Effect of Dextran Infusions on Destructive Processes in Liver Parenchyma in Prolonged Compression Syndrome

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Light microscopy and morphometry demonstrated that dextran infusions in prolonged compression syndrome increase the destruction of liver parenchyma, delay this process, and suppress the inflammatory reaction in the organ.

Key Words: *prolonged compression syndrome; liver parenchyma; dextran; destruction; inflammation*

Infusions of high-molecular plasma substitutes is the basic therapy for patients with prolonged compression syndrome (PCS) [3,10]. The lysosomotropism of these agents, their capacity to labilize lysosomal membrane [2,6,7] and accelerate the release of myoglobin degradation products into the blood during decompression of compressed tissues increase the concentration of these substances in the liver due to its cells' activity in endocytosis and the risk of liver injury in patients with PCS. We studied the development of destructive processes in liver parenchyma in "natural" PCS and during its treatment with dextran, a biodegraded lysosomotropic agent.

MATERIALS AND METHODS

Experiments were carried out on 75 male Wistar rats weighing 180-200 g fed standard laboratory ration. Medium-severe PCS was induced by 4-h clamping a 4 cm^2 area on the left hip. Group 1 consisted of rats with intact PCS and in group 2, the animals were intraperitoneally infused 10% dextran solution with molecular weight 30-40 kD in normal saline (10 ml/kg) three times every other day, according to the recommendations on first aid to victims with PCS. Group 3 consisted of intact animals.

Liver specimens were obtained 1, 3, and 7 days after decompression of the limb, which corresponded to the early, intermediate, and beginning of the late period of PCS development [5], fixed in 10% neutral Formalin, dehydrated in ascending alcohols, and embedded in paraffin. Sections (5-6 μm) were stained with Mayor's hematoxylin and eosin. Twenty-five sections were examined for each subgroup of rats (for each period). Stereometric analysis of tissue at magnification 100 and 1000 was carried out in 4 visual fields using a square test system. The size of inflammatory infiltrations was determined by the square test system at magnification 1000 and expressed in percent of the area taken for 100%. The volume of dystrophically and necrobiotically changed hepatocytes was estimated similarly. Macrophages, monocytes, and lymphocytes in inflammatory infiltrations were counted and their number expressed in percent of the total number of cell elements in infiltration. The differences were considered significant at $p<0.05$ according to Student's t test.

RESULTS

Examination of liver specimens showed hemocirculation congestion and predominance of vacuolar and

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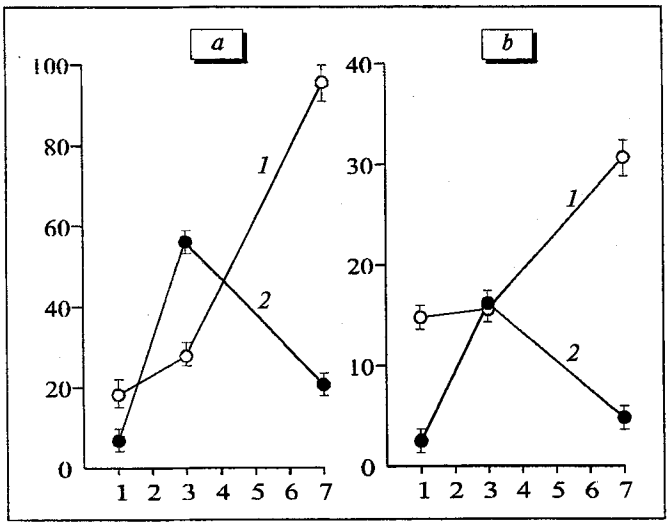

Fig. 1. Content of macrophages (*a*) and monocytes (*b*) in inflammatory infiltration in zones of liver parenchyma destruction. Abscissa: time from the beginning of hip limb compression, days. Ordinate: product of infiltration area and number of macrophages. *1*) no treatment; *2*) after dextran treatment.

balloon dystrophy with necrotic changes in hepatocytes. Destructive changes in liver parenchyma were extremely extensive as early as on day 1 of the limb decompression (Table 1). In rats treated with dextran, the total volume of destructive changes was 25% larger and of necrotic changes 47% lower. On day 3 of decompression, there was an obvious tendency to intensification of destructive processes in the liver of treated animals. On day 7 the total volume of necrotic hepatocytes in intact animals was less than 0.25% of the organ tissue, and the zone of dystrophic changes decreased more than 4-fold (Table 1). In dextran-treated rats, the volume of necrosis sharply increased and was many times greater and the zone of dystrophical hepatocytes was 4 times larger than in intact animals (Table 1). These data indicate that not all dystrophic changes in a cell are transformed into necrobiosis. Therefore, intracellular reparative regeneration is possible in parenchymatous (vacuolar) dystrophies. This is proven by a notable decrease in the volume of dystrophic hepatocytes in the liver without increase in the number of necrotic cells (and even with a drop in their number) (Table 1). The number of necrotically changed hepatocytes more rapidly increased in dextran-treated rats in parallel with gradual decrease in the volume of dystrophic hepatocytes. This means that the pool of cells weight with dystrophic changes was constantly replenished, rapidly transforming into a pool of necrobiotically changed cells. Relationship of these processes to dextran infusions is obvious. The above-described effects of dextran may be caused by increased rate of clearance of myoglobin degradation products from the limb tissues and directly of their low-molecular-weight fractions, and probably by fractions adsorbed on dextran, in hepatocytes. This can cause a more intense direct toxic damage to hepatocytes and an effect mediated by the lysosomotropic properties of dextran, due to increased of hepatocyte lysosomal membrane labilization [1,2,4] and, hence, of destructive effects of neurotoxins.

