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Morphological Condition of the Large Intestine in Chronic Intoxication with Pesticides Against the Background of Diabetes Mellitus

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ABSTRACT

This article presents experimental research and study of the peculiarities of alternative and reactive changes in the colon during prolonged exposure to the most widely used pesticides of various chemical groups (copper-containing, organochlorine, organophosphate) against the background of diabetes mellitus. The aim of the study was to identify morphological changes in the microcirculatory bed and tissue structures of the colon in chronic poisoning with pesticides "Neoron" and "Sumi-alpha" on the background of diabetes mellitus. Material and methods of research. The object of the study was the Ambassador of 68 white laboratory rats-males with an initial mass of 80-150 grams, who were in normal vivarium conditions. Modeling of alloxan diabetes was reproduced by a single intraperitoneal injection of 1.0 ml/100 g of alloxan in a phosphate-citrate buffer at the rate of 11 mg /100 g of mass. This study is *retrospective, with historical data coverage*, and *prospective preclinical, experimental*. Statistical processing of the obtained results was performed using standard student T-test methods to assess the reliability of differences using the *SPSS-21* version program. The average values are represented as M±SD. Differences at $p<0.05$ were considered reliable. Results. Long-term periods are characterized by an increase in atrophic processes, leading to a noticeable thinning of the wall throughout. There were pronounced phenomena of crypt polymorphism, and glued crypts were found in some areas. In some places, as a result of massive desquamation of the epithelium, there was a Baring of mucosal areas, as well as ulcerative defects, around which there was a massive infiltration of leukocytes and macrophages. In such areas, the area of non-vascular zones increases, which worsens the course of pathomorphological processes. Conclusion. The data obtained by us indicate that in the early periods (3-15 days) after acute priming with pesticides "Neoron" and "Sumi-alpha", animals show pronounced inflammatory and destructive changes in all layers of the colon wall, especially the mucosa.

Keywords: large intestine, pestecids, morphological changes, diabetes mellitus

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INTRODUCTION

Today, one of the global problems of modern ecology is the protection of the environment and the prevention of its pollution with various pesticides, in particular pesticides. Global climate change, population overpopulation in many areas, and food security challenges agriculture to ensure maximum efficiency in obtaining high yields. And, unfortunately, without the use of pesticides, it is virtually impossible to solve this problem. It is believed that if successful pest control in the world could be collected annually about 200 million tons of grain, which would be enough to feed 1 billion people. However, the downside of this is the presence of pronounced negative consequences for the environment, in General, and human health, in particular (Aspelin, 1997).

Today, the total number of known pesticides is hundreds of thousands, while 10-15 new chemical compounds are synthesized annually. In recent years, 3.2 million tons of pesticides have been processed on 4 billion hectares of land around the globe. In the United States, 750-800 million pounds of pesticides are used in agriculture every year (Yaglova et al., 2020). On the largest scale, pesticides are used in agriculture to control arthropods (insecticides and acaricides), nematodes (nematocides), fungal (fungicides) and bacterial (bactericides) diseases of plants and animals, as well as to control weeds (herbicides).

The circulation of pesticides can occur in the following ways: 1) air-plant-soil-plant-herbivores-human; 2) soil - water-zoophytoplankton-fish-human. And, therefore, the main way of getting pesticide residues into the human body is through food (Akhmedov B. X., 2000).

It should be noted that pesticides can enter the human body as a result of their professional activities. These are agricultural workers, and workers in the production of pesticides themselves. There are many cases of intoxication of pesticides in large quantities in factories that do not comply with safety regulations. The world health organization estimates that more than 4 million people are at risk of being poisoned by toxic pesticides each year, mainly due to a lack of safety knowledge .

The literature describes the term so-called "peasant syndrome" (peasant syndrome), which refers to the entire set of symptoms of physical or mental disorders that develop in farmers in connection with their work. For the first time this term was introduced by T. Kumagai (Kumagai, 1943) in 1943. Symptoms are diverse, including pronounced disorders of the digestive and nervous systems, and pronounced suppression of the

immune system.

