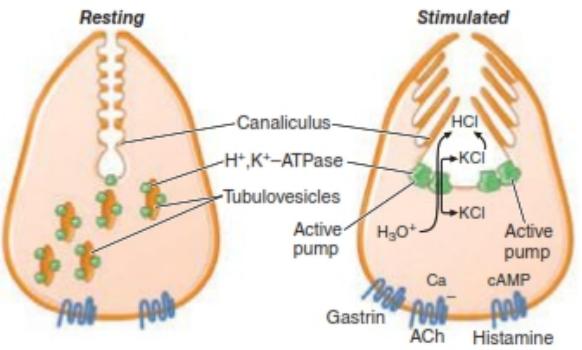


# MEDICINAL CHEMISTRY ROLE IN COMMUNITY PHARMACY SETTINGS



## ANALGESIC-ANTIPYRETIC AND ACID SUPPRESSANT MEDICATION

Disampaikan pada:

Kuliah Tamu- Fakultas Farmasi dan Sains UHAMKA

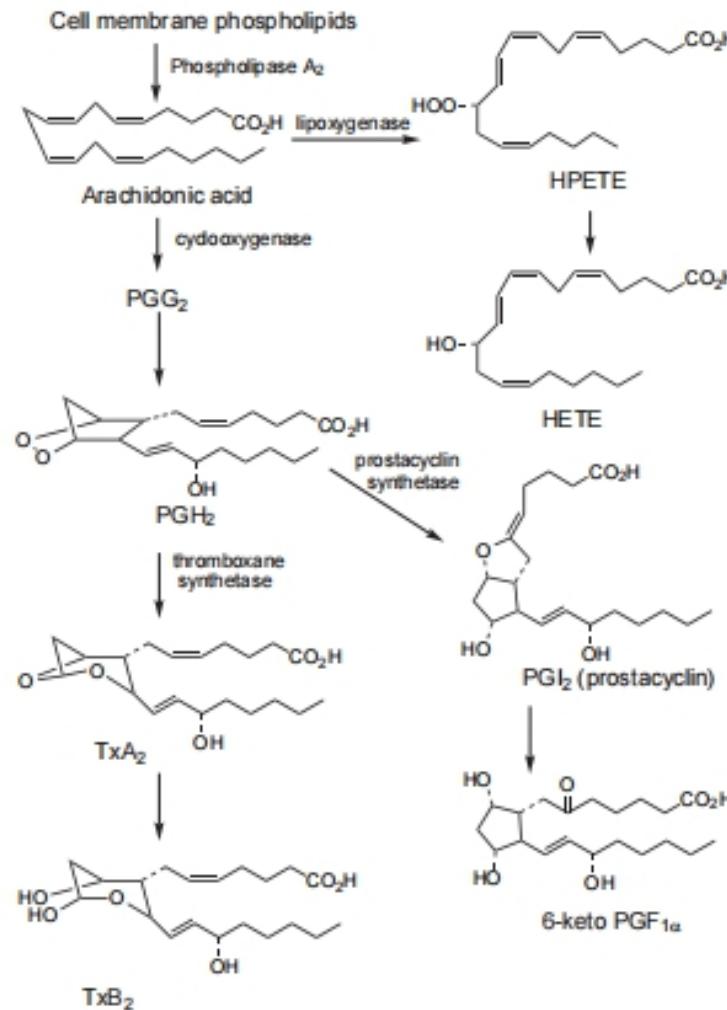
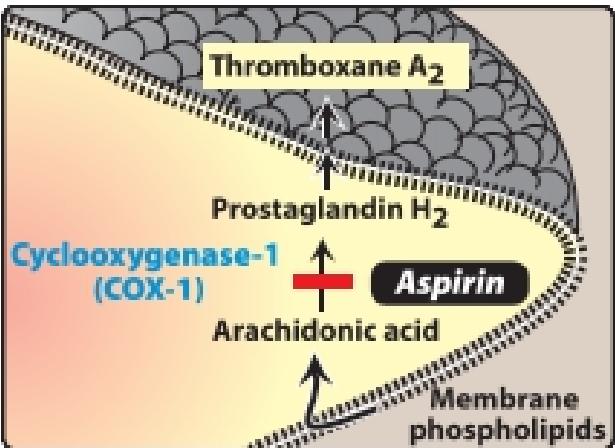
Sabtu, 29 Mei 2021

Primadi Avianto

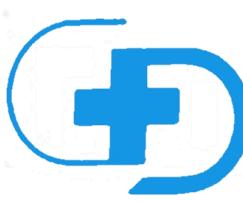
email: primadi-a-11@ff.unair.ac.id

Telegram: @primadi\_avianto

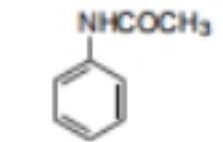
# BIOSYNTHESIS OF THROMBOXANES AND PROSTACYCLINE



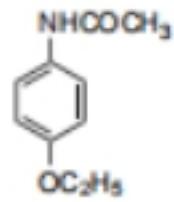
	PGE <sub>2</sub>	PGF <sub>2α</sub>	PGI <sub>2</sub>	TXA <sub>2</sub>
Uterus	Oxytocic dilation	Oxytocic constriction		
Bronchi	Dilates	Constricts		Constricts
Platelets			Inhibits	Aggregation
Blood vessels	Dilation	Constriction	Dilation	Constriction



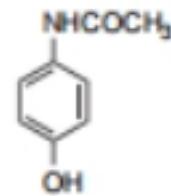
# ANALGESIC - ANTI PYRETIC



Acetanilide

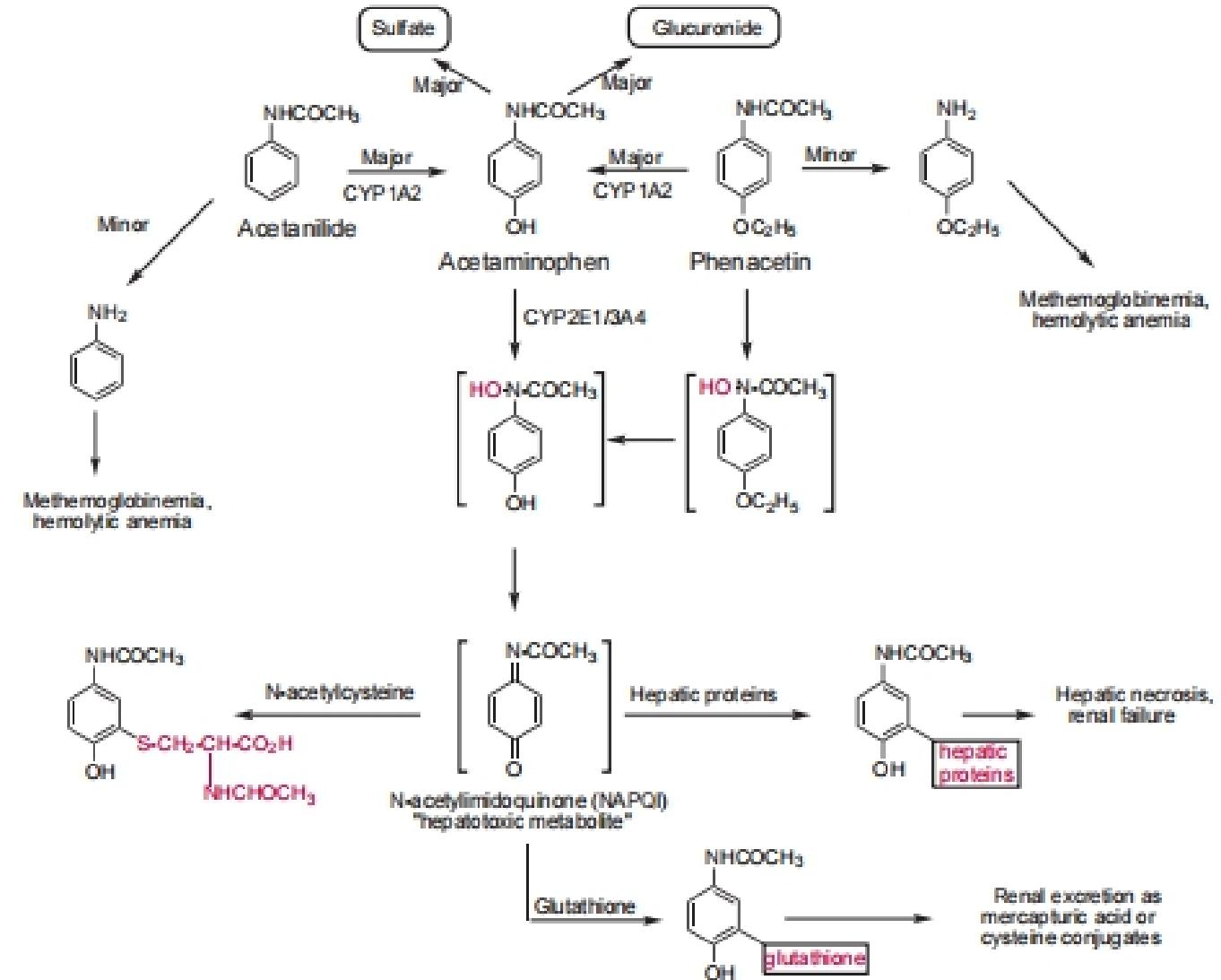


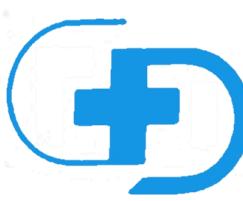
Phenacetin



Acetaminophen

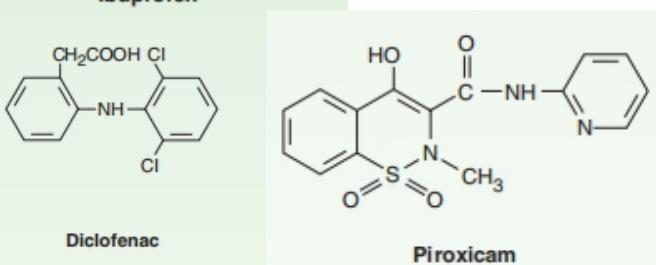
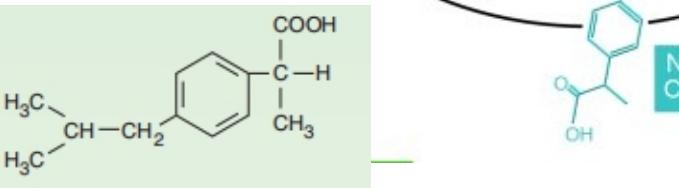
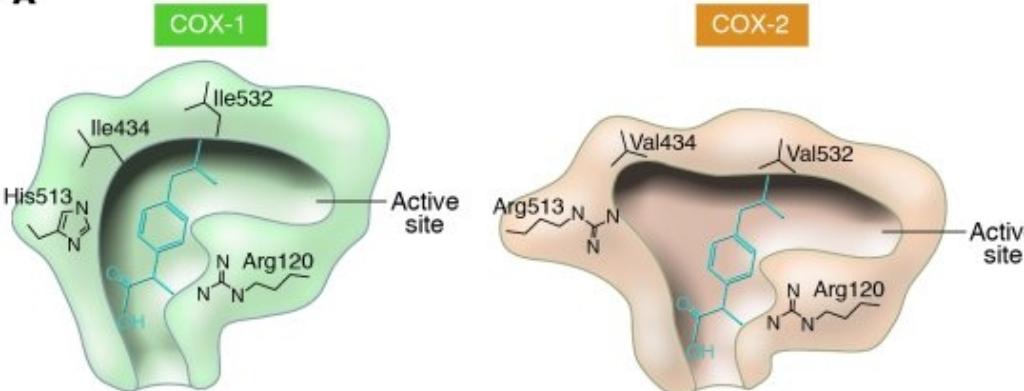
Drug	COX-1	COX-2	COX-3
Acetaminophen	>1,000	>1,000	460
Phenacetin	>1,000	>1,000	102
Aspirin	10	>1,000	3-1





