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PHARMACOLOGICAL AND TOXICOLOGICAL PROPERTIES OF ANTICOAGULANTOINTMENT

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ANNOTATION

Treatment of thrombosis and embolism is currently one of the urgent problems of medicine. It is known that the body has universal resistance to a sudden increase in blood clotting, and only a sharp violation of the neuro-humoral regulation of hemostasis leads to vascular wall damage and the formation of blood clots.This paper presents the results of research on the development of its dosage form - safinol ointment and also pharmacological and toxicological properties.

Keywords: Safinol, salicylic acid, ε -amino-enanthic acid, ointment.

INTRODUCTION

Treatment of thrombosis and embolism is currently one of the urgent problems of medicine. It is known that the body has universal resistance to a sudden increase in blood clotting, and only a sharp violation of the neuro-humoral regulation of hemostasis leads to vascular wall damage and the formation of blood clots.From the literature, it is known that heparin is a natural blood anticoagulant and is obtained by water-salt extraction from the lungs of cattle or pig mucose, followed by sorption on anion exchange resin and desorption with sodium chloride solution. The resulting heparin - raw is treated with potassium permanganate, which contributes to the release of heparin from impurities of proteins, nucleic acids, etc. However, severe oxidation conditions are carried out to the destruction of the heparin macromolecule and, as a result, its biological activity decreases.Heparin as a drug is a heterogeneous mixture of sulfonated polysaccharide chains made up of repeating units of D-glucosamine and either L-iduronic or D-glucuronic acids. It has an anticoagulant effect, due mainly to the modulating effect on antithrombin. Heparin is effective for the prevention and treatment of venous thromboembolism, for the early treatment of patients with unstable angina, acute myocardial infarction, for the treatment of patients undergoing cardiac surgery under an artificial blood circulation machine, during and after plastic surgery of the coronary vessels.[1,2]Anticoagulants widely used in medical practice, in particular, heparin have side effects. This complex technology, side effects that they have on the patient's body. Heparin can become an allergen, causing headaches, vomiting, lowering blood pressure. Long-term treatment leads to alopecia, especially noticeable in the temples, painful nodules and necrosis may appear at the injection sites.[2,3]Expanding the range of drugs for the treatment of thrombosis and thromboembolism is an important task.All this stimulates the search for new anticoagulants, the technology of which would be simple, the raw materials are affordable, and the anticoagulants themselves would be deprived of the above disadvantages, that is, they would not have side effects, they would be available to all categories of patients.It is known that salicylic acid preparations are widely used in clinical practice, as an analgesic and antipyretic agent. Inhibitors of the hemostatic function of platelets - active drugs are very effective in preventing and treating arterial thrombosis. Such drugs include aspirin, ticlopidine, clopidogrel, dipyramidol, absiximab, and other low molecular weight G11 in c 111 a antagonists.[4,6]Among them, sodium salicylate and acetylsalicylic acid (aspirin) are widely used. Salicylates also cause some reduction in prothrombin blood and are also used as anticoagulants. Aspirin is an effective antithrombotic agent that delays A2 thromboxane (TAX2). It is a potent pathogen of platelet aggregation and narrowing of blood vessels. By delaying the isoferment (COX1). Aspirin

prevents vascular death in almost 15% and non-fatal cases of cardiovascular diseases in about 30% of patients /1/.[3,4,7]Aspirin reduces the risk of myocardial infarction, sluggish myocardial ischemia or stable, unstable angina. Small doses of aspirin do not reduce the risk of maternal and intrauterine complications in pregnant women with hypertension, preeclampsia and eclampsia, renal disease, and intrauterine growth retardation. [4,5,8]A deterrent to the administration of salicylic acid preparations as antithrombotic agents is the development of side effects, such as gastritis, heartburn, nausea, epigastric pain, and vomiting.Obtaining drugs with the properties of acetylsalicylic acid, but lacking negative effects on the body - a task that needs to be addressed today. To reduce its toxicity, giving water solubility, obtaining the condensation products of salicylic acid with e-amino-enanthic acid.

