Design of Phase I Studies based on Mechanism of Action of Anti-Diabetic Drugs

Assessing power, precision and accuracy in a simulation study of glucose tolerance tests

Moustafa M. A. Ibrahim, Siti M. Sheikh Ghadzi, , Maria C. Kjellsson, Mats O. Karlsson

Pharmacometrics Research Group, Department of Pharmaceutical Biosciences, Uppsala University

Introduction

In anti-diabetic drug development, phase I studies usually involve short-term glucose provocations. With a highly nonlinear, complex system as the glucose homeostasis, the various provocations will contribute with somewhat different information upon which the probability of detecting drug effect will be highly dependent.

Objectives

The aim with this project was to investigate the most appropriate study design in phase I, for several hypothetical mechanisms of action (MoA) of a study drug. Power to detect drug effect and accuracy of quantification of drug effect was assessed using pharmacometric model based simulations

Methods

DRUG EFFECTS:

Stimulation of basal insulin (BINS), glucose clearance, either insulin dependent (CLG) and independent (CLGI), as well as inhibition of endogenous glucose production (EGP) and absorption of oral glucose (GABS).

STUDY DESIGNS:

Single meal tolerance test (sMTT), 24-hours meal tolerance test (MTT-24), Oral glucose tolerance test (OGTT), repeated fasting glucose sampling, i.e. no provocation (NO), intravenous glucose tolerance test (IVGTT) and graded glucose infusion (GGI). The models used were the different versions of the integrated glucose-insulin model (IGI) [1-3].

TITRATION OF DRUG EFFECTS:

The sMTT was used for titration of drug effects as it was assumed to be the most realistic & least invasive study design. Each drug effect was titrated to produce 10% decrease in plasma glucose area under the curve (AUC).

STUDY SCENARIO:

The titrated drug effects were used in all models as the true drug effects to simulate large data sets of thousand type 2 diabetic individuals with a cross over design. Each individual went through two occasions, without drug effect and with drug effect. The simulations of a typical individual are presented in figure 1. Monte carlo mapped power (MCMP) [4] was used to asses the study power of each model. Stochastic simulation and estimation (SSE) was used to calculate the precision and accuracy of these models with respect to the magnitude of the drug effect.

