STUDY OF THE THERAPEUTIC ACTIVITY OF THE GEL OF COMBINED ACTION

U.M. Tillaeva¹, R.T. Tulaganov²

¹Senior Lecturer, Candidate of Pharmaceutical Sciences, Department of Pharmaceutical Chemistry, Tashket Pharmaceutical Institute, email: author.uzb@mail.ru.
²Associate Professor, Doctor of Biological Sciences, Department of Pharmacology and Clinical Pharmacy, Tashket Pharmaceutical Institute, email: author.uzb@mail.ru.

ABSTRACT

Scientific research works were carried out on developed pharmaceutical composition “Fensin” (fensulcal, cetirizine) – the gel of combined action. The researches were carried out in order to study the safety and specific activity in comparison with the preparation "CINEPAR® ACTIVE" - a gel for external use manufactured by Marion Biotech® Pvt. Ltd, India in an experiment on white rats. Acute toxicity was assessed by changes in body weight and neuro-somatic parameters. The data obtained showed that the LD50 of the drug “Fensin” - a combined gel, was more than 10 g / kg and of practically non-toxic substances.

The results of the study of the specific action and therapeutic activity of the medication - the combined gel “Fensin” for external use showed that it relieves aseptic edema, is an anti-inflammatory active with a desensibilizing effect.

The studies were carried out in accordance with the requirements of Uzstandart GOST O'zDSt 276: 2013 "Good Laboratory Practice", Tashkent 2013

Key words: fensulcal, cetirizine, therapeutic activity, safety, gel.

I. INTRODUCTION

A number of works are known on the synthesis of new biologically active compounds based on aromatic α-keto acids and on the study of their pharmacological activity.

α-keto acids due to their high reactivity are the starting compounds in the synthesis of bioactive compounds. Thus, phenyl-glyoxylic acid is widely used for the synthesis of drugs. Protecting from radiation, it is used in the production of antibiotics, cephalosporins and drugs used in oncology. The anti-inflammatory drug Fensulkal has been developed on the basis of α-phenyl-glyoxylic acid and its ethyl ether [1, 2].

D.N. Ismatov and other authors [3] studied the anti-inflammatory activity of phenyl-glyoxylic and para-nitrophenylglyoxylic acid derivatives obtained by interaction with α-keto acids. Based on the studies carried out, it was found that all tests give an anti-inflammatory effect at a dose of 50 mg / kg (P <0.05). The study of toxicity showed that the picture of poisoning in mice after the introduction of the test substances was approximately the same and characterized mainly by the inhibition of their locomotor activity. The LD50 of phenyl-glyoxylic acid derivatives is in the range of 1756-2131 mg / kg. According to the relevant data, the (L) LD50 of butadione in oral administration to white mice is 430 mg / kg. The comparison shows that the tested compounds are several times less toxic than butadione.

Studies of the medico-biological properties of the synthesized complex compounds of biometals with phenyl-glyoxylic acid derivatives were carried out at the Department of Pharmacology of the Samarkand State Medical Institute under the leadership of PhD. D.N. Karshieva. Preclinical studies have shown that the synthesized phenyl-glyoxylic acid compounds are 1.5-2.5 times superior in anti-inflammatory effects to the butadione drug.
It is known that the dosage form is of great importance in the development and use of a medicinal product. Also, therapeutic activity is achieved by choosing a rational light form or combinations of drugs, or by combining to obtain synergism of action or adjusting to reduce side effects (4,5,6).

In fact, antihistamines occupy an important place in medical practice. It is necessary to study the pharmaceutical market for the assessment and prospects of producing and introducing active medicines (AM) in domestic pharmaceutics. Currently, an increase is noted worldwide in the frequency of allergic diseases - (AD), which is a serious problem for public health. ADs rank third after cardiovascular and oncological diseases (in some ecologically unfavorable regions, ADs come out on top) (7).