As a rule, intoxication with pesticides is acute or chronic, and the cumulative properties of many drugs should also be noted. Chronic poisoning in principle affects the entire population of the world, as a result of long-term intake of residual amounts of pesticides in finished agricultural products. Or possible accumulation of it on the surface of the skin among rural residents, as well as minimal amounts in drinking water. According to the Korea Ministry for Health (2015) in South Korea before 2000 the number of annual deaths from pesticide poisoning among farmers was 1200-1600 (Health, 2001).

As mentioned above, one of the main routes of entry of pesticides into the body is the gastrointestinal tract (GI), which naturally affects its morphological state, and in particular the colon. Of great scientific and practical interest is the study of the features of alternative and reactive changes in the colon during prolonged exposure to the most widely used pesticides of various chemical groups (copper-containing, organochlorine, organophosphate) against the background of diabetes mellitus. Literature data indicate that pathomorphological changes in the colon develop with many toxic effects on the body, especially under experimental conditions.

Analyzing literary sources, it was revealed that mostly covered only some morphological changes of the colon excluding the microcirculation of the body, and also nature of the current structural and functional rearrangements in the body to the effects of pesticides on diabetes mellitus.

As the studied chemical compounds, we used acarocide " Neoron "and insecticide" Sumi-alpha", which are allowed for use in the republics of Central Asia and Kazakhstan. The pesticide "Neoron" belongs to the class of acaricides, produced by the company "Siba-Geigi" (Switzerland). Designed for use in the processing of many crops, including cotton and vegetables. This pesticide is a contact acaricide. Toxicity of "Neoron": at a dose of LD5Q for rats-950 mg/kg and belongs to the class of medium-toxic pesticides.

The Sumi-alpha pesticide was developed by Sumitomo Chemical (Japan) and belongs to the class of contact insecticides. Highly toxic, especially for fish, the drug's toxicity is LD50 - 75 mg/kg.

The aim of the study

It was to identify morphological changes in the microcirculatory bed and tissue structures of the colon in chronic poisoning with pesticides "Neoron" and "Sumi-alpha" on the background of diabetes mellitus.

Material and methods

The object of the study was 68 white male laboratory rats with an initial weight of 80-150 grams, which were in normal vivarium conditions. The experimental animals were kept in separate cages at room temperature, with natural light and ventilation. The food was mixed and balanced.

Modeling of alloxan diabetes was reproduced by a single intraperitoneal injection of 1.0 ml /100 g of alloxan in a phosphate-citrate buffer at the rate of 11 mg /100 g of mass (Alavanja, Hoppin, & Kamel, 2004). The presence of glycemia was determined by glucose oxidase method; the amount of sugar in the blood was 6.5-10.5 mmol or more.

Before conducting experiments, the animals were carefully examined and their General condition was monitored. The period of quarantine before chronic priming is 14 days, which corresponds to the recommendations and guidelines for the comprehensive hygienic assessment of new pesticides of the Ministry of health of the Republic of Kazakhstan.

After the quarantine, all the animals were divided into groups. 1 group of 18 rats of the control. Rats of the following 2 groups were poisoned with pesticides "Neoron" and "Sumi-alpha" separately at a dose of 1/50 LD50 30 days after the creation of an experimental model of diabetes mellitus. The preparations were diluted in distilled water. The resulting solution was administered to experimental animals strictly in the morning (before feeding) intragastrically using a metal probe. The volume of the introduced suspension was introduced based on the calculation of 1.0 ml of an aqueous solution of the pesticide per 100 grams of animal weight. Modeling of chronic intoxication with these pesticides was reproduced by daily administration of pesticides for 3 months. Terms of observation: 3, 7, 15, 30, 60 and 90 days after the end of pesticide poisoning.

To study intra-organ vessels of the colon, we used the method of transcapillary injection of vessels with a mass of Gerot through the thoracic aorta in the modification of H. H. Kamilov (Strong et al., 2004). Then the organocomplex was fixed in a 10% solution of neutral formalin for 5 days or more. To study the vessels, cross sections were taken from 3 sections (proximal, middle and distal) of the colon, which were clarified in alcohols of increasing concentration using the accelerated method of a.m. Malygin (Hanke & Jurewicz, 2004), as well as by the method of T. A. Sagatov (Alavanja et al., 2004; McCauley et al., 2006). Circular sections 60-120 microns thick were enclosed in a balm.

