Quelles interactions lors de l'absorption digestive des médicaments ?

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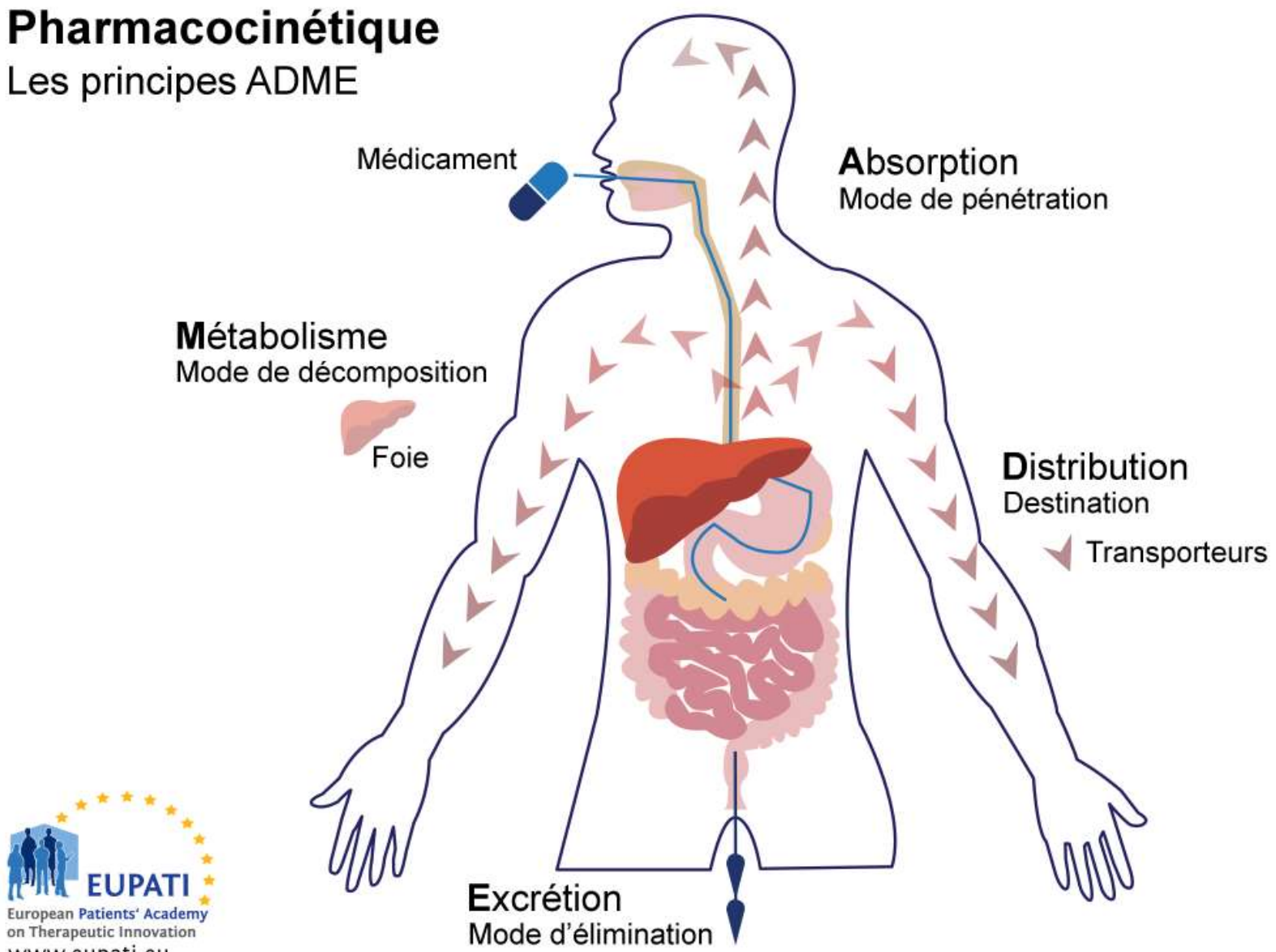
Absorption digestive



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European Patients' Academy on Therapeutic Innovation
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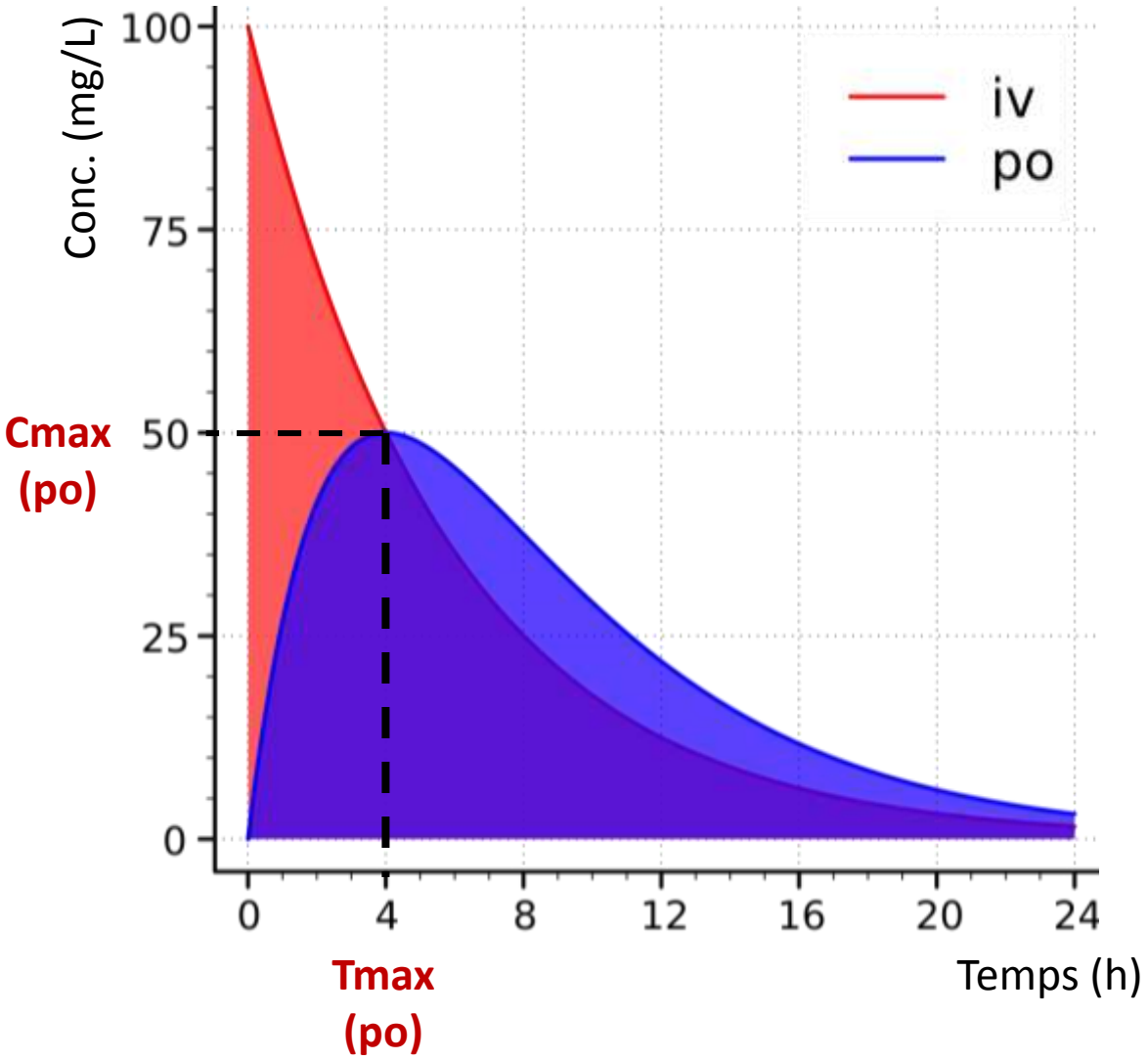
Absorption digestive



Biodisponibilité orale: F%= AUC(po)/AUC(IV) *100

Interactions médicamenteuses modifiant l'absorption digestive

Nombreux mécanismes possibles au niveau du tube digestif:

- Complexation
- Modification du pH gastrique
- Modification de la vidange gastrique
- Modification du péristaltisme intestinal
- Altération de la flore intestinale
- Modification du transport entérocytaire

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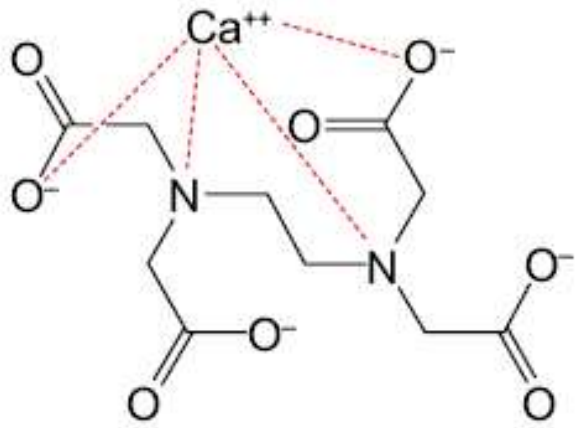
Complexation

Définition

Formation d'un complexe chimique à partir d'un ion ou d'un atome métallique.
Si la charge du complexe est neutre, celui-ci précipite en milieu aqueux.

