Meta-analysis of Magnetic Marker Monitoring (MMM) data to characterize tablet movement through the gastrointestinal (GI) tract

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Objectives

To develop a meta-model predicting tablet movement through the gastro-intestinal (GI) tract, based on Magnetic Marker Monitoring (MMM) data

MMM data & Meta model

Magnetic Marker Monitoring (MMM) technique:

- Visualize the transit of labeled tablet through GI tract
- Monitor tablet disintegration and drug release

5 MMM study data: in total 30 individuals in 94 occasions

- Tablet administered under 3 food conditions : fasted, at the begining of a meal, after the start of the meal
- GI locations : Proximal Stomach (PS), Distal Stomach (DS), Small Intestine (SI), Ascending Colon (AC), Transverse Colon (TC) and Descending Colon (DC), Sigmoid Colon (SC)

GI tablet transit model

Markov chain model for tablet position, where the probability of observing tablet in different GI position is dependent on the last observed position and time since last observation (Fig 1) [1].

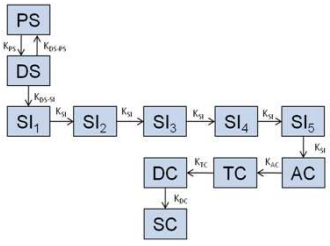

Figure 1: Schema of GI transit model
K: first-order rate constant for tablet movement

Estimated parameters

Table1 presents the estimated parameters from 3 different models, fitting all data simultaneously in NONMEM 7[2]

Mean Residence Time (minutes)	No Food effect	Food effet : Primary Meal	Primary Meal + GE function to Time
OFV	2036.30	1834.77	1820.07
Proximal Stomach	55.5 (16%)	11.6 (16%)	10.1 (21%)
Distal Stomach *	82.9 (14%)	13.0 (23%)	10.8 (27%)
Small Intestine	227 (7%)	231 (7%)	228 (7%)
Ascending Colon	545 (21%)	545 (21%)	545 (21%)
Transverse Colon	135 (39%)	135 (39%)	135 (39%)
Descending Colon	285 (21%)	285 (21%)	285 (21%)
Food effect			
- Prox. Stomach		7.3 (25%)	8.72 (28%)
- Distal Stomach		10.6 (30%)	20.1 (37%)
- Time to Fed status		34.9 (9%)	35.8 (8%)
GE Time Function			
- Slope			0.73 (53%)
- Time of increase			2.25 (10%)

Table 1: Estimated Mean Residence Times in GI tract and associated uncertainties (%SE) under 3 different models

* SE obtained using the Delta method [3]

Effects on tablet movement

Effect of simultaneous food intake:

- 8.7-fold prolongation of MRT in prox. stomach, 20.1-fold prolongation on MRT in distal stomach
- No effect on small intestine transit, nor on colon transit
- Probability of gastric emptying (GE) increased of 73% each hour from 2.25 hours after meal

Effect of a later meal (4 to 6 hours after tablet intake):

- No siginificant effect on stomach : increasing probability of GE could better describe the data
- No significant effect on SI: gastro-ileocecal reflex, described in the litterature [4] could not be retrieved in the present data

Effect of formulation-dependent disintegration rate:

- MMM data were censored by the limit of detection of the magnetic signal. No significant effect of time to censoring was found on estimated MRTs.

Model evaluation

Visual Predictive Checks (VPC): Comparison of observed probabilities to median and 90% confidence intervals (90%CI) computed from 500 simulated replicates.

Fig 2 shows VPC for the model including the primary meal effect and a time dependent function on GE probability.

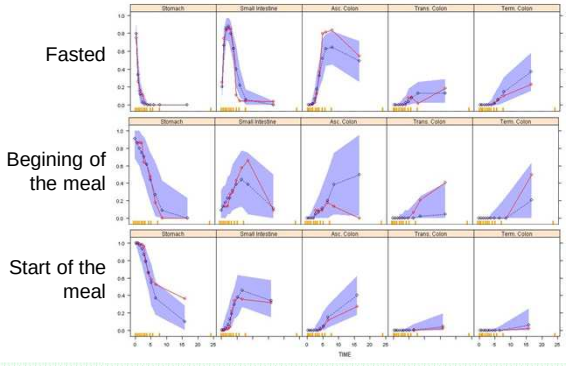

Figure 2: Visual Predictive Checks for each GI position under 3 food conditions
Observed probabilities (red) - Median and 90%CI for each probability obtained from 500 simulated replicates (blue line and area)
Since PS and DS were undistinguishable in few occasions, they were lumped together (stomach) in observations and simulations. As for "Terminal Colon" lumping DC and SC

Conclusions and Perspectives

This meta-model of MMM data represents an integration of information for tablet movement through GI tract under various food conditions.

This model–based knowledge can be used as prior information in semi-mechanistic model for drug absorption, involving tablet position [5,6]

References

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