

## Lecture

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### ANTACIDS CLINICAL PHARMACOLOGY

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Antacids clinical pharmacology is represented according to the international classification of drugs ATC (anatomical-therapeutic-chemical). The article elucidates antacids indications and contraindications, administration details and side effects.

**KEY WORDS:** antacids, clinical pharmacology

### КЛІНІЧНА ФАРМАКОЛОГІЯ АНТАЦИДІВ

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Представлена клінічна фармакологія антацидів відповідно до міжнародної класифікації лікарських препаратів АТХ (анатомо-терапевтично-хімічної). Висвітлено показання та протипоказання до застосування антацидів, особливості їх застосування та побічні ефекти.

**КЛЮЧОВІ СЛОВА:** антациди, клінічна фармакологія

### КЛИНИЧЕСКАЯ ФАРМАКОЛОГИЯ АНТАЦИДОВ

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Представлена клиническая фармакология антацидов в соответствии с международной классификацией лекарственных препаратов АТХ (анатомо-терапевтико-химической). Освещены показания и противопоказания к применению антацидов, особенности их применения и побочные эффекты.

**КЛЮЧЕВЫЕ СЛОВА:** антациды, клиническая фармакология

### INTRODUCTION

Antacids (gr. anti - against, lat. acidus - acid) - alkaline compounds used to neutralize hydrochloric acid in the stomach. Antacids have been used for more than 100 years in medical practice in the treatment of acid-related diseases of gastrointestinal tract. For a long time sodium carbonate (baking soda) was used as an alkalinizing agent [1].

### ANTACIDS CLASSIFICATION

#### ATC classification

A: Alimentary tract and metabolism

A02 Drugs for acid related disorders

A02A Antacids

A02AA Magnesium compounds

A02AB Aluminum compounds

A02AC Calcium compounds

A02AD Combinations of aluminum, calcium and magnesium compounds

A02AF Antacids with antifatulents

A02AG Antacids with antispasmodics

A02AH Antacids with sodium bicarbonate

A02AX Antacids, other combinations

#### The classification according to the digestive absorption

According to the digestive absorption

classification antacids are divided into 2 main categories which are very important in practice [1, 2]:

1. Absorbable:

- sodium carbonate (baking soda);
- magnesium oxide (magnesia);
- magnesium carbonates;
- calcium carbonates;
- Bourget mixture (sodium bicarbonates, sulphate, phosphate);
- Rennie mixture (calcium carbonates, magnesium carbonates);
- Tums mixture (calcium carbonates, magnesium oxide).

2. Non-absorbable:

- aluminum phosphate;
- aluminum hydroxide;
- magnesium silicate;
- magnesium hydroxide;
- aluminum-magnesium combination;
- aluminum-magnesium combination with other active ingredients (anesthetics, antifatulents, alginates, etc.).

### PHARMACOKINETICS

Absorbable antacids are rapidly dissolving substances that immediately react with hydrochloric acid in the stomach forming carbon dioxide and water. Carbon dioxide causes gastric distention which provokes gastroesophageal reflux and stimulates gastric secretion enhancement. Sodium carbonate is different from other antacids its systemic effects, as it is absorbed into the blood and affects the organism pH in whole. In patients with normal renal function, the excess of bicarbonate is rapidly excreted, and in case of parafunction it can be accumulated and may cause systemic alkalosis [2, 3].

Most antacids used in medical practice are non-absorbable, without systemic pharmacokinetics.

### PHARMACODYNAMICS

Absorbable antacids are rarely used in clinical practice due to the large number of systemic side effects. Such antacids come into direct neutralization reaction with hydrochloric acid in the stomach. They are characterized by quick onset of therapeutic action and short-term

effects, because after the administration of absorbable antacids, the level of intragastric pH increases up to 7 or more in a short period of time (15-20 min) that stimulates secondary acid hypersecretion (the «rebound» syndrome) [1, 4].