EDTA $\xrightarrow{Ca^{2+}}$



Calcium-EDTA

Complexation

Calcium et lévothyroxine

Etude prospective

N= 20 patients sous carbonate de **calcium 1200 mg/j + lévothyroxine 1 µg/kg**

	Baseline: Levothyroxine	Visit 1: Levothyroxine + Calcium	Visit 2: Levothyroxine + Calcium	Final Visit: Levothyroxine	Overall *P*†
Free T_4, ng/dL	1.34 ± 0.04‡	1.23 ± 0.04	1.22 ± 0.05	1.41 ± 0.06‡	<.001
TSH, mIU/L	1.60 ± 0.22‡	2.88 ± 0.41	2.71 ± 0.43	1.44 ± 0.21‡	.008
Total T_4, µg/dL	9.21 ± 0.46§	8.64 ± 0.43	8.55 ± 0.41	9.31 ± 0.39§	.03
Total T_3, ng/dL	141.50 ± 4.43	134.40 ± 6.59	142.10 ± 6.54	142.2 ± 7.03	.82

*All values are expressed as mean ±SE. T_4 indicates thyroxine; TSH, thyrotropin; and T_3, triiodothyronine. To convert free T_4 from ng/dL to pmol/L, multiply by 12.87; to convert total T_4 from µg/dL to nmol/L, multiply by 12.87; and to convert total T_3 from ng/dL to nmol/L, multiply by 0.0154.

†Overall *P* value from F test of repeated-measures multivariate analysis of variance (MANOVA) analyses that compare the means of the baseline levothyroxine group, the levothyroxine group plus calcium groups, and the final levothyroxine group.

‡*P*<.01 for between group comparison of levothyroxine plus calcium group (visit 1 + visit 2) from a repeated-measures MANOVA test.

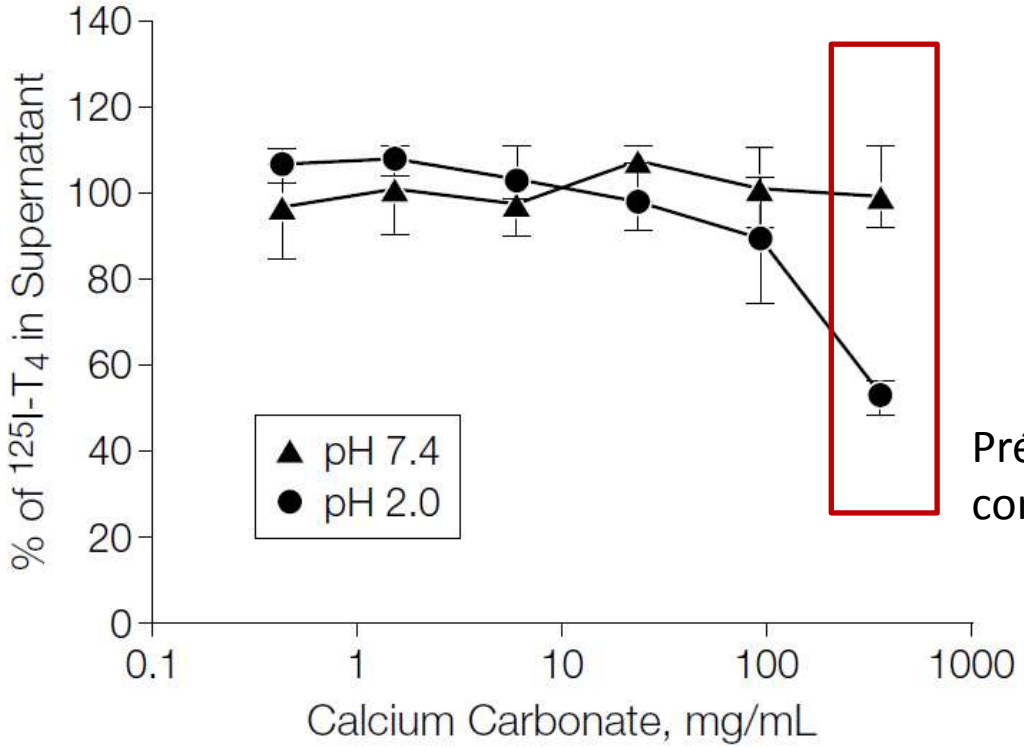
§*P*<.05 for between group comparison to levothyroxine plus calcium group (visit 1 + visit 2) from a repeated-measures MANOVA test.

Singh NA et al. JAMA. 2000;283(21):2822-2825.

Complexation

Calcium et lévothyroxine

Figure 2. In Vitro Studies With Calcium and Thyroxine (T_4)



Précipitation du complexe

Singh NA et al. JAMA. 2000;283(21):2822-2825.

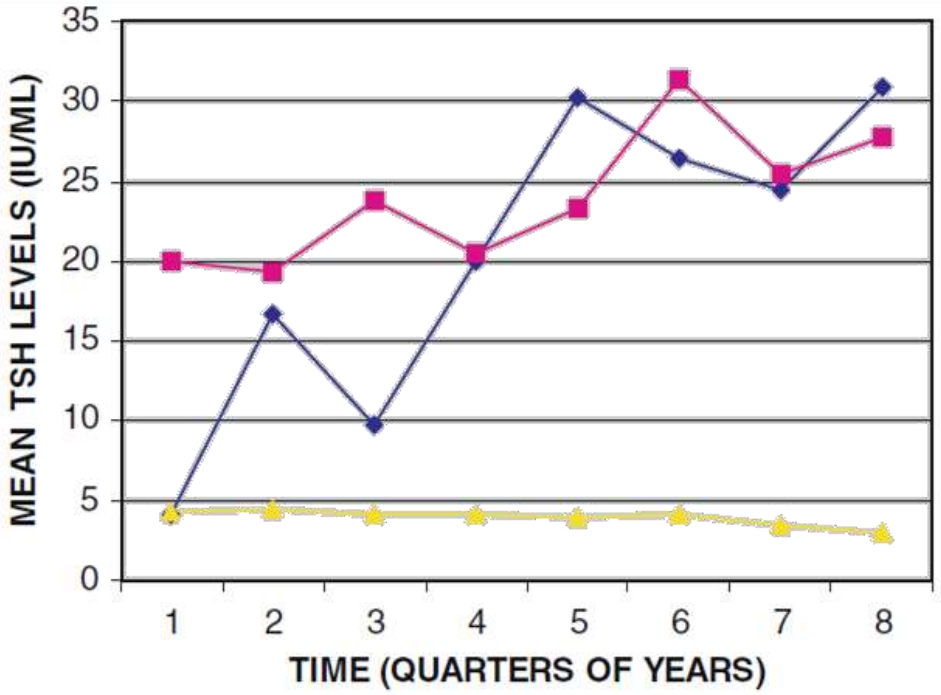
Complexation

Chélateurs du phosphate et lévothyroxine

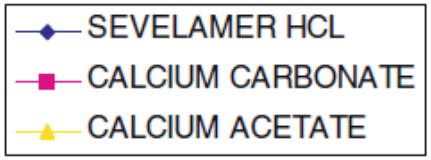
Table 1 Analysis of effect of phosphate binder on thyroid replacement dose

	Calcium acetate N=35	Calcium carbonate N=19	Sevelamer HCL N=13
Age (mean +/– SD)	71.82 +/– 13.70	76.25 +/– 7.31	76.15 +/– 10.62
Sex (Male/Female)	14/21	4/15	1/12
RACE (African American/Caucasian)	21/14	15/5	7/6
Levothyroxine dose (mean +/– SD)	95.00 +/– 83.75	98.68 +/– 45.24	173.08* +/– 25.94
TSH level (mean +/– SD)	3.92 +/– 7.83	23.7974 +/– 19.50	20.2908 +/– 30.83
Serum phosphorus (mean +/– SD)	5.911 +/– 2.02	5.516 +/– 2.02	6.931 +/– 1.822

* Significant at the 0.05 level



Etude observationnelle



Moins d'interaction avec l'acétate de Ca2+

Apport moindre de Ca^{2+} libre?

Mécanisme de l'interaction avec sevelamer?

Effet direct: adsorption

Effet indirect: modification du pH

Diskin CJ et al. Int Urol Nephrol (2007) 39:599–602

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Modification du pH gastrique

