Original article:

Experimental research of Harmine hydrochloride effect on internal organs

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Abstract:

Objective. The purpose of thisstudy was to determine the chronic toxicity of the drug "Harmine hydrochloride, capsules" for preclinical evaluation of its safety. ***Materials and methods.*** The experiment was performed on 48 CD-1 rats. Harmine hydrochloride was injectedto the animals intragastrically at doses of 2.5 mg / kg/per day, 5 mg / kg/per day, 9 mg / kg/per day, 10 mg / kg/per day for 3 months. After 3 months, the animals were withdrew from the experiment, internal organs (brain, heart, spleen, adrenals) were weighed and set in 10% neutral formalin. Histological specimenswere mounted in accordance with standard procedures. ***Results and Discussion.*** All morphological, histopathological changes, in addition to mortality and bodyweight changes were recorded.Microtome cuts, 5 micrometers thick, were stained with hematoxylin and eosin.***Conclusion***. As a result of the morphological study, there was no toxic effect of harmine hydrochloride at doses of 2.5 mg / kg, 5 mg / kg, 9 mg / kg and 10 mg / kg on the brain, at doses of 2.5 mg / kg and 5 mg / kg on the structure of the heart, spleen and adrenal glands. At doses of 9 mg / kg and 10 mg / kg, there is an initial toxic dose-dependent effect on the heart, spleen and adrenal glands.

Keywords: preclinical studies, chronic toxicity, harmine hydrochloride capsules, morphological examination, internal organs.

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Introduction

The search and development of herbal medicines is issue of the day[1-3].Recently, scientists are attracted by natural heterocyclic compounds, which are the richest source of production of broad-spectrum drugs[4,5].One of the most promising in the series of these compounds is the indole alkaloid harmine, which is comprehensively studied at present time[6-10]. According to the literature data, the neuroprotective effect[11] and the antitumor effect of harmine are discussed[12].According to the opinion ofseveral authors[13], harmine has great prospects, as far as an oncological drug and a combination ofharminee with an inhibitor of non-homologous end joining (NHEJ) can be an effective strategy of anticancer treatment.It has been shown that harmine can inhibit the proliferation of tumor cells and induce the arrest of the G2 / M cell cycle, accompanied by an increase in apoptotic cell death in SGC-7901 cancer cells. Harmine can exert antitumor activity at a dose of 15 mg / kg / day in vivo, which is also associated with the arrest of the cell cycle[14].

In addition, harmine has an anxiolytic effect[15] and other types of pharmacological activity, such as antimicrobial, antifungal, antitumor, cytotoxic, antiplasmic, antioxidant, antimutagenic,

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antigenotoxic and hallucinogenic properties[16-18]. It effects on gamma-aminobutyric acid (GABA) type A and monoamine oxidase A or B receptors, enhances insulin sensitivity and also causes vasorelaxing effect[19].Harmine prevents the loss of bone tissue, suppressing osteoclastogenesis[20]. Harmine activates both internal and external pathways of apoptosis, and also regulates some transcription factors and pro-inflammatory cytokines[21-23].Harminewas registered as an inhibitor of the hypotensive specific kinase (DYRK1A), which regulates cell proliferation and brain development[24].Harmine has a potential bioinsecticidal effect on the larvae of the insect pest, Plodiainterunctella[25]. The general trend for authors is the indication of the prospects for the investigation of harminee and its compounds[26].

A gap in the research is that the pathomorphological evidence of the influence of harminecompounds on the internal organs of animals is not numerous[27-29]. Thus, in the literature available to us, there are practically no pathomorphological data on the effect of various doses of hydrochloride garmin on the brain, heart, spleen, and adrenal glands oflaboratory animals.

During research of the pharmacological activity of harminea hydrochloride, its neurotropic activity was determined[30-34].A capsule dosage form was devised. Pharmacokinetic parameters ofharmine are known from the literature data[35-37]. The next stage in the development of the neurotropic drug was the preclinical evaluation of its safety.

