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THE EFFECT OF PLASMAPHERESIS ON THE COURSE OF EXPERIMENTAL TUBERCULOSIS AND THE TOLERANCE OF CHEMOTHERAPY BY PATIENTS WITH RENAL TUBERCULOSIS

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Plasmapheresis (PA) has not yet found a widespread application in phthisiology, despite the obvious usefulness in connection with the bacterial toxicosis that is characteristic for this infection, and the excessive medicinal load of tuberculosis patients.

The goal of this work consisted of experimentally substantiating the use of PA for tuberculosis and studying its effects on the manifestation of side effects of anti-tuberculosis medicine.

Under the conditions of long-term experiments on rabbits, it's not possible to apply the PA procedures that are technically analogous with those that are conducted on people. We developed an original model of using PA on this type of animal.

Under the conditions of vivisection, we drew animal donor blood from the common carotid artery into a container (Gemakon-500-300). We were able to draw about 200 ml of blood from 3-4 rabbits, which we used to separate erythrocyte mass by centrifugation. We drew up to 30 ml of blood from the animal recipients at first from the auricular vein. Then into the vein of the other ear, we introduced an adequate amount of physiological solution and erythrocyte mass.

During the first series of experiments conducted on 96 rabbits, we studied the effects of PA on the course of experimental tuberculosis. We inserted suspense culture of M. Bovis-8, in the amount of 0.1 mg, into the marginal vein of the ear. The animals were divided into 3 groups: the 1st was the contamination control group; the 2nd group of rabbits received 10 mg/kg of Isoniazid and Rifampicin daily; 7 courses of PA treatment were given to each of the animals in the 3rd group at the same time as the etiotropic treatment. The effectiveness of the therapy given was assessed according to the indexes of damage and coefficients of the lungs' mass. Rabbits were being killed via intravenous injection of 5 ml of 10% Hexobarbital solution.

In Table 1, it is evident that administering PA, in addition to antibacterial therapy, allowed a more benign tuberculosis process. Compared to the animals that only received etiotropic treatment, the index of lung damage was reduced from 2.1±0.2 to 1.0±0.14 (p<0.001).

The reactiveness of the animals was judged according to the lysosomal-cationic test, which is based on the cumulative cytochemical identification of granulocytes of enzymatic and non-enzymatic cationic proteins. These proteins have a wide spectrum of bactericidal effects, properties of mediators of inflammation, properties of permeability factors, and properties of phagocyte stimulation.

Table 1

The Effectiveness of Treating Experimental Tuberculosis in Rabbits

Group No.	Experiment conditions	Index of lung damage (relative units)	Coefficient of lung mass (relative units)
1	Contamination control (*n*=11)	3.9±0.07	3.14±0.25
2	Isoniazid 10 mg/kg + Rifampicin 10 mg/kg (*n*=16) p_{1-2}	2.1±0.2 <0.001	1.09±0.15 <0.001
3	Isoniazid + Rifampicin + PA (*n*=16) p_{2-3}	1.0±0.14 <0.001	0.7±0.17 >0.05

Table 2

Changes in the Cytochemical Coefficient and Content of Medium Peptide Molecules in Rabbit Blood

Grp. No.	Experiment conditions	Cytochemical coefficient (relative units)			Medium molecules (relative units)		
		Period of damage (week)					
		4	8	12	4	8	12
1	Contamination control (*n*=6)	1.22±0.02	-	-	0.309±0.03	-	-
2	Isoniazid 10 mg/kg + Rifampicin 10 mg/kg (*n*=7)	1.21±0.012 p_{1-2}>0.05	1.41±0.02	1.53±0.04	0.253±0.0065 p_{1-2}>0.05	0.237±0.009	0.217±0.003
	Isoniazid + Rifampicin + 1 PA treatment (*n*=7)	0.138±0.018 p_{1-3}<0.001 p_{2-3}<0.001	-	-	0.265±0.015 p_{1-3}>0.05 p_{2-3}>0.05	-	-
3	3 PA treatments (*n*=7)	-	1.41±0.02 p_{2-3}<0.05	-	-	0.166±0.05 p_{2-3}<0.001	-
	7 PA treatments (*n*=7)	-	-	1.5±0.016 p_{2-3}>0.05	-	-	0.187±0.007 p_{2-3}<0.001

Research from recent years has shown that there is a correlation between reinforcing the indicated test and favorable clinical x-ray dynamic, as well as the condition of the T- systems of immunity in patients with tuberculosis of the lungs.

As it is evident in Table 2, in animals that were given PA at the same time as the etiotropic treatment, the cytochemical index differs the most from the comparison group after 3 PA treatments. In Table 2, the meaning of the contents of medium peptide molecules in peripheral blood is also represented, which are evidence of the severity of destructive changes in

the body and toxicosis syndrome. The most significant change in the level of medium peptide molecules was also noted after 3 PA treatments.

