

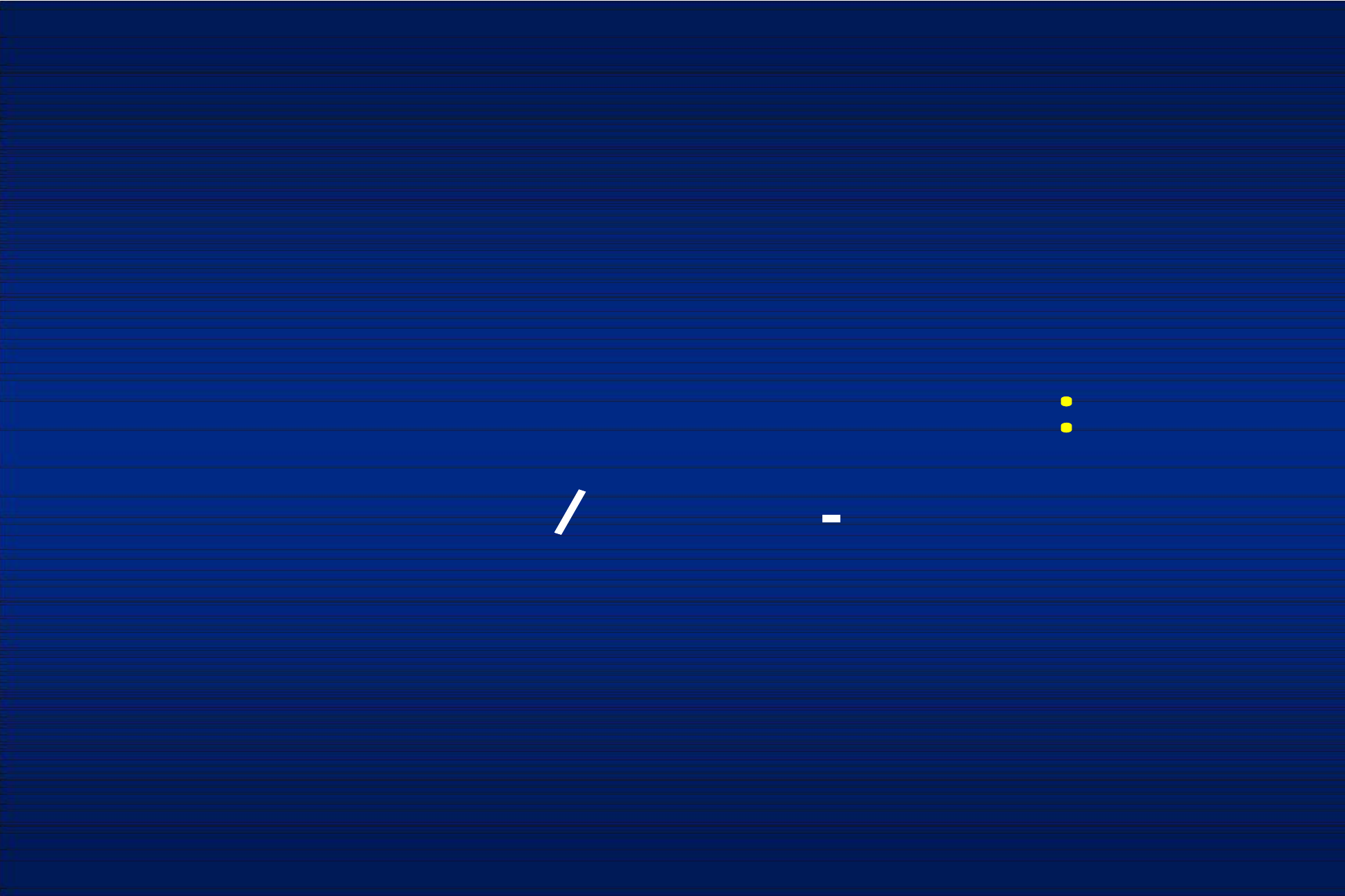
ГАСТРОЭНТЕРОЛОГИИ

И

НУТРИЦИОЛОГИИ



БЕЛМАПО



Rabeprazole

- pH (pH <1.3)
- (pH
- 1.3–2.3)
- /
- H⁺



/

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— pH

Joelsson B, et al. *Gut* 1989;30:1523-1525.
Smith JL, et al. *Gastroenterology* 1989;96:683-689.



Berardi RR, et al. *Am J Health Syst Pharm.* 1998;55:2289-2298.
Richardson P, et al. *Drugs.* 1998;56:307-335.
Hunt RH. *Aliment Pharmacol Ther.* 1995;9(Suppl 1):3-7.

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2003

20-40



24-

(mmol.h/L)

(pmol.h/L)

, 1996, UEGW

- Placebo 679 296
- Rabeprazole 10 mg 156*
- Rabeprazole 20 mg 131*
- Rabeprazole 40 mg 86*
- 2403*
- *p < 0.001 vs placebo
- C. Blanshard, et al 1996 (UEGW)



UEGW

1997,

• **Placebo**

• **Omeprazole**

• **Rabeprazole**

• ***p ≤ 0.001 vs placebo, #p ≤ 0.001 vs omeprazole,**

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**Mean 24-hour
intra gastric acidity
- Day 1 (mmol/L/h)**

**Mean 24-hour
intra gastric acidity
- Day 8 (mmol/L/h)**

1020

946

660*

352*

406*#

250*

/M. Williams, et all, London/



UEGW

1997,

	Intention to treat analysis %	Per protocol analysis %
RMC	100*	100*
RAC	95*	100*
RAM	90	88
RC	63	67