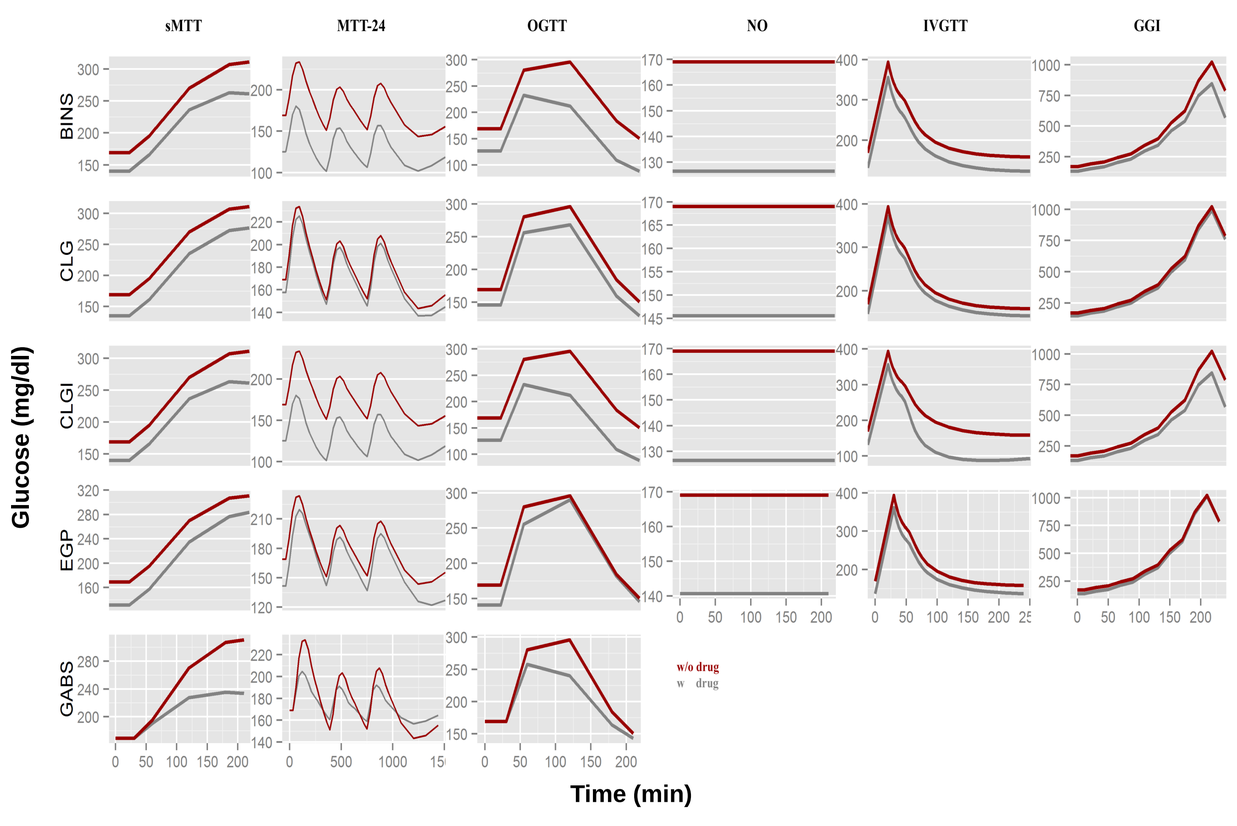

Figure 1: A schematic illustration of the simulated data for a typical individual through the two occasions, with and without drug treatment

Results and Discussion

Table 1 : The relative ratio of Likelihood ratio test statistic (LRT) of each model, for each drug effect to the corresponding LRT of sMTT.

		Study Designs					
		sMTT	MTT-24	OGTT	NO	IVGTT	GGI
Drug effects	BINS	1	8.7	1.5	2.0	5.8	5.4
	CLG	1	0.60	0.29	0.78	2.8	3.9
	CLGI	1	17	2.8	2.7	18	7.9
	EGP	1	2.0	0.58	1.7	4.2	4.8
	GABS	1	3.9	0.40	-	-	-

The study power of each model to detect a drug effect is shown in table 1 as how many times more individuals are needed relative to a sMTT to achieve equivalent power.

For all drug effects, except GABS, intravenous provocations were very powerful.

NO was surprisingly powerful and for many MoAs similar to sMTT. Notable though is that safety was not assessed in this study and NO may be associated with more hypoglycemia than other designs.

The results are in accordance with excepted and can be explained based on the provocation of the system, except for CLG, where 24-MTT and OGTT unexpectedly were the least powerful study designs, maybe because they through the incretin effect stimulate much more insulin and make CLG less important

The relative estimation errors of these models are visualized in figure 2.

The accuracy and precision of the parameters derived from OGTT, IVGTT and GGI were overall good for all MoAs. Thus, the most powerful study design, albeit including the two most invasive, is also producing accurate and precise estimates.

The precision and accuracy of MTT-24 and sMTT were dependant on the MoA of the drug. The precision of MTT-24 was the best for all MoAs.

The worst precision and accuracy in all MoAs were the sMTT for drug effect on CLGI, and NO for drug effect on CLG, despite these designs being rather powerful.

Conclusion

The most powerful, accurate and precise study designs are the Intravenous ones which are also the most invasive. From power perspective, MTT-24 is a good alternative, unless we are expecting effect on CLG like SGLT2-inhibitors, but it seems to be resulting in a biased parameter estimate.

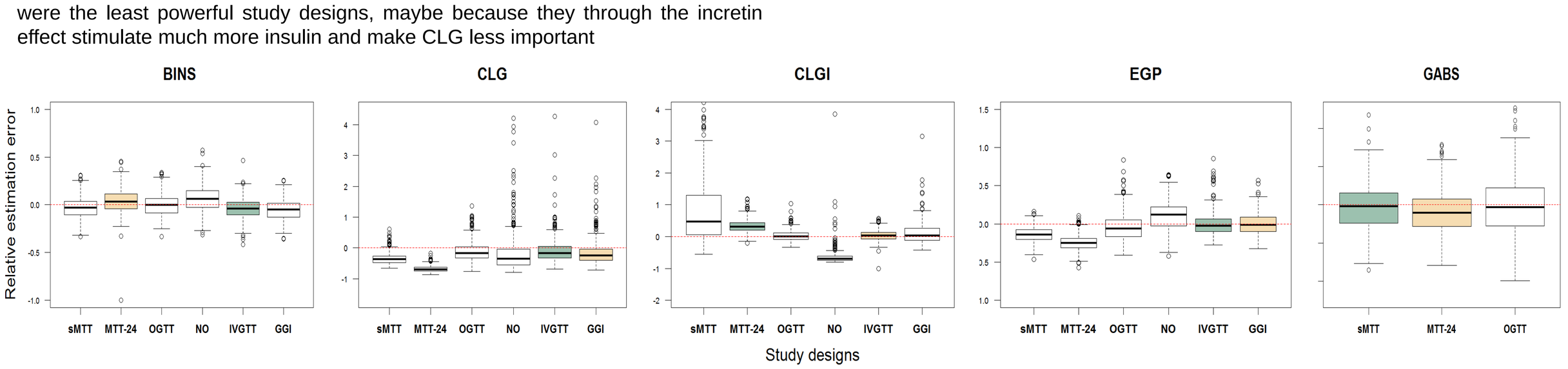

Figure 2: A descriptive representation of the distribution of relative estimation error of each drug effect for each study design

References

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