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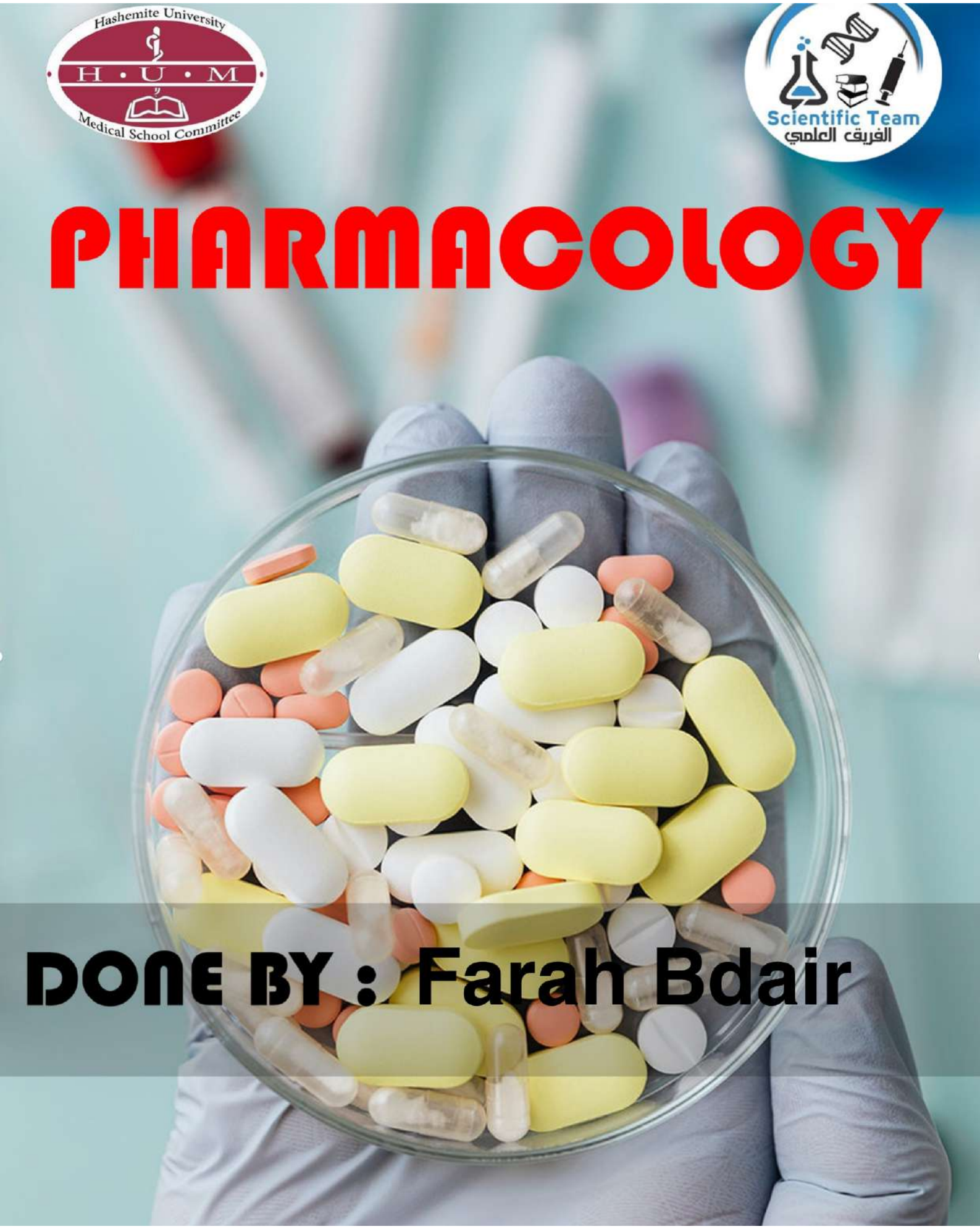
PHARMACOLOGY



DONE BY : Farah Bdair

PPIs & H2 antagonists

Lecture 2

Prof. Ahmed Shaaban

Professor of Pharmacology &

Senior consultant of Endocrinology

Proton Pump Inhibitors (PPIs)

1. Omeprazole & esomeprazole.
2. Lansoprazole.
3. Pantoprazole.
4. Rabeprazole.

Mechanism

A) Acid - suppression:

The most potent and highest efficacy acid – suppressant.

Absorbed in intestine reaching parietal cells from circulation and diffuse into secretory canaliculi where they are pronated and trapped.