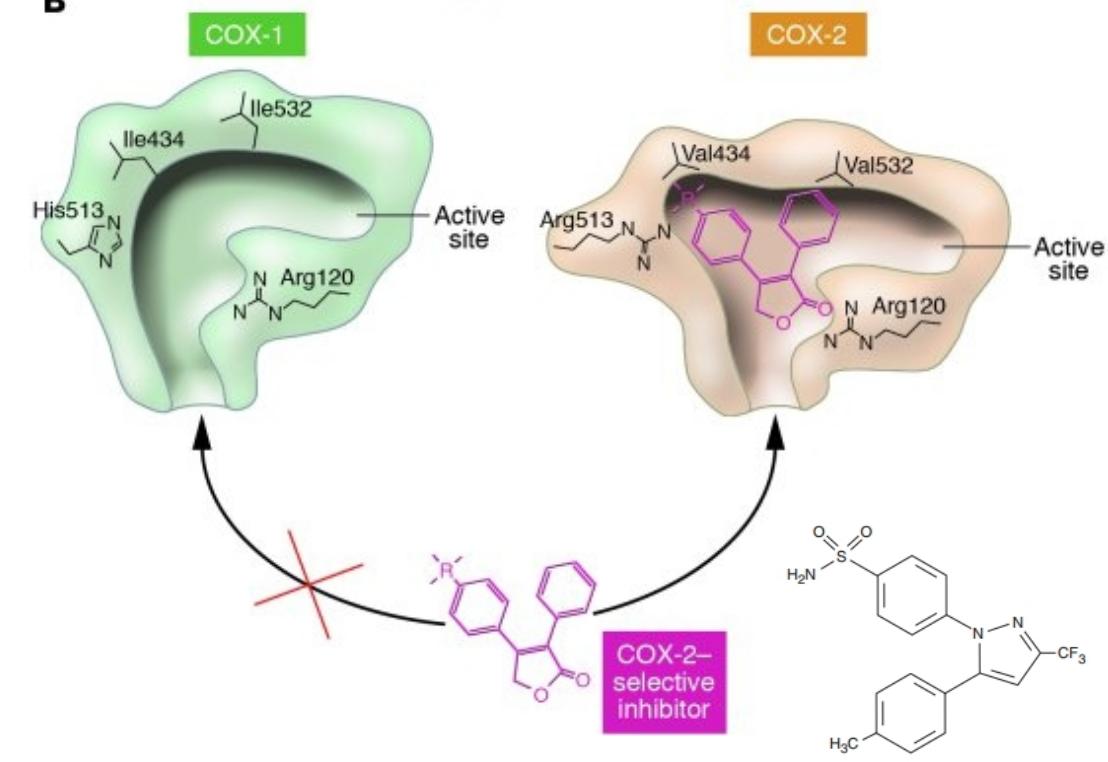
# COX-1 VS COX-2 INHIBITOR

A

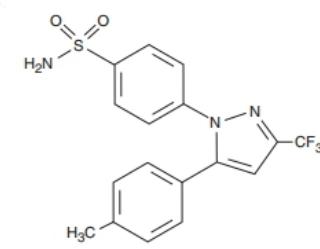


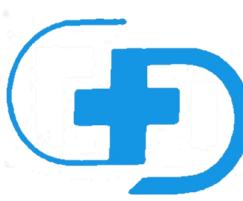
Piroxicam

B

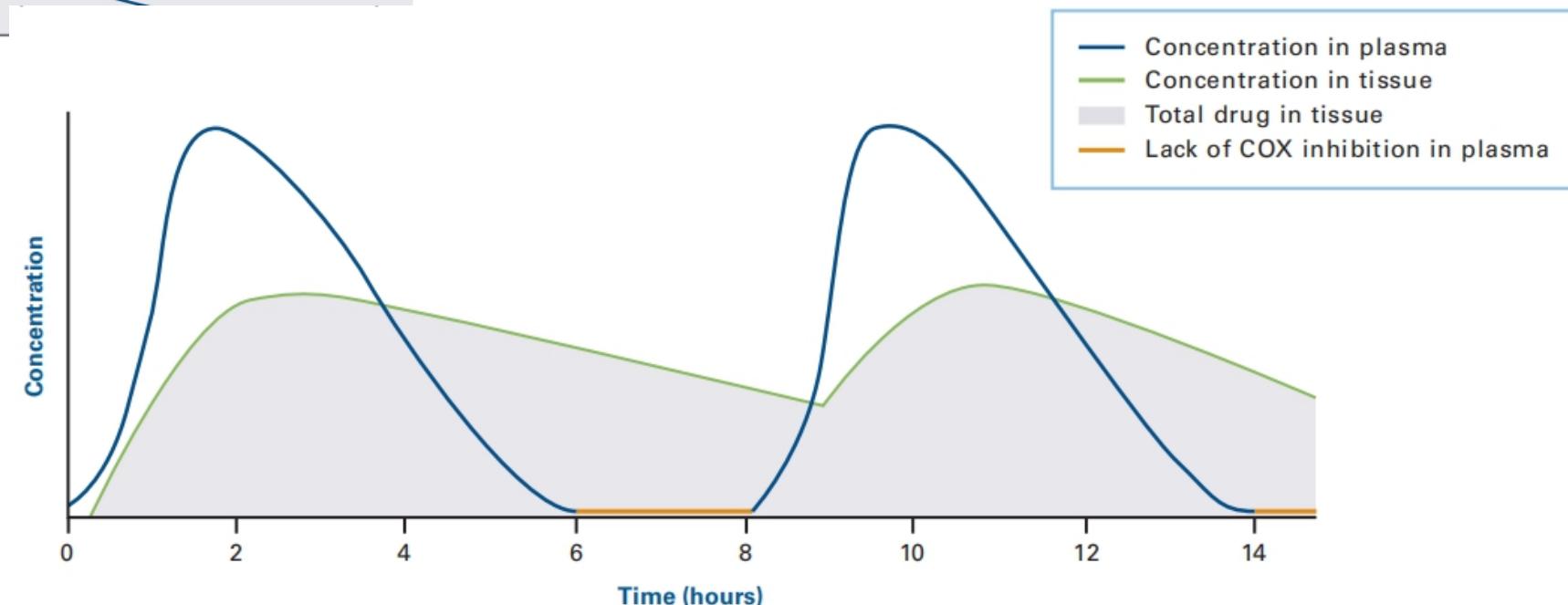
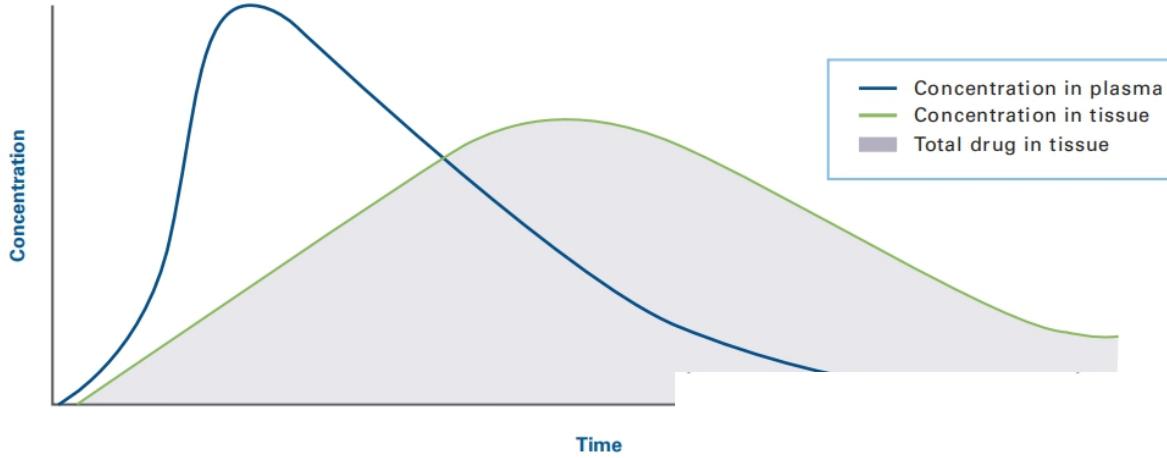


COX-2-selective inhibitor



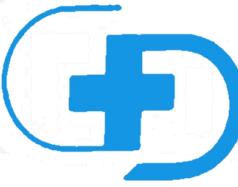


# PHARMACOKINETIC PARAMETER (1)





GeMa CerMat  
Gerakan Masyarakat Cerdas Menggunakan Obat



## PHARMACOKINETIC PARAMETER (2)

NSAIDs	Absosption	Distribution	Metabolism	Protein Binding	Excretion	t 1/2	pKa
Ibuprofen	1-2h	0.11-0.18L/kg	Hepatic	99%	Renal	1.8-2.4h	4.4
Ketoprofen	0.6-1.8h	0.1L/kg	Hepatic	99%	Renal	2.4h	5.9
Diclofenac Na	1.5-6.5	1.4L/kg	Hepatic	99%	Mainly renal	2h	4.0
Diclofenac K	1h	1.3L/kg	Hepatic	99%	Renal 65%	1-2h	4.0
Piroxicam	3-5h	0.1-0.2L/kg	Hepatic	99%	Renal 75%	50h	1.8
Meloxicam	4-8h	0.16-0.27L/kg	Hepatic	99%	Renal	26h	4.2
Ketorolac	44m	0.27L/kg	Hepatic	99%	Renal 90%	5.2h	3.5
Mefenamic acid	<60m	1.06L/kg	Hepatic	90%	Renal 52%	2h	4.2
Celecoxib	2.8h	7L/kg	Hepatic	97%	Renal 27%	11h	11.1
Etoricoxib	1.5h	1.9L/kg	Hepatic		Renal	22h	4.9



## PHARMACOKINETIC PARAMETER (3)

NSAIDs	Effects of Food
Ibuprofen	↑ Tmax
Ketoprofen	↑ Tmax, ↓ Cmax
Diclofenac Na	(IR) ↑ Tmax, ↓ Cmax (ER) ↑ Tmax, ↑ Cmax
Diclofenac K	↑ Tmax, ↓ Cmax
Piroxicam	↑ Tmax
Meloxicam	~ Tmax and Cmax
Ketorolac	High fat meal ↑ Tmax, ↓ Cmax
Mefenamic acid	~ Tmax and Cmax



# NSAIDs COX SELECTIVITY

More COX-1 Selective	Nonselective	5-50 fold COX-2 Selective	> 50 fold COX-2 Selective
Ketorolac Ketoprofen Acetocal (aspirin) Piroxicam	Ibuprofen	Diclofenac Celecoxib Meloxicam	Etoricoxib

