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EFFECT OF SYREPAR AND OXAPHENAMIDE ON LIVER FUNCTION IN EXPERIMENTAL HYPOKINESIA

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Previously (L. N. Skakun, 1976) we established that in contrast to other organs /465** and systems restricted movement for 30 days does not have a negative effect on the bile and cholate formation, synthesis and secretion of bilirubin and release of cholesterol. The cholate-cholesterol coefficient is also not diminished. Nevertheless, attention is drawn to the rapid depletion of the bile- and cholate-formation under conditions of temporary disengagement of the enterorenal circulation of the bile during hypokinesia.

The goal of this study was to reveal the peculiarities of the liver reaction to the introduction of syrepar and oxaphenamide during hypokinesia. The cholagogic preparation oxaphenamide has been well studied and is widely used in clinical practice (G. N. Karapetyan and A. M. Vecher, 1961; N. P. Skakun et al., 1970; Charlier and Vandersmissen, 1956). The action of the Hungarian preparation syrepar on bile-formation has not been studied, although it is used to treat liver diseases. According to our data (A. N. Oleynik and L. N. Skakun, 1975; L. N. Skakun, 1976) syrepar in acute liver dystrophy in rats accelerates the restoration of its structure and function. Here the intensity of bile secretion is normalized considerably earlier and more completely, as well as the ultrastructural organization of hepatocytes, the activity of hepatic enzymes, and the content of glycogen and cytoplasmic RNA.

Methods of Study

Experiments were done on 207 male rats weighing 140-170 g according to the

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**Numbers in margin indicate pagination in original foreign text.

technique of N. P. Skakun and A. N. Oleynik (1967). In all experiments the intensity of bile-formation was determined according to the rate of bile secretion during each of the 4 h experiments (in milligrams for 1 min per 100 g of animal weight), total quantity of bile obtained in each hour and in total for the time of the experiment (in milligrams per 100 g of weight). The bile was collected from all animals of the given group during each hour of the experiment. In hourly portions of bile the concentration was determined (in milligrams per 100 g of weight) of cholic acids, bilirubin and cholesterol. In addition, the cholic acids were separated by the method of ascending chromatography on paper with subsequent determination of the concentration and total quantity of tauro- and glycoconjugates.

In the control experiments the initial state of the liver was determined, as well as its reaction to the internal administration of oxaphenamide in doses of 25 and 50 mg per 100 g, or syrepar subcutaneously in 0.1 and 0.3 mg per 100 g in animals under conditions of free movement. In the remaining experiments the initial background of bile-formation was established on the 7th, 14th and 30th days of hypokinesia, and the reaction to oxaphenamide and syrepar. The model of hypokinesia was created by placing the animals in special box cages that sharply restricted their mobility. /466

Results

The experiments showed that the action of oxaphenamide affects not only the rate of secretion but also the chemical composition of the bile (table 1). Under the influence of the preparation in doses of 25 and 50 mg per 100 g of weight in the control rats the intensity of bile-emission was increased, in relation to which the total quantity of bile in the 4 h of the experiment was increased from 990$\pm$54.7 mg respectively to 1338$\pm$63.1 and 1386$\pm$110.6 mg per 100 g, or by 36 and 40%. In these experiments the choleretic reaction was the highest in the second-fourth hour. The cholagogic action of the oxaphenamide was manifest on the background of a reduction in the content of cholates and bile due to tauroconjugates, as well as decrease in the cholesterol level. In these experiments the content of bilirubin in the bile was increased, especially in the 2nd-4th hourly portion. Analysis of these shifts gives us the right to consider that oxaphenamide in albino rats significantly increases the intensity of the bile-emission, moderately inhibits

TABLE 1. EFFECT OF OXAPHENAMIDE ON FUNCTIONAL STATE OF LIVER IN ALBINO RATS UNDER CONDITIONS OF FREE MOVEMENT, AND IN HYPOKINESIA

