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STUDYING THE MECHANISM OF ACTION OF SOME CHEMICAL COMPOUNDS WITH ANTI-INFLAMMATORY PROPERTIES

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Abstract. Nonsteroidal anti-inflammatory drugs belong to the most widely used medications. This work is devoted to studying the effect of benzoic acid derivatives diphenyl-/bis-(benzoyloxy)/-silone and 1,4-bis-(bromobenzoyloxy)-butyne-2 on the exudative and proliferative phases of inflammation. Experiments conducted on animals showed that the mechanism of the anti-inflammatory action of the studied chemical compounds is associated with inhibition of the exudative and proliferative phases of the inflammatory process.

Key words: inflammation, anti-inflammatory effect, analgesic effect, antipyretic effect, benzoic acid derivative, mechanism of anti-inflammatory action, antiexudative effect, antiproliferative effect, antiallergic effect.

Introduction. The process of inflammation, being one of the central links in the pathogenesis of many diseases, is protective in nature, however, in some cases the inflammatory reaction has a negative effect on the body, which requires pharmacotherapeutic intervention. Increasing the effectiveness of pharmacotherapy for diseases whose pathogenesis involves an inflammatory process is one of the most important problems of modern medicine. Currently, clinical medicine has a large range of anti-inflammatory drugs belonging to various classes of compounds. However, many of these drugs do not meet the requirements of clinicians due to the insufficient therapeutic effect they cause, frequent adverse events and serious complications. Analysis of literature data shows that undesirable side effects of non-steroidal anti-inflammatory drugs are less pronounced and occur more favorably than those of steroidal anti-inflammatory drugs. Nonsteroidal anti-inflammatory drugs have a universal and unique combination of analgesic and anti-inflammatory effects for this class of drugs, which explains their leading place in modern medicine. The role of drugs of this pharmacological group in the practice of a doctor of any specialty is difficult to overestimate, however, this is what creates the main difficulty in choosing an adequate drug in each specific case. Nonsteroidal anti-inflammatory drugs are a class of pharmacological agents whose therapeutic activity is associated with preventing the development or reducing the intensity of inflammation. Currently, there are more than fifty dosage forms differing in chemical structure, classified as non-steroidal anti-inflammatory drugs, which in turn are divided into several main subclasses. Despite the huge variety of non-steroidal anti-inflammatory drugs, they remain one of the most popular drug groups. For this reason, the search and study of new highly active and low-toxic anti-inflammatory drugs among various classes of chemical compounds of non-steroidal

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structure is more appropriate and remains a very pressing problem in practical medicine [1,2,3,4,5,6].

Objectives of the work. Studying the anti-inflammatory activity of diphenyl-(bis-(benzoyloxy))-silane in various models of aseptic arthritis, as well as studying the effect of this compound on the exudative and proliferative phases of inflammation in comparison with known anti-inflammatory drugs, such as voltaren, indomethacin and butadione. Study of the anti-inflammatory, analgesic, antipyretic, antiallergic effects of 1,4-bis-(bromobenzoyloxy)-butine-2.

Material and research methods. A study of the anti-inflammatory effect of benzoic acid derivatives - diphenyl-(bis-(benzoyloxy))-silane and 1,4-bis-(bromobenzoyloxy)-butyne-2 - was carried out on white rats weighing 150-200 g. For comparison, well-known anti-inflammatory drugs were used - voltaren (10 mg/kg), indomethacin (15 mg/kg) and butadione (100 mg/kg). The anti-inflammatory effect of the studied chemical compounds was studied in well-known models of arthritis caused by formaldehyde, carrageenan, serotonin, histamine and dextran. Phlogogenic agents were injected in an amount of 0.1 ml into the dorsal surface of the aponeurosis of the rat ankle joint [7,8,9,10].

The anti-inflammatory activity of the drugs was determined by the difference in the volume of the paws of control and experimental animals. The test compounds were administered orally in the form of suspensions in 3% starch paste 48, 24 and 2 hours before the administration of phlogogenic agents at doses of 50, 100 and 150 mg/kg. Control animals received an equal volume of starch paste. The volume of the paws was measured at different time intervals depending on the nature of the phlogogenic agent.