Attention aux bases faibles peu solubles à pH ↑

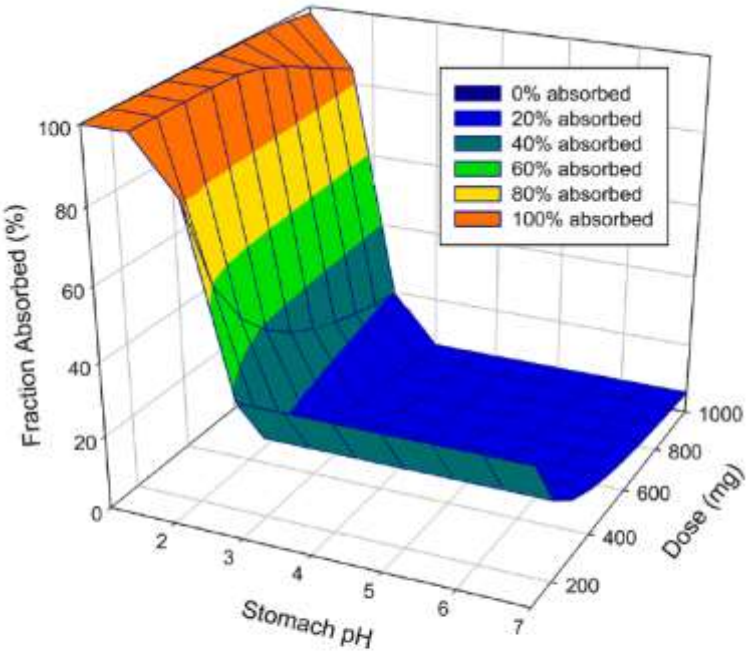
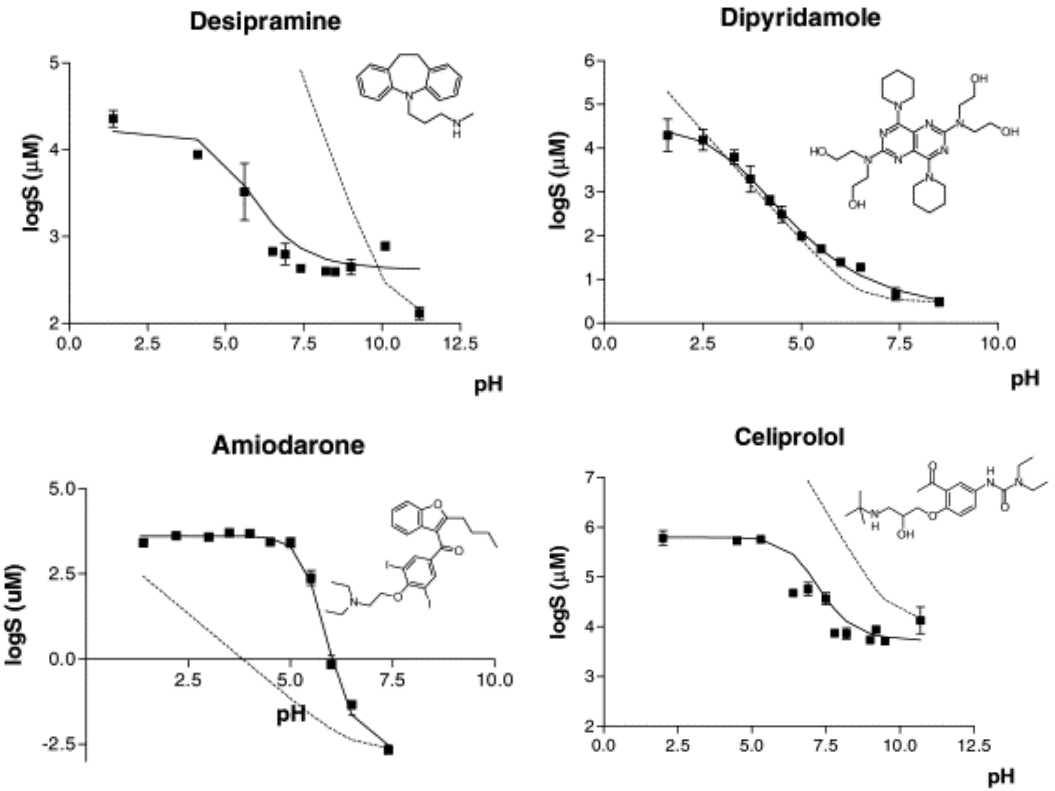


Figure 3. Parameter sensitivity analysis of fraction absorbed for a weak base BCS II drug compound as a function of stomach pH and dose. Simulations were conducted in GastroPlus using the default physiology model and assuming a precipitation time of 900 s. Compound solubility is more than 5 mg/mL at pH 2 but drops to 20 μg/mL at pH 6.0.

Parmi la Classe II FDA (classification BCS)
« low solubility, high permeability »



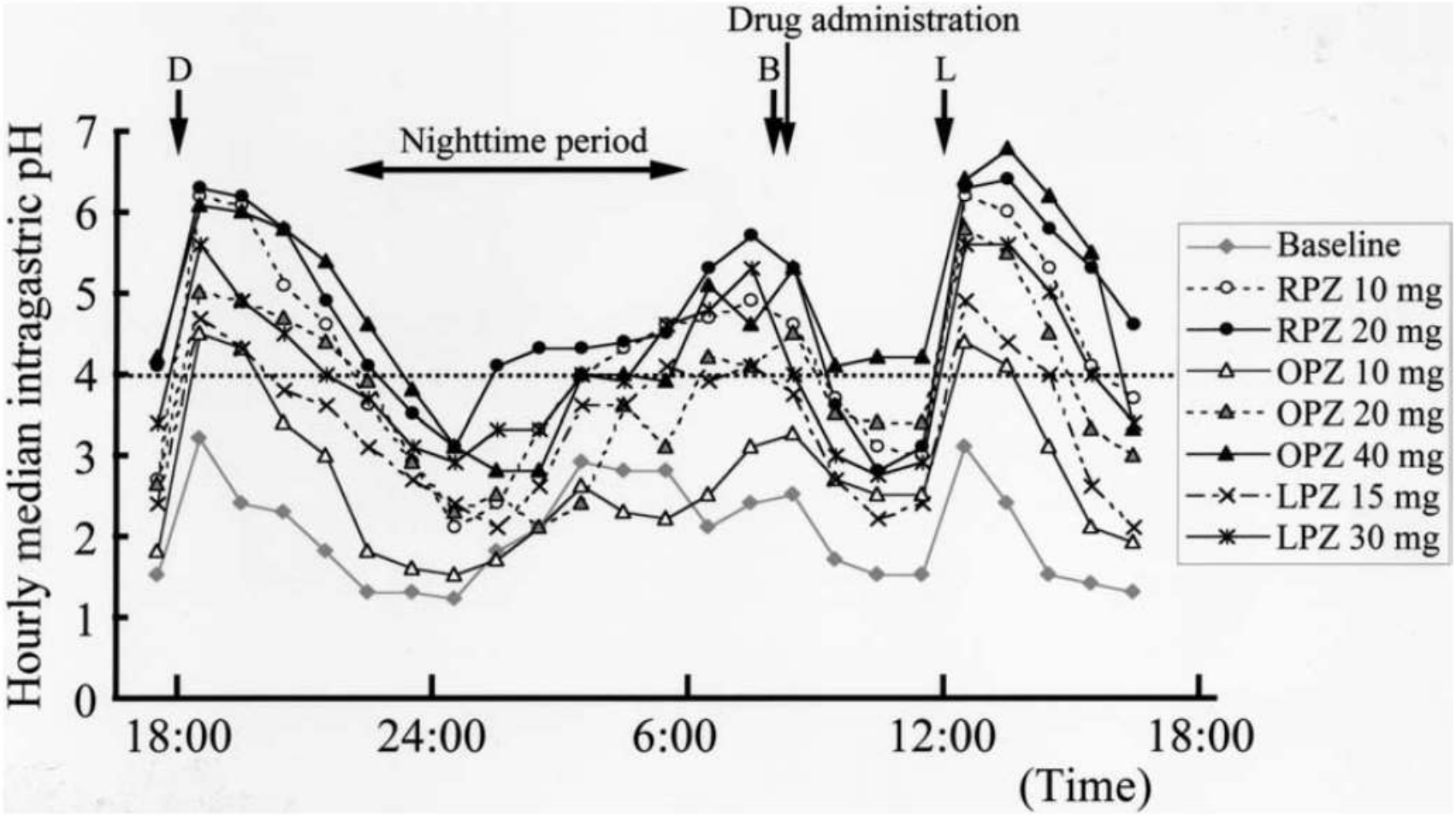
Mitra & Kesisoglou F. Mol Pharm. 2013 Nov 4;10(11):3970-9.

Bergström CA et al. Eur J Pharm Sci. 2004 Aug;22(5):387-98.

Modification du pH gastrique

Modification du pH gastrique sous IPP

Evolution du pH gastrique sur 24h après 7 jours de traitement (IPP 1x/jour)



D= Dinner ; B = Breackfast ; L = Lunch

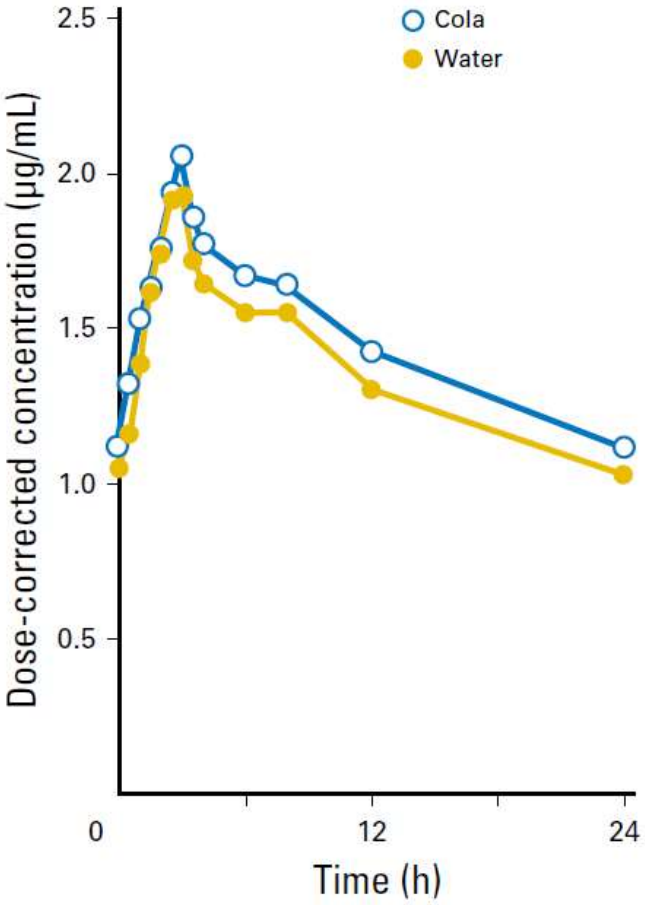
Shimatani et al. Clin Pharmacol Ther 2006;79:144–52.

