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The Leakage of Plasma Albumin Across Small Vessel Walls during Bleomycin Treatment

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Abstract—*To characterize the toxic side-effects of bleomycin physiologically, pulmonary function, transcapillary escape rate of albumin, plasma volume and intravascular mass of albumin were determined prior to and during combination chemotherapy including cisplatin, vinblastine and bleomycin in 11 patients with stages I and II embryonal carcinoma of the testis. Though the patients received the maximum tolerable dose of bleomycin (270 mg/m²), no change of the lung function was observed. Pretherapeutic subnormal values of the intravascular mass of albumin were normalized during treatment. The transcapillary escape rate was unaffected. It is concluded that the overall leakiness of the microvasculature does not change during bleomycin treatment. It is hypothesized that the function abnormalities of the vessels known to be induced by bleomycin are mainly confined to the lungs and only to a moderate degree to the skin, rather than being general in character.*

INTRODUCTION

BLEOMYCIN, an antineoplastic drug derived from *Streptomyces verticullus*, plays a major role in the treatment of patients with testicular cancer [1], malignant lymphoma [2, 3] and carcinoma of the head and neck [4].

Its dose-limiting effect is a potentially fatal interstitial pneumonitis reported to occur in 5–20% of all patients receiving bleomycin at a cumulated dose of more than 350 mg [5]. This effect is thought to reflect the fact that bleomycin persists in lung tissue much longer than in any other tissue except skin. The plasma half-life of bleomycin is 90 min and apart from the lung and the skin bleomycin cannot be demonstrated to remain in the body 24 hr after administration [6]. The skin is affected in 50% of the treated patients and the changes observed are erythema and desquamation, primarily located in the pressure areas [7].

There is evidence to support that the primary lesions induced in lung and skin tissue may be due to vascular changes. Thus Adamson and Bowden [8] have shown that in mice receiving bleomycin intraperitoneally twice weekly at a sublethal dose the first sign of toxicity to the lung was in the intima of the pulmonary arteries and veins, where swelling of the endothelial cells and separation from the underlying basement membrane were seen. Crooke and Bradner [9], reviewing available data, concluded that bleomycin increased cutaneous and visceral capillary permeability to a degree comparable to that induced by the same amount (10 mg/kg) of histamine.

We have therefore studied the leakiness of the microvasculature for plasma albumin in patients during bleomycin treatment. Our aim was to see if the normal leakiness of the intravascular albumin mass across the vascular wall to the interstitial fluid would increase during the treatment as a consequence of bleomycin toxicity.

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MATERIALS AND METHODS

Patients

Eleven patients (age 18–29) with embryonal carcinoma of the testis were included in the trial. None of the patients had a history, or clinical or radiological evidence, of cardiac failure, proteinuria, glucosuria, hypertension or extensive skin disease. None of the patients had previously received chemotherapy or irradiation.

Regimen

The patients received three drugs: *cis*-platinum, vinblastine and bleomycin. *cis*-Platinum was given in a dosage of 20 mg/m² as a 15 min intravenous infusion for 5 consecutive days (days 1–5) every 3 weeks for 6 courses. Vinblastine was given in a dosage of 6 mg/m² intravenously on

days 1 and 2 of each of the 6 *cis*-platinum courses. Bleomycin was given up to the level of toxicity [10] as an intravenous bolus at a dosage of 15 mg/m^2 on days 2, 9 and 16 of each of the 6 *cis*-platinum courses, to give a total dose of 270 mg/m^2.

Kidney function

Before the treatment and after the third and the sixth of the 6 *cis*-platinum courses [^{51}Cr]-EDTA clearance was determined according to the method of Bröchner-Mortensen [11]. Simultaneouly the urine was examined for the occurrence of albumin by means of Hema-Combistix®.

Pulmonary function

Plain chest roentgenograms and spirometry, including a single-breath helium dilution manoeuvre, was performed by means of a Hewlett-Packard computing pulmonary system before treatment and after each of the 6 *cis*-platinum courses. Total lung capacity, vital capacity, residual volume, forced vital capacity and forced expiratory volume in 1 sec were measured. Carbon monoxide diffusion capacity, DL_{CO}, was determined by a modified method of Ogilvie *et al.* [12]. All DL_{CO} values were normalized with respect to blood hemoglobin concentration by the method of Dinakara *et al.* [13].

Vascular leakiness

The investigative procedure and the theoretical basis for the calculation of the transcapillary escape rate of albumin (TER_{alb}) from the initial disappearance rate of labeled plasma albumin have been described in detail previously [14]. The patients were studied in the morning after at least 12 hr of fasting and 30 min of rest in the supine position. Human serum albumin labeled electrolytically with ^{131}I (Code Miak, Institute for Atomic Energy, Kjeller, Norway) was used. This tracer preparation contains less than 1% free radioactive iodide and has, by metabolic studies, been demonstrated to behave like endogenous albumin [15]. About 15 μCi of the tracer was used. The tracer was injected into one arm vein and nine venous blood samples were drawn from the other arm (10, 15, 20, 30, 35, 50, 55 and 60 min after injection). The radioactivity in each of the 3-ml samples was related to the total protein concentration of the sample determined by refractometry to cancel out the influence of accidental plasma volume fluctuations.

