DRUGS USED IN ACID-PEPTIC DISEASES

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Acid-peptic diseases

Gastrooesophageal reflux disease = GERD

Benign peptic ulcers of the stomach and duodenum

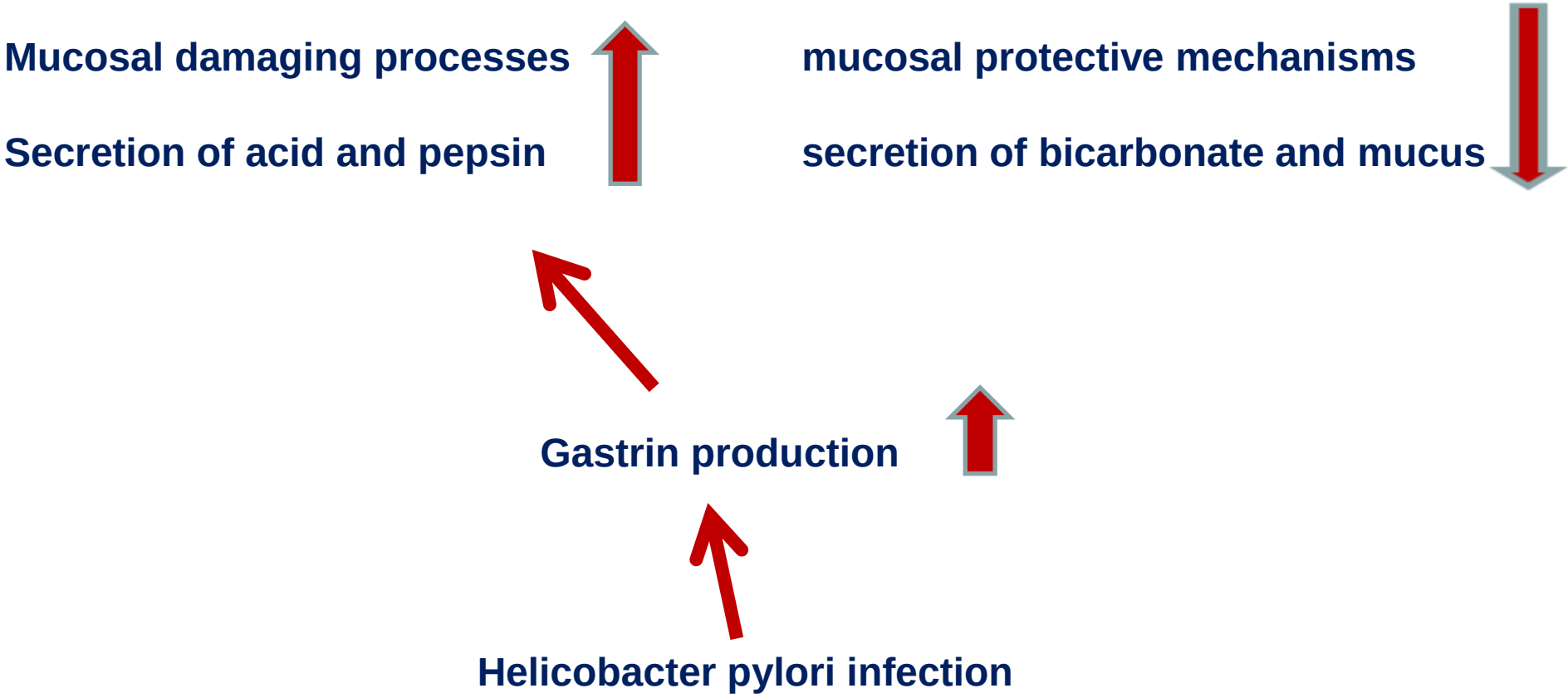
Ulcers secondary to the used conventional NSAIDs

Ulcers in the rare Zollinger-Ellison syndrome

Control of gastric acidity

is a cornerstone of therapy of these disorders

Peptic ulcer



Helicobacter pylori infection has a great importance in hyperacidity

Drugs for eradication Helicobacter pylori :

metronidazole **this antiprotozoal drug has also effect on anaerob bacteria**

+

antibiotics **from macrolide group (clarythromycin)**

or

penicillins with broad-spectrum (amoxicillin)

or

tetracyclines

bismuth salts

Therapy may be success if only the gastric pH is increased in a great extent using

