Oral Drug Dosing After Gastric Bypass and Diet-Induced Weight Loss: Simpler Than We Think? Lessons Learned From the COCKTAIL Study

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This article summarizes the lessons learned from the COCKTAIL study: an open, three-armed, single-center study including patients with obesity scheduled for treatment with Roux-en-Y gastric bypass (RYGB) or nonsurgical calorie restriction, and a normal- to overweight control group. The clinical implications of the results from multiple peer-reviewed articles describing the effects of RYGB, severe caloric restriction, weight loss, and type 2 diabetes on the *in vivo* activity and protein expression of drug-metabolizing enzymes (cytochrome P450 (CYP) 1A2, 2C9, 2C19, and 3A) and transporters (DMETs; organic anion-transporting polypeptide (OATP) 1B1 and P-glycoprotein (P-gp)) are discussed in the perspective of three clinically relevant questions: (1) How should clinicians get the dose right in patients after RYGB? (2) Will drug disposition in patients with obesity be normalized after successful weight loss? (3) Are dose adjustments needed according to obesity and diabetes status? Overall, RYGB seems to have a lower impact on drug disposition than previously assumed, but clinicians should pay close attention to drugs with a narrow therapeutic range or where a high maximum drug concentration may be problematic. Whether obesity-related alterations of DMETs normalize with substantial weight loss depends on the DMET in question. Obesity and diabetes downregulate the *in vivo* activity of CYP2C19 and CYP3A (only obesity) but whether substrate drugs should be dose adjusted is also dependent on other factors that influence clearance, that is, liver blood flow and protein binding. Finally, we recommend frequent and individualized follow-up due to high inter- and intraindividual variability in these patients, particularly following RYGB.

Bariatric surgery is established as the most effective treatment for severe obesity, offering superior long-term weight loss and improvement in comorbidities compared with nonsurgical treatment.[1] Due to the growing body of evidence showing that bariatric surgery also leads to improvement or remission of metabolic complications such as type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD),[2–5] the American Society for Metabolic and Bariatric Surgery (ASMBS) and the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) have moved away from the exclusive reliance on body mass index (BMI) and recently updated their indications for surgery to include a larger cohort of patients.[6] With the growing population of patients subjected to bariatric surgery, clinicians will increasingly be confronted with questions on how to manage oral drug dosing in these patients. However, many questions regarding pharmacokinetic changes after bariatric surgery remain unanswered.

The two most commonly performed bariatric procedures worldwide are sleeve gastrectomy (50%) followed by Roux-en-Y gastric bypass (RYGB) (37%).[7] While both procedures reduce the volume of the stomach (restrictive), RYGB also bypasses a significant part of the proximal intestine leading to reduced intestinal absorptive surface area (malabsorptive).[8] The anatomical and physiological alterations in the gastrointestinal (GI) tract following bariatric surgery in general, and RYGB in particular, may change various factors influencing the oral bioavailability of drugs.[9] Prediction of pharmacokinetic changes after RYGB are further complicated by the fact that the subsequent weight loss and thereby improvement in comorbidities may also influence the activity and expression of drug-metabolizing enzymes and -transporters (DMETs). A major

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Received January 31, 2024; accepted May 2, 2024. doi:10.1002/cpt.3307

limitation of previous studies is their inability to disentangle the surgical effects from the weight loss effect.[10,11]