*P < 0.05 compared with RC

RAC, RAM, RMC or RC (R = rabeprazole 20 mg bd, A = amoxycillin 1 g bd, C = clarithromycin 500 mg bd, M = metronidazole 400 mg bd)

RMC_W.A. Stack, et al London



, 1998, WCOG

Theophylline **CYP1A2**

Phenytoin **CYP2C9**

Warfarin **CYP2C9**

Diazepam⁽¹⁾ **CYP2C19**

- **Digoxin** **↑ AUC, Cmax, t1/2**

- **Ketoconazole** **↓ AUC, Cmax**

- T. Humphries, 1998, UEGW. 1-Clin Pharmacol Ther 1995; 58: 155-164

- (, ,)

/J.H. Walsh et all, 1998 WCOG/

- /
- 5 10 20 40 _____

• %	BAO	76	88	86	89
• %	GAO	82	81	95	94
• %	-	77	80-87 ¹	87	

-
- 20

•

/M. Kawaguchi et al

1998 WCOG

AUC (ng. hr/ml)	943 ± 605	1021 ± 713	901 ± 544	937 ± 617
Cmax (ng/ml)	631 ± 322	517 ± 270	453 ± 138	437 ± 237
t1/2 (hr)	1.1 ± 0.6	1.2 ± 0.7	1.1 ± 0.5	1.5* ± 0.7
<hr/>				(* p < 0.01)

• /G. Rindi et al, 1998 WCOG/
ECL

10 20

A. Spera et al, 1998, WCOG

AUC (ng. hr/ml)	1194.6 ± 398.8	631.2 ± 273.8	422 ± 293	613 ± 483	1776 ± 496	809 ± 544
Cmax (ng/ml)	668.9 ± 215.6	426.9 ± 143.9	236 ± 204	347 ± 238	635 ± 199	401 ± 246
t1/2 (hr)	1.2 ± 0.3	0.9 ± 0.4	0.95 ± 0.9	0.82 ± 0.5	3.7 ± 2.2	1.7 ± 1.7



1999 UEGW

Sukegawa, et al, 1999, UEGW/

CYP2C19

450,
/M.

CYP	n	pH		
			Omeprazole	Rabeprazole
wt/wt	6	1.3 ± 0.06	3.4 ± 0.44	4.5 ± 0.47
wt/mut	6	1.3 ± 0.12	3.6 ± 0.54	5.1 ± 0.46
mut/mut	6	1.3 ± 0.14	$5.9 \pm 0.40^{*/**}$	4.8 ± 0.44

\pm SE, * $P < 0.05$ vs. wt/mut, ** $P < 0.01$ vs. wt/wt.



2002
WCOG

,

RMC

RAC

RAM

RC

*P < 0.05 compared with RC

RAC, RAM, RMC or RC (R = rabeprazole 20 mg bd, A = amoxycillin 1 g bd, C = clarithromycin 500 mg bd, M = metronidazole 400 mg bd)

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RMC_W.A. Stack, et al London

Intention to treat
analysis %

Per protocol
analysis %

100*

95*

90

63

100*

100*

88

67

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: PARIET™ 10mg. PARIET™ 20mg.

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— 9.42 mg

— 18.85 mg

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20

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PARIET

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(PARIET)

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450(CYP450),
warfarin, phenytoin, theophylline, diazepam, cyclosporin

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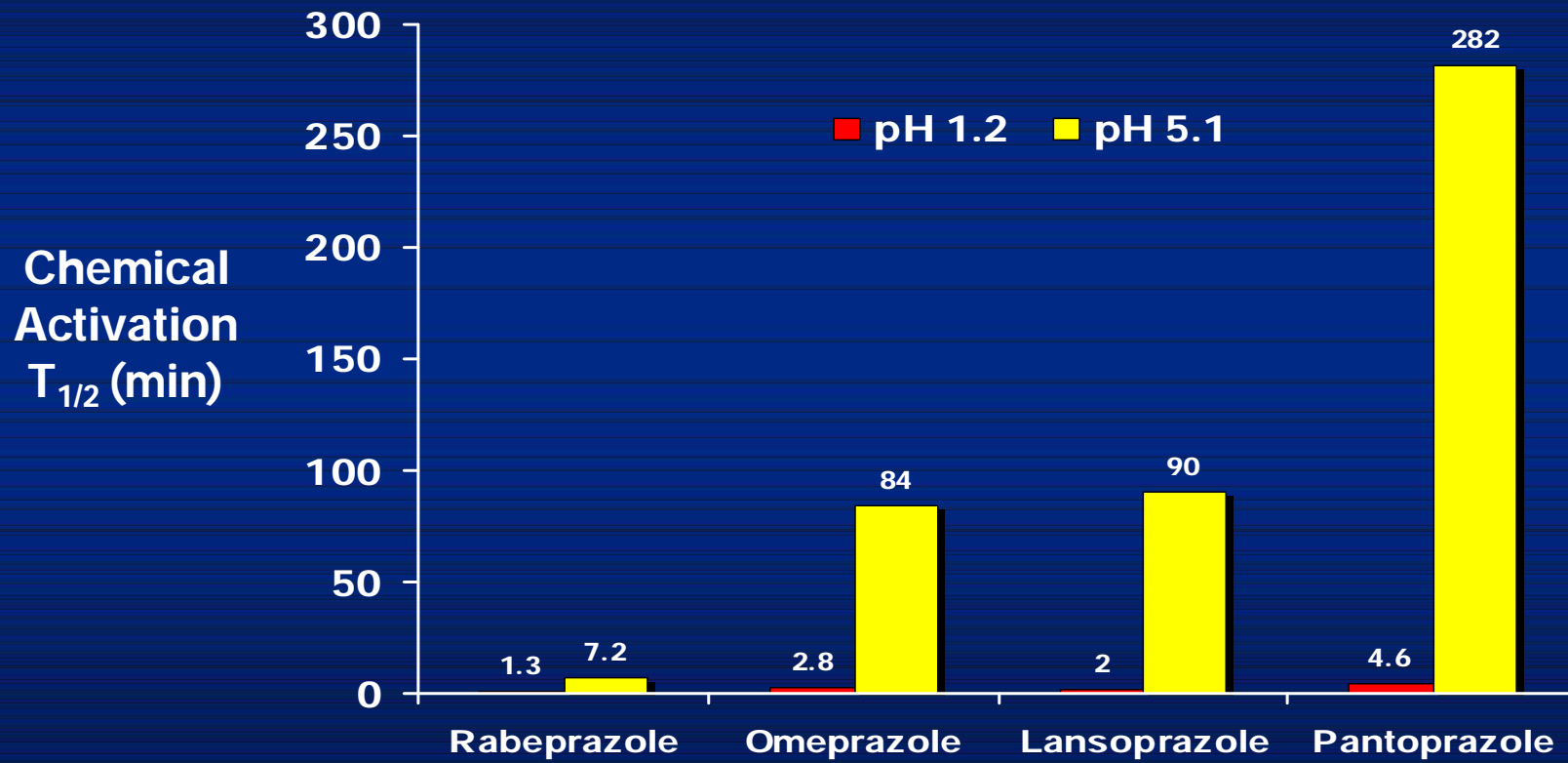
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33%, 22%.

