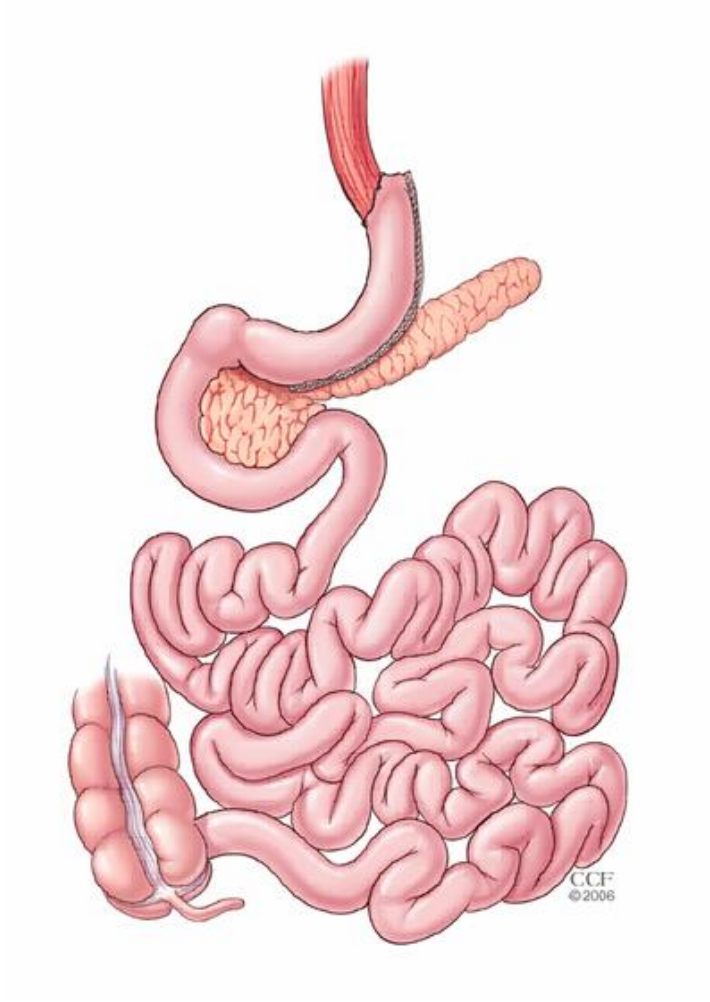
Geneesmiddelen en bariatrische chirurgie

Jurjen Kingma

AIOS ziekenhuisfarmacie

ST ANTONIUS
een santeon ziekenhuis


CCF
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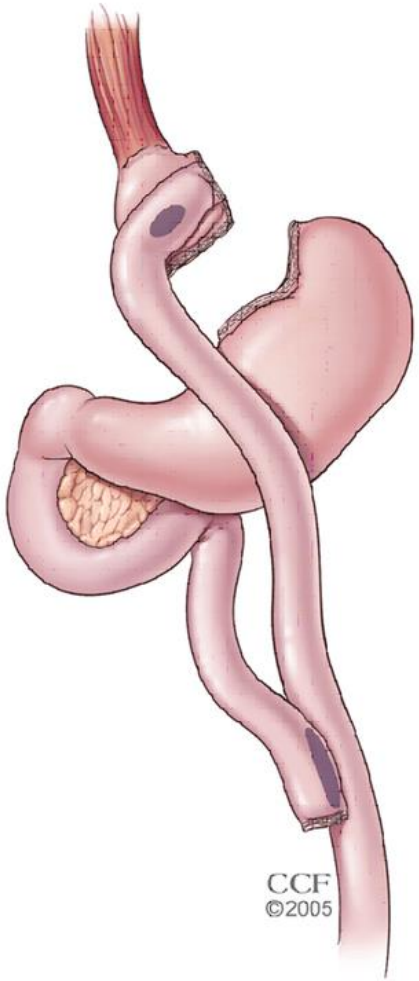
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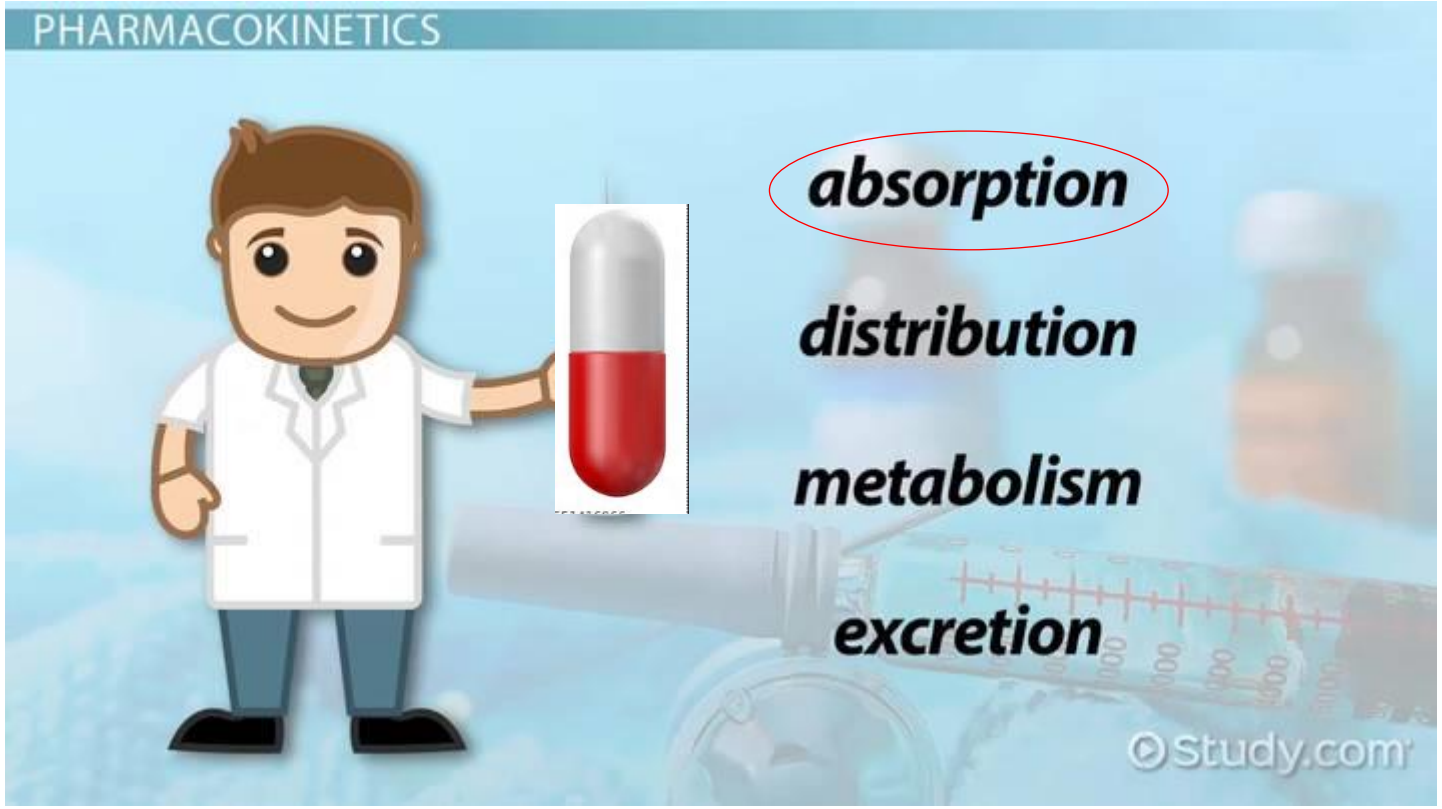
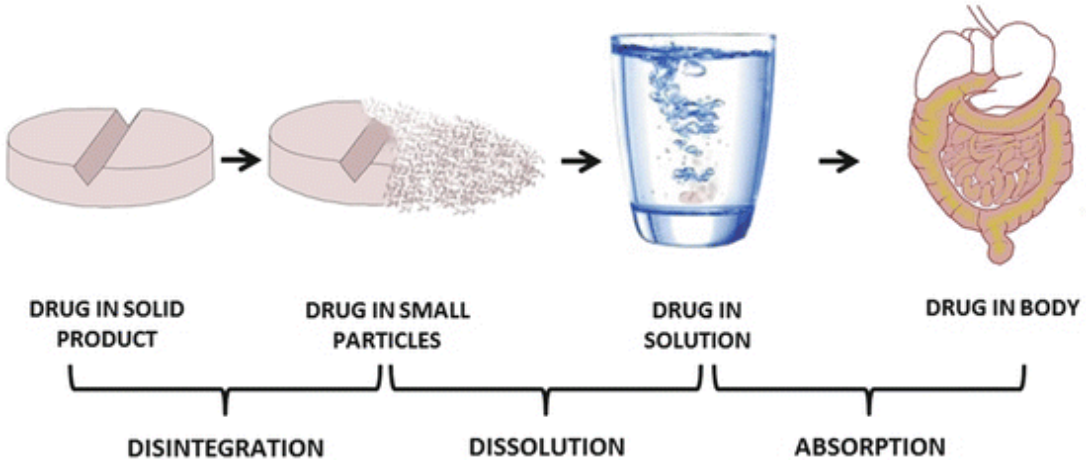
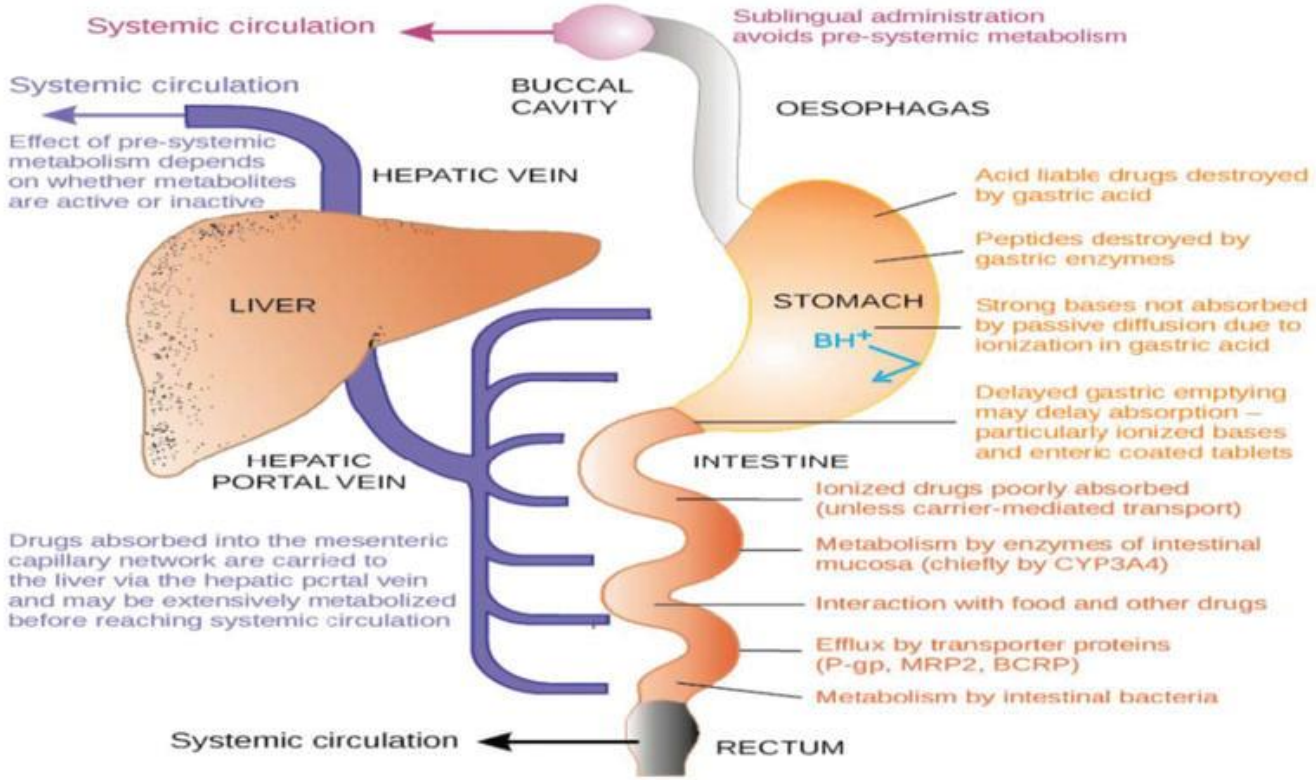
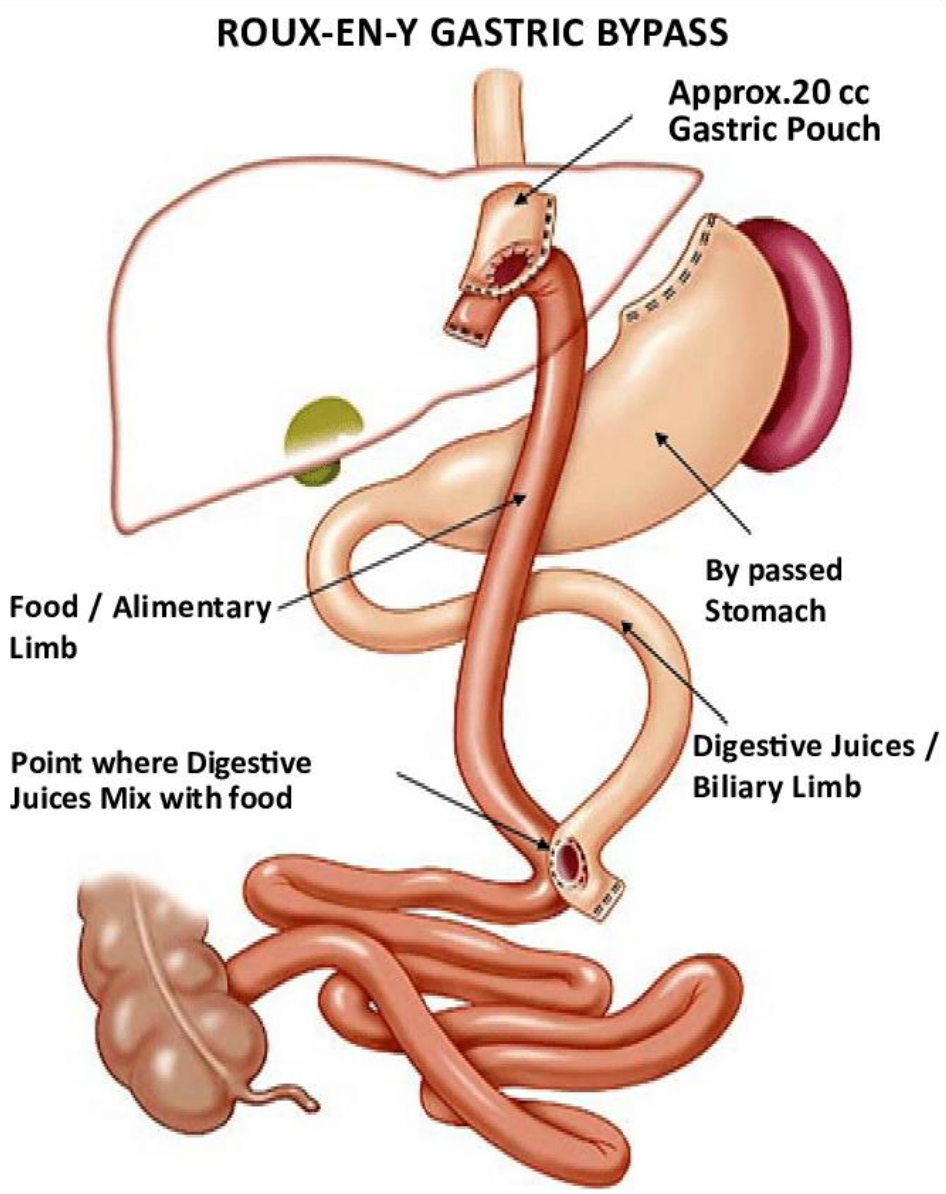
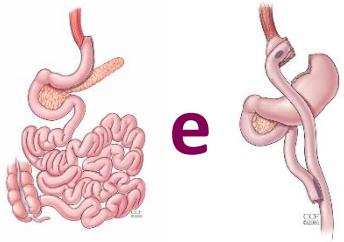

