Hypovolaemia after glucose/insulin infusions in volunteers

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ABSTRACT

High-dose intravenous infusion of 5% glucose promotes rebound hypoglycaemia and hypovolaemia in healthy volunteers. To study whether such effects occur in response to glucose/insulin, 12 healthy firemen (mean age, 39 years) received three infusions over 1–2 h that contained 20 ml of 2.5% glucose/kg of body weight, 5 ml of 10% glucose/kg of body weight with 0.05 unit of rapid-acting insulin/kg of body weight, and 4 ml of 50% glucose/kg of body weight with 1 unit of insulin/kg of body weight. The plasma glucose concentration and plasma dilution were compared at 5–10 min intervals over 4 h. Regardless of the amount of administered fluid and whether insulin was given, the plasma glucose concentration decreased to hypoglycaemic levels within 30 min of the infusion ending. The plasma dilution closely mirrored plasma glucose and became negative by approx. 5%, which indicates a reduction in the plasma volume. These alterations were only partially restored during the follow-up period. A linear relationship between plasma glucose and plasma dilution was most apparent when the infused glucose had been dissolved in only a small amount of fluid. For the strongest glucose/insulin solution, this linear relationship had a correlation coefficient of 0.77 (n = 386, P < 0.0001). The findings of the present study indicate that a redistribution of water due to the osmotic strength of the glucose is the chief mechanism accounting for the hypovolaemia. It is concluded that infusions of 2.5%, 10% and 50% glucose, with and without insulin, in well-trained men were consistently followed by long-standing hypoglycaemia and also by hypovolaemia, which averaged 5%. These results emphasize the relationship between metabolism and fluid balance.

INTRODUCTION

Glucose/insulin infusions have a use in anaesthesia and intensive care, although their precise roles are debated. Glucose/insulin is used to combat cardiac insufficiency in cardiovascular surgery [1,2] and might be given before general surgery begins as a means of reducing insulin resistance, the surgical stress response and the incidence of nausea [3,4]. Insulin given together with 10% glucose infusions resulted in a reduction in mortality in the ICU (intensive care unit) in a study by Van den Berghe et al. [5], and beneficial effects have been reported after acute myocardial infarction [6,7]. In animals, glucose/insulin makes the myocardium utilize glucose instead of fatty acids as the energy substrate, which might protect from permanent injury in ischaemic situations [8,9].

Glucose has an osmotic potential that affects the distribution of body water. Simple calculations suggest that each mmol of glucose attracts 3.6 ml of water, which is translocated from the extracellular to the intracellular fluid space along with the uptake of glucose by the cells, with or without the aid of exogenous insulin. The effects of glucose and glucose/insulin administration on the distribution of water have been poorly understood in the past. However, infusion of plain 5% glucose in volunteers was followed by mild hypovolaemia and hypoglycaemia.

Key words: fluid balance, glucose, hypoglycaemia, hypovolaemia, insulin, osmolality.
Abbreviations: CL, glucose clearance; ECF, extracellular fluid; Hb, haemoglobin; Hct, haematocrit; ICU, intensive care unit; MCV, mean corpuscular volume; RBC, red blood cell; Vd, distribution volume.
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30–45 min after the end of the infusion [10]. These effects were less apparent in those with a low glucose clearance, such as diabetic [11] and surgical patients [12], but may possibly be aggravated by exogenous insulin.

The aim of the present study was to evaluate the severity and time course of hypovolaemia developing in association with glucose/insulin therapy. On three occasions, volunteers were given an infusion with 2.5% glucose and electrolytes, a ‘mild’ glucose/insulin infusion and, finally, a ‘strong’ glucose/insulin infusion. The first solution is frequently given during anaesthesia and surgery [11,12], the second solution (10% glucose) is given post-operatively [5], and the third solution (50% glucose) is often used during intensive care. The amounts of insulin used were based upon the practices of thoracic anaesthesia clinics in Sweden. The volunteers were closely supervised by our team and followed with both laboratory and bedside testing of the glucose level to allow mild, but not severe, hypoglycaemia to develop.