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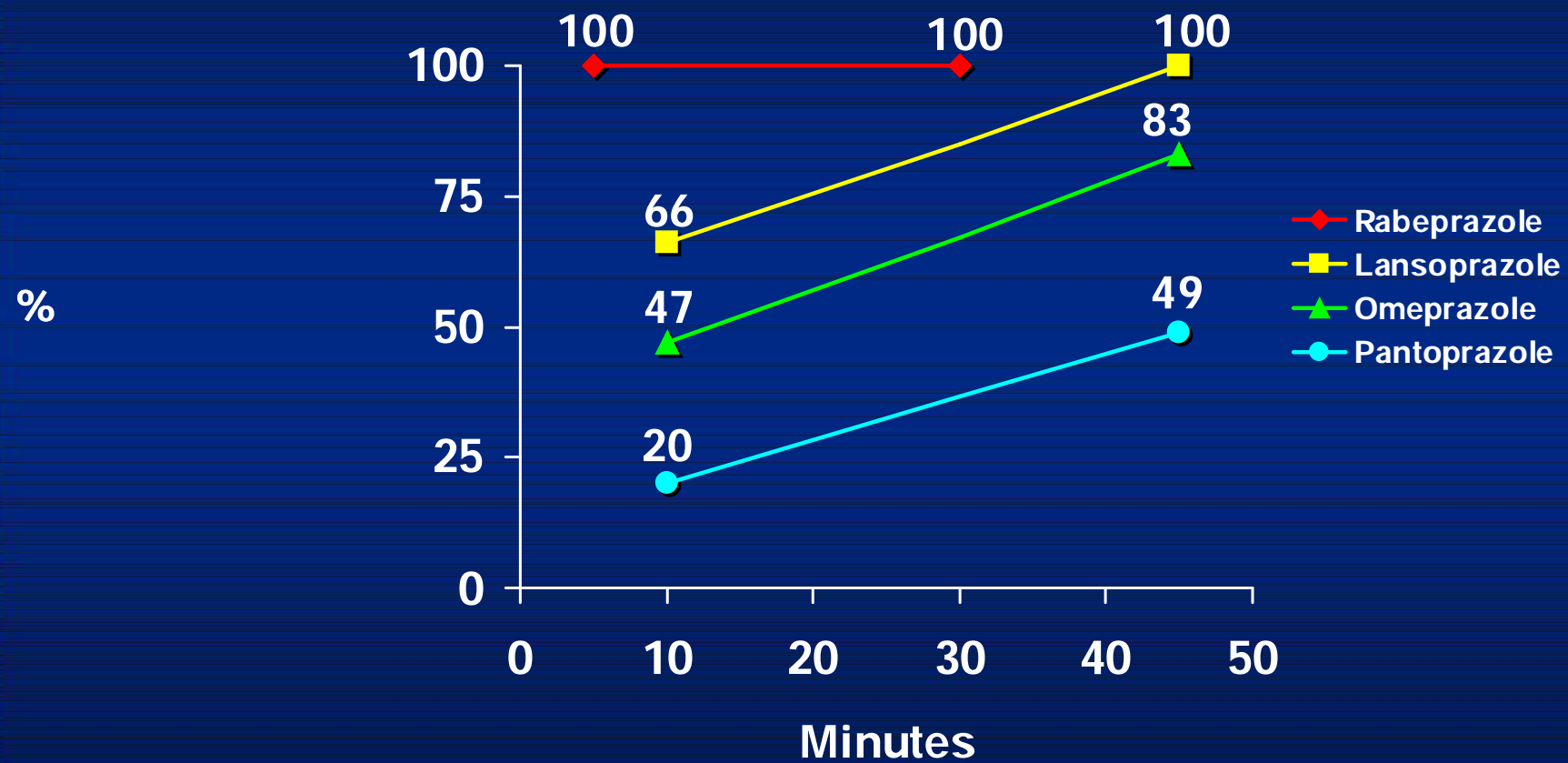
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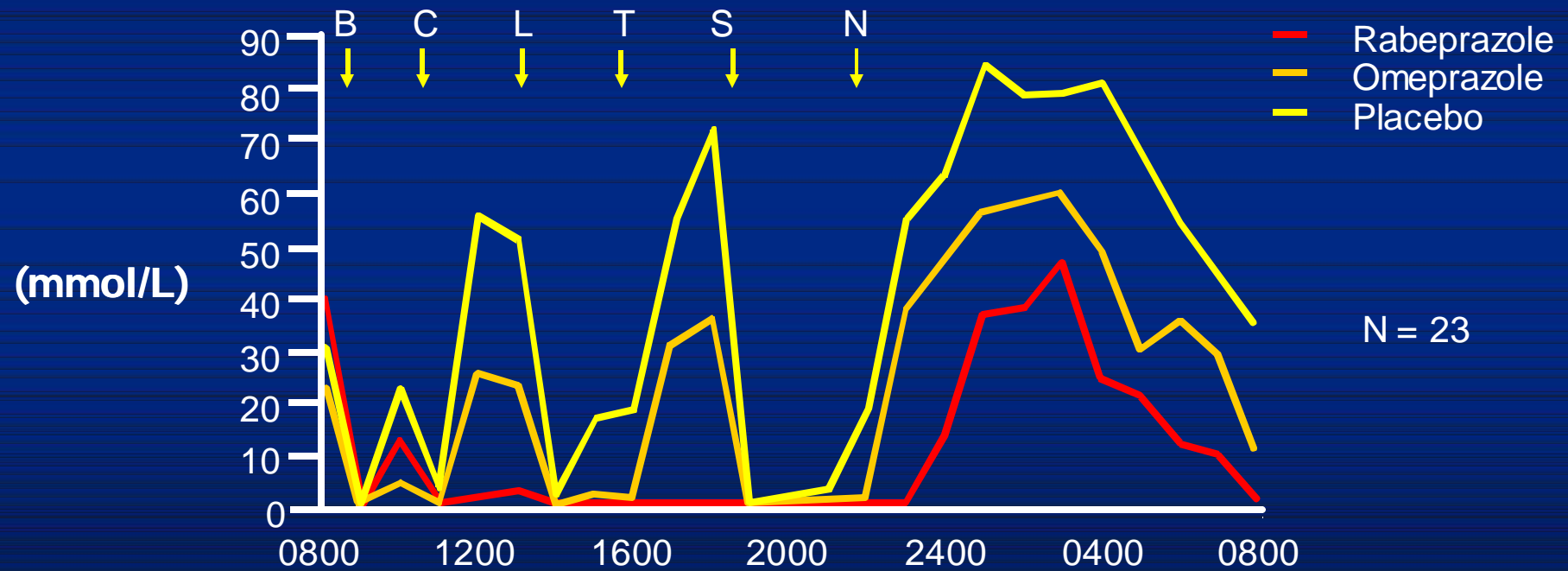
Kromer W, et al. *Pharmacology*. 1996;56:57-70.