PHARMACOKINETICS
absorption
distribution
metabolism
excretion
Study.com


DRUG IN SOLID PRODUCT
DRUG IN SMALL PARTICLES
DRUG IN SOLUTION
DRUG IN BODY
DISINTEGRATION
DISSOLUTION
ABSORPTION


Systemic circulation
Sublingual administration avoids pre-systemic metabolism
Systemic circulation
BUCCAL CAVITY
OESOPHAGAS
Effect of pre-systemic metabolism depends on whether metabolites are active or inactive
HEPATIC VEIN
Acid liable drugs destroyed by gastric acid
Peptides destroyed by gastric enzymes
LIVER
STOMACH
Strong bases not absorbed by passive diffusion due to ionization in gastric acid
BH+
Delayed gastric emptying may delay absorption – particularly ionized bases and enteric coated tablets
HEPATIC PORTAL VEIN
INTESTINE
Ionized drugs poorly absorbed (unless carrier-mediated transport)
Drugs absorbed into the mesenteric capillary network are carried to the liver via the hepatic portal vein and may be extensively metabolized before reaching systemic circulation
Metabolism by enzymes of intestinal mucosa (chiefly by CYP3A4)
Interaction with food and other drugs
Efflux by transporter proteins (P-gp, MRP2, BCRP)
Metabolism by intestinal bacteria
Systemic circulation
RECTUM

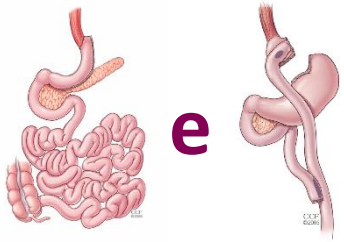

ROUX-EN-Y GASTRIC BYPASS
Approx.20 cc Gastric Pouch
By passed Stomach
Food / Alimentary Limb
Digestive Juices / Biliary Limb
Point where Digestive Juices Mix with food

Theoretische veranderingen *relevant?* voor orale genees e absorptie.



