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**ANALYSIS OF PHARMACOLOGICAL PROPERTIES OF ANTITUSSIVE  
DRUGS**

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**ABSTRACT.**

The role of respiratory defense mechanisms in airway protection and disease is addressed. Cough is a protective reflex that serves to clear the airways of excessive secretions and foreign matter and which sometimes becomes excessive, and troublesome to patients. Cough is one of the most common reasons why individuals seek medical attention. A range of drugs have been developed in the past with antitussive activity and different mechanisms of action, but there are still very few safe and effective treatments available. The poor tolerability of most available antitussives is closely related to their action on the central nervous system (CNS). An international group of experts specialized in cough met to discuss the need to identify an effective antitussive treatment with a good tolerability profile.

**Key words**

Cough; polysaccharides; respiratory, Glaucine, Libexin

**Introduction.** The cough reflex serves to clear the airways of excessive secretions and foreign matter and can also be voluntarily evoked. It has a protective role, but can sometimes become excessive, non-productive and troublesome to patients. Cough is one of the most common reasons why individuals seek medical attention [1,2]. The most common cause of acute cough (lasting less than 3–4 weeks) is an upper respiratory tract infection (URTI), but chronic cough (lasting more than 8 weeks) can be a feature of a number of pulmonary disorders such as asthma, chronic obstructive pulmonary disease (COPD) and lung cancer, or extra-



pulmonary disorders such as gastro-esophageal reflux disease [2,3]. Chronic cough can reduce the quality of life of patients and has been suggested to have a significant economic cost for the individual and society [2]. Chronic cough has a prevalence of more than 12% in the general population [1,4]. In patients, the cause of cough remains unexplained even after some low detailed assessments [5]. There are very few safe and effective treatments for cough and there is an urgent need for new treatments [2]. The poor tolerability of most antitussives on the market is closely related to central nervous system side effects. However, levodropropizine, a peripherally acting antitussive drug, has a good tolerability and safety profile. Levodropropizine has been demonstrated to show equivalent efficacy and less sedative effects compared to other antitussive agents such as the centrally acting cough suppressants dextromethorphan or dihydrocodeine [6]. Levodropropizine-containing products, for adults and children older than 2 years for the symptomatic therapy of cough, are approved for use in many countries in syrup, oral drop or tablet form. The mechanism of action of the drug is not fully characterized, but it does not act as an antitussive secondary to bronchodilation or muscarinic receptor antagonism. Some studies have suggested that levodropropizine has a peripheral site of action and can modulate the response of vagal C-fibers to chemical stimuli.

In this article we reviewed and summarized the current understanding of the mechanism and treatment of cough, as well as of the use of levodropropizine.

### **Antitussives are divided into two groups**

#### **1. Central influencers:**

A. Opioid (narcotic) drugs: codeine, ethylmorphine hydrochloride.

B. Nonopioid (nonnarcotic) drugs: glaucine hydrochloride, oxeladine citrate, butamirate.

#### **2. Peripheral agents: libexin.**

Located in the medulla oblongata, the central branches of the cough center depressant centrally acting drugs are somewhat more common in practical medicine used.

## 1. Antitussives

**Definition:** these drugs reduce the frequency or intensity of coughing.

**Classification:**



**Codeine (methyldmorphine)** is an alkaloid of the phenanthrene series included in opium (morphine group;). Opioid receptor agonist. It has strong cough suppressant properties. In addition, it has a weak analgesic effect. In therapeutic doses, codeine does not depress the respiratory center or this effect is manifested to a lesser extent. Regular from the drug may cause constipation when used. Also get used to and in some cases drug addiction may occur (mental and physical).

Mostly cough suppressants are used alone (codeine base) or codeine phosphate. In addition, codeine can be added to a number of other agents: Bekhterev's mixture: (adonis herb tincture, NaBr and codeine), "Codterpin" tablet (codeine expectorant

means - together with NaHCO<sub>3</sub> and terpene hydrate).