We have developed a technology for obtaining a drug with desired molecular characteristics for use as an effective and harmless antithrombotic drug in transfusion chemotherapy.Based on the above, one of the components we have chosen is salicylic acid. In order to reduce its toxicity (irritant effect on the stomach) and impart water solubility, synthesizing a copolymer of salicylic acid with amino compounds. One of such methods for the synthesis of such copolymers is a polycondensation reaction.The interrelation of changes in molecular mass characteristics and physico-chemical parameters of the drug, the condensation of salicylic acid with e-amino-enanthic acid with changing process conditions and the ratio of reacting components, which allowed to develop a progressive cost-effective and environmentally friendly technology for producing the anticoagulant.Previous studies by the authors found that safinol inhibits activated partial thromboplastin time, thrombin time, causes fibrin depolymerization and activates non-enzymatic fibrinolysis.

The urgency of the problem of hemostasiology in modern theoretical and clinical medicine is due to the prevalence of thromboembolitic lesions and their significant growth in recent years in many countries around the world. The solution to this problem, as well as the improvement of prevention of thrombosis control, depends on the purposeful systematic research of specialists of all profiles.

MATERIALS AND METHODS

Safinol is a light yellow powder with a weak specific odor, is hygroscopic, easily soluble in water, practically insoluble in sulfuric ether, acetone, chloroform.Safinol has rheological and antithrombotic properties; thanks to this, it improves circulation in the macro- and microcirculation system and stimulates diuresis and is not toxic.For this purpose, we have synthesized "Safinol" - a condensation product of salicylic acid and e-amino-enanthic acid. As shown by clinical trials of the dosage form of "Safinol" for intravenous administration carried out in three clinics of the Ministry of Health of the Republic of Uzbekistan, it has a pronounced anticoagulant effect. On the basis of clinical trials, the drug Safinol is recommended for use in practical medicine /2-7/Therefore, the development of various dosage forms based on safinol makes it possible to obtain drugs for the prevention and treatment of thromboembolitic complications in various diseases, prothrombophlebitis of the non-cough, etc.Based on the foregoing, and in order to simplify its application in medical practice, we decided to create a new dosage form of an anticoagulant blood safinol ointment.We studied the comparative pharmacological and toxicological properties of anticoagulants of blood of heparin and safinol ointment.Currently used heparin ointment is used externally for superficial thrombophlebitis of the extremities, phlebitis after repeated intravenous injections, thrombosis of hemorrhoidal veins, ulcers of the extremities.Gradually released from the ointment, heparin reduces the inflammatory process and has an anti-trobic effect, and nicotinic acid benzyl ester expands the surface vessels, promoting heparin absorption. Anesthesin has a pain-relieving effect.

Safinol has a pronounced anticoagulant effect and can be recommended for the prevention and treatment of thromboembolic complications in myocardial infarction, pulmonary and cerebral vessels thromboembolism, as well as blood transfusions, etc.This paper presents the results of research on the development of its dosage form - safinol ointment and also pharmacological and toxicological properties.We have developed a technology for producing an ointment base with the use of the substance safinoland auxiliary substances, which is carried out in table-1.

Table 1

The composition of the anticoagulant ointment on the basis of the substance Safinol

№	IngredientsName	Weightingr.
1.	SubstanceofSafinol (VFS 42-2793-2015)	0,200
2.	Anesthesin(FS 42-3024-00)	4,0
3.	Benzylnicotinate (FS 42-2160-84)	0,08
4.	Distilledglycerin (GOST 6824-96)	11,7

5.	Medicalvaseline (FS 42-2456-97)	5,5
6.	Cosmeticstearin (TU 10-04-02-83-91)	3,3
7.	Cornoil (GOST 8808-91, raf.)	5,5
8.	Emulsifier №. 1 (FS 42-3821-99)	8,0
9.	Nipagine (FS 42-1460-89, ND 42-7043-97)	0,15
10.	Pinazole (VFS 42-2079-91)	0,05
11	Thepurifiedwater (FS 42-2619-97)	100

The above composition of the safinol ointment differs from the heparin ointment, instead of heparin, we introduced the substance safinol into the ointment.The active ingredient in heparin ointment is heparin and in safinolointment the substance is safinol.We have studied the comparative acute toxicity of heparin ointment compared with safinol ointment.