On the basis of provided preclinical surveys is determined that harmine hydrochloride has antidepressant, antihypoxic (hypobaric hypoxia), activating (in 2.5 mg per kg dose in actometer) and antiparkinsonianeffects. Harmine hydrochloride in 2.5 mg/kg (in some tests in 5 mg/kg) eliminates catalepsy, caused by haloperidol among rats, decreasesoligokinesia and rigidity in the

Parkinson syndrome test, which was stimulated by 1-methyl-4-phenil-1,2,3,7-tetrahydropyridine (MFTP) neurotoxin to C57BL/6 mice line, but doesn`t effect on tremor, caused by arecoline or MFTP.The antiparkinsonian action is realized due to inhibition of monoamine oxidase as well as antagonism to GABA receptors[38-40].

The purpose of this research was to study the chronic toxicity of the drug "Harmine hydrochloride, capsules". When choosing the doses for the study of chronic toxicity of the drug "Harminee hydrochloride, capsules".

Methods

The investigated substance garmine hydrochloride is obtained as follows: 0.1 g (0.47 mmol) of garmin are dissolved in 12 ml of ethanol and 10 ml (40.5 mmol) of concentrated hydrochloric acid are added with stirring. The reaction proceeds at room temperature. The precipitated white precipitate is filtered off and dried. A crystalline water-soluble salt is obtained, garmine hydrochloride, m.p. 272-275 ° C (dec.), Yield 99%. The result of HPLC analysis shows that the purity of the substance corresponds to 99.9%, the retention time is 4.71 min, and the wavelength is 334 nm.

Ethical Issues:

This work got prior approval from Institutional Ethics Committee. The experiments were carried out in accordance with the requirements for the study of new pharmacological substances [Guidelines for the Experimental (Preclinical) Study of New Pharmacological Substances, Moscow, 2000] on mature CD-1 rats (30 rodents), equally females and males, initial body weight was 200-270 grams.The animals were in standard vivarium conditions on a normal diet and free access to water and food. Control and experimental animals were in similar conditions and had the same initial average weight, controlled by weekly weighing to correct the administered dose of the substance.The experiments were carried out, observing the necessary rules for carrying out work using experimental animals. Harmine hydrochloride was injected to rats intragastrically daily at doses of 2.5 mg / kg, 5 mg / kg, 9 mg / kg, 10 mg / kg (3 males and females in each test group) for 3 months. Control animals (3 males and 3 females) took an equivalent amount of intragastric drinking water also for 3 months. After 3 months, the animals were withdrew from the experiment in compliance with the rules of euthanasia.Blood was taken for biochemical studies. Internal organs (brain, heart, adrenal glands) were weighed and mounted in a 10% neutral formalin.The organs were evaluated macroscopically, then histological preparations were prepared, in accordance with the guidelines for the study of chronic toxicity.

Results

As a result of the study, it was found that the 3-month-long administration of the drug "Gargamine hydrochloride, capsules" at a dose of 2.5 mg / kg, 5 mg / kg 9 mg / kg and 10 mg / kg for 3 months orally did not cause significant changes in rats body weight, general condition and behavioral reactions of animals.

The increment in total weight in experimental animals receiving “Harmine hydrochloride capsules” at a dose of 10 mg / kg was slightly higher than in the control (Table 1).

Table I. Total Mass, G (Numerator) And Percentage Of Its Increase (Denominator) In Rats Within 3 Months Of The Administration Of The Drug “Gormina Hydrochloride, Capsules” (2.5 Mg / Kg, 5 Mg / Kg, 9 Mg / Kg And 10 Mg / Kg

Groups of animals	Termofstudy, weeks						
	Initial mass	2	4	6	8	10	12
Control	232,3± 25,0	251,7± 27,0	255,2± 26,0	252,3± 27,6	266,7± 31,5	282,0± 30,5*	287,8± 33,2*
	100%	8,4±0,2	9,9±1,8	8,6±2,3	14,8±2,7	21,6±4,9	23,9±3,2
2,5 mg/кg	258,7± 43,0	269,3± 49,7	271,3± 54,7	267,7± 53,7	277,8± 55,2	290,0± 62,2	298,2± 66,5
	100%	4,1±1,2	4,9±2,7*	3,5±2,1	7,4±2,0	12,1±4,2	15,3±2,8
5 mg/кg	284,0± 26,4	289,3± 24,5	288,3± 22,1	286,2± 24,1	294,0± 22,6	304,0± 24,3	305,0± 26,4
	100%	1,9±1,3*	1,5±3,3	0,8±3,4	3,5±2,1	7,0±3,4*	7,4±2,0
9 mg/кg	198,3± 44,0	211,0± 15,6	212,0± 11,1	204,0± 18,3	208,3± 22,5	217,3± 24,3	213,8± 21,0
	100%	6,4±2,1	6,9±4,7*	2,9±3,4	5,0±3,3	9,6±4,2	7,8±4,0
10 mg/кg	201,2± 21,5	202,7± 22,5	201,3± 19,4	202,0± 22,1	207,8± 24,2	209,7± 31,2	208,0± 33,6
	100%	0,7±1,2*	0,05±1,1*	0,4±1,4*	3,3±2,1*	4,2±3,2	3,4±3,0