**MATERIALS AND METHODS**

**Subjects**

The protocol was approved by the Ethics Committee in Umeå, Sweden and written informed consent was obtained from all volunteers. Twelve healthy male firemen aged between 26 and 50 years (median age 39 years) and with a body weight of 83 kg (72–100 kg) agreed to participate in three laboratory experiments conducted at the ICU at a university hospital with an interval of at least 1 month. A 13th volunteer abandoned the study after the first experiment and was excluded from the analysis.

**Experimental infusions**

The volunteers received three infusions: (i) ‘only glucose’, 20 ml of iso-osmotic 2.5% glucose with electrolytes (70 mmol/l sodium, 45 mmol/l chloride and 25 mmol/l acetate; Rehydrex; Pharmacia)·kg⁻¹ of body weight·h⁻¹ was infused over 1 h, no insulin was given; (ii) ‘mild’ glucose/insulin infusion, 5 ml of 10% glucose·kg⁻¹ of body weight·h⁻¹ was given over 1 h and 0.1 unit of rapid-acting insulin (Actrapid; Novo Nordisk)·kg⁻¹ of body weight·h⁻¹ over 30 min; and (iii) ‘strong’ glucose/insulin infusion, 2 ml of 50% glucose·kg⁻¹ of body weight·h⁻¹ over 2 h and 1 unit of Actrapid insulin·kg⁻¹ of body weight·h⁻¹ for 1 h.

Owing to the lag time before insulin exerts its effect, the insulin infusions were started 10 min before the glucose. The three experimental infusions contained different amounts of fluid, glucose and insulin, and also a period of glucose infusion after insulin had been discontinued. Details are compared in Table 1.

All volunteers arrived at the ICU in the fasting state at 07:00 hours and received a light standard breakfast consisting of 200 ml of water or coffee and one sandwich.

They were placed comfortably in a bed and, after instrumental preparation, they were left for haemodynamic equilibration for a period of 30 min. In the ‘only glucose’ experiment, the infusions were given via a peripheral venous cannula, whereas the insulin-containing fluids were infused via a central venous catheter placed in the axillary or subclavian vein via a cubital vein. Blood sampling was performed via an arterial catheter. A discard volume of 3 ml was drawn before each blood collection. This blood was then returned and the cannula flushed with 3 ml of acetated Ringer’s solution to prevent clotting.

**Measurements**

Blood was collected for measuring the blood Hb (haemoglobin) and plasma glucose concentrations, the Hct (haematocrit), MCV (mean corpuscular volume) and RBC [red blood cell (erythrocyte)] count every 5 min up to 1.5 h, and every 10 min up to 4 h of each experiment. All indices of the RBCs were reported as the mean of duplicate samples, whereas the baseline was taken as the mean of triplicate samples.

The serum sodium, potassium and insulin concentrations were measured every 30 min. However, insulin was not measured during the ‘only glucose’ experiments. In the ‘strong’ glucose/insulin experiments, lack of adequate dilution of the samples before analysis made all of the ones collected during the infusion show the maximum value for the kit (Roche Elecsys reagent), but all samples obtained from 1.5 h and onward were within the range of detection.

Blood analyses were conducted by the certified standard routine chemistry laboratory at Umeå University Hospital, Umeå, Sweden.

