Are insulin measurements needed in glucose provocation study? Comparisons of study power using Monte Carlo Mapped Power (MCMP) method

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Introduction

Most glucose provocation studies are performed according to the standard protocols. Recently, the needs for insulin measurements have been questioned when performing the glucose provocation studies especially with the aim to identify drug effects, as there is an increasing trend of neglecting insulin measurements for the analysis purposes. This condition is hypothesized to decrease the study power, as a result of loss of insulin information

Objective

This simulation study was performed with the aim of comparing the study power between the uses of glucose and insulin as opposed to only glucose in: (1) identifying hypothetical true drug effects compare to no drug effect (Part 1); (2) distinguishing the hypothetical true drug effect compare to false drug effect (Part 2), by using model-based analysis together with Monte Carlo Mapped Power (MCMP) method

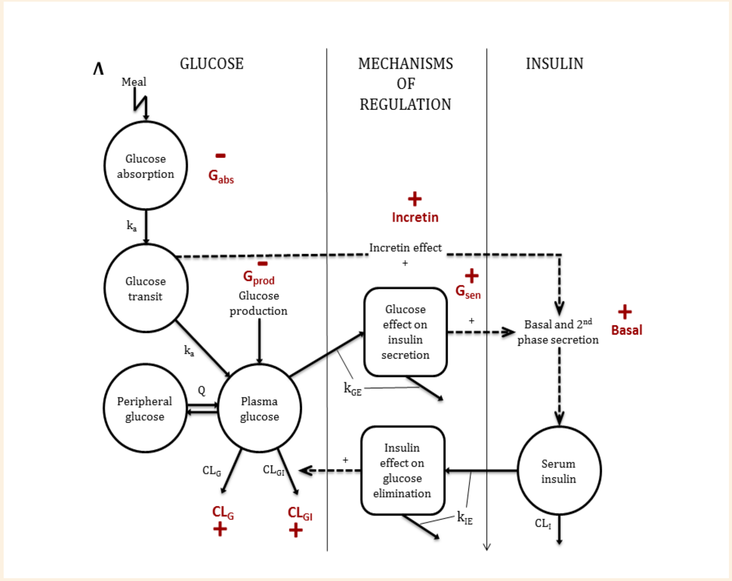
Methods

Study design

A cross-over study of meal tolerance tests (MTT) with and without drug treatment was simulated for 500 subjects. Placebo, on occasion 1, and study drug, on occasion 2, was administered at time 0, followed by the intake of meal (75000 mg glucose) 30 minutes later. Blood samples were taken at time 0, 30, 60, 90, 120, 150, 180, 210 and 240 minutes at both occasions. Seven different drug effects were investigated (Figure 1), all resulting in a 10% reduction in glucose AUC for drug treatment versus placebo. The simulation study set-up is shown to the right in Figure 2.

IGI-MTT with 7 drug effects

Figure 1: Integrated Glucose-Insulin Model of Meal Tolerance Test (IGI-MTT) with 7 drug effects

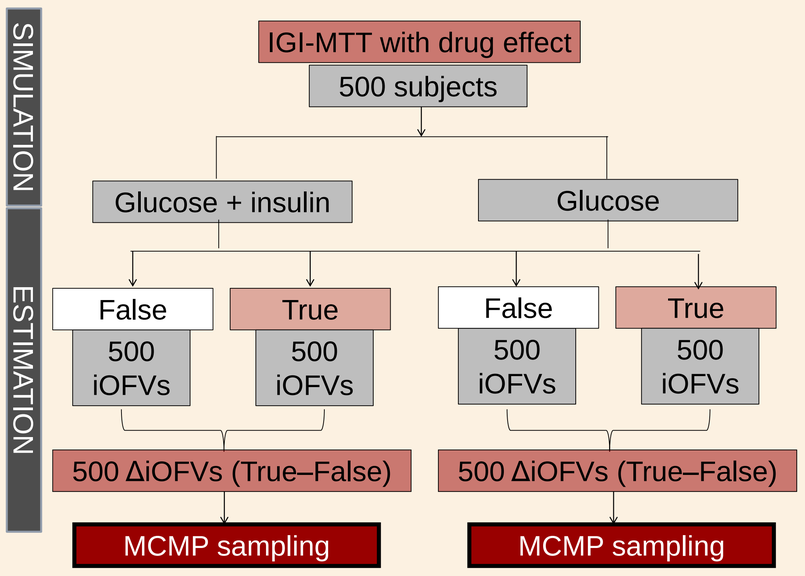


(Adapted from Jauslin et.al. (2011) [1])

*__Abbreviation__: **Incretin** = Incretin activity, **Basal** = Basal insulin secretion, **CL_G** = Insulin-independent glucose clearance, **CLGI** = Insulin-dependent glucose clerance, **G_{prod}** = Glucose production, **G_{abs}** = Glucose absorption, **G_{sen}** = Glucose sensitivity

Simulation study set-up

Figure 2: MCMP method comparing true vs false drug effects



Part 1
- *False model* = no drug effects
- *True Model* = true drug effects
- i.e. 7 true x 1 false = 7 runs
- Critical value = 5.991