To investigate if pharmacokinetic changes after RYGB are attributed to the surgery-induced anatomical changes *per se* or the subsequent weight loss, we designed the COCKTAIL study, an open, three-armed, single-center study including patients with severe obesity scheduled for treatment with RYGB or nonsurgical calorie restriction based on clinical indications, as well as a normal- to overweight control group scheduled for cholecystectomy (**Figure 1**).[12] To the best of our knowledge, this is the first pharmacokinetic study to include a dietary control group undergoing a similar severe caloric restriction (< 800 kcal/day) to induce a matched short-term (6 weeks; week 3–9) weight loss, as compared with an RYGB group. This enabled us to disentangle the effect of surgery from that of weight loss on the pharmacokinetics of a cocktail of probe drugs consisting of caffeine (cytochrome P450 (CYP) 1A2), losartan (CYP2C9), omeprazole (CYP2C19), midazolam (CYP3A), rosuvastatin (organic anion-transporting polypeptide (OATP) 1B1), and digoxin (P-glycoprotein (P-gp)). Another strength of the COCKTAIL study is that we were able to obtain paired tissue biopsies from the liver and intestine in patients undergoing RYGB, as well as liver biopsies in individuals undergoing cholecystectomy for microsome- and proteomics analyses. This allowed us to compare the *in vivo* activities of key DMETs with their respective *ex vivo* activities and protein concentrations. The study design also included a stratification based on T2DM status in the patients with obesity. In combination with data on genotype, a large patient cohort ($n = 108$), a long follow-up time of 2 years, and rich pharmacokinetic data, this formed the foundation for a comprehensive investigation that has resulted in multiple peer-reviewed publications. In this article, we describe and discuss the main results of the COCKTAIL study, focusing on the short-term and long-term effect of low-energy diet and RYGB as well as obesity and T2DM on key DMETs and their impact on drug dosing.[13–17]

STUDY DESIGN

The full details of the study have been described previously.[12,13] In short, patients aged 18 years and above with BMI ≥ 18.5 kg/m^2 scheduled for treatment with RYGB ($n = 44$), nonsurgical calorie restriction ($n = 44$), or cholecystectomy ($n = 20$) were eligible for inclusion. The pharmacokinetic cocktail investigation took place on four different occasions, at week 0, 3 (at which the RYGB group was subjected to surgery), 9, and year 2 (**Figure 1**). The drug cocktail administered at these in-depth pharmacokinetic investigations consisted of caffeine (100 mg, oral), losartan (25 mg, oral), omeprazole (20 mg, oral), midazolam (semi-simultaneous 1.5 mg oral, 1.0 mg intravenous), rosuvastatin (20 mg, oral), and digoxin (0.5 mg, oral) as measures of CYP1A2, CYP2C9, CYP2C19, CYP3A, OATP1B1, and P-gp phenotypes. The biopsies for omics analyses, including hepatic ($n = 38$) and jejunal ($n = 37$) biopsies from RYGB patients, as well as hepatic biopsies ($n = 18$) from cholecystectomy patients, were obtained on the day of surgery as previously described.[18] The RYGB- and diet groups were prescribed a low-energy diet (LED; < 1,200 kcal/day) the first 3 weeks of the study, followed by 6 weeks of a very-low-energy diet (VLED; < 800 kcal/day) or RYGB (< 800 kcal/day). The main objective was to compare the short-term (6 weeks) and long-term (2 years) effects of RYGB and nonsurgical calorie restriction on the pharmacokinetics of the six probe drugs. The primary outcomes were changes in all six probe drugs by absolute bioavailability and clearance for midazolam (CYP3A), area under the curve (AUC) for digoxin (P-gp), oral clearance for rosuvastatin (OATP1B1), metabolite to parent compound ratio for caffeine (CYP1A2) and omeprazole (CYP2C19), and parent compound to metabolite ratio for losartan (CYP2C9), as well as changes in the endogenous biomarker 4ß-hydroxycholesterol (4ßOHC) (CYP3A).

What were the main findings of the COCKTAIL study?

A summary of the *in vivo* activity of key DMETs according to obesity and diabetes status is presented in **Table 1**. Patients with obesity (mean BMI 43 ± 6 kg/m^2) demonstrated 63% lower

