Development and application of a mechanistic physiologically based pharmacokinetic model to assess oral drug bioavailability post bariatric surgery in morbidly obese patients

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Introduction

- Bariatric surgery, is a cost effective treatment for morbid obesity [1].
- Various types of bariatric surgery lead to changes in gastric emptying, pH, small intestinal transit (SIT), regional abundances of drug metabolising enzymes and efflux transporters [3]. Oral drug bioavailability (F_{oral}) might vary due to above physiological changes [2].
- Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion with duodenal switch (BPD-DS) lead to a reduction in gastric volume, bypass of the proximal small intestine and delayed bile inlet. The jejunoileal bypass (JIB) is limited to an extensive small intestinal bypass, whereas sleeve gastrectomy (SG) is limited to a gastric resection [3,4].
- PBPK models, such as the Advanced Dissolution Absorption Metabolism (ADAM) model incorporated into the population-based simulator Simcyp® [2], could be used to assess trends in F_{oral} post bariatric surgery (Figure 1).

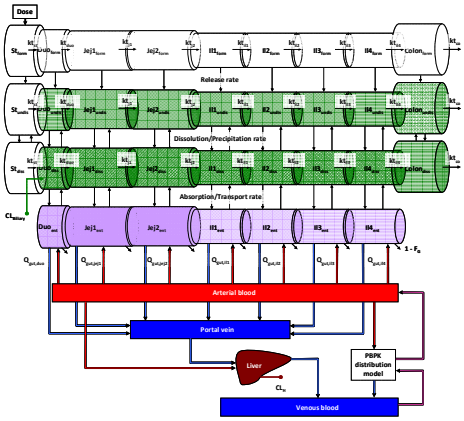

Figure 1. Schematic of the Advanced Dissolution Absorption and Metabolism (ADAM) model. Compartment size and purple colour intensity refer to segmental length and regional abundance of CYP3A4, respectively. St: stomach, Jej: jejunum, Il: ileum, form: drug trapped in formulation, undiss: undissolved drug, 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].

Objectives

- To create a model that incorporates post surgery anatomical, physiological and biological changes into a mechanistic framework (ADAM).
- To examine the impact of bariatric surgery on F_{oral} of drugs in morbidly obese (MO) patients.

Methods

- Relevant physiological parameters were implemented into the ADAM model in Simcyp® Simulator in the MO population template to mimic post RYGB, BPD-DS, JIB and SG [2,6,7].
- Drugs with potential use in bariatric surgery patients (simvastatin, omeprazole, diclofenac, fluconazole and ciprofloxacin) were simulated over therapeutic dose ranges and varying SIT.
- Post- to pre-surgery AUC, plasma concentration-time profiles, f_a and F_G were simulated and analysed.
- Two scenarios for SIT were assessed ([a] reduced time as a function of the bypass; [b] prolonged time due to reduced motility).
- Clinical data of atorvastatin acid and cyclosporine pre to post bariatric surgery were used as validation set [8,9].

Results

The simulated set of drugs displayed varied sensitivity to surgery procedures (Figure 2 A-C):

- Simvastatin immediate release (IR) displayed a post/pre surgery AUC ratio of 1.14 (±0.18) following RYGB (SIT=3.0h) at a low therapeutic dose, becoming less apparent at a higher dose, due to an increase in F_G counteracted by a reduced f_a (Figure 2A)
- Diclofenac enteric-coated (EC) post/pre surgery AUC ratio displayed a minor reduction following RYGB (SIT=3.0h) (Figure 2A).

