Khazar Journal of Science and Technology Volume 7 №2 2023, 19-27

DOI: 10.5782/2520-6133.2023.7.2.19

The effect of Mexidol on recovery of Liver Metabolic Disorder induced by X-RAYs

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Abstract

The aim of this study is to investigate the recovery of pathological changes in the liver occurred due to radiation, through pharmacological preparations. For this purpose, so called Mexidazole which is the biologically active substance, synthesized on the basis of palladium and Mexidaole was studied for its hepatoprotective properties at the Scientific Research Center. The experiments were carried out on 20 white rats of both sexes with unknown germ line. They were divided into five groups with five of rats in each. In the first group, the number of markers that characterized the normal liver metabolism were determined. In the second group the number of liver metabolic specific markers was evaluated after the X-ray exposure and in the third group the same markers were assessed 10 days after removing from the radiation area. In the fourth and fifth group the role of the biological active compound such as meksidazol on the recovery of the liver metabolic disorder induced due to the X-RAYs exposure was studied. In a way to assess the liver metabolism the concertation of the AsAT, A1AT, glutamyl transferase, KFK, LDH and alkaline phosphatase in the blood was tested.

Key words: Liver, enzymes, X-rays, meksidozol

Introduction

New technologies that were integrated to the manufactory and to household along with its positive features also brought certainly new challenges to society. Nuclear power plant, hydroelectric plant, loss and waste of radioactive substances, use of imperfect technologies and other sources enrich the environment with ionizing rays (Dyuzhev 2017; Me James 2017). On the other hand, high diagnostic tools used in medical institutions (x-ray machine, magnetic resonance tomogram and also computer tomogram) and a number of household devices are able to emit radioactive radiation, even though they are in low doses (Raya-Povedano 2021; Borges de Souza 2021). Irradiation with ionizing rays affects the living organism as a whole and

disrupts the physiological functions of individual organs, leading to the development of pathological processes. It has been established that any harmful impact directed at the organism primarily affects the liver and disrupts its physiological function (Ehrhardt 2020; Roth 2017). By this time, the metabolites formed as a result of the destructive process in hepatocytes become a source of endogenous intoxication (Pavlov 2021; Djuzhev 2018). The resulting endogenous intoxication aggravates subclinical and chronic diseases in the body. All above emphasizes the importance of the synthesis of new drugs to eliminate the effects of ionizing radiation.

Materials and methods

The research was conducted on 25 white rats of both sexes raised in the vivarium at the Scientific Research Center of the Azerbaijan Medical University. The experimental animals were kept in the vivarium at a temperature of $20C^0$ and were fed based on the received food regimen. Depending on the task and purpose, experimental animals were divided into 5 main groups, each contains 5 rats. In the 1st group rats were examined in an intact state and the results obtained from it were considered as normal. In the 2nd group rats were irradiated with X-rays. In the 3rd group rats were examined for the duration of the pathological process 10 days after the X-ray irradiation. Rats from the 4th group were injected with the complex compound synthesized on the basis of Palladium and Mexidol (Mexidazole) into their abdominal cavity for 3 days at a dose of 0.02 mg/kg per day after irradiating them with X-rays. In the 5th group rats were treated with the complex compound synthesized on the basis of Mexidazole via injection into the abdominal cavity at a dose of 0.02 mg/kg per day for 7 days after irradiating them with X-rays.

Based on the literature review the blood parameters that reflect the liver metabolism were choosed (Ivashkin 2019; Dibirov 2017; Joshi 2018; Podoluzhnyi 2018; Garayeva 2020). Therefore, to assess the functional state of the liver, blood level of Alat aspartate transaminase (AsAT GOT Ş Ac J; Aspartate Aminotransferase UJ 2.6.1.1), Alanine Aminotransferase (AlAT GRT 1 FsJ) Alanine Aminotransferase (EJ 2.6.1.2), Glutamine transferase, Creatine phosphokinase (KFK), Lactate dehydrogenase (LDH), Alkaline phosphatase was determined. In addition, based on the literature review, markers that are associated with the liver metabolism impairment as well as the recovery of the disturbed metabolism were determined and used as diagnostic tests (Styashkina 2017). For this purpose, the concentration of creatinine, urea, total bilirubin, residual nitrogen and total protein in the blood were determined. The concentration of the specified markers in the blood was carried out in the Bio Skreen MS-2000 brand analyzer manufactured in the USA, which works in fully automatic mode using reagent kits manufactured by the Human company.

The experimental animals were subjected to X-rays using the "RUM-17" device within the following parameters.

- Voltage – 180 kv;
- Current intensity – 15 m;
- Filters – 0.5 mm Cu + 1.0 mm Al.
- Focal distance factor - 3
- Dose strength without tube - 0.86 Gr/sec

Based on the recommendation of A.U. Eminov (2014), a single dose of 4 g was used during the irradiation of experimental animals. Experimental animals were irradiated with the indicated dose for 5 days.

