EFFECT OF AMINOETHYLISOTHIURONIUM ON THE SPECIFIC ACTIVITY OF CERTAIN ANTITUMOR PREPARATIONS

(UDC 615.771.7:615.21)

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 57, No. 5, pp. 73-76, May, 1964
Original article submitted April 19, 1963

Damage to normal tissues is one of the obstacles on the road to increasing the efficacy of chemotherapeutic preparations. Therefore, it is of importance to search for such chemical substances under whose protection it would be possible to use antitumor preparations in doses appreciably exceeding the maximum tolerable. Thus, a new pathway for increasing antitumor activity can be mapped out.

It was demonstrated in the works of a number of authors [5, 6, 8, 9, 10] that aminoethylisothiuronium (AET), cysteamine, and cysteine, by protecting the host from lethal doses of embichin and endoxan, enhance their antitumor effect with respect to certain transplantable tumors. The differential effect of AET on normal and tumor tissues was also elicited in roentgenotherapy of experimental tumors [4]. In certain ratios of doses, cysteamine does not affect the antitumor activity of dopan and at the same time reduces the inhibiting effect of this preparation on leukopoiesis [3].

In previous investigations [1, 2] we demonstrated the distinct protection of rats, mice, and monkeys under the effect of AET from the lethal action of embichin and dopan. Contrary to Haas [6], in whose experiments the preliminary injection of AET enhanced the toxicity of endoxan, we were able to obtain a noticeable drop in its toxicity when AET was used 30 min after injection of endoxan.

The purpose of the present investigation was to elucidate the effect of AET on the antitumor activity of dopan (5-[bis(2-chloroethyl)amino]-6-methyluracil]) and endoxan (cyclic ether of N, N-di-(2-chloroethyl)N', γ -hydroxypropyldiamide of phosphoric acid).

METHOD

More than 1000 rats with sarcoma 45 were used in the experiments.

In different series of experiments dopan was used in doses of 2.2, 1.7, 1.5, and 1.4 mg/kg every 72 h. AET in combination with lethal doses of dopan was injected intraperitoneally in doses of 150 mg/kg immediately before injecting dopan; AET was used less frequently than dopan so that the interval between the injections of AET was 144 h. The antitumor effect of AET + dopan was compared not only with the effect from dopan alone in lethal doses, but also with the effect of dopan in a maximum permissible dose of 0.75 mg/kg every 72 h.

RESULTS

We see from Fig. 1 that at dopan doses of 2.2 and 1.7 mg/kg, from which respectively 90 and 60% of the rats died, AET not only reduced the percent of rat death respectively to 60 and 45, but also weakened the antitumor effect of dopan. For example, under the effect of dopan alone in a dose of 2.2 mg/kg, the average weight of the tumor was 0.5 g, whereas in combination with AET it was 6.5 g. When dopan was used in a dose of 1.7 mg/kg the tumor

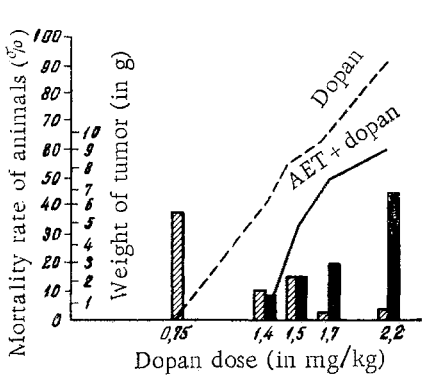

Fig. 1. Effect of AET on the antitumor activity of dopan. The curves depict rat death, the hatched columns the average weight of the tumor under the effect of dopan, the black columns under the effect of dopan combined with AET.

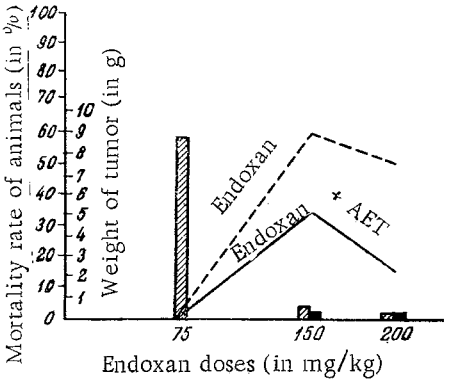

Fig. 2. Effect of AET on antitumor activity of endoxan. The curves depict rat death, the hatched columns the average weight of the tumors under the effect of endoxan, the black columns under the effect of endoxan combined with AET.

averaged 0.3 g, and when dopan was used in combination with AET it was 2.8 g. Thus, the use of AET in doses of dopan exceeding LD_{50} reduces both the toxic and the antitumor action of the latter.

