Modelling the Dynamics of Glucose, Insulin, Insulin Sensitivity and Beta-Cells in Subjects with Insulin Resistance and Patients with Type 2 Diabetes

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Ribbing J, Hamrén B, Svensson MK, and Karlsson MO A Model for Glucose, Insulin, Beta-Cell and HbA1c Dynamics in Subjects with Insulin Resistance and Patients with Type 2 Diabetes (Manuscript)
Scope

• Covered
  – Mechanisms of type 2 diabetes
  – BIG model by Topp et al.
  – The usual suspects: Method, Results and Conclusions

• Not covered
  – Previously developed PK-PD models
Mechanism of Type 2 Diabetes

- Glucose
- Type 2 Diabetes (T2DM)
- Insulin resistance
  - Due to FFA
- Reduction in beta-cell mass (BCM)

Beta cells → Glucose → Type 2 Diabetes (T2DM)

- Insulin
Topp et al. - BIG Model

- **Beta-cell mass, Insulin and Glucose (BIG)**
- Three differential equations
  - Includes adaptation of beta-cell mass (BCM)
- Not fitted simultaneously
  - Derived from sources in literature
  - Mean parameter values for normal subject
- No pharmacological treatment

1. Glucose is Regulated by Insulin

\[ \frac{dFPG}{dt} = R_0 - \left( E_{GO} + S \cdot FI \right) \cdot FPG \]
1. Glucose is Regulated by Insulin

\[ \frac{dFPG}{dt} = R_0 - \left( E_{GO} + S \cdot FI \right) \cdot FPG \]
2. Insulin is regulated by Glucose!

\[
dFI/dt = BCM \cdot \sigma \cdot FPG^2 / (\alpha^2 + FPG^2) - k \cdot FI
\]
2. Insulin is regulated by Glucose!

\[ \frac{dFI}{dt} = BCM \cdot \sigma \cdot \frac{FPG^2}{(\alpha^2 + FPG^2)} - k \cdot FI \]
3. Beta-Cell Mass (BCM) Adapting to Glucose Level

\[ \frac{dBCM}{dt} = (-d_0 + R_1 \cdot FPG - R_2 \cdot FPG^2) \cdot BCM \]
3. Beta-Cell Mass (BCM) Adapting to Glucose Level

\[ \frac{dBCM}{dt} = (-d_0 + R_1 \cdot (FPG - \text{Offset}) - R_2 \cdot (FPG - \text{Offset})^2) \cdot BCM \]
Tesaglitazar – A dual PPAR agonist

• Tesaglitazar PPAR $\alpha$-$\gamma$ agonist

• Development discontinued in phase III
  – Reduced renal function

• Anti-diabetic effects similar to $\gamma$ agonists, pioglitazone and rosiglitazone
  – Increased insulin sensitivity
    • Due to decrease in FFA
  – Increased beta-cell mass?
Aim

• Develop an integrated population PK-PD model for glucose, insulin and BCM
  – Treatment effects
    • Tesaglitazar
    • pre-treatment in drug experienced
  – Patient heterogeneity
    • Random IIV
    • Disease stage
Method – Tesaglitazar data

• **SIR** — Study in Insulin Resistance
  – 3-months, insulin resistant non-diabetics

• **GLAD** — Glucose and Lipid Assessment in Diabetes
  – 3-months, treatment experienced and naïve

• **GALLANT6**
  – 6-months, treatment experienced and naïve

• Fasting measurements from 1460 subjects
Method - New Model Structure Based on BIG

Pre-treatment or tesaglitazar exposure
Overview - Drug and System Specific Parameters

Physiological Parameters
- Glucose-dependent growth rate of BCM
- Glucose dependent death rate of BCM
- BCM death rate at zero glucose (extrapol)
- Maximum insulin secretion per unit BCM
- EC$_{50}$, glucose stimulated insulin secretion
- Hill factor, glucose stimulated insulin secretion
- First order elimination rate of insulin
- Glucose production at zero glucose (extrapol)
- Total glucose effectiveness at zero insulin

Pathophysiological parameters
- OFFSET in BCM adaptation
- Insulin sensitivity

Mixed origin parameters
- K$_{out}$, insulin sensitivity
- Relation btw insulin elimination & insulin sensitivity

Pharmacology parameters
- E$_{max}$, insulin sensitivity
- EC$_{50}$, insulin sensitivity
- EC$_{50}$, OFFSET
- Hill coefficient, OFFSET
- Pre-treatment effect, insulin sensitivity
- Pre-treatment effect, OFFSET

Fixed and random effects estimated in NONMEM
Results - Drug Naïve Diabetic Patients, GLAD

Treatment stopped

Time after start of treatment (days)
Results - Insulin Resistant Non-Diabetic Subjects

Time after start of treatment (days)
Result – Median Response in IRS Subjects and Naïve Diabetics

![Graph showing response levels over time](image-url)

- BCM
- S
- IRS (SIR)
- Drug Naive, GLAD

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Discussion

• Naïve T2DM patients, 40% of normal BCM
  – Well in line with literature
  – Decrease in actual *beta-cell function* mainly decrease in *BCM*

• Strong relation between *insulin elimination* and *insulin sensitivity*
  – Well in line with literature
  – FFA common link
  – Important when assessing beta-cell function!
Conclusions

• Describes FPG, FI and BCM well
  – mechanistic manner

• Allows incorporation of
  – Short-term experiments
  – Observations of FFA
  – Observations of BCM (future)
  – Treatment duration of 1-2 years
    • Long term disease progression
    • Long term disease modifying effects