REDUCING THE TOXIC EFFECTS OF LETHAL DOSES OF ANTITUMOR PREPARATIONS BY MEANS OF AMINOETHYLISOTHIOURONIUM

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A series of chemical compounds having a markedly selective action on certain human tumors has not been synthesized. Unfortunately the difference in the sensitivity of individual forms of tumors is so great that many tumors, especially carcinomas, are resistant to the action of even the best existing preparation in use at the present time. However, by further progress in chemotherapy it may be possible both to obtain new substances having a different spectrum of action, and to improve the utilization of the existing compounds. As an example we may cite the technique of regional administration into the body cavities, intra-arterially or, in particular, by perfusion.

One way of increasing the therapeutic effect of existing preparations may be by the use of toxic, essentially lethal doses, under the protective cover of certain chemical substances. This field of chemotherapy has been inadequately studied, even experimentally. The basis of research in this field is the fact that the antitumor effect can be greatly increased by changing from tolerated doses of preparations to toxic doses. As an example of this phenomenon we may cite the results showing the effect of sarcolysin and other preparations on sarcoma 45 in tolerated doses and in LD50 (see Fig. 1).

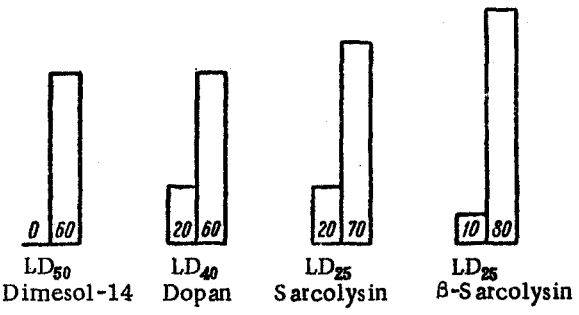

Fig. 1. The antitumor effect (absorption of tumors, in %) of different preparations given in maximal tolerated doses (figures on the left) and lethal doses (right).

The investigations of workers abroad [3-8] have shown that the toxic action of embichin can be weakened by sulfur-containing compounds – cystein, mercaptoethylamine, and aminoethylisothiouronium, – if these substances are given a few minutes before the embichin. In similar experimental conditions these compounds may also weaken the effect of ionizing radiation on the organism. N. I. Shapiro and co-workers [2] have discovered the interesting fact that aminoethylisothiouronium, while weakening the harmful action of roentgen rays on the organism, does not at the same time protect tumor cells from the harmful action of these rays. By the use of another protective substance – mercamine – A. B. Syrkin [1] also observed a weakening of the effect of toxic doses of dopan on rats, but found no weakening of the toxic action of sarcolysin.

We undertook the study of the possibility of weakening of the toxic action of certain antitumor preparations when administered in lethal doses.

Effect of AET on Survival of Rats and Mice After Administration of a Single Dose of Embichin and Dopan

Species of animal	Compounds and order of administration	Dose of compound (mg/kg)	Interval between injections (in minutes)	No. of animals	Mortality (in %)	R
Rats	Embichin	4	–	5	100	–
	AET + embichin	150 +4	2-3	5	100	–
	Embichin	2	–	20	100-70	4.8
	AET + embichin	150 +2	2-3	20	40-0	3.87-4.8
	Embichin + AET	2 + 150	2-3	10	20 ±12.65	2.5
	AET + embichin	150 +2	30	10	60 ±15.49	0.46
	Embichin + AET	2 + 150	30	10	80 ±12.65	1.6
Mice	Embichin	4.6	–	10	100	–
	AET + embichin	200 +4.6	2-3	10	40 ±15.49	3.2
	Embichin + AET	4.6 +200	5	10	100	–
Rats	Dopan	3	–	15	100	
	AET + dopan	150 +3	2-3	15	25 ±11.18	6.8
	Dopan	2.5	–	10	80 ±12.65	
	AET + dopan	150 +2.5	2-3	10	0	6.3
	Dopan	2.2	–	10	90 ±9.48	
	AET + dopan	150 +2.2	2-3	10	20 ±6.3	6.1
Mice	Dopan	12	–	12	58 ±14.25	2.27
	AET + dopan	200 +12	2-3	7	14 ±13.1	
	Dopan + AET	12 +200	2-3	8	62	–