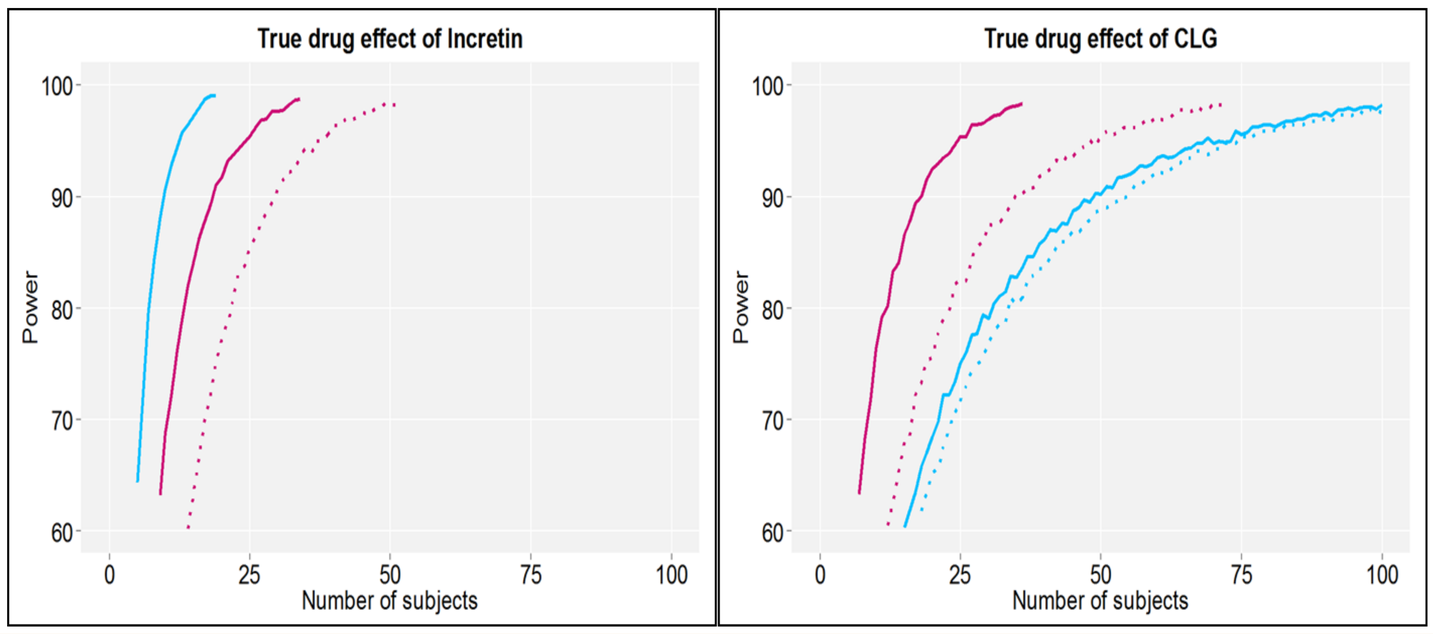
Part 2
- *False model* = false drug effects
- *True Model* = true drug effects
- i.e. 7 true x 6 false = 42 runs
- Critical value = 10

Results and Discussion

Table 1 : Difference between number of individuals to detect drug effects
Part 1 : True drug effects compared to no drug effect (for 95% power)
Part 2 : True drug effects compared to false drug effects (for 80% power)

	Part 1	Part 2						
Drug effect	**No drug effect**	**Incretin**	**Basal**	**CL_G**	**CL_{GI}**	**G_{prod}**	**G_{abs}**	**G_{sen}**
Incretin								
gi	6	-	43	5	8	6	5	14
g	8	-	>100	12	>100	21	21	24
Basal								
gi	5	37	-	4	7	7	5	10
g	7	>100	-	14	>100	25	26	31
CL_G								
gi	**15**	13	12	-	31	54	**86**	12
g	**12**	25	28	-	35	57	**41**	24
CL_{GI}								
gi	6	10	8	15	-	48	**43**	8
g	8	>100	>100	20	-	50	**40**	34
G_{prod}								
gi	10	10	10	22	39	-	20	9
g	10	44	41	24	59	-	23	17
G_{abs}								
gi	6	7	7	12	12	12	-	6
g	8	8	25	23	27	21	-	28
G_{sen}								
gi	4	8	5	3	4	3	3	-
g	6	33	28	8	23	7	14	-

Figure 3: Graphs for selected drug effects



*Note that the false drug effect of CL_{GI} for only glucose data in the left graph is absent because the number of subjects far exceeds 100 subjects for as low as 60% power, that it cannot be plotted in the graph.

Results and discussion (Part1)

The power to detect a drug effect is overall high with a model-based approach, but the power is, for most drug effects, even higher when insulin measurements are included in the analysis. Glucose production is unaffected by insulin inclusion while the power is higher for insulin-independent glucose clearance when excluding insulin.

Results and discussion (Part2)

In contrast to detecting drug effects, the power to identifying the true mechanism of drug effect was largely affected by the exclusion of insulin for most drug effects, but in particular, when separating a true drug effect on an insulin parameter from other drug effects. Inclusion of insulin does only marginally affect the power to identify a drug effect on glucose absorption and it was even higher excluding insulin for the separation of true glucose absorption from insulin-independent glucose clearance effects. For CL_{GI} vs G_{abs} , the power from including and excluding insulin was almost the same. It was easier to differentiate true drug effects from false drug effects when the mechanism of drug was related to insulin regulation, such as incretin effect. The presence of insulin measurements however might made it more difficult to distinguish true from false, when the drug's mechanism was unrelated to insulin, for example insulin-independent glucose clearance. The insulin model in the absence of insulin is aiding the identification of the correct mechanism.

Conclusion

The power to detect a drug effect was high with a model-based analysis and only marginally affected when insulin measurements were excluded. The power to identify the true mechanism of drug effect from a false was in most cases severely harmed by not sampling insulin.

References
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