+

proton pump inhibitors

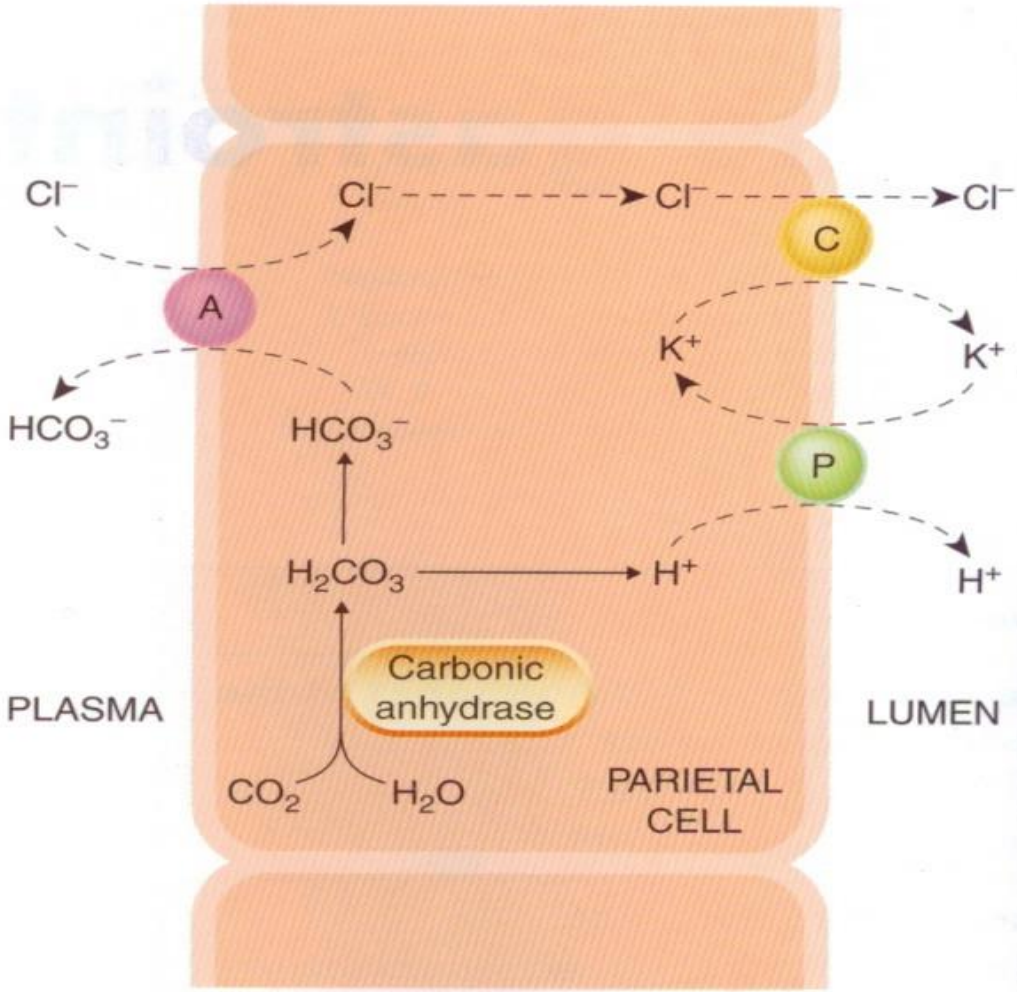


Fig. 25.1 A schematic illustration of the secretion of hydrochloric acid by the gastric parietal cell. Secretion involves a proton pump (P), which is an H^+/K^+ ATPase, a symport carrier (C) for K^+ and Cl^-, and an antiport (A), which exchanges Cl^- and HCO_3^-. An additional Na^+/H^+ antiport situated at the interface with the plasma may also have a role (not shown).

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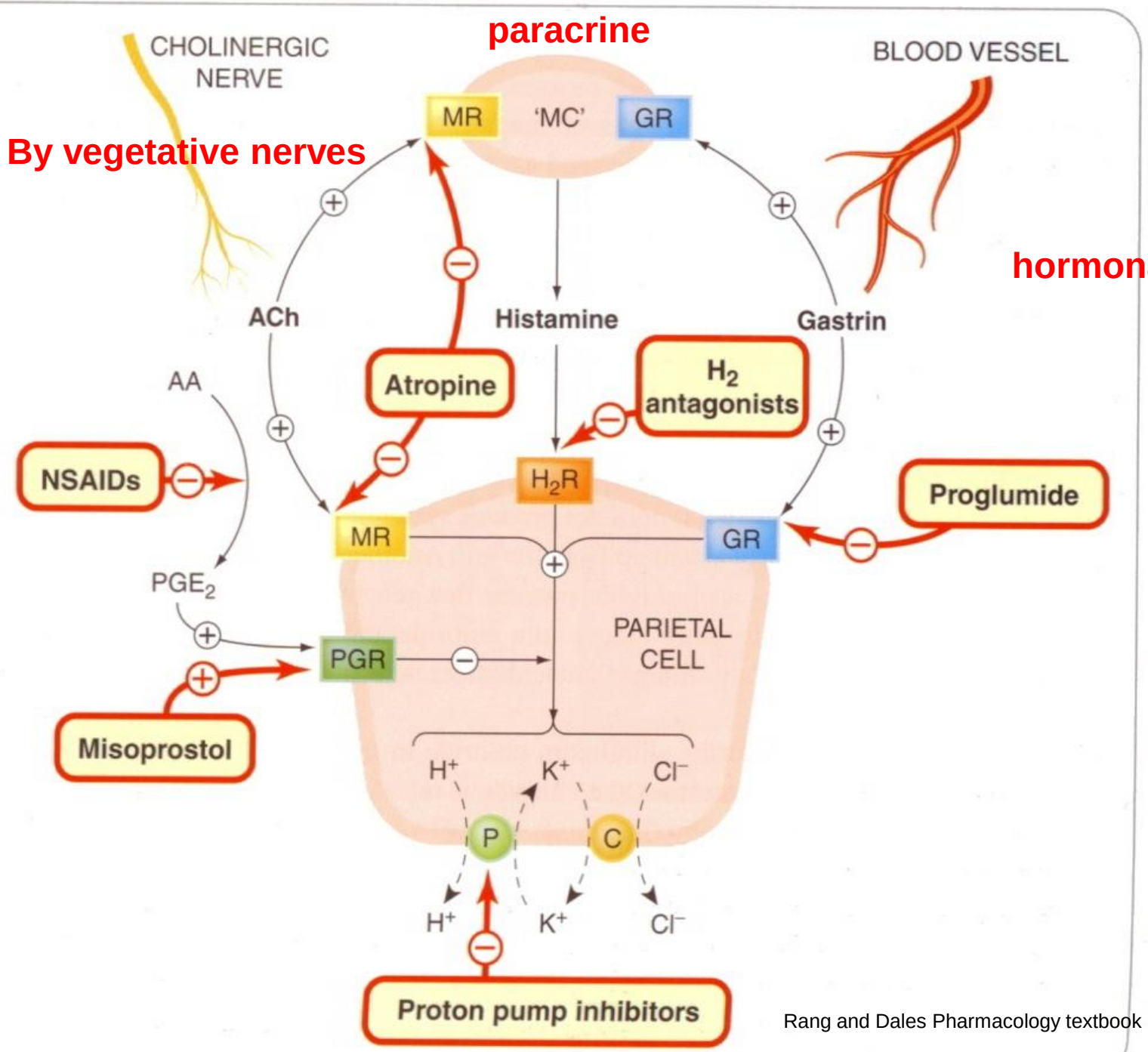

