A Population PK model to evaluate variability in oral absorption using gamma scintigraphy

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Introduction

- GSKX is a weak base with good solubility at gastric pH and good permeability, it belongs to BCS class II (Biopharmaceutical Classification System).
- GSKX showed high PK variability (CV% 70-100% in Cmax and AUCs) when orally administered as an immediate release tablet in fasted conditions. This variability could be related to a variety of factors such as differences in gastric emptying patterns or poor formulation performance [1]. In phase I studies, variability was limited by food.
- A 3-way cross-over study in human volunteers was carried out to assess the relationship(s) between GSKX absorption and gastric emptying time and to guide formulation development. Treatments were: 1) solution in capsule, 2) IR tablet – fasted state, 3) IR tablet –fed state.
- Gamma scintigraphy was used to evaluate formulation performance by visualizing the disintegration process and by measuring the gastric emptying time in relation to the use of food or of different formulations.

Objectives

To develop a population PK model to assess any relationship(s) between gamma scintigraphy emptying profile and GSKX plasma disposition after administration of a solution or a tablet formulation in fasted and fed states.

Methods

- A GI-transit-absorption kinetics model was developed. Different number of sequentially linked compartments (stomach, intestine,…) were explored [2].
- The drug was measured as radioactivity in the stomach and GI transit process from the stomach to the jejunum was described by a rate-limited process:

$$Ka = \frac{\text{Rate}_{max} \times \text{Time}^{\gamma}}{\text{T50}^{\gamma} \times \text{Time}^{\gamma}}$$

- Where Rate_{max} is the fastest transit rate, T50 is the time at which rate is the 50% maximum rate and γ is the sigmoidicity factor.
- The disposition PK model connected to this GI absorption model was a three compartment model with first order elimination rate constant (k_{20}) from the central compartment and distribution (k_{23}, k_{32}, k_{24}, k_{42}) into 2 additional peripheral compartments.
- A Mixed effect modelling (NONMEM, version VI) was used to estimate the model parameters.

Results

Dosage forms landed in a formulation and food dependent manner.

1) Solution in capsules: esophagus
2) Tablet fasted: antrum
3) Tablet fed: fundus

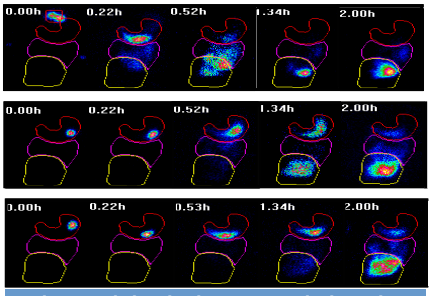

Fig. 1. Abdominal gamma scintigraphy images of Subject 2 after administration of solution (top), tablet fasted (middle), tablet fed (bottom) from time 0 to 2 hr

- In one subject, tablet was immediately visualized in duodenum when administered in fasted state (gastric scintigraphy not available, subject excluded from analysis). Systemic exposure was low (30% of solution or tablet in fed state).
- The rate and pattern of transit of radioactivity from the stomach to the duodenum was formulation and food dependent.
- When a solution was administered, T50 was estimated to be negligible and the equation describing Ka simplified to $Ka=Rate_{Max}$
- When a tablet was administered T50 was estimated to be higher in fed than in fasted conditions.

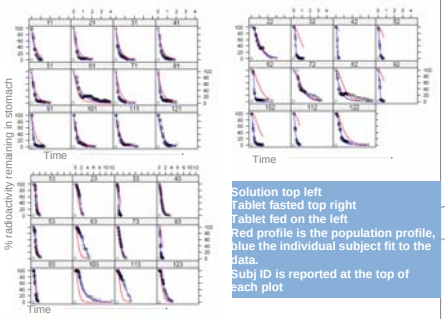

Fig. 2. Individual fit and time-course of radioactivity transit through the stomach

- Using the sequential approach (stomach + intestine) the transit rate from stomach to central compartment was overestimated (K up to $20h^{-1}$).
- The final absorption model (stomach only) was characterized by an absorption rate proportional to gastric emptying rate (scintigraphy) directly linked to central compartment with a lag time. This model accurately predicted the overall absorption process if the tablet disintegrate within the stomach.

- A relative bioavailability F (to solution) was estimated for tablet in fasted and fed conditions.
- F for tablet (fasted and fed) was not statistically different from solution; variability was much higher.

Parameter		Estimate	Inter-individual variability (CV%)
Fixed Effect Parameter			
θ_1	Vc (L)	333 ±90	28%
θ_2	K23 (h^{-1})	0.235±0.045	99%
θ_3	K32 (h^{-1})	0.14±0.042	<10%
θ_4	K24 (h^{-1})	0.42±0.066	100%
θ_5	K42 (h^{-1})	0.00885±0.0002	48%
θ_6	K20 (h^{-1})	0.0904±0.017	100%
θ_7	LAG TIME (h)	0.25±0.0027	<10%
	F for solution	1	<10%
θ_8	F for tablet in fasted conditions	0.89±0.22	66%
θ_{10}	F for tablet in fed conditions	1.28±0.40	100%
σ^2	Additive residual error	1	
σ^2	Proportional residual error	0.288	

Tab. 1 Population PK parameters by treatment

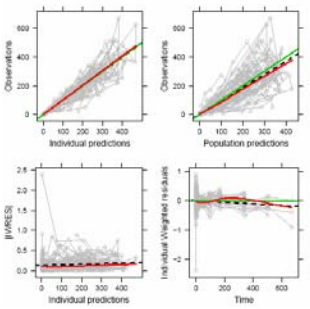

Fig. 3 GSKX PK Goodness of fit plots

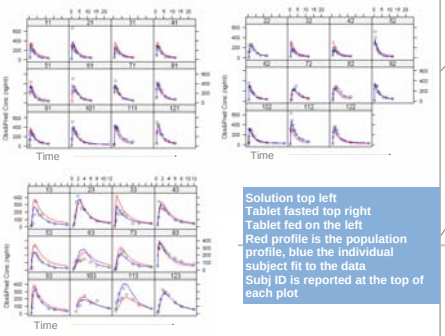

Fig. 4. Individual fit for plasma conc vs time (hr) of GSKX

Conclusions

- GSKX individual absorption rate (Ka) was controlled by disappearance of radioactivity from the stomach (gamma-scintigraphy).
- Once tablet disintegrated in the stomach, despite different gastric transit patterns, the extent and variability of exposure did not change.
- The high PK variability observed in phase I studies (fasted) was possibly due to lack of tablet disintegration in stomach (observed in one subject here).

References

[1] Kilian K. et al, Comparison of the Rates of Disintegration, Gastric Emptying, and Drug Absorption Following Administration of a New and a Conventional Paracetamol Formulation, Using Gamma Scintigraphy, *Pharm. Res., 20, 1668-1673, 2003*
[2] Honghui Z., Pharmacokinetic Strategies in Deciphering Atypical Drug Absorption Profiles, *J. Clin. Pharmacol.* 43 211-227, 2003