

Title: Optimal design of the intravenous glucose tolerance test in type 2 diabetic patients

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Background/Objective: Intravenous glucose provocations are very informative for studying the glucose-insulin system. They are, however, both time consuming and intensive in sampling which makes them less appealing compared to the oral tolerance test which is much easier to perform. The intravenous glucose tolerance test (IVGTT) was originally designed to be analyzed with simple methods and individual data fitting. For improved measurement of the insulin efficiency in diabetic subjects an insulin modified IVGTT was proposed as an alternative to the previously suggested tolbutamide modification by Bergman et al in 1985.¹ To our knowledge, the design of the insulin modified IVGTT has not changed since then. The standard frequently sampled IVGTT design contains approximately 30 blood samples of glucose, insulin and sometimes also labeled glucose during 4 hours following an intravenous bolus dose of glucose. In the insulin modified IVGTT, a 5-minute insulin infusion is given at 20 minutes. Previously, a reduced sampling schedule with 14 samples has been suggested by Cobelli et al and was based on the minimal models for both glucose and insulin.²

Optimal experimental design can be used to increase the efficiency of clinical trials by optimizing the sampling schedule or other design parameters, e.g. dose. When optimal experimental design is used together with population techniques for data analysis we expect the over all trial design of the IVGTT to be improved and made more efficient with respect to precision of parameter estimates.

The objective of this study was to evaluate the possibilities of an improved study design of the insulin modified IVGTT in type 2 diabetic patients.

Methods: A previously published model developed for glucose and insulin regulation in type 2 diabetic patients was implemented in the optimal design software PopED.^{3,4} The model was originally developed based on data from intravenous provocations (glucose, insulin and labeled glucose) from both healthy volunteers and diabetic patients. For this project only the patient model was used, see figure 1, and in order to decrease run times the number of samples was reduced from 30 to 10 (0, 2, 10, 15, 30, 45, 70, 100, 150, 240 minutes). Several aspects of the study design of the insulin modified IVGTT were evaluated including; (1) glucose dose, (2) insulin dose (start and stop time and total insulin dose), (3) combination of glucose and insulin dose, (4) sampling times of a reduced sampling schedule and reduction in total sampling time, (5) optimal design without labeled glucose. Constraints were incorporated into the optimal designs to avoid prolonged hyper- and/or hypoglycemia. Efficiency was calculated as a measure of the improvement with an optimal design compared to the basic design. The efficiency also corresponds to the reduction in number of subjects that need to be included when an optimal design is used.

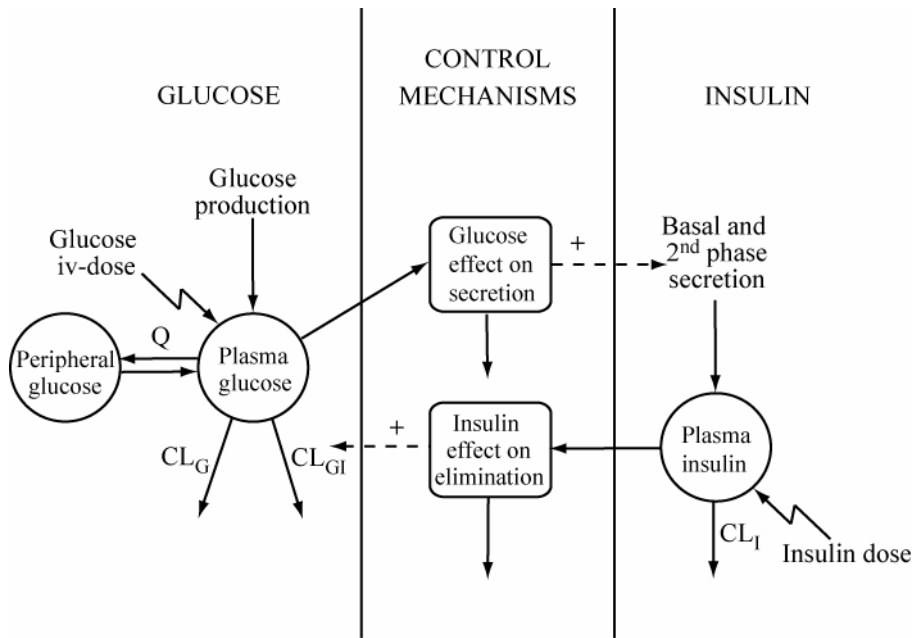


Figure 1. Model of glucose and insulin regulation in type 2 diabetic patients developed by Silber et al.³ The model contains sub-models for glucose, insulin and labeled glucose (not shown) as well as control mechanisms for glucose uptake and insulin secretion.

Results: The results show that the design of the insulin modified IVGTT can be substantially improved by the use of an optimal design compared to the standard design. Despite the comparably low number of samples included the predicted uncertainty of parameter estimates was low in all tested cases. By adjustment of the magnitude and timing of the insulin dose the efficiency of the design could be increased by 300%.

Conclusions: We conclude that improvement can be made to the design of the insulin modified IVGTT. Also when the number of samples is reduced parameters are predicted to be estimated with a high certainty. The use of the intravenous provocation experiments are expected to be favored by an improved design.

References:

1. Bergman R N, Finegood D T, and Ader M. Assessment of insulin sensitivity in vivo. *Endocr Rev* 1985; 6: 45-86.
2. Cobelli C and Ruggeri A. A reduced sampling schedule for estimating the parameters of the glucose minimal model from a labeled IVGTT. *IEEE Trans Biomed Eng* 1991; 38: 1023-9.
3. Silber H E, Jauslin P M, Frey N, Gieschke R, Simonsson U S H, and Karlsson M O. An integrated model for glucose and insulin regulation in healthy volunteers and type 2 diabetic patients following intravenous glucose provocations. *J Clin Pharmacol* 2007; 47: 1159-71.
4. Foracchia M, Hooker A, Vicini P, and Ruggeri A. POPED, a software for optimal experiment design in population kinetics. *Comput Methods Programs Biomed* 2004; 74: 29-46.