

**Title:** Pharmacokinetic / Pharmacodynamic Modeling of Glucose Clamp Effects of Inhaled Insulin

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**Objectives:** The euglycaemic glucose clamp technique is considered one of the gold standard methods to measure insulin sensitivity. While glucose clamp data have been assessed using a ‘biophase direct effect’ model [1], the underlying basis was not clear. The pharmacokinetics and pharmacodynamics (PK/PD) of inhaled insulin have not been modeled. Therefore we sought to rationalize a model to describe and predict the effects of inhaled insulin during a glucose clamp study. We intended to 1) build a PK/PD model based on the mechanism of insulin action, 2) describe the effect of inhaled insulin on glucose infusion rate during a euglycemic clamp study, and 3) compare the PD parameter estimates between subcutaneous and inhaled insulin.

**Methods:** Published data of insulin concentrations and glucose infusion rates (GIR) from a study by Brunner et al. [2] were digitized. The crossover study was performed in 18 type 1 diabetic patients who received regular human insulin by inhalation (1.8, 1.2, 0.6, or 0.3 IU/kg) or subcutaneously (0.12 IU/kg) at the start of a 10 h glucose clamp study. All data were modeled simultaneously in NONMEM VI.

**Results:** The insulin PK was described by a one compartment model with one (inhaled) or two (sc insulin) first-order absorption processes and first-order elimination (Figure 1). Plasma glucose amounts (G) during stimulation of glucose utilization by insulin can be described as:

$$\frac{dG}{dt} = k_{in} - k_{out} \cdot \left( 1 + \frac{S_{max} \cdot (I_s - I_s^0)}{SC_{50} + (I_s - I_s^0)} \right) \cdot G_{ss} \quad \text{Equation 1}$$

$G_{ss}$ : glucose amount in plasma at steady-state,  $k_{in}$ : zero-order rate constant for glucose input,  $k_{out}$ : first order rate constant for glucose disappearance,  $I_s$  insulin concentration,  $I_s^0$ : baseline insulin concentration,  $S_{max}$ : maximum stimulation of glucose utilization by insulin,  $SC_{50}$ : insulin concentration at half-maximal stimulation. For the case of a glucose clamp study where plasma glucose concentrations are held constant, from equation 1 in several steps a direct effect equation can be derived that describes the baseline adjusted GIR ( $GIR_A$ ) as follows:

$$GIR_A = \frac{GIR_{max} \cdot Ce(I_s - I_s^0)}{SC_{50} + Ce(I_s - I_s^0)} \quad \text{Equation 2}$$

$GIR_{max}$ : maximum GIR,  $Ce$ : Insulin concentrations in the biophase. By inclusion of a biophase compartment the delay in insulin effect on GIR could be described. Simultaneous modeling of all data suggested that the relative bioavailability of inhaled insulin decreased with increasing dose, while the absorption rate constant increased with increasing dose. All other parameters were the same between doses. PD parameter estimates were 12.0 mg/min/kg for  $GIR_{max}$  and 65.9 mIU/L for  $SC_{50}$ . The model showed good predictive performance as evaluated by visual predictive checks (Figure 2). As the GIR after both inhaled and subcutaneous insulin could be well described by the same PD parameters, this suggests similar potency for both formulations and routes of administration.

**Conclusions:** This model was developed based on fundamental principles of insulin action and turnover of glucose and predicted the effects of several doses of inhaled and subcutaneous insulin well. The results from the modeling suggest that the potency of inhaled insulin was similar to the potency of subcutaneous insulin.

**References:**

- [1] Tornøe et al. (2004) J Math Biol 48: 591-604.
- [2] Brunner et al. (2001) Diabetologia 44: 305-308.

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Figure 1: Model diagram

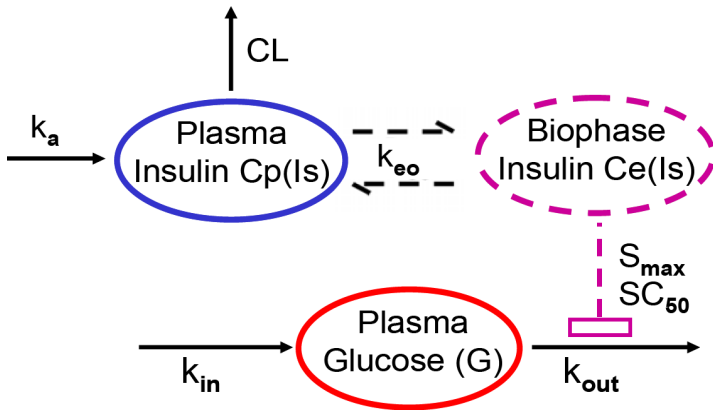


Figure 2: Visual predictive checks for the 10 mg inhaled and the subcutaneous dose