Non-absorbable antacids have fewer systemic adverse effects than absorbable ones. Their main mechanism of action is associated with the absorption of hydrochloric acid. Non-absorbable antacids begin acting later (within 10-30 minutes), however, they have longer period of therapeutic action – nearly 2.5-3 hours [5]. Buffer (neutralizing) capacity of non-absorbable antacids is higher than of the absorbable. Their neutralizing activity lasts until the pH does not exceed 3.0-4.0 (the physiological pH when there is a normal digestion and hydrochloric acid has an antimicrobial action). Non-absorbable antacids have many others favorable properties:

- absorb pepsin, resulting in reduced proteolytic activity of gastric acid;
- connect lysolecithin and bile acid, which have a damaging effect on the gastric mucosa;
- possess cytoprotective function through the activation of prostaglandin synthesis, which stimulate a secretion of mucin and bicarbonates, improve microcirculation;
- possess ambient function, forming a protective film on the gastric mucosal surface;
- able to bind epithelial growth factor and fix it in the ulcerous defect region effectively stimulating cell proliferation, angiogenesis and angiogenesis.

Antacids efficiency is evaluated by their acid neutralizing capacity (ANC) which is expressed in mEq of hydrochloric acid that is neutralized by a standard dose of antacids raising the pH to approximately 3.5 during a predetermined time (usually – about 15 minutes). ANC varies widely and is dissimilar among the various antacids. The average daily dosage of antacids should provide 200 to 400 mEq neutralizing capacity, ANC is considered to be low if it is less than 200 mEq / day and high if it is more than 400 mEq / day.

Pharmacodynamics properties of antacids depend on their cationic composition (tab. 1).

Characteristic of the antacids cationic composition

| Effect         | Cations  |           |         |         |
|----------------|----------|-----------|---------|---------|
|                | Aluminum | Magnesium | Calcium | Bismuth |
| Neutralizing   | ++/+++   | +++       | +       | –       |
| Absorbing      | +        | –         | –       | –       |
| Ambient        | +        | –         | –       | +++     |
| Astringent     | +++      | +         | +       | +       |
| Cytoprotective | +++      | –         | –       | +       |

Remarks: «-» No effect, «+» low activity, «++» average activity, «+++» high activity.

Antacids containing aluminum cations, have the greatest medicinal effect (along with hydrochloric acid neutralization, such antacids possess high cytoprotective function and bind effectively bile acid) [2, 5]. However they promote a slowdown of intestinal motility and may cause constipation, magnesium salts, vice versa, – possess slight laxative action. The administration of combined antacid containing aluminum and magnesium hydroxide provides more rapid onset of therapeutic effect (due to magnesium hydroxide), increases period of action (due to aluminum hydroxide) and minimizes side effects. The exposure to the drug on motility depends on the quantitative ratio of aluminum / magnesium at the combined antacid: the closer this ratio to 1, the less likely this effect.

## INDICATIONS AND PRINCIPLES OF CLINICAL USE

### Antacids therapeutic indications

In the treatment of acid disorders the proven effectiveness belongs to proton pump inhibitors (PPIs), H<sub>2</sub> antagonists (H<sub>2</sub> blockers) and eradication therapy of infection *Helicobacter pylori* (Hp). In this regard, antacids are mainly examined as an adjunctive therapy. Due to quick symptomatic effect, convenient presentation (suspensions, chewable tablets), pleasant organoleptic properties, high security antacids are the drugs of choice for self-treatment.

### 1. Gastroesophageal reflux disease (GERD)

Antacids neutralize hydrochloric acid, inactivate pepsin, absorb bile acids, stimulate the synthesis of bicarbonates, raise the tone of the lower esophageal sphincter, thus affecting

on the majority of units in the GERD pathogenesis. Along with that antacids possess cytoprotective effect on the esophageal and gastric mucosa that allows achieving positive clinical and endoscopic dynamics faster.

When GERD is non-erosive (NERD), antacids may be used as monotherapy. In case of monotherapy failure (heartburn saving), and in erosive form of GERD antacids are prescribed as a co-drug to the PPIs main course [5, 6].

It is better to use liquid form of non-absorbable combined antacids: antacid containing aluminum phosphate, as well as pectin gel and agar; aluminum-magnesium antacids; aluminum magnesium antacids with alginic acid (is derived from seaweeds). Alginic acid produces a gel foamy layer in the cardiac orifice, which in case of backflow, instantaneously gets into the esophagus and prevents aggressive action of gastric acid. Besides, alginic acid increases the residence time of antacid in the esophagus and stomach, thereby prolonging their cytoprotective effect to the mucous membrane.

### 2. Gastric and duodenal ulcers

In gastric and duodenal ulcers, antacids are used for severe pain management during the screening phase and within first day of PPIs administration before the acid production blockade (after 1-3 days).