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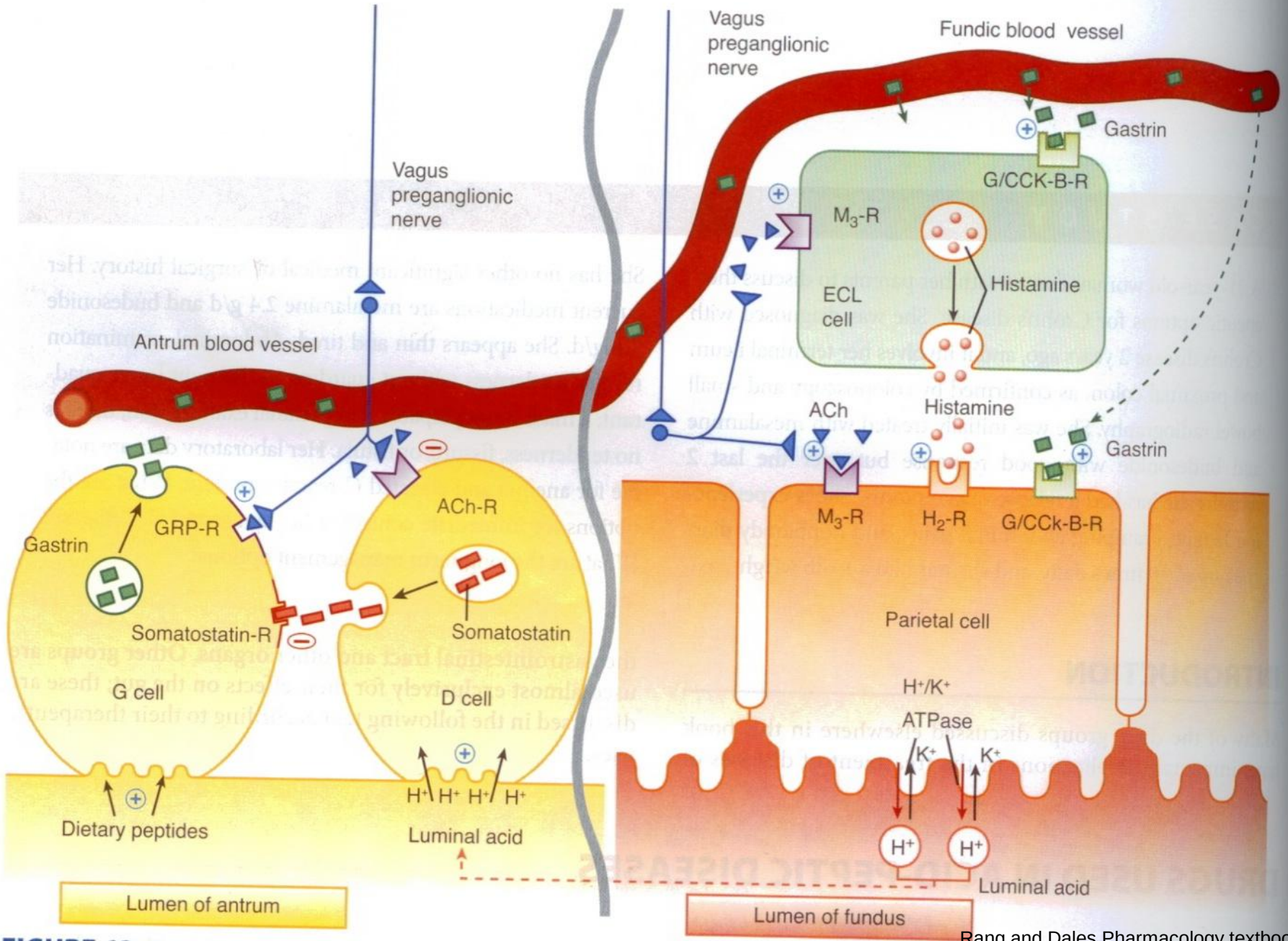