⋮

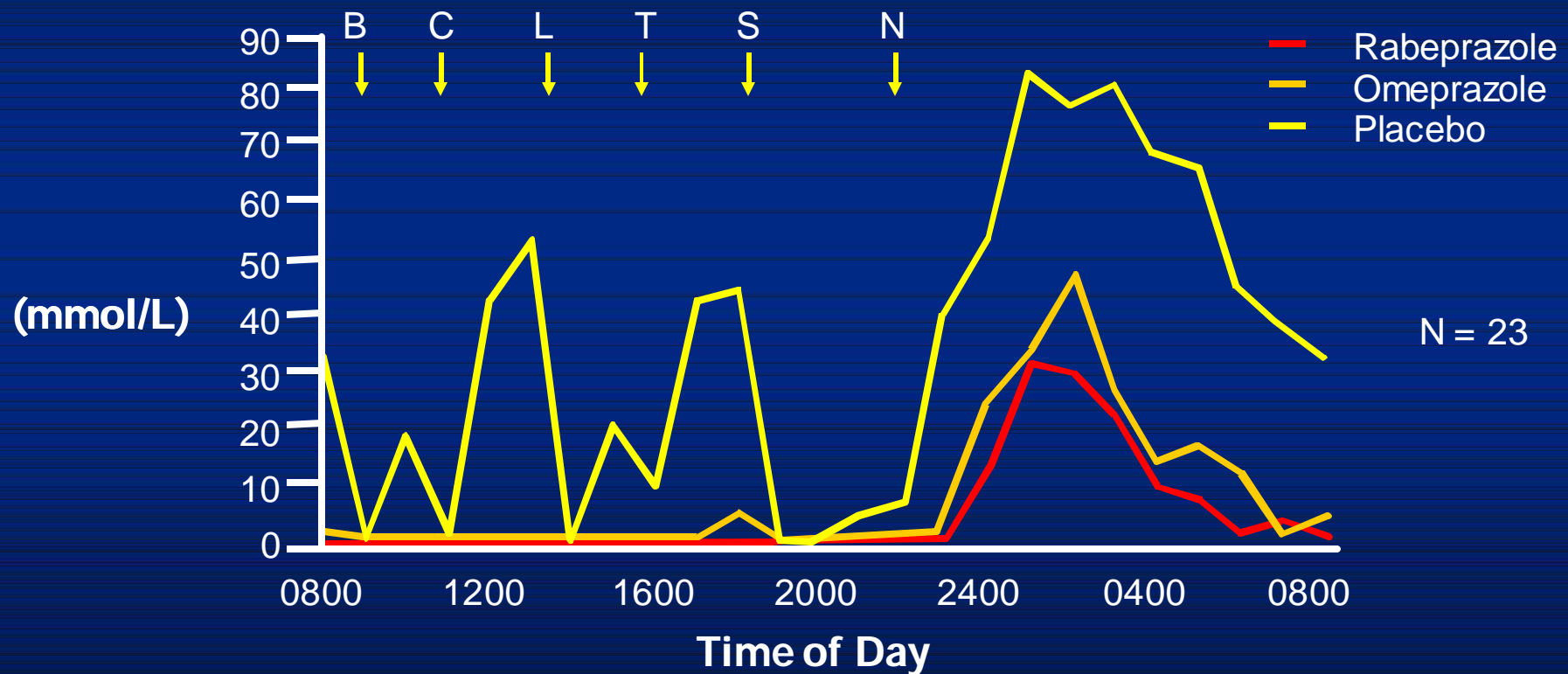


Rabeprazole

Omeprazole:

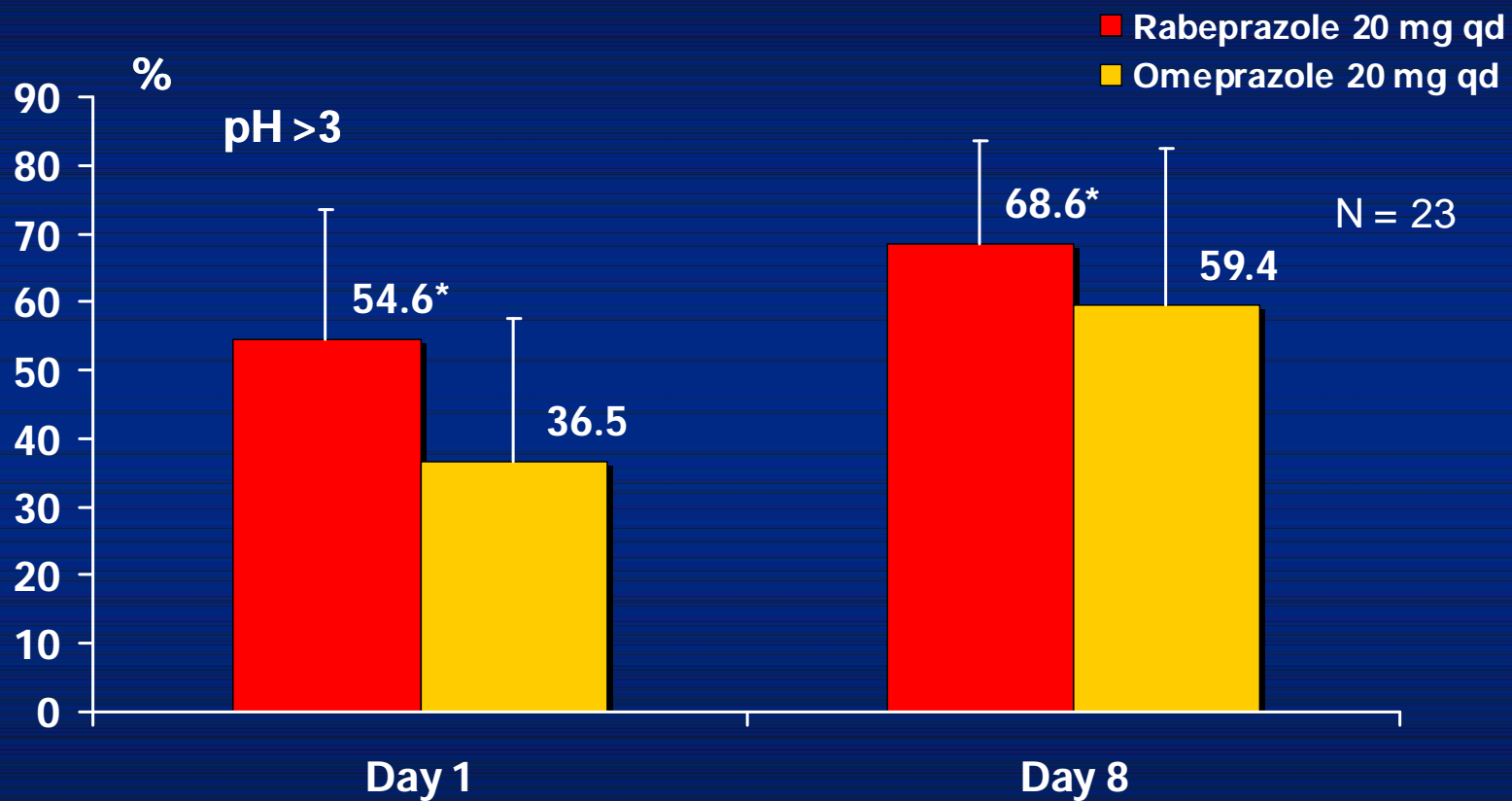


Rabeprazole vs Omeprazole:



Williams MP, et al. *Aliment Pharmacol Ther.* 1998;12:1079-1089.

pH:



A cause and effect relationship between these data and clinical effect has not been established

* $P < .001$ vs omeprazole

Williams MP, et al. *Aliment Pharmacol Ther* 1998;12:1079-1089.

