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# PK/PD Modeling of Glucose Clamp Effects of Inhaled Insulin

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American Conference on Pharmacometrics  
(ACoP), March 9-12, 2008  
Tucson, Arizona

## BACKGROUND

The euglycemic glucose clamp technique is considered one of the gold standard methods to measure insulin sensitivity. Generally, a constant rate insulin infusion is given that results in insulin concentrations higher than physiological baseline. Blood glucose is measured frequently and maintained within the euglycemic range by administration of a glucose infusion with variable rate. As hepatic insulin production is assumed to be completely inhibited by the exogenous insulin infusion, glucose infusion rate (GIR) equals glucose utilization rate. Effects of exogenous insulin are often measured by comparing the areas under the GIR vs. time curve after various doses of insulin (to baseline GIR). With this approach the doses in a study can be compared but effects of other doses or modes of administration cannot be predicted and the underlying mechanism cannot be described. While glucose clamp data have been assessed using a 'biophase direct effect' model, the underlying basis was not clear [1]. The effect of spray instilled insulin in rats was modeled previously [2]. Therefore we sought to rationalize a model to describe and predict the effects of inhaled insulin during a glucose clamp study in healthy volunteers and diabetes patients.

## OBJECTIVES

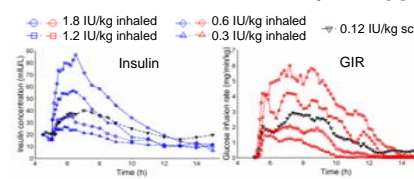
- 1) To build a PK/PD model based on the mechanism of insulin action.
- 2) To describe the effect of inhaled insulin on glucose infusion rate during a euglycemic clamp study.
- 3) To compare the PD parameter estimates between subcutaneous (sc) and inhaled insulin.

## METHODS

**Data.** Published data from 18 type 1 diabetic patients (T1DM, Brunner et al. [3]) and 13 healthy volunteers (HV, Rave et al. [4]) were digitized. Each subject received 4 different doses of regular human insulin by inhalation and 1 to 3 different doses subcutaneously at the start of a 10 h euglycemic glucose clamp.

**Computation.** All modeling and simulation utilizing NONMEM® version VI level 1.0 (NONMEM Project Group) with the method FOCE with interaction. All data were modeled simultaneously.

FIGURE 1: Literature data from T1DM patients [3]



## RESULTS

The PK was described by a one compartment model with one (inhaled) or two (sc insulin) parallel or sequential first order absorption processes and first-order elimination.

### Development of the PD model equations

Insulin stimulates utilization of glucose:

$$\frac{dG}{dt} = \underbrace{k_{in}}_{GIR} - \underbrace{k_{out} \cdot \left(1 + \frac{S_{max} \cdot (I_s - I_s^0)}{SC_{50} + (I_s - I_s^0)}\right)}_{Tissue\ utilization} \cdot G_{ss} = 0$$

$$GIR = k_{out} \cdot \left(1 + \frac{S_{max} \cdot (I_s - I_s^0)}{SC_{50} + (I_s - I_s^0)}\right) \cdot G_{ss}$$

At baseline of glucose and insulin:

$$k_{in} = k_{out} \cdot G^0 = k_{out} \cdot G_{ss}$$

During insulin dosing: 'Biophase direct effect' to capture glucose time shift

$$GIR = k_{in} \cdot \left(1 + \frac{S_{max} \cdot Ce(I_s - I_s^0)}{SC_{50} + Ce(I_s - I_s^0)}\right)$$

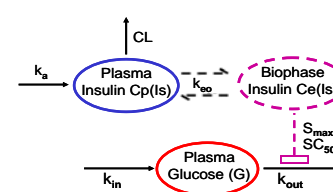
Baseline adjusted GIR ( $GIR_A$ ):

$$GIR_A = \frac{GIR_{max} \cdot Ce(I_s - I_s^0)}{SC_{50} + Ce(I_s - I_s^0)}$$

Insulin concentrations in the biophase:

$$\frac{dCe}{dt} = k_{in} \cdot (Cp(I_s - I_s^0) - Ce(I_s - I_s^0))$$

FIGURE 2: Model diagram



G: Glucose amount in plasma (mg)  
 $G_{ss}$ : Glucose amount in plasma at steady-state (mg)  
 $G^0$ : baseline glucose amt. in plasma (before insulin dose, mg)  
 $k_{in}$ : zero-order rate constant for glucose input (mg/min)  
 $k_{out}$ : first-order rate const. for glucose disappearance ( $min^{-1}$ )  
 $I_s$ : insulin concentration (mIU/L)  
 $I_s^0$ : baseline insulin concentration (before insulin dose, mIU/L)  
 $SC_{50}$ : insulin concentration at half-maximal effect (mIU/L)  
 $S_{max}$ : maximum effect of insulin on GIR  
 $GIR$ : Glucose infusion rate (mg/min or mg/min/kg)  
 $GIR_{max}$ : maximum glucose infusion rate (mg/min or mg/min/kg)  
 $k_{in}$ : first-order rate constant between plasma and biophase

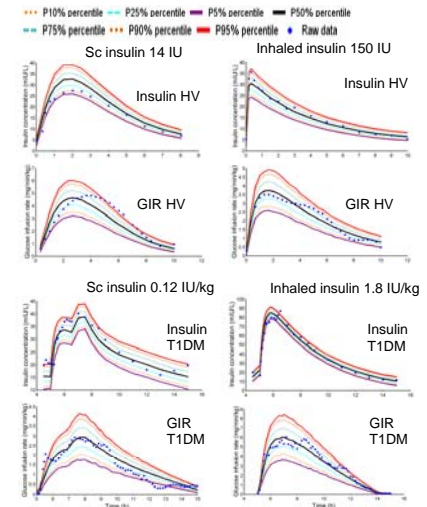
TABLE 1: Population parameter estimates

Parameter	Unit	Estimate HV	Estimate T1DM
CL	L/h	131	26.5
V	L	8.36	8.36*
$k_{in}$	1/h	1.35	1.35*
$GIR_{max}$	mg/min/kg	15.2	15.2*
$SC_{50}$	mIU/L	63.2	88.5
$Ce(I_s^0)$	mIU/L	4.5	14.9

\*Parameters were the same for HV and T1DM

When the  $SC_{50}$  was estimated for inhaled and sc insulin independently, the estimates were similar in both HV and T1DM. This result suggests a similar efficacy for inhaled and sc insulin. The lower  $Ce(I_s^0)$  and slightly larger  $SC_{50}$  in T1DM compared to HV suggests the presence of a small degree of insulin resistance in the T1DM patients.

FIGURE 3: Visual predictive checks



## CONCLUSIONS

- 1) Our model was developed based on fundamental principles of insulin action and turnover of glucose.
- 2) The effects of inhaled and sc insulin were predicted well in both HV and T1DM.
- 3) Assuming the same maximum effect, the model suggests that the efficacy of subcutaneous insulin was similar to that of inhaled insulin.

## ACKNOWLEDGMENT

This work was supported by the UB - Pfizer Strategic Alliance.

## References:

- [1] Tornøe et al. (2004) J Math Biol. 48: 591-604. [2] Gopalakrishnan et al. (2005) J Pharmacokinetic Pharmacodyn 32: 485-500. [3] Brunner et al. (2001) Diabetologia 44: 305-308. [4] Rave et al. (2004) Diabetic Medicine 21: 763-768.