Introduction

- Bariatric surgery, 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 jejunoleal 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).

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, $f_{oral}$ and $F_{oral}$ 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 data 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 $F_{oral}$ counteracted by a reduced $f_{oral}$ (Figure 2A).
  - Diclofenac enteric-coated (EC) post/pre surgery AUC ratio displayed a minor reduction following RYGB ($SIT=3.0h$) (Figure 2A).

- Following BPD-DS a more extensive reduction in $f_{oral}$ 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 $f_{oral}$ as compared to RYGB and BPD-DS (Figure 2C).
- Simulations post SG did not significantly alter the drug exposure (data not shown) [7].

Discussion and Conclusions

- 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 $f_{oral}$ counteracted by an increase in $F_{oral}$ (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].

- 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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References