In case when ulcer is unassociated with Hp, antacids are administered in combination with PPIs (in order to enhance cytoprotective effect when ulcers are nonhealing).

When ulcer is Hp-associated, antacids (in combination with PPIs) are recommended in case of difficultly cicatrizing ulcer (the phenomenon of growth factors fixation) after eradication therapy or on retention of

dyspeptic symptoms. Antacids administration during the eradication therapy is undesirable because of its potential self-tapering action [7].

Antacids are the drugs of choice for contraindications to antisecretory agents' administration, side effects of PPIs and H<sub>2</sub>-blockers. They are also recommended for H<sub>2</sub>-blockers administration and their withdrawal in order to relieve the «rebound» phenomenon. Long-term maintenance administration of antacids is effective as an anti-relapse treatment.

### **3. Acute gastritis / gastroduodenitis**

Antacids are used in addition to PPI therapy, H<sub>2</sub>-blockers in the treatment of acute gastritis, gastroduodenitis, especially with severe pain and dyspeptic syndromes [7].

### **4. Chronic gastritis / gastroduodenitis**

To prevent recurrences, antacids are used either alone or in conjunction with antisecretory agents. They are the drugs of choice for treatment and prevention of reflux gastritis, where bile acids and lysolecithin are the main disturbing factors.

### **5. Gastropathy caused by nonsteroidal anti-inflammatory drugs (NSAIDs - gastropathy)**

Antacids can be taken alone or in addition to antisecretory drugs in order to prevent gastro- and duodenopathies affected by the administration of nonsteroidal anti-inflammatory drugs (NSAIDs).

### **6. Pain and dyspeptic syndromes**

Antacids are recommended for healthy people with discomfort or epigastric pain, dyspeptic symptoms (heartburn, belching, meteorism). Non-absorbable antacids are used as the essential drug to relieve heartburn in pregnancy, which occurs in approximately (50-80) % [2, 4].

### **6. Cholecystitis, biliary dyskinesia**

Antacids are included in the treatment regimen for patients with acalculous and calculus cholecystitis, biliary dyskinesia's to eliminate the symptoms of bail and mixed refluxes. Antacids efficacy is associated with their ability to absorb bile acids and lysolecithin, which get into the esophagus and stomach in case of duodenogastric and gastroesophageal refluxes. Thus, antacids prevent damaging effect of bile acids on the

gastric and esophageal mucosas and their stimulating effect on the secretion of hydrochloric acid.

### **7. Chronic pancreatitis in the exacerbation phase**

Taking into account the role of gastric acid in the stimulation of pancreatic secretion during the exacerbation of chronic pancreatitis, PPIs, H<sub>2</sub>-blockers and antacids are necessary components of treatment. By raising the stomach pH, antacids promote the evacuation process normalization, reduce intragastric and intraduodenal pressure, thereby negating the flatulent distention. Enzyme drugs are used in chronic pancreatitis to correct a digestion and in order to reduce pain syndrome. But the action of hydrochloric acid leads to rapid inactivation of the main components of enzyme drugs - lipase and trypsin. Besides, during chronic pancreatitis a normal process of duodenal contents «alkalinity» is disrupted and consequently the release and activation of enzyme drugs particles with enteric coating (activated only in the alkaline environment) is disrupted as well. Therefore, to increase the effectiveness of enzyme therapy it is advisable to use a co-administration of antacids and / or anti-secretory drugs. Even if a starvation for 2-3 days is prescribed to the patient, antacids and antisecretory drugs are recommended from the first day of treatment [8].

### **8. Prevention of «stress» ulcers**

Antacids are used in the intensive care units to prevent so-called «stress» ulcers (in patients after a major operation, with craniocerebral traumas - Cushing's ulcers or with severe burns – Curling's ulcers, etc.).

#### **Administration principles**

Antacids are used in the form of tablets and suspensions. These presentations are differ significantly in the ANC. Solubility affects the ANC, as antacids react with hydrogen ions only in a solute form. In comparison with tablets, suspensions consist of smaller particles, they have a larger surface area and are dissolved faster in the acid environment of the stomach. Thus, antacids are more active in the form of suspension [1, 2].

