Mechanistic Modeling of Magnetically Marked Extended Release Formulation of Felodipine

Martin Bergstrand (1), Erik Söderlind (2), Mats O Karlsson (1)

(1) Division of Pharmacokinetics and Drug Therapy, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden.; (2) Product Development, AstraZeneca R&D Mölndal, Sweden

Objectives: To assess information gained by a mixed effect modeling approach to data from studies with magnetically marked monitoring of formulations in gastrointestinal transit.

Methods: Magnetic Marker Monitoring is a novel technique for visualising the transit of a solid oral dosage form through the GI tract. For dosage forms with erosion controlled drug release, the technique can also be used for obtaining an in-vivo drug release profile [3].

In a clinical crossover study the gastrointestinal transit and the in-vivo drug release of magnetically labeled extended release tablets containing felodipine were monitored under fasting and fed conditions in six healthy volunteers using Magnetic Marker Monitoring [4]. Observations from this study were of three kinds: GI location of the tablet, remaining non-disintegrated tablet and plasma concentration of felodipine. These data were combined with concentration data following i.v. infusion [1] to build an integrated population mixed effect model.

Model development was carried out by step-wise modeling of different parts of the complete system. Finally the entire model was fitted to all data simultaneously. GI position was included in the model as a covariate, governing the turning on and off drug release into corresponding absorption compartments. Two different approaches to handle transitions from one GI position to another in-between the observation periods (10 min with 20 min intervals) were applied. A simple approach of setting unknown time of transit to halfway between the surrounding observations was compared to a more elaborate approach, were time of transit was estimated.

Results and Discussion: Parameter estimates and their imprecision are reported in Table 1. The in vivo drug release was best described with three different zero order rate constants depending on the position of the non-disintegrated tablet (D1, D2/D3 and D4/D5). A relatively slow release rate was seen for the proximal stomach (D1). An approximately three times faster release rate was estimated for the distal stomach and the proximal small...
intestine (D2/D3). In the distal part of the small intestine and colon the drug release rate was estimated to be intermediate in comparison to D1 and D2/D3. The interindividual variability for the different rate constants was highly correlated and sufficiently described with only one variability term affecting all rate constants. The magnitude of the interindividual variability was also seemingly small, 9%.

Mixing of gut content in the proximal stomach is low which is manifested in the model by a slow first order distribution constant for released drug content passing down to the distal stomach (K23). As the tablet moves down to the distal part however, it is likely that released drug in the proximity of the tablet is also moved in a sudden fashion. This effect has been incorporated in the model. The distribution rate from distal stomach to small intestine (K34) was estimated to be considerably faster than K23 but showed the same pattern in terms of acceleration after tablet movement. Absorption can be rate limited by either dissolution or permeability. An observed three-fold faster absorption rate in small intestine (K47 and K57) compared to colon (K67) is thought to be due to a lower dissolution rate in colon. It was hypothesized during the model development that the pre-hepatic bioavailability (FA) might differ over the different GI parts, however no such significant effect was detected.

It has previously been concluded that concomitant food intake alter GI transit of the formulation, primarily by prolonging time in the proximal stomach [3]. The model further suggests that food intake decreases the rate with which released drug substance in the distal stomach is passed down to the stomach (K34 -70 %) and increases pre-hepatic bioavailability (FA +70 %).

Estimating the time of transit between GI-positions did offer a small, statistically significant improvement in the model fit to the data. However since there was no major change to the estimated parameters and that it rendered difficulties in characterizing the uncertainty around the parameter this feature was not included in the final model.

**Conclusions:** The interaction between tablet GI location, in-vivo drug release and plasma concentration can be described in a mechanistically informative way with an integrated mixed effect model.

**References:**