## GI Adverse Effect

Dyspepsia  
Nausea/ vomiting  
GI ulcer  
GI bleeding



Nausea



Diarrhea

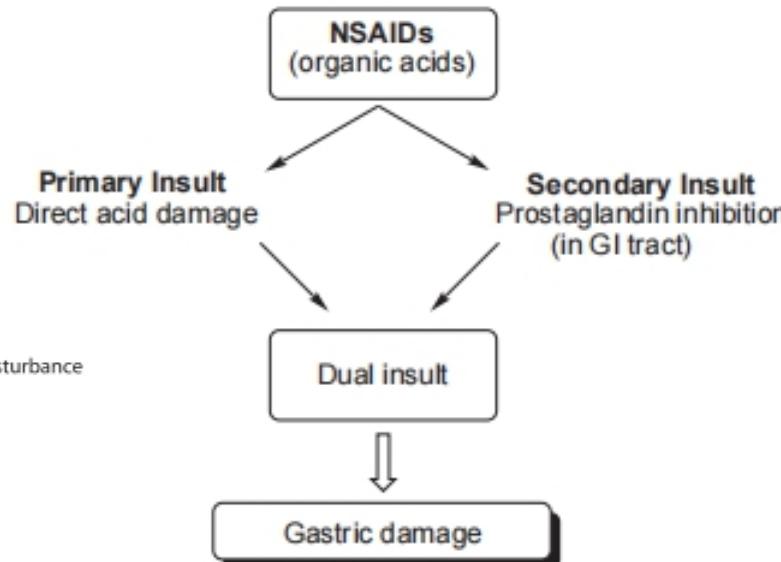


GI disturbance



## CV Adverse Effect

Myocardial infarction  
Ischemic stroke



SYSTEMATIC REVIEW

Drug Saf 2012; 35 (12): 1127-1146  
0114-5916/12/0012-1127

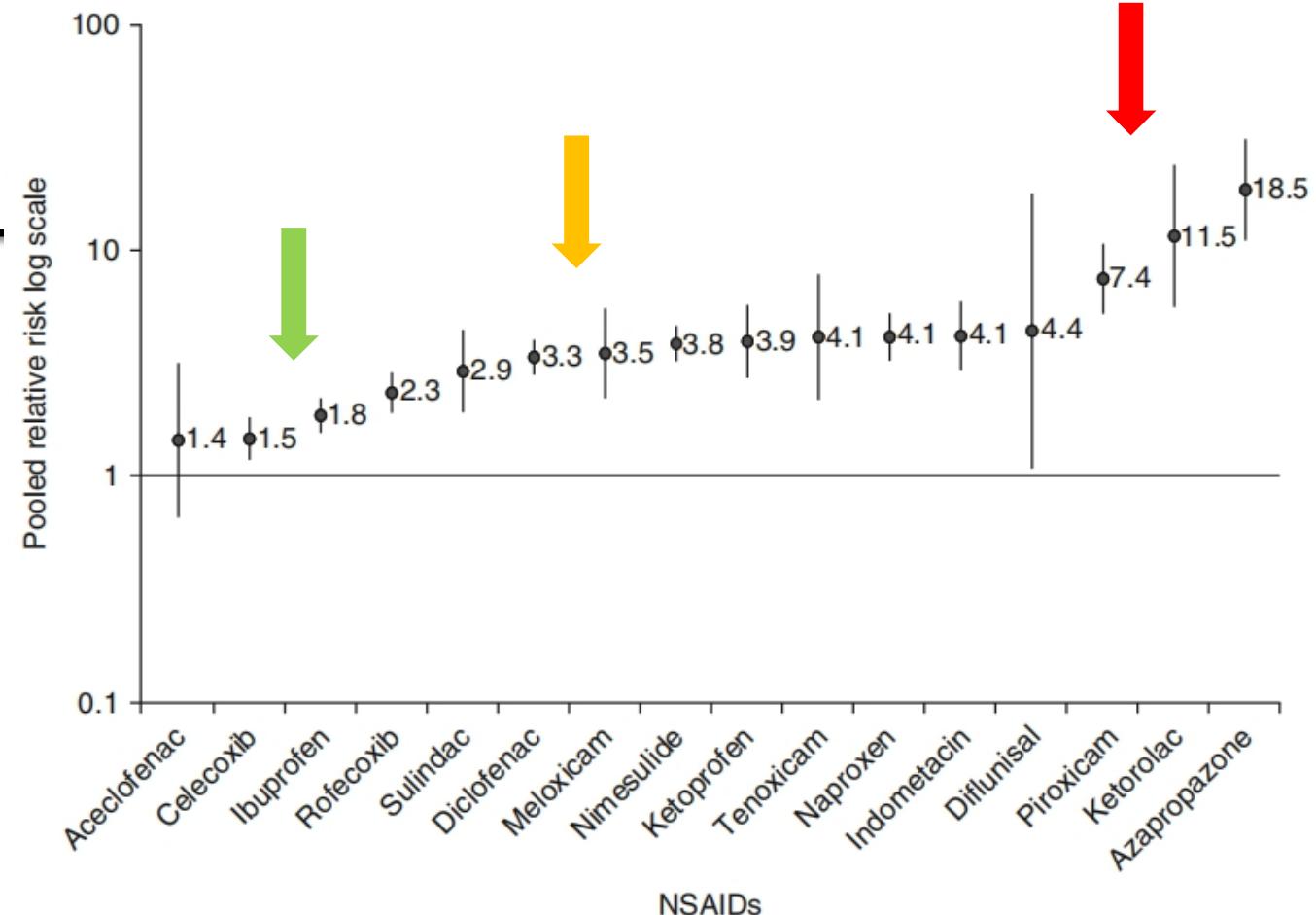
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provided the original work is properly cited and not altered.

# Individual NSAIDs and Upper Gastrointestinal Complications

A Systematic Review and Meta-Analysis of Observational Studies (the SOS Project)

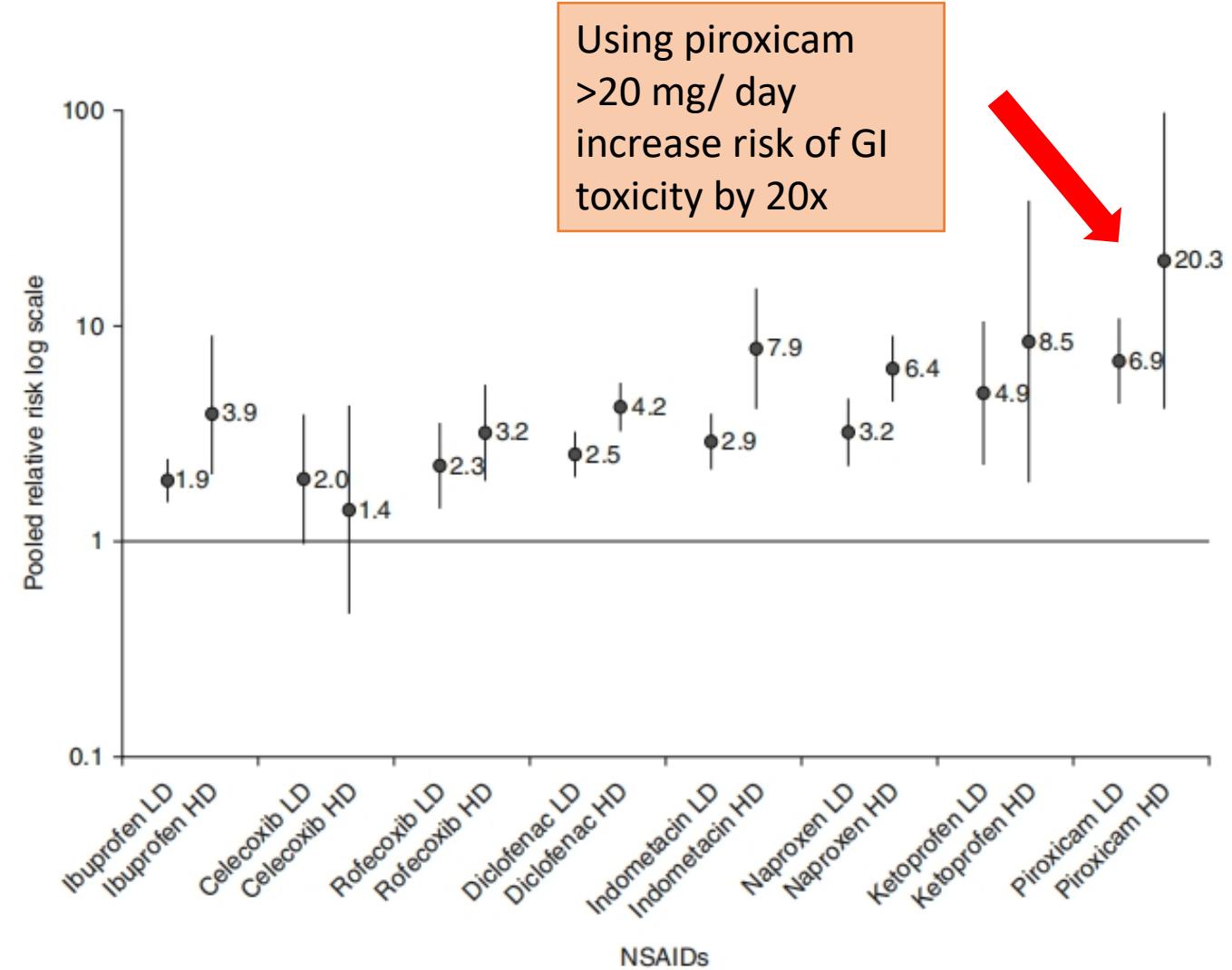
GI bleeding, peptic ulcer, duodenal lesion,

Using any NSAIDs increase risk of GI Toxicity, as high as 11.5 fold!! **(KETOROLAC)**

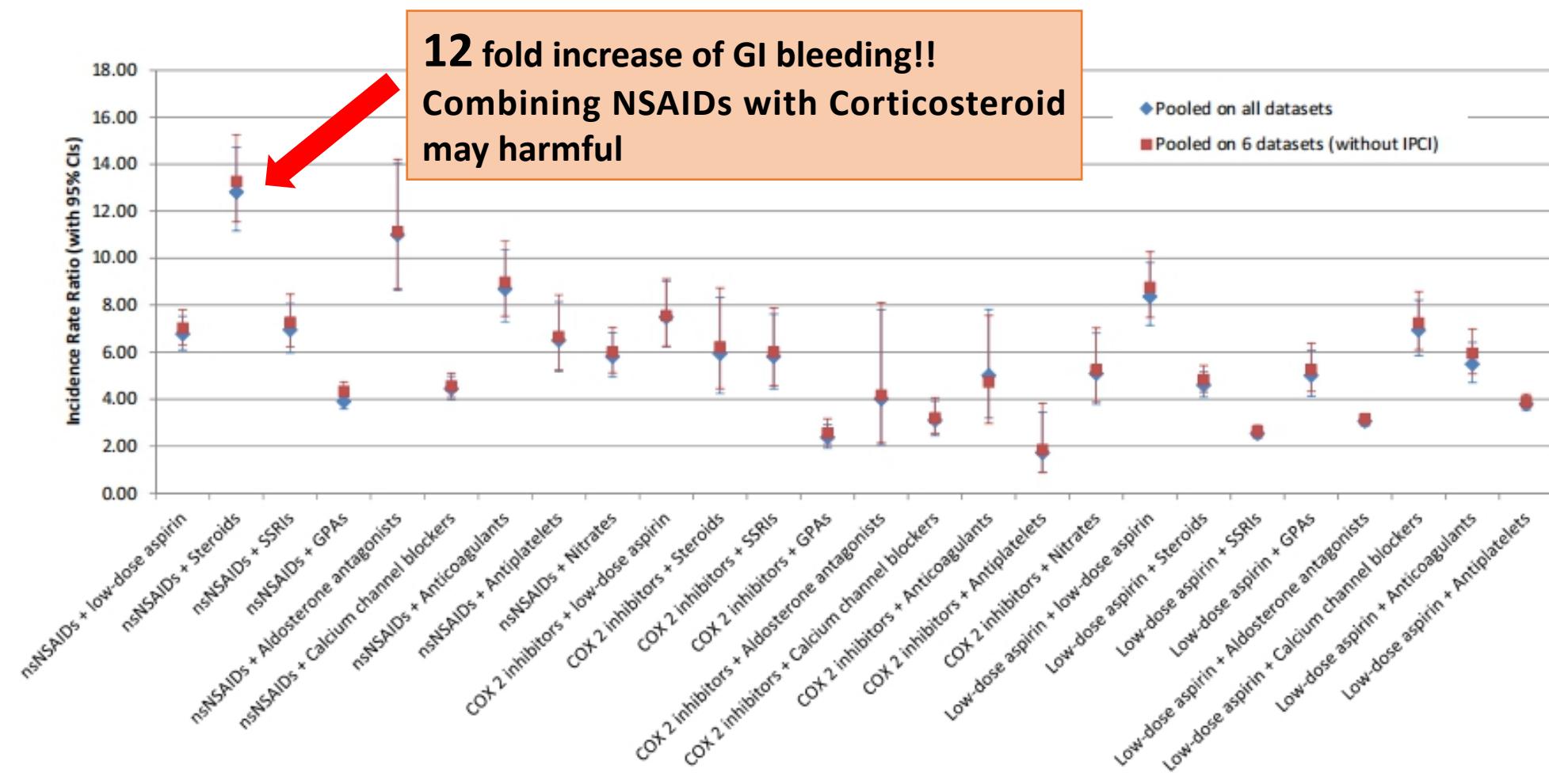


# DOSE DEPENDENT GI TOXICITY

NSAIDs	Low- Medium Dose (mg/ day)	Usual Dose Regiment
Ibuprofen	≤ 1200	3 x 400 mg
Diclofenac	≤ 100	2 x 50 mg
Ketoprofen	≤ 150	2 x 50 mg
Piroxicam	≤ 20	1 x 20 mg