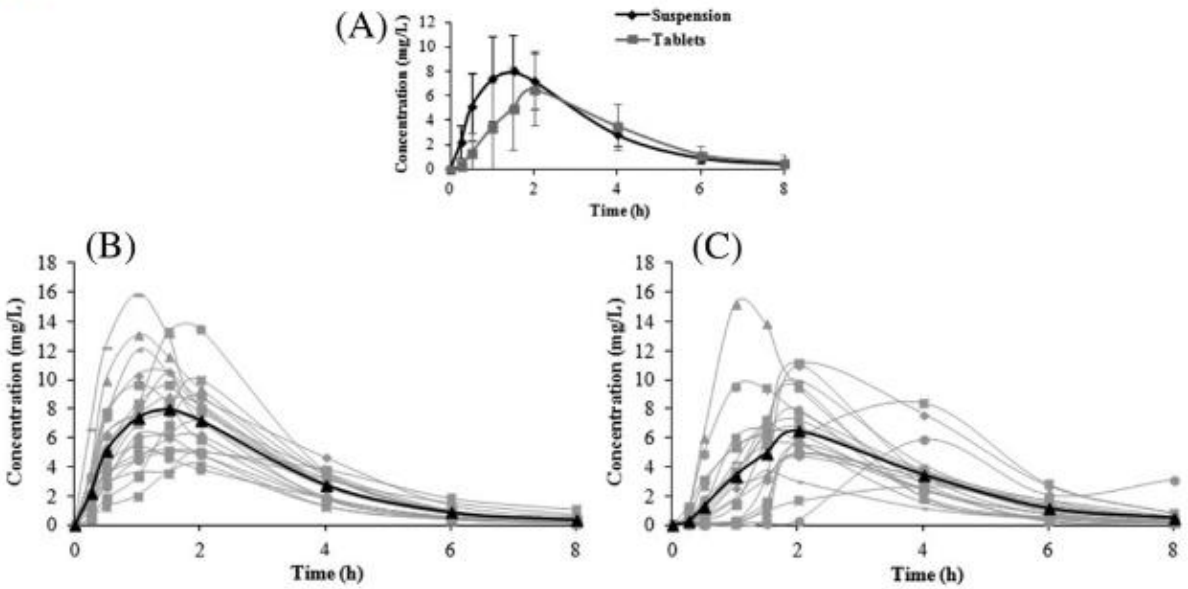
	Gastric Sleeve	Roux-en-Y gastric bypass
Volume van de maag neemt af	✓	✓✓
Verminderd contact met verteringssappen / enzymen	✓	✓
Verhoogde pH in de maag	Conflicterende resultaten	✓
Verminderde absorptieoppervlakte in de dunne darm		✓
Verminderde blootstelling aan galzouten		✓

Theoretische veranderingen *relevant?* voor orale genees e absorptie.



	Gastric Sleeve	Roux-en-Y gastric bypass
Volume van de maag neemt af	Dus tabletten lossen mogelijk niet goed op > drank?	
Verminderd contact met verteringssappen / enzymen	✓	✓
Verhoogde pH in de maag	Conflicterende resultaten	✓
Verminderde absorptieoppervlakte in de dunne darm		✓
Verminderde blootstelling aan galzouten		✓

DRANK VS TABLETTEN



IGURE 1 Spaghetti plotting of amoxicillin plasma concentrations *vs* time. (A) Mean suspension and tablet pharmacokinetic profiles. (B) ndividual suspension pharmacokinetic profiles (mean in bold line). (C) Individual tablet pharmacokinetic profiles (mean in bold line)

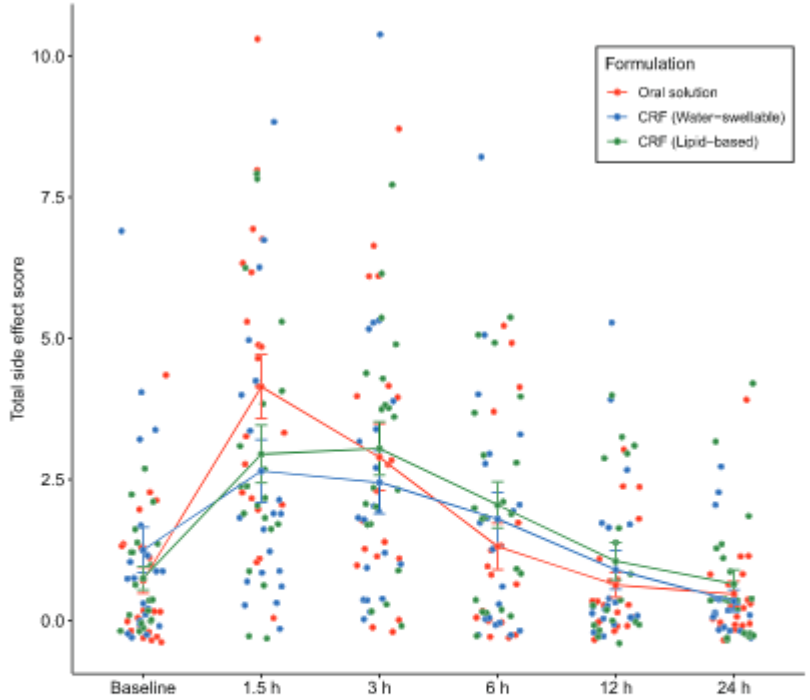


FIGURE 6 Total rating of side effects over time for each oxycodone formulation. No overall difference in total side effect scores was found between any of the formulations ($P > 0.05$). Vertical lines represent the standard error of the mean. Dots represent individual side effect scores. CRF, controlled-release formulation; h, hours

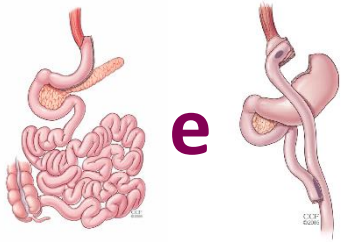
Montanha et al. BJCP 2019 | Ladebo et al. Basic Clin Pharmacol Toxicol. 2021

DRANK VS TABLETTEN

Figure 1 Pathophysiology of dumping syndrome. Abbreviations: GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; VIP, vasoactive intestinal peptide.

Van beek et al. Obes Rev. 2017 | G Standaard

Theoretische veranderingen *relevant?* voor orale genees e absorptie.



	Gastric Sleeve	Roux-en-Y gastric bypass
Volume van de maag neemt af	Dus tabletten lossen mogelijk niet goed op > drank?	
Verminderd contact met verteringssappen / enzymen	✓	✓
Verhoogde pH in de maag	Conflicterende resultaten	✓
Verminderde absorptieoppervlakte in de dunne darm	Dus verminderd darm oppervlak > geen MGA!	
Verminderde blootstelling aan galzouten		✓

MGA VS IR

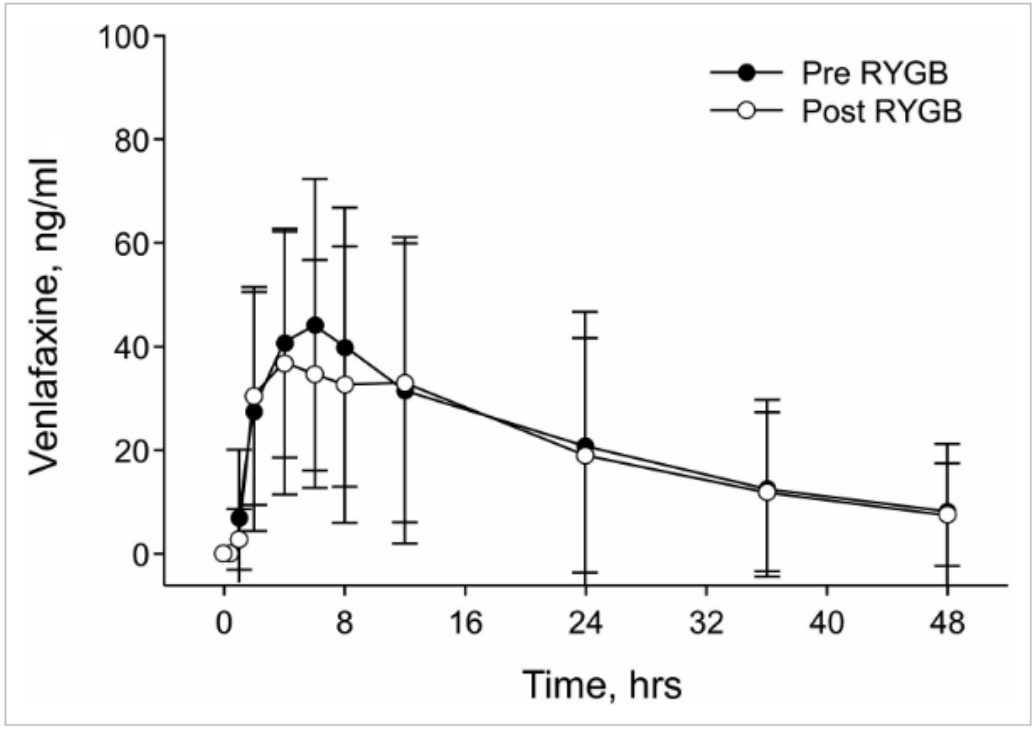


Figure 3 Open in figure viewer | PowerPoint

Mean (SD) values for the time course of venlafaxine plasma concentration from 0–48 hours for the 10 study patients before (Pre) and after (Post) Roux-en-Y gastric bypass (RYGB) surgery. (Adapted from16 with permission of Mayo Foundation for Medical Education and Research.)