Arterial blood pressure and heart rate were measured via the arterial line every 5 min and displayed on a GE

### Table 1 Composition of the three infused solutions and excreted urine

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>‘Only glucose’</th>
<th>‘Mild’ glucose/ ‘Strong’ glucose/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose infusion time (min)</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Volume infused (ml)††</td>
<td>1660 (163)</td>
<td>430 (42)</td>
</tr>
<tr>
<td>Glucose concentration (mg/ml)</td>
<td>2.5</td>
<td>10</td>
</tr>
<tr>
<td>Dose of glucose (g)</td>
<td>41.6 (3.6)</td>
<td>41.6 (3.6)</td>
</tr>
<tr>
<td>Insulin infusion time (min)</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>Insulin infusion rate (units·kg⁻¹·h⁻¹)</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>of body weight·h⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infused insulin (units)</td>
<td>0</td>
<td>4.2 (0.4)</td>
</tr>
<tr>
<td>Urine volume (ml)</td>
<td>1649 (529)</td>
<td>510 (394)</td>
</tr>
<tr>
<td>Sodium infused (mmol/l)</td>
<td>115 (37)</td>
<td>0</td>
</tr>
<tr>
<td>Sodium excretion (mmol/l)</td>
<td>85 (50)</td>
<td>66 (40)</td>
</tr>
<tr>
<td>Potassium excretion (mmol/l)</td>
<td>23 (8)</td>
<td>19 (9)</td>
</tr>
</tbody>
</table>

†† ‘Flush’ volumes, rescue injections of glucose and the amount of sampled blood are not included.
Solar 8000 M (General Electric). Voiding was allowed whenever needed, but the subject then remained in the recumbent position.

The volunteers were always attended by a registered nurse and by at least one member of the study team. Blood glucose was monitored at the bedside every 5 min by using a system which requires only one drop of blood for each analysis (HemoCue). Any sign of sweating and discomfort, which was checked continuously, as well as blood glucose levels of 2 mmol/l or lower, as detected by HemoCue, was treated with one or several intravenous ‘rescue’ injections of 30 % glucose. This was necessary in 19 experiments. Data on plasma glucose and the dilution obtained during, and for 15 min after, emergency injections were excluded from analysis. The research team had telephone contact with the volunteers 24 h after each experiment. The volume of the ‘rescue’ injections averaged 50 ml and the ‘flush’ volume was 66 ml. The volume of sampled blood amounted to 300–350 ml.

Calculations

Glucose

The kinetics of the ‘only glucose’ infusion was analysed to characterize how effectively the volunteers handled an exogenous glucose load. The pharmacokinetics were analysed using a one-compartment turnover model. The plasma concentration ($C$) at any time ($t$) is increased by an exogenous infusion rate ($R_{in}$) and the endogenous production of glucose ($k_{en}$), which result in the glucose concentrations $C_{ex}$ and $C_{en}$ respectively. Hence $C = C_{ex} + C_{en}$. The contribution of $R_{in}$ to the measured $C$ was assessed from the following differential equation [10–12] (eqn 1):

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

where $V_d$ is the volume of distribution and $CL$ is the clearance of glucose. The glucose concentration resulting from endogenous production of glucose ($C_{en}$), which is responsible for the baseline concentration in these fasting volunteers, was simplified as (eqn 2):

$$C_{en} = \frac{R_{in}}{CL}$$

The model parameters ($V_d$, $CL$ and $R_{in}$) were calculated from eqn (2) and the analytical solution eqn (1) simultaneously on a PC using Matlab version 6.5 (Math Works), operating with a non-linear least-squares regression routine based on a modified Gauss–Newton method [11]. Since glucose enters the cells by active transport, a decreasing amount of glucose in $V_d$ corresponds, in the absence of glucosuria, to the uptake of glucose into the cells of the body.

The half-life of the exogenous glucose was obtained as the product of $V_d$ and the natural logarithm of 2 (0.693) divided by $CL$.

The $CL$ during each 5 min or 10 min period was estimated for all 36 experiments by inserting the values of $V_d$ and $R_{in}$ obtained during the ‘only glucose’ experiments into eqn (1).

The serum half-life of insulin during the post-infusion period was obtained from the coefficient in a simple linear regression analysis of the relationship between the logarithm-transformed serum insulin concentration and time after the infusions ended.