FIGURE 62–1 Schematic model for physiologic control of

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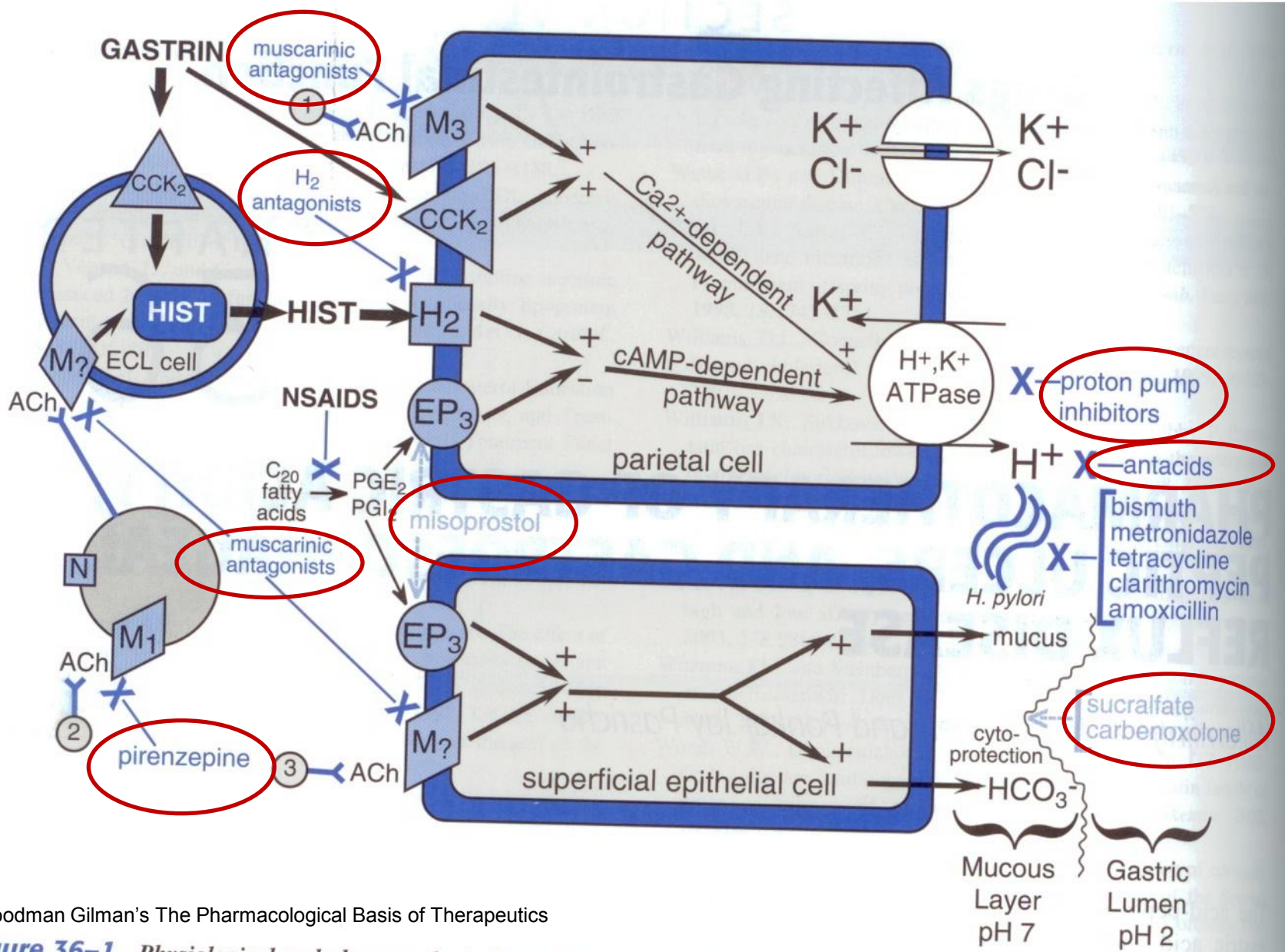

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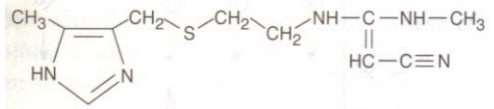
Figure 36–1. ***Physiological and pharmacological regulation of gastric secretion: the basis for therapy of acid-peptic disorders.***
Shown are the interactions among an enterochromaffin-like (ECL) cell

duction in volume of distribution.



Cimetidine

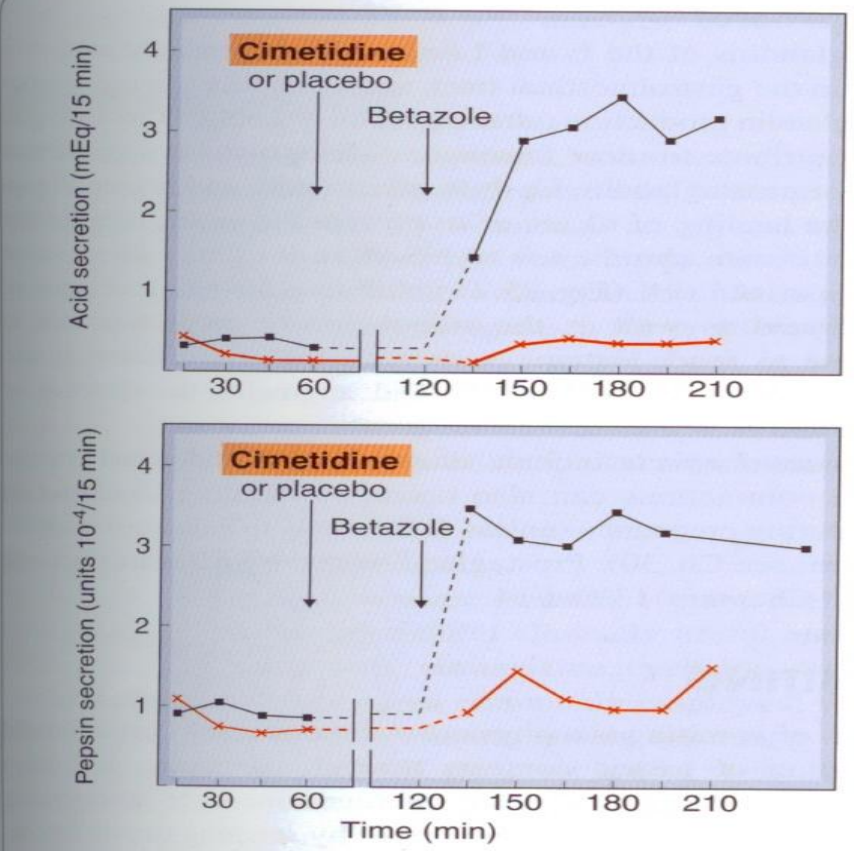


Fig. 25.3 The effect of cimetidine on betazole-stimulated gastric acid and pepsin secretion in humans. Either cimetidine or a placebo was given orally 60 minutes prior to a subcutaneous injection (1.5 mg/kg) of betazole, a relatively specific histamine H_2 receptor agonist that stimulates gastric acid secretion. (Modified from Binder H J, Donaldson R M 1978 Gastroenterology 74: 371–375.)