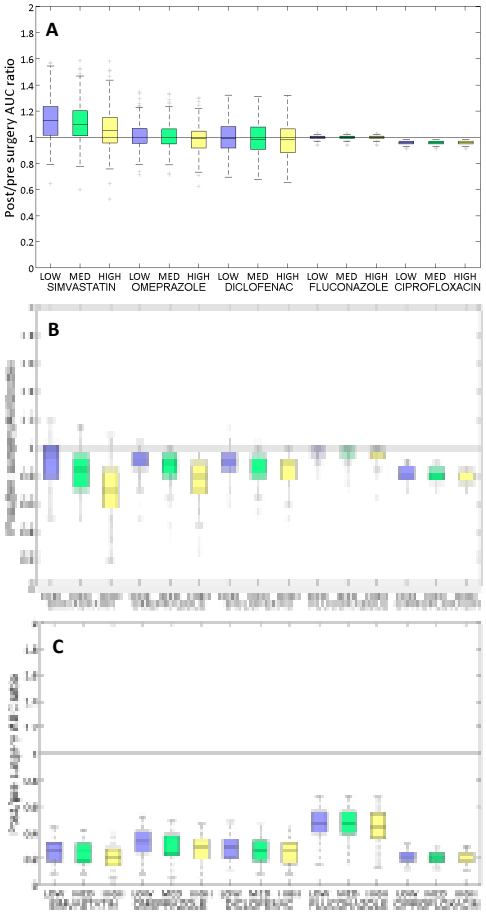

Figure 2. Simulated post/pre surgical AUC ratio following A: Roux-en-Y gastric bypass (small intestinal transit [SIT]=3.0h), B: biliopancreatic diversion with duodenal switch (SIT=2.2h), C: jejunoileal bypass (SIT=0.4h), over a range of selected drugs at a low (LOW), medium (MED) and high (HIGH) therapeutic dose: Simvastatin Immediate Release (IR), omeprazole enteric-coated (EC), diclofenac EC, fluconazole IR and ciprofloxacin IR.

- Following BPD-DS a more extensive reduction in f_a resulted in a lower AUC ratio as compared to RYGB (Figure 2B).
- Post JIB, drugs displayed an extensive reduction in AUC due to a more apparent reduction in f_a as compared to RYGB and BPD-DS (Figure 2C).
- Simulations post SG did not significantly alter the drug exposure (data not shown) [7].

- Simulated atorvastatin acid post RYGB (SIT=3.0h; n=10·10) displayed an overall median pre/post surgery AUC ratio of 1.26 (0.85-1.76) as compared to an observed AUC ratio of 1.18, due to a reduction in fa counteracted by an increase in F_G (Figure 3 A-J) [8].
- Simulated F_{oral} of cyclosporine displayed a dose dependent reduction in exposure post JIB (SIT=0.7). The concentration range observed in the control subjects were well described within the 95% confidence interval of the simulated data in this morbidly obese group (Figure 4) [9].

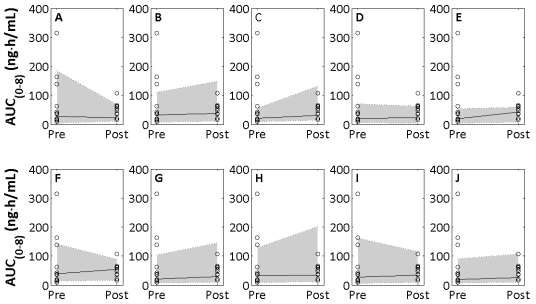

Figure 3. Simulated 95, 50 and 5% confidence interval of oral drug exposure of atorvastatin acid in randomised trials of age, sex, dose and BMI matched patients pre to post surgery as compared to observed data **A-J:** Roux-en-Y gastric bypass simulated 10 trials (12 subjects in each trial), observed n=12 (○), [6].

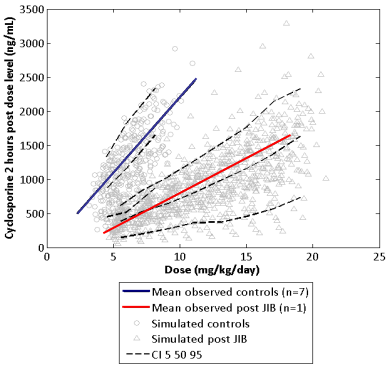

Figure 4. Observed mean plasma concentration of cyclosporine emulsion 2 h post dose 7 to 107 days administering drug twice daily (BID) in controls (n=7) and post jejunoileal bypass (JIB; n=1). Simulated sex and age matched controls (n=300) and post JIB (n=800) (small intestinal transit=0.7h) over dose range of 300 to 1,000 mg BID 2 hours post dose at 7 days including 5th, 50th and 95th confidence interval (CI 5, 50, 95) [8].

Discussion and Conclusions

- Simulating F_{oral} post bariatric surgery identified several potential pharmacokinetic parameters that influence exposure post operatively.
- Trends in F_{oral} pre to post bariatric surgery resulting in restriction of the small intestine (*i.e.* RYGB, BPD-DS and JIB), seem to be highly dependent on drug specific parameters such as affinity to CYP3A4, solubility and permeability, where the extent of these effects will be dependent on the surgery.
- Following SG alterations in pre to post surgical F_{oral} are limited to potential solubility issues. In this work we developed and demonstrated the potential of a pharmacokinetic modelling approach in the clinical application of assessing oral drug exposure post bariatric surgery.

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