Modification du pH gastrique

IPP et erlotinib

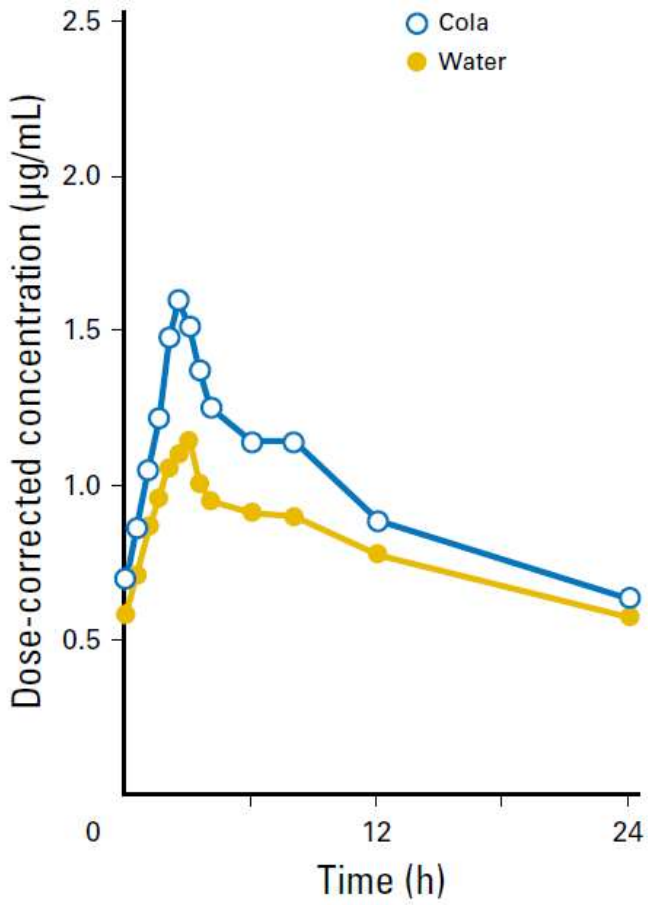
Erlotinib

(n= 14 patients)



Erlotinib + Esoméprazole

(n= 14 patients)



Erlotinib + IPP *vs.* Erlotinib seul → **AUC -52%**

Erlotininb + IPP + Cola *vs*. Erlotininb + IPP → **AUC +39%**

van Leeuwen RW et al. J Clin Oncol. 2016;34(12):1309-14.

Modification du pH gastrique

IPP et erlotinib

Gastric Acid Suppression Is Associated With Decreased Erlotinib Efficacy in Non–Small-Cell Lung Cancer

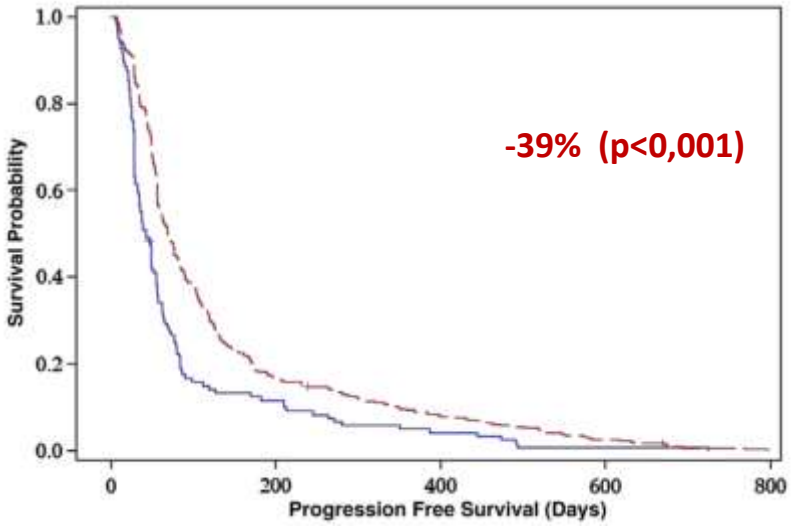
Michael P. Chu,[1] Sunita Ghosh,[1] Carole R. Chambers,[2] Naveen Basappa,[1] Charles A. Butts,[1] Quincy Chu,[1] David Fenton,[3] Anil A. Joy,[1] Randeep Sangha,[1] Michael Smylie,[1] Michael B. Sawyer[1]

Clin Lung Cancer. 2015 Jan;16(1):33-9

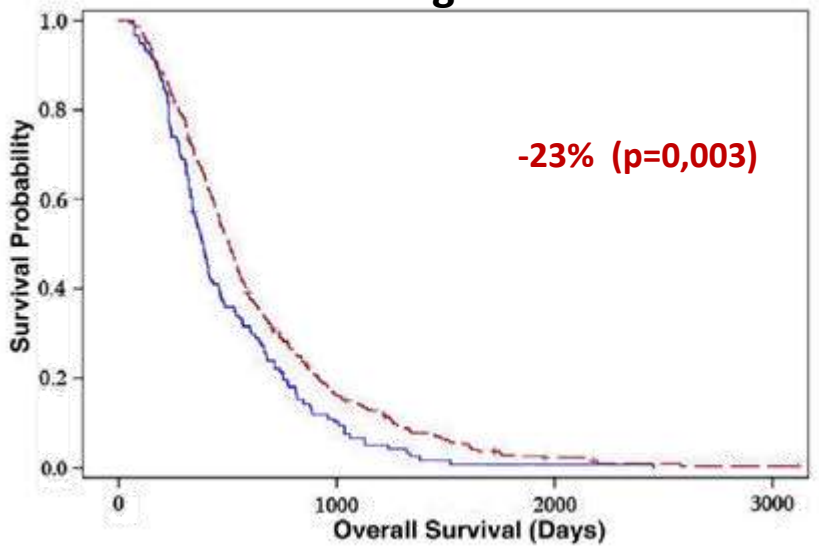
Etude rétrospective

N= 507 patients avec CBNPC (124 sous IPP ou AntiH2 versus 383)

Survie sans progression



Survie globale



Modification du pH gastrique

IPP/antiH2/anti-acide et inhibiteurs de tyrosine kinase

Effect of food and acid regulation drugs on smTKI absorption and administration advices.

Drug	Food		Antacids		Reference(s)
	Exposure (AUC)	Advice	Exposure	Advice	
Afatinib	−39%	WO	↔	–	
Axitinib	+19%	WO/F	↔	–	[193]
Bosutinib	+70%	F	↓	A	[194]
Cabozantinib	+57%	WO	(↓)[1]	–	
Crizotinib	−14%	WO/F	(↓)	–	
Dabrafenib	−31%	WO	(↓)	–	
Dasatinib	+14%	WO/F	↓	A	[195]
Erlotinib	+109%	WO	↓	A	
Gefitinib	−14 to +37%	WO/F	(↓)	A	
Imatinib	?	F[2]	↔	–	[196,197]
Lapatinib	+80–161%	[3]	↓	A	[146]
Nilotinib	+29–82%	WO	↓	A	
Pazopanib	+100%	WO	↓	A	[198]
Ponatinib	−3 to +9%	WO/F	(↓)	A	[199]
Regorafenib	+36–48%	F	(↔)	–	
Ruxolitinib	?	WO/F	↔	–	
Sorafenib	−29 to +14%	WO	(↓)	A	
Sunitinib	+12%	WO/F	↔	–	[200]
Vandetanib	?	WO/F	(↓)	–	
Vemurafenib	+200%	WO/F[4]	?	?[4]	[147]

↑, Increased exposure; ↓, lowered exposure; ↔, no effect; ?, unknown effect; (↑)/(↓)/(↔), possible effect; –, no avoidance needed; A, avoidance needed. WO, without food; F, with food. Source: EPARs and FDA label texts, additional sources indicated where appropriate.

[1] No formal studies done.

[2] Food serves as gastrointestinal protection.

[3] 1 h before or after meal (see text).

[4] Advice not (yet) given.

Herbrink M et al. Cancer Treat Rev. 2015 May;41(5):412-22.

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Modification de la vidange gastrique

Agents « procinétiques »

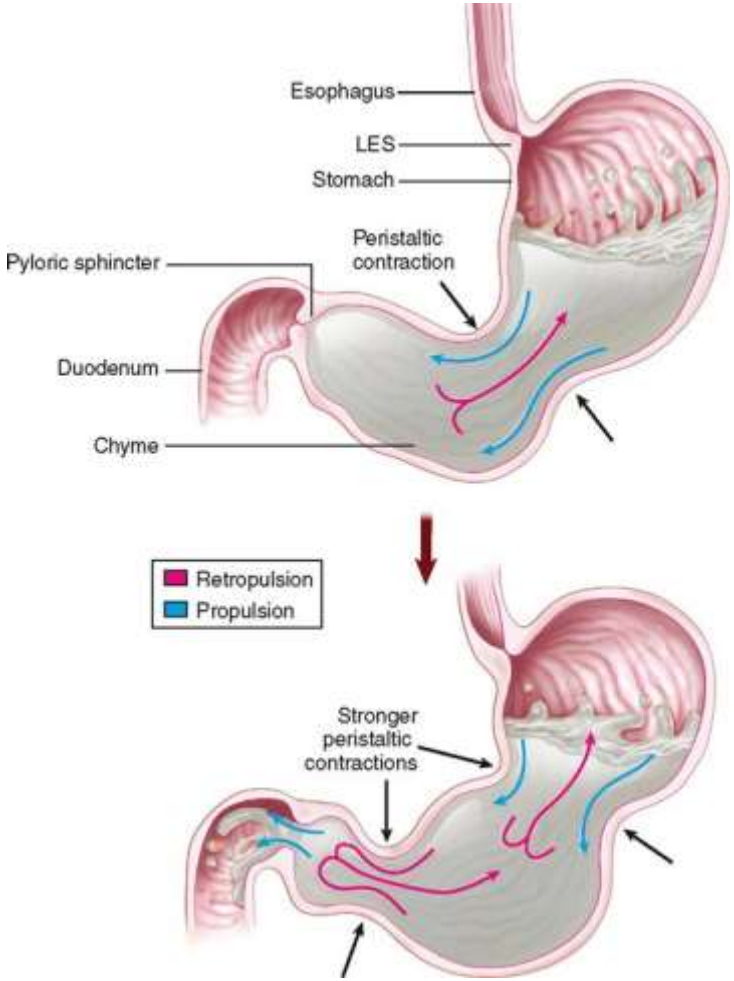

Table 3. Prokinetic agents

Agent	Mechanism	Dosage
Metaclopramide	dopamine D_2 receptor antagonist	5–20 mg q.i.d.
Domperidine	dopamine D_2 receptor antagonist	10–30 mg q.i.d.
Erythromycin	motilin receptor agonist	50–250 mg q.i.d.
Bethanechol	muscarinic receptor agonist	25 mg q.i.d.
Pyridostigmine	acetylcholinestrase inhibitor	30–60 mg t.i.d.
Tegaserod	5-HT_4 receptor agonist	withdrawn in US
Cisapride	5-HT_4 receptor agonist	withdrawn in US
Loxiglumide	CCK receptor antagonist	under study