This group of substances also includes ethylene hydrochloride (dionine), which is synthetically obtained from morphine. It is an opioid receptor agonist. Pharmacologically similar to codeine, but compared to it inhibits the excitability of the cough center more strongly, has a stronger anesthetic effect. Opioid analgesics (morphine hydrochloride, etc.) have a strong antitussive effect have However, they weaken the respiratory center. In addition, this drugs can cause dangerous drug addiction in the short term.

Therefore, they can be used only temporarily when codeine and other antitussives are ineffective.

A number of drugs have been created that only selectively suppress the cough center, do not cause the development of learning addiction and habituation.

These drugs are called **nonopioid (nonnarcotic)** antitussives. **Glaucine** them



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include hydrochloride (glauvent) and oxeladine citrate (tusuprex). Glaucine is an alkaloid obtained from plants, while tusuprex is obtained synthetically. Medicines are well absorbed by the body. Glaucin can cause dizziness, nausea.

**Libexin** is included in antitussives with peripheral effect. Its mechanism of action is related to the anesthetic effect on the mucous membrane of the upper respiratory tract, as well as certain broncholytic properties. Libexin central nervous system does not affect the system. Libexin does not develop drug dependence. Thus, libexin belongs to non-opioid (non-narcotic) antitussives.

If the humidity of the mucous membrane of the bronchi is reduced (dry), thick, sticky sputum is released from the bronchial glands, increasing the secretion of the glands in the mucous membrane of the bronchi, as well as reducing cough by liquefying sputum possible For this, expectorants, including inhalation of alkaline liquid aerosols, are prescribed.

**Sinecod- active ingredient: butamirate (butamirate)**

Clinical and pharmacological group: Antitussive drug

Pharmacotherapeutic group: Centrally acting antitussive  
pharmacologic effect

Butamirate is a centrally acting antitussive. However, the exact mechanism of action of the drug is not known. Butamirate citrate has nonspecific anticholinergic and bronchospasmolytic effects.

Suppresses cough, having a direct effect on the cough center. Has a bronchodilator effect (expands the bronchi). Helps make breathing easier by improving spirometry (reduces airway resistance) and blood oxygenation (saturates the blood with oxygen).

In therapeutic doses, the drug is well tolerated. Butamirate in the form of an oral solution has a soothing effect on an irritated throat due to the moisturizing properties of glycerol.

**Pharmacokinetics**

Based on available data, it is assumed that butamirate ester is rapidly and completely absorbed and hydrolyzed in plasma, turning into 2-phenylbutyric acid and diethylaminoethoxyethanol. The effect of food on absorption has not been studied. The change in the concentration of 2-phenylbutyric acid and diethylaminoethoxyethanol occurs in proportion to the dose taken in the range of 22.5-90 mg.

Butamirate is rapidly and completely absorbed when taken orally, measured concentrations are detected in the blood 5-10 minutes after administration in doses of 22.5 mg, 45 mg, 67.5 mg and 90 mg. Cmax in blood plasma is achieved within 1 hour when taken in all 4 doses, the average is 16.1 ng/ml when taken orally at a dose of 90 mg.



After taking 150 mg of butamirate, C<sub>max</sub> in plasma of the main metabolite (2-phenylbutyric acid) is reached after approximately 1.5 hours and is 6.4 µg/ml. When the drug is re-administered, its concentration in the blood remains linear, no accumulation is observed

Average plasma concentrations of 2-phenylbutyric acid are achieved within 1.5 hours; C<sub>max</sub> was observed at a dose of 90 mg (3052 ng/ml); average plasma concentrations of diethylaminoethoxyethanol are reached within 0.67 hours; C<sub>max</sub> is observed after taking a dose of 90 mg (160 ng/ml).