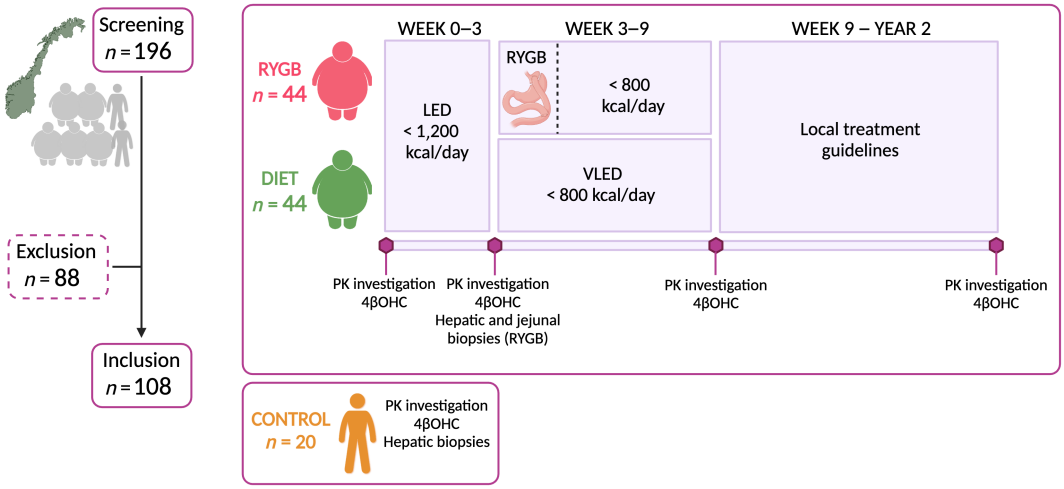

Figure 1 Study design of the COCKTAIL study. Re-used from[24] with permission from the author. Created with BioRender.com. 4βOHC, 4β-hydroxycholesterol; LED, low-energy diet; PK, pharmacokinetic; RYGB, Roux-en-Y gastric bypass; VLED, very-low-energy diet.

Table 1 Summary of the *in vivo* activity of key drug-metabolizing enzymes and transporters in patients with obesity, and in patients with obesity and T2DM

	Obesity vs. Controls[a]	Obesity and T2DM vs. obesity only[b]
	n = 29	*n* = 53
CYP1A2 activity (paraxanthine/caffeine)	↔	↔
CYP2C9 activity (losartan/losartan carboxylic acid)	↔	↔
CYP2C19 activity (5-hydroxyomeprazole/omeprazole)	↓ (−63%)	↓ (−63%)
CYP3A activity (midazolam absolute bioavailability)	↓ (153%)	↔
CYP3A activity (midazolam clearance)	↑ (46%)	↔
CYP3A4 activity (4ßOHC)	↓ (−44%)	↔
OATP1B1 activity (CL/F)	↔	ND
P-gp activity ($AUC_{0-\infty}$)	↑ (−26%)	ND

Statistically significant differences are illustrated as ↑ (higher) or ↓ (lower) (mean difference, percentage).
$AUC_{0-\infty}$, area under the concentration–time curve from zero to infinity; CYP, cytochrome P450; ND, not determined; OATP1B1, organic anion-transporting polypeptide 1B1; P-gp, p-glycoprotein; T2DM, type 2 diabetes mellitus; 4ßOHC, 4-beta hydroxycholesterol.
[a]Patients with obesity with and without T2DM (RYGB + diet group) compared with normal- to overweight individuals scheduled for cholecystectomy at baseline (controls) (week 0). [b]Patients with obesity and T2DM compared with patients with obesity only. Both patients with obesity and T2DM and patients with obesity only had undergone a 3-week LED before the study investigation.

in vivo CYP2C19 activity than the normal- to overweight controls (mean BMI 25 ± 3 kg/m^2) (**Table 1**).[14] When comparing patients with obesity and T2DM with patients with obesity only, we also demonstrated that *in vivo* CYP2C19 activity was less than half the respective *in vivo* CYP2C19 activity in patients with obesity only (**Table 1**).[17] For CYP3A, we observed a higher absolute bioavailability of midazolam (threefold) in the patients with obesity than the normal- to overweight controls, suggesting a lower intestinal and/or hepatic *in vivo* CYP3A activity. Surprisingly, patients with obesity had higher clearance of midazolam (~50%; suggesting a higher hepatic *in vivo* CYP3A activity) but lower levels of 4ßOHC (44%; suggesting a lower hepatic *in vivo* CYP3A activity) than the normal- to overweight controls.[13] Considering our finding of lower hepatic CYP3A4 protein concentrations with increasing BMI ($R = -0.35$, $P = 0.0091$), and that patients with obesity have higher hepatic blood flow,[19] we speculate that this discrepancy may be attributed to the fact that midazolam is a medium to high extraction ratio drug leaving patients with obesity with higher midazolam clearance than normal weight individuals despite that hepatic *in vivo* CYP3A activity and expression seem to be lower. T2DM did not influence any of the investigated CYP3A metrics.[17] Neither obesity nor T2DM influenced *in vivo* CYP1A2 and CYP2C9 activities. With regards to the drug transporters, *in vivo* P-gp activity was slightly higher (26% lower AUC) in the patients with obesity compared with the normal- to overweight controls (**Table 1**).[15] The patients with obesity also had slightly higher protein expression of hepatic P-gp (29%). There was no difference in *in vivo* OATP1B1 activity between patients with obesity and normal- to overweight controls.[16]

