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Research Article

COLCHICINE AS A NATURAL TOXICANT AND METHODS OF ITS ANALYSIS

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Abstract:

Colchicine is an indispensable medical alkaloid of the Colchicaceae family. It is still used in the treatment of gout, recurrent illness, Behcet's disease and many other diseases. Despite the centuries-old experience of using this alkaloid by humans, fatal cases of poisoning are still encountered. Materials and methods. The authors analyzed specialized literature in databases and search engines Google Scholar, PubMed, Web of Science, Scopus, eLibrary on the toxicological, pharmacological, technological and clinical significance of colchicine. Results. Pharmacodynamics, clinical signs and pathological changes in case of colchicine poisoning are described based on the data of contemporary literature. In addition, the basic principles of the qualitative and quantitative determination of substances from biological material are illustrated.

Keywords: *colchicine; Colchicum autumnale; toxicology; poisoning; extraction.*

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INTRODUCTION:

The aim of our study is to determine the value of colchicine as a toxicant poison, consider its pathophysiological effects on the body, based on clinical cases, qualitative and quantitative determination and isolation from biologic material.

Relevance: colchicine -is an alkaloid that is isolated from plants of the Colchicaceae - Colchicum autumnale and Gloriosa superba. Colchicine has been used in medicine for the treatment of gout for more than 2000 years [1]. Colchicine is also used in the treatment of a wide range of diseases, in particular for the prevention of the development of amyloidosis in patients with Mediterranean familial fever (FMF) [2].

This herbal preparation is of interest from the point of clinical toxicology, because along with its unique healing properties, it has high toxicity, expressed in violation of almost all organs and systems of the body.

In addition, colchicine has a rather narrow therapeutic window, which can be difficult to determine for a particular patient [3, 4]. Accidental colchicine poisoning is periodically observed when *C. autumnale* or *G. Superba* are mistaken for *Allium ursinum* and *Ipomoëa batatas*, respectively [5-8].

MATERIALS AND METHODS:

The toxicological, pharmacological, technological and clinical significance of colchicine was analyzed in specialized literature using electronic databases and search engines Google Scholar, PubMed, Web of Science, Scopus, eLibrary etc.

RESULTS AND DISCUSSION:

Colchicine binds to the intracellular protein tubulin, preventing the formation of microtubules, which inhibits normal mitotic cell division. In addition, colchicine slows down endo- and exocytosis, biomodification of proteins in the Golgi apparatus, stabilizes lysosome membranes, and generally changes the cell geometry [9]. The mechanism of action of the drug is associated with a decrease in the migration of leukocytes to the area of inflammation and the suppression of phagocytosis of microcrystals of uric acid salts. In addition, it blocks cell division in the anaphase and metaphase stages, prevents the degranulation of neutrophils and the development of amyloidosis, as it reduces the formation of amyloid

Formulae of the active substances:

fibrils. These mechanisms explain both the therapeutic use of colchicine and its toxicological effect. The active substance quickly stops an acute attack of gout. The effect of it is observed in the first 12 hours after the start of treatment in 75% of patients.

Colchicine is used for treatment of:

- acute gout and for the prevention of exacerbations, especially during the first few months of treatment with allopurinol or agents that promote the excretion of uric acid; [10]
- recurrent illness (familial Mediterranean fever) [2, 11];
- primary AL amyloidosis;
- Behcet's syndrome;
- idiopathic thrombocytopenic purpura;
- pericarditis;
- primary biliary cirrhosis;
- gangrenous pyoderma, etc. [12]

There is no clear boundary between therapeutic, toxic and lethal doses of colchicine in both children and adults, but it is believed that the drug is relatively safe at a dose of up to 0.015 mg / kg, toxic - over 0.1 mg / kg, and can cause death in dose over 0.8 mg / kg [13].

The fatal cases of colchicine poisoning by the enteral route in a dose of 7 to 26 mg are described [14-16]. However, in 1966 a clinical case of 350 mg of orally taken colchicine was described and the patient survived [17]; although some authors doubt the accuracy of calculating the claimed dose [18].

