6% respectively (median). There were no significant differences in the kinetic parameters between the two infusion regimes.

**Fluid kinetics**

The infusion rates during the 30-min and 60-min infusions of a 2.5% glucose solution became reasonably similar due to the early correction made possible by the bedside measurement of blood glucose. The rates
Intravenous hydration with a glucose solution in Type II diabetes

Figure 4  Blood glucose (A and B) and the plasma C-peptide (C) and insulin (D) concentrations during and after infusions of a 2.5% glucose solution in patients with Type II diabetes

Data are means (S.D.). B-glucose, blood glucose; P-insulin, plasma insulin.

Figure 5  Plasma dilution during and after the 30-min (A) and 60-min (B) infusion of a 2.5% glucose solution

Values are means (S.D.).

were 0.21 (0.07) and 0.22 (0.08) mg·kg⁻¹ of body weight·min⁻¹ respectively, which corresponded to a fluid volume of 622 (221) ml during the 30-min infusion and 1176 (367) ml during the 60-min infusion.

The maximum plasma dilution was 11 (4) and 14 (4)% respectively (Figure 5). There were no significant differences in $V_1$ or $k_s$ between the two infusions. Overall, $V_1$ amounted to 3.67 (1.86) litres and $k_s$ to 99 (46) ml/min. These parameters were estimated with an uncertainty (S.D.) of 15.4 and 15.7% respectively. The parameter $k_{31}/V_3$ differed between the infusions, being $9 (2–44) \times 10^{-3}$/min for the 30-min infusion and $27 (6–49) \times 10^{-3}$/min for the 60-min infusion. The average parameter values were entered into the computer simulation program and used to create the nomograms shown in Figure 6 (right-hand panels).

According to the volume kinetic model, accumulation of fluid in $V_3$ amounted to 140 ml after the 30-min infusion and to 232 ml after the 60-min infusion (median). These results agreed reasonably well with the ones obtained with the sodium balance, which were 99 and 219 ml respectively.

Urinary excretion and haemodynamics

No significant change in blood pressure or heart rate occurred during the 24 experiments. The urinary excretion
Figure 6  Nomograms showing the effect of infusing a 2.5 % glucose solution in healthy volunteers (left-hand panels) and in patients with Type II diabetes (right-hand panels)

Plasma dilution, blood glucose (b-Glucose) concentration and the volume expansion of $V_1$ (plasma) are shown. The isobars represent estimated effects when infusing a 2.5 % glucose solution at a certain rate (vertical axis) over a certain infusion time (horizontal axis). The ‘maintain’ box on the right indicates the rates of infusion that maintain the levels reached. Computer simulations were based on kinetic data from patients with Type II diabetes (the present study) and healthy individuals ([10]).

amounted to 72 (32) % of the infused fluid volume. The fluid volumes given were fairly high, but all patients felt well and showed no signs of peripheral oedema.

No patient had glycosuria at baseline. The median glucose excretion amounted to 0.9 (0.2–5.7) % of the infused amount during the 30-min infusion and to 0.8 (0.4–3.3) % during the 60-min infusion. Seven of the nine experiments associated with glycosuria in excess of 1 % reached a maximum glucose level that was higher than 12 mmol/l ($P < 0.01$, as determined by $\chi^2$).

Sodium retention was greater when larger amounts of fluid were infused, the excretion being 118 % of the amount given after the 30-min infusion and 71 % after the 60-min infusion (values are medians; $P < 0.01$).

**Bedside guidance of blood glucose**

Fluid given intravenously yielded a maximum glucose level of 11.6 (0.8) mmol/l during the 30-min infusion and 12.0 (0.7) mmol/l during the 60-min infusion. Without the correction of the infusion rate, the computer simulations predicted that the patients would have a 0.3 (0.1–0.6) mmol/l lower glucose level at the end of the 30-min infusion and 0.5 (0.1–0.9) mmol/l lower at the end of the 60-min infusion.

**DISCUSSION**

Controlling the glucose level and preventing excessive plasma volume expansion in patients with insulin
resistance is important in both medical and surgical specialties. The results of volume kinetic studies characterize different patient groups with respect to how they handle these components of glucose solutions. Nomograms can serve as a guide when planning such therapy, although further validation is needed before using them in the clinic. In the present study, we infused a 2.5% glucose solution into patients with Type II diabetes who were devoid of apparent complications from their disease. This fluid is appropriate to prescribe when hydration is desired in addition to supplementation of calories, such as in patients who are dehydrated due to poor fluid intake, surgical wounds or diarrhoea.