It is known that Cetirizine hydrochloride is a competitive antagonist of histamine, a metabolite of hydroxyzine, blocking H1-histamine receptors. It facilitates the course of allergic reactions and prevents their development. It carries antipruritic and anti-exudative actions. It influences on the early stage of allergic reactions, limits the release of inflammatory mediators at the late stage of an allergic reaction, reduces the migration of eosinophils, neutrophils, and basophils. It reduces capillary permeability, prevents the development of tissue edema, relieves smooth muscle spasm.

It eliminates skin reactions from the introduction of histamine, specific allergens, as well as from cooling (with cold urticaria).

In therapeutic doses, it practically does not cause sedation. It refers to antihistamines of the II generation. The onset of action after a single dose of 10 mg of cetirizine - after 20 minutes (in 50% of patients) and after 60 minutes (in 95% of patients), lasts more than 24 hours. After stopping treatment, the effect lasts up to 3 days.

**Purpose of the research:** to study the therapeutic activity and safety of the drug “Fensin” - a gel of combined action consisting of Fensulkal and Cetirizine.

The drug “Fensin” is a combined gel developed at the Department of Pharmaceutical Chemistry of Tashkent Pharmaceutical Institute. The tests were carried out at the Testing Scientific Center for the Standardization of Medicines.

The comparing drug is CINEPAR® ACTIVE gel for external use, manufactured by Marion Biotech® Pvt. Ltd, India.

It is used as a local symptomatic agent for the treatment of pain, inflammation and swelling in:
- trauma in chordas, ligaments, muscles, and joints, for example, due to sprains, back pain after overexertion, bruises;
- localized forms of soft tissue rheumatic diseases such as tendinitis, shoulder-arm syndrome, bursitis, periarthropathy;
- osteoarthritis of small to medium-sized joints and superficial joints such as the knuckles or knee.

Dosage regimen: externally, 2-4 g of gels (which is comparable in volume to the size of a cherry or walnut and sufficient for treating a body surface area of 400-800 cm2) is applied in a thin layer, rubbing slightly onto the skin over the inflammation focus, 2-3 times per day.

**Research objectives:** the gel Fensin consists of:

- **active substances** - fensulcal - 2 g, cetirizine hydrochloride - 0.01 g;

- **excipients:** carbopol, glycerin, sodium hydroxide qs, purified water.

1. Study of acute toxicity of the drug “Fensin” - a combined gel developed at the Department of Pharmaceutical Chemistry of Tashkent Pharmaceutical Institute.

2. Study of the specific activity of the drug “Fensin” - a combined gel developed at the Department of Pharmaceutical Chemistry of Tashkent Pharmaceutical Institute, in comparison with CINEPAR® ACTIVE gel for external use, manufactured by Marion Biotech® Pvt. Ltd, India.
STUDY OF ACUTE TOXICITY

II. MATERIAL AND METHODS

The acute toxicity of the compared drugs was studied on white rats, weighing 180-200 g, of both sexes by the method of Noakes and Sanderson (Noakes, Sanderson 1969). The rats were divided into 2 groups of 6 animals each. The animals were kept in a separate room in standard plastic cages on sawdust bedding. The air temperature was maintained within 20-25 °C, relative humidity - 40-70%. Access to water and food was free. All animals participating in the experiment were healthy, without any physiological abnormalities.

The day before the experimental studies, the wool was cut off on the skin of the back, in an area of 7.5 x 4 cm. On the clipped skin area of the rats of the experimental groups, the drug “Fensin” (Uzbekistan) was applied at a dose of 10 g / kg. The animals were observed hourly during the first day of the experiment. Then, every day, for 2 weeks, animals of both groups were monitored for the general condition and activity, and behavioral reactions were taken into account. All experimental animals were kept in the same conditions and on a common diet with free access to water and food. Acute toxicity was assessed according to the changes in body weight and neurosomatic parameters:

- animal’s general condition,
- particulars of deportment,
- the intensity and the character of locomotor activity,
- the presence and the nature of seizures,
- motion coordination,
- reaction to tactile, painful, sound and light stimuli,
- frequency and depth of breathing,
- condition of the hair and skin, as well as macroscopic changes in the skin [9].