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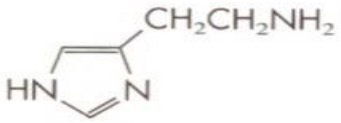
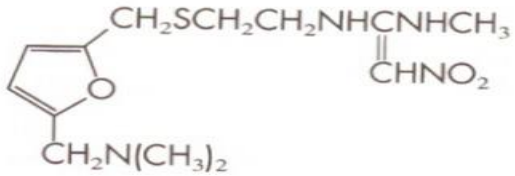
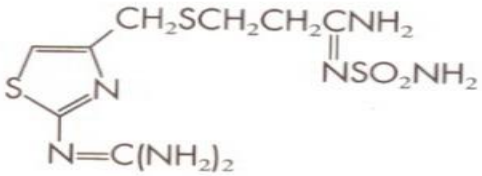


HISTAMINE

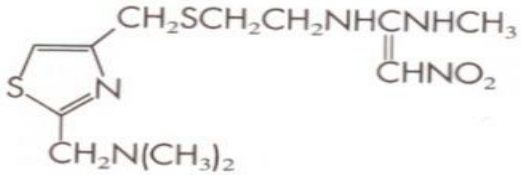
CIMETIDINE



RANITIDINE



FAMOTIDINE

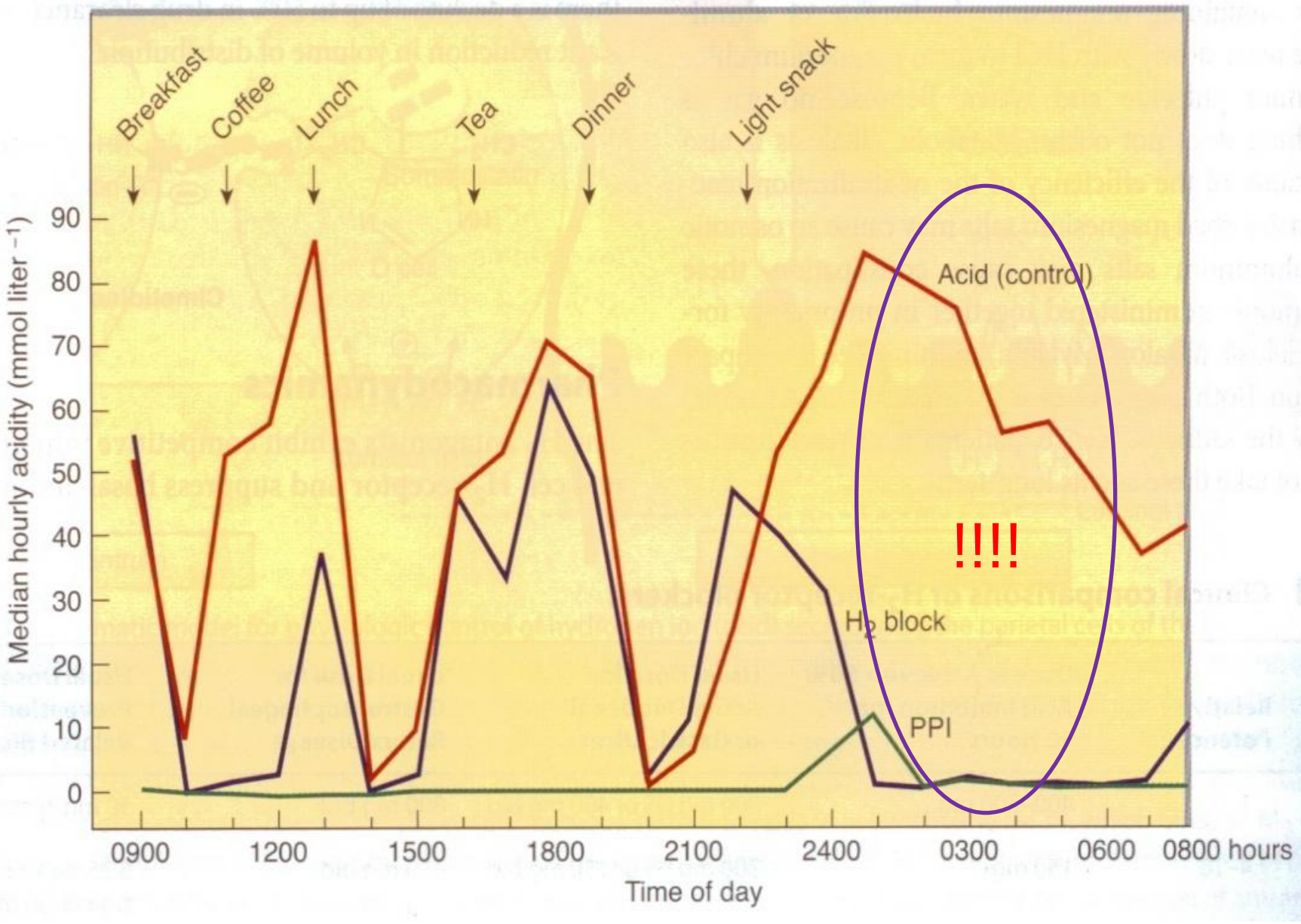


NIZATIDINE

ure 36–3. *Histamine and H receptor antagonists*

Safety is good

OTC drugs



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Pharmacokinetics of H2 blocking drugs

Absorption is good and rapid with peak concentration 1-3 hours after administration

Protein binding is low

Metabolism is small in the liver with exception of cimetidine , which has many metabolites and drug interactions on CYP enzimes

Excretion by the kidney –drug interactions : cimetidine and ranitidine inhibit tubular secretion of basic drugs

Cross the placenta and excreated in breast milk !!

