Simultaneous fitting of the Minimal Model to IVGTT & Glucose Clamp Data

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Introduction

The minimal model of glucose kinetics developed by Bergman et al in 1979 has been extensively used to provide quantitative estimates of insulin sensitivity and glucose effectiveness in both healthy and diabetic subjects. It has previously been shown that the minimal model can be successfully fitted to data from an intravenous glucose tolerance test (IVGTT) and data from a glucose clamp experiment. Here is presented the findings of fitting the minimal model to IVGTT and clamp data alone and a novel approach of fitting the minimal model simultaneously to both IVGTT and clamp data.

Methods

IVGTT and Clamp Study

Data from a two-period euglycaemic clamp study performed in 28 healthy volunteers was used. An IVGTT was performed prior to the first clamp period during which 0.3 g/kg of a 20% glucose solution was administered. Blood samples were then taken at -15, -5, 0, 2, 4, 6, 10, 15, 20, 25, 30, 40 minutes and 1, 1.33, 2, 3 and 4 hours post glucose dose to measure the insulin and glucose concentrations. In each of the two clamp periods of the study, a single s.c. dose of 0.2 IU/kg Actrapid® was administered. Blood glucose concentration was monitored every five minutes using HemoCue® measurements for the duration of the 6-hour clamp. Based on these glucose concentration measurements the amount of glucose to be infused to keep glucose at the clamp target value and this was determined using the manual clamping method. The measurement of blood glucose levels prior to treatment administration allowed the fasting blood glucose level of each individual to be measured on each day of administration to be measured, this was used as the target clamp glucose concentration. Blood samples for the measurement of insulin and C-peptide were taken at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7 and 8 hours post dose with time 0 being immediately prior to insulin administration on dosing in each period. Blood samples taken at the above times were also measured in the laboratory for the blood glucose levels prior to treatment administration allowed the fasting blood glucose level of each volunteer to be measured on each day of administration to be measured.

The mean and individual glucose, insulin and GIPR against time profiles from the IVGTT and clamp data are shown in Figures 1 to 6.

Minimal Model

The minimal model as presented by Voicu et al is shown in Figure 6 with its uniquely identifiable parameters described in Figure 7.

\[
\frac{dG_t}{dt} = -\left(\frac{G_t}{x} + \alpha \right) \left( q + G_t \right) + D(t) \left( G_b \right)
\]

Where \( G_b \) is the basal plasma glucose concentration, \( \bar{G} \) is the basal insulin plasma concentration, \( q \) is glucose mass, \( D(t) \) is insulin plasma concentration, \( G_t \) is glucose plasma concentration, \( \frac{dG_t}{dt} \) the glucose volume of distribution, \( x \) and \( \alpha \) describe insulin action, \( D(t) \) is the dose of drug. \( S_o \) describes the insulin sensitivity - the ability of insulin to enhance glucose disposal and inhibit glucose production. \( S_b \) describes the glucose effectiveness - the ability of glucose to stimulate glucose disposal and inhibit endogenous glucose production. NHKRef refers the net hepatic glucose balance.

Data fitting Methods and Fisher Information Matrix (FIM)

Model fitting and minimal model parameter estimates were estimated using the first order estimation method in NONMEM®. Four parameters were estimated \( S_b, S_o, G_t, \) and \( \bar{G} \) along with the observed insulin concentrations were supplied in the dataset. The NONMEM® estimates were used to compute the FIM for the fixed effect parameters (\( S_b, S_o, \bar{G} \) and \( \bar{G} \)) using Matlab®.

Results

Parameter estimates are presented in Table 1 for fitting of the minimal model to the three types of data: IVGTT alone, clamp alone and IVGTT & clamp together. Plots of observed glucose concentrations versus population and individual predictions and time are present in Figures 8 & 9 for the clamp alone data and in Figures 10 & 11 for the simultaneous fit of IVGTT and clamp data. Parameter estimates for the simultaneous fit of IVGTT and Period 1 clamp data were used to predict the glucose concentrations for the second clamp period. Figure 12 shows some individual observed and predicted Period 2 glucose concentrations. Results from the FIM are presented in Table 2.

Fisher Information Matrix

Table 2 – Results of the Fisher Information Matrix

Table 3 – Estimated parameters of the minimal model

Conclusion

As indicated by the FIM, minimal model parameters were estimable from fitting to clamp data alone and by simultaneous fitting to both IVGTT and clamp data. Fitting of IVGTT alone was not successful as the parameters \( S_b \) and \( \bar{G} \) were not identifiable, again as indicated by the FIM.

Appendix

References:

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