Gumaste et al. Digestion 2008;78:173–179

Modification de la vidange gastrique

Métoclopramide et ciclosporine

N= 14 patients transplantés rénaux

J1 = Ciclosporine seule
J2 = Ciclosporine + métoclopramide

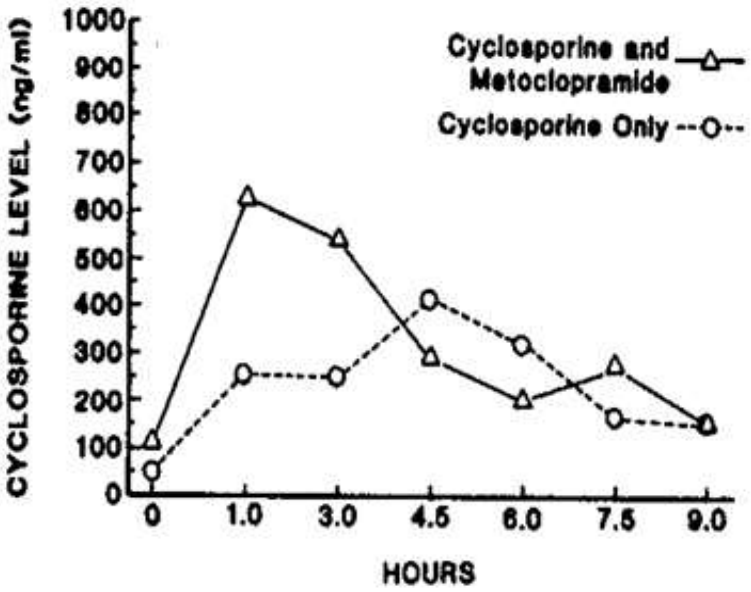

TABLE 2. Cyclosporine pharmacokinetic parameters with and without metoclopramide coadministration

Parameter	Cmax (ng/ml)	Tmax (Hr)	AUC (ng·hr/ml)
CsA	388[a] (354, 425)	3.3±0.2[b]	3370±220[b]
CsA + MET	567 (515, 625)	2.9±0.2	4120±230
P	0.00005	0.01	0.003

[a] Geometric mean, with the figures in parentheses 1 SEM below or above the mean.
[b] Arithmetic mean ± SEM.

+ 46% **-24 min** **+ 22%**

Wadhwa NK et al. Transplantation. 1987 Feb;43(2):211-3.

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Modification du péristaltisme intestinal

Opioïdes et péristaltisme intestinal

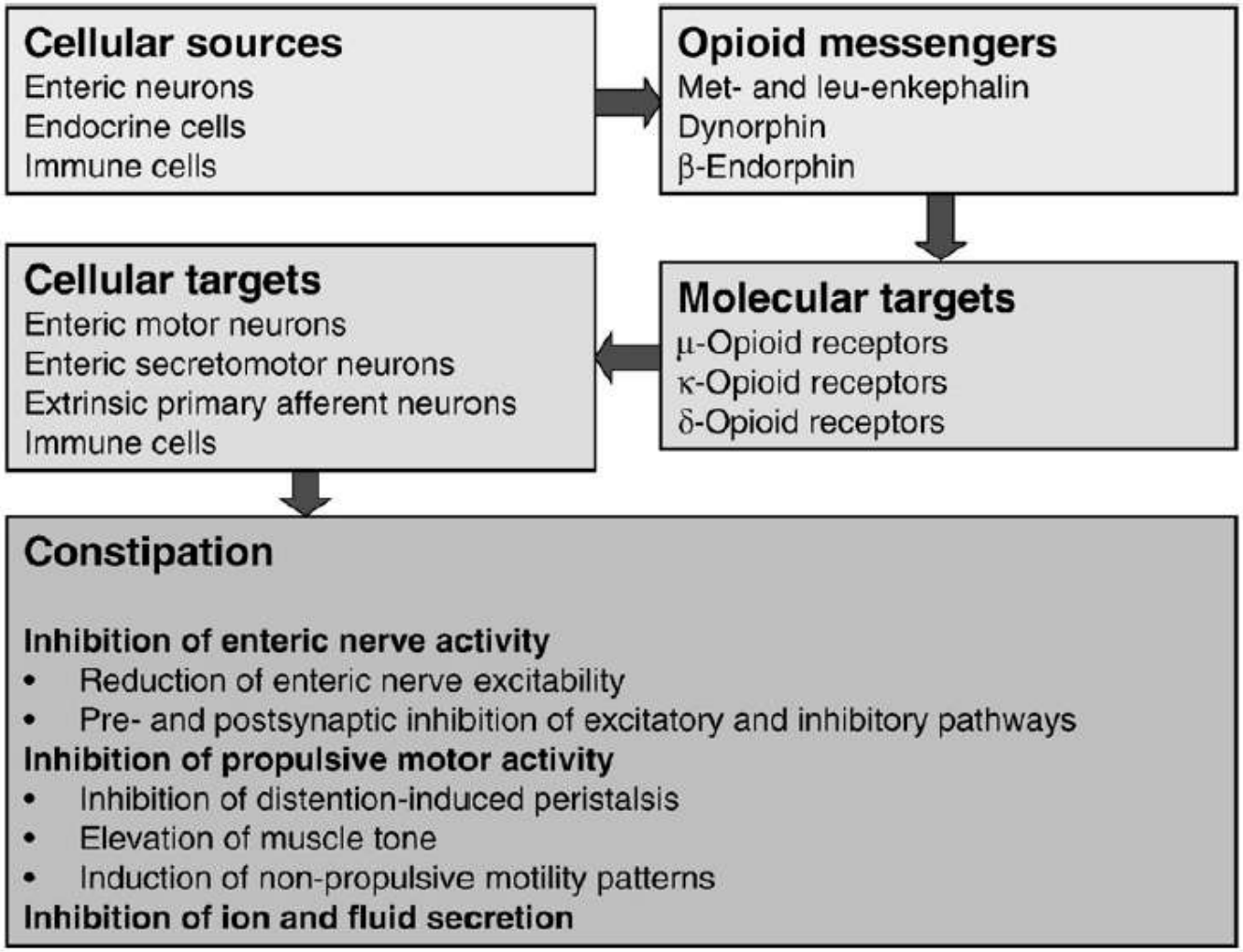

Fig. 1. Overview of the gastrointestinal opioid system.

Modification du péristaltisme intestinal

Morphine et antiagrégants plaquettaires

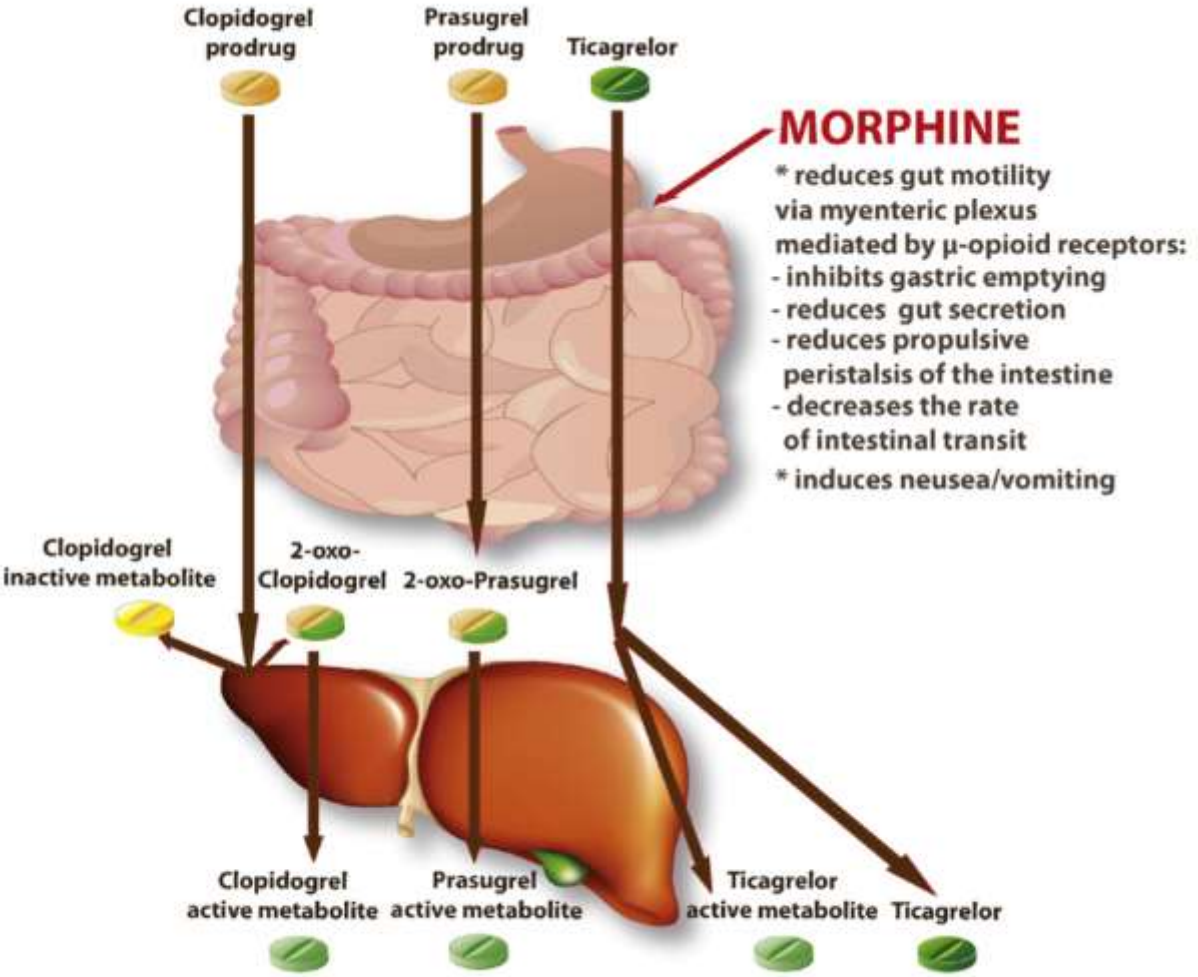

Fig. 1. The possible route of interaction between morphine and P2Y12 receptor inhibitors.