They interact with SH-groups of H+ / K+ ATPase → enzyme inhibition → ↓H+ pump → ↓ Hcl secretion. This maintains intragastric pH more than 4 for at least 20 hours, causing effective nocturnal and day - time acid suppression.

B) Anti H pylori:

Lansoprazole is the most potent PPI against H pylori.

* كلهم (acid - labile) يعني destroyed by HCl in stomach، وبالتالي من أجل نمنع ال destruction by HCl rapidly

يعملوا protection من خلال Delayed release preparation تكون acid resistant من خلال enteric coated capsules or tablets

• بالتالي، بنحط عليه outer cover ← isn't dissolved in stomach ← بوصل لل intestine، لأنه قاعدي وما بتذوب ال coat بتذوبه ال dissolving وبصير release لل drug particles.

Pharmacokinetics

PPIs are acid – labile prodrugs. For protection from rapid destruction within gastric lumen, oral formulations for delayed release as acid resistant, enteric coated capsules or tablets are used. In alkaline intestinal lumen, enteric coatings dissolve causing absorption of prodrugs.

Absorption orally is rapid, pantoprazole more than lansoprazole than omeprazole.

IV injection allows more of drugs to reach site of action in parietal cell canaliculi without degradation.

لكونه الدواء systemic، بالحالات ال acute/severe لو أعطيت المريض الدواء IV رح يوصل أسرع.

Onset of action: 1 hour.

Peak: 2 hours.

→ . Lipophilic الدواء، سريعة :.

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* لما أقول انه الدواء فقدت نصفه لا يعني انه ⇒ ∴ halfing of the dose doesn't mean halfing of pharmacological response.
الـ response بيقل للنصف ، لانه بعتمد على الـ MEC علاقة بالـ Concentration-time curve ، وفي حالة كان الـ dose اللي نصفنا الـ effect ما بيقل الـ MEC (Minimal Effective Concentration)

Bioavailability

Pantoprazole (90%), lansoprazole (80%) & omeprazole (60%).

Decrease markedly (50%) by food in case of lansoprazole & omeprazole (must be given at least 30 minutes before meals). Pantoprazole is unaffected by food (given before, during or after meals).

* لا تأخذوا after meals بتأثر فعاليتهم

Bioavailability of omeprazole is increased after repeated dosing.

Esomeprazole is S- isomer of omeprazole. It has 80% bioavailability. → بجهاز الأفلاج بقل الـ bioavailability

Rapid 1st pass and systemic hepatic metabolism (affected by liver function). → isn't affected by kidney disease. → Lipophilic.

Serum t ½ is 1 hour but duration of action is more than 24 hours due to prolonged inhibition of H+ / K+ ATPase.

Short plasma/serum half life

but long biological half life → وهاد اللي بهمني

وبالتالي الريض بوخذ الدواء غالباً once daily قبل الإفطار مباشرة.

بكون بقوته ، ما وهاد لا low effect

ولا الانزيم regenerate again بدون مفعوله.

Uses

1st line in PU disease.

1.DU: for 2-8 weeks.

most potent anti-ulcer drug

Specially in severe and non responding mild or moderate cases.

It produces faster pain relief and more rapid ulcer healing than H2 antagonists. Healing rates are higher. Pantoprazole is more potent and has higher efficacy and produces faster symptom relief than lansoprazole than omeprazole.

(PPIs) more potent, lipophilic

2. GU: for 4-8 weeks.

3. Prevention of rebleeding from PU and stress bleeding. High oral dose or IV infusion increases intragastric pH > 6 and increases coagulation and platelet aggregation.

4. GERD: Longer term use is frequently required. (It may need more than 8 weeks).

- Mild cases: lansoprazole is the drug of 1st choice because its rapid absorption leads to more efficient acid suppression. (more anti H.pylori).
- Severe cases: omeprazole is the drug of 1st choice because, unlike lansoprazole and pantoprazolc, it produces dose - dependent acid - suppression.
- In erosive esophagitis PPIs cause healing in 85%. In 10% of cases and in extraesophageal complications doses may be given twice daily for 3 months.