# TOXIC COMBINATION



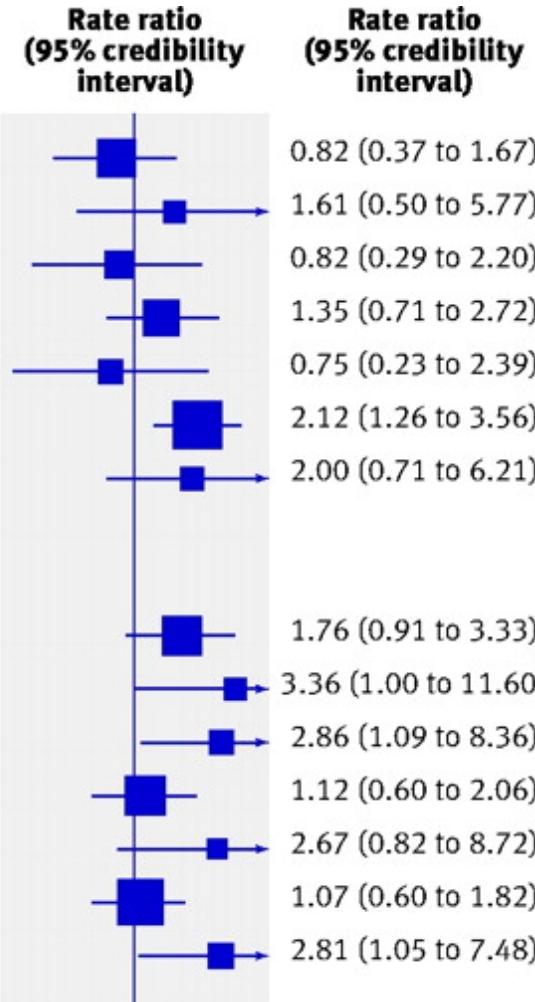
**12 fold increase of GI bleeding!!  
Combining NSAIDs with Corticosteroid  
may harmful**

If Possible avoid combining NSAIDs with

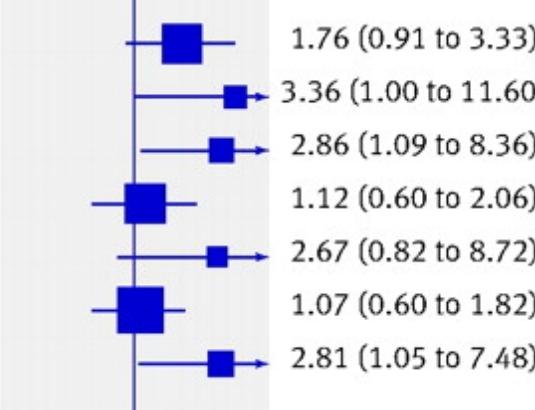
- other NSAIDs
- Corticosteroid
- Anticoagulant
- Aldosteron ant.

# NSAIDs AFFECTING CARDIOVASCULAR SYSTEM

## Myocardial infarction



## Stroke

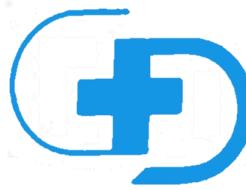


## Mechanism

- Fluid and Sodium retention
- Increasing blood pressure
- Affecting platelet aggregation

## How to manage?

- Use lowest dose possible
- Use shortest duration possible
- Avoiding use in unstable px.
- Closely monitor and adjust if necessary



### Therapeutic disadvantages of selected NSAIDs\*

Upper GI disturbances are common

No antipyretic effect

Very potent; should be used only after less toxic agents have proven ineffective

CNS disturbances are common

Potential to increase myocardial infarctions and strokes

### Therapeutic advantages of selected NSAIDs

Low cost; long history of safety

Less GI irritation than aspirin

Long half-life permits daily or twice-daily dosing

Lower toxicity and better acceptance in some patients. Naproxen is considered by some experts as one of the safest NSAIDs

#### Salicylates:

Aspirin  
Salicylate salts  
*Diflunisal*

#### Acetic acids:

*Indomethacin*  
*Sulindac*  
*Tolmetin*

#### Propionic acids:

*Ibuprofen*  
*Fenoprofen*  
*Flurbiprofen*  
*Ketoprofen*  
*Naproxen*  
*Oxaprozin*

#### Oxicams:

*Piroxicam*  
*Meloxicam*

#### Fenamates:

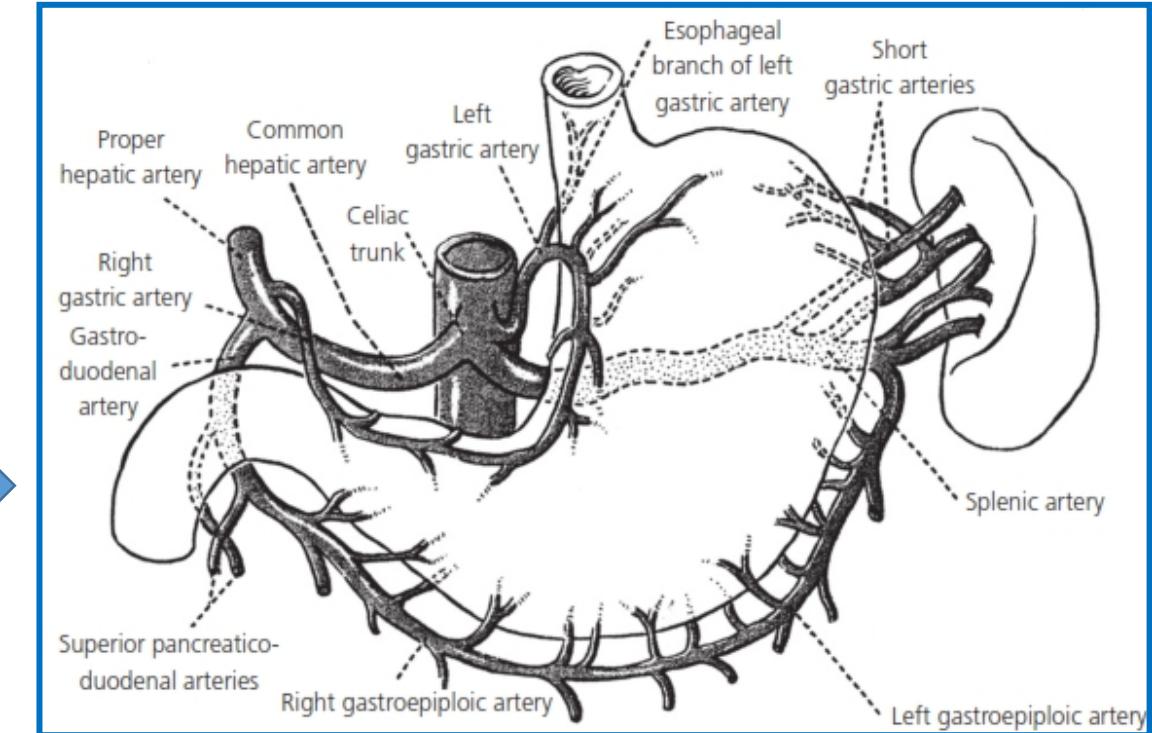
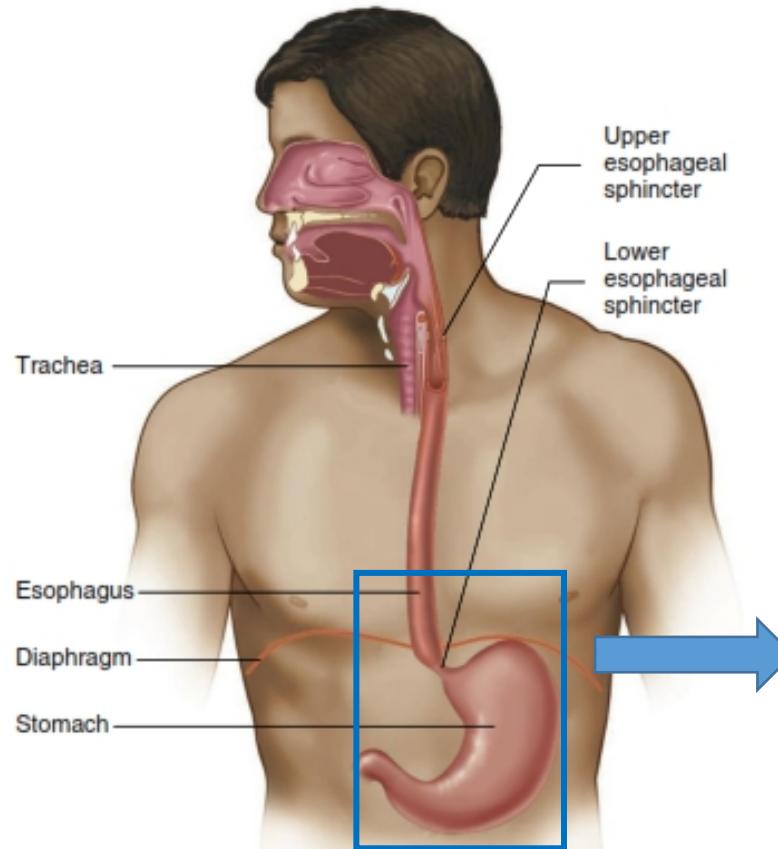
*Mefenamic acid*  
*Meclofenamic acid*