24- pH Lansoprazole, Omeprazole, Rabeprazole

/ Median pH*		
Lansoprazole 15 mg	2.9	
Lansoprazole 30 mg	2.99	
Lansoprazole 60 mg	3.79	$P < .05$ vs lansoprazole 15 & 30 mg
Omeprazole 20 mg	3.01	
Omeprazole 40 mg	4.15	$P < .01$ vs lansoprazole 15 & 30 mg and $P < .05$ vs omeprazole 20 mg
Basal	2.15	
Rabeprazole 10 mg	5.05	$P < .016$ vs basal
Rabeprazole 20 mg	5.90	$P < .016$ vs basal, $P = .34$ vs 10 mg

* At day 5 of treatment for lansoprazole and omeprazole, at day 4 for rabeprazole

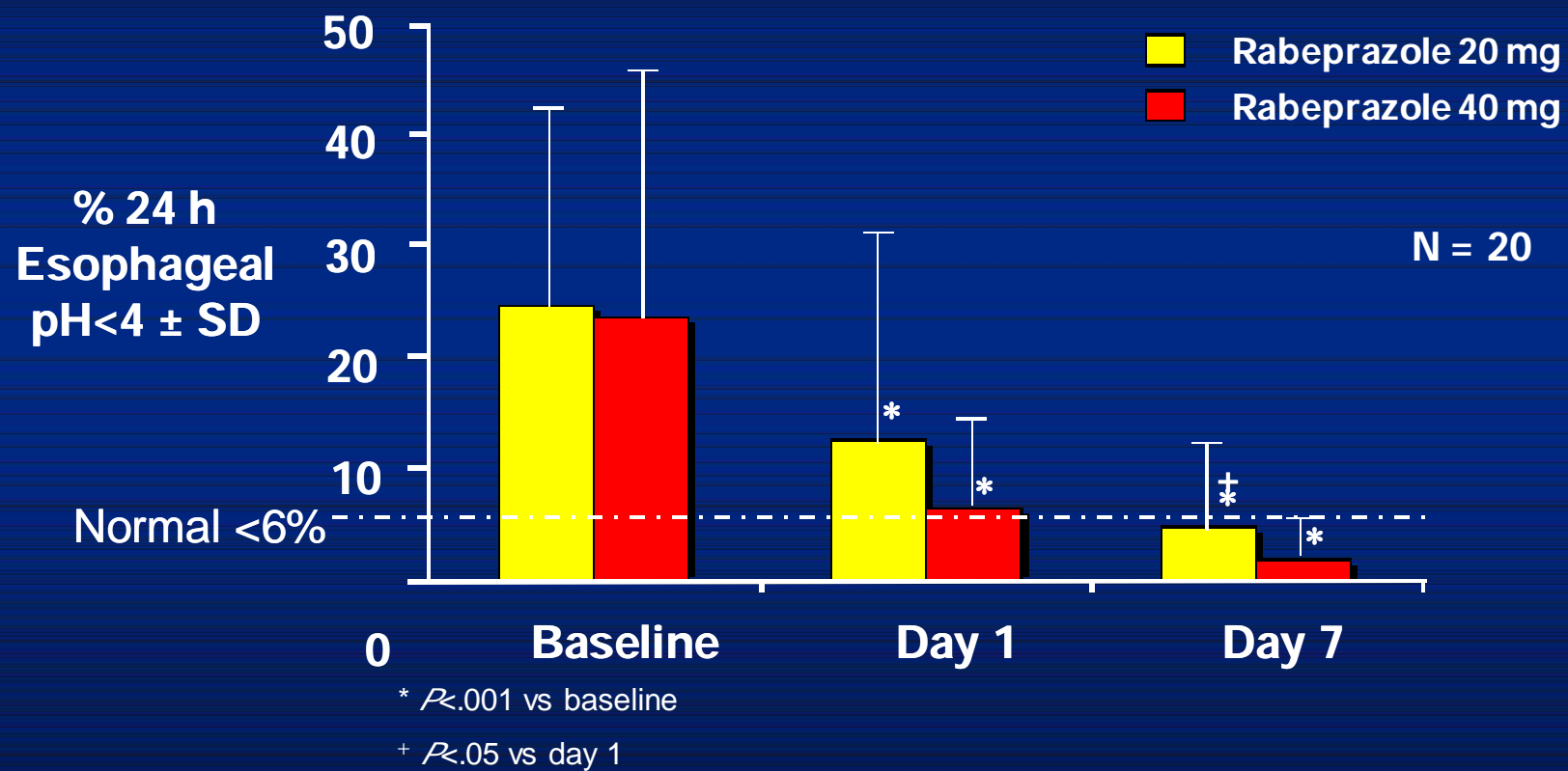
Seensalu R, et al. *Gastroenterology*. 1995;108:A215. Abstract.

Hongo M, et al. *J Exp Med*. 1998;186:43-50.

