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Development of a population-based ADME simulation to assess variability in raltegravir pharmacokinetics

Darren Moss, Marco Siccardi, David Back, Andrew Owen. University of Liverpool, Liverpool, UK

Introduction Raltegravir (RAL) is a first in class integrase inhibitor used as part of Highly Active Antiretroviral Therapy (HAART). Oral absorption of RAL shows high inter- and intra-patient variability (Siccardi et al, Ther Drug Monit 2012;34:232-5). This variability remains largely unexplained and complicates patient management owing to difficulty in predicting RAL pharmacokinetics (PK). Our previous investigations have shown that pH and divalent metals (e.g. magnesium reduces transcellular permeation of RAL across Caco-2 cell monolayers) influence RAL disposition *in vitro* (Moss et al, Antimicrob Agents Chemother. 2012;56(6):3020-6) and may help explain PK variability. In this investigation we have determined the influence of pH on the dissolution rate of standard 400 mg RAL tablets *in vitro*. This information was combined with other drug properties determined in-house or from the literature to create a physiologically-based pharmacokinetic (PBPK) model. This model was used to simulate the influence of gastrointestinal pH and ingestion of divalent metals on RAL exposure. **Methods** The dissolution rate of standard 400 mg RAL tablets was assessed *in vitro* using different buffered solutions (30 min, 37°C, 10 rpm, pH 1 - 7) and dissolved drug was quantified using a validated HPLC assay. RAL PK properties were simulated using the full PBPK model implemented through the Simcyp Population-based Simulator (Version 11.0, Simcyp Limited, UK) by adding drug parameters determined in-house and from the literature. The model was then used to simulate RAL (400 mg, single dose) plasma PK in healthy, fasted subjects (20-50 years old, 0.5 proportion female) over 12 hours. Simulated PK results were compared with published PK data from patients and used to calculate the geometric mean values for C_{max} (ng/mL), $AUC_{0\text{-}12hr}$ (ng/mL.hr), C_{trough} (ng/mL) and fa (fraction of dose absorbed). The influence of magnesium on RAL PK was also assessed. An independent *t* test was used to determine whether differences were statistically significant. Pearson correlation was used for all bivariate analyses. A two-tailed p value of less than 0.05 was accepted as being statistically significant. **Results** Percentage of tablet dissolution was 11%, 17%, 24% and 53% in pH 1, 3, 5 and 7, respectively, following 30 minutes incubation. Simulated PK values C_{max} (2091 ng/mL), $AUC_{0\text{-}12hr}$ (8255 ng/mL.hr) and C_{trough} (77 ng/mL) fell within the range of PK values observed in published clinical studies. Both intestinal transit time and duodenal pH strongly correlated with the fraction of RAL dose absorbed ($p<0.001$), with an increase in intestinal transit time and duodenal pH resulting in increased RAL absorption. Co-administration of 25 mM magnesium solution caused a 40% decrease in RAL $AUC_{0\text{-}12hr}$ ($p<0.01$), which led to more than twice as many of the simulated subjects in the magnesium group having a C_{trough} less than 15 ng/mL (IC_{95} of RAL) compared to control group (17% versus 8%). **Discussion** Gastrointestinal pH and divalent metal binding are likely to influence the exposure of RAL and both provide a possible explanation of high RAL PK variability. RAL tablet dissolution rate is pH-dependent and an improved formulation may be required to reduce variation in RAL exposure.