#### COX-2 inhibitor:

*Celecoxib*

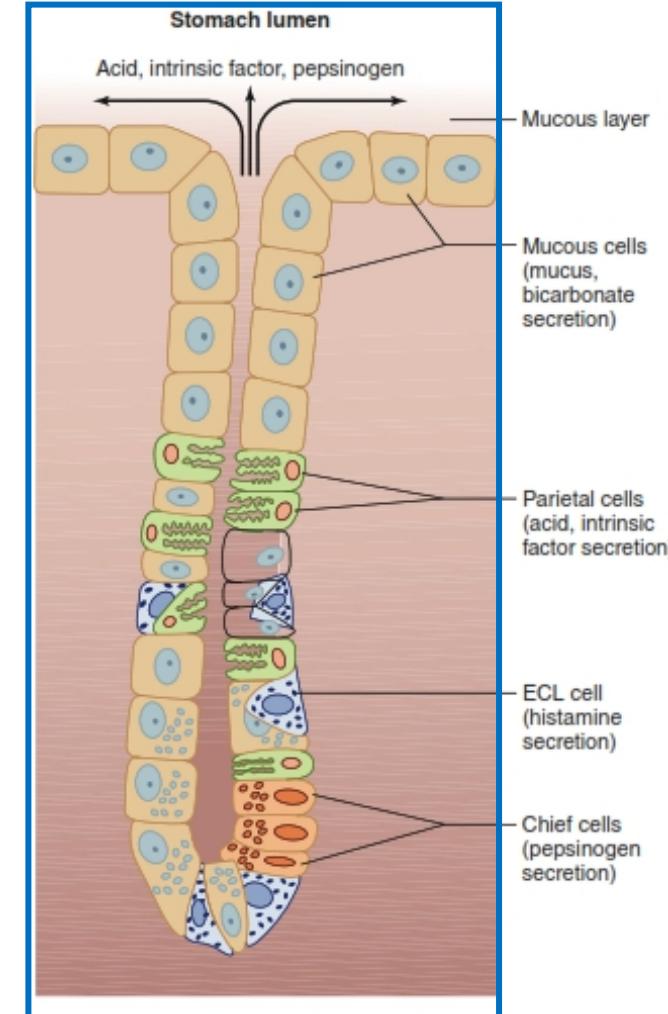
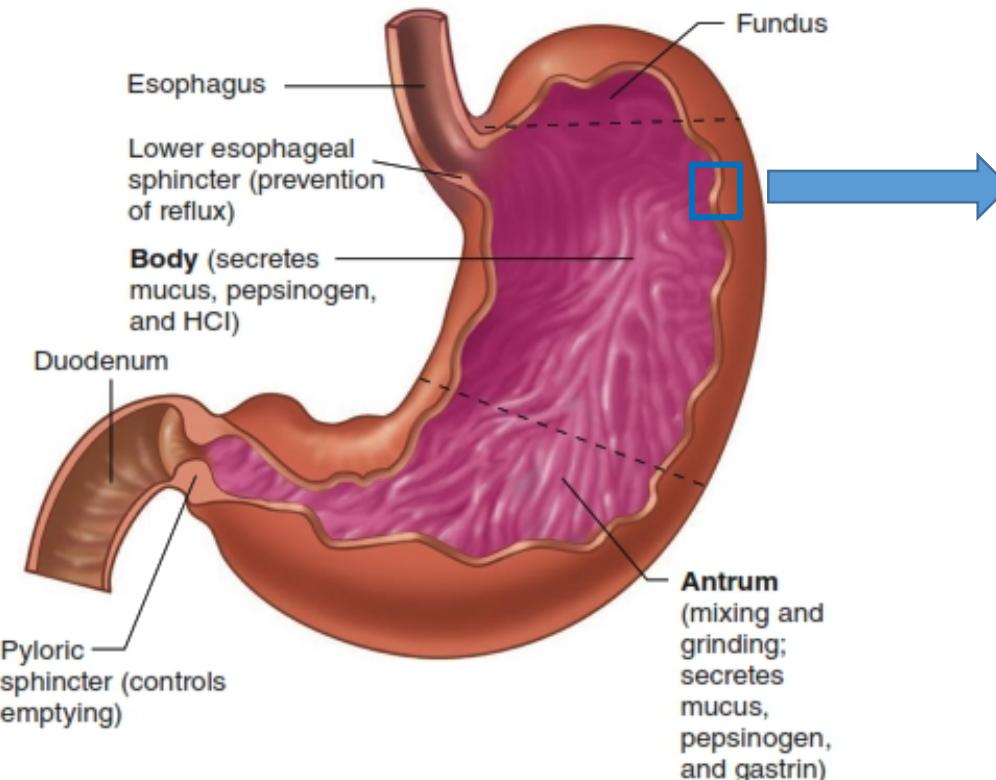
Less GI irritation than aspirin

# GASTRIC PHYSIOLOGY

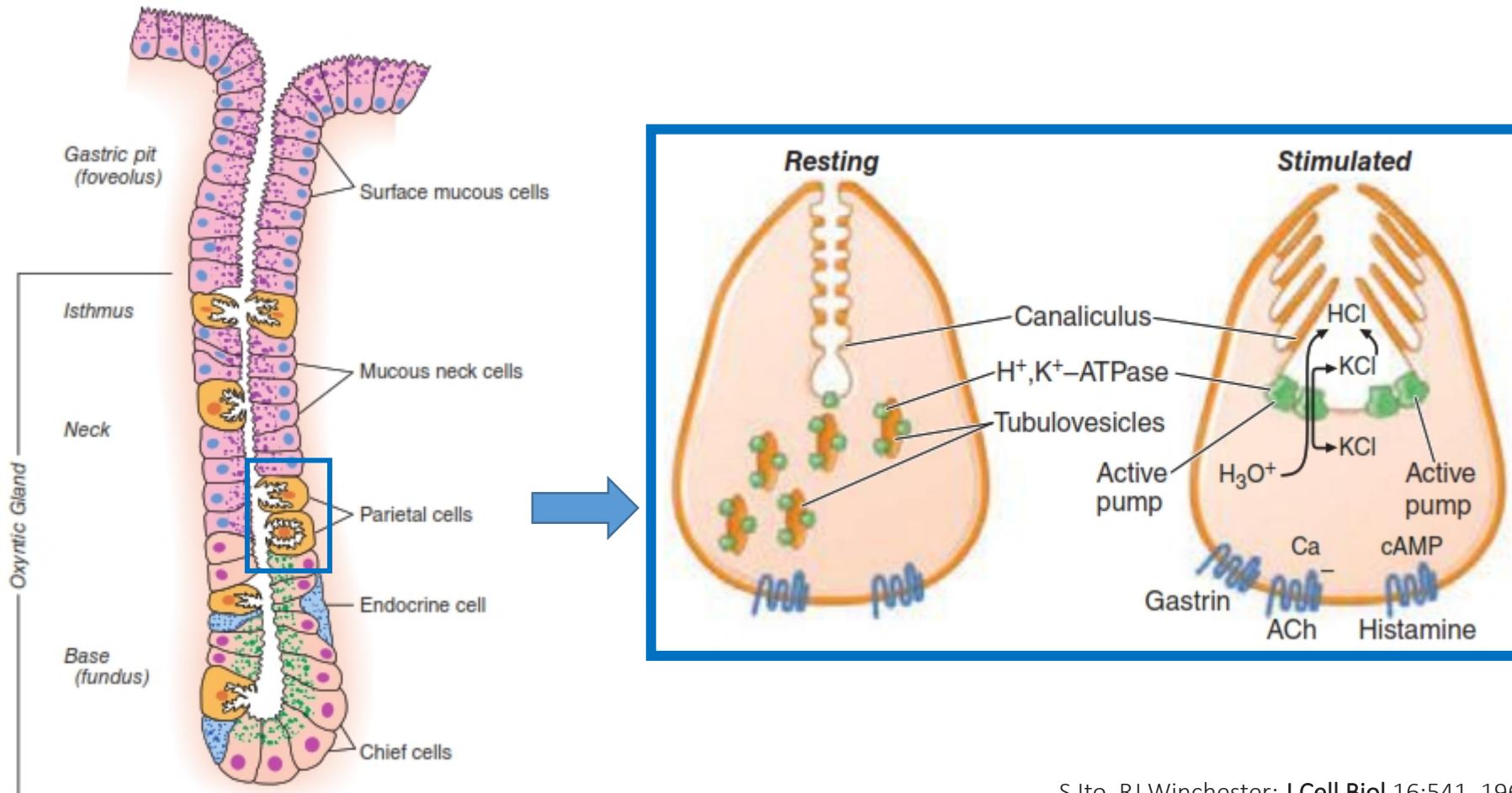




# GASTRIC PHYSIOLOGY

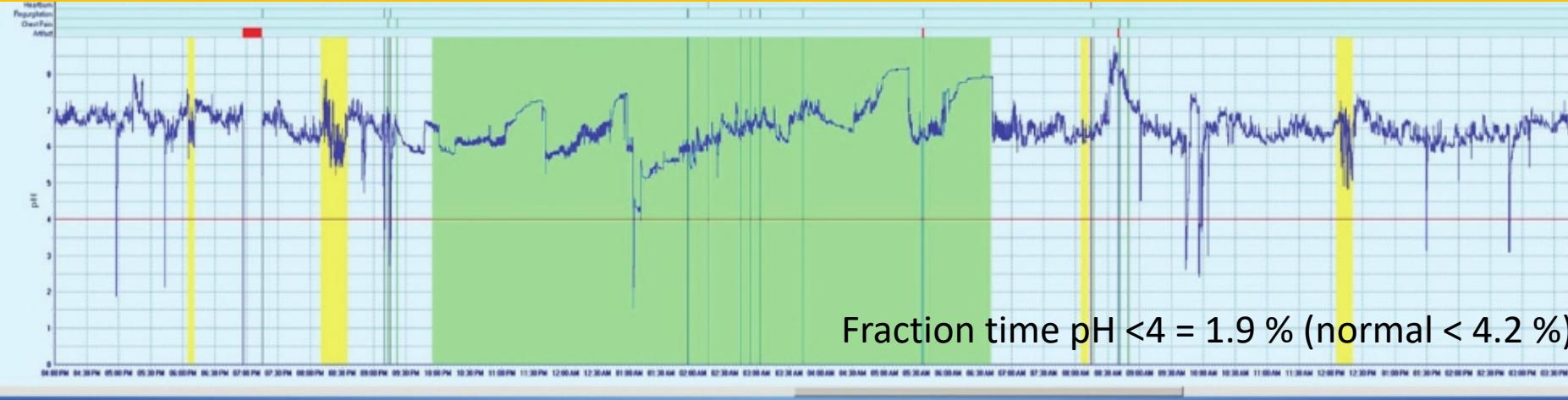


# GASTRIC PHYSIOLOGY

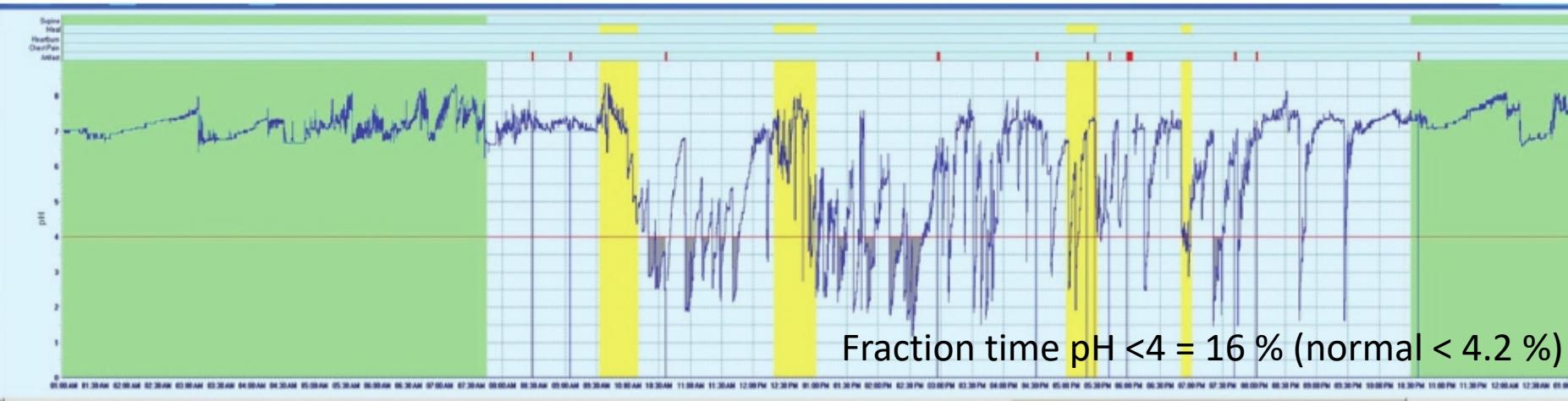


S Ito, RJ Winchester: J Cell Biol 16:541, 1963

SJ Hersey, G Sachs: Physiol Rev 75:155, 1995



(a)



(b)