### **Metabolism**

Hydrolysis of butamirate, which results in the formation of 2-phenylbutyric acid and diethylaminoethoxyethanol, which have an antitussive effect, occurs very quickly, the concentrations of metabolites are detected after 5 minutes. 2-phenylbutyric acid undergoes further partial metabolism by hydroxylation at the para position.

Excretion of the three metabolites occurs primarily by the kidneys; After conjugation in the liver, the acidic metabolites are largely bound to glucuronic acid. Conjugates of 2-phenylbutyric acid are determined in urine in significantly higher concentrations than in blood plasma. Butamirate is detectable in urine within 48 hours, and butamirate excreted in urine during the 96-hour sampling period accounts for approximately 0.02, 0.02, 0.03, and 0.03% of the 22.5 mg, 45 mg, 67.5 mg, and 90 mg doses, respectively. . As a percentage, butamirate is excreted in the urine in greater quantities and in the form of diethylaminoethoxyethanol than unchanged butamirate or unconjugated 2-phenylbutyric acid. The measured T<sub>1/2</sub> of 2-phenylbutyric acid, butamirate and diethylaminoethoxyethanol is 23.26-24.42, 1.48-1.93 and 2.72-2.90 h, respectively.

There is no data on changes in the pharmacokinetics of the drug in patients with impaired liver or kidney function.

Indications for the drug Sinekod

symptomatic treatment of dry cough of various etiologies.

Dosage regimen

The drug is taken orally.

Do not exceed the recommended dose.

The maximum duration of use of the drug without consulting a doctor is 7 days.

The drug is taken before meals using a measuring cap (supplied). The measuring cap should be washed and dried after each use. If the drug is used by several patients, the measuring cap should be washed and dried between uses on different patients.

Adults - 15 ml (22.5 mg) 4 times a day.



The maximum daily dose is 60 ml (90 mg).

Children over 12 years old - 15 ml (22.5 mg) 3 times a day.

The maximum daily dose is 45 ml (67.5 mg).

Children aged 6 to 12 years - 10 ml (15 mg) 3 times a day.

The maximum daily dose is 30 ml (45 mg).

Children aged 3 to 6 years - 5 ml (7.5 mg) 3 times a day.

The maximum daily dose is 15 ml (22.5 mg).

If symptoms worsen or do not improve after 7 days of treatment, as well as if there is a fever, rash or persistent headache, you should consult a doctor for further examination.

#### Side effect

The adverse reactions presented below are listed according to the damage to organs and organ systems and the frequency of occurrence. The frequency of occurrence is defined as follows: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1000$  and  $< 1/100$ ), rare ( $\geq 1/10000$  and  $< 1/1000$ ), very rare ( $< 1/10000$ , including isolated cases), frequency unknown (frequency cannot be estimated based on available data).

From the nervous system: rarely - drowsiness.

From the digestive system: rarely - nausea, diarrhea.

From the skin and subcutaneous tissues: rarely - urticaria; the development of allergic reactions is possible.

### **SYRUPUS TUSSIFENE**

Active substances (XPN): aminophenazone and ephedrine hydrochloride

Drug form: syrup

Contents: 100 ml of syrup contains:

active substances: aminophenazone - 0.6 g and ephedrine hydrochloride - 0.18 g;

excipients: sodium benzoate, sugar, saccharin, sodium bromide, liquid extract of sunflower, liquid extract of togjambil, ethyl alcohol, purified water.

Description: a syrupy liquid with a characteristic smell and a sweeter taste.

#### Pharmacological properties

A mucolytic drug with a pronounced expectorant effect. The drug liquefies sputum by stimulating the serous cells of the mucous membrane of the bronchi. By normalizing the ratio of serous and mucous components of sputum, it stimulates the production of enzymes that break down the bonds between mucopolysaccharides of sputum, and the formation of surfactant. Due to the increase in the production of surfactant, the drug has an anti-inflammatory effect, has antioxidant properties and increases local immunity.