Note: * - p <0,05 in comparison with the values in the animals of the control group

At the same time, the control animals were in good condition: the lymph nodes were normal, normal motor activity remained, healthy fur.

A biochemical study of blood serum showed that as a result of chronic use of the drug “Harmine hydrochloride, capsules” for 3 months, the content of aspartate aminotransferase increased in rats as compared to the control group.

The average values of the other biochemical indices studied did not differ from their control values (Table 2).

Table Ii. Effect Of The Drug "Harmine Hydrochloride, Capsules" For Chronic Use During 3 Months Of Administration (2.5 Mg / Kg, 5 Mg / Kg, 9 Mg / Kg And 10 Mg / Kg Intragastric, Daily) For Biochemical Blood Rats

Groups of animals	Total protein, g/l	Glucose, Mmol/l	Cholesterol, Mmol/l	Bilirubin, Mcmol/l	Triglycerides, Mmol/l	AsAT U/l
Control, n=6	75,2±2,9	5,5±0,01	1,9±0,05	10,0±6,3	1,3±0,01	0,5±0,6
2,5mg/кg, n=6	74,3±5,7	5,6±0,02	1,9±0,02	17,5±4,9	1,3±0,02	0,5±0,2
5 mg/кg, n=6	74,5,±9,0	5,8±0,03	2,0±0,01	9,8±9,1	1,4±0,02	0,7±0,2
9 mg/кg, n=6	70,3±5,5	5,7±0,02	1,9±0,02	13,5±7,7	1,5±0,02	0,9±1,0
10 mg/кg, n=6	68,9±13,9	5,6±0,02	2,1±0,04	9,8±6,7	1,4±0,01	1,9±1,3*

Note: * - p <0,05 in comparison with the values in the animals of the control group

The results of the study of macro- and micro-preparations of the brain showed that in the control preparations and, during whole period of survey of chronic toxicity irrespective of the consumed dose of the harmine hydrochloride, a similar pattern was observed. Macroscopically, the following picture was noted: the cerebral hemispheres were symmetrical; the sulci are narrow, the gyri are flattened.

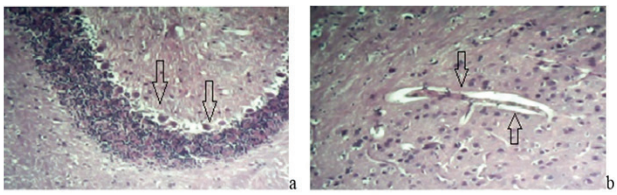

Figure 1. The brain. Control group: a) minor pericellular edema; b) perivascular edema, vessels full-blooded. Staining:HematoxylinandEosin. Magnification: 10x40.

On Figure 1a shows a fragment of the cerebellum gyrus. The vessels are lined with squamous endothelial cells, the nuclear part of which protrudes somewhat into the lumen of the vessel. Vessels are somewhat narrowed due to perivascular edema, which is clearly seen as a light zone around the vessels. Vessels are full-blooded.In the lumen of the vessels, both freely lying red blood cells and single sludgesare defined. Moderate edema of the brain tissue was observed. A similar picture was observedat other cases of the experiment, up to the maximum dose we used 10 mg / kg (Fig. 2).