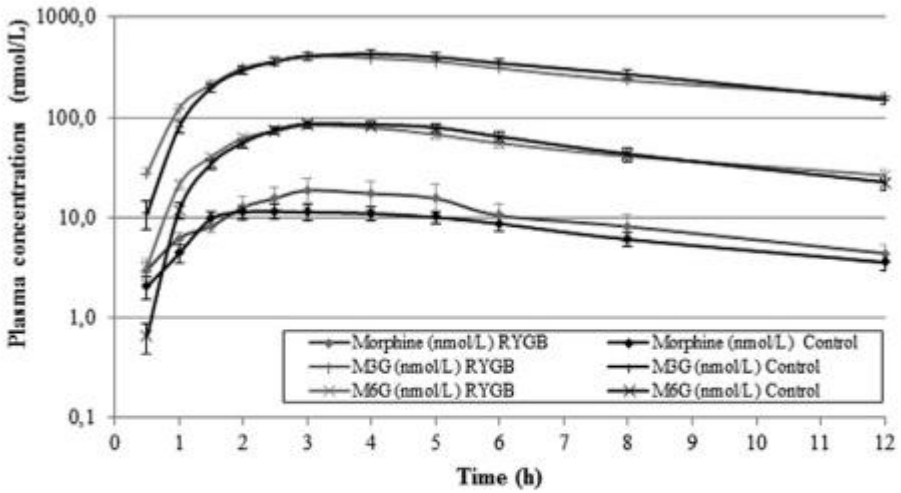


Fig. 1. Plasma pharmacokinetics of morphine, morphine-3-glucuronide, and morphine-6-glucuronide after a single oral dose of 30 mg of sustained release morphine for the 12-matched Roux-en-Y gastric bypass and control patients (data are expressed as mean ± standard error of the mean).

Krieger et al. Pharmacotherapy 2017 | Hachon et al. Surgery for Obesity and Related Diseases 2017 |

MGA VS IR

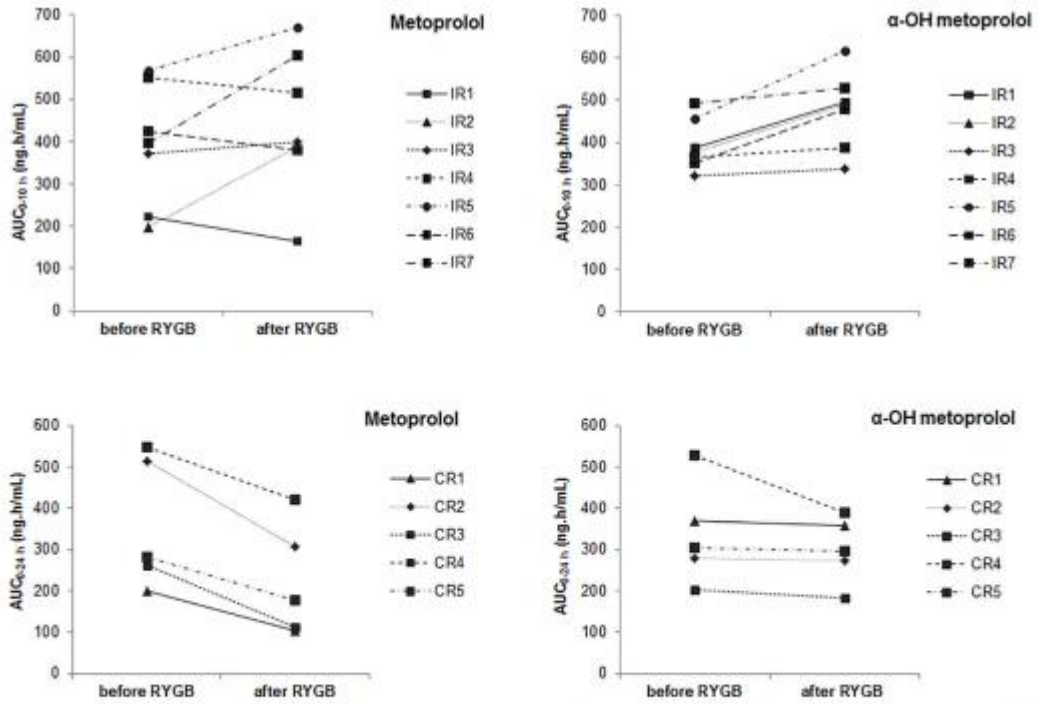
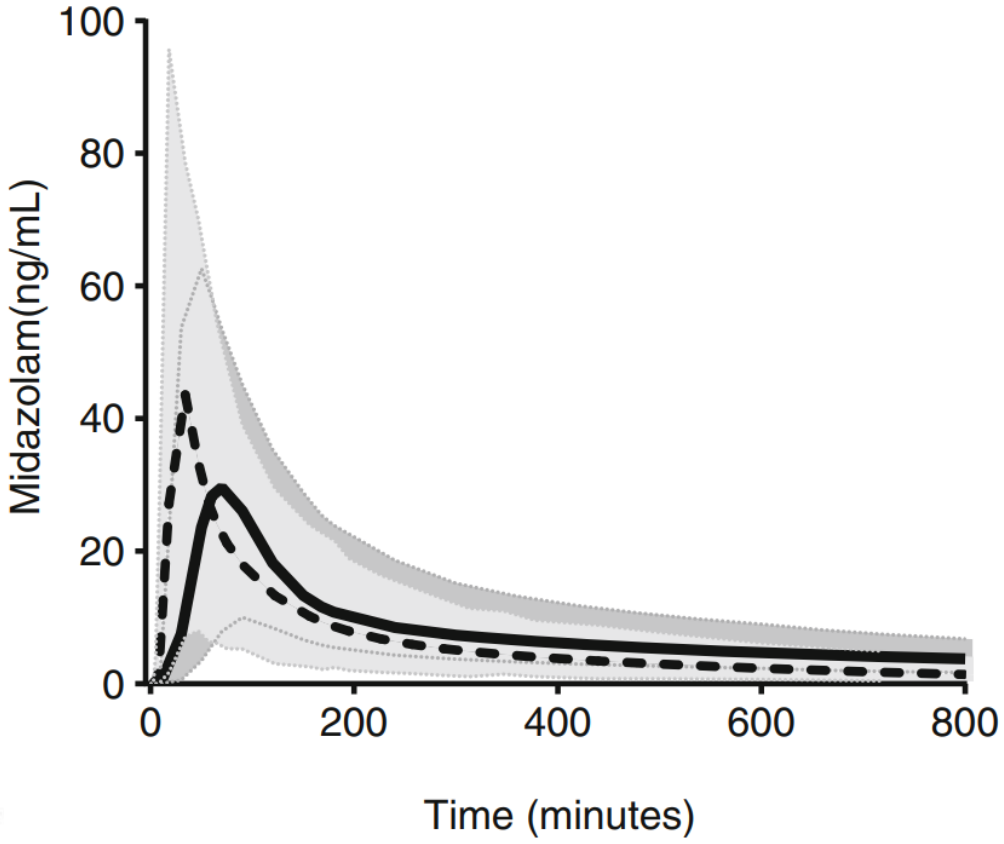


Figure 1 $AUC_{0-10\ hours}$ after administration of a single oral dose of metoprolol tartrate 100 mg immediate release (IR) tablet (upper windows) and $AUC_{0-24\ hours}$ after administration of a single oral dose of metoprolol succinate 95 mg controlled release (CR) tablet (lower windows) before and after Roux-en-Y gastric bypass (RYGB). AUC, area under the serum concentration versus time curve.

Yska JP, *et al. Eur J Hosp Pharm* 2020;**27**:e19–e24. doi:10.1136/ejhpharm-2018-001804 e21



Yska2017 Eur J Hosp Pharm 2020 | Brill Pharm Res. 2015

Stappen plan, hoe doseer ik geneesmiddelen?

1. G-standaard

Stappen plan, hoe doseer ik geneesmiddelen?

1. G-standaard

2. Reviews

> Obes Rev. 2019 Sep;20(9):1299-1311. doi: 10.111

The influence of bariatric s bioavailability in patients w review

Review > Obes Rev. 2016 N

Philip Carlo Ange
Julie Skattebu [5],

Affiliations + ex

PMID: 31232513

Review > Br J Clin Pharmacol. 2021 May 14. doi: 10.1111/bcp.14913. Online ahead of print.

Oral drug dosing following bariatric surgery – general concepts and specific dosing advice

Jurjen S Kingma [1 2], Desirée M T Burgers [1], Valerie M Monpellier [3], Marinus J Wiezer [4], Heleen J Blussé van Oud-Alblas [5], Janelle D Vaughns [6 7], Catherine M T Sherwin [8], Catherijne A J Knibbe [1 9]

Affiliations + expand

PMID: 33990981 DOI: 10.1111/bcp.14913

FULL TEXT LINKS

BJCP

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Oral drug therapy following bariatric surgery: an overview of fundamentals, literature and clinical recommendations

Review > Obes Surg. 2013 Jun;23(6):819-25. doi: 10.1007/s11695-013-0882-6.

FULL TEXT LINKS

Influence of pharmacoki

Jan Peter Yska [1], Susan
Erik R Totté, Bob Wilffer

Affiliations + expand

Review > Health Sci Rep. 2022 Apr 26;5(3):e605. doi: 10.1002/hsr2.605. eCollection 2022 May.