*Tumor in delta cells of pancreas secreting much gastrin → multiple extensive peptic ulcers. (not common)

more steep بكون dose - response curve ال

Severe cases: ال dose شوي، يعني لو زدت ال response زاد كتير بال شوي بلاش ال

5. Zollinger - Ellison syndrome: Drugs of 1st choice. ⇒ (↑ HCl, multiple peptic ulcer)

6. Chronic idiopathic urticaria:

* Uses:

* الأدوية مهمة جداً بال DU و GU فشكل دواء بين الاثنين مختلفة ولكن بنلاحظ انه ال maximum بال ٣ ← 8 weeks وهذا معناه انه اهم ال Adverse effect بخاف منها ، ولكن بحالة ال DU بنقدر نعطي الدواء ل 2 weeks وال GU ل ٤ weeks ، لانه بحالة ال DU المشكلة هي ال HCl وبالتالي ال acid suppression drugs بهاي ال ح يكون أسرع وال healing أكثر فال 2 weeks ممكن يكفوا ، أما بال GU المشكلة من ال defense loss مع انه خلي الضرر susceptible لل HCl normal / low ولكن بحتاج ٤ weeks.

* شرح نقطة [٣] :

تابعة لنقطة ٢ ولكنها Severe وهي bleeding أو Stress ulcer وبكون خطر على حياة المريض ، فممكن أعطي High oral dose أو الأفضل أعطيه rapid IV infusion السبب بإعطائهم ← بدل ما ال intragastric pH كانت توصل ل ٤ بوصلها ل 7 كمان + ال coagulation process & platelet aggregation بزيدوا من ال high pH.
وهذا مهم جداً حتى يمنع ال bleeding

* شرح نقطة (٤) (فرع ٣) :

ال erosion بكون أقل شي من ال ulcer يعني ما في complete loss of mucosal continuity وبالتالي نسبة كويسة انه يوصل ال healing ل 85%.

- ال GERD أحياناً ممكن يكون منها extraesophageal complications يعني ممكن يوصل ال regurgitation لل Respiratory tract و ال Pharynx -

أحياناً بيصير manifestation بلعب فيتذكرها tonsillitis ، و أحياناً بيشخصها خطأ كـ myocardial infarction الخ ...

معلومة خارجية * myocardial infarction is a serious result of coronary artery disease.

Both GERD and coronary artery disease are frequently co-exist & can cause chest pain, and GERD can cause cardiac symptoms. ⇐ عشان هيك ممكن تتشخص غلط غالباً.

* Acid from stomach irritates the surface of the throat and tonsils, causing a sore throat.

- نفس حالات الـ extraesophageal بنغير كالتالي :

1) بدل ما أعطيها once daily بعطيها twice daily.

2) وبدل ما الـ maximum duration of therapy ⇐ 8 weeks ممكن توصل لـ 3 months.

وهاد بسبب انه الحالة severe.

* نقطة [6] + [7] :

جدول المرضى ما الهم علاقة بالـ HCl ولكن وجدوا انهم لديهم بسبب الـ H.pylori

وبجدول الحالات بختار الـ lansoprazole لانه يعتبر أقوى من ناحية الـ anti H.pylori من باقي الأدوية (كما ذكرنا سابقاً) و بما انه الـ H.pylori بكتيريا ، العلاج بكون Combination therapy مع other antibiotic مثل الـ Amoxicillin .

much gastrin → multiple extensive peptic ulcers. (not common)

ال dose - response curve بكون more steep شوي، يعني لو زدت ال dose شوي ح نلاحظ ال response زاد كثير بال severe cases.

5. Zollinger - Ellison syndrome: Drugs of 1st choice. ⇒ (↑ HCl, multiple peptic ulcer)

6. Chronic idiopathic urticaria:

Caused by H pylori. Lansoprazole is given combined with amoxicillin.

7. Immunomodulator: They inhibit several leukocyte functions, reduce killer cell cytotoxicity, chemotaxis and superoxide anion generation.

Dose : orally as capsules, once daily, in the morning. Also twice daily in severe cases.

Omeprazole : 20 & 40 mg. (has dose-dependent response).

Lansoprazole: 30 mg.

Pantoprazole: 40mg.

Rabeprazole : 20 mg.

PPIs are given 30 - 60 minutes before breakfast, but pantoprazole may be given before, during or after breakfast.

- Also by repeated IVI or IV infusion.

IVI → intravenous injection.

Adverse effects

Duration & dose - dependent:

1. Recurrence: less than H2 antagonists. (because PPIs more potent + longer acting)
2. Hypochlorhydria:

More than H2 antagonis • harmful bacteria / normal intestinal bacterial flora balance

Long term use ↓Hcl → colonization of stomach by bacteria (intestinal dysbiosis) → reduction of salivary or dietary nitrates to nitrites → carcinogenic nitroso compounds. (>8 weeks) (intestinal dysbiosis; Hcl suppression)

Also ↑gastrin → ↑cell growth. This → malignancy. (↓HCl —negative feedback→ ↑ gastrin).