Result and discussion

In the first group the blood concentration of chosen parameters was as follows; the concentration of AST enzyme was 25-33 u/l, ALT enzyme was 30-40 u/l, glutamine transferase enzyme was between 28-58 u/l, LDH enzyme was 270-440 u/l, KFK was between 243-275 u/l, and the concentration of alkaline phosphatase enzyme varied between 150-300 u/l. In the second experimental group, the average concentration of AST enzyme in the blood was 27% ($P<0.05$), the ALT enzyme was 30% ($P<0.05$), the glutamine transaminase enzyme was 17%, the average concentration of the LDH enzyme increased by 31% ($P<0.05$), the KFK enzyme by 52% ($P<0.001$) and the alkaline phosphatase by 29% ($P<0.05$).

Based on the obtained results, the effect of the X-rays irradiation on the blood level of enzymes that are associated with the physiological function of the liver, was higher in compare with the normal stage. It was determined that the concentration of KFK enzyme increased due to the effect of X-rays exposure. In comparison with other parameters, the increase of concentration of γ-glutamine transferase enzyme was slightly increased.

It was observed that in the 3rd group the elevated blood concentration of liver enzymes modestly decreased (Table 1). Thus, in compare to the intact condition, the average concentration of AST enzyme increased by 22% ($P=0.05$),of ALT enzyme by 23%, of glutamyl transferase enzyme by 13%, the LDH enzyme by 27% ($P<0.05$), the KFK enzyme by 34% ($P<0.05$), and the alkaline phosphatase increased by 22%.

Based on the obtained results from 2nd and 3rd groups, X-rays have a serious negative effect on the enzyme synthesis and function of the liver. In addition, the function of the liver damaged by X-rays cannot be restored even after the transfer of the experimental animals from the radiation area.

The results obtained from the 4-th group showed that the injection of mexidazole at a dose of 0.02 mg/kg per day into the abdominal cavity of experimental animals irradiated with X-rays for a period of 3 days prevents abnormal liver enzyme synthesis at a certain extent.

Thus, in compare with the normal condition the average concertation of the AST enzyme increased by 14% (P=0.05), while the average concentration of ALT enzyme increased by 15% (P=0.05). In contrast to AST and ALT enzymes, the average concentration of glutamine transferase enzyme remained at the same level as in the intact state. Meanwhile, the average concentration of LDH enzyme decreased by 20% and the concentration of CFC decreased by 39.5% (P<0.01).

The average concentration of alkaline phosphatase enzyme was 16% (P=0.05) higher than that in the normal state. Thus, based on the results obtained from the 4th group, it can be concluded that as a result of injecting the mexidazole drug into the abdominal cavity for 3 days, the increased concentration of enzymes in the blood during the irradiation was significantly reduced (Table 1). Meanwhile, the results obtained from the 5th group showed that with the increase of the duration of intra-abdominal injection of mexidazole, the elevated concentration of enzymes in the blood approaches the normal level.

Thus, after the injection of mexidazole drug into the stomach of experimental animals that were exposed to X-rays for 7 days, the average concentration of AST enzyme in the blood reached the same level as it was in a normal state. The average concentration of ALT and LDH enzyme was only 6% and 10% higher respectively (P=0.05) in compare to the concentration of those in the blood of experimental animals included in the 1st group. However, the average concentration of KFK enzyme in the blood was significantly higher by 32% (P<0.01) than that in the normal stage.

Positive dynamics were observed in the concentration of alkaline phosphatase due to the effect of mexidazole in the blood. In all white rats included in the 5th group, the concentration of alkaline phosphatase enzyme in their blood was the same as the level in the intact state.

Thus, due to intra-abdominal injection of mexidazole for 7 days, the blood concentration of enzymes that are markers for the liver disorder decreased significantly.

The following results were obtained from the non-enzymatic marker of liver metabolism. The mean concentration of creatinine in the blood of white rats exposed to X-rays increased dramatically by 43.5% (P<0.05) compared to the intact

condition. The concentration of urea in the blood also increased dramatically by 72% ($P<0.05$) compared to the level in the intact state. The concentration of total bilirubin was 70% ($P<0.05$) higher than that in the intact state.

Due to the effect of X-rays, there was a significant difference (51%) in the concentration of residual nitrogen in the blood in compare with the intact state.

Unlike the mentioned markers, the total protein concentration in the blood decreased slightly by 7% in compare to the intact state.

Thus, based on the obtained results, the elevated blood concentration of creatinine, urea, total bilirubin, and residual nitrogen that were determined in the 2nd group proved that hepatitis develops in the liver of white rats under the influence of X-rays.

Table 1. Effect of mexidazole on elevated blood enzymes cocncetration of white rats exposed to X-rays.