TABLE 62–1 Clinical comparisons of H_2-receptor blockers.

Drug	Relative Potency	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	1	400–800 mg	800 mg HS or 400 mg bid	800 mg bid	50 mg/h continuous infusion
Ranitidine	4–10	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	4–10	150 mg	300 mg HS or 150 mg bid	150 mg bid	Not available
Famotidine	20–50	20 mg	40 mg HS or 20 mg bid	20 mg bid	20 mg IV every 12 h

BID, twice daily; HS, bedtime.

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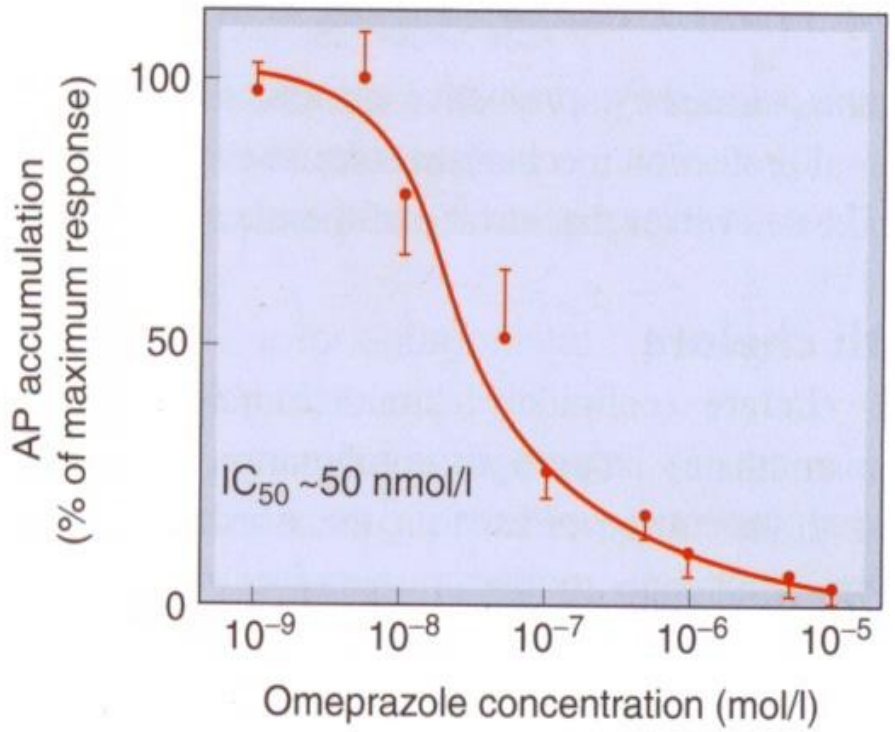
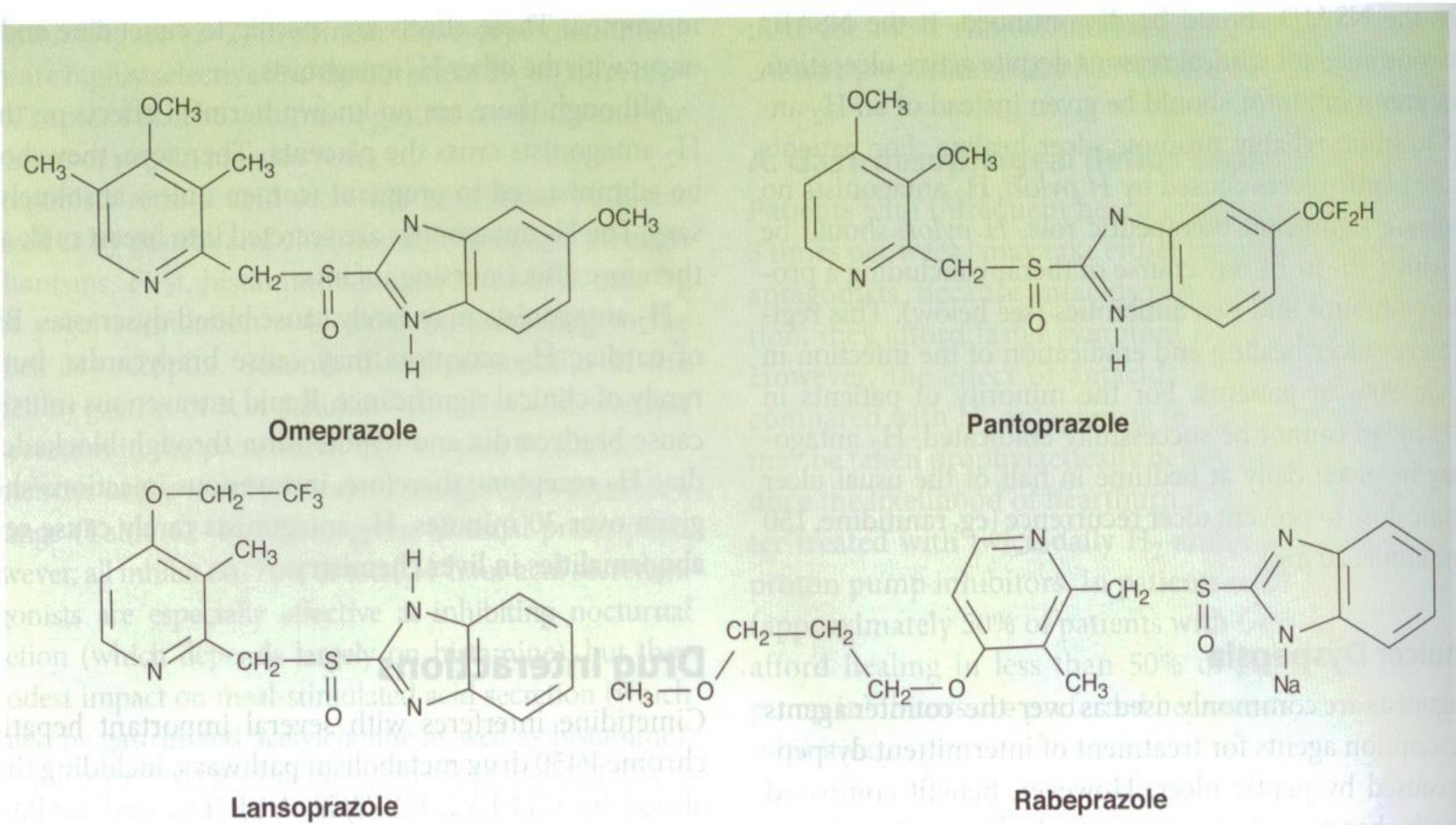