Drug absorption in bariatric surgery patients: A narrative review

Abdullah Abdulaziz Alalwan [1 2], Jeffrey Friedman [3], Osamah Alfayez [1], Abraham Hartzema [2]

Affiliations + expand

PMID: 35509385 PMCID: PMC9059175 DOI: 10.1002/hsr2.605

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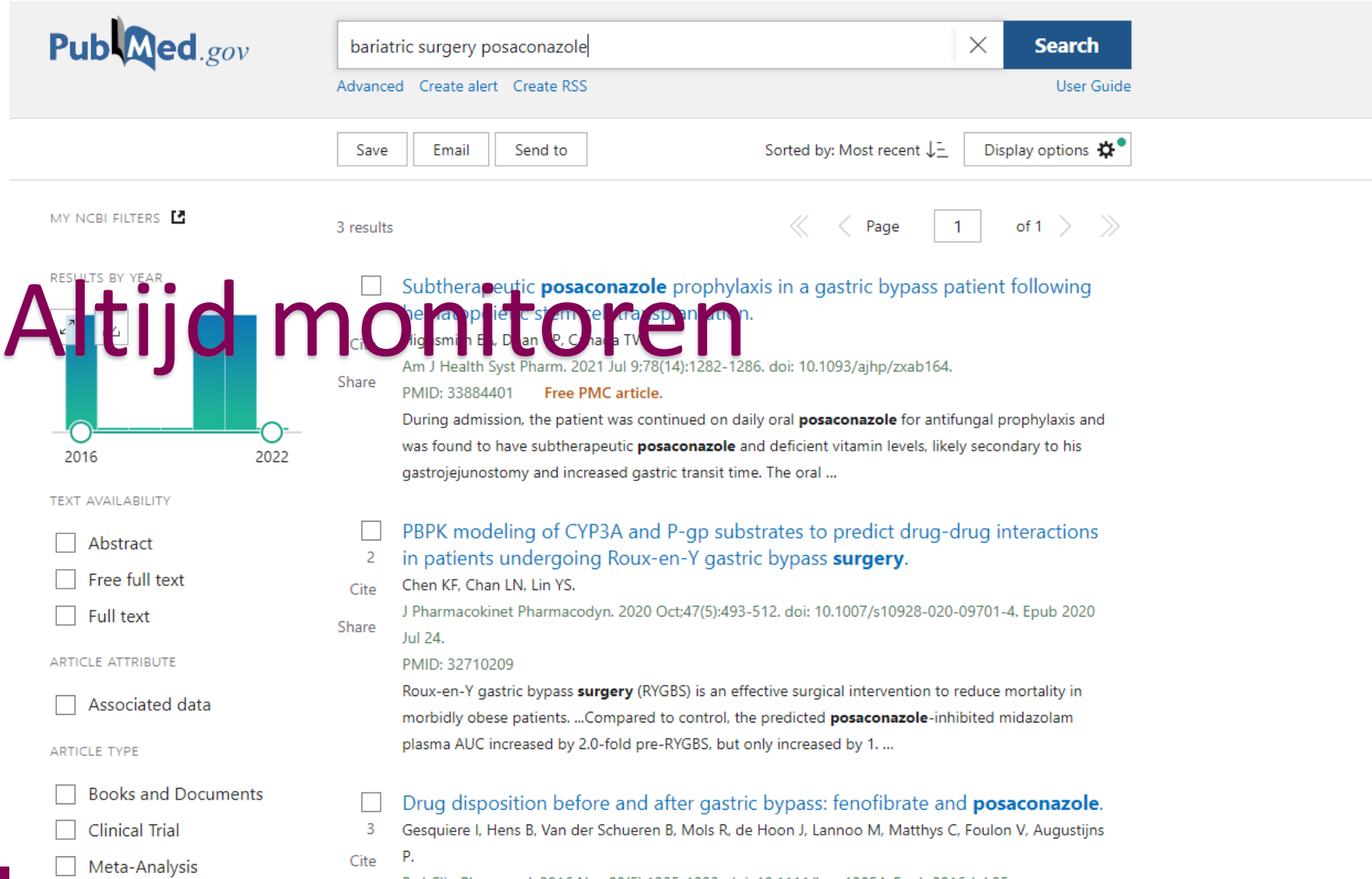
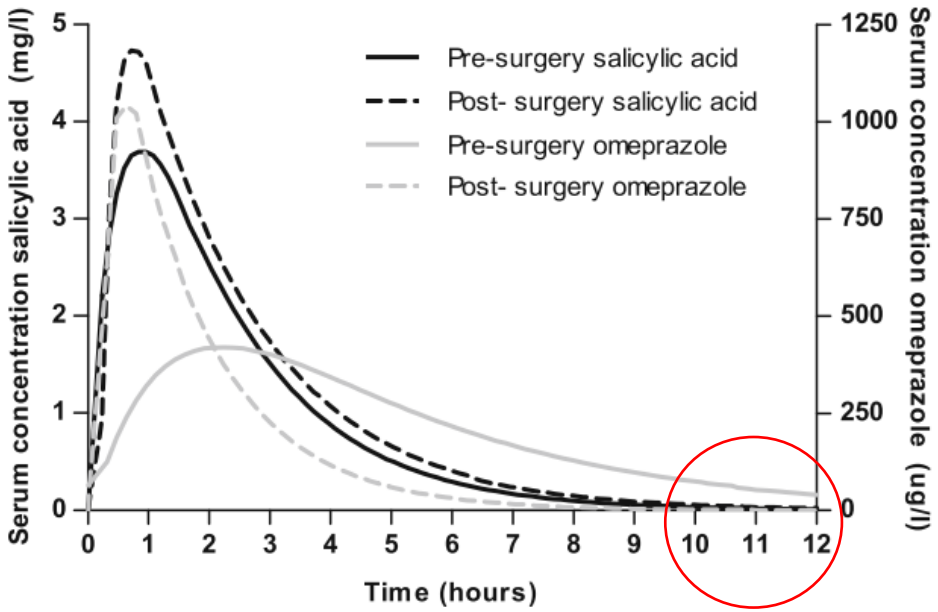
Stappen plan, hoe doseer ik geneesmiddelen?

1. G-standaard
2. Reviews
3. Literatuur



Altijd monitoren

Monitoren obv TDM



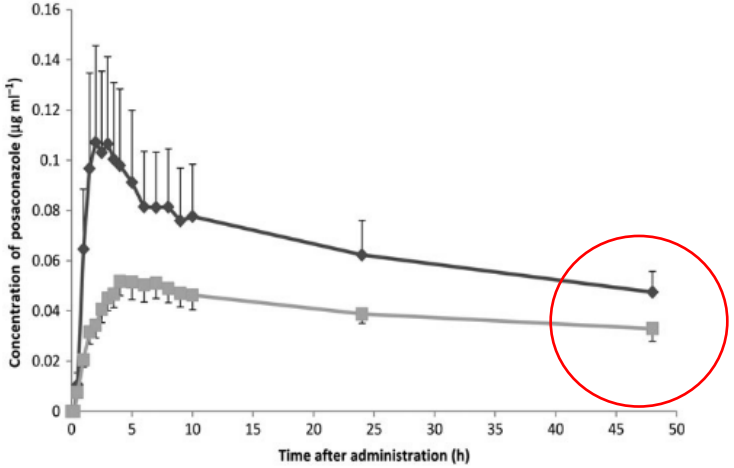
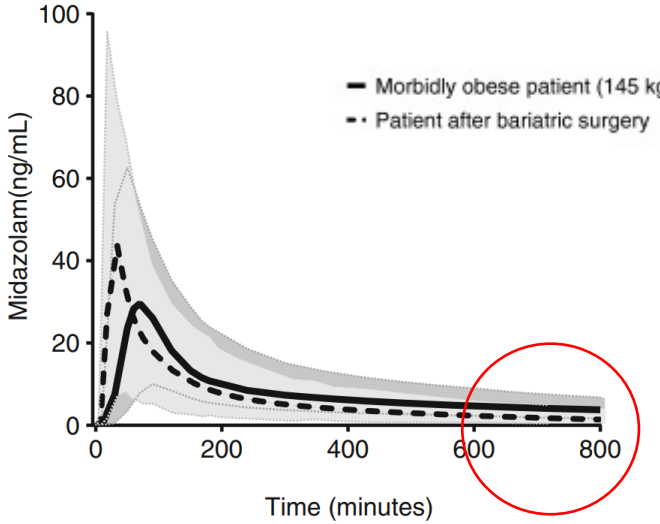


Figure 2

Observed plasma concentration–time profiles of posaconazole over 48 h after oral administration, shown as mean concentration ± standard error of the mean. Preoperative, Postoperative

Wat valt jullie op?



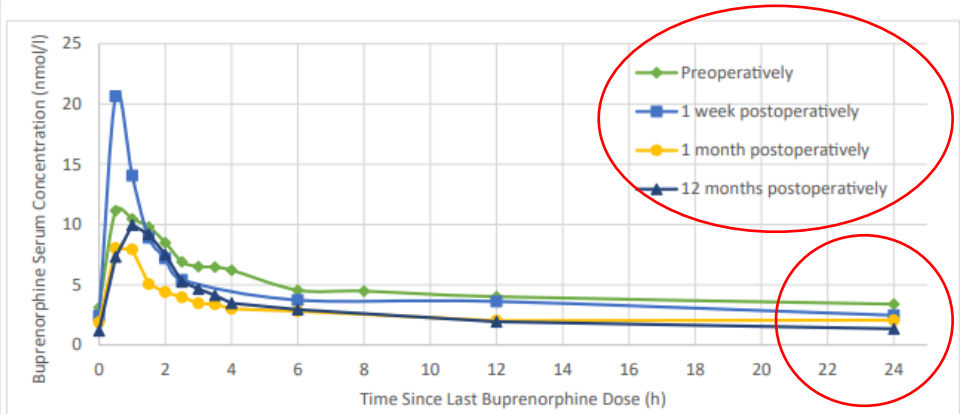


Figure. Serum concentrations of buprenorphine in a patient undergoing sleeve gastrectomy.

Mitrov-winkelmolen et al. Obes Surg. 2016 | Gesquiere et al. Br J Clin Pharmacol.. | Brill M.J. et al. Pharm Res. 2015

Stappen plan, hoe doseer ik geneesmiddelen?