Plasma dilution

The dilution of arterial plasma was calculated based on the blood haematology obtained at baseline (zero time) and at any later time ($t$). The principle is to convert haemodilution into plasma dilution based on the average of the Hb and RBC dilutions, as these are measured by different laboratory methods (photometry and laser-beam dispersion respectively). Hence (eqn 3):

$$\text{Plasma dilution} = 0.5 \left( \frac{0.5}{1 - Hct_t} \right) (\text{Hb}_0/\text{Hb}(t) - 1) + \left( 1 - \frac{0.5}{1 - Hct_0} \right) (\text{RBC}_0/\text{RBC}(t) - 1)$$

Before use, this expression was corrected for ‘iatrogenic’ dilution resulting from the sampling (7 ml per sample) and also by the ratio MCV$_v$/MCV$_t$ to account for changes in RBC cell size [13].

Statistics

Results are means (S.D.). The relationship between parameters was analysed by linear regression analysis. Significant changes from baseline were studied by repeated-measures ANOVA. $P < 0.05$ was considered statistically significant.

RESULTS

Plasma glucose and plasma dilution

In the ‘only glucose’ experiments, the plasma glucose concentration decreased quite rapidly after the infusion was finished and remained below baseline ($P < 0.0001$) from 30 min onward (Figure 1, upper left-hand panel). The half-life of the exogenous glucose averaged 7 min (Table 2).

The plasma dilution was also significantly below baseline ($P < 0.01$; indicating haemoconcentration) from 30 min after the infusion ended (Figure 1, upper right-hand panel).

The ‘mild’ glucose/insulin infusion resulted in a gradual reduction in the plasma glucose and the plasma dilution (Figure 1, middle panels). Rescue injections of 30 % glucose needed to be given to seven volunteers after the infusion ended, despite the fact that insulin was stopped 30 min before the infusion of 10 % glucose.
Figure 1 Plasma glucose concentrations (left-hand panels) and plasma dilution (right-hand panels) in experiments with an infusion of 2.5% glucose (top panels), 10% glucose with insulin (middle panels) and 50% glucose with insulin (bottom panels). Values are means ± S.D.

Table 2 Pharmacokinetic parameters for glucose when 20 ml of 2.5% glucose · kg⁻¹ of body weight · h⁻¹ was infused in 12 volunteers.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (litre/min)</td>
<td>0.78</td>
<td>0.19</td>
</tr>
<tr>
<td>CL (litre)</td>
<td>7.1</td>
<td>3.9</td>
</tr>
<tr>
<td>CL (mmol/min)</td>
<td>3.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Half-life (min)</td>
<td>7.1</td>
<td>5.0</td>
</tr>
</tbody>
</table>

The ‘strong’ glucose/insulin solution increased plasma glucose significantly only during the first hour of the 120 min infusion, and it fell to below baseline within 30 min after it was stopped (Figure 1, bottom left-hand panel). The plasma dilution both increased and decreased during the infusion, but it decreased to significantly below baseline from 30 min and up to the end of the study (P < 0.01; Figure 1, bottom right-hand panel and Table 3).

A linear relationship between individual changes in plasma glucose and plasma dilution was most apparent when a small volume of fluid accompanied the glucose infusion. Hence this relationship was statistically significant during infusion of the ‘strong’ glucose/insulin solution, between 0 and 30 min after and >30 min after these infusions ended (Figure 2). The pooled data from all of the periods of time during infusion of the ‘strong’ glucose/insulin solution further illustrated the consistent linear relationship between these parameters (Figure 3).

The estimates of CL over time indicated that the CL was twice as high during the glucose/insulin infusions as compared with ‘only glucose’ (Figure 4, left-hand panel).

Haemodynamics

With ‘only glucose’, the diastolic arterial pressure increased gradually from baseline 66 (6) mmHg and remained elevated during the last 15 min of the infusion and beyond, when it averaged 73 (5) mmHg (P < 0.001). The systolic arterial pressure tended to increase at the end of the infusion but the change was not significant. The heart rate showed no trend.