The effect of the compounds on the exudative phase of inflammation was studied in a model of aseptic peritonitis caused by the introduction of a silver nitrate solution into the abdominal cavity. The drugs were administered orally 48, 24 and 2 hours before the administration of silver nitrate. The anti-inflammatory activity of the drug was assessed by the difference in the amount of exudate in control and experimental animals.

The effect of drugs on the exudative-proliferative phase of inflammation was studied using the “cotton ball” method. The drugs were administered before implantation and once within 7 days after implantation of cotton balls. On the eighth day, the animals were killed, cotton balls were removed and their wet weight was determined, then dried at a temperature of 70° C to constant weight and weighed again in dry form.

When studying diphenyl-(bis-(benzoyloxy))-silane, the technique proposed by Selye was also used: after introducing an irritant into the cavity of the air sac under the skin of the rat’s back, a pocket granuloma appears. The study drug was administered orally in doses of 50, 100 and 150 mg/kg for 7 days, once a day. On the eighth day, the pocket granuloma was separated, the exudate was sucked out with a syringe, it was weighed to a constant weight and weighed in dry form, the volume of exudate in the bag and the total protein content in it were determined.

The effect of 1,4-bis-(bromobenzoyloxy)-butine-2 on pain sensitivity was studied in rats using the method of A.K.Sangailo. The antipyretic effect of the drug was studied on white

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laboratory mice against the background of preliminary administration of a standard solution of pyrogenal. The antiallergic effect of this chemical compound was studied in guinea pigs using the generally accepted method [11,12,13,14,15,16,17,18].

The resulting digital material was subjected to statistical processing using the standard software package using the well-known method of variation statistics with assessment of the significance of indicators and differences in the samples under consideration using the Student's t-test.

Research results and discussion.

A study of the anti-inflammatory effect of diphenyl-(bis-(benzoyloxy))-silane showed its high activity in various aseptic arthritis. Thus, this chemical compound had a pronounced inhibitory effect on the course of formaldehyde arthritis, starting with small doses. The drug at a dose of 50 mg/kg suppressed the development of the inflammatory process by 40.3%; with an increase in dose to 100 and 150 mg/kg, a significant increase in the effect was noted by 47.3% and 52.8%, respectively. Whereas, in the formaldehyde edema model, comparison drugs reduced edema as follows: voltaren by 38.4%, indomethacin by 36.1% and butadione by 27.3%. Consequently, the drug under study turned out to be more active and superior to voltaren, indomethacin, and butadione.

A comparison of the data presented in Table 1 shows that the drug under study is noticeably superior to the comparison drugs in its ability to suppress inflammation caused by various phlogogenic agents.

Table 1

Effect of diphenyl-(bis-(benzoyloxy))-silane, voltaren, indomethacin and butadione on inflammation caused by various phlogogenic agents

(at P<0.05)

A drug	Dose, mg/kg	Number of animals in the group	Inhibition of inflammation (%) caused				
			Formalin	Corragenine	Serotonin	Histamine	Dextran
Diphenyl-(bis-(benzoyloxy))-silane	50	10	40,9	39,1	38,0	37,3	36,2
Diphenyl-(bis-(benzoyloxy))-silane	100	10	47,9	46,3	46,1	45,4	44,1
Diphenyl-(bis-	150	10	52,8	51,9	50,3	50,8	49,8

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(benzoyloxy))-silane							
Voltaren	10	10	38,4	40,9	38,2	39,4	38,2
Indomethacin	15	10	36,1	35,3	33,4	35,8	35,6
Butadion	100	10	27,3	28,1	25,0	26,9	26,1

A study of the anti-inflammatory effect of 1,4-bis-(bromobenzoyloxy)-butine-2 revealed its high activity in various types of aseptic arthritis. The drug had a pronounced inhibitory effect on the course of formaldehyde arthritis, starting with small doses: at a dose of 50 mg/kg it suppressed the development of the inflammatory process by 48.1%. With an increase in dose to 100 and 150 mg/kg, an increase in effect was observed by 53.5% and 59.8%, respectively. Whereas in this model, voltaren at a dose of 10 mg/kg suppressed the development of the inflammatory process by 40.1%, indomethacin at a dose of 15 mg/kg - by 40.1%, and butadione at a dose of 100 mg/kg - by 28.4%. Consequently, the drug under study is more active and exceeds voltaren and indomethacin by 1.5 times, butadione by 2.5 times.