1. G-standaard
2. Reviews
3. Literatuur

Doe geen aannames
&
Monitoren

Wat kan ik nog meer doen voor de bariatrische chirurgie patient?

Ga eens in gesprek / doe een review met de patiënten uit je praktijk

Veel te verbeteren rondom bijvoorbeeld: inname momenten, therapietrouw (MVS, Calcium), veel over gebruik van bijv PPI of CVD medicatie, astma medicatie (kan allemaal vaak afgebouwd worden) > deprescriben

Vaak onverwachte hulpvragen

& Veel *DRPs:*

	Patient-reported DRPs	Expert panel: yes or possible DRPs	Expert panel: unlikely DRPs
Total DRPs per patient, n, mean (SD)	3.4 (2.3)	5.9 (3.3)	1.9 (1.7)
Patient-reported symptoms [f]	2.0 (1.7)	2.0 (1.8)	1.0 (0.8)
Practical problems [g]	1.0 (1.0)	0.9 (0.9)	0.1 (0.4)
Based on medication review [h]	-	3.0 (2.2)	0.8 (1.3)

[f] Het afbeeldingmateriaal heeft niveau-nl 1(B) (zie het aangehaalde in het bijblad).

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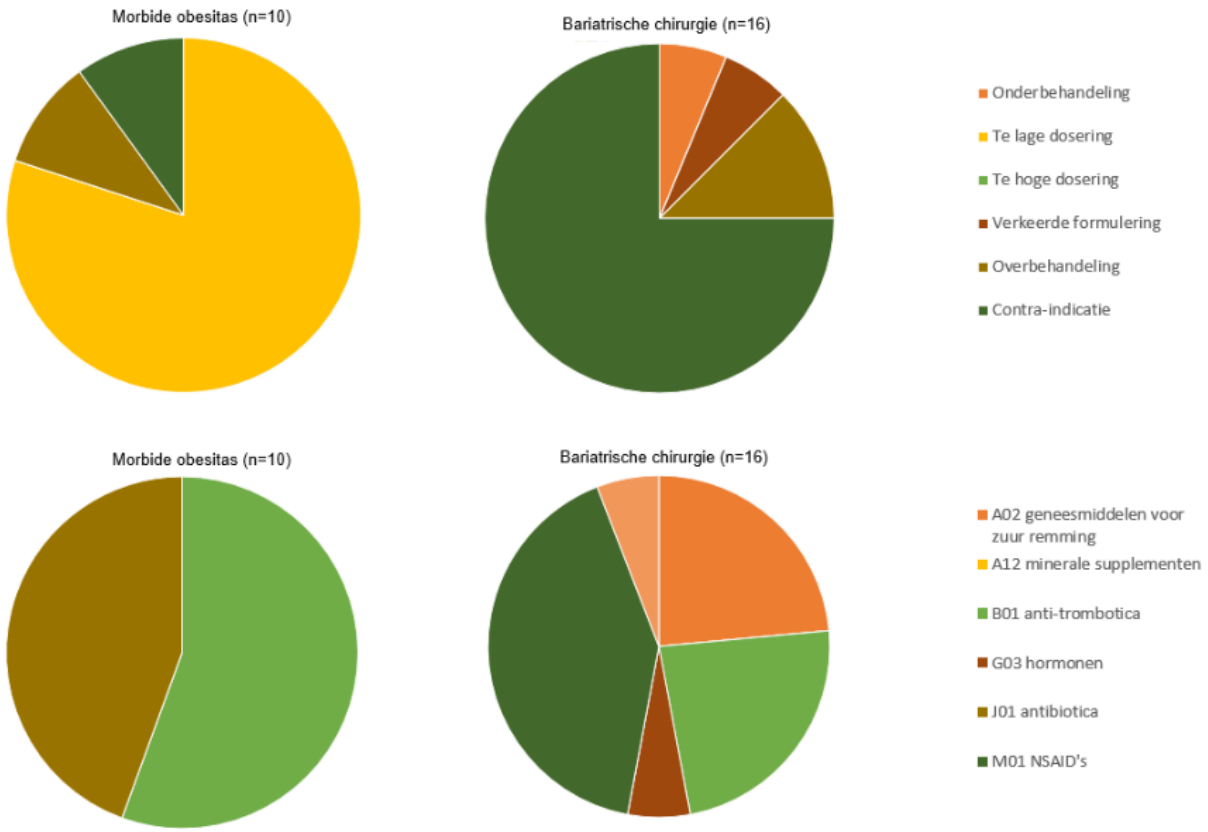
Vaak onverwachte hulpvragen & Veel *DRPs (5,7 gemiddeld)*

Registreer de contra-indicatie

Hoe identificeer je deze patiënten?

Registreer de contra-indicatie bariatrische chirurgie!



- 22 / 157 (14 %)
- 1 / 49 (2%)
- OR 0,13 (95% BI: 0,02 – 0,97)

Wat kan ik nog meer doen voor de bariatrische chirurgie patient?

Ga eens in gesprek / doe een review met de patiënten uit je praktijk

Veel te verbeteren rondom bijvoorbeeld: inname momenten, therapietrouw (MVS, Calcium), veel over gebruik van bijv PPI of CVD medicatie, astma medicatie (kan allemaal vaak afgebouwd worden) > deprescriben

Vaak onverwachte hulpvragen & Veel *DRPs (5,7 gemiddeld)*

Registreer de contra-indicatie

Hoe identificeer je deze patiënten?

Controleer de protocollaire geneesmiddelen

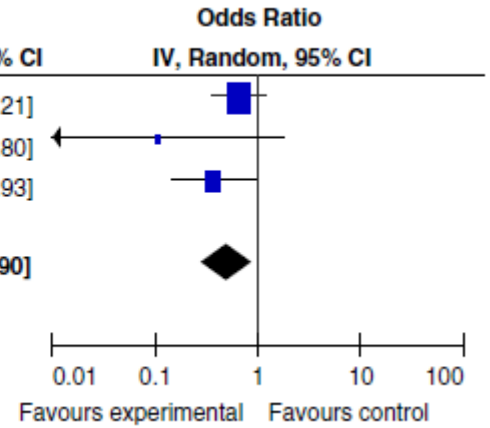
Protocollaire medicatie na chirurgie

Fig. 3 Forest plot showing pooled odds ratio of receiving PPI versus no PPI for marginal ulcer

Study or Subgroup	PPI Events	PPI Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
D'Hondt 2010	18	210	30	239	63.0%	0.65 [0.35, 1.21]
Gumbs 2006	0	73	16	274	4.1%	0.11 [0.01, 1.80]
Wilson 2006	6	32	75	194	32.8%	0.37 [0.14, 0.93]
Total (95% CI)		**315**		**707**	**100.0%**	**0.50 [0.28, 0.90]**
Total events	24		121			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 2.28$, df = 2 (P = 0.32); $I^2 = 12\%$

Test for overall effect: Z = 2.33 (P = 0.02)



1. PPI (6mnd)

2. Suppletie

   Calcium/vitamine D: 2 of 3 maal daags

   Multivitamine (WLS)

   LEVENSLANG

Suppletie van vitamines en mineralen

Na een gastric sleeve of gastric bypass is altijd suppletie van vitamines en mineralen nodig. Wij adviseren om hier zo spoedig mogelijk na de operatie mee te starten. Indien dit na 1 week nog niet is gelukt dient patiënt contact op te nemen met de kliniek.

Multivitamines
Patiënten wordt geadviseerd een gespecialiseerde multivitamine (WLS multivitamine) te gebruiken die geschikt is voor de ingreep die zij hebben ondergaan. In de kliniek krijgen zij informatie met betrekking tot geschikte soorten en merken. Van belang is te weten dat deze preparaten niet tegelijk met zuivel en/of calciumpreparaten mogen worden ingenomen. WLS multivitamines zijn met name hoog gedoseerd in ijzer, vitamine B12 en vitamine D.

Vitamine B12
Additionele orale of parenterale suppletie dient gebaseerd te zijn op plasma spiegels.

Calcichew/D3, 500/400
Naast de geadviseerde multivitamine wordt ter voorkoming van calcium en vitamine D deficiëntie extra calcium en vitamine D suppletie geadviseerd: na een Gastric Sleeve 2dd1, na een Gastric Bypass en andere malabsorptieve operaties 3dd1. Voor een optimale opname dient calcium minimaal 1 uur voor de maaltijd te worden ingenomen, of 's avonds op een lege maag voor het slapen. Overigens dient ook tussen de inname van calcium en multivitaminen minimaal een tijdsinterval van 2 uur te zitten. Aanpassing van de calcium en vitamine D suppletie dient te geschieden op basis van metingen van de plasma calcium, vitamine D en parathormoon spiegels. De vitamine D spiegel dient minimaal > 50 nmol/L te zijn, bij voorkeur rond de 75 nmol/L, en niet hoger dan 150 nmol/L.