The ‘mild’ glucose/insulin infusion was followed by a 10–15% reduction in the systolic and diastolic arterial pressures during the last 2 h of the experiment (P < 0.006). The heart rate increased from 62 (11) to 67 (12) beats/min during the first hour post-infusion, after which it decreased to below baseline [to 56 (9) beats/min; P < 0.0001].

During the last hour of the ‘strong’ glucose/insulin experiments, the systolic and diastolic arterial pressures also fell by approx. 10% from baseline (P < 0.05). The heart rate tended to rise post-infusion, but this change was not statistically significant.

Insulin, electrolytes and urine

The baseline serum insulin concentration was 24 (16) pmol/l. The maximum concentration at the end of the ‘mild’ glucose/insulin infusion was 2325 (1964–2635) pmol/l (median, 25–75th percentiles). The baseline insulin level had been reached again at 120 min, the half-life being 27 (2) min. In the ‘strong’ glucose/insulin experiments, the half-life of insulin in serum was 32 (4) min and the baseline level had been reached at 210 min.

There was a statistically significant relationship between CL and log₁₀ of the plasma insulin concentration at the points in time when the insulin level had been assessed successfully (Figure 4, right-hand panel).

Serum sodium decreased during the ‘only glucose’ infusion [from 140.5 (2.0) to 136.6 (3.6) mmol/l; P < 0.001] but the baseline level was restored 30 min later. Serum sodium was unchanged or increased slightly during the two glucose/insulin experiments (results not shown).

Serum potassium decreased to a similar degree during the two glucose/insulin infusions, from 3.85 (0.22) to 3.55 (0.21) mmol/l (P < 0.001), after which it was slowly restored to 3.78 (0.41) mmol/l at 240 min.
Table 3 Change in plasma glucose from baseline and the plasma dilution for various periods of time during the glucose/insulin experiments
Values are means (S.D.).

<table>
<thead>
<tr>
<th>Experiment</th>
<th>During infusion</th>
<th>After infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma glucose (mmol/l)</td>
<td>0–30 min</td>
</tr>
<tr>
<td>'Only glucose'</td>
<td>+ 3.5 (1.3)</td>
<td>− 0.4 (1.6)</td>
</tr>
<tr>
<td></td>
<td>Plasma dilution (%)</td>
<td>− 1.1 (4.3)</td>
</tr>
<tr>
<td>'Mild' glucose/insulin</td>
<td>− 1.5 (1.3)</td>
<td>− 3.7 (1.2)</td>
</tr>
<tr>
<td></td>
<td>Plasma dilution (%)</td>
<td>− 3.1 (4.5)</td>
</tr>
<tr>
<td>'Strong' glucose/insulin</td>
<td>+ 1.4 (2.6)</td>
<td>− 0.2 (3.2)</td>
</tr>
<tr>
<td></td>
<td>Plasma dilution (%)</td>
<td>− 1.3 (3.7)</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

Figure 2 Change in plasma glucose from baseline against the Hb-derived plasma dilution for three different time periods (vertical rows) for a series of three experiments (horizontal rows)
The regression line is shown whenever linear regression analysis indicated that the relationship was statistically significant by $P < 0.05$. Each circle represents a single time point during one experiment.

The volunteers voided all or nearly all of the infused fluid during the experiments (Table 1).

**DISCUSSION**

Hypoglycaemia and hypovolaemia were common after the intravenous infusions of glucose in well-trained males, regardless or whether the glucose load was accompanied by exogenous insulin or a fluid volume of 1.6 litres. Blood glucose and plasma dilution regularly fell to below baseline within 30 min after the glucose infusion ended. At 3 h later these alterations in body physiology were only partially restored, despite the fact that plasma insulin had returned to baseline. Other findings include that nearly all of the fluid infused with the glucose was excreted during the experiments, which was hardly expected when considering the long-standing state of mild hypovolaemia. Haemodynamic responses consisted mainly of a modest increase in heart rate and a decrease in arterial pressure after the glucose/insulin infusions were ended. Reduction in
serum potassium was a minor issue, although glucose/insulin is usually provided together with potassium to prevent hypokalaemia from developing. In the present study, potassium was not added as it would increase the risk of pain on infusion of the strong glucose solutions. The fact that haemoconcentration developed which corresponds to a reduction in the plasma volume by up to 15% (average 5%) can be explained by the osmotic strength of the glucose molecule. When administered intravenously, this molecule attracts water that is either recruited from the intracellular fluid space or else is provided with the infusion. The fluid stimulates a diuretic response but the same fluid should also, by virtue of osmosis, accompany the glucose into the cells. The end-result of these events is a diuretic response and a matched load of glucose and water entering the cells. Hypovolaemia develops as the diuresis competes with the osmotic forces for the same fluid volume [14].

