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 (F_{oral}) 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].

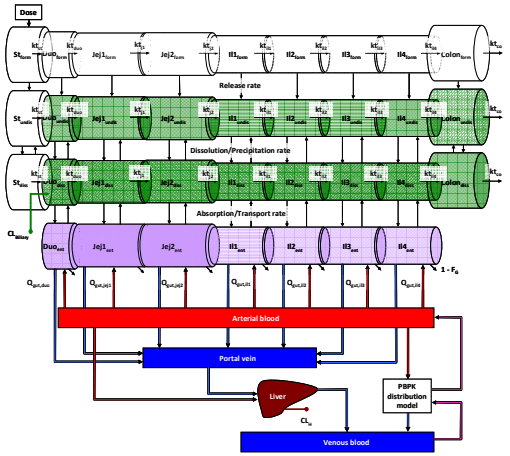

Figure 1. Schematic of the Advanced Dissolution Absorption and Metabolism (ADAM) model. Compartment size and purple colour refer to segment length and regional abundance of CYP3A. St: stomach, Jej: jejunum, Il: ileum, form: drug trapped in formulation, undiss: undissolved drug, diss: dissolved drug, ent: fraction absorbed drug in enterocytes, kt_n: transit rate, Q_n: blood flow, F_G: fraction of drug escaping gut wall metabolism, CL_H: hepatic clearance, $CL_{biliary}$: biliary clearance [2].

Aim and objectives

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

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

Methods

- 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 F_{oral}.
- Pre- to post-surgery AUC, plasma concentration-time profiles, f_a and F_G 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 F_{oral} was caused by a reduction in f_a (Figure 2). Assuming a reduced small intestinal motility post RYGB (SIT=5.0h) overpredicted the post surgical F_{oral} [4].

Cyclosporine: Jejunoileal bypass

F_{oral} 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 f_a, 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].

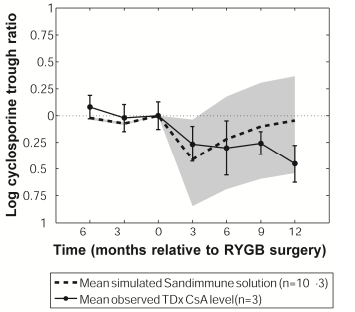

Figure 2. Mean (±standard deviation) observed and simulated cyclosporine trough levels at steady state pre to post Roux-en-Y gastric bypass [4].

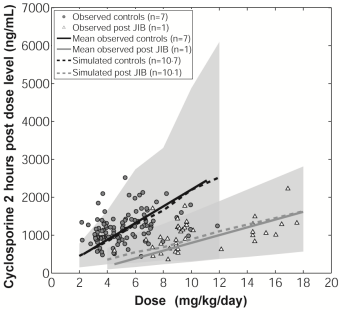

Figure 3. Observed mean blood concentration of cyclosporine microemulsion 2 hours post dosing in controls (n=7) and post jejunoileal bypass (JIB; n=1). Simulated controls and post JIB (small intestinal transit=0.7 hours) including 5, 50 and 95% prediction interval (grey) [5].

Atorvastatin acid: Roux-en-Y gastric bypass

Atorvastatin acid post RYGB (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 f_a counteracted by an increase in F_G (Figure 4). Assuming a reduced small intestinal motility (SIT=5.0h) an overprediction was evident [6].

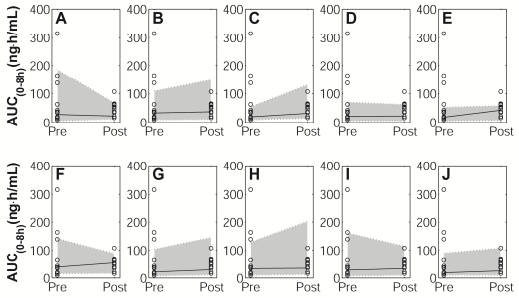

Figure 4. Simulated 95, 50 and 5% confidence interval of oral drug exposure of atorvastatin acid in randomised trials of sex, age, BMI and dose matched patients pre to post Roux-en-Y gastric bypass as compared to observed data **A-J:** Simulated 10 trials (12 subjects per trial), observed n=12 (○), [6].

Atorvastatin acid: Biliopancreatic diversion with duodenal switch

Simulated oral atorvastatin acid post BPD-DS (SIT=1.2h) failed to recover the observed 2-fold increase in AUC (n=10). Parameters able to explain the observed data in post BPD-DS exploratory sensitivity analysis included: SIT, villous blood flow and intestinal permeability (Figure 5) [7].

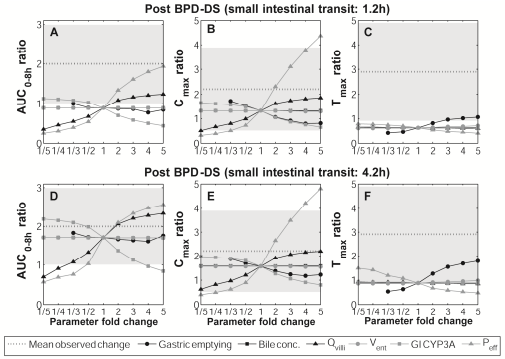

Figure 5. Simulated post/pre biliopancreatic diversion with duodenal switch (BPD-DS) AUC_{0-8h}, C_{max} and t_{max} ratio examining physiological parameters: Gastric emptying, ileal bile concentration (Bile conc.), villous blood flow (Q_{villi}), the enterocytic volume post BPD-DS (V_{ent}), Gastrointestinal CYP3A content and intestinal permeability [7].

Discussion & conclusions

Developed bariatric surgery PBPK models were able to recover observed data for CsA and atorvastatin acid post JIB and RYGB well 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 modelling approach may serve as a tool in examining the impact of physiological alterations on F_{oral} in the absence of clinical data. The demonstrated approach may allow a framework for optimisation of oral drug therapy post bariatric surgery.

Acknowledgements

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