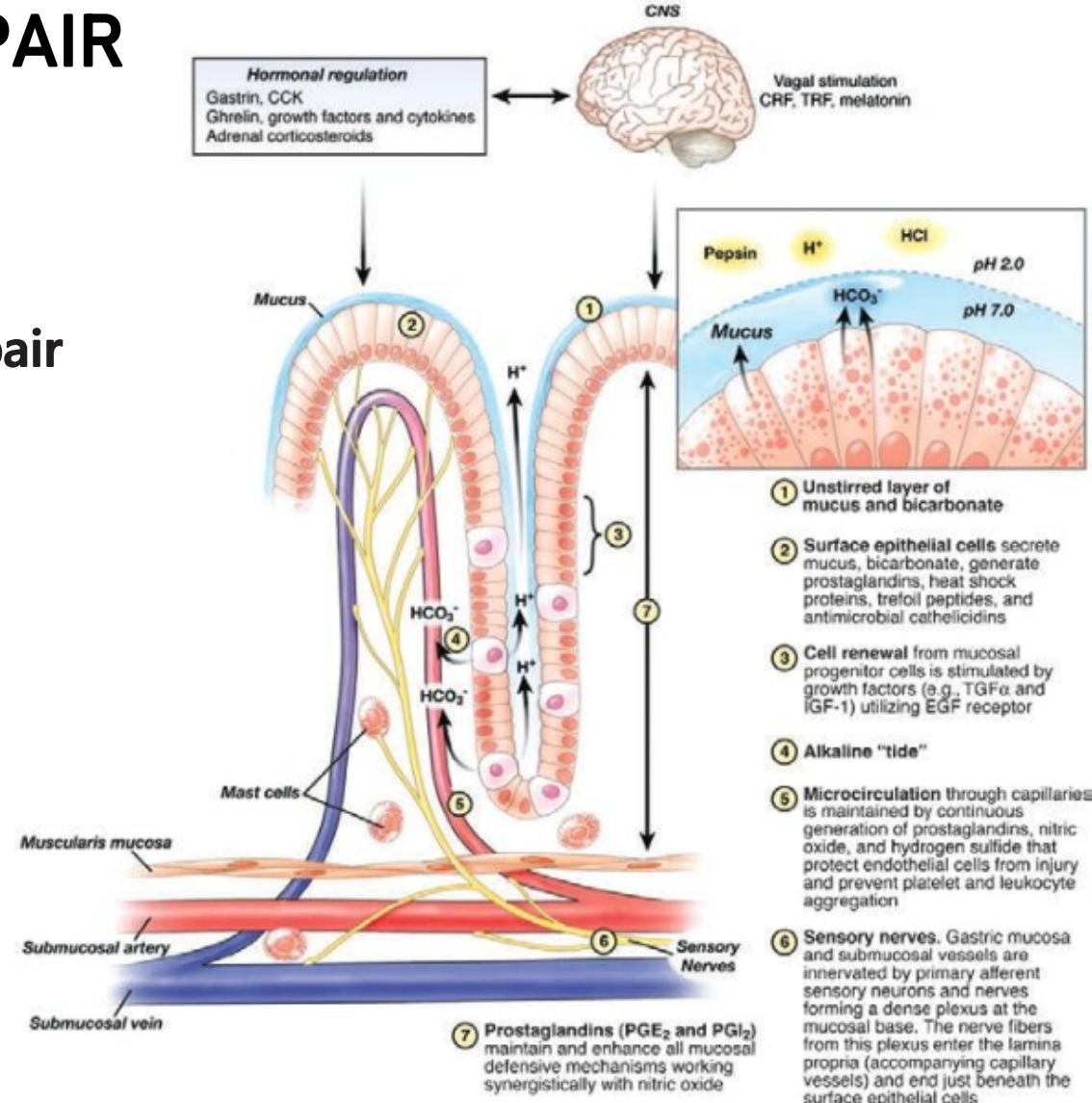
- a. Normal people
- b. People with GERD

Krishnan, K., Pandolfino, J. E. & Kahrilass, P. J., 2016. Gastroesophageal reflux disease. In: D. K. Podolsky, ed. *Yamada's Atlas of Gastroenterology*. New York: John Wiley & Sons, p. 75.

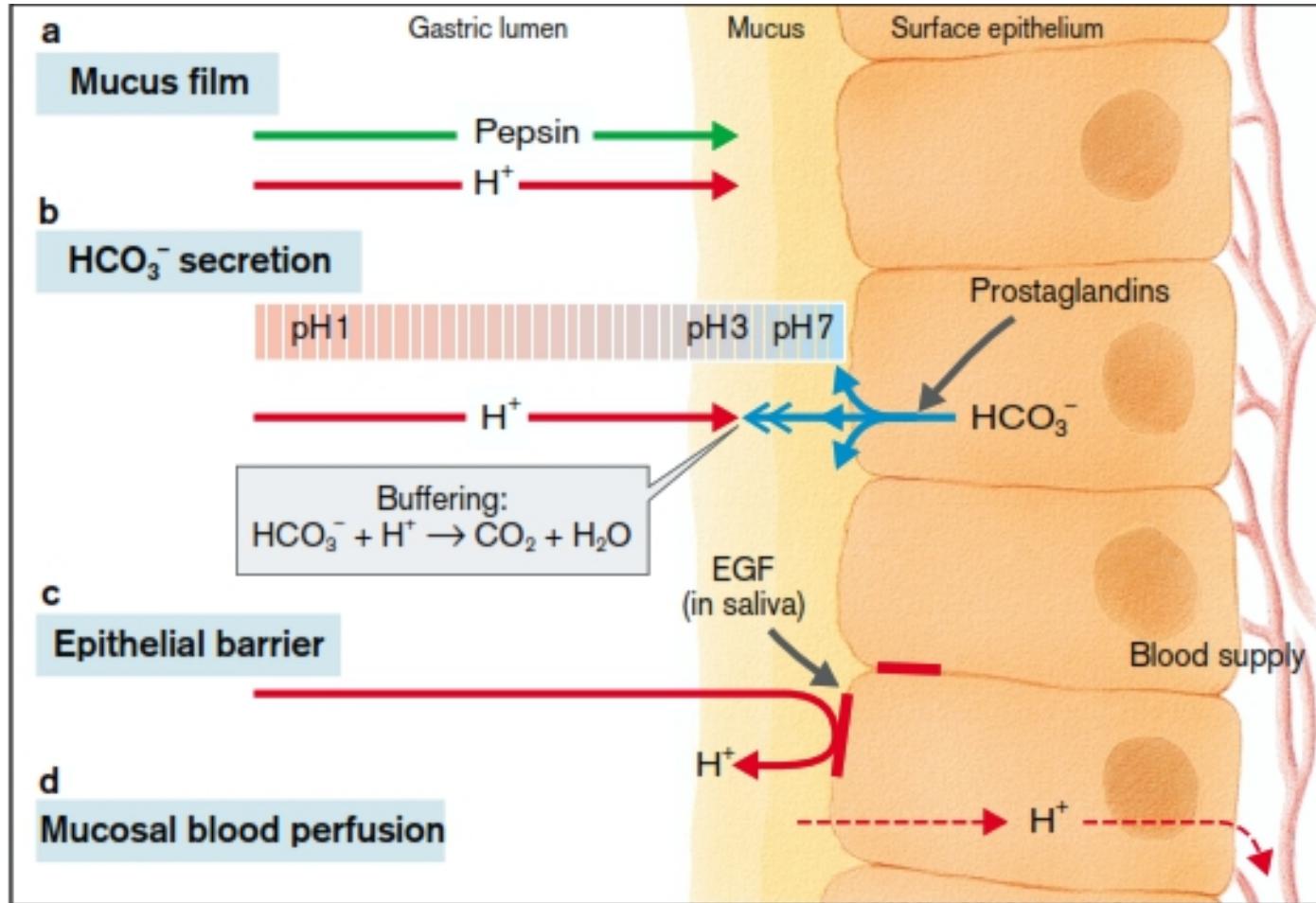
# MUCOSAL DEFENSE AND REPAIR

## Components involved in providing gastroduodenal mucosal defense and repair

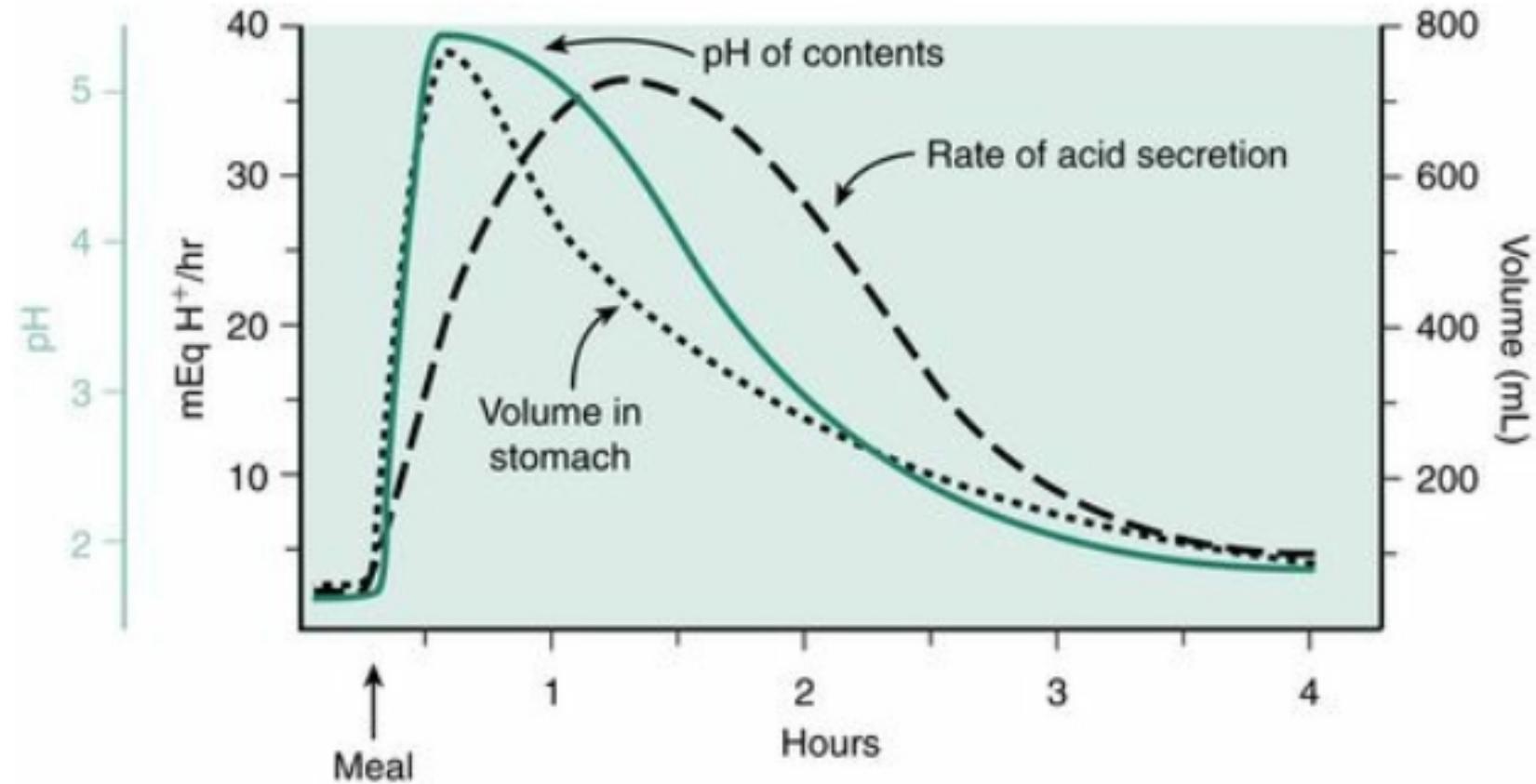
Tarnawski A. Cellular and molecular mechanisms of mucosal defense and repair. In: Yoshikawa T, Arakawa T. *Bioregulation and Its Disorders in the Gastrointestinal Tract*. Tokyo, Japan: Blackwell Science, 1998:3–17

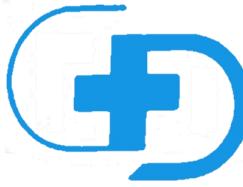


# MUCOSAL PROTECTION



The relationship between gastric secretory rate, intragastric pH, and volume of gastric contents during a meal.