Kubica J et al. Int J Cardiol. 2016

Modification du péristaltisme intestinal

Morphine et clopidogrel

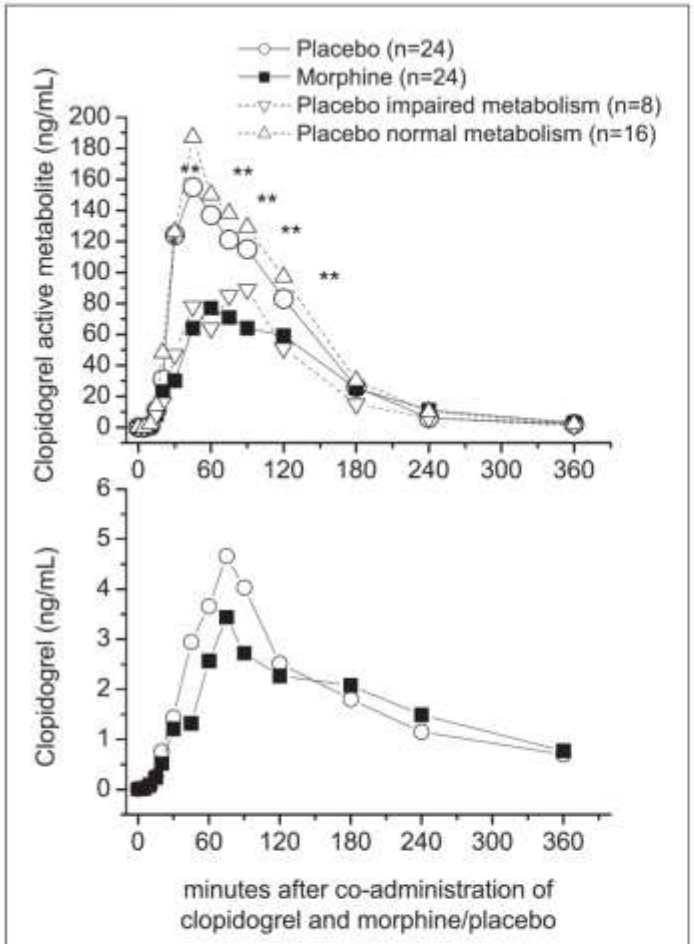

Figure 2 **Morphine Lowers Plasma Concentrations of Clopidogrel Active Metabolite**

Healthy volunteers (n = 24) received a 600-mg loading dose concomitantly with a placebo or 5 mg morphine. $p < 0.001$ repeated measures analysis of variance; $*p < 0.05$; $**p \leq 0.01$ designate differences between treatments (Wilcoxon test). Data present medians without error bars for reasons of clarity.

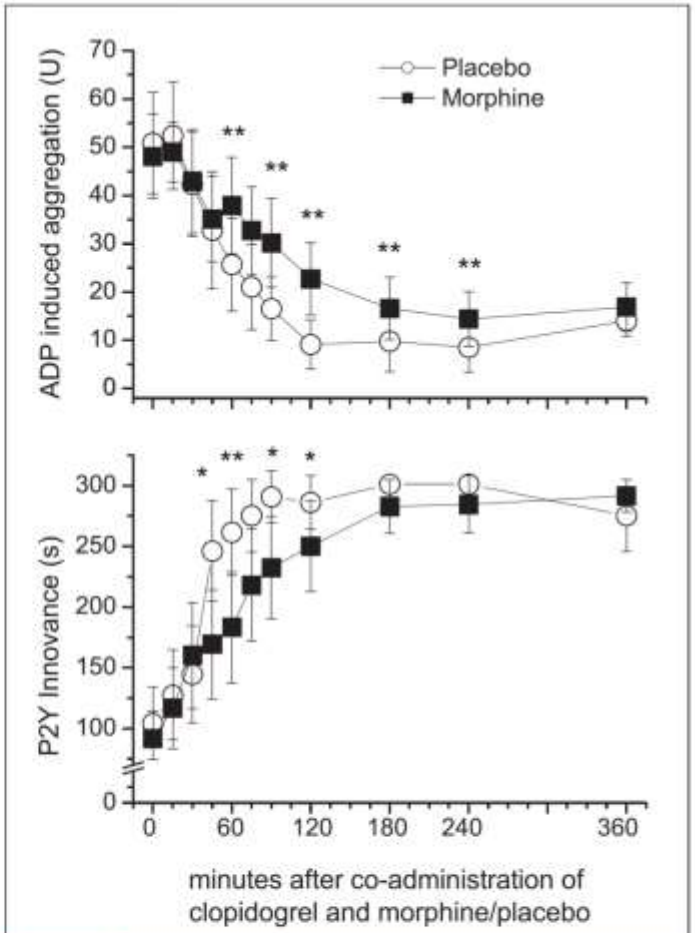

Figure 3 **Morphine Retards and Decreases Clopidogrel Effects**

Adenosine-diphosphate (ADP)-induced aggregation was measured by whole-blood aggregometry (n = 24) and with the P2Y- cartridge of the platelet function analyzer (n = 21). $p < 0.001$ repeated measures analysis of variance; $*p < 0.05$; $**p \leq 0.01$ designate differences between treatments (Wilcoxon test). Data present mean ± 95% confidence interval.

Hobl EL et al. J Am Coll Cardiol. 2014 Feb 25;63(7):630-5.

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Altération de la flore intestinale

Antibiotiques et AVK

Concurrent Use of Warfarin and Antibiotics and the Risk of Bleeding in Older Adults

Jacques Baillargeon, PhD,[a,b] Holly M. Holmes, MD,[c] Yu-Li Lin, MS,[b] Mukaila A. Raji, MD, MSc,[b,d] Gulshan Sharma, MD, MPH,[b,d] Yong-Fang Kuo, PhD[a,b,d]

[a]Department of Preventive Medicine
Galveston, Tex; [c]Department of Ger
of Internal Medicine, University of

Am. J. Med. 2012

Serious Bleeding Events due to Warfarin and Antibiotic Co-prescription in a Cohort of Veterans

Michael A. Lane, MD, MSc,[a] Angelique Zeringue, MS,[a,b] Jay R. McDonald, MD[a,b]

[a]Washington University, St. Louis, Mo; [b]St. Louis Veterans Affairs Medical Center, St. Louis, Mo.

Am. J. Med. 2014

N= 38762 patients > 65 ans sous warfarine –> rôle de l'exposition à un ATB dans les 15 jours qui ont précédé l'hospit pour saignement

Table 3 Association between Specific Antibiotic Agent Exposure and Hospitalization for Bleeding in Older Patients Receiving Warfarin

Antibiotic Drug	Matched Controls[a] n (%)	Cases n (%)	Univariate OR (95% CI)	Multivariable[b] OR (95% CI)
Azole antifungals	8 (0.33)	17 (2.13)	6.49 (2.79-15.10)	4.57 (1.90-11.03)
Macrolides	35 (1.46)	24 (3.01)	2.09 (1.24-3.54)	1.86 (1.08-3.21)
Quinolones	56 (2.34)	40 (5.01)	2.20 (1.46-3.33)	1.69 (1.09-2.62)
Cotrimoxazole	22 (0.92)	22 (2.76)	3.06 (1.68-5.55)	2.70 (1.46-5.05)
Penicillins	50 (2.09)	31 (3.88)	1.89 (1.20-2.99)	1.92 (1.21-2.07)
Cephalosporins	39 (1.63)	36 (4.51)	2.85 (1.80-4.52)	2.45 (1.52-3.95)

OR = odds ratio; CI = confidence interval.
[a]See Table 1.
[b]Multivariable analyses were adjusted for: all drug groups; comorbidity index; having stayed in a nursing home in the 90 days before event/index date.