3. ↑ GIT bacteria → ↑risk of community - acquired & nosocomial respiratory infections and also GIT infections. * e.g. pneumonia, by respiratory regurgitation.
4. Long term PPIs decrease absorption of vitamin B12, iron and calcium causing their deficiency. * Some vitamins & minerals depend on acidic medium in their absorption.

This may cause hip, wrest & spine fracture. So, give calcium supplement.

5. Enzyme inhibition: more significant clinically by omeprazole.
6. Diarrhea, abdominal pain, nausea & vomiting.
7. Headache, dizziness & asthenia.

(dizziness → drowsiness & blurring of vision.)

(calcium supplement → very important clinically; females, old age; menopause → 20%; fractured neck of femur.)

H2 antagonists

1. Ranitidine.
2. Famotidine.

Memo No.

Date / /

* Adverse effects:

* نقطة ٥ : هنا انه الأدوية lipophilic وبالتالي بتأثر على الـ enzymes وهاي مشكلة لو عملوا combination therapy.

* نقطة ٦ : local action on GIT.

وظيفة الـ HCl انه بساعد على digestion of food بالمعدة عن طريق انه بخلي إنزيم الـ pepsin يكون activated، طبعا بعد ← جزء من الأكل رح يضل undigested رح يعمل Diarrhea وباقي الـ effects.

H2 antagonists

1. Ranitidine. →
2. Famotidine.
3. Nizatidine.

Mechanism

A) Acid suppression:

H2 receptors are linked via Gs proteins to adenyl cyclase.

H2 antagonists are reversible competitive H2 blockers decreasing intracellular cAMP particularly in parietal cells.

↓Hcl secretion mediated by histamine completely and by Ach & gastrin partially.

Marked reduction in fasting and nocturnal acid secretion (main effect) and less reduction in meal stimulated and day time acid secretion (duration of secretion inhibition is 12 hours). In a linear dose - dependent manner.

Efficacy is higher when given twice daily than once daily even if we double the once daily dose.

B) H pylori suppression by ranitidine.

Famotidine is more potent than ranitidine, but ranitidine has higher efficacy due to H pylori suppression.

* H2 antagonists :

- some preperations of ranitidine, especially Zantac → شكّوا انه carcinogenic بعد التحاليل وجدوا انه فيه مادة معينة الشركة حاطيها (for preservation) حتى تحافظ على الدواء و يكون slow release ويضل مدة بالأسواق ، واحيانا موجودة بكميات أكثر من الطبيعي (Maximum daily allowance) فالـ health authority فاتت و سحبت الدواء للاصلاح لعمل الأبحاث واتأكد. ولكن ليس في بدائل زي ولكن المادة الحافظة ما بتكون carcinogenic .

Pharmacokinetics

Rapid absorption orally.

Peak effect: 2 hours.

Nizatidine has high (100%) oral bioavailability but the other H2 blockers have low bioavailability. 50% of ranitidine has 1st pass metabolism and 50% of famotidine is decomposed by acid.

So, famotidine is used in liver diseases and ranitidine in patients with delayed gastric emptying.

Plasma t1/2 is 3 hours.

Not cumulative.

Clearance is mainly renal (affected by renal diseases). Also hepatic.

CL is decreased in up to 50% of old patients.

Due to non specificity of cimetidine (the 1st H2 blocker), its use is markedly decreased to avoid its more frequent and more severe adverse effects.

USES

1. DU:

USES

1. DU:

A. Short term (acute therapy) leads to healing rate of 70% (4 weeks therapy) and 90% (8 weeks).

Oral dose: ranitidine & nizatidine 150 mg and famotidine 20 mg in the morning and at bed time. Total dose may be given at bed time but efficacy is reduced.

B. Maintenance therapy: only bed time dose for 1-5 years.

2. GU:

Less effective because there is normal or low Hcl. So there is lower healing rate and healing is delayed than DU by 2-4 weeks. Also in acute gastritis and gastric erosion e.g. by NSAIDs.

3. GERD:

In GERD, 50% have erosive esophagitis. H2 antagonists cause healing in 50%.

Low healing rates and recurrence rate is higher than PU.

*In GERD we prefer PPIs.

* موجودة عند أغلب الناس، بعد أكل وجبة دسمة / irritant
↳ يحدث عسر هضم.

