Monte Carlo Analysis of a Subcutaneous Absorption Insulin Glargine Model: Variability in Plasma Insulin Concentrations

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Abstract. Absorption kinetics of long acting insulin such as Glargine often shows significant intra and inter-individual variability. To add this variability to the pharmacokinetics model of Glargine, ranges of variation for Glargine model parameters were introduced into 1000 Monte Carlo simulations. This assessment and analysis portray the likely intra-individual and inter-individual variability that could be expected clinically. The Monte Carlo analysis thus defines a range and distribution of identified and validated model parameter variations to consider in designing a glycaemic control protocol using Glargine.

Keywords: Insulin Glargine, Monte Carlo, subcutaneous insulin protocol.

1. Introduction

Limited research has been done in terms of modelling the absorption process of Glargine, since its introduction in 2000. Pharmacokinetics and pharmacodynamics (PK/PD) modeling analysis have been used to support licensing dose of drugs. The FDA (US Food and Drug Administration) states that PK/PD might be the supporting evidence of clinical trial efficacy. Hence, there is a definite importance of PK/PD modeling with the widespread confidence. To date, only [2, 3] and [4] reported comprehensive pharmacokinetic models. [2,3] constructed an extensive physiologically consistent ten-compartment model for the pharmacokinetics of several rapid acting, regular and long acting insulins including Glargine.

Using such deterministic models to determine the pharmacokinetics of insulin, physicians and nurses can better overcome barriers to effective glucose management. The use of model-based methods in Type 1 and Type 2 diabetes has shown the potential for developing successful therapeutic methods for effective glycaemic control [3]. However, models can not give meaningful prediction or portray the underlying physiology unless their parameters are determined and justified with clinical data. In addition, significant intra- and inter-patient variability in the PK and PD of insulin offer further barriers to model-based control.

To capture the dynamics and variability of Glargine's absorption kinetics, this paper presents a robust model that accounts for variability seen clinically among patients under Glargine therapy. Intra- or inter-individual variation in insulin absorption can range from 35% to 50% [5]. Thus, a robust model will give a good prediction and sufficient time for intervention and adjustment of insulin before glucose concentrations drift from desired ranges. As a result, hypo or hyperglycaemia can be better avoided. It is intended that this subcutaneous absorption model development would eventually offer a safe means to develop and compare control algorithms using Glargine prior to clinical testing.

2. Glargine Compartmental Model

A four compartment description of subcutaneous insulin kinetics is presented, where Glargine is modelled to appear in its precipitate, hexameric, dimeric / monomeric, and (local) interstitium states. The
underlying structure of this pharmacokinetics model is adopted from [2, 3]. The model describes the pharmacokinetics processes following subcutaneous administration of Glargine:

Precipitate State:

\[ \dot{p}_{\text{gla}}(t) = \frac{-k_{\text{prep},\text{gla}}p_{\text{gla}}(t)}{1 + k_{\text{prep},\text{gla}}/r_{\text{dis,max}}P_{\text{gla}}(t)} + u_{\text{p},\text{gla}}(t) \]  

\[ (1) \]

Hexameric State:

\[ \dot{x}_{\text{h},\text{gla}}(t) = -(k_1 + k_2)x_{\text{h},\text{gla}}(t) + k_{\text{prep},\text{gla}}p_{\text{gla}}(t) \frac{k_{\text{prep},\text{gla}}/r_{\text{dis,max}}P_{\text{gla}}(t)}{1 + k_{\text{prep},\text{gla}}/r_{\text{dis,max}}P_{\text{gla}}(t)} + u_{\text{h},\text{gla}}(t) \]  

\[ (2) \]

Dimeric/ Monomeric State:

\[ \dot{x}_{\text{d},\text{gla}}(t) = -(k_3 + k_4)x_{\text{d},\text{gla}}(t) + k_1 x_{\text{h},\text{gla}}(t) + u_{\text{m},\text{gla}}(t) \]  

\[ (3) \]

Interstitium:

\[ \dot{x}_i(t) = -(k_3 + k_4)x_i(t) + k_2 x_{\text{d},\text{gla}}(t) \]  

\[ (4) \]