Altération de la flore intestinale

Antibiotiques et AVK

Réduction de dose préemptive (10 à 20%) vs. surveillance de l'INR seulement

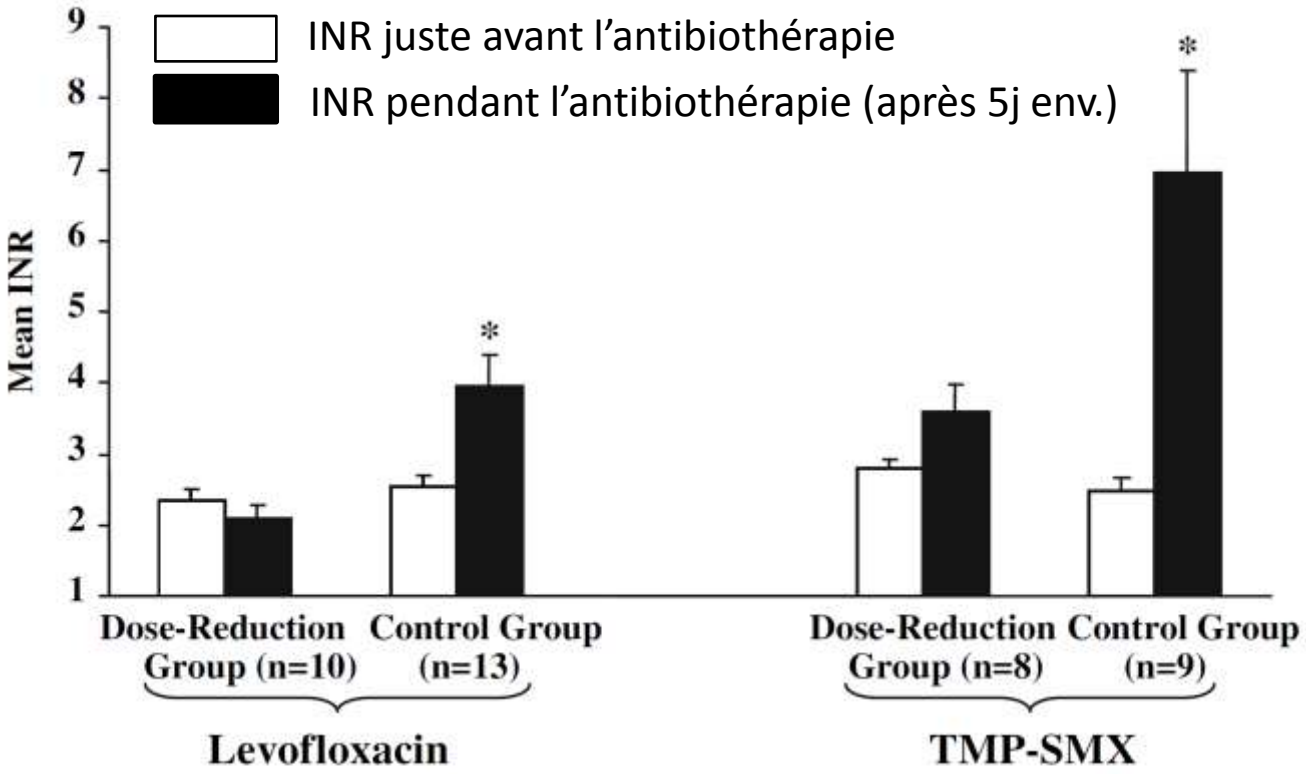
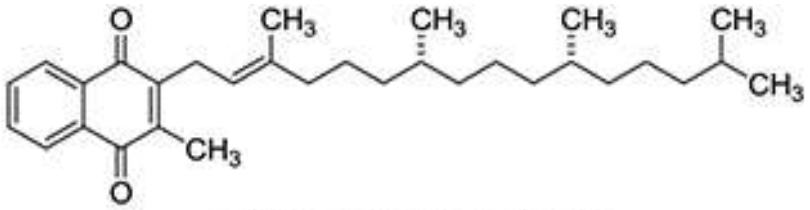


Fig. 1 Mean pre-antibiotic (empty bars) and post-antibiotic (black bars) INR values for the warfarin DR and control groups, for TMP-SMX- and levofloxacin-treated patients. *$P < 0.02$ vs. corresponding pre-antibiotic INR

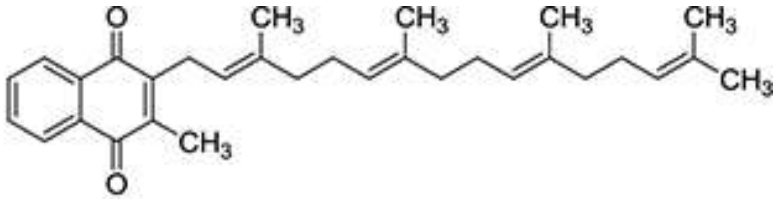
Ahmed A et al. J Thromb Thrombolysis. 2008 Aug;26(1):44-8.

Altération de la flore intestinale

Vitamine K et microbiote intestinal



vitamin K_1 (phylloquinone)



vitamin K_2 (menatetrenone, MK-4)

Altération de la flore intestinale

Amoxicilline/Acide clavulanique et MPA

Pharmacokinetic Drug Interaction of Mycophenolate With Co-Amoxiclav in Renal Transplant Patients

Ratna P. et al. Transplantation. 2011 Mar 27;91(6):e36-8.

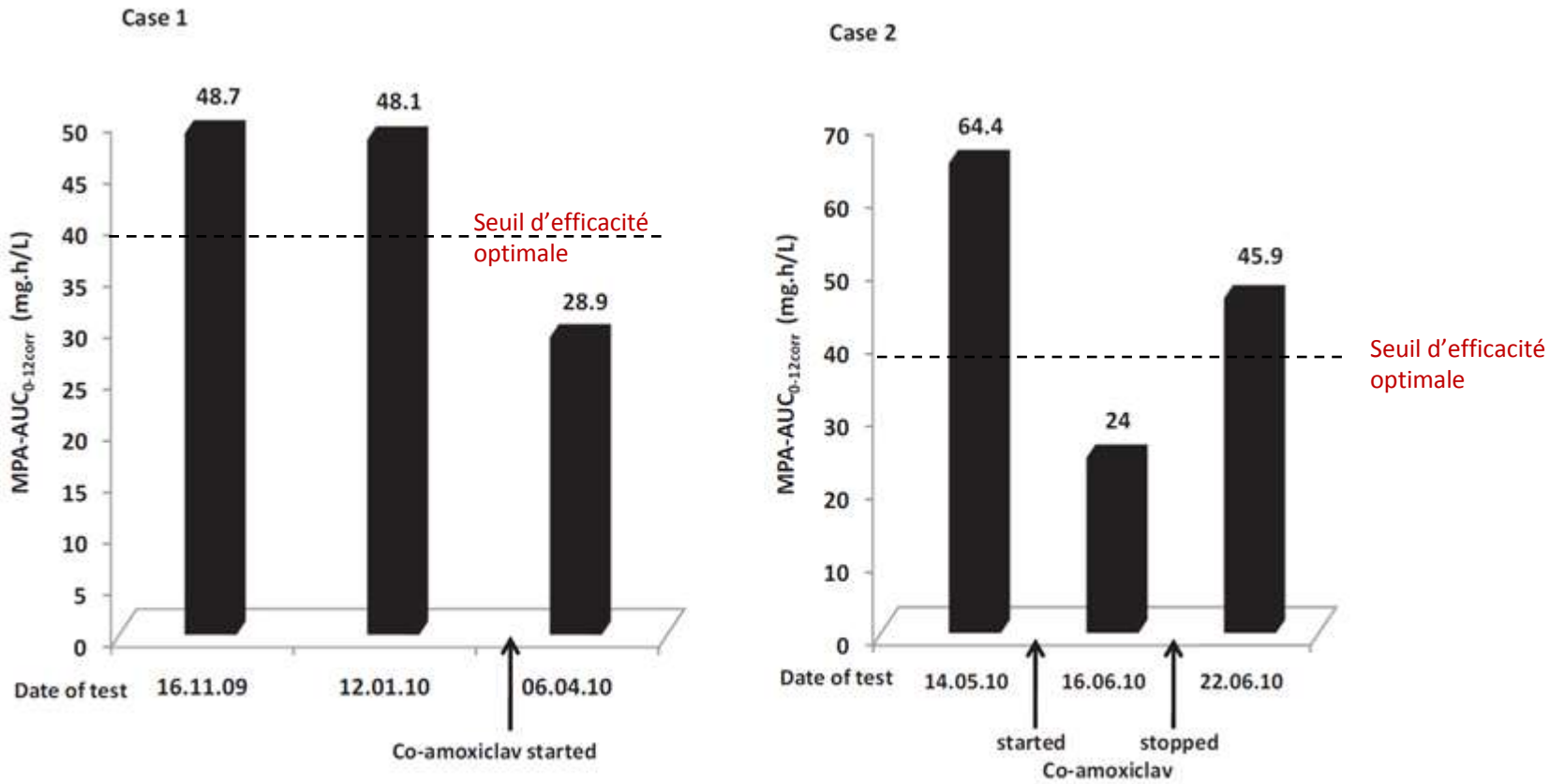
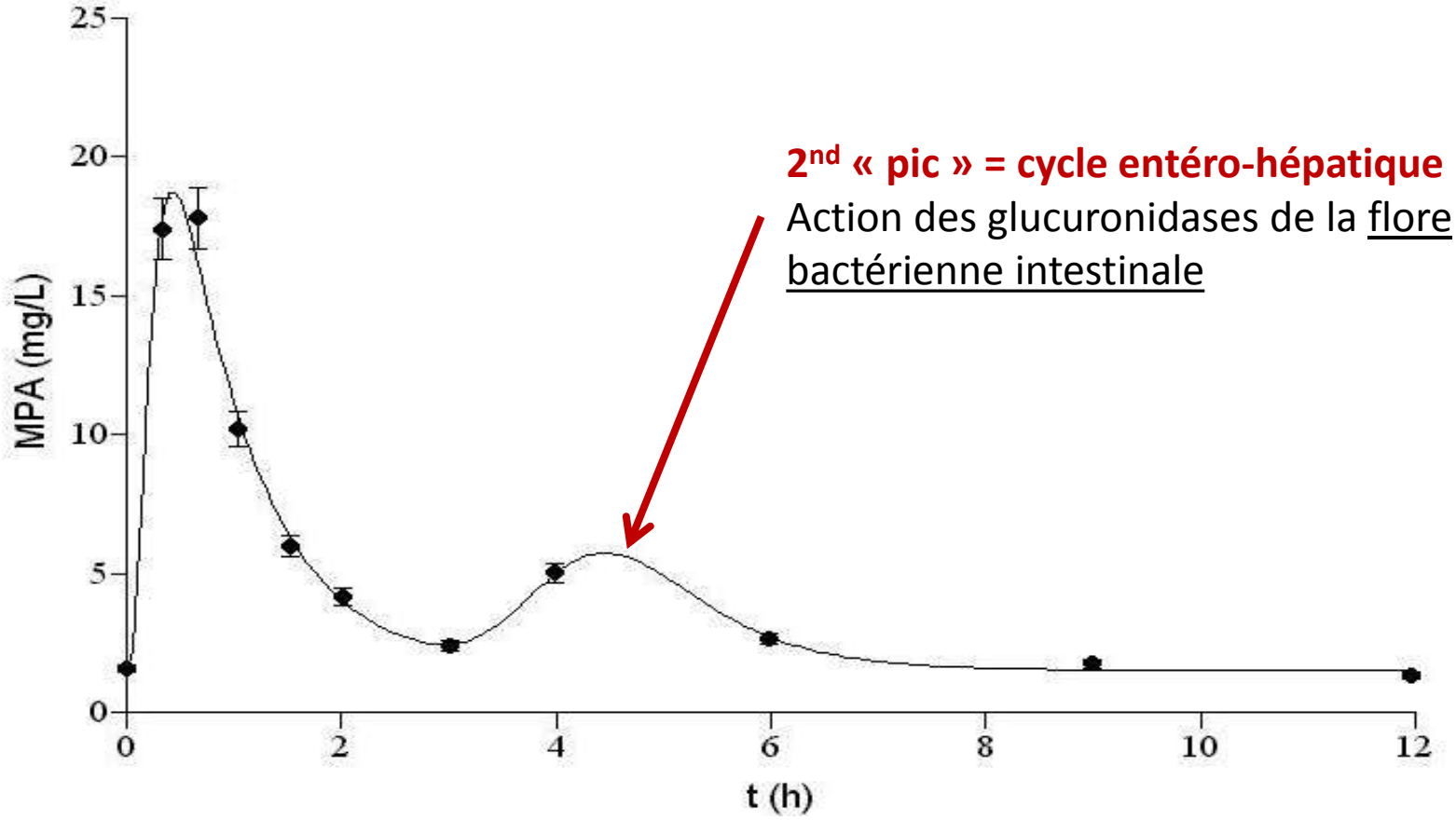