Table 2 contains a summary of changes in the *in vivo* activity of key DMETs after a preoperative LED and RYGB or nonsurgical calorie restriction. Overall, the pharmacokinetic changes that we observed for the six probe drugs administered in the COCKTAIL study in the early phase after RYGB (6 weeks) were significantly lower than what we expected.[13–16] Particularly surprising was the fact that the absolute bioavailability of midazolam (CYP3A probe drug) was unaltered shortly after RYGB (**Table 2**). This was unexpected since the proximal part of the intestine rich in CYP3A enzymes is bypassed, placing drugs directly into a more distal part with lower metabolic capacity.[13] This may suggest that the body adapts quickly to GI alterations following RYGB. At year 2, there was a moderate increase in *in vivo* CYP3A activity (shown by a decreased midazolam absolute bioavailability (−36%) and increased levels of 4ßOHC (57%)) (**Table 2**), suggesting that with substantial weight loss and sufficient time, the downregulated CYP3A activity in patients with obesity seems to recover. Midazolam clearance was unaltered throughout the study. The only probe drug where a clinically meaningful change was observed in the early phase of the study was omeprazole (CYP2C19). The *in vivo* activity increased by nearly 50% after the LED (week 0–3) in both the RYGB- and diet group, suggesting that calorie restriction (< 1,200 kcal/day) and/or a moderate weight loss (~5%) has a significant impact on CYP2C19.[14] In the RYGB group, an additional increase of 30% was observed 6 weeks post-surgery (week 3–9), while no change was observed in the diet group (**Table 2**). This suggests that RYGB may have an additional effect on CYP2C19, given that the two groups in our study had a comparable weight loss from weeks 3–9 (~7–9%). Overall, the main contributing factor leading to changes *in vivo* CYP2C19 activity seems to be an initial moderate weight loss of about 5%, which is further amplified by the surgical alterations *per se*, but not the additional weight loss. This notion was supported by the fact that regained body weight, as observed in the diet group from week 9 to year 2, resulted in a moderate reversal of the short-term increase *in vivo* CYP2C19 activity (**Table 2**). For CYP1A2, CYP2C9, OATP1B1, and P-gp, we did observe some statistically significant changes during the study period; however, the magnitude of these changes was not considered to be clinically meaningful, suggesting that these isoforms are less susceptible to be influenced by RYGB or nonsurgical weight loss.[14–16] A faster absorption post-RYGB, both short-term and long-term, was observed for all the probe drugs for which we had rich pharmacokinetic data (midazolam, digoxin, and rosuvastatin).[13,15,16]

CLINICAL IMPLICATIONS OF FINDINGS IN THE COCKTAIL STUDY

How should clinicians get the dose right in patients subjected to RYGB?