To fully characterize the anti-exudative effect of the first test drug, experiments were conducted to study its effect on the amount of exudative fluid in the abdominal cavity of rats with intraperitoneal administration of 1 ml of 0.2% silver nitrate solution.

It was noted that in animals of the control group after administration of silver nitrate, the amount of exudative fluid averaged 2.3 ± 0.04 ml, and in rats that had previously received the drug, it was less. Thus, when the drug was administered at a dose of 50 mg/kg, the amount of peritoneal fluid averaged 1.4±0.02 ml, and at doses of 100 and 150 mg/kg - 1.31±0.03 ml and 1.25±0 .04 ml respectively. This means that the drug reduced the formation of exudative fluid at a dose of 50 mg/kg by 39.2%, at a dose of 100 mg/kg by 43.1%, and at a dose of 150 mg/kg by 45.7%. The formation of peritoneal fluid was also suppressed under the influence of known anti-inflammatory drugs. Thus, with the introduction of butadione, the amount of peritoneal fluid decreased compared to the control by 26.1%, and with indomethacin and voltaren by an average of 32.2% and 34.8% (Table 2).

Table 2

Effect of diphenyl-(bis-(benzoyloxy))-silane, voltaren, indomethacin and butadione on aseptic peritonitis caused by silver nitrate in rats (at P<0.05)

A drug	Number of animals in the group	Dose, mg/kg	Amount of exudate in the abdominal cavity in ml	Antiexudative effect in %
Control	10	-	2,3 ±0,04	0
Diphenyl-(bis-(benzoyloxy))-	10	50	1,4 ±0,02	39,2

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silane				
Diphenyl-(bis-(benzoyloxy))-silane	10	100	1,31 ±0,03	43,1
Diphenyl-(bis-(benzoyloxy))-silane	10	150	1,25 ±0,04	45,7
Voltaren	10	10	1,5 ±0,04	34,8
Indomethacin	10	15	1,56 ±0,03	32,2
Butadion	10	100	1,7 ±0,04	26,1

These data indicate that the drug has a fairly pronounced anti-exudative activity and in this ratio is approximately 1.7 times higher than butadione, 1.4 and 1.3 times higher than indomethacin and voltaren, respectively.

When studying the effect of the second drug under study on the exudative phase of inflammation, a decrease in the amount of fluid in the abdominal cavity was noted compared to the control; in this indicator, 1,4-bis-(bromobenzoyloxy)-butyne-2 is 2 times superior to the comparison drugs.

Thus, analysis of the data obtained allows us to conclude that benzoic acid derivatives: diphenyl-/bis-(benzoyloxy)/-silone and 1,4-bis-(bromobenzoyloxy)-butyne-2 are quite active in terms of anti-exudative effect, and in this significantly superior to comparison drugs: voltaren, indomethacin and butadione.

In the next series of experiments, we studied the ability of 1,4-bis-(bromobenzoyloxy)-butine-2 to have an inhibitory effect on the formation of granulomas during subcutaneous implantation of “cotton balls” in rats. As can be seen from the data presented in Table 3, on the eighth day of the experiment, the weight of wet balls in control animals was 233.9 ± 4.42 mg. This indicator in experimental rats who were orally administered the drug for seven days was equal to: at a dose of 50 mg/kg - 179.17 ± 3.11 mg, at a dose of 100 mg/kg 139.64 ± 3.01 mg and at dose of 150 mg/kg – 127.7±2.88 mg. Consequently, the activity of diphenyl-(bis-(benzoyloxy))-silane was 23.4% at a dose of 50 mg/kg, and 40.3% and 45.4% at doses of 100 mg/kg and 150 mg/kg, respectively. Under similar conditions, voltaren, indomethacin and butadione inhibited exudative impregnation of granulation tissue around cotton balls by 24.9%, 22.4% and 16.5%, respectively. Consequently, the drug under study has a more pronounced anti-exudative effect than voltaren, indomethacin and butadione.