Day of hypoki-nesia	Conditions of experiment	Quantity of bile in 4 h, mg per 100 g of weight (M±m)	Quantity of cholates in 4 h, mg per 100 g of weight			Quantity of choles-terol in 4 h	Quantity of bili-rubin in 4 h	Cholate-cho-lesterol coefficient
			total	tauro-conju-gates	glyco-conju-gates			
con-trol	Initial back-ground	990±54,7	10,465	9,166	0,934	0,185	0,096	57
	Dose of prep. mg/100g:							
	25	1338±63,1	8,206	7,269	0,872	0,096	0,114	85
	50	1386±110,6	8,027	6,826	1,104	0,139	0,119	58
7th	Init. bckgrnd	1272±40,4	27,998	20,547	6,326	0,278	0,121	101
	Dose of prep. mg/100 g							
	25	1458±105,2	28,195	25,991	2,145	0,114	9,151	247
	50	1290±96,5	21,193	16,566	4,032	0,077	0,148	275
14th	Init.bckgrnd							
	Dose of prep. mg/100 g	1422±48,7	15,146	11,344	3,053	0,286	0,092	53
	25	1326±79,3	24,580	20,746	2,624	0,143	0,149	172
	50	1434±130,3	27,080	23,758	1,809	0,166	0,179	163
30th	Init. bckgrnd.	1044±66,5	18,270	11,141	7,175	0,105	0,140	174
	Dose of prep. mg/100 g							
	25	870±67,4	16,813	13,687	3,029	0,097	0,161	173
	50	1224±101,9	25,519	21,245	3,984	0,122	0,261	209

synthesis of cholic acids and their conjugation with taurine, but somewhat stimulates the formation of glycoconjugates.

In addition, it inhibits the excretion of cholesterol with bile, which increases the release of bilirubin. Here the cholate-cholesterol coefficient of bile is increased, an important index of the functional state of the liver (Yu. A. Petrovskiy, 1947; A. N. Ardamatskaya, 1964; A. M. Nogaller, 1969).

During hypokinesia the action of oxaphenamide on bile secretion was manifest to a lower degree. Apparently, this is governed by the higher level in the initial background of the bile-formation. On the 14th day of hypokinesia when hypersecretion of the bile was the maximum, the cholagogic action of the preparation was not manifest. Moderate choleretic reaction was observed on the 7th day of hypokinesia under the influence of the preparation in a dose of 25 mg per 100 g and on the 30th day with its administration in a larger dose. /467

In these experiments the total concentration of cholates in the bile was reduced on the 7th day of hypokinesia, but rose on the 14th and 30th days. These shifts depended both on the initial content of cholates in the bile, and on the dose of the preparation. As in the control, the decrease in the total quantity of cholates released in the bile was observed on the 7th day of hypokinesia, but the increase--on the 14th and 30th days, primarily due to the tauroconjugates (see table 1).

During hypokinesia the release of cholesterol with the bile under the influence of oxaphenamide was reduced on the average 1.5-2-fold, and on the 7th day--2-3.5-fold. In this respect there was a sharp reduction in the cholate-cholesterol coefficient, especially on the 7th and 14th days. The release of bilirubin with the bile also rose: on the 7th day on the average by 22-25%, on the 14th day--by 15-86%, and on the 30th day--by 15-86% versus 20-24% in the control.

Consequently, during hypokinesia the degree of cholagogic action of oxaphenamide is reduced, the exchange is possible of its inhibiting effect for a stimulating effect on the synthesis of the cholic acids, the effect on bilirubin secretion is increased. In addition, the cholesterol-stabilizing properties of the bile are considerably improved.