Although bariatric surgery has several beneficial effects on weight-related comorbidities, most patients who undergo these

Table 2 Summary of changes in the *in vivo* activity of key drug-metabolizing enzymes and transporters after a preoperative low-energy diet and RYGB or nonsurgical calorie restriction (LED + VLED)

	RYGB			Diet		
	Week 0–3	Week 3–9[a]	Week 9–Year 2	Week 0–3[a]	Week 3–9	Week 9–Year 2
	LED (< 1,200 kcal/day)	RYGB (< 800 kcal/day)	Local treatment guidelines	LED (< 1,200 kcal/day)	VLED (< 800 kcal/day)	Local treatment guidelines
Weight change	−5%	−13%	−20%	−5%	−11%	+9%
CYP1A2 activity (paraxanthine/caffeine)	↔	↔	↑ (19%)	↔	↔	↔
CYP2C19 activity (5-hydroxyomeprazole/omeprazole)	↑ (43%)	↑ (30%)	↔	↑ (48%)	↔	↓ (−36%)
CYP2C9 activity (losartan/losartan carboxylic acid)	↑ (−24%)[b]	↔	↔	↔	↔	↔
CYP3A activity (midazolam absolute bioavailability)	↔	↔	↑ (−36%)	↔	↔	↔
CYP3A activity (midazolam clearance)	↔	↔	↔	↔	↔	↔
CYP3A4 activity (4ßOHC)	↔	↔	↑ (57%)	↔	↔	↔
OATP1B1 activity (rosuvastatin CL/F)	↓ (−16%)	↔	↑ (57%)	↓ (−23%)	↔	↔
P-gp activity (digoxin $AUC_{0-\infty}$)	↔	↔	↔	↑ (14%)	↔	↔

Statistically significant changes are illustrated as ↑ (increase) or ↓ (decrease) (mean change, percentage).
$AUC_{0-\infty}$, area under the concentration–time curve from zero to infinity; CYP, cytochrome P450; DMET, drug-metabolizing enzyme or transporter; LED, low-energy diet; ND, not determined; OATP1B1, organic anion-transporting polypeptide 1B1; P-gp, p-glycoprotein; RYGB, Roux-en-Y gastric bypass; SD, standard deviation; VLED, very low-energy diet; 4ßOHC, 4-beta hydroxycholesterol.
[a]Six weeks post-surgery. [b]The RYGB group had higher CYP2C9 *in vivo* activity than the diet group at baseline. Logically, it should be comparable with the DIET group. We do not have an explanation for this, but the effect diminished after the LED as CYP2C9 *in vivo* activity decreased significantly in the RYGB group from weeks 0 to 3, while it remained unchanged in the diet group.

procedures also require pharmacological treatment after surgery. The lack of clarity regarding appropriate drug dosing adjustments of oral drugs after bariatric surgery has therefore been a long-time concern among clinicians. It is generally accepted that RYGB leads to an increased absorption rate of orally administered drugs, meaning that the time to maximum concentration (T_{max}) is reduced.[9,20] Maximum concentration (C_{max}) has been shown to both increase and decrease depending on the drug.[9] In the case of higher C_{max}, this may be of clinical importance for some drugs, such as drugs with a narrow therapeutic range and where high peak concentrations are associated with side effects (e.g. lithium, phenytoin, tacrolimus, digoxin, lamotrigine, and opioids). However, for the most part, it seems like the changes in the absorption rate do not cause any major changes to the systemic exposure of orally administered drugs. The findings from the COCKTAIL study demonstrated negligible or minor changes in the activities of CYP1A2, CYP2C9, CYP3A, OATP1B1, and P-gp shortly after surgery, suggesting that orally administered drugs with clearance primarily dependent on these DMETs can be dosed as before surgery. The short-term rapid increase in CYP2C19 *in vivo* activity induced by a 3-week LED and RYGB may be relevant for dosing of drugs where clearance mainly depends on this isoform (such as omeprazole, pantoprazole, clopidogrel, proguanil, diazepam, escitalopram, and amitriptyline). Another point worth noting is that drug disposition may also slowly change with time (and weight loss) after RYGB, as we observed for some of the probe drugs. Oral drug dosing after bariatric surgery is further complicated by considerable variability in drug disposition between patients, but also within patients. A large interindividual variability was observed for all the probe drugs in the COCKTAIL study. Overall, it seems that for many drugs dose adjustments are not necessary, but patients should be monitored more closely with regards to side effects or therapeutic failure.

May drug disposition in patients living with obesity be normalized after successful weight loss?