#### Pharmacokinetics



After oral administration, ambroxol is practically completely absorbed from the gastrointestinal tract. The maximum concentration (S<sub>max</sub>) in the blood plasma is reached after about 0.3-0.5 hours. The bioavailability of the drug is 70-80%. Accumulation has not been determined.

Plasma protein binding is about 90%. It quickly enters the tissues and the highest concentration is determined in the lungs. It crosses the blood-brain barrier (GET) and the placental barrier and is excreted in breast milk.

It is metabolized in the liver by conjugation, forming pharmacologically inactive metabolites.

The plasma elimination half-life (T<sub>1/2</sub>) is 7-12 hours. Approximately 90% of the drug is excreted through the kidneys.

#### Application

It is used in the mucolytic treatment of acute and chronic respiratory tract diseases accompanied by sticky sputum (acute and chronic bronchitis, pneumonia, obstructive bronchitis, bronchial asthma with impaired secretion secretion, bronchiectatic disease, and to improve mucus thinning in nasopharyngeal inflammation).

#### Method of administration and doses

The drug should be taken after meals. During treatment, it is necessary to drink a lot of liquid (juice, tea, water), because it enhances the mucolytic effect of the drug.

In the absence of other indications, the following dosage is recommended:

The duration of treatment depends on the severity of the disease and is determined by the treating physician. It is impossible to take the drug for more than 4-5 days without a doctor's recommendation.

#### Side effects

The drug is usually well absorbed. In some cases, allergic reactions: skin rash, urticaria, angioneurotic edema, in rare cases, allergic contact dermatitis, in very rare cases, acute severe reactions of the anaphylactic type (anaphylactic shock), increased salivation, dry mouth, difficulty urinating, when taking large doses for a long time - stomach pain, heartburn, gastralgia, nausea, vomiting, constipation can be observed.

#### Circumstances that cannot be used

Hypersensitivity to the drug or other components of the drug, pregnancy (first trimester) and lactation period, stomach and duodenal ulcer disease, and antitussive drugs cannot be taken at the same time.

#### Drug interactions



Taking the drug and antibacterial agents (amoxicillin, cefuroxime, doxycycline, erythromycin) at the same time contributes to the penetration of antibiotics into the lung tissue. Proportionate with birth control drugs.

When the drug is used in combination with antitussive drugs, due to suppression of the cough reflex, liquefied secretions can be dangerously humidified. Therefore, antitussives should be taken only according to the instructions of the attending physician.

#### Special instructions

Syrup can be taken only after consultation with the attending physician and under the supervision of a doctor in cases of impaired motility of the bronchi and in cases of increased mucus (for example, dangerous eyelash syndrome). In case of severe renal or hepatic dysfunction, it is necessary to use smaller concentrations or increase the interval between drug administrations.

Syrup can be taken during breastfeeding or especially during the II and III trimesters of pregnancy only on the recommendation of the attending physician.

**Conclusion.** Cough remains a serious unmet clinical problem, both as a symptom of a range of other conditions such as asthma, chronic obstructive pulmonary disease, gastroesophageal reflux, and as a problem in its own right in patients with chronic cough of unknown origin. This article reviews our current understanding of the pathogenesis of cough and the hypertussive state characterizing a number of diseases as well as reviewing the evidence for the different classes of antitussive drug currently in clinical use. For completeness, the review also discusses a number of major drug classes often clinically used to treat cough but that are not generally classified as antitussive drugs. We also reviewed a number of drug classes in various stages of development as antitussive drugs. Perhaps surprising for drugs used to treat such a common symptom, there is a paucity of well-controlled clinical studies documenting evidence for the use of many of the drug classes in use today, particularly those available over the counter. Nonetheless, there has been a considerable increase in our understanding of the cough reflex over the last decade that has led to a number of promising new targets for antitussive drugs being identified and thus giving some hope of new drugs being available in the not too distant future for the treatment of this often debilitating symptom.

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