The results of the other series of experiments demonstrated that syrepar in animals under conditions of free movement does not have a significant effect on the bile-forming function of the liver. The rate of bile secretion was increased only in the 2nd and 3rd hours of the experiment: on the average by 12-13% under the influence of the preparation in a dose of 0.1 ml per 100 g and by 25-30% with its triple increase. In these experiment the total concentration of cholic acids, cholesterol and bilirubin was somewhat reduced. Nevertheless, the total quantity of cholates and bilirubin released in the bile was not altered, but the content of cholesterol was reduced (on the average by 22-24%). Here the cholate-cholesterol coefficient was increased (table 2).

During hypokinesia under the influence of syrepar a moderate reduction was observed in the rate of bile secretion: on the average by 24-25% on the 7th day, by 33-36% on the 14th day and by 13-19% on the 30th day. The degree of this inhibition depended on the initial background of the bile hypersecretion. The total concentration of cholates in the bile was usually reduced in the case of high initial index, but was increased with a comparatively low background. These

shifts occurred due to the conjugates with taurine and glycine. In addition, the content of cholesterol in the bile was reduced, with the exception of the 30th day of hypokinesia. As a consequence of this the cholate-cholesterol coefficient was increased: on the 7th day on the average 1.6-1.7-fold, on the 14th day--2.3-2.5-fold and on the 30th day--1.1-1.6-fold. In addition to this the syrepar stimulated the secretion of the bilirubin: correspondingly to the periods of observation by 19 - 34, 23-96 and 29%.

Thus, one can consider that syrepar in doses of 0.1 and 0.3 ml per 100 g of weight does not have a negative effect on the functional state of the liver under conditions of the prolonged hypokinesia.

Bile formation is a very labile function of the liver. It is altered under the influence of numerous xenobiotics and endogenous factors (Yu. A. Petrovskiy, 1947; A. S. Saratikov, 1962; N. P. Skakun, 1964). The sensitivity of the liver to cholagogic preparations is sharply disrupted during affection of the liver with CCl_4, bacterial toxins, during the effect on the organism of ionizing radiation /468
and others (L. L. Fedorovskiy, 1961; I. Kh. Pasechnik, 1969; S. M. Drogovoz, 1972, and others).

Our experiments demonstrate that the liver reaction to the introduction of oxaphenamide and syrepar is altered also with sharply restricted mobility of animals. In the mechanism of these changes, apparently, not only the initial background of bile-formation has great value, but also the presence of functional reserves of the liver, changes in the system of regulation, and others.

Conclusions

1. In albino rats during their free maintenance oxaphenamide stimulates secretion of bile, increases release of bilirubin, but moderately inhibits the synthesis of cholic acids and their conjugation with taurine, and the excretion of cholesterol. Under these conditions the action of syrepar on the given processes is manifest to a lower measure.

2. During hypokinesia the degree of cholagogic action of oxaphenamide is reduced, the exchange is possible of its inhibiting effect for the stimulating effect on the synthesis of cholic acids, and the effect on the bilirubin secretion rises.

TABLE 2. EFFECT OF SYREPAR ON FUNCTIONAL STATE OF LIVER OF ALBINO RATS NORMALLY AND IN HYPOKINESIA

Day of hypokinesia	Conditions of experiment	Quantity of bile in 4 h mg/100 g (M±m)	Quantity of cholic acids in 4 h, mg/100 g			Quantity of cholesterol in 4 h	Quantity of bilirubin in 4 h	Cholate-cholesterol coefficient
			total	tauro-conjugates	glyco-conjugates			
Control	Initial backgrnd	990±54,7	10,465	9,166	0,934	0,185	0,096	57
	Dose of prepar. ml/100 g							
	0.1	996±68,0	9,355	7,380	1,548	0,140	0,073	66
	0.3	1116±69,1	9,893	8,376	1,306	0,144	0,111	69
7th	Init. bckgrnd	1272±40,4	27,998	20,547	6,326	0,278	0,121	101
	Dose of prep. ml/100 g							
	0.1	968±46,7	15,036	13,812	0,991	0,088	0,144	171
	0.3	952±56,0	15,033	12,968	1,653	0,090	0,162	167
14th	Init. bckgrnd	1422±48,7	15,146	11,344	3,053	0,286	0,092	53
	Dose of prep. ml/100 g							
	0.1	910±67,7	16,863	13,363	2,694	0,129	0,180	131
	0.3	948±71,6	18,920			0,156	0,113	121
30th	Init. bckgrnd	1044±66,5	18,270	11,141	7,175	0,105	0,140	174
	Dose of prep. ml/100 g							
	0.1	906±83,9	19,289	14,771	4,361	0,070	0,124	276
	0.3	816±89,5	20,215	17,442	2,388	0,107	0,180	189