Median Intragastric pH (Range) During Lansoprazole and Pantoprazole Treatment of 12 Normal Subjects

Basal: 1.5 (1.1 – 2.0)			
	Lansoprazole	Pantoprazole	Lans vs Pant
Day 1 (24 hours)	4.0 (1.8 – 5.0)	2.1 (1.5 – 5.0)	$P = .007$
Day 7 (24 hours)	4.0 (2.0 – 5.0)	3.05 (1.8 – 7.5)	$P = \text{NS}$
Day 1 Daytime	4.55 (2.1 – 5.5)	2.18 (1.5 – 4.5)	$P = .003$
Day 7 Daytime	4.75 (2.4 – 6.3)	3.5 (2.0 – 7.1)	$P = .025$
Day 1 Nighttime	2.88 (1.6 – 6.0)	1.94 (1.4 – 5.0)	$P = .025$
Day 7 Nighttime	3.09 (1.3 – 5.0)	2.72 (1.6 – 7.7)	$P = \text{NS}$

Lans: Lansoprazole, Pant: Pantoprazole * $P \geq .05$, NS = $P \geq .05$, † $P = .046$, ‡ $P = .036$



Robinson M, et al. *Aliment Pharmacol Ther.* 1997;11:973-980.

Rabeprazole:

20 mg dose

$T_{1/2}$

0.82 – 1.7 h

C_{max}

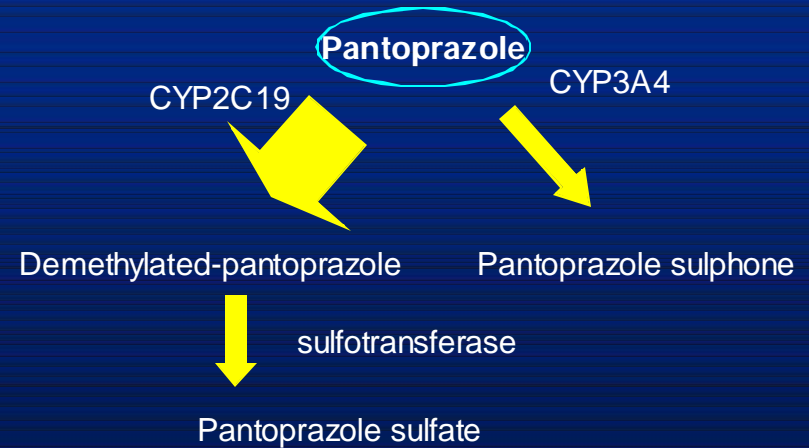
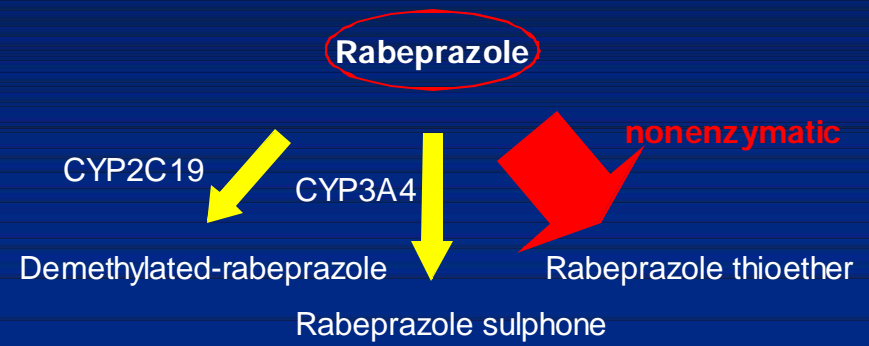
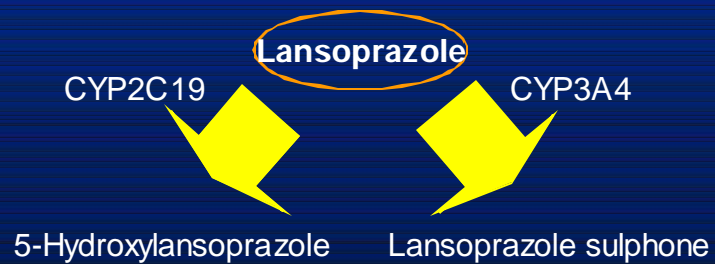
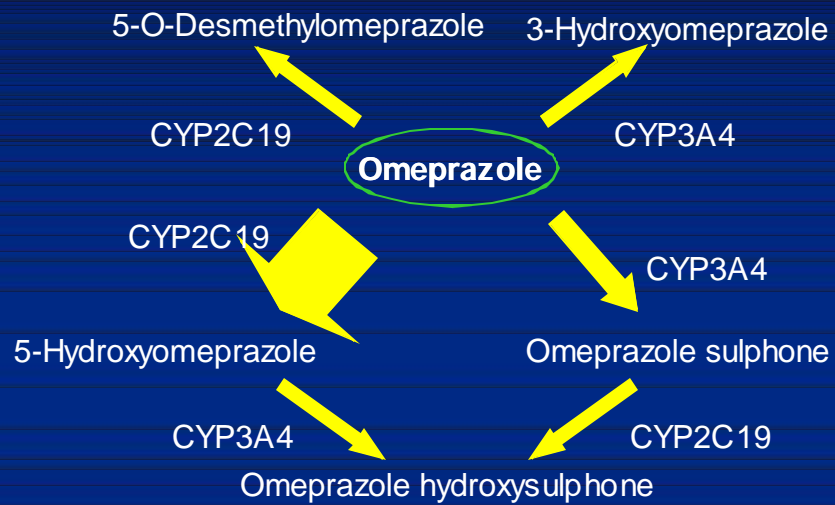
347 – 427 ng/mL

