Development and Application of an *In Silico* Pharmacokinetic 'Post Bariatric Surgery Model' in a Morbidly Obese Population to Assess Drug Absorption and Metabolism from the Gastrointestinal Tract

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Introduction

Bariatric surgery, involving partial restriction of the gastrointestinal (GI) tract, has proven to be clinically and cost effective for treating morbid obesity [1]. Oral drug bioavailability (BA) is dependent on physiological parameters, such as gastric emptying, pH, small intestinal transit (SITrans) and regional abundances of drug metabolising enzymes and efflux transporters [2]. These parameters are altered to differing extents following surgery. Roux-en-Y gastric bypass (RYGBP) and biliopancreatic diversion with duodenal switch (BPDDS) lead to a reduction in gastric volume, bypass of the proximal small intestine and delayed bile inlet, whereas sleeve gastrectomy (SG) [3], results in a reduced gastric volume. As a consequence of these events, altered oral drug exposure has been reported following bariatric surgery [4].

The Advanced Dissolution Absorption Metabolism (ADAM) model, incorporated into the population-based PKPD simulator Simcyp, is an *in silico* mechanistic platform for integrating *in vitro* data and predicting oral BA. The model considers all available information related to regional intestinal abundances of CYP3A and relative distribution of p-glycoprotein (P-gp) efflux transporter in addition to the segregated blood flows to each region of intestine (Figure 1) [2]. ADAM might be used to asses expected BA in various GI surgeries.

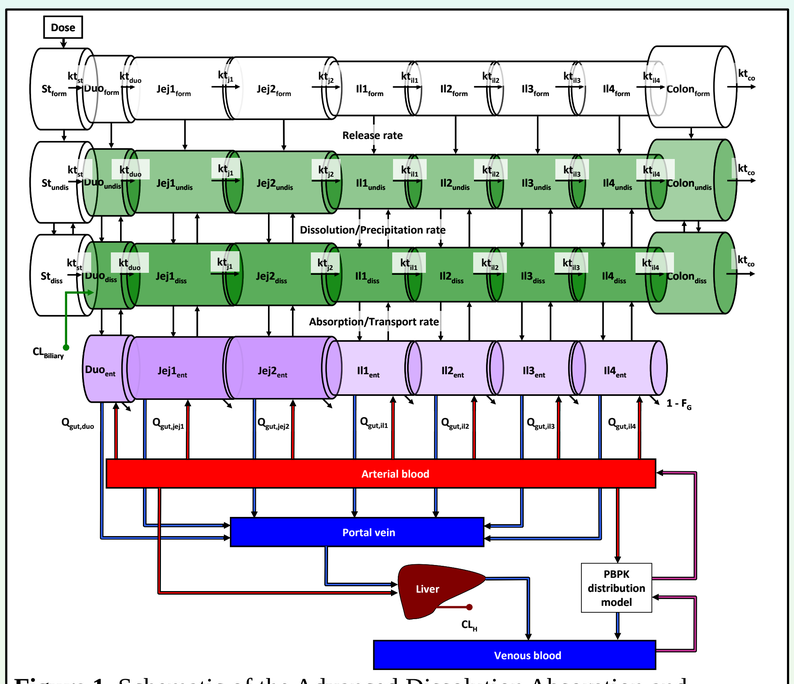

Figure 1. Schematic of the Advanced Dissolution Absorption and Metabolism (ADAM) model. Compartment size, and purple colour intensity refer to segmental length and regional abundance of CYP3A4, respectively. Other intensity schemes applied for Pgp. St: stomach, Jej: jejunum, Il: ileum, form: drug trapped 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, CLbiliary: Biliary clearance [2].

Objectives

To examine the impact of bariatric surgery on oral BA of drugs in morbidly obese patients through incorporation of post surgery anatomical, physiological and biological changes into a mechanistic modelling framework, and to assess trends in AUC, f_a (fraction of dose absorbed) and F_G (fraction escaping gut wall metabolism).

Methods

An extensive literature search was carried out to obtain anatomical, physiological and biological parameters corresponding to bariatric surgery. The ADAM model of the Simcyp Simulator (v10) was adapted to mimic the identified changes in the GI tract.

Due to conflicting literature data regarding SITrans following surgery, two scenarios were evaluated, one corresponding to a reduction in SITrans and related to the extent of bypass, and the other reflecting an increased transit time recorded following Roux-en-Y with total gastrectomy [5].