Table 3

The influence of diphenyl-(bis-(benzoyloxy))-silane, voltaren, indomethacin and butadione on the weight gain of wet and dry cotton swabs after

7 day subcutaneous implantation

A drug	Dose	Numb	Wet	Reductio	P	Weight	Reductio	P

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	, mg/kg	er of animals in the group	weight of granulation tissue, mg	n in the weight of wet granulation tissue compared to control in %		of granulation tissue after drying	n in the weight of dry granulation tissue compared to control in %	
Контроль	-	10	233,9±4,42	0	-	33,9±3,18	0	-
Diphenyl-(bis-(benzoyloxy))-silane	50	10	179,17±3,11	23,4	<0,05	25,12±2,06	25,9	<0,05
Diphenyl-(bis-(benzoyloxy))-silane	100	10	139,64±3,01	40,3	<0,05	19,63±2,01	42,1	<0,05
Diphenyl-(bis-(benzoyloxy))-silane	150	10	127,7±2,88	45,4	<0,05	17,83±1,65	47,4	<0,05
Voltaren	10	10	175,66±3,09	24,9	<0,05	25,15±2,68	25,8	<0,05
Indomethacin	15	10	181,5±3,18	22,4	<0,05	26,01±2,74	23,2	<0,05
Butadion	100	10	195,3±3,91	16,5	<0,05	28,0±2,91	17,4	<0,05

This drug had a clear inhibitory effect on the development of granulomas according to the Selye method. This effect of the drug at doses of 50, 100 and 150 mg/kg was expressed by a decrease in the weight of the wet granuloma sac by 60.1%, 50.3%, 47.5%, respectively, and the dried one - by 48.1%, 40.8%, 39 .0%. The effectiveness of voltaren, indomethacin and butadione was slightly lower. At the same time, voltaren reduced the weight of the wet granuloma sac by 61.4% and dry by 53.5%, and indomethacin and butadione, respectively, by 64.8% and 56.4%, by 74.3% and 65.4% (Table 4).

Table 4

Effect of diphenyl-(bis-(benzoyloxy))-silane, voltaren, indomethacin and butadione on the weight of the granuloma sac in exudative inflammation

according to Selye (P<0.05)

A drug	Dose, mg/kg	Number of animals in the group	Wet sac weight		Dry sac weight	
			г	%	г	%

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Control	-	10	3,142±0,11	100	2,12±0,09	150
Diphenyl-(bis-(benzoyloxy))-silane	50	10	1,911±0,08	60,8	1,02±0,04	48,1
Diphenyl-(bis-(benzoyloxy))-silane	100	10	1,580±0,06	50,3	0,865±0,04	40,8
Diphenyl-(bis-(benzoyloxy))-silane	150	10	1,486±0,05	47,3	0,827±0,03	39,0
Voltaren	10	10	1,929±0,08	61,4	1,134±0,07	53,5
Indomethacin	15	10	2,036±0,08	64,8	1,196±0,06	56,4
Butadion	100	10	2,334±0,09	74,3	1,386±0,07	65,4

The drug under study reduces the intensity of the development of exudative phenomena. This is evidenced by a decrease in the volume of exudate in the granuloma sac. If the volume of exudate in the granuloma sac in animals of the control group averaged 6.3 ± 0.3 ml, then in experimental animals that were administered the first test drug, the amount of exudate in the granuloma sac was 4.4 ± 0.15 ml, 3. 9±0.1 ml and 3.1±0.12 ml according to the administered doses. At the same time, the effectiveness of voltaren, indomethacin and butadione was slightly lower: the volume of exudate in the granuloma sac upon administration of voltaren was 4.4±0.21 ml, and for indomethacin and butadione 4.6±0.22 and 4.9±0.24 ml respectively.

Thus, the studies have convincingly shown that the studied chemical compound diphenyl-(bis-(benzoyloxy))-silane exhibits a pronounced anti-inflammatory effect, which is expressed by a significant decrease in the mass of the granuloma sac (wet and dry) and the amount of exudate in it. According to these indicators, it is superior to Voltaren, indomethacin and butadione.

