Semi-mechanistic PK/PD modeling of Paracetamol and Sulfapyridine to characterize effects on gastric emptying and small intestinal transit

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Objective

Demonstrate how mechanistic modeling of paracetamol and sulfapyridine can characterize pharmacologically induced changes in gastrointestinal transit under fed and fasting conditions.

Background

- Drug-induced changes in gastric emptying (GE) and small intestinal transit time (SITT) can cause altered absorption of other drugs as well as constipation and diarrhea.
- The paracetamol (PCM) & sulfapyridine (SP) double marker technique[1]
  - Combined gastric administration of PCM and sulfasalazine followed by plasma concentration measurements for PCM and SP.
  - PCM is rapidly absorbed from duodenum ⇒ Marker for GE
  - Sulfasalazine is poorly absorbed in the small intestine and is in colon rapidly metabolized by bacteria into SP. As SP is absorbed from colon only it serves as a marker for SITT.

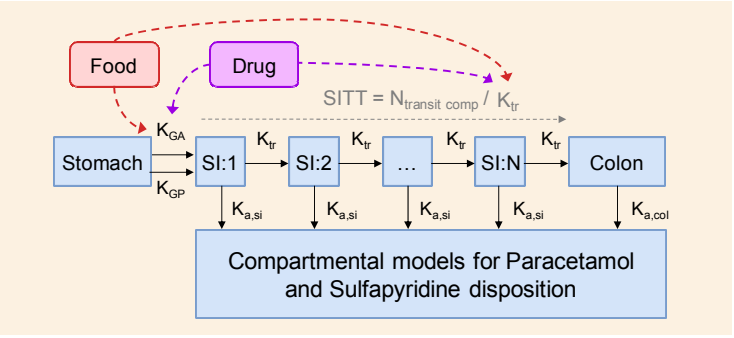

Figure 1. Schematic model structure.
Rate of gastric emptying is divided into two parts an active (K_{GA}) and an passive emptying (K_{GP}), Mean small intestinal transit time (SITT) estimated as number of transit compartments divided by transit rate constatant (K_{tr}), first order absorption rate constants from small intestine ($K_{a,si}$) and colon ($K_{a,col}$). Food and drug (atropine/erythromycin) effects on K_{GA} and K_{tr}.

Results

Gastric emptying (GE):
- Described with two first order rate constants, K_{GA} and K_{GP}
- Mean time for 50% GE (fasting) estimated to 8 min

Small intestinal transit:
- Described with 5 transit compartments (Figure 1)
- Fasting SITT estimated to 7 h and 45 min

Atropine:
- Inhibits K_{GA} and cause initial >20 fold decrease in GE (K_{GA} + K_{GP})
- Has no significant effect on SITT
- A time dependent decrease in atropines effect was described with an inhibitory E_{max} model and prior information on atropine half-life (2 h)[2]

Erythromycin:
- Prolongs SITT and stimulates K_{GA} (fasting)
- Stimulating effect on K_{GA} not seen with concomitant food intake
- Literature information on half-life (1.5 h)[3] in dogs was used to explain how the effect was decreasing with time

Food intake:
- Decrease rate of GE in a transient time dependent manner (Figure 3)
- Stimulates K_{tr} transiently ⇒ shorter average SITT (Figure 3)

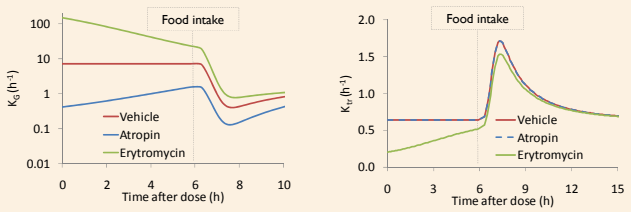

Figure 3. Food and drug effects on GE (K_G = K_{GA} + K_{GP}) (left graph) and SITT (K_{tr}) (right graph) illustrated for the fasting drug administration study.

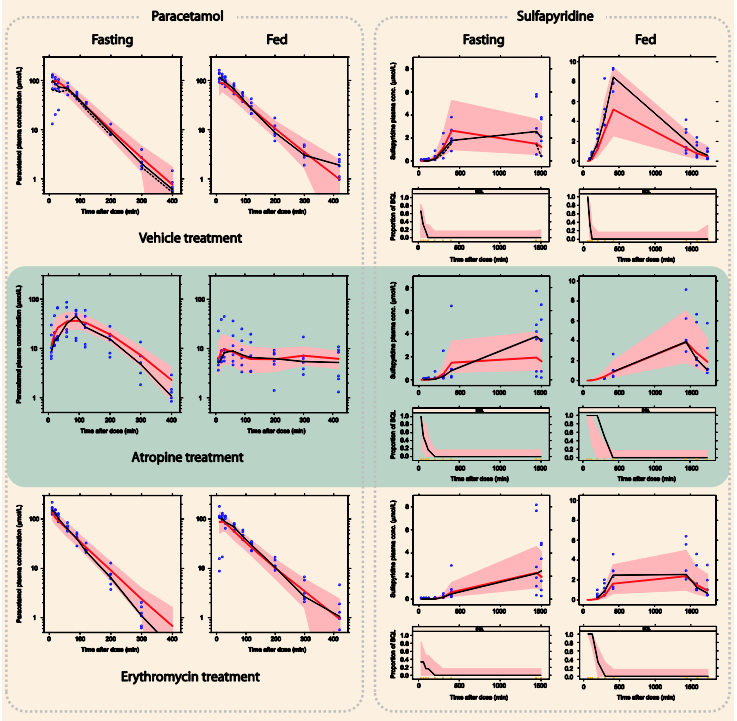

Figure 2. VPC for PCM and SP plasma concentration and BQL stratified for food and drug treatment. Observed median (—), simulated median (—) and it's 95% CI (▭) for plasma concentration of PCM (left) and top panels for SP (right). Lower panels for SP shows proportion of observed BQL (—) and a 95% CI (▭) for the simulated proportion of BQL samples ($LLOQ_{fed}$= 0.05 µmol/L, $LLOQ_{fasting}$ = 0.002 µmol/L).

Methods

- Two similar double marker studies, one with fed and one with fasting administration (6 + 6 dogs)
  - Gastric administration of PCM and Sulfasalazine
  - Three way cross-over design; atropine (0.06 mg/kg), erythromycin (1 mg/kg), and vehicle treatment
- Two dogs receiving gastric administration and i.v. infusion of PCM
- A semi-mechanistic model implemented in NONMEM VI 2.0 for simultaneous analysis of PCM and SP plasma concentration.

Conclusion

Simultaneous modelling of paracetamol and sulfapyridine can facilitate mechanistic understanding of effects on gastric emptying and small intestinal transit.

[1] Mizuta H, Kawazoe Y, Ogawa K. Gastrointestinal absorption of chlorothiazide: evaluation of a method using salicylazosulfapyridine and acetaminophen… 1990 Oct;38(10):2810-3.

[2] Smallridge RC, Chernow B, Teich S, Kinzer C, Umstott C, Geelhoed G, et al. Atropine pharmacokinetics are affected by moderate hemorrhage and hypothyroidism. Crit Care Med 1989 Dec;17(12):1254-7.

[3] Duthu GS. Interspecies correlation of the pharmacokinetics of erythromycin, oleandomycin, and tylosin. J Pharm Sci1985 Sep;74(9):943-6.