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[1], 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 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, safer and can be performed anywhere

✓OABT measures the rate $^{13}CO_2$ is 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

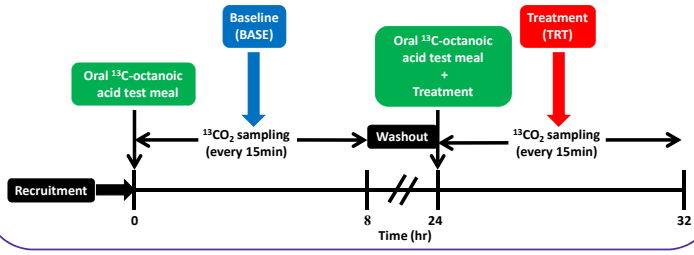
✓A semi-mechanistic model was recently proposed for the analysis of OABT data which is based on repeated/parallel experiment and a constraint[5]

✓The model incorporate 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

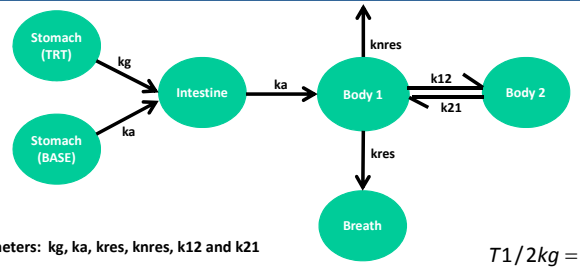
Objective

✓To assess the performance of the semi-mechanistic model using simulation against three currently used methods (modified exponential model[6], Ghoos[1] method and Wagner-Nelson method[7]) that have bee used to convert parameter (halt emptying time) from OABT to scintigraphy equivalents

Repeated Study Design



The Model (kg model)



Parameters: kg, ka, kres, knres, k12 and k21

$$T1/2kg = \ln 2/kg$$

Other Methods

Modified Exponential Model

$$PDR(\%dose/hr) = mk\beta e^{-kt}(1-e^{-kt})^{\beta-1}$$

$$T1/2\exp = (-1/k)\ln(1-2^{-1/\beta})$$

Ghoos Method

$$PDR(\%dose/hr) = at_j^b e^{-ct}$$

$$T1/2ghoos = gammainv(0.5; b+1; 1/c)$$

Wagner-Nelson Method

$$F(t) = (A + PDR/0.65)A_\infty, \quad A_\infty = A_n + PDR/0.65$$

$$y(t) = 100(1-F(t)), \quad y(t) = e^{-kt}, \quad T1/2wag = \ln 2/k$$

Parameter Values

Parameter	Sim 1		Sim 2		Sim 3		Sim 4	
	Mean	Var	Mean	Var	Mean	Var	Mean	Var
kg (hr^{-1})	1.8	0.03	1.8	0	1.8	0.03	1.8	0
ka (hr^{-1})	1.2	0.03	1.2	0	1.2	0.03	1.2	0
kres (hr^{-1})	4.5	0.01	4.5	0.01	4.5	0	4.5	0
knres (hr^{-1})	3	0.01	3	0.01	3	0	3	0
k12 (hr^{-1})	100	0.01	100	0.01	100	0	100	0
k21 (hr^{-1})	7.5	0.01	7.5	0.01	7.5	0	7.5	0

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

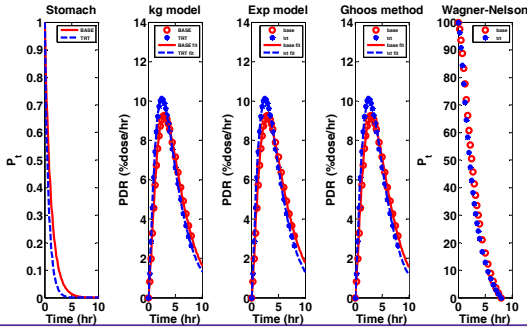
✓**Sim 3** – variability on kg and ka only **Sim 4** – no variability on all parameters

✓Simulations were based on baseline and treatment OABT (treatment by a hypothetical prokinetic drug that increases kg by 50%)

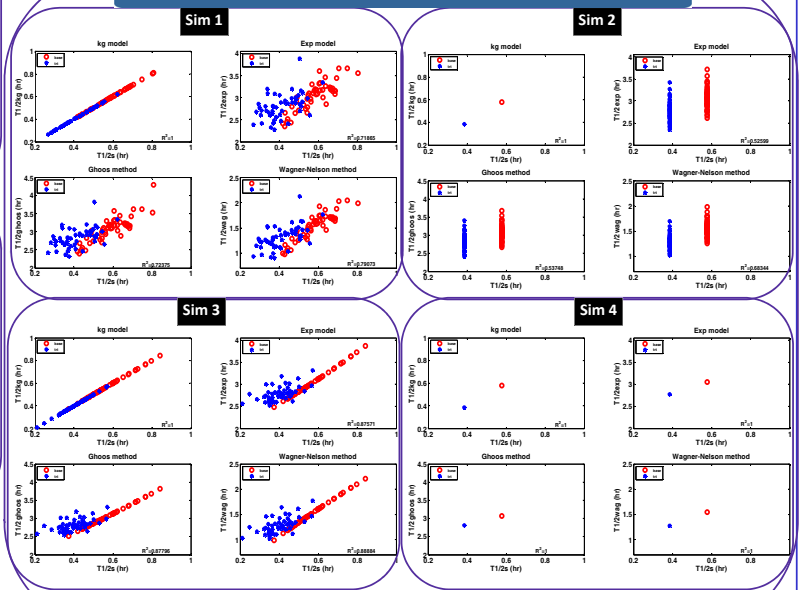
✓Fittings were done for individual simulated breath profile in MATLAB using lsqnonlin and kg model and the other three methods

✓The true half emptying times from stomach profiles (T1/2s) were compared with the half emptying times obtained by the kg model (T1/2kg) and the other three methods (T1/2ghoos and T1/2wag)

Typical Profiles and Fittings



Results



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 the 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 PD model or part of a PK/PD model and the use of this model will allow efficient assessment of the rate of GE especially during drug development

References

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