Simulations were carried out for 3 therapeutic dose levels (low, medium and high) of simvastatin [immediate release (IR)], omeprazole [enteric coated (EC)], diclofenac [EC], cyclosporine [IR], fluconazole [IR] and ciprofloxacin [IR], in 100 virtual morbidly obese, post surgical (RYGBP, BPDDS and SG) patients.

Results

Population Characteristics

The post RYGBP population template displayed a gastric emptying of 7 (±3) minutes, restricting fluid intake to 30 mL as compared to 250 mL in morbidly obese. Gastric pH was set to 6.4. The small intestinal bypass corresponded to ADAM model segment Duo and Jej1 (88 cm); whereas the bile inlet was diverted to Il2 segment (113 cm; Figure 1). Small intestinal transit was set to 2.5 and 5.0 hours [2,3,6,7].

In the post BPDDS population fluid intake was restricted to 150 mL. Segments Jej1 and 2 were bypassed (132 cm); whereas the bile inlet was diverted to Il4 (322 cm) (Figure 1). Small intestinal transit was set to 2.2 and 3.3 hours [2,3].

Further, regional abundances of CYP3A were adjusted in accordance to the small intestinal bypass, through recalculating total and regional gastrointestinal abundances [2].

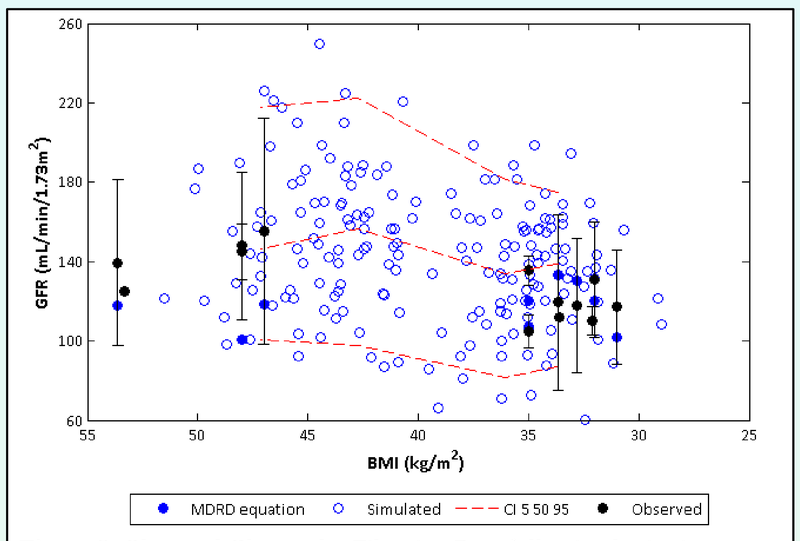

Figure 3. Observed Glomerular Filtration Rate following bariatric surgery induced weight loss, calculated and simulated GFR utilising the Modification of Diet in Renal Disease (MDRD) [9-12].

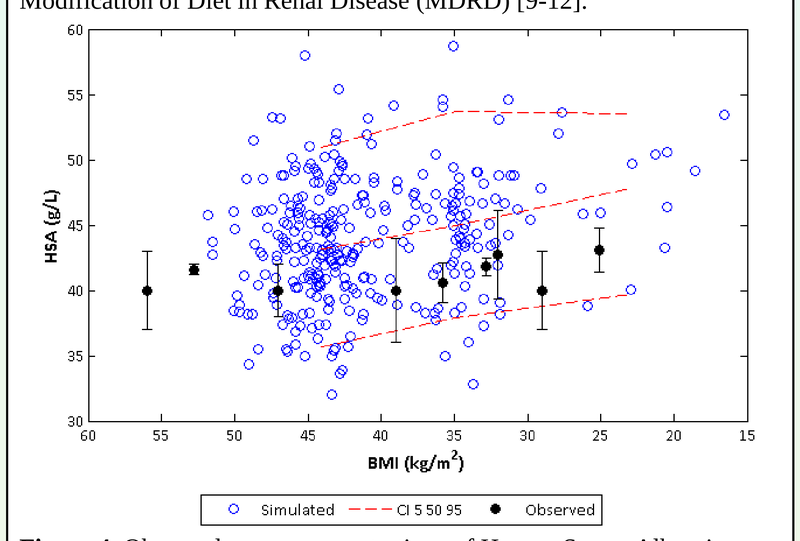

Figure 4. Observed serum concentrations of Human Serum Albumin (HSA) in morbidly obese subject to bariatric surgery induced weight loss as compared to simulated HSA levels [13-16].

The SG condition displayed a restriction of concomitant fluid intake to 80 mL and a reduction in gastric emptying time to 14 (±12) minutes; whereas gastric pH was assumed to remain unchanged [8].