Plasma Insulin:

\[ \dot{I}(t) = \frac{-nI(t)}{1 + \alpha I(t)} + \frac{k_3 x_i(t) + u_x(t)}{m_{I} V_i} \]  

\[ (5) \]

where all variables in Equations (1)-(5) are defined in Table 1 and the model’s schematic is in Fig. 1:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Parameter</th>
<th>Description</th>
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<tbody>
<tr>
<td>( x_{\text{h},\text{gla}}(t) )</td>
<td>Mass in glargine hexameric compart. [mU]</td>
<td>( k_{\text{prep},\text{gla}} )</td>
<td>Glargine precipitate dissolution rate [min(^{-1})]</td>
</tr>
<tr>
<td>( p_{\text{gla}}(t) )</td>
<td>Mass in glargine precipitate compart. [mU]</td>
<td>( k_1 )</td>
<td>Hexamer dissociation rate [min (^{-1})]</td>
</tr>
<tr>
<td>( x_{\text{d},\text{gla}}(t) )</td>
<td>Mass in dimer/monomer compartment [mU]</td>
<td>( k_{1\text{gla}} )</td>
<td>Glargine hexamer dissociation rate [min (^{-1})]</td>
</tr>
<tr>
<td>( x_i(t) )</td>
<td>Mass in the interstitium compartment [mU]</td>
<td>( k_2 )</td>
<td>Dimeric/monomeric insulin transport rate into interstitium [min(^{-1})]</td>
</tr>
<tr>
<td>( r_{\text{dis,max}} )</td>
<td>Max glargine precip. dissolution rate [mU/min]</td>
<td>( k_3 )</td>
<td>Interstitium transport rate into plasma [min(^{-1})]</td>
</tr>
<tr>
<td>( u_{\text{total},\text{gla}}(t) )</td>
<td>Insulin glargine input [mU/min]</td>
<td>( k_{dI} )</td>
<td>Rate of loss from interstitium [min(^{-1})]</td>
</tr>
<tr>
<td>( u_{\text{p},\text{gla}}(t) )</td>
<td>Glargine precipitate state insulin input [mU/min]</td>
<td>( k_d )</td>
<td>Rate of diffusive loss from hexameric and dimeric/monomeric state compartments [min(^{-1})]</td>
</tr>
<tr>
<td>( u_{\text{h},\text{gla}}(t) )</td>
<td>Glargine hexamer state insulin input [mU/min]</td>
<td>( u_{\text{m},\text{gla}}(t) )</td>
<td>Glargine dimer/monomer state insulin input</td>
</tr>
<tr>
<td>( n )</td>
<td>Decay rate of insulin from plasma [min(^{-1})]</td>
<td>( I(t) )</td>
<td>Plasma insulin [mmol/L]</td>
</tr>
<tr>
<td>( \alpha_1 )</td>
<td>Saturation of plasma insulin disappearance [L/mU]</td>
<td>( m_b )</td>
<td>Body Mass [kg]</td>
</tr>
<tr>
<td>( u_{\text{ex}} )</td>
<td>Exogenous insulin input [mU/min]</td>
<td>( V_I )</td>
<td>Insulin distribution volume [L]</td>
</tr>
</tbody>
</table>
Equations (1) and (2) differ from the original non-linear model in [2] and [3] with the introduction of the Michaelis-Menten saturation terms in these equations. The rate of Glargine precipitate dissolution, $k_{\text{prep, gl}}$, is a saturable process and is slower with the introduction of the Michaelis-Menten saturation function. There is a need to model this saturation as the solubility of the Glargine precipitate is limited due to the shifted pH of Glargine molecules [4]. Glargine injection is completely soluble at a pH of 4.0, and once injected in a neutral subcutaneous state with pH 7.4, Glargine is neutralized and formed microprecipitates [10]. Specifically, this model adds non-linear transport saturation based on the impact of Glargine molecule's own pH on the surrounding depot pH, which limits and extends the process to give Glargine its characteristically flatter profile. Hence, the model development with Michaelis-Menten saturation has a greater physiological relevance.

![Fig. 1: Structure of Glargine absorption kinetics model, beginning from subcutaneous Glargine injection, to precipitate compartment, $p_{\text{gla}}(t)$, hexameric compartment, $x_{h, \text{gla}}(t)$, dimeric/monomeric compartment, $x_{d,m}(t)$, interstitium, $x_i(t)$ and finally to the plasma insulin compartment, $I(t)$.](image)

3. Monte Carlo Study

Subcutaneous insulin absorption varies from one person to another, and can also be influenced by temperature, exercise, depth of injection, and many other insulin-dependent/independent factors [5]. Clinical experience has shown that under comparable patient conditions, the same injected subcutaneous dose often does not produce the same metabolic effect [1]. To model Glargine absorption variability in this study, lognormal distributions in several critical parameters are combined to produce variability matching reported ranges in Glargine dose-response studies. Lognormal distributions are used because the varied model parameters must be positive, which using a normal distribution does not guarantee. Parameters $k_{\text{prep, gl}}$, $k_{1, \text{gla}}$ and $\alpha_{\text{gla}}$ are the critical parameters given lognormal distribution in this study, producing variations in maximal plasma insulin concentrations, $C_{\text{max}}$, matching published data. These parameters are critical as they partly define the hexameric compartment. The Glargine pharmacokinetic responses are computed for 1000 Monte Carlo simulations to produce the expected variability distribution.