Morphological examination of the brain

On microscopic examination of the brain, there is a slight pericellular, perivascular edema (Fig. 1a); in the lumen of the vessels are determined freely lying red blood cells, single sludges; vascular plexuses are full-blooded (Fig. 1b)

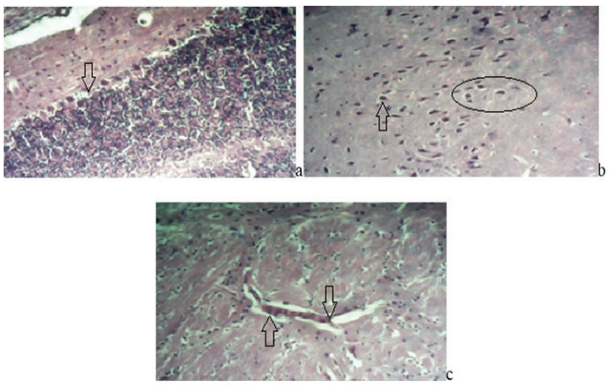

Figure 2. The brain. Chronic toxicity of harmine hydrochloride. Dose 10 mg / kg: a, b) a slight pericellular edema; c) perivascular edema, vasoconstriction of blood vessels. Staining:HematoxylinandEosin. Magnification: 10x40.

Morphological examination of the heart

A macroscopic examination of the heart showed that the animals in all the experimental groups had the same pattern.

At a microscopic examination of the heart of intact

animals, the pattern of the structure is preserved. There is edema of the stroma; vessels full-blooded, free-lying red blood cells are determined in their enlarged lumen (Fig. 3a). The majority of cardiomyocytes on the longitudinal section of a rectangular shape, have 1-2 nuclei and well-expressed striated striation, form functional "fibers" (Fig. 3b).Cardiomyocytes are covered with a sarcolemma consisting of a plasmolemma and a basal membrane, into which thin collagen and elastic fibers are intertwined, forming the "outer skeleton" of cardiomyocytes.

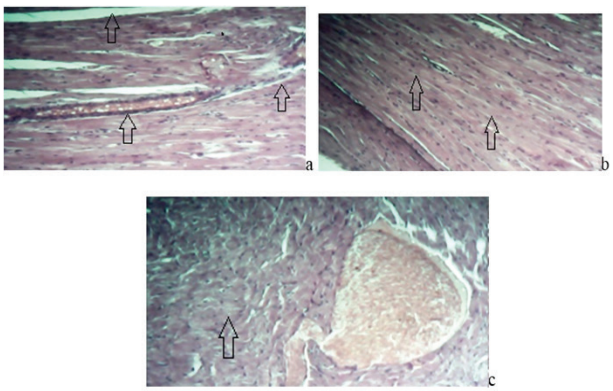

Figure 3. Heart. Control group: a) edema of the stroma; a full-blooded vessel with an enlarged lumen where free-lying red blood cells are determined; b) cardiomyocytes with well-defined transverse striated striation; c) tortuosity of functional myocardial muscle fibers. Staining: Hematoxylinand Eosin. Magnification: 10x40.

Morphological examination of the heart of animals treated with harmine hydrochloride at doses of 2.5 mg / kgand 5 mg / kg for 3 months showed no change compared to the control group.

Morphological picture of the heart of animals receiving harmine hydrochloride at a dose of 9 mg / kg, slightly differs from previous series of studies. The picture of the structure is partially broken. There is a swelling of the stroma with massive foci of hemorrhages, in the lumen of the vessels slugs and single erythrocyte thrombi are determined (Figure 4a). Instromafociofhemorrhagesareseen.

At a microscopic examination of the heart of animals receiving harmine hydrochloride at a dose of 10 mg / kg for 3 months, changes are observed, similar to those observed in the previous group, but their severity increases.

Morphological examination of the spleen

In the study of the spleen, the same pattern is observed for all periods of the study: the organ is elongated; capsule is pale violet, slightly wrinkled; pulp cherry color, scraping the pulp does not.

The wall of the arterioles is thickened, due to plasma impregnation, homogeneous, pink in color (Fig. 5a, b). The stroma is well expressed (Fig. 5c).