Fig. 25.4 The inhibitory action of omeprazole on acid secretion from isolated human gastric glands stimulated by 50 μmol/l histamine. Acid secretion was measured by the accumulation of a radiolabelled weak base, aminopyrine (AP), in the secretory channels. The data represent the mean and standard error of measurements from eight patients. (Adapted from Lindberg P et al. 1987 Trends Pharmacol Sci 8: 399–402.)



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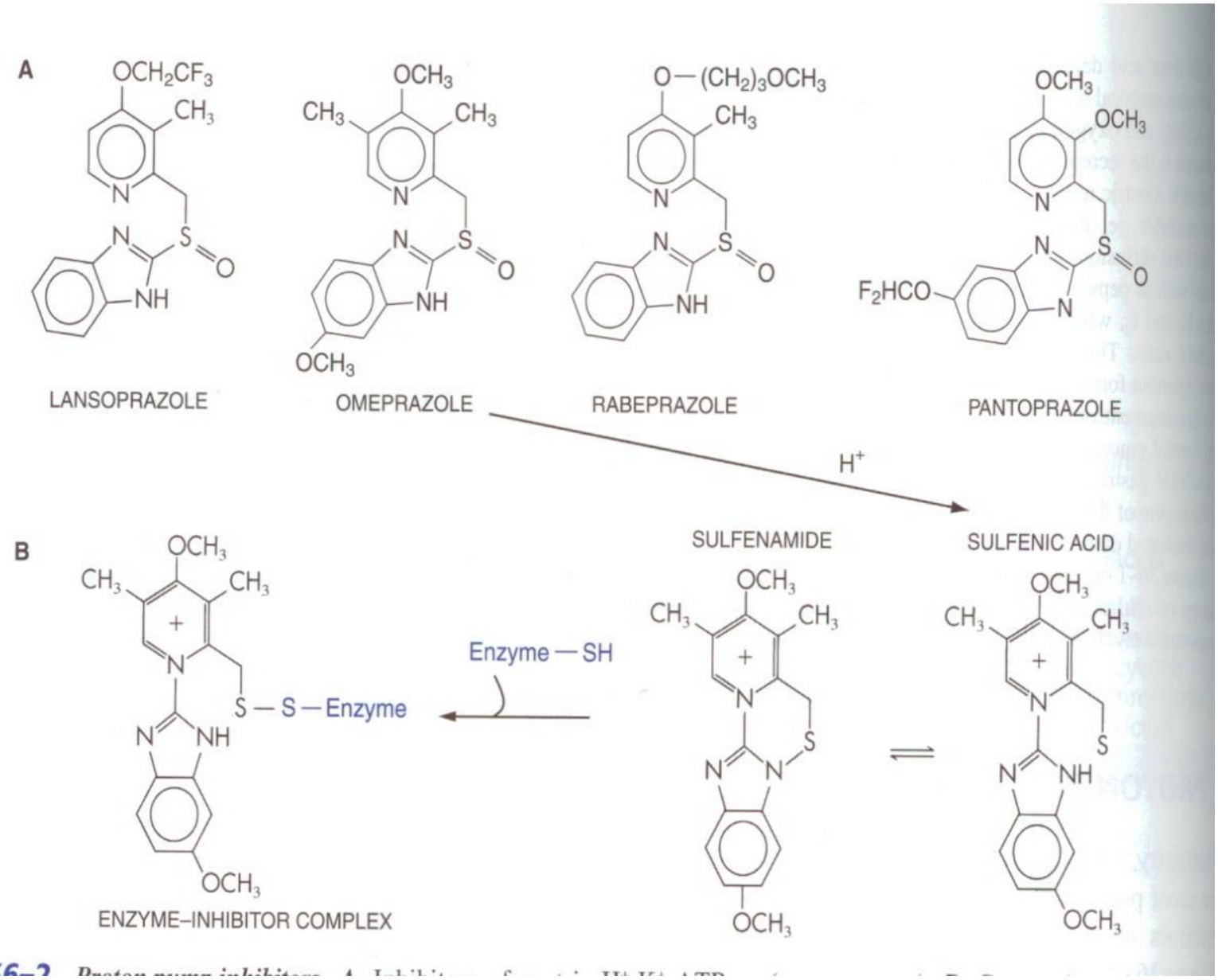

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TABLE 62–2 Pharmacokinetics of proton pump inhibitors.