The glucose/insulin protocols used in the present study are similar to those used in the clinic. The Department of Thoracic Anaesthesia in Lund, Sweden, gives 50 units of insulin in 500 ml of 30% glucose at a rate of 1.2 ml·kg⁻¹·h⁻¹ of body weight·h⁻¹. Our ‘mild’ composition provided 30% more glucose and less than half as much insulin per h but, to assure volunteer safety, the glucose infusion alone was continued for twice as long as the insulin infusion. The composition of the ‘strong’ glucose/insulin infusion was derived from the Department of Thoracic Anaesthesia in Umeå, Sweden. Here, too, the glucose administration was continued for twice as long as the insulin infusion to limit the risk of hypoglycaemia. In both cases, the precautions proved to be insufficient. Several bolus injections of 30% glucose had to be given and the volunteers were often at the limit of experiencing blunt hypoglycaemia. However, the monitoring of the volunteers was extensive. They were kept at the ICU of a university hospital and received attention similar to that given to cardiothoracic surgical patients. One drop of blood was also taken every 5 min for a bedside check-up of blood glucose, and the volunteers were asked to read a book and to report every experience of lost attention, blurred vision or nausea to the research team.

Our volunteers were well-trained physically and had a $CL$ of 0.8 litre/min when no insulin was provided, which is fairly high. Previous studies using the same one-compartment model yielded a $CL$ of 0.72 and 0.54 litre/min [10] and 0.6 litre/min [15] in healthy volunteers, which corresponded to half-lives for exogenous glucose of between 11 and 16 min. $CL$ in patients with diabetes averaged 0.37 litre/min [11] and those undergoing laparoscopic cholecystectomy only 0.21 litre/min [12]. Hence, although the two groups of patients had a half-life of glucose that was slightly longer than that for insulin, the opposite has been the case for all healthy volunteers in which rebound hypoglycaemia was also more apparent.

$CL$ for the glucose/insulin experiments could not be calculated by conventional methods owing to the many periods of hypoglycaemia. However, one purpose of conducting the ‘only glucose’ experiments was to obtain a value for the $V_d$ and baseline endogenous glucose production in the present group of volunteers. Estimates of $CL$ over time for all experiments could then be obtained by inserting those values into eqn (1). Such calculations indicate that the exogenous glucose doubled $CL$. Moreover, $CL$ was only slightly higher during the ‘strong’ experiments despite the marked difference in insulin dose between the two series of glucose/insulin infusions. In the present study, $CL$ should be understood to express the overall effectiveness of the body to lower plasma glucose as it summarizes the effects of the true $CL$ of glucose from the ECF (extracellular fluid) space and the insulin-induced depression of the endogenous glucose production.

\[ CL = \frac{G}{I} \]

\[ CL \text{ should be understood to express the overall effectiveness of the body to lower plasma glucose as it summarizes the effects of the true } CL \text{ of glucose from the ECF (extracellular fluid) space and the insulin-induced depression of the endogenous glucose production.} \]
The longer half-life for insulin than for glucose might provide an indication about the risk of ‘rebound hypoglycaemia’ when exogenous glucose administration is halted. The shorter half-life for glucose can, in turn, be understood from the logarithmic relationship between CL and the insulin concentration (Figure 4, right-hand panel) which maintains a rapid glucose elimination despite decreasing insulin concentrations.