In the next series of experiments, the effect of 1,4-bis-(bromobenzoyloxy)-butine-2 on the pain sensitivity threshold of animals was studied. First, the pain sensitivity threshold was determined in all male rats, then the animals were divided into four groups. The first group is the control group. Animals in this group were administered a suspension of 3% starch paste. Rats of the second group were administered the study drug at a dose of 50 mg/kg, the third - at a dose of 100 mg/kg, and the fourth - at a dose of 150 mg/kg. Pain sensitivity was measured every 30 minutes for 5 hours. During the experiments, it was found that the threshold of pain sensitivity in animals in the control group remained the same as before the introduction of a suspension of 3% paste, while the drug at a dose of 50 mg/kg increased the threshold of pain sensitivity by 42.3% compared to the initial level. As the dose of the drug increased, an increase in the threshold of pain sensitivity was observed.

Consequently, the drug under study quite significantly increases the threshold of pain sensitivity in rats.

An increase in body temperature is one of the main components of the inflammatory process and occurs as a result of destructive changes in tissue, which leads to the formation and entry into the general bloodstream of protein breakdown products, polysaccharides, etc.

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In this regard, studying the effect of the drug on the body temperature of animals is of particular interest. In the first series of experiments, the effect of the drug on the temperature of intact animals was studied. Analysis of the results showed that the body temperature of animals in the control group, which were administered a starch suspension, fluctuated during the observed period by only 0.1-0.2 degrees. In experimental mice, after administration of the drug, a tendency to a decrease in body temperature was observed within 30 minutes. Thus, the drug at a dose of 50 mg/kg caused a decrease in body temperature by 0.5 degrees, at a dose of 100 mg/kg - by 0.6 degrees, and at a dose of 150 mg/kg - by 0.7 degrees Celsius. The duration of action of the drug was 3-4 hours.

In the second series of experiments, the effect of the drug on the body temperature of animals that had previously received pyrogenal was studied. In all experimental animals, approximately 2 hours after the administration of pyrogenal, an increase in body temperature of 2.3-2.5 degrees Celsius was noted. Subsequent administration of the drug after 30 minutes caused a decrease in body temperature. This effect gradually increased and reached its maximum 2-3 hours after administration of the drug.

Thus, in animals, 3 hours after administration of the drug at a dose of 50 mg/kg of weight, a decrease in body temperature was observed, at a dose of 100 mg/kg - by 1.6-1.7 degrees, and at a dose of 150 mg/kg - by 1. 9-2.0 degrees. Then a gradual decrease in the body temperature of the animals was observed almost to normal.

Therefore, based on the data obtained, we can conclude that the drug, under conditions of a febrile reaction caused by the administration of pyrogenal, clearly lowers the body temperature of animals, that is, it has a pronounced antipyretic effect.

A study of the antiallergic effect of the drug under study showed that 1,4-bis-(bromobenzoyloxy)-butine-2 exhibits an antiallergic effect, which is manifested by a mild course of anaphylactic shock and a decrease in the number of dead animals. Thus, if in the control group, after the introduction of a permissive dose of horse serum, 10 (100%) out of 10 guinea pigs died, then when the drug was administered at a dose of 50 mg/kg, 8 (80%) out of 10 died, and at doses of 100 and 150 mg/kg kg - 7 (70%) out of 10 and 6 (60%) out of 10, respectively.

Thus, the successful combination of anti-inflammatory, analgesic, antipyretic and antiallergic properties of the drug makes it promising in the treatment of various inflammatory diseases, including those with an allergic component.

Conclusions:

1. Diphenyl-/bis-(benzoyloxy)/-silone and 1,4-bis-(bromobenzoyloxy)-butyne-2 are highly active anti-inflammatory drugs and are superior in their activity to comparison drugs.

2. The drug under study, 1,4-bis-(bromobenzoyloxy)-butine-2, exhibits analgesic, antipyretic and antiallergic effects.

3. Diphenyl-[bis-(benzoyloxy)]-silone and 1,4-bis-(bromobenzoyloxy)-butyne-2 are of some theoretical and practical interest as potential anti-inflammatory drugs.

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