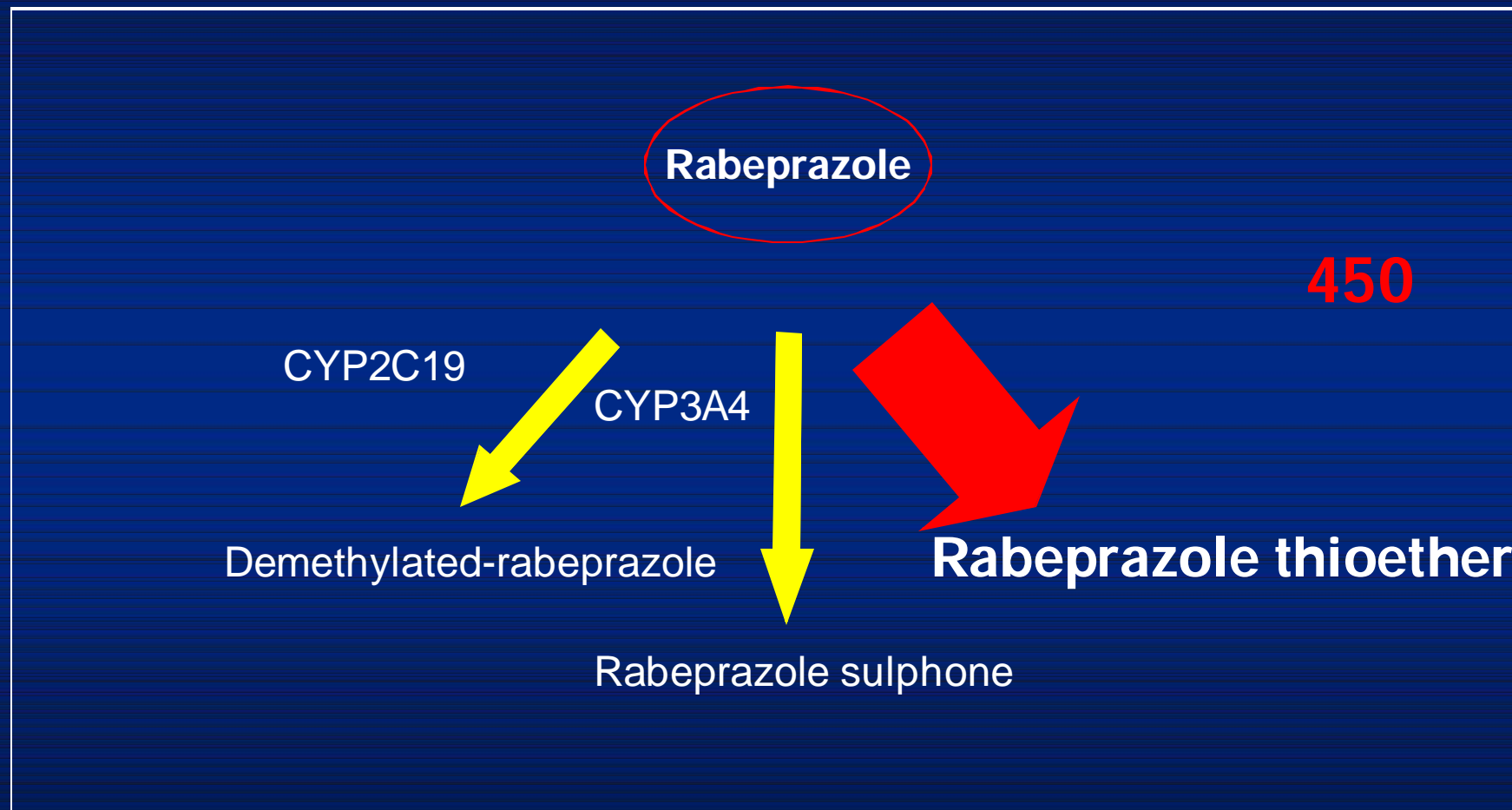
T_{max}

3.45 – 3.7 h

Metabolism

Nonenzymatic,
CYP450 3A4, 2C19





450,

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I:

CYP450

PPI	Diazepam	Warfarin	Phenytoin	Theophylline
Rabeprazole	—	—	—	—
Omeprazole	+	+	+	—
Lansoprazole	—	—	—	+ *
Pantoprazole	—	—	—	—

* No inhibition, possible induction

Humphries TJ, et al. *Gastroenterology*. 1996;110(Suppl):A138. Abstract.

Humphries TJ, et al. *Gut*. 1996;39(Suppl 3):A47. Abstract.

Ishizaki T, et al. *Clin Pharmacol Ther*. 1995;58:155-164.

Andersson T. *Clin Pharmacokinet*. 1996;31:9-28.

Rabeprazole:

US •

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Europe •

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	(N = 79)	(ITT)
RAC	Rabeprazole 20 mg bid Amoxicillin 1000 mg bid Clarithromycin 500 mg bid	95%
RAM	Rabeprazole 20 mg bid Amoxicillin 1000 mg bid Metronidazole 400 mg bid	90%
RCM	Rabeprazole 20 mg bid Clarithromycin 500 mg bid Metronidazole 400 mg bid	100%
RC	Rabeprazole 20 mg bid Clarithromycin 500 mg bid	63%

* Rabeprazole is currently licensed for eradication of *H pylori* in the US and Europe.

Stack W, et al. *Am J Gastroenterol*. 1998;93:1909-1913.

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2003