Estimation of the initial distribution volume of glucose by an incremental plasma glucose level at 3 min after i.v. glucose in humans

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Aims The initial distribution volume of glucose (IDVG) could be a clinically useful indicator of the central extracellular fluid (ECF) space volume, namely the interstitial fluid volume status of highly perfused organs. In this study, we determined the formula of IDVG using incremental plasma glucose levels after i.v. glucose.

Methods One hundred and fifty patients admitted to the general intensive care unit of the University of Hirosaki hospital were entered into this prospective study which was conducted in two stages. In the first stage 300 data points from 100 patients were used to measure the IDVG (3 determinations for each patients). This utilized a one compartment model to describe the incremental plasma glucose decay curve following an intravenous bolus injection of glucose which, in turn, was used to derive the parameters of an equation for IDVG prediction following a single plasma sample. The second stage was a validation of the equation using a separate data set (150 points) from a further 50 patients.

Results A one phase exponential decay model was well-fitted for the IDVG-postadministration glucose level curve, and indicated that the incremental glucose level at 3 min after i.v. glucose was best-correlated to the IDVG compared with those at 1, 2, 4, 5 and 7 min postadministration. The formula of the IDVG was obtained from the curve: $IDVG = 24.44 \times e^{-0.0298 \times \Delta GL} + 2.70$, where ΔGL = incremental glucose level at 3 min after i.v. glucose. Another 150 samples showed that the measured-IDVG from a one compartment model and predicted-IDVG from the formula were 7.24 ± 1.63 and 7.27 ± 1.52 l, respectively, and that there was a significant correlation between the two IDVGs ($r = 0.966$, $P < 0.0001$).

Conclusions Using an incremental glucose level at 3 min after i.v. glucose, we have established the reliable formula for determination of the IDVG which could be a clinically useful indicator of the central ECF volume.

Keywords: extracellular fluid space, glucose, pharmacokinetics

Introduction

The initial distribution volume indicates the central compartment when describing the kinetics of drug disposition [1]. Since radioisotopic studies have demonstrated that insulin does not affect extracellular glucose distribution kinetics or volumes in human and rats [2, 3], we speculate that the initial distribution volume of glucose (IDVG) could indicate the central ECF volume, namely the interstitial fluid volume status of highly perfused organs as well as plasma volume during altered states of fluid volume in the body. We previously found

a significant linear correlation between the initial distribution volume of sucrose, which is commonly used to estimate the ECF volume [4, 5], and the IDVG [6–8]. In addition, we also found that the IDVG may correlate to cardiac output in dogs with normovolaemic and hypovolaemic status [6], and critically ill patients except patients with congestive heart failure [9, 10]. These findings suggest that the IDVG could be a good indicator of the central ECF volume, which would be important for fluid management in postoperative or critically ill patients. However, as 14 ml of blood (2 ml $\times$ 7 times) is required to obtain the IDVG and it takes at least 7 min for the blood collection, patients sometimes can refuse to give the informed consent. In this study, to reduce the amount of blood sampled as well as turnaround time for measurements, we determined the formula of IDVG

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Received 14 April 1998, accepted 1 October 1998.

using only two blood samples obtained before and after i.v. glucose.

Methods

After approval of the research protocol by our University Ethics Committee, 150 patients admitted to the general intensive care unit of the University of Hirosaki hospital were entered into this prospective study which was conducted in two stages. In the first stage 300 data points from 100 patients were used to measure the IDVG (three determinations for each patient). This utilized a one compartment model to describe the incremental plasma glucose decay curve following an intravenous bolus injection of glucose which, in turn, was used to derive the parameters of an equation for the IDVG prediction following a single plasma sample. The second stage was a validation of the equation using a separate data set (150 points) from a further 50 patients.

Initial study

One hundred patients were given a bolus of 25 ml of 20% glucose (5 g) over 30 s through a central venous catheter whose tip was located at the superior vena cava. Serial blood samples (2 ml each) were obtained via an indwelling radial artery catheter just before and at 1, 2, 3, 4, 5, 7, 9 min after i.v. glucose. Plasma was separated immediately by centrifugation. Plasma glucose concentrations were determined using a glucose oxidase method (Kyoto Dai'ichi Kagaku Co Ltd GA1150, Kyoto, Japan). This IDVG measurement was performed once a day for 3 days. All sample measurements were performed in duplicate and averaged. The coefficient of variation was less than 1% for repeated glucose measurements.