# COMPARISON OF COMMON FORMS OF PEPTIC ULCER

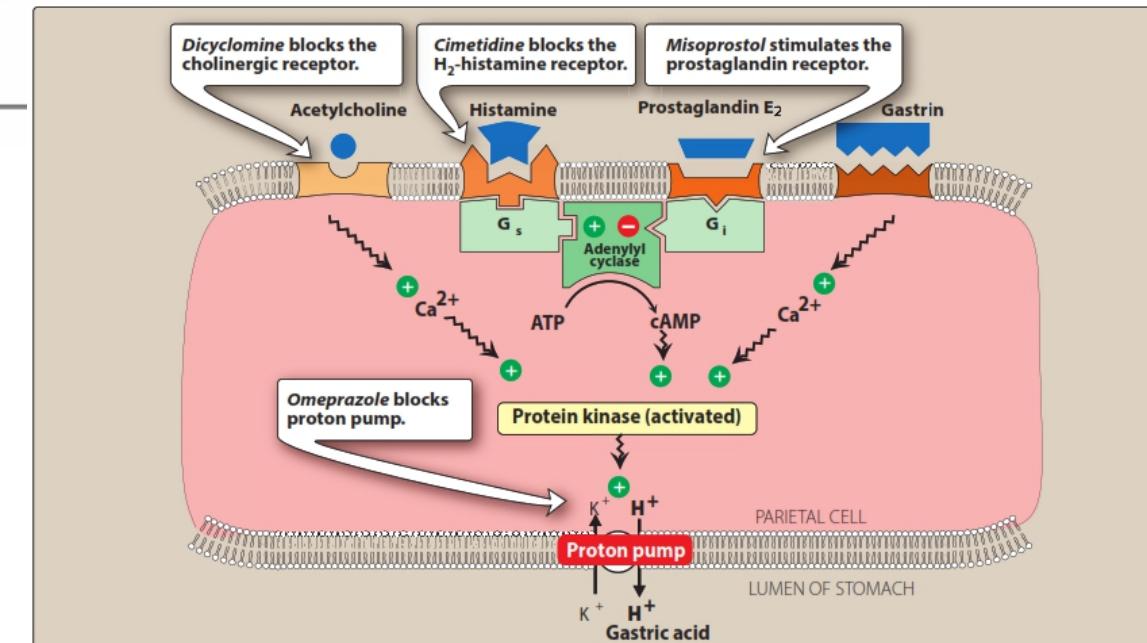
Characteristic	<i>H. pylori</i> Induced	NSAID Induced	SRMD
Condition	Chronic	Chronic	Acute
Site of damage	Duodenum > stomach	Stomach > duodenum	Stomach > duodenum
Intragastric pH	More dependent	Less dependent	Less dependent
Symptoms	Usually epigastric pain	Often asymptomatic	Asymptomatic
Ulcer depth	Superficial	Deep	Most superficial
GI bleeding	Less severe, single vessel	More severe, single vessel	More severe, superficial mucosal capillaries

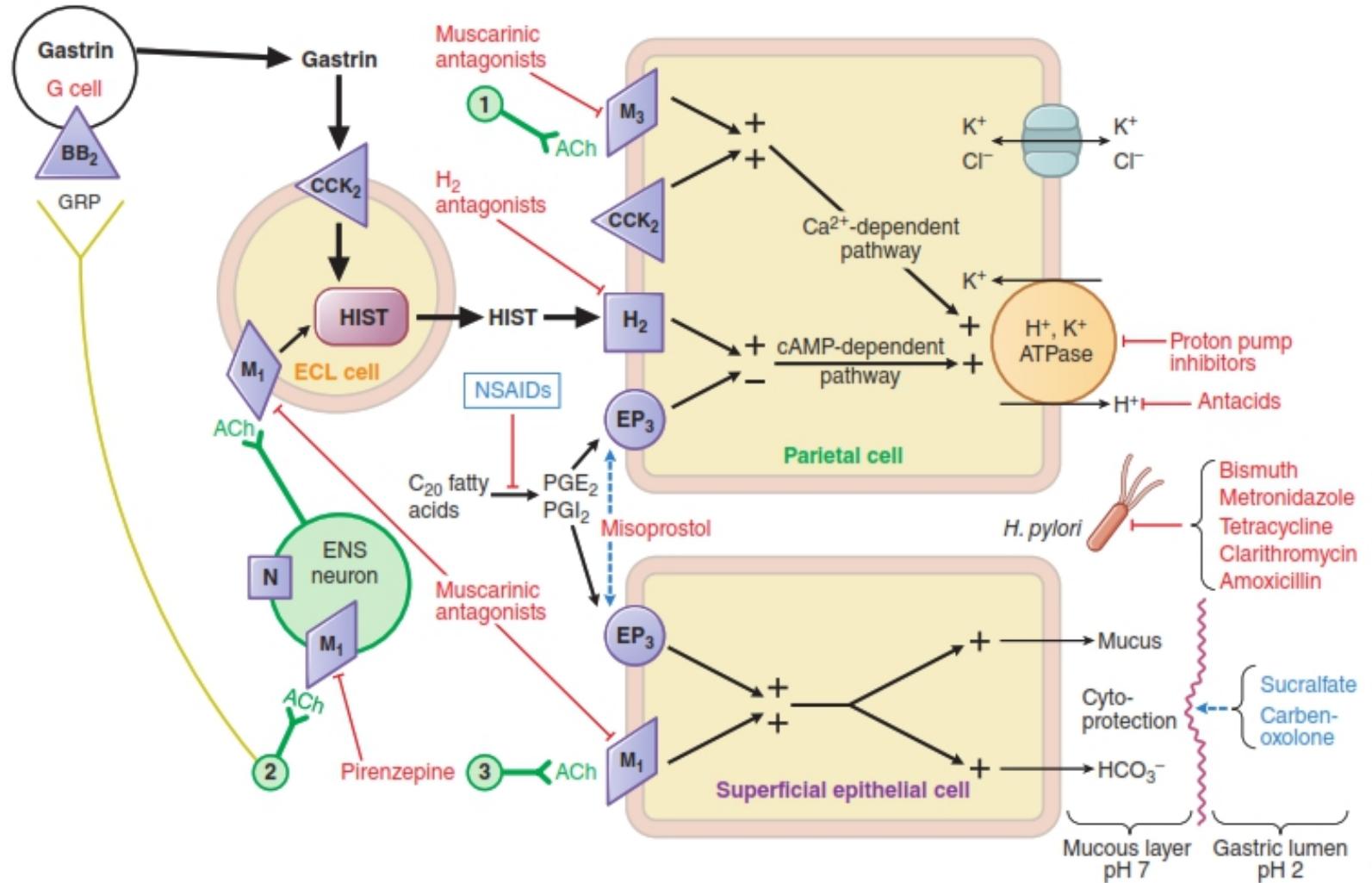
*H. pylori*, *Helicobacter pylori*; NSAID, nonsteroidal antiinflammatory drug; SRMD, stress-related mucosal damage.

# ACID SUPPRESSIONS IN PREVENTING PEPTIC ULCER

Intragastric pH	Physiologic Activity
≥3.5	Decreased incidence of stress-induced bleeding
>4.0	<b>Target pH - Prevention of stress related mucosal bleeding</b>
≥4.5	Pepsin inactivation
5.0	99.9% acid neutralization
5.1–7.0	Alterations in coagulation and platelet aggregation
>6	<b>Target pH - Prevention of peptic ulcer recurrence</b>
≥7.0	Potential decrease in incidence of rebleeding
≥8.0	Pepsin destruction

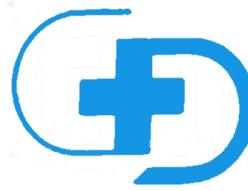
<sup>a</sup>Based on in vitro and animal studies.







Gerakan Masyarakat Cerdas Menggunakan Obat



## ANTACID (ANTI - ACID)

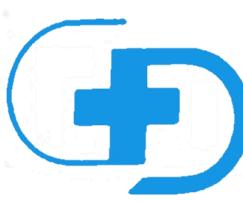
Contituent	Neutralizing Capacity	Salt Formed in Stomach	Solubility of Salt	Adverse Effects
NaHCO <sub>3</sub>	High	NaCl	High	Systemic alkalosis, fluid retention
CaCO <sub>3</sub>	Moderate	CaCl <sub>2</sub>	Moderate	Hypercalcemia, nephrolithiasis, milk-alkali syndrome
Al(OH) <sub>3</sub>	High	AlCl <sub>3</sub>	Low	Constipation, hypophosphatemia
Mg(OH) <sub>3</sub>	High	MgCl <sub>2</sub>	Low	Diarrhea, hypermagnesemia

- Less effective than PPI or H2RA
- But widely available, relatively cheap and have rapid action

- Determinant of effectiveness = ANC (acid neutralizing capacity)
- ANC Suspension > ANC Tablet

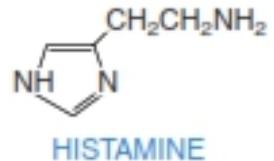
- USP ANC test (in vitro) → pH > 3.5 in 15 min
- Some preparation can achieve gastric pH as high as 8, but mainly at pH 3 – 5 for up to 1.5 - 3 h
- Aluminum-magnesium compounds appear to provide steadier buffering than carbonate compounds

- Antacid may alter gastric pH and urine, also chelating others substance → potentially affect ADME other drug(s)

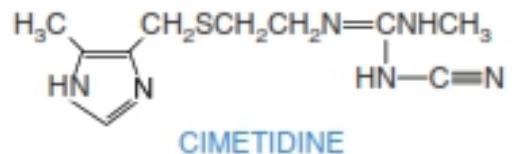


# H<sub>2</sub>RA

Drug	Dose to Achieve >50% Acid Inhibition for 10 Hours	Usual Dose for Acute Duodenal or Gastric Ulcer	Usual Dose for Gastroesophageal Reflux Disease	Usual Dose for Prevention of Stress-Related Bleeding
Cimetidine	400–800 mg	800 mg HS or 400 mg bid	800 mg bid	50 mg/h continuous infusion
Ranitidine	150 mg	300 mg HS or 150 mg bid	150 mg bid	6.25 mg/h continuous infusion or 50 mg IV every 6–8 h
Nizatidine	150 mg	300 mg HS or 150 mg bid	150 mg bid	Not available
Famotidine	20 mg	40 mg HS or 20 mg bid	20 mg bid	20 mg IV every 12 h



- Reversibly bind to H<sub>2</sub> receptor in parietal cell
- May develop tolerance after 72 h



Drug	Trade name	R	X	Y
Burimamide		H	CH <sub>2</sub>	S
Metiamide		CH <sub>3</sub>	S	S
Cimetidine	Tagamet	CH <sub>3</sub>	S	N=C≡N
		<chem>ArCS-CC(=NH)C(=O)N</chem>		
Drug	Trade name	Ar		
Ranitidine	Zantac	<chem>CC1=CC=C(O)C=C1</chem>		
Nizatidine	Axid	<chem>CC1=CC=C(S)C=C1</chem>		
		<chem>CC1=CC=C(N)C=C1N(C)C#NCCSCC2=CC=C(N)C=C2</chem>		
		Famotidine (Pepcid)		