The therapeutic use of colchicine in the treatment of recurrent illness according to current clinical guidelines is considered safe [19]; however, adverse reactions from the gastrointestinal system are often encountered in the treatment of acute attacks of gout, even taking into account clinical recommendations: in 80% of patients, before the onset of clinical improvement or at the same time, there are undesirable reactions from the gastrointestinal tract [20].

When analyzing cases of poisoning by plants, for example, *Colchicum autumn*, it should be taken into account that in addition to colchicine (Fig. 1) (C₂₂H₂₅NO₆), the plant also contains colchamine (Fig. 2) (C₂₁H₂₅NO₅). The amount of alkaloids in the seeds can reach 1% or more; less in tubers and flowers and least in leaves. In addition, colchicum contain a certain amount of saponin substances [2].

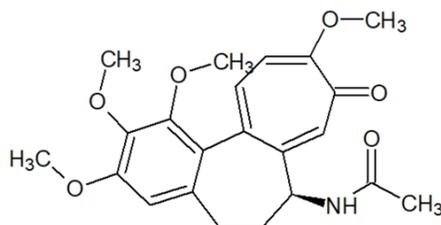


Fig. 1. Colchicine

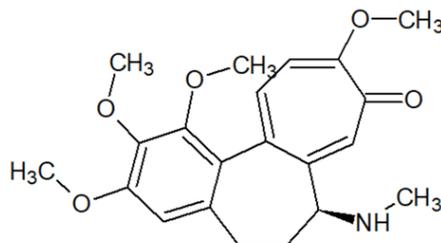


Fig. 2. Colchamine

Toxicological significance:

Colchicine is a capillary poison; it causes severe circulatory disturbance, in particular severe hyperemia of the mucous membrane of the stomach and intestines, causing an increase in excitability and violent peristaltic movements of the intestine (cholera-like diarrhea). Colchicine also affects the kidneys, causing polyuria, albuminuria, hematuria, even anuria; paralyzes the central nervous system, causing death from respiratory paralysis. External clinical manifestations in case of colchicine poisoning do not occur immediately, but after a few hours, since they are apparently the result of the action of products of the conversion of colchicine in the body of a mammal (into dioxicolchicine) [20].

Since colchicine blocks mitosis, in case of poisoning with this substance, the greatest disorders develop in tissues with high mitotic activity: in the bone marrow, gastrointestinal tract, and hair follicles [21, 22].

In many patients with impaired renal function, the usual doses of colchicine can cause colchicine myoneuropathy, which often remains unrecognized. Skeletal muscle damage usually occurs to a greater extent than damage to peripheral nerve fibers, and is expressed in proximal muscle weakness and increased serum creatine kinase. The abolition of colchicine contributes to the remission of these symptoms within a few weeks, and the resolution of the neuropathic component is slower. Examination of the proximal muscles reveals a noticeable pathological spontaneous activity, but at first the condition itself is usually

mistakenly diagnosed as polymyositis or uremic myopathy. An analysis of the sources confirms that impaired renal function is the primary risk factor for the development of colchicine myoneuropathy, and adjusting the dosage of colchicine is recommended as a priority measure [23, 24, 25].

There is evidence that colchicine myoneuropathy can occur in people with normal kidney function.

The occurrence of rhabdomyolysis was also described. Potentially fatal effects include neutropenia, thrombocytopenia, pancytopenia, acute renal failure, and congestive heart failure [7].

Clinical picture:

The first signs of poisoning appear after 6-24 and even 48 hours. The first symptoms of the toxic effects of colchicine are usually: loose bowels, nausea and vomiting, abdominal pain. Their appearance should be a signal for the abolition of colchicine or a decrease in its dose. If this is not done or, conversely, the dose is increased, then diarrhea becomes profuse, gastrointestinal bleeding may occur, a rash may appear on the skin, and renal and liver failure develops.

The appearance of a reaction similar to toxic epidermal necrosis is described; within 10 days, alopecia, leukocytosis (recurrent type), stomatitis may appear. Death with acute overdose of colchicine can occur due to respiratory depression, cardiovascular collapse, sepsis (with the development of pancytopenia) [8].

