Pharmacokinetic model to simulate oral drug bioavailability of atorvastatin acid and cyclosporine post bariatric surgery

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Background
An increasing prevalence of morbid obesity has led to dramatic increases in the number of bariatric surgeries performed. Altered gastrointestinal physiology post surgery can result in modified oral drug bioavailability (Foral) depending on the surgery in question [1):

- Roux-en-Y gastric bypass (RYGB): Reduced gastric volume, partial bypass of duodenum and proximal jejunum, delayed bile inlet to distal jejunum.
- Biliopancreatic diversion with duodenal switch (BPD-DS): Partial resection of the stomach, bypass of jejunum and proximal ileum, delay in bile inlet.
- Jejunoileal bypass (JIB): Most invasive surgery, retaining only distal ileum.

In previous work a post bariatric surgery model was created utilising the Advanced Dissolution, Absorption and Metabolism (ADAM) model (Figure 1), incorporated into the Physiologically-Based Pharmacokinetic (PBPK) simulator, Simcyp®. The developed post bariatric surgery models included all known physiological alterations following RYGB, BPD-DS and JIB [2,3].

Figure 1. Schematic of the Advanced Dissolution Absorption and Metabolism (ADAM) model. Compartment size and purple colour refer to segment length and regional abundance of CYP3A4: Stomach, jejunum, ileum, form: drug trapped in formulation, undis: undissolved drug, diss: dissolved drug, ent: fraction absorbed drug in enterocytes, k, transit rate, Vb, blood flow, Foral: fraction of drug escaping GI tract metabolism, CLint, hepatic clearance, CLint, biliary clearance [2].

Methods

To evaluate previously developed bariatric surgery PBPK models for RYGB, BPD-DS and JIB and estimate the impact of bariatric surgery on Foral of:

- Cyclosporine (CsA) following RYG and JIB.
- Atorvastatin acid following RYG and BPD-DS.

Clinical data on CsA and atorvastatin acid pre to post bariatric surgery were used as a validation set for previously developed PBPK models [3-7].

Sex, age and weight of virtual studies matched those of clinical investigations.

Trials explored two scenarios for the post operative small intestinal transit (SIT) time, assuming it to be a function of (a) intestinal length or (b) reduced motility post operatively. This assessment was carried out due to conflicting clinical data and the significant impact of SIT on Foral.

- Pre- to post-surgery AUC, plasma concentration-time profiles, Foral and Fb were simulated and compared to observed data through visual predictive checks.

Results

- Cyclosporine: Roux-en-Y gastric bypass
  Simulated CsA trough levels pre to post RYGB following oral administration of Sandimmune solution (SIT=3.0h) displayed a reduction comparable to observed data. A 194% dose increase recovered pre-surgical trough levels in accordance to observed data (n=3). The simulated reduction in Foral was caused by a reduction in Fb (Figure 2). Assuming a reduced small intestinal motility post RYGB (SIT=5.0h) overpredicted the post surgical Foral [4].

- Cyclosporine: Jejunoileal bypass
  Foral of simulated CsA levels following oral administration on Neoral microemulsion pre to post JIB (SIT=0.4h) displayed a reduction in oral exposure due to an extensively reduced Fb, recovering observed data of the control group and patient within the 95% prediction interval (Figure 3). A slower SIT of 0.7h overpredicted post surgical CsA levels [5].

Atorvastatin acid: Roux-en-Y gastric bypass
Atorvastatin acid post RYG (SIT=3.0h) displayed an overall simulated median post/pre surgery AUC ratio of 1.13 (CI95: 0.27-3.80) compared to an observed AUC ratio of 1.12 (0.34-2.33) (n=10). This was due to a reduced Fb, counteracted by an increase in Fb (Figure 4). Assuming a reduced small intestinal motility (SIT=5.0h) an overprediction was evident [6].

Discussion & conclusions

Developed bariatric surgery PBPK models were able to recover observed data for CsA and atorvastatin acid post RYGB and JIB within the 95% prediction interval. In majority of the cases, a reduction in small intestinal transit as a function of bypass was the most descriptive scenario with the exception of atorvastatin acid post BPD-DS [4-7].

These findings suggest that additional physiological parameters, such as impairment in permeability or redistribution of intestinal blood flow, may play an important role in governing trends in oral drug exposure pre to immediately post BPD-DS. The findings are further supported by post BPD-DS rat models [8-10].

A mechanistic PBPK modeling approach may serve as a tool to examine the impact of physiological alterations on Foral in the absence of clinical data. The demonstrated approach may allow a framework for optimisation of oral drug therapy post bariatric surgery.

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References