Recovery of renal clearance in the post surgical populations were well described utilising Modification of Diet in Renal Disease (MDRD) equation, accounting for post surgical weight loss (Figure 3) [9-12]. Plasma protein concentrations of Human Serum Albumin (HSA) were within the 95% confidence interval of predicted levels (Figure 4) [13-16].

Simulating oral drug exposure

Following RYGBP (SIT=5h) simvastatin (low solubility, eliminated via CYP3A) [17,18] displayed an increase in AUC at a low therapeutic dose, with a mean post/pre surgery ratio of 1.18, becoming less apparent at higher dose levels, with a ratio of 1.09 at 80 mg; due to an increase in F_G by 22% counteracted by a reduction in f_a (19-31%) (Figure 5A). The increase was less apparent at a SIT of 2.5h due to a more extensive reduction in f_a.

Cyclosporine (low solubility, low permeability, metabolised by CYP3A4) [19] displayed a reduction in AUC post RYGBP, with a simulated ratio in AUC of 0.43 at low dose level further reducing to 0.35 at a high dose level due to a 56-62% reduction in f_a (Figure 5A). Assuming a reduced SIT post RYGBP, this reduction became more pronounced with an observed ratio of 0.22 at a high therapeutic dose.

The reduction in oral drug exposure of cyclosporine was more extensive following BPDDS when compared to RYGBP, displaying a post/pre surgical AUC ratio of 0.22-0.18 and 0.16-0.13 at SIT of 3.3 and 2.2 h, respectively. Due to a more extensive reduction in f_a, simvastatin displayed a reduction in AUC at higher dose levels post surgery (Figure 5B). Atorvastatin (40mg) displayed an increase in exposure (AUC: 1.77 fold) post BPDDS due to a higher F_G. Overall, SG displayed an unaltered pre to post surgery BA with the exception of cyclosporine, displaying a post/pre surgery AUC ratio of 0.89 (±0.37) at a low therapeutic dose, becoming more apparent at higher dose levels due to a reduction in f_a (Figure 5C). Bariatric surgery had a limited impact on the oral BA of the remainder of studied drugs (Figure 5A-C).