TER_{alb} was calculated as the rate constant of the practically monoexponential decrease in specific plasma activity over the first 60 min after injection and calculated by the least squares method; plasma volume (PV) was determined by extrapolation to time zero of the plasma disappearance curve of tracer albumin and the injected volume of tracer measured by weighing. Plasma albumin concentration was measured according to Laurell [16]; intravascular mass of albumin (IVM_{alb}) is equal to the plasma volume × plasma albumin concentration. TER_{alb}, PV and IVM_{alb} were all determined at regular intervals of 3 weeks over a period of 18 weeks of treatment. All data obtained concerning PV, IVM_{alb} and TER_{alb} were compared with those previously obtained in 13 normal adults by exactly the same technique [17].

RESULTS

Clinical course

During the 18 weeks of antineoplastic treatment all the patients developed skin changes (WHO grade 3). All the patients achieved complete or partial remission during the treatment and 24 months after the initiation of the treatment only one patient had relapsed.

Kidney studies

During the course of treatment [^{51}Cr]-EDTA clearance showed a statistically significant decrease from an initial 150 ml per 1.73 m^2 to 87 ml/min per 1.73 m^2 ($P < 0.02$), but none of the patients developed proteinuria.

Pulmonary studies

Neither before nor during treatment did radiological signs of interstitial pneumonitis develop. The lung function parameters, including the DL_{CO}, remained normal throughout the investigation.

Vascular leakiness studies

In Table 1 it is shown that all the patients had normal plasma volume before the treatment and that no significant trend occurred during the course of treatment. As seen from Table 1, the IVM_{alb} increased from initial statistically significant subnormal values to completely normal values after treatment. This was reflected by a moderate, but insignificant, increase in albumin concentration. Thus the initial albumin concentration of the patients was significantly lower than that of the previously mentioned 13 normal adults, whereas the difference between the treated patients and the normals, with respect to albumin concentration, was statistically insignificant.

TER_{alb} for the group of patients was not significantly different from the control values either before or after treatment (Fig. 1). However, there was a great intervariation between the

Table 1. Plasma volume (PV), intravascular mass of albumin (IVM_{alb}), plasma albumin concentration and the transcapillary escape rate (TER_{alb}) of the 11 patients in the study and the 13 controls

	Plasma volume (l/m^2)		IVM_{alb} (g/m^2)		Plasma albumin concentration (g/l)		TER_{alb}	
	Before	After	Before	After	Before	After	Before	After
$\bar{x}$	1.72	1.86	47.87	69.92	32.02	34.30	7.18	6.03
S.D.	0.54	0.54	20.3	21.12	3.81	4.35	2.03	2.32
Controls	1.67		63.8		38.2		5.6	
S.D.	0.16		22.0		3.2		2.1	

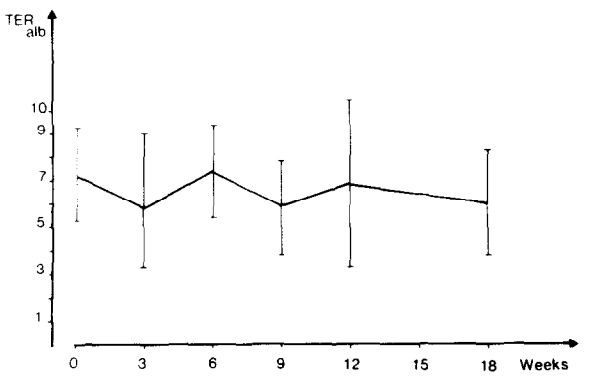

Fig. 1. TER_{alb} (± S.D.) in eleven patients during bleomycin treatment.

patients. TER ranged from 4.5 to 9.7% per hour before treatment was initiated, and this variation was also present by the end of the study.

DISCUSSION

The TER of macromolecules such as albumin is a reliable parameter to monitor the leakiness of the microvasculature seen in various systemic engagements or infections of larger organs such as the skin [18]. Also, in hypertension and cirrhosis of the liver there is a marked increase in TER_{alb} due to a general or splanchnic increase in filtration pressure [19, 20]. Diabetes mellitus and myxedema are characterized by changes in the endothelial lining of the microvasculature, with increased leakiness as a consequence [21, 22]. Extensive skin diseases show increased TER_{alb} values [18], probably because the dermal microvasculature is an extensive fraction of the total microvasculature.

During bleomycin treatment the first toxic changes seen are damages in the vascular endothelium of the lung and the skin. If this endothelial damage was universal an increase in the TER_{alb} as described could be expected. This, however, was not found.

Before treatment the TER_{alb} ranged from normal to moderately elevated. During the 18 weeks of treatment no changes in the TER_{alb} were seen.

As the patients were treated with bleomycin up to the level of toxicity, the lack of increase in the TER_{alb} must be explained by the fact that if functional abnormalities are present they are confined to the lung and that the changes in dermal microvasculature are moderate, either in degree or in extensiveness, when compared with generalized dermal diseases.

The finding of an increasing intravascular albumin mass during treatment to partial or complete remission of the malignancy agrees with the previous findings of an increased albumin catabolic rate as long as the neoplastic disease is active. The normalization of the intravascular albumin mass may thus be a consequence of the treatment.

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