The experiments showed that after a single cutaneous application of the test drug at a dose of 10 g / kg, no visible changes were observed in the behavior and functional state of the animals and the consumption of food and water was normal. All rats were active and no signs of intoxication were observed. The rats responded adequately to tactile, painful, sound and light stimuli. The frequency and depth of respiratory movements were normal. Macroscopic changes in the skin and pathological changes in the hair of the animals were not observed. There was no mortality of rats within 2 weeks. The results of the experiment are shown in Table 1.

Table 1: Determination of acute toxicity of the drug “Fensin”

<table>
<thead>
<tr>
<th>№ animals</th>
<th>weight, gramm</th>
<th>Dose g/kg</th>
<th>«Fensin» administration way</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>185</td>
<td>10 g/kg</td>
<td>Cutaneously</td>
<td>No death</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td></td>
<td></td>
<td>No death</td>
</tr>
<tr>
<td>3</td>
<td>188</td>
<td></td>
<td></td>
<td>No death</td>
</tr>
<tr>
<td>4</td>
<td>195</td>
<td></td>
<td></td>
<td>No death</td>
</tr>
<tr>
<td>5</td>
<td>192</td>
<td></td>
<td></td>
<td>No death</td>
</tr>
<tr>
<td>6</td>
<td>180</td>
<td></td>
<td></td>
<td>No death</td>
</tr>
<tr>
<td>LD50</td>
<td></td>
<td>&gt;10 g/kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
To sum up, the data obtained show that the LD50 of the drug “Fensin” - a combined gel, developed at the Department of Pharmaceutical Chemistry, Tashkent Pharmaceutical Institute, was more than 10 g / kg and of practically non-toxic substances.

STUDY OF SPECIFIC ACTIVITY

Specific activity: The effect of drugs on acute aseptic inflammation was studied on 18 white rats of both sexes weighing 180-200 g. The initial paw volume (ml) in rats was preliminarily measured [5].

For the experiment, the rats were divided into groups of 6 animals each:

Group 1 - control - cutaneous gel - basis + 0.1 ml of 6% dextran solution;

Group 2 - experimental - cutaneous medicine “Fensin” + 0.1 ml of 6% dextran solution;

Group 3 - experimental - cutaneous preparation “Fensulkal” + 0.1 ml of 6% dextran solution;

Group 4 - experimental - cutaneous preparation “CINEPAR® ACTIVE” manufactured by Marion Biotech® Pvt. Ltd, India at a dose of 10 g / kg + 0.1 ml of 6% dextran solution.

Acute inflammatory reaction (edema) was reproduced by subplantar (between 1 and 2 toes of the left hindfoot) injection of 0.1 ml of 6% dextran solution. Compared preparations were applied in a thin layer on the skin before and after dextran administration every hour for 3 hours. The severity of the inflammatory response was assessed 1 h, 2 h, 3 h and 4 h after the induction of inflammation by changing the paw volume using a plethysmometer.

Anti-inflammatory activity (AIA) is calculated by the formula:

\[ \text{IVe AIA} = \frac{\text{IVe} - \text{IVc}}{\text{IK}} \times 100, \text{ means:} \]

IVe - increase in paw volume in the experimental group;

IVc - increase in paw volume in the control group.

The data obtained were statistically processed using the software program STATISTICA for Windows 9.5.

The results of the studies showed that in intact animals, under the influence of dextran, the volume of the paws increased after an hour by 165.8%, after 2 hours by 130.4%, after 3 hours by 104.8% and after 4 hours by 95% in comparison with the initial state (table 2). At the same time, the greatest increase in the volume of the paws was noted after 1 hour from the beginning of the experiment, which was statically significantly preserved for the next four hours. In contrast, in the animals of the experimental group, who had been applied the Fensin gel, the maximum increase in the volume of the paws was 113.4% 1 hour after the administration of dextran. After 2, 3 and 4 hours this figure was 84%, 73.2% and 47.6%, respectively. These indicators are statistically less by 19.7%, 20.1%, 15.4%, 24.4% in comparison with the data of control animals after 1, 2, 3 and 4 hours. The AIA of the medication was 31.7-49.9%.