Experimental Method and Results

The 4 preparations embichin, dopan, sarcolysin, and thiophosphamide (ThioTEP) were investigated. As protective substance we used aminoethylisothiouronium (AET). The experimental animals were 620 rats and 500 mice. As a rule a single dose of AET was injected intraperitoneally, and in individual experiments, subcutaneously. Immediately before injection of AET solution was neutralized with a 1.8N solution of alkali. The antitumor preparations were injected once only. Embichin, sarcolysis, and thio-TEP were injected intraperitoneally and dopan was given into the stomach. The results were assessed in terms of the survival rate of the animals.

The results of the experiments with embichin [methyl-bis-(β-chloroethyl)amine], are given in Table 1, from which it can be seen that when a dose of 4 mg/kg of embichin was used, causing death of all the rats, AEG had no obvious protective action. However, the preliminary injection of AET immediately before injection of embichin in a dose of 2 mg/kg had a significant protective effect. Whereas after injection of embichin in a dose of 2 mg/kg from 100 to 70% of rats died, the preliminary injection of AET in a dose of 150 mg/kg lowered the mortality among the rats to 40%, and sometimes led to tolerance of a lethal dose of embichin. An obvious protective effect was also observed when rats received an injection of AET immediately after embichin (i.e., within 2-3 minutes). When the interval between the injections of embichin and AET was increased to 30 minutes, the latter had no protective effect.

A protective effect of AET was demonstrated not only in rats but also in mice, in experiments on which the protective effect was observed to bear the same relationship to the size of dose and to the order and time of administration of embichin and of the protective substance.

Similar results were obtained in experiments with dopan [4-methyl-5-bis(b-chloroethyl)-aminouracil]. The degree of protection afforded by AET against dopan was slightly greater than against embichin (see Table 1). In the experiments with dopan the modes of administration of the antitumor and protective substances were different (oral and intraperitoneal), in contrast to the experiments with embichin, in which both compounds were injected intraperitoneally.

In the experiments with sarcolysin [p-di-(2-chloroethyl)-aminophenylalanine] on rats, no weakening of the toxicity of lethal doses of the compound was obtained. In a series of experiments the mortality among the rats was actually increased after administration of AET. For instance, when the dose of sarcolysin was 20 mg/kg, the mortality rate was 70%; administration of AET whether before or after sarcolysin increased the mortality among the rats to 80-100%. A slight reduction (by 20%) in the mortality rate was obtained in the experiment with a smaller dose of sarcolysin (18 mg/kg), but this slight protective effect was not statistically significant. It was observed when the compounds were given at different times and in different orders.

The results of the experiments on mice were different. The mortality could be lowered by 30% if AET was given 60 minutes before the injection of sarcolysin. If the intervals were shorter (15 minutes or 2-3 minutes) hardly any protective effect was observed. If AET was injected after sarcolysin, the protective effect was entirely absent at intervals of both 60 and 15 minutes.

In experiments on mice with thioTEP in doses of 25 and 30 mg/kg, AET led to no lowering of toxicity. Only when the dose of thioTEP was 20 mg/kg was its toxicity slightly lowered as a result of the preliminary administration of AET.

Our experiments thus showed that the general toxic action of embichin and dopan can be considerably reduced or even abolished by means of AET, the best results being obtained by a preliminary injection of AET 2-3 minutes before administration of the antitumor preparation. On the other hand, a decrease in the general toxic action of sarcolysin and thioTEP cannot always be obtained, and even if it is obtained it is slight. The results give hope that we shall be able to increase the therapeutic effect of existing preparations by means of the administration of lethal doses of antitumor preparations under the protective cover of other compounds. The object of our future research will be to study the possibility of using protective substances in the chemotherapy of tumors.

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