In the next series of experiments that were carried out on healthy rabbits, the effect of PA on hepatotoxicity symptoms of anti-tuberculosis therapy was studied. Damage to the liver required a long (12 week) course of treatment using Isoniazid (20 mg/kg) and Rifampicin (10 mg/kg). Animals in the main group received 4 treatments of PA (1 procedure per animal every 3 weeks). The excretory function of the liver was assessed 2-3 days after the PA treatment. The half-life period ($T_{1/2}$) was registered for Bromsulphalein with the following calculations of relative parenchymal clearance (RC) and hepatic blood flow (PK). It is evident in Table 3 that starting with week 6 of the experiment, a significant increase in Bromsulphalein $T_{1/2}$ and decrease in hepatic blood flow were identified. The most extreme changes were observed during the 12^{th} week of the experiment. Using PA allowed the liver to be preserved from damage caused by the anti-tuberculosis medication. Bromsulphalein $T_{1/2}$ decreased by a factor of 1.8, and relative parenchymal clearance increased (from 20.40 to 34.97%; $p<0.01$) and hepatic blood flow increased (from 12.04 to 20.63 ml/min; $p<0.01$).

The results of the biochemical research were histologically proven. 90% of the animals in the control group developed course-grained hydropic degeneration. In half of the cases, completing 4 treatments of PA led to a substantial reduction of these symptoms; and in the other half of cases, it eliminated them completely.

Table 3

Indicators of Functional Status of the Liver in Rabbits

Grp. No.	Experiment conditions	Background			Experiment period (week)		
					6		
		$T_{1/2, min.}$	Relative parenchymal clearance (RC), %	Hepatic blood flow (PK), ml/min.	$T_{1/2, min.}$	RC, %	PK, ml/min.
1	Rifampicin 10 mg/kg, internal + Isoniazid 20 mg/kg, internal (n=6)	1.88 (1.6-1.8)	37.04 (33.0-43.31)	21.86 (19.47-25.55)	2.63 (2.2-3.3)	26.84 (21.0-31.5)	15.83 (12.39-18.59)
2	Rifampicin + Isoniazid + PA (n=8) p_{1-2}	1.83 (1.7-2.0)	38.09 (34.65-40.76)	22.38 (20.44-24.05)	1.93 (1.8-2.1)	35.94 (33.0-38.5)	26.26 (19.47-37.46)

Table 3 continued

Experiment period (week)							
Grp. No.	Experiment conditions	9			12		
		$T_{1/2, min.}$	RC, %	PK, ml/min.	$T_{1/2, min.}$	RC, %	PK, ml/min.
1	Rifampicin 10 mg/kg, internal + Isoniazid 20 mg/kg, internal (*n*=6)	3.68 (3.0-4.95)	20.40 (11.75-23.90)	11.43 (8.26-13.63)	3.60 (2.9-5.9)	20.40 (11.75-23.9)	12.04 (6.93-14.1)
2	Rifampicin + Isoniazid + PA (*n*=8)	2.73 (1.85-3.0)	26.87 (20.38-37.46)	18.42 (12.03-20.97)	2.04 (1.6-2.6)	34.97 (26.65-43.31)	20.63 (15.73-25.55)
	p_{1-2}	<0.05		<0.01	<0.01	<0.01	<0.01

Because the percentage of side effects to the anti-tuberculosis medicine increases when there is kidney damage, we used PA during the experiment in 90 patients with various forms of renal tuberculosis and poor tolerance to chemo-therapeutic agents. 10% of patients experienced skin itching when taking the specified medications; 25% of patients experienced toxicoderma; 20% experienced allergic reactions such as hives, and 15% experienced reactions such as Quincke's edema. In 20% of patients, a combination of side effects was noted (Quincke's edema and toxicoderma, or hives). Only eosinophilia was observed in the remaining 10% of patients. Additionally, general toxicosis symptoms were noted in all of the patients: weakness, sweating, headache, and nausea.

Centrifugation of the blood was completed using the refrigerated centrifuge RS-6P at the speed of 2,000 RPM for 10 minutes.

The patients received 6-8 PA treatments along with an exfusion of 500 ml of blood during one operation and replacement of plasma with an adequate amount of physiological solution. After 3-4 PA treatments, the signs of general toxicosis normally disappeared from the patients and indicators normalized, such as the number of eosinophils and activity of alanine transaminase. After this, etiotropic therapy was resumed. Adverse reactions were generally not observed. There was a reoccurrence of intolerance in only 10% of the patients and this was eliminated by repeating the PA treatment, which allowed for the full course of chemotherapy to be completed.

Conclusions

1. An experimental model was developed for treatment using plasmapheresis (PA) in long-term studies on rabbits.
2. Using PA in experimental tuberculosis increases the effectiveness of etiotropic therapy and reduces the severity of adverse effects on the liver.
3. The suggested method for eliminating the adverse reactions of tuberculosis therapy in patients with renal tuberculosis is simple from a technical standpoint, and it is highly effective and economical.