The study of the specific activity of the drug Fensin showed that after 1 hour, the edema of the inflamed paw increased by 101.2%, after 2 hours - by 84.8%, after 3 hours - by 80.2%, and after 4 hours - by 56.9 % compared to the original one. During the experiment, in applying Fensin gel, the severity of paw edema is significantly less by 20.6%, 15.8%, 7.7%, 15.6% compared to the data of control animals. The AIA of the drug was 36.9-37%.

Study of the specific activity of the drug "CINEPAR® ACTIVE” manufactured by Marion Biotech® Pvt. Ltd, India showed that after 1 hour, the swelling of the inflamed paw increased by 125%, after 2 hours - by 96.4%, after 3 hours - by 71.4%, and after 4 hours - by 70.2% compared to the original volume of the foot. During the experience, in application of the preparation "CINEPAR® ACTIVE” manufactured by Marion Biotech® Pvt. Ltd, India, the severity of paw edema is statistically significantly less by 13.3%, 12.3%, 14.2%, 10.6% compared to the control animals. The AIA of the drug was 23.1-40%. The results of the experiment are presented in Table 2.
Table 2: Study of the specific activity of the preparations “Fensin”, Uzbekistan and “CINEPAR® ACTIVE” produced by Marion Biotech® Pvt. Ltd, India (M ± m, n = 6)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Volume of paws, ml/AIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>initial</td>
</tr>
<tr>
<td>Control (gel based) + 6% dextran solution</td>
<td>0.82±0.02</td>
</tr>
<tr>
<td>“Fensin” + 6% dextran solution</td>
<td>0.82±0.02</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>“Fensulkal” + 6% dextran solution</td>
<td>0.86±0.03</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>CINEPAR® ACTIVE + 6% dextran solution</td>
<td>0.84±0.04</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: * - reliable in relation to the initial indicators at P <0.05;
# - reliable in relation to control at P <0.05.

Consequently, the studied gel Fensin has a distinct anti-edematous effect, indicating the presence of anti-inflammatory activity. According to AIA, the drug Fensin gel was more active after 2 hours by 0.95 times, after 3 hours by 0.92 times and after 4 hours by 0.89 times compared to the gel “Fensulkal”.

III. CONCLUSION

In conclusion, the study of the specific action of the drug “Fensin” - a combined gel, developed at the Department of Pharmaceutical Chemistry of Tashkent Pharmaceutical Institute, produced by IP Ltd “Well Med Pharm”, Uzbekistan in comparison with the drug “CINEPAR® ACTIVE” - a gel for external use (2027 - 02/2023, registration number and date DV / X 00600/07/15 17/07/15 B-250-95 33705 RUz 15/09/05 rev. 27/04/18) manufactured by Marion Biotech ® Pvt. Ltd, India showed that the medicinal product belongs to practically non-toxic substances, relieves aseptic edema, has an anti-inflammatory effect with desensitizing effect.

The research results are presented in the form of a scientific report on research work in accordance with the requirements of Uzstandard GOST O'zDSt 276: 2013 “Good Laboratory Practice”, Tashkent 2013.

CONFLICT OF INTERESTS AND CONTRIBUTION OF AUTHORS

The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article and report on the contribution of each author.

SOURCE OF FINANCING

No funding was required for this research.

REFERENCES:

5. Жалилов Ф.С., Бекчанов Б.С., Тиллаева Г.У. Значение комбинированных лекарственных форм в современной фармакотерапии. Фармацевтический вестник Узбекистана. 2019 г., № 2, С.75-79.

8 Беленький М. Л. Элементы количественной оценки фармакологического эффекта. Л. Медгиз 1963, -152 с.