FIGURE 1. Changes in mycophenolic acid (MPA) concentration time profile with and without Co-amoxiclav.

Altération de la flore intestinale

Amoxicilline/Acide clavulanique et MPA

Exemple : concentrations plasmatiques de MPA au cours de temps après administration d'une dose par voie orale



2nd « pic » = cycle entéro-hépatique

Action des glucuronidases de la flore bactérienne intestinale

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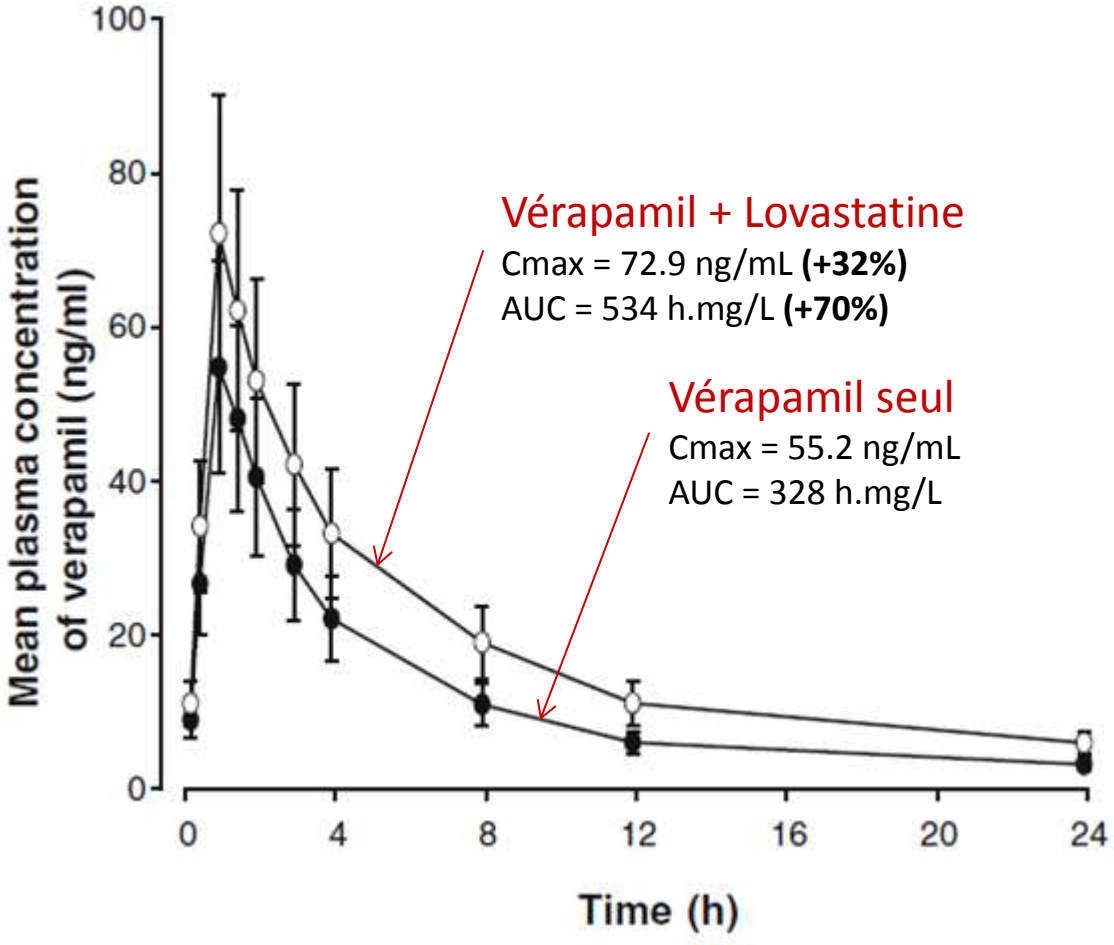
- Altération de la flore intestinale
- **Modification du transport entérocytaire**

Modification du transport entérocytaire

Lovastatine et Vérapamil

N= 14 volontaires sains (22-28 ans)

Etude en crossover



Vérapamil + Lovastatine

Cmax = 72.9 ng/mL **(+32%)**

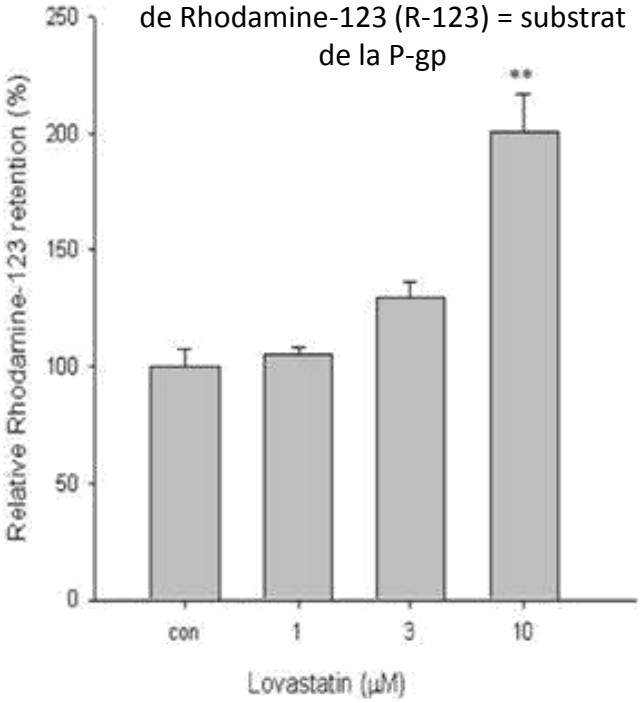
AUC = 534 h.mg/L **(+70%)**

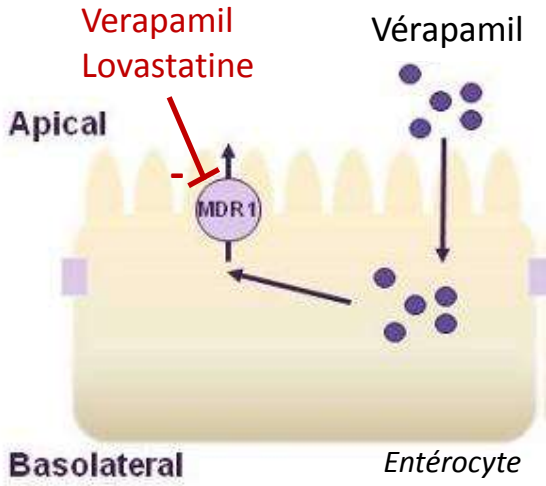
Vérapamil seul

Cmax = 55.2 ng/mL

AUC = 328 h.mg/L

Effet sur l'accumulation intracellulaire de Rhodamine-123 (R-123) = substrat de la P-gp





Choi DH et al. Eur J Clin Pharmacol. 2010 Mar;66(3):285-90

Modification du transport entérocytaire

Lovastatine et Vérapamil

Effet sur la pression artérielle

Table 1 Mean blood pressures (mmHg) after the oral administration of verapamil and lovastatin in normal subjects (n=14)

Time[a]	Drug	
	Verapamil (alone)	Verapamil with lovastatin
0 (control)	121±9.4	120±9.0
1	116±10.0	108±8.1*
3	112±8.8	104±8.1*
6	113±9.0	106±8.3*
12	116±9.4	111±9.0
24	119±9.2	116±9.2

Values are given as the mean ± standard deviation (SD)

*P<0.05; difference is significant compared to the control (before administration of verapamil with lovastatin)

[a] 0 (control), before drug administration

- 8 mmHg

- 8 mmHg

- 6 mmHg

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Conclusion

Nombreux mécanismes possibles au niveau du tube digestif:

- Complexation (ex: calcium et lévothyroxine)
- Modification du pH gastrique: (ex: IPP et erlotinib)
- Modification de la vidange gastrique: (ex: métoclopramide et ciclosporine)
- Modification du péristaltisme intestinal: (ex: morphine et clopidogrel)
- Altération de la flore intestinale: (ex: antibiotiques et AVK)
- Modification du transport entérocytaire: (ex: lovastatine et vérapamil)

Les interactions cliniquement pertinentes sont probablement fréquentes mais très peu documentées!

Merci de votre attention !

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