4. Functional possibly acid - related dyspepsia. Small dose for short period. (one tablet for 1-3 days) * الدكتور لازم يكتب المدة.
5. Stress ulcer: IV injection or infusion is preferred.
6. GIT bleeding.
7. Before anesthesia in e.g. cesarean section to avoid aspiration pneumonia (Mendelson's syndrome).

- Ranitidine is used in combination therapy for H pylori.
- H2 blockers can be given by slow IV injection or infusion in acute and severe cases.
- Because H2 antagonists have less efficacy than proton pump inhibitors they are second choice in GERD and severe PU.

* نقطة (V) : في العمليات الدكتور يعطي المريض يهدم عشان الـ HCl ما يتكون، وبالعملية ما تكون موجودة لانه عكسه وهو anesthesia نتيجة الـ deglutition reflexes الـ reflexes في أثناء العملية يراجع الـ acid secretion من الـ stomach ويروح لـ respiratory tract فيصير respiration pneumonia، وبالتالي لو أعطيت هاي الأدوية قبل الـ Cesarean Section راح يصير ↓ incidence of this pneumon

- Cesarean section يعني الولد بده ينزل ولو ما نزل بسرعة بتصير bleeding ،

fetal asphyxia ، rupture of uterus يعني الام والبيبي مهددين بالموت

وبالتالي ما بقدر أكيلها صيدي لغاية ما أطلع العملية وأضمن انه رح يكونوا

ماتوا ، ولو أعطيتها ال anesthetic رح يصير لها aspiration pneumonia وفي

نص كثير ماتوا بسببها وبالتالي الحل بكون بانه نعطيها H2 antagonist ،

فلما يصير regurgitation of gastric content ما بكون so acidic فبتقل marked aspiration pneumonia

نتيجة ال destruction of mucosa ← (respiratory mucosa) .

Adverse effects

A) Caused by all H2 antagonists:

1. Tolerance due to up regulation of H2 receptors and rebound hyperacidity.
   - Negative Feedback نتيجة ال
   - يعملها الجسم كـ Feedback نتيجة ↓ HCl
2. Recurrence on withdrawal ⇒ because → It doesn't so potent. / → of tolerance.
3. Hypochlorhydria: .....

This adverse effect is much more significant by PPIs.

4. Rapid IV injection may cause decrease cardiac output, arrhythmias or heart block.

- in parietal cells ← mainly adenyl cyclase & cAMP حكينا انه بشتغل على ال
- heart و منتجبوها اشتركنا للمقارنة بين الأدوية لكنه ممكن يحصل بأماكن ثانية مثل ال
- بحيث انه يعتبروها سيئة للدواء عشان يشتغوا المشتري يشتري دواء آخر ← بدون ما يعرفوا انه
- كل أدوية ال H2 antagonist بتأثر على القلب ⇐ ∴ common adverse effect of all H2 antagonists

* ملاحظة :

١- بسبب الـ tolerance نلجأ لـ combination therapy أو تغيّر الدواء .

٢- بسبب الـ recurrence نلجأ لـ تقديم الدواء لفترة أطول ← prolonged therapy / interrupted therapy.

كل النشاط بيعتمد عليها → more lipophilic → اللي بيعدي حاجة بيعدي كل حاجة.

Caused more by ranitidine:

1. CNS manifestations, specially in old patients: confusion, hallucination, insomnia and depression.
2. Impotence and loss of libido, gynecomastia and galactorrhea (weak antiandrogen).
3. Enzyme inhibition.

* impotence = erectile dysfunction.
* Libido = sexual desire.

C) Caused by famotidine:

1. Diarrhea.
2. Bronchial asthma.
3. Headache.

* الـ famotidine بيشتغل أكثر على الـ smooth muscle stimulation
لأنه لو الـ H2 تسكرت فالـ H1 بتوخذ الـ upper hand
والهستامين كله بيروح عليه ، الـ H1 بيعمل allergic response ~
ضمنها الـ contraction of SM وبيسبب ① + ②

D) Caused by nizatidine: ← مهم + خطر

1. ↑Cholinergic effects: Lacrimation, salivation, emesis, miosis & diarrhea.
2. Mild increase in (serum cholesterol) and (uric acid.)

emesis → vomiting
diarrhea → ↑GIT movement
serum cholesterol ⇓ hyperlipidemia
uric acid ⇓ gout

∴ this drug is not commonly used.

+ بيسبب changes in vasculature of brain vessels

∴ Headache فيعمل