3. Under conditions of hypokinesia syrepar moderately inhibits the secretion of bile, but stimulates the release of bilirubin. Its effect on the synthesis of cholic acids and excretion of bilirubin in different periods of hypokinesia is manifest to an unequal measure.

4. In hypokinesia, as in the control, oxaphenamide and syrepar increase the cholate-cholesterol coefficient of bile.

References

Ardamatskaya, A. N. Opredeleniye kholatov i kholato-kholesterinnovogo koeffitsiyenta v diagnostike funktsii pechenii pri eye zabolevaniyakh i kholetsistite v svete zadach khirurgicheskogo lecheniya ["Determination of Cholates and the Cholate-Cholesterol Coefficient in Diagnosing the Function of the Liver in Its Diseases and Cholecystitis in Light of the Tasks of Surgical Treatment"] Author's abstract of candidate dissertation, Leningrad, 1964.

Drogovoz, S. M. Sravnitel'noye izucheniye i osobennosti deystviya zhelchegonnykh preparatov na zhelcheobrazovatel'nuyu funktsiyu pecheni v norme i patologii ["Comparative Study and Peculiarities of the Effect of Cholagogic Preparations on the Bile-Forming Function of the Liver in the Normal and Pathological"] Author's abstract of doctoral dissertation, Khar'kov, 1972.

Karapetyan, G. N.; and Vecher, A. M. Klin. med. No. 6 (1961), p.103.

Nogaller, A. M. Zabolevaniya zhelchnogo puzyrya i zhelchnykh putey ["Diseases of the Gallbladder and Bile Ducts"], Moscow, 1969.

Oleynik, A. N.; and Skakun, L. N. Vengersk. farmakoter., No. 2 (1975), p. 79-81.

Pasechnik, I. Kh. Materialy po farmakodinamike i effektivnost nekotorykh lekarstvennykh sredstv pri ostrom gepatite ["Materials on Pharmacodynamics and Effectiveness of Certain Medicines in Acute Hepatitis"], Author's abstract of doctoral dissertation, Khar'kov, 1969.

Petrovskiy, Yu. A. Vneshnyaya sekretsiya pecheni (Fiziologiya, patologiya i farmakologiya zhelche-otdeleniya) ["External Secretion of the Liver (Physiology, Pathology and Pharmacology of Bile-Secretion"], L'vov, 1947.

Saratikov, A. S. Zhelcheobrazovaniye i zhelchegonnye sredstva ["Bile-Formation and Cholagogic Resources"], Tomsk, 1962.

Skakun, L. N. Farmakol. i toksikol., No. 3 (1976), p. 333-335.

Skakun, N. P. Zovnyshn'osektretorna funktsiya pechinki i zhovchorinni zasobi [in Ukrainian], Kiev, 1964.

Skakun, N. P.: Drogovoz, S. M.; and Bezkorovaynaya, N. M. Farmakol. i toksikol. No. 4 (1970), p. 446-448.

Skakun, N. P.; and Oleynik. A. N. Farmakol. i toksikol., No. 3 (1967), p. 334-337.

Fedorovskiy, L. L. Med. radiol., No. 1 (1961), p. 83-84.

Charlier, R.; and Vandersmissen, L. Arch. int. Pharmacodyn. Vol. 107 (1956), p. 461-464.

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