4. Results

The results in Fig. 2 illustrate how Glargine pharmacokinetics parameter variability yields expected variability in maximal plasma insulin, $C_{\text{max}}$. The range produced in Fig. 2 is the best achieved to replicate the reported values of $C_{\text{max}}$ by studies in the literature for similar injection doses [6, 7, 8, 9]. For example, a 24U of subcutaneous Glargine as reported by [9], has variations of $C_{\text{max}}$ from $7 \pm 1.3$ mU/L, and this is presented by the boxed area in Fig. 2(b). The range of $C_{\text{max}}$ produced covers the reported area. The plot of $C_{\text{max}}$ is expressed as a log normal distribution. This distribution maximizes the likelihood of accounting for variability among patients receiving the subcutaneous injection. As absorption rate is dose dependent, where a small dose is absorbed faster than a larger dose, the variability of $C_{\text{max}}$ as portrayed in Fig. 2 increases at higher volume of Glargine injection, as expected. Fig.3 shows the randomly selected model parameter variability of the Glargine pharmacokinetics parameters, $k_{\text{prep, gl}}$, $k_{1, \text{gla}}$ and $\alpha_{\text{gla}}$ for 1000 Monte Carlo simulations. The theoretical lognormal functions are also shown in Fig.3.

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Fig. 2: Distribution of maximal plasma insulin concentration, $C_{max}$, computed 1000 Monte Carlo runs with variability in $k_{prep,gla}$, $k_{1,gla}$ and $\alpha_{gla}$. Fig. 2(a): A 32U dose, boxed area refers to range quoted in [7]. Fig. 2(b): A 24U dose, boxed area refer to range quoted in [9] and Fig. 2(c): a 12U dose. No quoted range [8].

Fig. 3: Variability of Glargine pharmacokinetics parameters, $k_{prep,gla}$, $k_{1,gla}$ and $\alpha_{gla}$ computed with 1000 Monte Carlo runs as seen in (a), (b) and (c). The darker histogram shows the actual variability while the lighter histogram is the theoretical distribution of a lognormal distribution.

5. Discussion

Clinical experience has found that subcutaneous administration of insulin does not result in highly reproducible metabolic effects, even when the same dose is administered [1]. Thus, designing any protocol (clinical or model-based) for efficient subcutaneous insulin dosing in an attempt to achieve good blood glucose control has always been a challenge. The major limitation is in the pharmacokinetics profile of subcutaneous insulin and its intra-subject variability. Variable absorption and day to day variability are major factors that contribute to the instability of resulting intra-subject glycaemic levels. Glargine, in comparison to other long acting basal analogues, like NPH and Ultralente, has the lowest reported intrasubject variability [10]. However, its variability is still considered a significant aspect in insulin treatment, affecting glycaemic control and the risk of developing hypoglycaemia [11].

A reliable system for insulin dosing should thus be able to consider all sources of variation. The decision to vary only three model parameters, $k_{prep,gla}$, $k_{1,gla}$ and $\alpha_{gla}$ is deemed sufficient, as these parameters most influence the modelled variability of Glargine absorption kinetics. In addition, they are Glargine-specific parameters and their variability is thus independent, in this model, of other insulin types, which may have a different variability for the same subjects. Physiologically and clinically, the rate of dissolution and absorption of Glargin can be affected by the state of Glargin forming an amorphous microprecipitate at the injection site. The resulting observed and considerable variability of insulin action is considered here with a Monte Carlo analysis.

The outcomes of the Monte Carlo analysis portray the likely intra-individual and inter-individual variability of maximal plasma insulin concentrations, $C_{max}$ that could be expected clinically. Thus, the result of the Monte Carlo analysis defines a range of distribution of variation to consider in designing a glycaemic control protocol using Glargin. These ranges are seen to (broadly) capture those reported in the literature, further validating the overall model and approach. Hence, the main target is to develop control protocol that would be feasible to all the variations often see among patients. Specifically, by defining what might be
expected, the overall glycaemic control system model can be adapted to the observed insulin variability encountered clinically among patients. More importantly, such validated model variations may also be used to aid therapy selection and decision support [12]. The ability to predict subcutaneous insulin absorption using these results based on glycaemic response at the bedside would thus allow further patient-specific optimization of insulin treatment, with the potential to reduce or better manage the patient-specific outcome glycaemic variability.

6. Conclusion

The impact of maximal plasma insulin’s, C\text{max} variability, assessed with Monte Carlo increases the potential of the subcutaneous absorption model to be used effectively in a Glycaemic control protocol. The resulting Glargine absorption time-action with expected variability seen intra- and inter- individually would help in designing dosage regimens. Understanding the pharmacokinetic properties of insulin is one of the major sources in dosage designs. It is intended that this model development with introduced parameter variability would eventually offer a safe means to develop and compare control algorithms for the less critically ill patients, prior to a clinical testing.

7. References