For histological examination, tissue fragments were taken from 3 sections (proximal, middle and distal) of the colon, and they were fixed in a neutral 10% solution of formalin, Carnois liquid. After the corresponding wiring, the material was poured into paraffin. Then sections 4-6 microns thick were stained with hematoxylin and eosin after dewaxing for morphological and morphometric studies.

For electron microscopy, samples of the mucous membrane of various parts of the large intestine of rats were fixed in a 1% buffered solution of glutaraldehyde, and dopixation was performed in a 1% solution of osmium tetrachloride for 1.5-2 hours at a temperature of 4°C (pH 7.3-7.5). After dehydration in alcohols of increasing concentration of the pieces of fabric embedded in panaramitee mixture. After contrasting with uranyl acetate and lead nitrate, ultra-thin sections were viewed in an electron microscope Hitachi H-600 (Japan).

For scanning electron microscopy (SEM), the vessels of the colon were filled with polymerized methacrylate, then the corrosion casts after spraying a thin layer of gold were placed in the IB-3 sprayer and viewed in the s-405 electron microscope.

Morphometrically, using an eyepiece-micrometer MBR-1-15x, the thickness of the wall shells of the 3 sections of the colon and the diameters of the vessels of the microcirculatory bed of the colon were measured. Using the method of A. A. Gutsol (Hanke & Jurewicz, 2004), the total density of microvessels distribution per 1 mm2 was determined.

Statistical processing of the obtained results was performed using standard methods of variation statistics using the student's t-test to assess the reliability of

differences using the SPSS-21 version program. The average values are represented as M±SD (average value ± average standard error). Differences at $p<0.05$ were considered reliable.

Results and discussion

Our data indicate that in the early periods (3-15 days) after the end of chronic intoxication with pesticides "Neoron" and "Sumi-alpha" in animals, inflammatory and destructive changes in the vascular-stromal elements of the colon wall, especially the mucosa, are noted.

In particular, there is edema and diffuse infiltration of the stroma of the entire wall of the colon, more pronounced in the proximal part. The epithelium of the mucosa is flattened, many cells with polymorphic, randomly decomposed nuclei. Among these cells there is a large number of goblet cells in various stages of secretion. The number of epithelial cells in comparison with the control group decreased by 74% in the proximal, 64% on average and 76% in the distal, respectively. The lumen of the crypts is sharply expanded, contains microorganisms and mucus.

On the surface of the mucosa, there were often areas with desquamation of the epithelial layer from the stroma, sometimes atrophied tissue elements. It should be noted that as the progression of atrophic processes, enterocytes lining the distal sections of the crypts, as it were, move away from the subject's own plate due to increasing tissue edema. In this case, enterocytes are rejected from their own plate fall into the intestinal lumen, as a result of which the underlying tissues are directly affected by the intestinal contents. Further, due to the violation of epithelial integrity, the absorption of the toxic substance from the lumen of the intestine into the stroma occurs, which further aggravates the picture of pathomorphological changes.

Vessels of the microcirculatory bed in different States. Thus, the precapillaries are sinuous, expanded, and blood-filled. The lumen of the capillaries is not uniform, sometimes spasmodically narrowed, in other areas varicose. The integrity of the capillary wall is broken in places, this is manifested by the release of the injection mass into the stroma. Narrowed and blindly ending capillaries are detected, as well as vascular-free zones, which lead to a decrease in the density of microvessels distribution. The postcapillaries were at a standstill.

In the submucosal basis, connective tissue loosening and infiltration by lymphoid cells were observed in all parts of the large intestine. Ordinal arterial vessels are dilated, full-blooded, and the wall of some vessels is thickened. In contrast, the venous vessels in almost all areas are varicose, which indicates the beginning of venous congestion, sometimes extravasate.

During these periods, the serous-muscular membrane has a swelling and loosening of smooth muscle bundles, desquamated mesothelial cells. Morphological changes in microvessels are represented in the form of lumen expansion, their blood filling, violations of the integrity of the vessel wall.