The average therapeutic dose of antacid is 10-15 ml (1 tablespoon or 1 package content) of liquid or 1-2 tablets 3-4 times a day. Tablets should be chewed or dissolved well

before swallowing. In some patient information leaflet of antacids it is recommended to take them before a meal. However, when antacids are taken on an empty stomach they are rapidly emptied into the duodenum, in addition their effect is negated because food acts as a buffer for antacids. It is advisable to take antacids 1-1.5 hours after meals or at bedtime (to reduce the aggressive action of hydrochloric acid on the gastric mucosa during the night). Additional intake of antacids 3-4 hours after a meal can be recommended in special cases, for example, when there are long intervals between meals. Antacids can be used singly as a symptomatic treatment in case of complaints («on-demand therapy») or on a regular basis as a course. Course duration may range from 1 to 3-4 weeks.

#### **Antacids side effects**

1. When administered absorbable antacids (sodium hydrogencarbonate, rarely - calcium carbonate) after a short-term effect of acid neutralization a secondary acid hypersecretion (the «rebound» syndrome) occur in the result of pH increases up to 7 and / or as a result of a direct effect of calcium ions. In long-term treat and in high doses antacids can cause systemic metabolic alkalosis (with a headache, sicchasia, vomiting).

2. Sodium bicarbonate may adversely affect the water-salt metabolism: 2 g of sodium retains fluid as well as 1.5 g of sodium chloride. In elderly patients with pathology of the cardiovascular system may rise blood pressure, appear or enlarge swelling, increase signs of cardiovascular failure.

3. Antacids containing carbonates (sodium hydrogencarbonate, calcium and magnesium carbonate) in reaction with hydrochloric acid produce carbon dioxide gas. This causes gastric distension (pain syndrome), belching and meteorism which are especially undesirable in case of GERD.

4. Urinary alkalization occurs under the influence of sodium hydrogencarbonate and magnesium drugs (oxide, hydroxide and carbonate), which may lead to settling phosphates forming phosphate stones.

5. Antacids containing calcium may cause hypercalcemia, which promotes kidney stones formation and reduces parathormone

production. Consequently, the excretion of phosphorus is delayed and calcium phosphate is accumulated. That causes tissue calcification and nephrocalcinosis progression.

6. The combination of calcium antacids and milk is undesirable, because such intake promotes «milk-alkali» syndrome (sicchasia, vomiting, polyuria, mental disorders).

7. Non-absorbable antacids have fewer adverse effects than absorbable ones and more frequently these effects are caused by long-term and uncontrolled drug administration. With long-term administration of aluminum hydroxide, the intestinal absorption of phosphate can be decreased that sometimes may cause hypophosphatemia. That complication is more common in patients who abuse alcohol. In patients with severe renal failure, antacids may cause clinically significant increased aluminum and magnesium levels in the blood. In such cases the cumulation of aluminum can lead to encephalopathy and osteomalacia. During the antacids treatment in patients with normal or moderately reduced kidney function a visible increase of aluminum level in the blood does not occur.

8. The most common adverse reaction in the aluminum hydroxide administration is constipation, magnesium hydroxide have a laxative effect that may cause diarrhea. In the combined aluminum / magnesium antacids the exposure to the drug on motility of the gastrointestinal tract depends on the quantitative ratio of aluminum / magnesium. If this ratio is 1 or a shade more, the drug has no effect on motility or, in rare cases may cause a laxative effect (as a rule, at a dose increase).

#### **CONTRAINDICATIONS**

Currently, the administration of absorbable antacids is undesirable. Contraindications for non-absorbable antacids are severe kidney failure, Alzheimer's disease. Aluminum phosphate is contraindicated in pregnancy [5].

#### **Antacids interaction with other drugs**

Antacids that contain calcium, magnesium and aluminum ions are chelators. They bind a great number of drugs such as digitoxin, tetracycline, bishydroxycoumarin, indomethacin, aspirin, cimetidine, ranitidine, famotidine, theophylline etc. Antacids administration reduces the bioavailability of weak acids: barbiturates, sulfonamides,

penicillins and others. The absorption of weak bases increases (atropine, chlorpromazine, propranolol etc.) [1, 2].

It is advisable to combine antacids with M-anticholinergics (to prolong the effect of antacids) and with PPIs (to reduce their destruction in the stomach).

Because of pharmacodynamic drug incompatibility, antacids cannot be combined with bismuth subcitrat and sucralfate.

To avoid undesirable interactions, antacids are usually used 2 hours before or after taking any medication.

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