However, by reducing the dopan dose to 1.5 and 1.4 mg/kg we can obtain a differential influence of AET on normal and neoplastic tissue (see Fig. 1). Under the effect of dopan in a dose of 1.5 mg/kg 50% of the rats died, and the average weight of the tumors was 2.2 g. The preliminary use of AET reduces the percent of rat death to 35, however, the antitumor effect is fully retained, i.e., the average weight of the tumor of the rats that survived was as before, 2.2 g. At a dopan dose of 1.4 mg/kg, from which 40% of the rats died, AET yielded complete protection against the lethal effect; at the same time the average weight of the tumor in the animals of the protected group (1.5 g) proved to be somewhat less than under the effect of just dopan with LD_{40} (1.7 g) and vastly less than the average weight of the tumor at a maximum dose of dopan (5.5 g). Consequently, in this case it was possible to obtain with AET complete protection against the lethal effect of dopan, and also to retain and even elevate the antitumor effect of dopan in comparison with the maximum which this preparation yields at tolerable doses.

Thus, with the use of dopan a differential action of AET is detected only under certain circumstances, mainly when dopan is used in doses not exceeding LD_{50}. At larger doses of dopan the differential effect of AET is not demonstrated. This can be explained by the fact that when the dopan dose is reduced there is a different degree of lesion of the normal and neoplastic tissues: normal tissues are less affected than the tumor; in this manner favorable conditions are created for the appearance of the differential effect of AET.

Endoxan was used in doses of 200, 150, and 75 mg/kg in a single intraperitoneal injection. AET was injected in a dose of 150 mg/kg 30 min after injection of endoxan.

Endoxan in a dose of 150 and 200 mg/kg killed 50-60% of the rats (Fig. 2). AET reduced the toxicity of endoxan: only 14-35% of the rats died from these same doses. In this case the antitumor effect was completely retained. The combined use of endoxan and AET, just as the use of endoxan alone in doses of 200 and 150 mg/kg, caused total regression of the tumors. At the same time, at a maximum dose of endoxan regression of tumors was observed only in individual rats, and the average weight of the tumor was 6 g. Thus, under the effect of AET at the endoxan doses use, the antitumor effect was not only distinctly retained but also noticeably enhanced in comparison with the maximum dose. True, this enhancement of the antitumor effect was accompanied by incomplete protection, i.e., we were not able in these experiments to achieve survival of all rats.

Summarizing the results of our experiments, we can make the following conclusions. By using AET with such antitumor preparations as dopan and endoxan, we can obtain protection of normal tissues and avoid the weakening influence of AET on the antitumor effect. Therefore, it becomes possible to use antitumor substances in doses exceeding the maximum doses, and thus, increase the antitumor effect. This differential influence of AET depends apparently on its dissimilar distribution in various tissues. In the work of N. I. Shapiro and group [3] on mice with

Ehrlich's subcutaneous tumor it was established that AET labeled for sulfur (S^{35}) was primarily accumulated in the marrow and spleen and in small concentrations in the tumors and testicles. True, our experiments were set up on a different tumor, sarcoma 45, therefore, these data on the distribution of AET can serve here only as an indirect explanation. On the other hand, in the work of the same authors [3] it was demonstrated that sarcoma 45 is a tumor which is not protected by AET in roentgenotherapy. One of the causes for the differential action of AET can also be the different pH values in normal tissues and in tumors [11].

The data obtained can serve as grounds for elaborating a method of using elevated doses in the chemotherapy of tumors in the clinic.

SUMMARY

A study was made of the effect produced by AET—a protective agent—on the antiblastic activity of dopan and endoxan.

It is proved that the use of AET may, under certain conditions, provide the protection of rats against the lethal action of dopan and endoxan precluding at the same time, the weakening influence of the preparation on the antitumor effect. The latter circumstance enables it to employ the antitumor preparations in doses exceeding the maximum permissible limits thus enhancing the antiblastic effect.

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