**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

### 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**

<table>
<thead>
<tr>
<th>A02A Antacids</th>
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<tr>
<td>A02AA Magnesium compounds</td>
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<tr>
<td>A02AB Aluminum compounds</td>
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<tr>
<td>A02AC Calcium compounds</td>
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<tr>
<td>A02AD Combinations of aluminum, calcium and magnesium compounds</td>
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<tr>
<td>A02AF Antacids with antiflatulents</td>
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<tr>
<td>A02AG Antacids with antispasmodics</td>
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<td>A02AH Antacids with sodium bicarbonate</td>
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<td>A02AX Antacids, other combinations</td>
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</table>

**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, antiflatulents, 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).
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), H2 antagonists (H2 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, instantly 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 H₂-blockers. They are also recommended for H₂-blockers administration and their withdrawal in order to relief 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, H₂-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 duodenopaties 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 biliary 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, H₂-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 antisecretory 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 calcifi-
cation 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 admi-
nistration. With long-term administration of 
alaninum 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 osteoalisteresis. 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 quan-
titative 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 absorb-
able antacids is undesirable. Contrain-
dications 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.

REFERENCES