IDVG calculation

The IDVG was calculated using a one compartment model from the excess or incremental plasma glucose decay curve after i.v. glucose. In a one compartment model, the volume of distribution (V_d) is calculated as follows: $V_d = \text{Dose}/C_0$, Dose = amount of drug administered, C_0 = initial plasma concentration at time zero assuming instantaneous distribution, but before the start of elimination [1]. The IDVG was determined using a 'least squares' regression technique to find the line of the best fit. Akaike's information criterion (AIC) [11] was examined as described previously [3, 6–10] to evaluate the exponential term of the pharmacokinetic model as follows: $AIC = -N \times \ln(SSQ_w) + 2P$, where N = the number of data points, P = the number of parameters identified in the model, SSQ_w = the weighted residual

sum of squares. Low AIC values indicate a superiority of the selected model.

Statistical analysis

All data are expressed as mean $\pm$ s.d. The formula using incremental glucose levels after i.v. glucose was determined by a one phase exponential decay ($Y = Ae^{-BX} + C$) using computer software (GraphPad Prism 1.03): Predicted IDVG = $A \times e^{-B \times \Delta GL} + C$, where ΔGL = incremental glucose level after i.v. glucose.

Formula validation study

To validate the formula, we compared measured IDVG from a one compartment model with predicted IDVG from the formula in 150 samples from 50 patients. The agreement between predicted and measured IDVG was assessed by Bland and Altman plots [12] and Pearson's correlation coefficient with a least squares linear regression line.

Results

Initial study

As the AIC value of the IDVG was 23.13 ± 5.22 , convergence was assumed in the IDVG.

A one phase exponential decay model indicates that the incremental glucose level at 3 min after i.v. glucose correlated best to the IDVG (Table 1). Constants (A, B and C) of the formula obtained from the curve (Figure 1) were 24.44 ± 1.22 , 0.0298 ± 0.0018 and 2.70 ± 0.25 , respectively. Therefore, the formula of the predicted IDVG was: IDVG = $24.44 \times e^{-0.0298 \times \Delta GL} + 2.70$, where ΔGL = incremental glucose level at 3 min after i.v. glucose.

Formula validation study

AIC value of the IDVG was 23.12 ± 5.50 and consistent with that in the 'Initial study'.

In 150 samples, measured and predicted IDVG were 7.24 ± 1.63 and 7.27 ± 1.52 l, respectively, and the indi-

Table 1 Correlation between the IDVG and incremental plasma glucose levels before and after i.v. glucose.

	Time after i.v. glucose (min)					
	1 min	2 min	3 min	4 min	5 min	7 min
r^2	0.888	0.790	0.944	0.898	0.822	0.721
ASS	16872	20386	3542	5200	8034	9277

r^2 : Square of correlation coefficient, ASS: Absolute sum of squares.

Figure 1 Relationship between IDVG and incremental plasma glucose level at 3 min after i.v. glucose.

Figure 2 Agreement between measured IDVG and predicted IDVG shown by a least square linear regression line with Pearson's correlation coefficient (a) and Bland and Altman plots (b).

vidual difference between two IDVGs was also 0.30 ± 0.43 l (Figure 2a). There was also a significant correlation between two IDVGs ($r=0.966$, $P<0.0001$, Figure 2b).

Discussion

The formula obtained in this study may accurately predict the IDVG and the incremental plasma glucose levels at 3 min after i.v. glucose could be the best to use in the

formula. Since the complete mixing within the initial distribution volume is achieved generally within 3 min postinjection [13, 14], data at 3 min following i.v. glucose showed the best correlation to the IDVG in the present study. In addition, due to reduction of the total amount of blood sampled to 4 ml, patients may give consent more easily.

Although a one compartment model was used to obtain the IDVG, a two compartment model is generally required to analyse the entire glucose kinetics [3, 15]. The central compartment which consists of both the plasma and the extravascular space of the highly perfused tissues such as brain, heart, liver and kidney is not insulin dependent [13]. In the extravascular space of the highly perfused tissues, iv glucose equilibrates rapidly with the plasma glucose. The peripheral compartment consists of less perfused tissues such as the skeletal muscles and the adipose tissues where glucose is slowly metabolized and is insulin dependent [3, 13]. Therefore, the longer the interval after i.v. glucose, the greater the metabolism of glucose which would affect plasma glucose concentrations more. In addition, we previously reported that glucose metabolism could not modify the IDVG by a one compartment model even during insulin and/or vasoactive drug infusions [9, 10], and that the two compartment model misleadingly showed small IDVG in hypervolaemic dogs [8]. Therefore, to evaluate the central ECF volume by IDVG, a one compartment model should be applied.

The evidence that intravenously administered glucose distributes throughout the ECF space is based on the findings that the IDVG correlates with the initial distribution volume of sucrose and that the IDVG correlates with the cardiac output [6, 9, 10]. However, further study will be required to determine whether the IDVG consistently indicates this volume.

In conclusion, we have established a formula using incremental glucose level at 3 min after i.v. glucose for determination of the IDVG which could be a clinically useful indicator of the central ECF volume.

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