The productive phase of inflammation was studied. The volume of inflammatory infiltration in zones of hepatocyte necrobiosis and number of macrophages and monocytes in these zones were assessed. In intact animals, the number of macrophages in infiltrates gradually increased and reached the maximum by day 7 of decompression. By this term their level in the limb was 5.1 times higher than on day 1, when necrobiosis was the minimal (Table 1, Fig. 1, *a*). The count of monocytes was also increased (Fig. 1, *b*). By contrast, in dextran-treated animals the number of macrophages and monocytes in infiltrates on day 1 was lower than in intact ones (Fig. 1). On day 3, the content of macrophages in dextran-treated animals was 3.5 times higher than in intact ones. The count of monocytes increased only 2.3 times in comparison with the previous period in in-

Table 1. Rat Liver in PCS and Its Dextran Treatment (*M±m*)

Parameters (volume compactness, % of section area)	Day after decompression					
	1		3		7	
	no treatment	dextran	no treatment	dextran	no treatment	dextran
Dystrophy (vacuolar)	56.7±1.94	78.4±1.0*	56.4±2.05	65.0±2.18*+	13.4±1.65*+	55.2±1.36*
Necrosis	11.8±0.63	6.84±0.87*	8.5±0.61*+	12.2±0.89*	0.24±0.11*+	31.9±1.21*+
Sum of destructive changes (dystrophy, necrosis)	68.4±2.57	85.2±1.39*	64.9±2.66	77.2±3.07*	13.6±1.76	87.5±2.55*
Inflammatory infiltration	0.4±0.14	0.1±0.08*	0.5±0.19	0.8±0.21+	1.5±0.37*+	0.3±0.13*+

Note. $p<0.05$: *vs.* intact animals, +*vs.* previous period of observation.

tact animals (Fig. 1), though both values differed significantly from that in dextran-treated animals on day 1 of decompression. Administration of rheopolygluquin (dextran) involves an increase in the content of macrophages in the liver of animals with iron-deficiency anemia. Rheopolygluquin, possessing lysosomotropic properties, was believed to create a high chemotactic gradient while accumulating in the vacuolar system of parenchymatous and sinusoidal cells of the liver [1]. This can cause macrophage migration from other organs to the liver, the largest compartment of mononuclear phagocytes. The ability of resident liver macrophages to migration has been discussed [7,8]. A lower content of macrophages and monocytes in the liver of dextran-treated rats on day 1 of decompression can be caused by a more severe (than in intact animals) shock because of higher blood concentration of neurotoxins. So-called "bone marrow locking" effect could have taken place [11,12] because of high blood concentration of glucocorticoid hormones. By day 3, chemotactic effect of dextran as if "overlapped" the glucocorticoid effect, while in intact rats the counts of macrophages and of monocytes changed less in comparison with decompression day 1 (Fig. 1). Between the third and seventh days, the stress phenomena reduced in intact animals, and the zone of hepatocyte destruction significantly decreased. Presumably, glucocorticoid concentrations decreased both due to their lower production and to recovery of the metabolic potential of hepatocyte population. During this period, the content of macrophages in infiltrations increased 3.4 times and of monocytes 2.3 times (Fig. 1, *a*) in comparison with decompression day 3 and still more so, on day 1. In dextran-treated animals, the number of macrophages dropped again and was no higher than initially (on day 1 of decompression), which might be due to almost 4 times decreased count of monocytes. Half-life for dextran of this molecular weight is 3 days, and by day 7, only 15% of its initial amount is left [9]. Therefore, by day 7 chemotactic gradient of dextran dropped, causing macrophage and monocyte migration from the liver. During this period, the bone marrow "locking" effect presumably once more caused changes in mononuclear content of infiltrates, because even in normal production of glucocorticoid hormones their blood concentration increased, since 87% hepatocytes could not adequately participate in their metabolism because of injury (Table 1).

These data indicate that dextran (rheopolygluquin), although possessing many positive properties, should be used with great care because of a probability of delayed necroses and direct and indirect modulation of the mononuclear phagocyte functions. This is true for other high-molecular-weight plasma substitutes and high-molecular-weight iron-containing agents with potent lysosomotropic effects.

REFERENCES

1. T. A. Ageeva, V. A. Shkurupii, and M. I. Loseva, *Byull. Eksp. Biol. Med.*, **116**, No. 12, 642-645 (1993).
2. T. A. Korolenko, in: *Lysosomotropic Agents* [in Russian], Novosibirsk (1984), pp. 101-114.
3. E. A. Nechaev, A. K. Revskoi, and G. G. Savitskii, *Prolonged Compression Syndrome* [in Russian], Moscow (1993).
4. T. I. Pospelova, T. A. Ageeva, M. I. Loseva, *et al.*, *Gematol. Transfuziol.*, **37**, No. 9-10, 25-28 (1992).
5. S. I. Stomatin, *Zdravookhraneniye* (Kishinev), No. 4, 60-62 (1978).
6. V. A. Shkurupii, *Byull. Eksp. Biol. Med.*, **102**, No. 9, 362-365 (1986).
7. V. A. Shkurupii and V. N. Gavrilin, *Tsitologiya*, No. 5, 537-542 (1987).
8. V. A. Shkurupii and I. N. Indikova, *Ibid.*, **20**, No. 3, 269-274 (1978).
9. V. A. Shkurupii, T. G. Chernova, and Yu. N. Kurunov, *Probl. Tub.*, No. 1, 38-40 (1993).
10. O. S. Better, *Am. J. Med. Sci.*, **25**, 69-72 (1989).
11. R. T. Nozava and T. Yokota, *J. Cell. Physiol.*, **100**, No. 2, 351-364 (1979).
12. J. Thompson and R. van Furth, in: *Mononucear Phagocytes*, Oxford (1970), pp. 225-264.