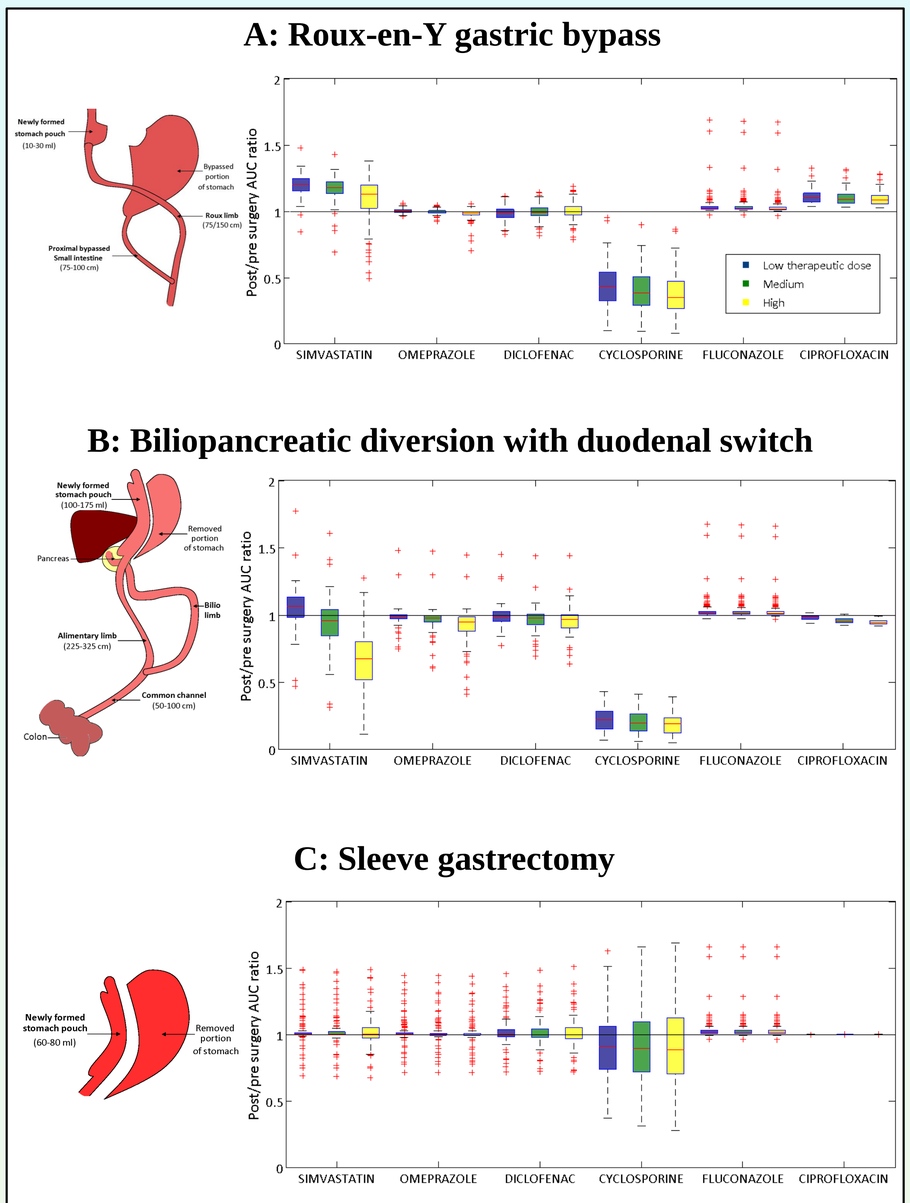

Figure 5. Schematics of surgical procedures and median and inter-quartiles of post/pre surgery AUC ratio of a set of drugs at low, medium and high therapeutic dose, following **A:** RYGBP SIT 5h, **B:** BPDDS SIT 3.3h and **C:** SG, of simvastatin IR at 10, 20 and 80 mg; omeprazole EC 10, 20 and 40 mg; diclofenac EC 25, 50 and 75 mg; cyclosporine IR 1 mg·kg^{-1}, 2.125 mg·kg^{-1} and 7.5 mg·kg^{-1}; fluconazole IR 50, 200 and 400 mg and ciprofloxacin IR 250, 500 and 750 mg.

Discussion and Conclusions

Simvastatin displayed the most significant increase in BA, due to reduced exposure to intestinal CYP3A; whereas cyclosporine showed the most extensive reduction in BA following surgery, as a possible consequence of delayed bile inlet [20]. The latter was consistent with a reported reduction in AUC following jejuno-ileal bypass [21]. The results provide insight into factors influencing the BA of each drug following surgery (solubility, reduced absorptive area, time for absorption and altered gut wall metabolism). The impact of each of these factors is specific to each type of surgery. Hence, the consequential change in BA is a complex interplay between drug characteristics and modifications to the GI tract in each surgery. ADAM may be an ideal tool to estimate these in the absence of clinical data.

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References

[1] Picot, J., *et al. Health technol Assess* 13 (2009)
[2] Jamei, M., *et al. AAPS J.* 11:225-237 (2009)
[3] Wittgrove, A.C., *et al. Obes Surg* 10:233-239 (2003)
[4] Padwal, R., *et al. Obes Rev* 11:41-50
[5] Pellegrini, C.A., *et al. Am J Surg* 151:117-125 (1986)
[6] Horowitz, M., *et al. Br J Surg* 69:655-657 (1982)
[7] Smith, C.D., *et al. Ann Surg* 218:91-96 (1993)
[8] Braghetto, I., *et al. Obes Surg* 19:1515-1521 (2009)
[9] Chagnac, A., *et al. J Am Soc Nephrol* 14: 1480-1486 (2003)
[10] Navarro-Diaz, M., *et al. J Am Soc Nephrol* 17:S213-217 (2006)
[11] Saliba, J., *et al. Surgery* 147:282-287
[12] Serra, A., *et al. Clin Nutr* 25:400-408 (2006)
[13] Barker, K.B., *et al. Am J Gastroenterol* 101:368-373 (2006)
[14] Benedek, I.H., *et al. Br J Pharmacol* 18:941-964 (1984)
[15] Mattar, S.G., *et al. Ann Surg* 242:610-617 (2005)
[16] Stratapoulos, C., *et al. Obes Surg* 15:1154-1160 (2005)
[17] Lennernäs and Fager. *Pharmacokinet* 32:403-425 (1997)
[18] Prueksaritanont, T., *et al. Drug Metab Dispos* 25:1191-1199 (1997)
[19] Wojcikowski, J., *et al. Br J Pharmacol* 138:1465-1474 (2003)
[20] Mehta, M.U., et al. Br J Clin Pharmacol 25:579-584 (1988)
[21] Chenhsu, R.Y., *et al. Ther Drug Monit* 25:665-670 (2003)