The ‘rebound’ phenomenon has been reported for infants whose mothers were given glucose infusions before delivery [16,17] and is common in response to a rapid infusion of 5 % glucose in volunteers [10], as well as during intravenous glucose tolerance tests, which use glucose solutions with a strength of between 20 % and 50 % glucose [18]. In the present study, rebound hypoglycaemia became apparent even after infusion of a glucose solution of very low strength, only 2.5 %. A check-up of plasma glucose appears to be warranted 30 min after infusing a fixed combination of glucose and insulin, which is often done in the clinic to create a ‘safe’ match between the two compounds. Prolonging of the half-life for glucose associated with ‘insulin resistance’ would make seriously ill and trauma patients less susceptible to rebound hypoglycaemia if glucose alone is infused [14]. Such resistance would cause a rightward shift in the relationship shown in the right-hand panel of Figure 4. At very low and high CLs, this curve is also expected to flatten out [18]. On the other hand, if insulin is also given, the dose is likely to be raised to cope with any insulin resistance, as shown by the schemes used at the thoracic anaesthesia departments mentioned above. In those cases, it appears probable that rebound hypoglycaemia can occur despite insulin resistance.

Many views encouraged by the present results merit further study. Insulin promotes intravascular fluid loss in patients with diabetes [19], but we would like to know whether rebound hypoglycaemia is associated with hypovolaemia in other clinical conditions. This is important in patient groups that are more sensitive to hypovolaemia than others, such as trauma patients, patients with sepsis and burns, and those with chronic ischaemic heart disease. The reduction in plasma glucose created in patients treated for diabetic ketoacidosis might follow the same basic relationship as that shown in Figure 3, which could then be used as a reference for rehydrating the ECF volume.

It is difficult to find a good alternative explanation for the hypovolaemia found in the present study other than rapid uptake of glucose by the cells, sustained by prolonged insulin action, which translocates water from the ECF to the intracellular fluid space by virtue of osmosis. The plasma volume reduction by 5 % observed after our glucose/insulin infusions would then represent a fluid deficit that is evenly distributed throughout the ECF volume, meaning that the deficit would amount to approx. 800 ml if the ECF volume equals 20 % of the body weight. As 1 mmol of glucose attracts 3.6 ml of water, 800 ml corresponds well to the amount of fluid that can be expected to be translocated into the cells along with the infused glucose in the ‘glucose only’ experiment.

Dehydration can probably be prevented by infusing additional sodium along with the glucose. A previously published sodium-fluid redistribution equation suggests that 200 mmol of sodium, or 160 ml of 7.5 % saline, would offer sufficient prevention [20]. A benefit with sodium treatment is the relatively long duration of its plasma volume support, although blunt hypoglycaemia must still be carefully observed. Another way to prevent the osmosis-induced hypovolaemia would be to provide fluid 30 min after the glucose load; infusing it together with the glucose will only result in a prompt diuretic response, as seen in our ‘only glucose’ series of experiments.

The bolus injections of 30 % glucose that were given to combat clinical hypoglycaemia resulted in major increases in plasma glucose (15–25 mmol/l) and plasma dilution (10–15 %), but they lasted for only 10–15 min. Those results were not included in the Figures or calculations because plasma dilution could lag one sample behind plasma glucose. This can be explained by the arterial line used for sampling while the blood needed to pass the capillaries before water could be recruited from the intracellular fluid space. However, these acute changes indicated that an increase in plasma glucose of 30 mmol/l corresponded to a plasma dilution of 20 %, which further illustrates the osmotic strength of glucose.

In conclusion, the present results show that hypoglycaemia is associated with hypovolaemia, which both developed 30 min after intravenous infusion of glucose with and without insulin in well-trained firemen. High glucose clearance despite falling insulin levels and the osmotic strength of glucose are proposed to be the key mechanisms explaining these findings.

ACKNOWLEDGMENTS

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