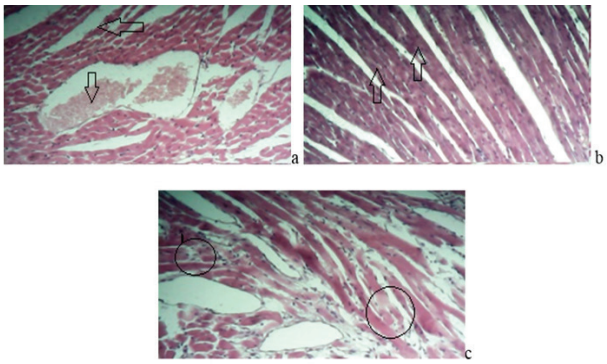

Figure4. Heart. Chronic toxicity of harmine hydrochloride. Dose 9 mg / kg: a) edema of the stroma, sludge; b) cardiomyocytes with well-defined transverse striated striation; c) fragmented cardiomyocytes; cytoplasm of cells of homogenous pink color with a cluster of pink grains, nucleus weakly basophilic, in places picnotic. Staining:HematoxylinandEosin. Mag: 10x40

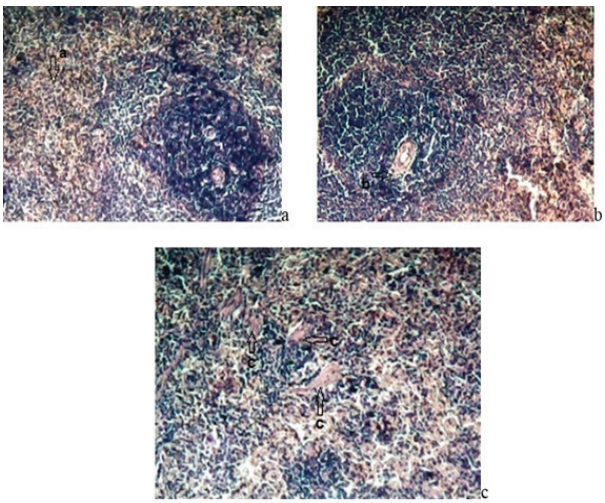

Figure 5. The spleen. Control group: a) the fullness of blood vessels and stasis; b) thickening of the arteriolar wall; c) proliferation of the stroma. Staining:Hematoxylin and Eosin. Mag: 10x40.

Some of the lymphoid follicles are reduced in size (Fig. 6a). Vessels are expanded, full-blooded. In the capillaries stagnant phenomena-stasis are seen. The wall of arterioles is thickened, due to plasma impregnation, homogeneous, pink color (Fig. 6b).The stroma is well expressed (Fig. 6c) in comparison with the animals of the control group, a partial reduction of the lymphoid follicles is observed and the stroma is more distinguished.

Morphological examination of the adrenal glands

Microscopically in control preparations zoning of the cortex of the adrenal gland is weakly expressed (Figure.8). The glomerular zone is not always well distinguishable, which is characteristic of the organ of rats. Epithelial strands form a zona glomerulosa , which consists of light polygonal cells with a gently

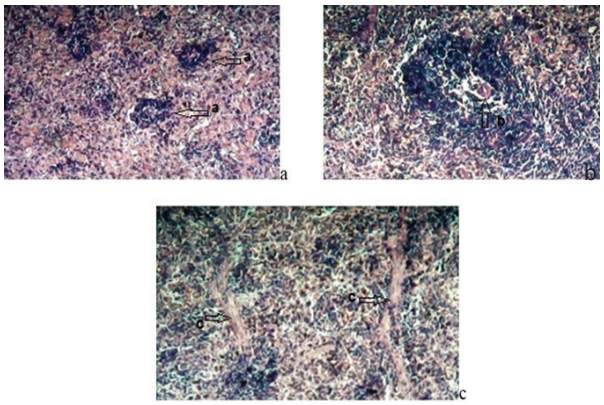

Figure 6. The spleen. Chronic toxicity of harmine hydrochloride. Dose 2.5 mg / kg: a) partial reduction of follicles; b) thickening of the arteriolar wall; c) proliferation of the stroma. Coloration: Hematoxylin and Eosin. Mag: 10x40

When microscopic examination of the spleen of animals with priming drug Harmine hydrochloride at a dose of 10 mg / kg in the parenchyma of the spleen visible white and red pulp. Lymphoid follicles of large and medium size, without a clear division into zones, reactive centers are not determined. Some follicles are reduced in size (Fig.7a). The vessels are dilated, full-blooded. In the capillaries are visible stagnant phenomena-rhinestones. The wall of arterioles is thickened, due to plasma impregnation, homogeneous, pink (Fig.7b). Stroma thickened (Fig.7b).

