LIVER NONSPECIFIC OXIDASE ACTIVITY AND BIOLOGICAL EFFECTS OF THE ANTITUMOR ANTIBIOTIC ADRIAMYCIN

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The therapeutic effect of many drugs, including some antitumor preparations, is exhibited in the course of their metabolism by nonspecific oxidases of the liver. The activity of this enzyme system may be modified by means of various agents and by administration of certain antitumor preparations [1, 3, 5]. Under these circumstances the toxic and therapeutic action of many antitumor preparations and other drugs which may be used in chemotherapy is modified by activation or inhibition of this enzyme system [7-9].

The object of the present investigation was to study the effect of the antitumor antibiotic adriamycin (AD), widely used in clinical practice, on the activity of the nonspecific oxidases of the liver, and also the effect of phenobarbital (PB), an inducer of this enzyme system, and its inhibitor SKF525-A, on the toxic action of AD.

EXPERIMENTAL METHOD

Experiments were carried out on male CBA mice aged 3-4 months. AD (Farmaceuticil S.P.A., Gruppo Montedison, Milan, Italy) was injected subcutaneously as a single dose. Activation of nonspecific liver oxidases was judged by the duration of sleep after intraperitoneal injection of 0.01 mg/g of a 0.75% solution of hexobarbital (HB, official preparation), the substrate of this enzyme system. When the metabolic capacity of the liver is inhibited, sleep due to HB is prolonged, whereas stimulation shortens sleep. PB (from Farmakhim) in a dose of 60 mg/kg was injected intraperitoneally once a day for three days, and AD was given to the animals one day after the last injection. SKF525-A (Smith, Kline and French, USA)

TABLE 1. Effect of AD on Duration of Hexobarbital Sleep (M ± m)

Expt. No.	Dose of AD, mg/kg	Time after injection of AD, days	Duration of sleep, min		P
			control	experiment	
1	20	2	36,6±2,7	142,2±7,6	<0,001
2		2	27,8±3,4	62,0±3,1	<0,001
	20	3	25,0±1,8	62,6±2,7	<0,001
		4	28,3±2,1	79,2±3,9	<0,001
3	15	1	20,0±1,9	24,8±1,8	>0,05
		2	34,2±2,6	79,8±5,1	<0,001
		3	21,2±3,1	39,4±4,1	<0,01
		5	17,0±2,0	50,2±3,4	<0,001
		6	18,4±1,7	59,6±2,8	<0,001
		9	34,0±2,8	105,4±15,5	<0,001
4	5	1	35,2±3,1	37,4±2,7	>0,1
		2	34,2±3,3	46,2±1,7	<0,01
		3	49,3±2,1	67,6±4,2	<0,01
		5	26,8±3,4	26,4±1,9	—
		6	37,8±2,6	31,0±3,5	>0,1

Legend. Data subjected to statistical analysis by Fisher–Student method. Level of significance of differences $P \leq 0.05$.

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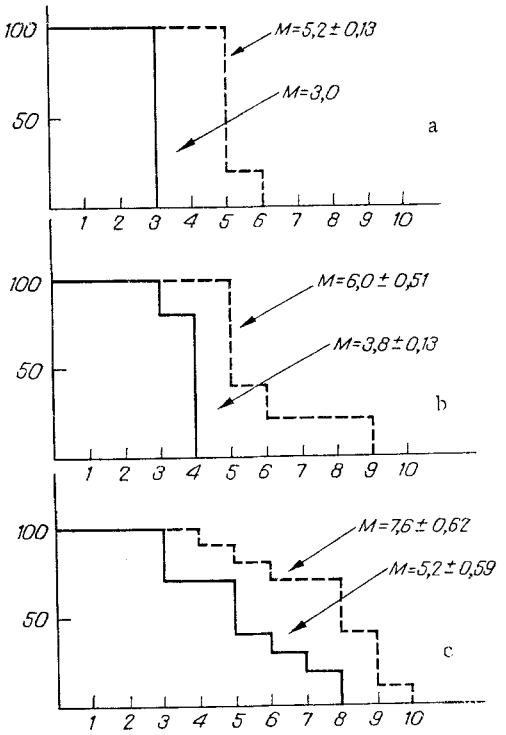

Fig. 1. Effect of PB on toxic action of AD. Continuous line, AD; broken line, AD + PB (60 mg/kg, 3 times). Doses of AD: a) 45, b) 30, c) 20 mg/kg. M) Mean length of survival of animals (in days). In all experiments difference in survival of animals between groups statistically significant ($P < 0.01$). Abscissa, days after injection of AD; ordinate, number of surviving animals (in percent of initial). Statistical analysis of results by Wilcoxon's matched pairs signed ranks test.

was injected intraperitoneally in a dose of 60 mg/kg 1.5-2 h before the injection of AD. At least 10 animals were tested in each group.