RESULTS

Experiments were conducted on laboratory mice. To do this, we first trimmed the back of the mice from wool on an area in a volume of 1 cm^2, then a clean, 0.5, 0.75 and 1.0 g dose of the safinol ointment was applied to this cleared area.The survey was conducted in the laboratory, for 2 days and 14 days in vivarium conditions, the data are given in table 2.Observations on the condition of the animals were carried out in the laboratory for 2 days and in vivarium conditions for 14 days. During the observation period in a state of animals, negative reactions were not detected.

table 2

Results of acute toxicity of heparin and safinol ointment in mice

Weightingrams	Amount of heparin in grams	Weightingrams	Amount of safinol in grams
19,0	Heparin ointment in the amount of 0.5 g.	18,0	Introduced safinol ointment in the amount of 0.5 g.
20,0		20,0	
18,5		22,0	
22,0		21,0	
21,0		18,0	
19,0		19,0	
18,0	Heparin ointment was introduced in aamount of 0.75 g.	19,0	Safinol ointment was introduced in aamount of 0.75 g.
20,0		21,0	
21,0		20,0	
19,0		18,0	
19,5		19,0	
22,0		22,0	
18,5	Heparin ointment in the amount of 1.0 g.	18,5	Introduced safinol ointment in the amount of 1.0 g.
19,0		21,0	
22,0		19,0	
20,0		20,0	
21,0		18,0	
19,0		22,0	

The effect of the ointment on the cut back dorsal wound in 18 rats weighing 165-190 g of both sexes was also studied. An incision made with a surgical scalpel on the dorsal surface of rats 1.5 cm long and 1-2 mm deep, then the rats were divided into 3 groups of 6 pcs. In the first group, the effect of the Vaseline base was investigated. In the second group - the effect of heparin ointment, in the third - safinol ointment.

The test ointment was applied in a volume of 0.75 g once a day for three days. The control group received an equivalent amount of vaseline. In the course of the experiments, it was revealed that in animals of the control group wound healing occurs on the 5-6th day. In rats treated with heparin and safinol ointment, the disappearance of inflammatory changes was observed on the 3-4th day. It can be concluded that healing in the experimental groups compared with the control occurs 1-2 days earlier. This experiment should be carried out on a large group of animals and on a different model of surface inflammation.

For this purpose, experimental rats in the rectum to a depth of 2-3 cm were injected with a 25% formalin solution and thereby created a surface proctosigmatid. Then the rats were divided into three groups. Experimental animals 3 hours after the introduction of formalin and then twice a day for 7 days were administered prototypes of heparin and safinol ointment at 0.5 g. The control animals were given a vaseline base.

Experiments have shown that in rats receiving the studied ointments, excretion of fecal masses was observed. Soreness has decreased, the general condition of animals has improved: their appearance, decreased aggressiveness, appetite, mobility appeared. In the control group, painful symptoms persisted for 3-5 days, narrowing of the anus, swelling of hyperemia, impaired formation of feces and temperature increase of 2-2.50°C were observed. Further, diarrhea was added to the above symptoms, in some animals - discharge of pus, this lasted for 7-8 days. Ofthesixrats, onediedfromintoxication.

DISCUSSION

From the above pharmacological and toxicological studies, we can conclude:

1. Comparative pharmacological and toxicological studies of heparin and safinol ointments, conducted at the base of the Department of Pharmacology and Clinical Formation of Tashkent Pharmaceutical Institute at the Ministry of Health of the Republic of Uzbekistan on laboratory mice and rats of both sexes, showed that the studied safinol ointment was of low toxicity, and it also has a pronounced anti-coagulant action effectiveness is not inferior to the well-known heparin ointment

2. Safinol ointment enhances the regeneration of incised wounds and contributes to a more rapid healing of the resulting destruction-surface wound.

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