Pathological changes:

Autopsy data correspond to the clinical manifestations of poisoning. The mucous membrane of the stomach and intestines is severely inflamed and has a large number of hemorrhages. In severe cases, these changes can be hemorrhagic, especially in the large intestine, the mucosa of which is very swollen, vitreous, with a mass of small or continuous hemorrhages.

Intestinal contents are often bloody stained. Hemorrhages are present on the mucous and serous membranes of other organs. The kidneys and brain are strongly hyperemic and also have hemorrhages. The heart muscle is altered.

Pharmacokinetics:

The maximum concentration of colchicine in blood plasma occurs approximately 2 hours after ingestion. Bioavailability is less than 50% (approximately 45%) [26]. It is believed that absorption of colchicine from the gastrointestinal tract is limited by the action of P-glycoprotein. Absorbed colchicine is found in high concentrations in the kidneys, liver and spleen. It undergoes oxidative demethylation in the liver with the participation of the cytochrome P450 isoenzyme CYP3A4, 2 main metabolites (metabolites of the 1st phase of biotransformation) are formed and 1 is a secondary (metabolite of the 2nd phase of biotransformation); the concentration of metabolites in plasma is negligible. Excretion of colchicine and its metabolites occurs through hepatobiliary secretion into the intestine, then with feces. Such a mechanism of excretion determines the effectiveness of the use of adsorbents even a day after poisoning [4]. With preserved renal function, their excretion of colchicine

is only 10–20% of the total. The mean half-life is approximately 28 hours [27]. Enterohepatic circulation is detected 4–6 hours after oral administration. Most of the administered dose is excreted through the intestines.

Interaction of colchicine with other drugs:

Colchicine is a substrate for P-glycoprotein and cytochrome P450 isoenzyme CYP3A4. If treatment with a P-glycoprotein inhibitor or CYP3A4 inhibitor is really necessary, then the dosage of colchicine needs to be adjusted if the patient's kidneys and liver function well, otherwise such combinations should be avoided [28]. Cases of myopathy and rhabdomyolysis have been reported in those who took statins, fibrates, cyclosporin (Ciclosporin) or digoxin (Digoxin) together with colchicine.

Thiazide diuretics can increase serum uric acid levels and interfere with colchicine activity.

Chemo-toxicological analysis of colchicine:

In modern chemo-toxicological analysis, liquid-liquid extraction is one of the main methods for the isolation of alkaloids and other toxic substances from biological material of a corpse, biological fluids (urine, blood), gastric lavage, and a number of other objects.

For each alkaloid, there is a pH range at which it is extracted with maximum amounts of water-immiscible organic solvents. The maximum degree of colchicine extraction is achieved in an acidic environment [24]. As an extractant, it is advisable to use ethyl alcohol, diethyl ether.

Table 1

Organic solvent	pH
Chloroform	1,5
Dichloroethane	1,5
Benzene	1,5

Qualitative, quantitative analyses and chromatography are well described in special literature [29].

The content of the total alkaloids of colchicine and colchamine in terms of colchicine in percent (X) is calculated by the formula (Formula 1):

$$X = \frac{S \times a_0 \times 1 \times 10 \times P \times 100}{S_0 \times 10 \times 10 \times a \times 100} = \frac{S \times a_0 \times P}{S_0 \times 10 \times a}$$

Formula 1

where: S – the sum of the areas of two peaks of alkaloids in the chromatogram of the test solution;
 a_0 – weight of colchicine, g;
 P – colchicine content, %;
 S_0 – peak area in colchicine chromatogram;
 a – extraction sample, g.

CONCLUSION:

At excessive doses, colchicine can cause serious systemic toxicity. Acute colchicine poisoning is uncommon, but is associated with a high mortality rate. It is essential, therefore, that clinicians recognize

and are familiar with colchicine poisoning symptoms, first aid and the basics of pathological changes and chemo-toxicological analysis.

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