EXPERIMENTAL RESULTS

Data on the duration of hexobarbital sleep in the animals at different times after administration of AD are given in Table 1. On the second day after injection of toxic doses of AD (15 or 20 mg/kg) there was a marked increase in the duration of sleep (by two or more times) compared with that in intact animals, and this continued during nine days of observation. The toxicity of AD was exhibited as a fall in body weight of the mice on average by 30% compared with the control. In addition, on the 9th day after injection of 15 mg/kg AD three of the ten animals died.

After injection of a nontoxic dose of AD (5 mg/kg) an increase in the duration of hexobarbital sleep by 1.4 times was observed only on the 2nd-3rd day. The effect was reversible, and on the 5th-6th day after injection of AD the duration of sleep of the animals in the control and experimental groups was equal.

The results of experiments to study the effect of PB on the toxic action of AD showed that (Fig. 1) with all doses of AD the length of survival of the animals was shorter than when AD and PB were given. After receiving 45 or 30 mg/kg AD all the animals died on the 3rd-4th day of observation, whereas animals receiving both AD and PB began to die only on the 5th day. With a smaller dose of AD (20 mg/kg) the number of animals which died at all

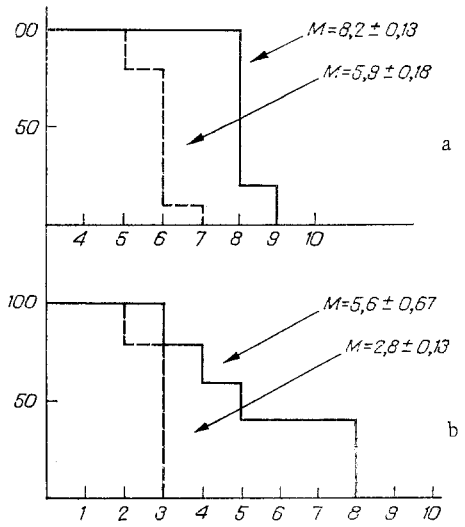

Fig. 2. Effect of SKF525-A on toxic action of AD. Continuous line, AD (20 mg/kg); broken line, AD + SKF525-A (60 mg/kg). Remainder of legend as to Fig. 1.

times of observation also was smaller after administration of both AD and PB than after AD alone.

SKF525-A had the opposite action on the toxicity of AD. Animals receiving 20 mg/kg AD and SKF525-A died sooner than after receiving AD alone. By the time of death of all the animals after receiving AD and SKF525-A, 80-100% of animals in the group receiving AD alone were still alive.

The investigation thus showed that AD, in a nontoxic dose (5 mg/kg) such as is often used for the treatment of animals with tumors, can evoke reversible inhibition of activity of the nonspecific oxidases of the liver, and this effect increased considerably and continued for 9 days of observation during administration of toxic doses of AD. The experiments also showed that the toxic effect of AD is reduced by preliminary administration of PB, an inducer of the nonspecific liver oxidases, to the animals and is intensified by administration of SKF525-A, an inhibitor of oxidases.

In the writers' opinion, these results must be taken into account during clinical use of AD. For example, administration of the drug to patients with various liver diseases, when the activity of the nonspecific liver oxidases is depressed [6, 8, 10], must evidently be carried out with caution, for in this case the toxic action of AD may be potentiated. Reports of clinical cases confirming this suggestion have been published [2]. Moreover, when the toxic action of AD is exhibited, persistent inhibition of the liver oxidases may arise and, as was shown above, it is these enzymes which metabolize many antitumor drugs. In this case, the use of drugs which are activated by this enzyme system, such as cyclophosphamide, 6-mercaptopurine, natulan, bleomycin, etc. [4, 7, 8, 10, 11], may prove ineffective. In that situation it is evidently better to use a combination of AD with antitumor preparations that are not metabolized by the nonspecific oxidases of the liver.

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