A semi-mechanistic gastric emptying pharmacokinetic model for \(^{13}C\)-octanoic acid: an evaluation using simulation

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Introduction

- Gastric emptying (GE) is important for human nutritional health and oral drug absorption.
- There are three main methods for studying GE: scintigraphy\(^2\), paracetamol absorption test\(^2\) and \(^{13}C\)-octanoic acid breath test (OABT)\(^3\).
- Scintigraphy is very accurate and it is the gold standard. However, it is unsafe, requires expensive equipment and is not generally available.
- \(^{13}C\)-octanoic acid breath test (OABT) is used for indirect assessment of the rate of GE.
- Compared to scintigraphy OABT is cheaper and safer and can be performed anywhere.
- OABT measures the rate of \(^{13}CO_2\) exhaled in breath and this is converted to scintigraphy GE equivalents.
- There are inconsistencies when results from OABT are compared with simultaneous and direct measurements using scintigraphy\(^4\).
- Parameters from OABT do not reflect only GE but other processes: absorption, metabolism, distribution and elimination.
- A semi-mechanistic model was recently proposed for the analysis of OABT data which is based on repeated/parallel experiment and a constraint\(^5\).
- The model incorporates all processes (absorption, metabolism, distribution and elimination) involved between the ingestion of \(^{13}C\)-octanoic acid meal and elimination of \(^{13}CO_2\) in breath.

Objective

To assess the performance of the semi-mechanistic model using simulation against three currently used methods (modified exponential model\(^6\), Ghoos\(^7\) method and Wagner-Nelson method\(^8\)) that have been used to convert parameter (half emptying time) from OABT to scintigraphy equivalents.

Repeate Study Design

![Repeated Study Design Diagram](image)

**The Model (kg model)**

\[
\begin{align*}
\text{Stomach (BASE)} &\rightarrow \text{Intestine} \rightarrow \text{Body 1} \rightarrow \text{Body 2} \rightarrow \text{Breath} \\
\text{ka} &\rightarrow \text{kg (hr)} &\rightarrow \text{ka} &\rightarrow \text{kg (hr)} &\rightarrow \text{ka} &\rightarrow \text{kg (hr)}
\end{align*}
\]

Parameters: \(k_g, k_a, k_b, k_n, k_{12}, k_{21}\)

\[T/2kg = \ln 2/\text{kg}\]

**Other Methods**

- **Modified Exponential Model**
  \[PDR(\% \text{dose/hr}) = \frac{mk}{\exp}\left( -\frac{1}{1/2} \right) \]
  \[T/2exp = \left( -\frac{1}{1/2} \right) \]

- **Ghoos Method**
  \[PDR(\% \text{dose/hr}) = 2\ln a \exp -b \]
  \[T/2ghoos = \frac{1}{2} \ln \left( \frac{1}{2} \right) \]

- **Keller Method**
  \[\frac{F(t)}{A_0} + PDR(0.65)A_0 = \frac{A_0}{A_0} + PDR(0.65)A_0 \]
  \[y(t) = \exp -\frac{1}{2} \]
  \[T/2wag = \ln 2/k \]

**Typical Profiles and Fittings**

![Typical Profiles and Fittings](image)

**Results**

- **Simulations**
  - Breath profiles were simulated using ordinary differential equations based on the semi-mechanistic model and the parameter values under four settings assuming 50 subjects and repeated study design.
  - Sim 1 - variability on all parameter Sim 2 - no variability on kg and ka
  - Sim 3 - variability on kg and ka only Sim 4 - no variability on all parameters.
  - Simulations were based on baseline and treatment OABT (treatment by a hypothetical prokinetic drug that increases kg by 50%).
  - Fittings were done for individual simulated breath profile in MATLAB using lnsapln and kg model and the other three methods.

  The true half emptying times from stomach profiles (T/2s) were compared with the half emptying times obtained by the kg model (T/2kg) and the other three methods (T/2mod, T/2ghoos and T/2wag).

**Parameter Values**

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**Conclusion**

- Only the semi-mechanistic model can estimate accurately gastric half emptying times from breath profiles obtained during OABT.
- The semi-mechanistic model incorporates all processes involved between the ingestion of \(^{13}C\)-octanoic acid meal and elimination of \(^{13}CO_2\) in breath, all of which are modeled simultaneously.
- Half-emptying times obtained using modified exponential model, Ghoos method and Wagner-Nelson method are the time taken for half of the total cumulative dose of \(^{13}C\) to be recovered as \(^{13}CO_2\) in breath and not the time taken for half of \(^{13}C\)-octanoic acid to be emptied from the stomach.
- These half emptying times do not reflect only the rate of GE but are affected by other processes such as absorption, distribution, metabolism and elimination.
- The new semi-mechanistic model can be used as a PK/PD model and the use of this model will allow efficient assessment of the rate of GE especially during drug development.

**References**