№	Groups	Statistical parameters	ASTul	ALTul	QTul	LDHul	KFKul	QFul
1	I	Min	25	30	28	270	243	150
		Max	33	40	58	440	275	300
		M	29,4	35,2	43,2	368	260,4	23,4
		m	1,50	1,85	5,43	28,53	6,00	27,13
2	II	Min	28	33	33	320	315	280
		Max	50	57	60	590	463	330
		M	37,4**	45,8**	50,6*	482**	394,8***	302**
		m	3,78	4,53	5,18	45,54	24.25	8,60
3	III	Min	48	52	67	560	426	420
		Max	70	73	110	800	625	600
		M	58,6****	63,8****	88,2***	724****	528,4****	530****
		m	4,24	4,50	8,45	43,89	38,94	35,92
4	IV	Min	24	30	28	300	285	240
		Max	45	52	53	530	420	300
		M	33,6*	40,6*	43,4*	422*	363,2***	272*
		m	3,44	4,07	4,72	36,80	23,32	10,68
5	V	Min	23	27	0-	300	277	220
		Max	40	47	-	480	410	260
		M	29,6*	37,4*	-	404*	344,8***	240
		m	3,04	3,76	-	33,26	22,59	7,07

* - p = 0,05
** - p < 0,05
*** - p < 0,05

**** - p < 0,05

In the table 2 the results obtained 10 days after stopping irradiation are shown. In compare to the normal state the blood concentration of following markers were increased: creatinine by 39% (P<0.05), urea content by 68% (P<0.05), total bilirubin content by 62.5% (P<0.05), residual nitrogen content by 46% (P<0.05). In contrast the total protein concentration decreased by 2% (P=0.05).

Thus, based on the experimental results, it can be concluded that X-rays permanently disrupt the metabolism of the liver. Since, even 10 days after of transporting the white rats from the radiation area, the average concentration of non-enzymatic markers characterizing the liver metabolism in the blood were still significantly higher than the level in the steady-state.

It was shown that administration of mercidozole at a dose of 0.02 mg/kg for 3 days to white rats exposed to X-rays led to the stabilization of the level of metabolic indicators via improving the detoxification function of the liver.

It was determined that the concentration of urea in the blood taken from the experimental animals was significantly decreased by 33.5% (P<0.05), but it was still higher (14.5% (P=0.05)) than the concentration of that in the unexposed state.

The concentration of the total bilirubin, which is one of the antitoxic indicators of the liver, decreased by 26.5% (P<0.05) and its blood concentration of most of the experimental animals was within the normal range. However, despite this positive dynamics, the average concentration of bilirubin in the blood was 25% (P=0.05) higher than that in the unexposed state.

In contrast to these indicators, the concentration of residual nitrogen in the blood has sharply decreased, but was by 2% higher than that in the unexposed state.

Positive dynamics were also observed for the total protein concentration in the blood. So, its average concentration increased by 4% (P=0.05) in compare to the 3rd group. However, it did not fall to the level of the unexposed state, and remained to be by 3% (P=0.05) higher than that.

Thus, as a result of intraperitoneal injection of 0.02 mg/kg of mexidazole for 3 days in white rats irradiated with X-rays, the elevated amount of specific indicators of liver damage was significantly reduced and approached the normal range (table 2).

In order to study the therapeutic effect of mexidazole the treatment duration was extended up to 7 days after irradiating white rats in 5th group with X-rays. Since the elevated level of other indicators in the blood was close to the normal limit, the concentration of total bilirubin and total protein in the blood in the 5^{th} group was determined.

It was determined that as a result of injecting mexidazole into the abdominal cavity for 7 days, the increased concentration of total bilirubin in the blood due to the effect of X-rays was sharply reduced. Compared to 2nd group, the difference was by 34% ($p<0.01$), but the concentration of total bilirubin in the blood could not reach the level of the intact state, by being 12.5% higher.

Meanwhile, the average concentration of total protein decreased by 3% compared to the 2nd group and reached the normal level.

Thus, the results of our experiments have shown that liver metabolism is seriously disturbed by exposure to X-rays. According to the results obtained from the examinations of its markers in the blood, X-rays cause the development of hepatitis in the liver. Positive dynamics of metabolic indicators in the blood were recorded after administration of a newly synthesized biologically active substance so called mexidazole into the body. Based on the result it can be conclude that mexidazole has radioprotective properties.

Table 2. Effect of mexidazole on the concentration of non-enzymatic markers of liver metabolism in the blood of white rats exposed to X-rays.

№	Groups	Statistical parameters	Creatinine	Urea	Total bilirubin	Residual nitrogen	Total protein
1	I	Min	0,7	16	0,3	6	66
		Max	1,2	45	1,1	18	85
		M	0,92	33	0,8	12,2	75,4
		m	0,09	5,08	0,14	2,06	3,47
2	II	Min	1	32	1,1	10	59
		Max	1,7	74	1,6	27	81
		M	1,32	56,8	1,36	18,4	70,2
		m	0,12	7,60	0,09	2,80	4.71
3	III	Min	1	32	1,1	10	61
		Max	1,7	70	1,5	25	81
		M	1,28**	53,6**	1,3**	17,8**	71,4**
		m	0,12		0,07	2,46	4,27
4	IV	Min	0,7	22	0,8	8	63
		Max	1,3	54	1,2	20	82
		M	0,94	37,8	1	12,4	73
		m	0,10	5,82	0,07	2,25	3,86
5	V	Min	-	-	0,7	-	67
		Max	-	-	1,1	-	83
		M	-	-	0,9	-	75
		m	-	-	0,07	-	3,21

* - p = 0,05

** - p < 0,05

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