The main outcome of the present study is the nomograms (Figure 6) showing the increase in blood glucose and the accompanying plasma dilution for a large number of infusion rates and infusion times in patients with Type II diabetes with a normal creatinine clearance, successful antidiabetic medication and under no stress. The volume increase of the central volume $V_1$ is also given, although it is not known whether this corresponds precisely to the plasma volume expansion. Plots for healthy volunteers based on kinetic parameters obtained in a previous study [10] are also shown in Figure 6 for comparison.

One of the benefits of kinetic analysis is that the outcome of experiments not performed can be indicated. Hence the multiple predictions made in the nomogram for patients with Type II diabetes are based on only two series of experiments, although the results cannot be extrapolated to other patient groups. Two series of observations still had to be made because otherwise it would be uncertain whether the kinetic parameters differed between different volume loads and infusion times. A more detailed evaluation showing that kinetic parameters are reasonably stable for different infusion rates has been performed previously by applying this mathematics in healthy volunteers [10]. As in the volunteers, the 2.5% glucose solution infused in patients with Type II expanded $V_1$ to a size similar to the expected plasma volume, and the relatively high clearance constant for the infused fluid ($k_3$) shows that the elimination of excess fluid was effective [9,10]. In contrast, the rate at which water returned to $V_1$ from the cells ($k_{31}/V_1$) differed between the experiments. However, the importance of the latter finding is small, as changes in $k_{31}/V_1$ affect the predictions to a limited extent [15].

The disposition of the exogenous glucose was more aberrant than the disposition of infused fluid in the patients with Type II diabetes. Interestingly, $V_d$ for the exogenous glucose molecules was twice the volume previously found in healthy volunteers and in patients during and after surgery [5,9–11]. Although many of the patients with Type II diabetes were slightly overweight, the glucose clearly distributed over a larger proportion of their body fluids than expected. This makes the glucose level increase more slowly than expected from the patient's capacity to clear glucose, whereas the situation is the opposite after the infusion ends.

Glucose clearance was almost 40% lower than in healthy volunteers [9,10], but in the same range as in non-diabetic females 2 days after major surgery [5]. The aberrant handling of glucose is relevant to the disposition of infused fluid as these two kinetic systems are connected by the osmotic strength of the glucose molecules. The only 'normal' kinetic parameter estimate was the endogenous glucose production, which is used in the present study to account for the baseline blood glucose. However, having been obtained without radioisotopes, this estimate might reflect the true situation only at the beginning of the experiment.

The kinetics of exogenous glucose are often described by two- or three-compartment models [17], although a one-compartment model offers reasonably good precision for clinical use [9–11]. For glucose molecules in non-diabetics, the most remote compartment equilibrates slowly with plasma and parts of the extracellular fluid space and, therefore, $V_d$ in the one-compartment model corresponds to two-thirds of the expected size of the extracellular fluid space volume [18]. In patients with Type II diabetes, exogenous glucose is quickly distributed over 21% of the body weight and thus seemed to fill virtually the entire extracellular fluid space.

This unexpected finding, the physiological background of which should be clarified in future studies, means that a slightly larger amount of glucose per kg of body weight had to be infused to fill up $V_d$ in patients with Type II diabetes than in healthy volunteers, despite the fact that the patients with Type II diabetes had a reduced capacity to clear administered glucose. An illustration of this finding was obtained as early as during the infusions, as a target glucose level of 12 mmol/l had been set to reduce the impact of glycosuria on the results. When the rise in blood glucose was tested at the bedside after one-third of the infusion, more glucose had to be given consistently as the measured glucose levels were lower than expected (Figure 1). The clinical implications of this finding have been illustrated in the nomograms; a 50% lower infusion rate would be required in patients with Type II diabetes to keep the glucose level at steady state. This is consistent with the results of the insulin clamp. Similarly, the volume nomograms show that approx. 25% lower infusion rates were required to reach or maintain a predetermined plasma volume expansion in patients with Type II diabetes. This difference from healthy subjects is explained by insulin resistance as their fluid kinetics were normal.

In conclusion, the volume kinetic model for isosmotic 2.5% glucose solutions was a reliable guide to reach a predetermined target level for blood glucose and plasma volume expansion in patients with Type II diabetes and insulin resistance in the present study. The
results imply that a 50% lower infusion rate for this group of patients is required to keep the target glucose level at steady state. Additionally, these patients with Type II diabetes with normal creatinine clearance had a larger plasma volume response to the intravenous infusion of a 2.5% glucose solution than healthy subjects. The study was, however, performed on a limited number of patients and, hence, a study on a larger patient group is necessary to forward any recommendations on fluid therapy to be used clinically in the future. Furthermore, these patients had normal kidney function and the clearance of the infused fluid was within normal range, hence, the nomograms cannot be applied to patients with reduced elimination of fluid.

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