Drug	pK_a	Bioavailability (%)	$t_{1/2}$ (h)	T_{max} (h)	Usual Dosage for Peptic Ulcer or GERD
Omeprazole	4	40–65	0.5–1.5	1–3.5	20–40 mg qd
Esomeprazole	4	> 80	1.2–1.5	1.6	20–40 mg qd
Lansoprazole	4	> 80	1.5	1.7	30 mg qd
Pantoprazole	3.9	77	1.0–1.9	2.5–4.0	40 mg qd
Rabeprazole	5	52	1.0–2.0	2.0–5.0	20 mg qd

GERD, gastroesophageal reflux disease.

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Duration of action **is not directly related to their short plasma half - lives**

because they covalently bind to proton/potassium ATPase enzyme.

Therefore once daily dosing results in acid inhibiting effect for 24-48 hours or more, until the new enzyme molecules are synthesized.

PPIs are weak bases and acidic pH destroy them

enteric-coated tablets (pantoprazole is more resistant)

Administration: **with meals !!**

Inhibition CYP2C19 and CYP3A4 → **drug interactions !!**

Clearance of e.g. benzodiazepines, phenytoin, warfarin ↓

Side effects:

Not too frequent

Nausea, abdominal pain, constipation, flatulance, diarrhea,

myopathy, arthralgias, headache, skin rashes

Absorption of vitamin B12 decreases

5-10 % in chronic use:

Hypergastrinaemia !! → **Rebound effect**

Maybe teratogenic
Do not use them in pregnancy if it is possible !

ANTACIDS I.

Also systemic effects:

$Na+HCO_3^-$ + HCl → Na Cl + H_2CO_3 → CO_2 + H_2O

↓ blood ↓ metab. alkalosis

↓ CCK ↓ ic Ca++ ↓ HCl ↑ in the gastric juice

Ca salts more rarely used (Rennie tablets contain them)

Milk –alkali syndrome: CaCO3 or NaHCO3

hypercalcemia, phosphate retention , PTH secretion,
Ca precipitation in the kidney

ANTACIDS II.

local effect in the stomach:

magnesium salts → diarrhea

aluminium salts → constipation

$Mg(OH)_2 + 2HCl \rightarrow \underline{MgCl_2} + 2H_2O$

$Al(OH)_3 + 2HCl \rightarrow \underline{AlCl_3} + 3\ H_2O$

hydrotalcite Al-Mg carbonate in hydroxylated form

OPTACID is a buffer system containing $NaHSO_4$ + NaH_2PO_4 in combination

Acid-Neutralizing Capacities of Popular Antacid Preparations

PRODUCT	$Al(OH)_3$*	$Mg(OH)_2$*	$CaCO_3$*	SIMETHICONE*	ACID NEUTRALIZI CAPACITY†
Tablets					
Gelusil	200	200	0	25	10.5
Maalox Quick Dissolve	0	0	600	0	12
Mylanta Double Strength	400	400	0	40	23
Riopan Plus Double Strength	Magaldrate, 1080			20	30
Calcium Rich Rolaids		80	412	0	11
Tums EX	0	0	750	0	15
Liquids					
Maalox TC	600	300	0	0	28
Milk of Magnesia	0	400	0	0	14
Mylanta Maximum Strength	400	400	0	40	25
Riopan	Magaldrate, 540			0	15

*Contents, milligrams per tablet or per 5 ml. †Acid-neutralizing capacity, milliequivalents per tablet or per 5 ml. The United States marketpla antacids is fluid. The current trend of "reusing" well-known brand

Recommendations for Treatment of Gastroduodenal Ulcers

DRUG	ACTIVE ULCER	MAINTENANCE THERAPY
H_2 Receptor Antagonists		
Cimetidine	800 mg at bedtime/400 mg twice daily	400 mg at bedtime
Famotidine	40 mg at bedtime	20 mg at bedtime
Nizatidine/ranitidine	300 mg after evening meal or at bedtime/150 mg twice daily	150 mg at bedtime
Proton Pump Inhibitors		
Lansoprazole	15 mg (DU; NSAID risk reduction) daily 30 mg (GU including NSAID-associated) daily	
Omeprazole	20 mg daily	
Rabeprazole	20 mg daily	
Prostaglandin Analogs		
Misoprostol	200 μg four times daily (NSAID-associated ulcer prevention)*	

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Severity of GERD	Medical Management
Stage I Sporadic uncomplicated heartburn, often in setting of known precipitating factor. Often not the chief complaint. Less than 2-3 episodes per week. No additional symptoms.	Lifestyle modification, including diet, positional changes, weight loss, *etc.* Antacids and/or histamine H_2-receptor antagonists as needed.
Stage II Frequent symptoms, with or without esophagitis. Greater than 2-3 episodes per week.	Proton pump inhibitors more effective than histamine H_2-receptor antagonists.
Stage III Chronic, unrelenting symptoms; immediate relapse off therapy. Esophageal complications (*e.g.*, stricture, Barrett's metaplasia)	Proton pump inhibitor either once or twice daily.

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