It is still uncertain if an individual with obesity who normalizes his/her body weight will attain drug disposition features comparable with a normal weight person with no obesity history. In the COCKTAIL study, patients subjected to RYGB demonstrated a total mean weight loss of ~30% at year 2, but the majority of patients were still in the obesity category (mean BMI: 31 ± 5 kg/m^2). Even though patients in our study did not lose enough

weight to answer this question, we still made some interesting findings. When comparing the patients with obesity and the normal- to overweight controls at baseline, we found that *in vivo* P-gp activity was slightly higher (26% lower AUC) in the obesity group. Surprisingly, *in vivo* P-gp activity remained unaltered 2 years after RYGB, despite the considerable weight loss.[15] This is in contrast to what we observed for CYP2C19 and CYP3A. The *in vivo* activity of these isoforms was downregulated in patients with obesity.[13,14] While *in vivo* CYP2C19 activity increased rapidly with weight loss and also reverted with regained body weight, CYP3A took a longer time to recover. These findings suggest that whether obesity-related alterations of DMETs will normalize after successful weight loss depends on the DMET in question. Further, a normalization of body weight may lead to changes in the liver blood flow (and fraction unbound, f_u) which may influence drug disposition depending on the extraction ratio and physicochemical properties of the drug in question.

Are dose adjustments needed according to obesity and diabetes status?

Whether DMETs are altered in patients with metabolic conditions depends on the CYP isoform or drug transporter in question. Clinicians may want to pay additional attention to how patients with obesity respond to drugs primarily dependent on clearance via CYP2C19 (such as clopidogrel or escitalopram) and CYP3A (such as many statins) to ensure optimal effect, depending on the extraction ratio of the drug, given that the activity of these isoforms are downregulated in patients with obesity. Interestingly, the presence of T2DM seems to downregulate *in vivo* CYP2C19 activity beyond that of obesity. Patients with obesity and T2DM may therefore have a higher risk for side effects (active drug) or treatment failure (prodrug) when drugs primarily dependent on clearance mediated by CYP2C19 are prescribed. Most patients with T2DM in the COCKTAIL study had good metabolic control (mean glycated hemoglobin; 50 mmol/mol (6.7%)). As such, we cannot exclude that the effect on CYP2C19 may be different in patients with poorly controlled T2DM. Clinicians are therefore advised to follow-up with these patients more closely and adjust the dose depending on the drug response. The higher P-gp activity in patients with obesity may also be relevant for dosing of some P-gp substrates. Metabolic conditions did not seem to have any impact on the *in vivo* activity of CYP1A2, CYP2C9, and OATP1B1, meaning that no special precautions are needed when drugs with clearance primarily dependent on these DMETs are prescribed.

METHODOLOGICAL CONSIDERATIONS

Probe drugs for phenotyping: Current challenges and future landscape

Phenotyping using exogenous probe drugs is the standard approach to determine the *in vivo* activity of DMETs. However, this approach has some challenges that should be addressed. The pharmacokinetics of probe drugs is usually not only dependent on the metabolic/transporter capacity, but also on other processes such as protein binding and blood flow to the eliminating organ. This was demonstrated for midazolam in the COCKTAIL study. Neither hepatic CYP3A4 protein expression and *in vivo* midazolam clearance nor hepatic microsomal CYP3A4 activity and *in vivo* midazolam clearance correlated.[13,21] Similarly, there was no correlation between *in vivo* midazolam clearance and the endogenous CYP3A4 biomarker 4ßOHC. We speculated that this discrepancy may be explained by the fact that midazolam is a medium- to high extraction ratio drug,[22] meaning that clearance also is dependent on hepatic blood flow which is higher in patients with obesity. This illustrates how disease states or physiological alterations during an intervention may influence the pharmacokinetics of probe drugs in clinical studies. Another interesting finding was that both hepatic CYP3A4 protein expression and hepatic microsomal CYP3A4 activity correlated with 4ßOHC, suggesting that 4ßOHC may be a valuable biomarker for *in vivo* hepatic CYP3A4 activity.[21] Based on our experience from the COCKTAIL study, we suggest that future studies should consider implementing endogenous biomarkers such as 4ßOHC and methodology to assess changes in physiology, for example, hepatic blood flow, in phenotyping studies using exogenous probe drugs, given that they may give complementary information that is valuable for correct interpretation of the results.