As a result of chronic intoxication in terms of up to 30 days, along with inflammatory phenomena in all the membranes of the colon, the development of atrophic processes was observed. Along with this, macrophage and lymphocytic infiltration of the stroma, sometimes fibrosis, randomly arranged bundles of collagen fibers are significantly expressed. The number of epithelial and mitotic dividing cells in all parts of the colon was significantly lower compared to previous periods. Enterocytes unevenly covered the crypts, the height of enterocytes is noticeably lower, and there is no brush border in places. The interstitial slits are narrowed, and the crypts themselves are enlarged. Goblet cells in various stages of secretion. The thickness of the mucosa and the depth of the crypts are noticeably reduced.

Dyscirculatory changes in the vessels of the microvasculature of the mucosa continue to increase. In most cases, the capillaries in the crypts are narrowed, blindly ending, and in places there are small and vascular - free zones. Postcapillaries remain varicose, which leads to an average increase in the lumen of 1.2-1.3 times. The overall density of microvessel distribution is noticeably reduced.

The picture of pathomorphological transformations is presented in the form of a decrease in lymphohistiocytic infiltration against the background of stroma fibrosis progression. The ordinal vessels are in different States, and the venous vessels are varicose. In places, the arterial vessels are noticeably narrowed, their wall is thickened.

In the serous-muscular membrane, cellular infiltration persists, smooth muscle fibers are thinned in places, loosened. Many vessels are noticeably narrowed, and the precapillaries are sinuous. The postcapillaries were varicose, and in places there was a bulging of the vessel walls in the form of glomeruli. All this leads to a decrease in the thickness of the shell.

On the 60th day of observation, previously detected atrophic changes increase, which leads to a decrease in the wall thickness in all departments, especially in the proximal one.

Atrophic changes are most pronounced in the mucous membrane. So, in the mucosa, polymorphism of crypts is histologically noted, in some areas there are a lot of glued crypts. The crypt stroma remains infiltrated, and the crypt Depth is significantly reduced. Crypts covered with low-prismatic epithelium became short. The lumen of many crypts is expanded, it contains microorganisms and mucus. the number of goblet-shaped, epithelial, and mitotic dividing cells also significantly decreased. Cells with pycnotic altered nuclei appear. Signs of venous congestion increase against the background of a noticeable decrease in the density of microvessels.

In the serous-muscular membrane throughout the entire length of the large intestine, edema and infiltration by cellular elements has significantly decreased, and muscle fibers are atrophied.

Long-term periods are characterized by an increase in atrophic processes, leading to a noticeable thinning of the wall throughout. There were pronounced phenomena of crypt polymorphism, and glued crypts were found in some areas. In some places, as a result of massive desquamation of the epithelium, there was a Baring of mucosal areas, as well as ulcerative defects, around which there was a massive infiltration of leukocytes and macrophages. In such areas, the area of non-vascular zones increases, which worsens the course of pathomorphological processes.

Microaneurysmal expansion of the vascular wall, especially of the venous part, was also observed against the background of a noticeable decrease in the density of the distribution of vessels. However, it should be noted that in these periods of observation, the walls of the arteries and precapillaries were thickened, i.e. microangiosclerosis developed.

Thus, chronic intoxication with pesticides at a dose of

1/50 LD50 on the background of diabetes leads to pronounced morphological changes in the wall of the colon in the form of atrophy and necrosis in all tissue structures of the intestinal membranes, especially the mucosa. And changes in the vessels of the microcirculatory bed come to the fore, which, apparently, is the result of the direct action of the pesticide on the intestinal wall and its vessels. The identified shifts are more pronounced when priming "Sumi-alpha", compared to" Neoron", which is probably due to the toxicity of the pesticide. Therefore, knowledge of the mechanisms of development of chronic intoxication opens up broad prospects in terms of developing ways to prevent and correct the resulting shifts in poisoning.

CONCLUSIONS

The development of inflammatory-reactive and atrophic processes in chronic intxication with pesticides is based on deep pathomorphological changes in the hemocirculatory system and tissue structures of the colon, leading to progressive atrophy of all wall membranes.The depth of violations depends on the chemical composition of the pesticide used, the duration of its action and the way it enters the body. If there is any pathological process in the body, in particular diabetes, the action of the pesticide further aggravates it.

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