Ying et al. Surg Endosc. 2015 | Nederlandse Obesitas kliniek

Received: 12 December 2020 | Revised: 6 April 2021 | Accepted: 1 May 2021
DOI: 10.1111/bcp.14913

INVITED REVIEW

Oral drug dosing following bariatric surgery: General concepts and specific dosing advice

Jurjen S. Kingma[1,2] | Desirée M. T. Burgers[1] | Valerie M. Monpellier[3] | Marinus J. Wiezer[4] | Heleen J. Blussé van Oud-Alblas[5] | Janelle D. Vaughns[6,7] | Catherine M. T. Sherwin[8] | Catherijne A. J. Knibbe[1,9]

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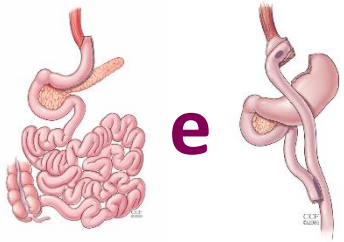
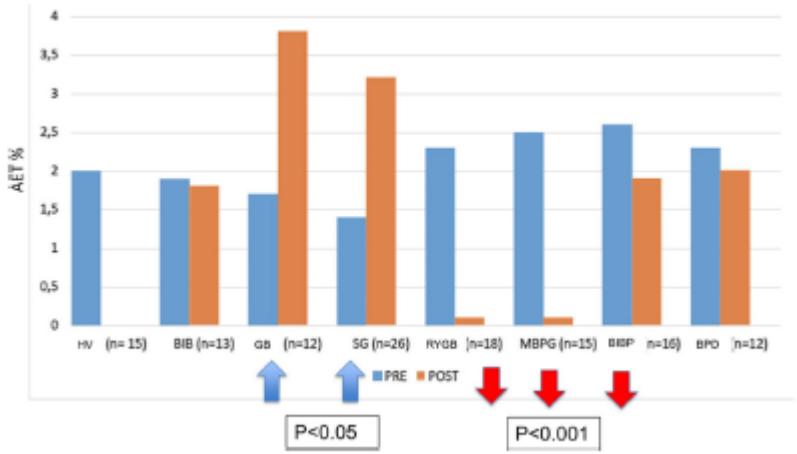


	Gastric Sleeve	Roux-en-Y gastric bypass
Volume van de maag neemt af	Dus tabletten lossen mogelijk niet goed op > drank?	
Verminderd contact met verteringssappen / enzymen	✓	✓
Verhoogde pH in de maag	Oplosbaarheid zwakke basen en zuren verminderd	
Verminderde absorptieoppervlakte in de dunne darm	Dus verminderd darm oppervlak > geen MGA!	
Verminderde blootstelling aan galzouten		✓

pH in de maag na bariatrische chirurgie

Gemm 17 (3-38) maanden na ok >

NB: tevens veel gebruik PPI post OK
(profylaxe voor ulcera)



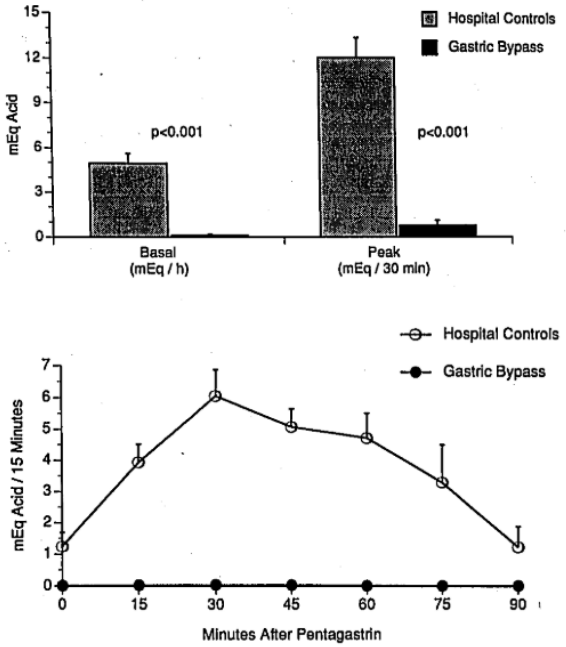
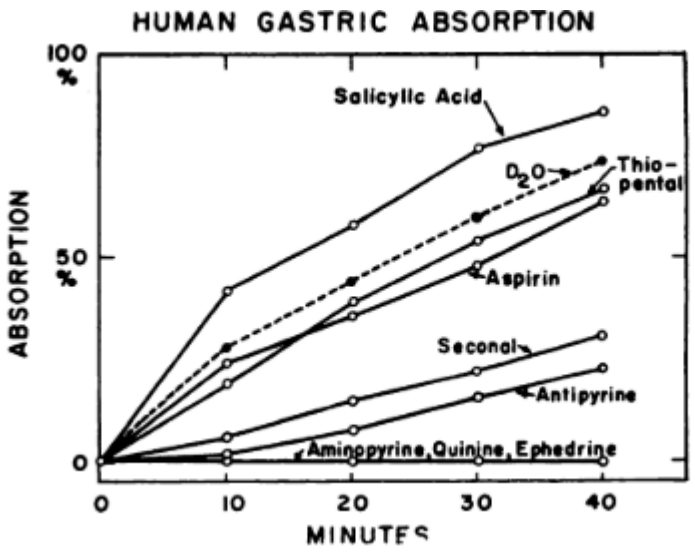


Figure 3. For gastric bypass patients and hospital control subjects, (A) basal and pentagastrin-stimulated acid output and (B) changes in acid output after pentagastrin stimulation (6 μg/kg subcutaneously).

Smith et al. Ann Surg. 1993 Jul;218(1):91-6. | Steinemann et al. Obes Surg. 2014 May;24(5):741-6.| Tolone et al. J Gastrointest Surg. 2020 Jan;24(1):1-



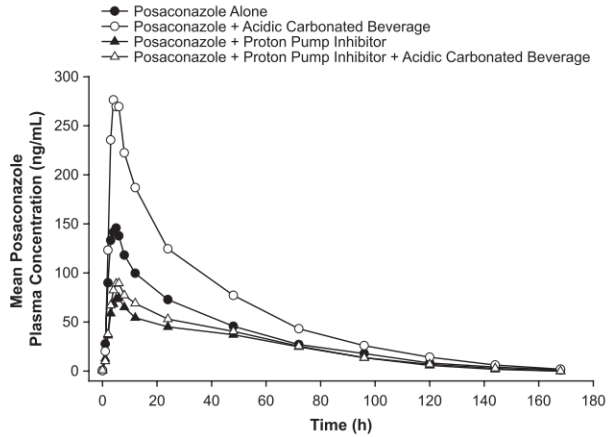
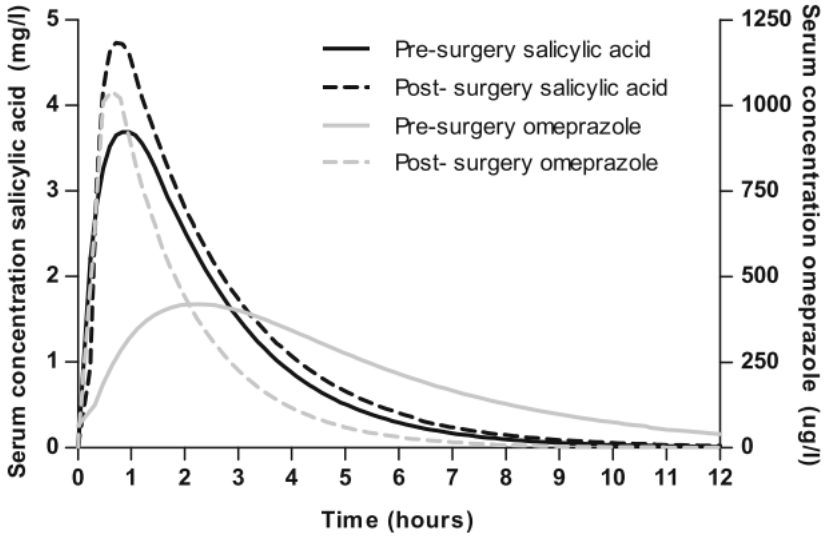


FIG. 1. Mean posaconazole plasma concentration-time profiles following administration of a single oral dose of posaconazole at 400 mg alone, with an acidic carbonated beverage, with esomeprazole, or with both an acidic carbonated beverage and esomeprazole.



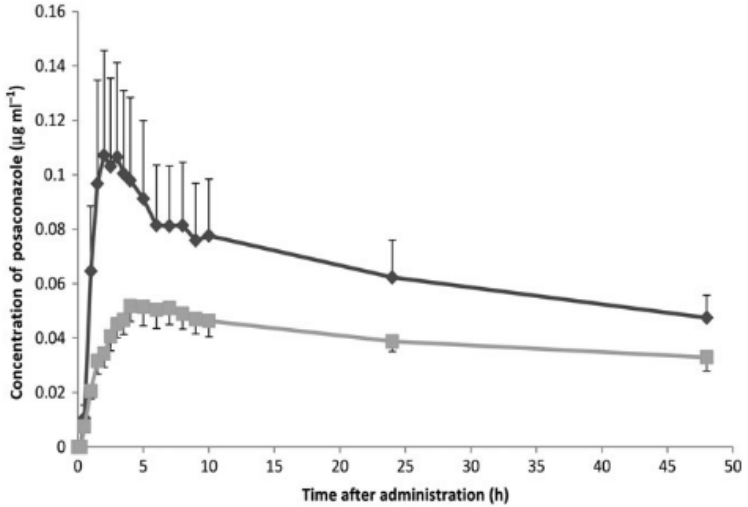
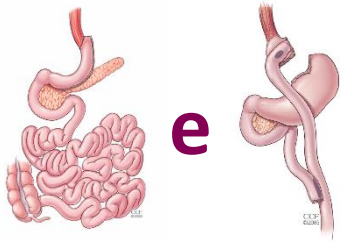


Figure 2

Observed plasma concentration–time profiles of posaconazole over 48 h after oral administration, shown as mean concentration ± standard error of the mean. Preoperative, Postoperative

Krishna et al. Antimicrob Agents Chemother. 2009 | Gesquiere et al. Br J Clin Pharmacol. 2016 | Mitrov-winkelmolen et al. Obes Surg. 2016| Hogben et al. J Pharmacol Exp Ther. 1957

Theoretische veranderingen *relevant?* voor orale genees e absorptie.