Other limitations

The COCKTAIL study has limitations that should be addressed. First, we were not able to obtain rich pharmacokinetic data for all six probe drugs due to cost and logistical constraints, and as a result, we did not have detailed pharmacokinetic information for caffeine, losartan, and omeprazole. CYP1A2-, CYP2C9-, and CYP2C19 activities were therefore determined using a single timepoint metabolic ratio with carefully selected timepoints, meaning that differences in the absorption may have influenced the metabolic ratios. However, assuming that CYP protein expression corresponds to CYP activity, the data on hepatic protein concentrations of CYP1A2, CYP2C9, and CYP2C19 supported that the metabolic ratios to a large extent reflected the *in vivo* activities of CYP1A2, CYP2C9, and CYP2C19 in this study. Second, a cocktail approach increases the risk of drug–drug interactions. The potential for any interaction between the probe drugs was investigated thoroughly when designing this study, but only parts of the probe cocktail have been properly validated.[23] Another limitation is the fact that differences in substrate specificity, extraction ratio, and physicochemical properties between the probe drugs and other drugs make it challenging to extrapolate the results. Furthermore, the COCKTAIL study only included patients subjected to bariatric surgery by RYGB. The findings in this study may therefore not be generalizable to other bariatric procedures.

CONCLUSION

Based on our experience from the COCKTAIL study, it seems that RYGB has a much lower impact on drug disposition than previously assumed for the investigated probe drugs. Overall, the faster absorption of oral drugs that is observed after surgery does not seem to influence the systemic exposure of drugs to any clinically meaningful degree. The take-home message from the COCKTAIL study is therefore that for most drugs where clearance is mainly dependent on CYP1A2, CYP2C9, CYP3A,

OATP1B1, and P-gp, dose adjustment is likely not necessary in the early phase after RYGB. However, clinicians should be cautious when prescribing drugs with a narrow therapeutic range or where a high peak (C_{max}) is undesired. They should also pay more closer attention to how these patients respond to drugs that are CYP2C19 and CYP3A substrates, given that the *in vivo* activity and/or expression of these isoforms are dependent on body weight, and diabetes status for CYP2C19. Another aspect to take into consideration is that patients with obesity have higher hepatic blood flow, which may compensate for the downregulated enzyme activity and lead to an overall higher clearance of intermediate- to high extraction ratio drugs such as we observed for midazolam. Overall, there is both a high interindividual- and intraindividual variability in drug response in patients subjected to RYGB. The general recommendation to clinicians is therefore to follow-up with patients frequently and adjust their treatment based on their drug response.

ACKNOWLEDGMENTS

First, we will thank all patients who participated in the COCKTAIL study. We would also like to thank the coauthors of the previously published articles; Veronica Krogstad, Christine Wegler, Marianne K. Kringen, Jens K. Hertel, Maria Heijer, Eva Skovlund, Tommy B. Andersson, Philip Carlo Angeles, Birgit M. Wollmann, Kristine Hole, Espen Molden, and Per Artursson. Last but not least, we thank the dedicated personnel at Vestfold Hospital Trust and the University of Oslo who contributed to recruitment, retention, monitoring, investigational procedures, and patient follow-up in the COCKTAIL study.

FUNDING

Vestfold Hospital Trust, Norway, Department of Pharmacy, University of Oslo, Norway, and AstraZeneca, Sweden founded and funded the COCKTAIL study. The authors prepared this article without any funding.

CONFLICT OF INTEREST

Rasmus Jansson-Löfmark, Shalini Andersson, and Cecilia Karlsson are AstraZeneca employees and own shares in AstraZeneca. Kine Eide Kvitne, Markus Hovd, Jøran Hjelmesæth, Rune Sandbu, Line Kristin Johnson, Hege Christensen, Anders Åsberg, and Ida Robertsen declared no competing interests for this work.

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