## H<sub>2</sub>RA PHARMACOKINETIC

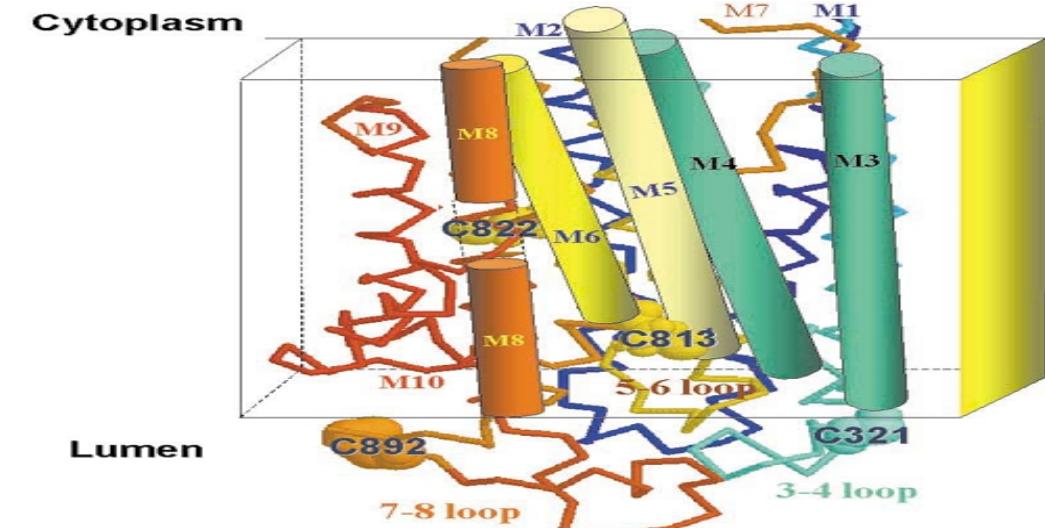
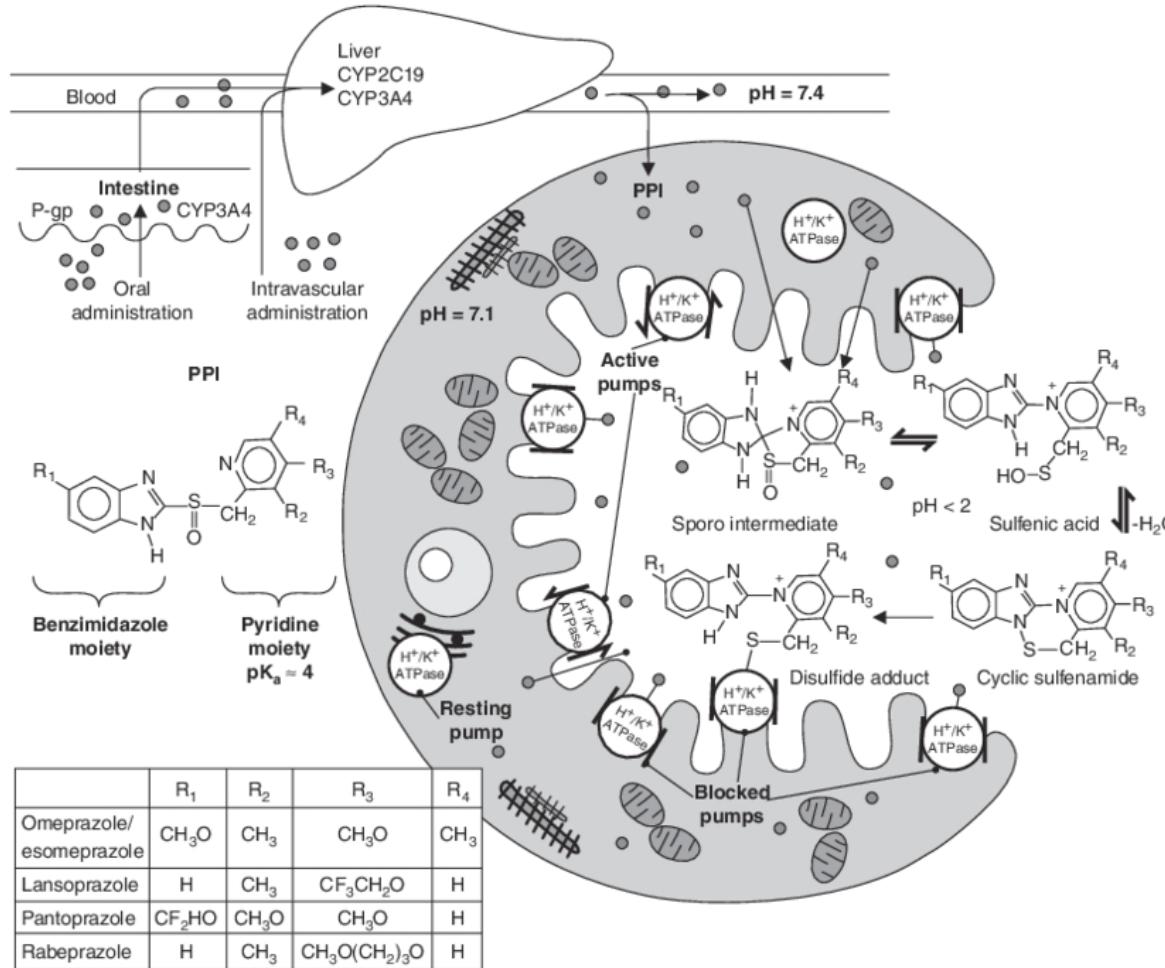
Characteristic	Ranitidin	Cimetidin	Famotidine	Nizatidine
Tmax (oral)	1 – 3 h	0.5 – 1.5 h	1 – 3 h	0.5 – 3 h
Bioavailability (oral)	50 – 60%	60 – 70%	40 – 45%	> 90%
Protein binding	15%	13 – 24 %	15 – 20%	30 – 35%
Half-life	2 h	2 – 3 h	2.5 – 3.5 h	1 – 2 h
Excretion	Urine 30%	Urine 48%	Urine 25%	Urine 60%
Renal impairment	Need dosage adjustment			
Hepatic impairment	No dosage adjustment is needed, but monitor closely			
Relative potency	4 – 10	1	4 - 10	20 - 50

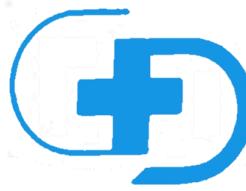
Higher potency ≠ higher efficacy

## H2RA

- Cimetidine have many interaction with other drug(s) due to capability to inhibit CYP.
- If possible use ranitidine or famotidine especially when patients also receive warfarin, theophylline, phenytoin, lidocaine, clarithromycin .
- Anti-androgen → gynecomastia (long term therapy > 1 mo)

# PROTON PUMP INHIBITOR

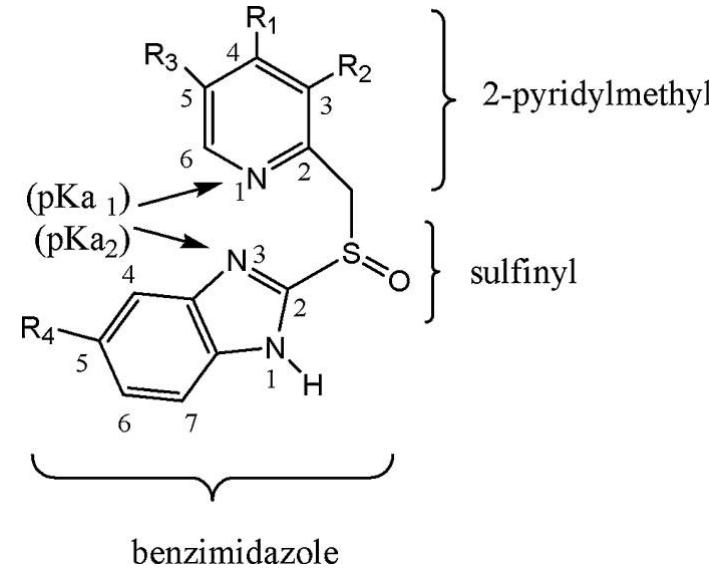




# PROTON PUMP INHIBITOR



Drugs	Trade name	X	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
Omeprazole	Prilosec	CH	OCH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>
Esomeprazole (S-enantiomer)	Nexium	CH	OCH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>
Tenatoprazole		N	OCH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>
Lansoprazole	Prevacid	CH	H	CH <sub>3</sub>	CH <sub>2</sub> CF <sub>3</sub>	H
Dexlansoprazole (R-enantiomer)	Dexilant	CH	H	CH <sub>3</sub>	CH <sub>2</sub> CF <sub>3</sub>	H
Rabeprazole	Adiphex	CH	H	CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>3</sub>	H
Pantoprazole	Protonix	CH	OCHF <sub>2</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	H



Proton Pump Inhibitor	pKa1	pKa2
Omeprazole/esomeprazole	4.06	0.79
Lansoprazole	3.83	0.62
Pantoprazole	3.83	0.11
Rabeprazole	4.53	0.62



## PROTON PUMP INHIBITOR

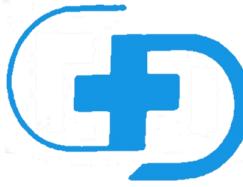
- A Prodrug, stay inactive during absorption and distribution
- Accumulate in the parietal cell canalculus by more than 1000-fold its plasma concentration due to Henderson-Hasselbach trapping
- Irreversibly bind to H<sup>+</sup>/K<sup>+</sup> ATPase by disulfide bond

- Not all proton pumps inactivated with first dose
- Maximal suppression in 2 – 5 days with once daily dosing
- Acid secretion suppressed for more than 48 h until new proton pumps are synthesized

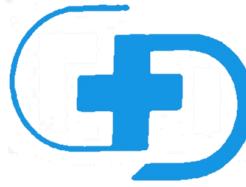
- PPI may alter gastric pH → potentially affect ADME other drug(s)



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Characteristic	Omeprazol	Lansoprazol	Pantoprazol	Rabeprazol	Esomeprazol
<b>Onset</b>	1h	1 h	1,75 h	1.75 h	1.5 h
<b>Peak effect</b>	72 h	> 24 h	> 24 h	24 hours	
<b>Bioavailability</b>	30-40%	80-85%	77%	52%	64%
<b>Protein binding</b>	95%	98%	97%	94,8-97,5%	97%
<b>Half-life</b>	0,5-1 h	1 h	2 h	1-2 h	1-1,5 h
<b>Excretion</b>	Urine (77%); feces	Urine (33%) Feces (67%)	Urine (71%); feces(18%)	Urine (90%); feces	Urine (80%); feces (20%)
<b>Renal impairment</b>	No dosage adjustment is needed (no significant changes)				
<b>Hepatic impairment</b>	Need dosage adjustment				
<b>Factors that affect absorption</b>	Food	Antacids food	none	Food not studied	Food
<b>PPI used 30-60 minutes before meals, recommended in the morning</b>					



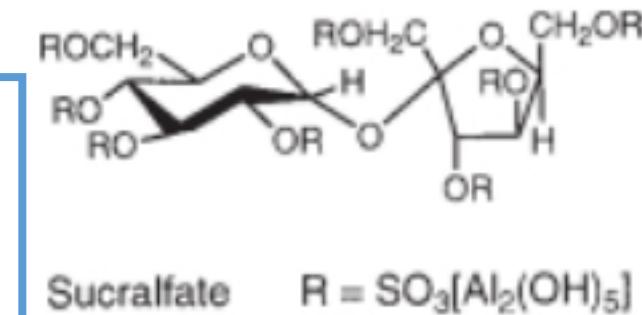
## SUCRALFAT

- Sucralfat breaking down to sucrose sulfate (negatively charged) in **acidic environment (preferably at pH < 4)**

- Bind to positively charged protein in the base of ulcer erosion
  - Forming physical barrier
  - Stimulate mucosal PG
  - Stimulate bicarbonate secretion

- Sucralfate binding to ulcer persist up to 6 hours

- Sucralfate may bind to other medication given orally, impairing their absorption





**GeMa CerMat**

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# TERIMA KASIH