In the microscopic structure of the spleen, compared with animals with priming with the drug harmine hydrochloride at a dose of 9 mg / kg, most of the lymphoid follicles are reduced, the thickening of the arterioles and stroma walls is more distinguished.

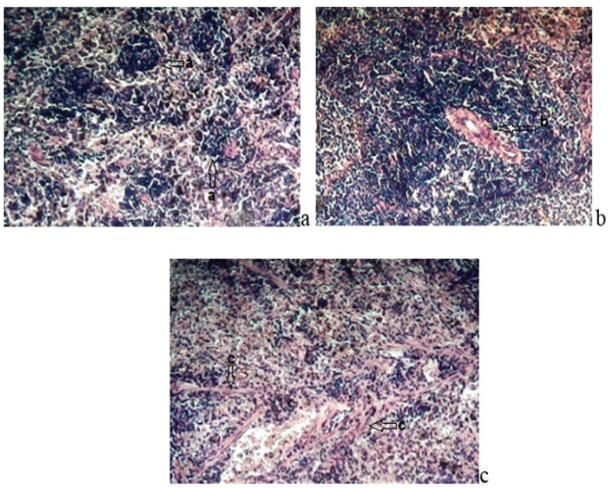

Figure 7. The spleen. Chronic toxicity of harmine hydrochloride. Dose 10 mg / kg: a) partial reduction of follicles; b) thickening of the arteriolar wall; c) proliferation of the stroma. Staining:Hematoxylin and Eosin. Mag .: 10x40

grainy cytoplasm and rounded basophilic nuclei. In the medulla, comparatively large endocrinocytes of round shape are defined, between which there are blood vessels.

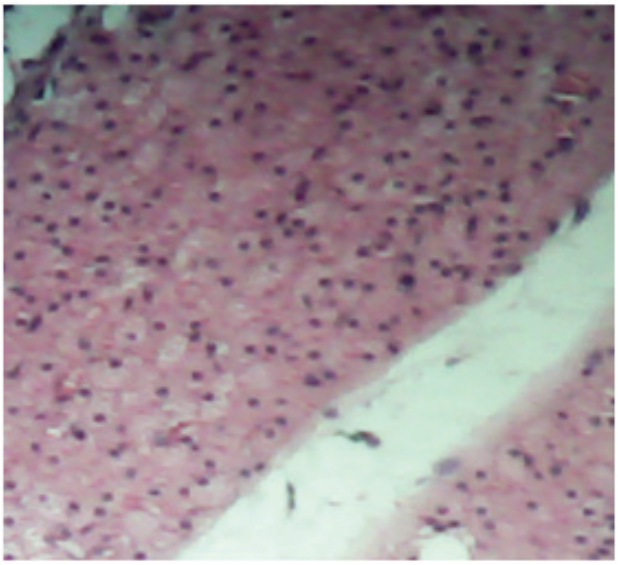

Figure 8. Adrenal gland. Control group: the zoning of the cortex is poorly expressed. Empty blood vessels and contain a small amount of blood inside. Staining:Hematoxylin and Eosin. Mag.10x40.

In the experimental group of animals receiving the harmine hydrochloride at a dose of 2.5 mg / kg, the histological pattern of the structure characteristic of the organ is preserved. Cortical endocrinocytes form epithelial cords, which are represented by light cells. (Figure 9a). In the cortex layer, relatively large endocrinocytes are determined, more rounded, lying more randomly (Figure 9b). Between their cords there are blood vessels. Vessels in most cases are either empty or contain a small amount of red blood cells in the lumen.

The microscopic structure of the adrenal gland is not changed in comparison with the control.

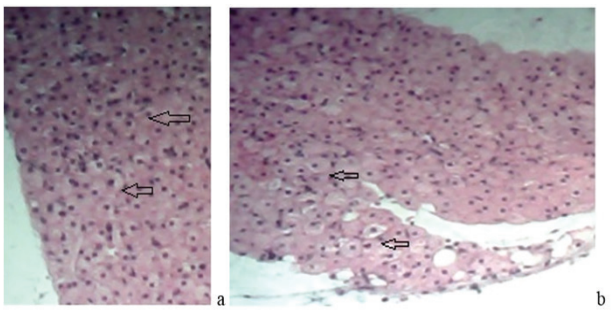

Figure 9. The adrenal gland. Chronic toxicity of harmine hydrochloride. Dose 2.5 mg / kg: a) cells of the cortex of the organ. в) large cells of adrenal medulla. Staining:Hematoxylin and Eosin. Mag.: 10x40.

