ESM Methods

The pharmacokinetic parameters were estimated using compartment modelling. In the present study, a two-compartment model described insulin aspart kinetics as in our previous work [1-4]:

\[
\frac{d i_1(t)}{dt} = u(t) - \frac{i_1(t)}{t_{\text{max}}} \\
\frac{d i_2(t)}{dt} = -\frac{1}{t_{\text{max}}} (i_2(t) - i_1(t))
\]

where \(i_1(t)\) and \(i_2(t)\) is the amount of insulin in the two subcutaneous insulin depots (U) and \(u(t)\) denotes the exogenous insulin delivery (U/h; model input) representing jointly prandial insulin bolus (appropriately represented as a short high-burst insulin infusion) or basal insulin infusion entering the compartment \(i_1\) and then the insulin is transferred into the compartment \(i_2\) at a fractional rate of \(1/t_{\text{max}}\), where \(t_{\text{max}}\) is the time-to-peak of plasma insulin (min).

The plasma insulin concentration is obtained assuming instantaneous equilibration between insulin appearance in plasma and plasma insulin reflecting a short plasma insulin half-life relative to the frequency of plasma insulin measurements:

\[
I_{\text{plasma}}(t) = \frac{1000}{t_{\text{max}} \cdot MCR_i W} i_2(t) + ins_c
\]

where \(I_{\text{plasma}}(t)\) is the plasma insulin concentration (mU/l; model output), \(MCR_i\) is the metabolic clearance rate of insulin (l/kg/min), \(ins_c\) is the background insulin (mU/l) which is assumed constant throughout the study period and may explain insulin concentration due to previously unabsorbed insulin left in the insulin depot, and \(W\) is subject’s weight (kg).

\(t_{\text{max}}, MCR_i\) and \(ins_c\) are the individual pharmacokinetic (PK) model parameters estimated by fitting a Bayesian statistical model to each subject’s data set.
To introduce the Bayesian approach, let $\mathbf{p}_i = [t_{\text{max},i}; MCR_{i}; \text{insc},i]$ represent the PK parameter vector for subject $i$ and $\mathbf{y}_i$ the plasma insulin concentration data set for subject $i$. According to the Bayes theory,

$$f(\mathbf{p}_i | \mathbf{y}_i) = \frac{f(\mathbf{y}_i | \mathbf{p}_i)f(\mathbf{p}_i)}{f(\mathbf{y}_i)} \propto f(\mathbf{y}_i | \mathbf{p}_i)f(\mathbf{p}_i)$$

(4)

where $f(\mathbf{p}_i | \mathbf{y}_i)$ is the posterior density of the unknown parameter $\mathbf{p}_i$, $f(\mathbf{y}_i | \mathbf{p}_i)$ is the likelihood function, $f(\mathbf{p}_i)$ is the prior density of $\mathbf{p}_i$, and $f(\mathbf{y}_i)$ performs as a scale factor. $f(\mathbf{y}_i | \mathbf{p}_i)$ is determined by solving Eq. (1) and (2) and calculating the plasma insulin concentration using Eq. (3). The model was numerically identified using WinBUGS (Bayesian inference Using Gibbs Sampling for Windows) software version 1.4 (MRC Biostatistics Unit, Cambridge, UK). We derived a closed-form solution of the model given in Eqs. (1)-(3). The WinBUGS extension ‘WBDev’ was utilized to implement this solution into WinBUGS through a separate module.

Parameter mean/median and credible intervals can be derived from the posterior density. Median values of parameters obtained from the posterior density functions were subjected to the statistical analysis.

The prior density reflects our previous knowledge about unknown parameters. In the present study, we used vague log-normal prior distributions for PK parameters (see below) with $t_{\text{max}}$, $MCR_i$ and $\text{insc}$ centred at 60 min, 0.01 l/kg/min and 36 pmol/l, respectively, with a large coefficient of variation of $10^4$. 
Table. Uninformative prior distributions of pharmacokinetic parameters used in the Bayesian analysis.

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Prior distribution$^a$</th>
</tr>
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<tbody>
<tr>
<td>$t_{\text{max}}$ (min)</td>
<td>$\log(t_{\text{max}}) \sim N(\log(60),10^2)$</td>
</tr>
<tr>
<td>$MCR_f$ ($10^{-2} \times \text{l/kg/min}$)</td>
<td>$\log(MCR_f) \sim N(\log(0.01),10^2)$</td>
</tr>
<tr>
<td>$ins_c$ (pmol/l)</td>
<td>$\log(ins_c) \sim N(\log(36),10^2)$</td>
</tr>
</tbody>
</table>

$^a$ Log-normal distributions to guarantee parameter positivity

References