	Gastric Sleeve	Roux-en-Y gastric bypass
Volume van de maag neemt af	Dus tabletten lossen mogelijk niet goed op > drank?	
Verminderd contact met verteringssappen / enzymen	✓	✓
Verhoogde pH in de maag	Oplosbaarheid zwakke basen en zuren verminderd	
Verminderde absorptieoppervlakte in de dunne darm	Dus verminderd darm oppervlak > geen MGA!	
Verminderde blootstelling aan galzouten	Verminderde absorptie van geneesmiddelen afhankelijk van galzuren	

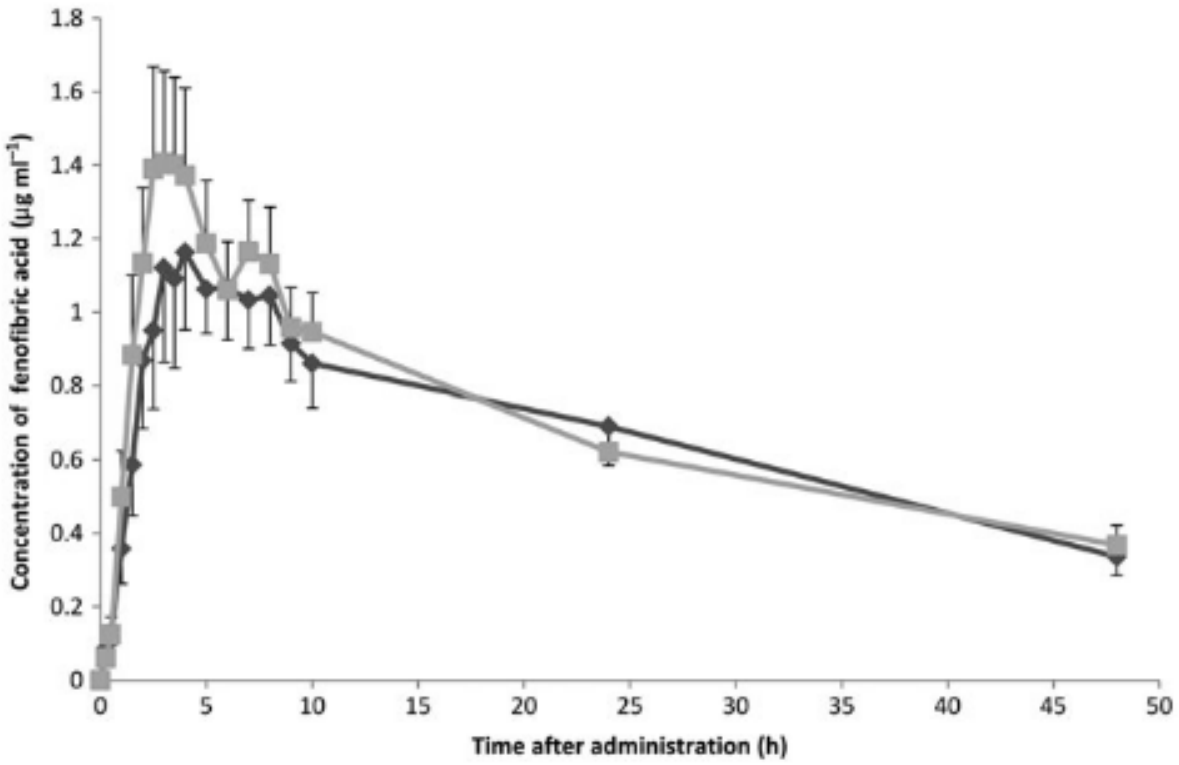


Figure 1

Observed plasma concentration–time profiles of fenofibrate over 48 h after oral administration, shown as mean concentration ± standard error of the mean. Preoperative, Postoperative

Gesquiere et al. Br J Clin Pharmacol. 2016 Nov;82(5):1325-1332.

APB study

Table 2
Pharmacokinetic properties C_{max}, T_{max}, AUC, and $t_{½}$

Visit	RYGB	*P* value versus preop visit	VSG	*P* value versus preop visit	*P* value RYGB versus VSG	Total	*P* value versus preop visit
C_{max} (ng/mL), mean (SD)							
Preop	80.5 (23.5)		85.7 (23.6)			83.1 (23.3)	
1 month postop	84.7 (35.2)	.65	91.9 (20.0)	.33	.85	88.3 (28.4)	.34
6 months postop	79.0 (30.2)	.85	88.9 (33.5)	.61	.64	83.9 (31.7)	.87
12 months postop	73.8 (22.3)	.34	91.0 (28.7)	.34	.18	82.4 (26.7)	.88
T_{max} (h), median (IQR)							
Preop	3 (2–3)		2 (2–3)			2.5 (2–3)	
1 month postop	3 (3–4)	.12	2 (1–2)	.032*	.014*	3 (2–3.5)	.95
6 months postop	2.5 (2–3)	.63	2 (1–3)	.032*	.52	2 (2–3)	.10
12 months postop	2.5 (2–3)	.45	2 (1–2)	.044*	.28	2 (2–3)	.042*
$AUC_{0–72}$ (ng/mL/h), mean (SD)							
Preop	1006.9 (212.4)		1011.3 (249.1)			1009.1 (227.1)	
1 month postop	1302.3 (497.0)	.012*	1163.5 (366.8)	.07	.27	1232.9 (434.4)	.002*
6 months postop	989.0 (410.0)	.84	1012.8 (383.0)	.98	.86	1000.9 (389.5)	.88
12 months postop	840.6 (299.2)	.035*	843.0 (306.5)	.016*	.98	841.8 (297.2)	.001*
$t_{½}$ (hr), mean (SD)							
Preop	9.43 (1.94)		9.57 (2.21)			9.50 (2.04)	
1 month postop	12.18 (2.90)	.0039*	10.44 (2.21)	.26	.09	11.31 (2.68)	.0031*
6 months postop	10.53 (3.18)	.15	10.10 (3.22)	.51	.60	10.31 (3.14)	.13
12 months postop	9.24 (2.60)	.79	8.83 (2.39)	.38	.60	9.04 (2.46)	.38

RYGB = Roux-en-Y gastric bypass; VSG = vertical sleeve gastrectomy; preop = preoperatively; postop = postoperatively; C_{max} = maximum/peak serum concentration; T_{max} = time to maximum/peak serum concentration; $AUC_{0–72}$ = area under the concentration-time curve up to 72 hours; $t_{½}$ = elimination half-life from T_{max} to 72 hours.

* Significant at $P < .05$.

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APB study

Table 3
Pre- and postdose change in chromogenic factor X activity by time after surgery

Visit	RYGB, mean (SD), % activity	*P* value versus preop visit	VSG, mean (SD), % activity	*P* value versus preop visit	*P* value RYGB versus VSG	Total, mean (SD), % activity	*P* value versus preop visit
Predose chromogenic factor X activity, hr 0							
Preop	107.5 (22.4)		118.6 (25.3)			113.0 (24.1)	
1 month postop	100.5 (18.2)	.36	98.0 (21.3)	.001*	.14	99.3 (19.5)	.0054*
6 months postop	89.6 (30.3)	.039*	105.9 (19.2)	.008*	.56	97.7 (26.2)	.0015*
12 months postop	87.7 (15.1)	.002*	91.8 (25.1)	.002*	.42	89.8 (20.4)	<.0001*
Decrease in chromogenic factor X activity from hour 0 to hour 3							
Preop	52.7 (24.6)		71.7 (23.4)			62.2 (25.5)	
1 month postop	61.4 (20.7)	.34	59.3 (18.6)	.07	.059	60.3 (19.3)	.74
6 months postop	51.2 (33.5)	.89	60.7 (20.7)	.044*	.44	55.9 (27.7)	.30
12 months postop	55.0 (9.2)	.76	49.7 (26.4)	.062	.073	52.4 (19.6)	.16
Decrease in chromogenic factor X activity from hour 0 to hour 6							
Preop	45.0 (21.6)		55.7 (16.0)			50.4 (19.4)	
1 month postop	57.4 (22.1)	.054	48.8 (22.8)	.31	.037*	53.1 (22.4)	.56
6 months postop	45.1 (25.5)	.99	51.4 (18.3)	.24	.58	48.2 (22.0)	.59
12 months postop	41.0 (11.5)	.48	36.2 (21.9)	.007*	.071	38.6 (17.3)	.011*
AUC_{0-6}							
Preop	419.4 (93.2)		412.7 (98.0)			416.0 (93.9)	
1 month postop	332.8 (82.3)	.018*	337.0 (82.2)	.0007*	.77	334.9 (80.8)	.0001*
6 months postop	316.4 (71.4)	.0002*	376.1 (84.0)	.067	.021*	346.2 (82.3)	.0001*
12 months postop	299.8 (62.5)	<.0001*	347.2 (123.3)	.012*	.084	323.5 (98.9)	<.0001*

RYGB = Roux-en-Y gastric bypass; VSG = vertical sleeve gastrectomy; preop = preoperatively; postop = postoperatively; AUC_{0-6} = area under the factor X–time curve from 0–6 hours.

The assay for factor X activity is calibrated to read between 10% and 136% using calibrators supplied by the vendor. In our laboratory, a chromogenic factor X activity of 20%–40% corresponds to an international normalized ratio of 2.0–3.0, and the normal range for patients not on anticoagulants is 72%–138%.

* Significant at $P < .05$.

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