The following indicators characterize morphological picture of the adrenal glands with dose increased to 5 mg/ kg of harmine hydrochloride. The histological structure of the organ is preserved. Cortical endocrinocytes form epithelial cords, which are represented by light cells (Figure. 10a, b). Cells have in most cases a gritty structure, sometimes cells with a more clarified cytoplasm are found. In such endocrinocytes, light small-vesicular structures are defined.

The dramatic plethora of blood vessels is observed.

Discussions

We have data of the toxic effect of the extract (Peganum Harmala) on the kidneys and liver. In this case, large doses of 100-150 mg / kg were used[40]. Another study also with alkaloids of Peganum Harmala in the study of acute toxicity did not reveal a pronounced toxic effect on internal organs[28].

Thus, all of the foregoing concerns the study of extracts obtained from Peganum Harmala. Studies on the toxicity of the derivative of the individual compound harmine-harmine hydrochloride have not been found in the available literature.

Morphological examination of the state of the internal organs of rats in the study of chronic toxicity of harmina hydrochloride showed that when administered continuously for 3 months, the hormin hydrochloride at doses of 2.5 mg / kg, 5 mg / kg, 9 mg / kg, 10 mg / kg had no toxic effects on the brain, in doses of 2.5 mg / kg and 5 mg / kg on the structure of the heart, spleen and adrenal glands.At doses of 9 mg / kg and 10 mg / kg, there is an initial toxic dose-dependent effect on the heart, spleen and adrenal gland.

Violation of parenchymal-vascular relationships in the adrenal glands leads to an initial dose-dependent toxic action of the drug, which is manifested in the increase in the size of cells of the cortical substance, the presence in the beam the area of the plots of disconnecktie cellular bands, alternating extended areas of blood vessels with a sharp hyperemia and narrowed their divisions.

Violation of the vascular system in the form of stasis and the formation of hypoxia as a result of this state is a stressful situation for the adrenal glands and leads to the development of characteristic changes in the adrenal glands: hyperplasia of the cortical beam zone, increased functional activity of neuroendocrinocytes of the brain substance, inhibition of morphofunctional activity of endocrinocytes of the glomerular zone and fetal cortex.

The conducted studies show that the drug “Harmine hydrochloride, capsules 0.025” does not have a toxic effect at the recommended effective therapeutic dose of 2.5 mg / kg and can later be used for clinical studies in patients to confirm the antiparkinsonian action.

It was shown that garmin hydrochloride under conditions of single and subchronic oral consumption at doses of 2.5-10 mg / kg revealed a psychotropic effect of the stimulating type; was most active in terms of indicators characterizing the impact on motor activity and behavior in the conditions of an unavoidable situation. Garmine hydrochloride 2.5 mg / kg and 5 mg / kg also eliminates catalepsy in rats caused by haloperidol, reduces oligokinesia and rigidity in the parkinsonism test caused by the neurotoxin MCPP in C57BL / 6 mice.

In a pathomorphological study, it was found that the drug “harmine hydrochloride, capsules 0.025g” with daily intake for 3 months does not have toxic effects at doses of 2.5 mg / kg, 5 mg / kg, 9 mg / kg and 10 mg / kg per brain condition, in doses of 2.5 mg / kg and 5 mg / kg per heart, spleen and adrenal structure.In doses of 9 mg / kg and 10 mg / kg, there is an initial toxic dose-dependent effect on the heart, spleen and adrenal glands, which manifests itself in developing circulatory disorders and reversible stages of cardiomyocyte dystrophy (protein, granular), signs of decreased immunity (reduction of lymphoid follicles)in peripheral endocrine system.

Conflict of interst:

The authors declare no conflict of interest.

Individual Authors Contribution:

Data gathering and idea owner of this study: Galina Zhanaidarova, Roza Seidakhmetova, Leila Arystan, Sergazy Adekenov,

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Writing and submitting manuscript: Galina Zhanaidarova,

Editing and approval of final draft:Galina Zhanaidarova,

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