THE EFFECT OF (THIAZOLYL-2) AMIDE OF N-ACETYLSARCOLYSIN (ASAZOL) ON THE GROWTH OF TRANSPLANTABLE TUMORS

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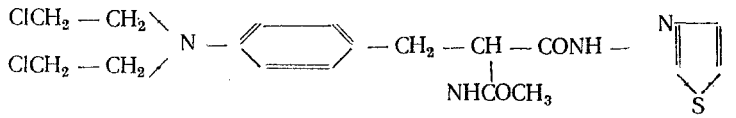
During recent years intensive research has been conducted in the Laboratory of Experimental Chemotherapy of the Institute of Experimental and Clinical Oncology in the quest for antitumor preparations among the complex alkylating metabolites, i.e., substances in which various metabolites, for example amino acids, vitamins, heterocyclic compounds and so on, are combined with amino acid derivatives of chloroethylamine or with phenylalkanecarbonic acids by means of a peptide, amide or ester bond [2, 3]. In particular, the peptides of sarcolysin, which show high experimental antitumor activity, have been obtained in this way [4].

In the present communication we describe experimental data concerning a new preparation of this type, which is an amide of N-acetylsarcolysin and amino-thiazole, the thiazole ring of which is a component of vitamin B_1. This preparation, which is called "asazol," has the following structure:



(thiazolyl-2) amide of N-acetylsarcolysin.

Asazol was synthesized by Berlin and Bronovitskaya [1] in the Laboratory of Chemical Synthesis of the Institute of Experimental and Clinical Oncology. The preparation is stable on storage, readily soluble in chloroform and alcohol, and insoluble in water.

EXPERIMENTAL METHOD

Asazol was investigated experimentally in mongrel mice, rats and cats, suspensions of the preparation in starch paste being administered intraperitoneally or by mouth. In order to assess the antitumor properties of asazol we used rats with developing transplanted tumors, namely spindle-cell sarcoma 45, polymorphocellular sarcoma M-1, Jensen's sarcoma, Gueren's carcinoma, Walker's carcino-sarcoma, alveolar carcinoma of the liver RS-1, and the following tumors of mice: sarcoma 298, carcinoma of the mammary gland RMZh, squamous cell carcinoma of the forestomach OZh-5, Crocker's sarcoma, Ehrlich's tumor and lymphosarcoma LI0-1. The criterion of the antitumor activity of the preparation was the degree of inhibition (in %) of growth of the tumors, calculated from the mean weights of the tumors in the control and experimental groups. The statistical significance of the results was verified in accordance with Student's formula. For the difference calculated by this method to be significant, the value of "P" must be not less than 0.955.

EXPERIMENTAL RESULTS

A single intraperitoneal injection of the drug showed that asazol is a compound of low toxicity. MLD_{100} of the compound for rats is 1 g/kg body weight, and MLD_{25} is 0.5 g/kg body weight. Because asazol is not completely absorbed when given by intraperitoneal injection, we subsequently gave it by mouth. In experiments in which asazol was given in frequent doses by mouth it was found that the therapeutic dose for rats is 25 mg/kg once daily, 40 mg/kg once every two days, or 60-65 mg/kg once every three days. The best therapeutic results and the optimal tolerance of the drug were observed when it was given at intervals of 48 and 72 hours. Mice were found to be less sensitive to asazol than rats. For instance, the daily therapeutic dose for mice is 100 mg/kg, and when given at intervals of 48 hours, 350 mg/kg body weight (Table 1).

TABLE 1

Sensitivity of Mice and Rats to Asazol

Animal	Method of administration of preparation	MLD_{100} (in mg/kg)	MLD_{25} (in mg/kg)	Therapeutic dose
Rat	Intraperitoneally	1 000	500	15/24, 30/48
	By mouth	—	—	25/24, 40/48, 60—65/72
Mouse	Intraperitoneally	—	—	100/48
	By mouth	—	—	100/24, 350/48

Note: Numerator: sessional dose of preparation (mg/kg body weight), denominator: interval between administration of individual doses (hours).

The results of the antitumor action of asazol are shown in Table 2. It will be seen from Table 2 that asazol inhibits the growth of sarcoma 45 by 99.4% and causes total regression of tumors in 60% of treated rats. Close to sarcoma 45 in its sensitivity is sarcoma 298, which not only reacts to asazol by considerable inhibition of growth, but also undergoes complete absorption in 50% of treated mice.

The study of the action of asazol on the other transplantable tumors showed considerable inhibition of growth not only of sarcomas (strains M-1 and Jensen), but also of some epithelial tumors (Gueren's carcinoma, carcinoma of the liver RS-1, and carcinoma of the mammary gland RMZh). Asazol had no effect, however, on growth of the squamous-cell carcinoma of the forestomach OZh-5 and lymphosarcoma LI0-1. An unexpected discovery was that, in these doses, asazol stimulated growth of the undifferentiated Crocker's sarcoma.

Comparison of asazol with sarcolysin shows certain differences in the spectrum of their antitumor action. According to Trusheikina [5], for instance, sarcolysin causes considerable inhibition of growth of lymphosarcoma LI0-1 (by 90%) and leads to complete absorption of the tumors in individual mice, whereas asazol has no effect on this tumor. As Trusheikina's investigations [5] showed, moderate inhibition of growth of Crocker's sarcoma (by 45%) takes place as a result of the action of sarcolysin. Asazol, however, showed the opposite action on Crocker's sarcoma, and caused appreciable stimulation of its growth.

Therapeutic experiments on rats with sarcoma 45 showed that asazol causes moderate depression of hemopoiesis. Under the influence of a therapeutic dose of 65 mg/kg body weight, given every 72 hours, at the end of treatment the white cell count in the peripheral blood of the rats had decreased by 60%.

TABLE 2

Action of Asazol on Transplantable Tumors

Tumor strain	Inhibition (in %)	Absorption (in %)	Criterion of reliability
Sarcoma 45	99.4	60	1.0
Sarcoma M-1	98.0	–	0.997
Jensen's sarcoma	97.0	–	1.0
Gueren's carcinoma	93.0	–	1.0
Sarcoma 298	88.0	50	1.0
Carcinoma of liver RS-1	79.0	–	1.0
Carcinoma of mammary gland RMZh	76.0	–	1.0
Ehrlich's tumor	64.0	–	0.997
Walker's carcino-sarcoma	61.0	–	0.988
Carcinoma of forestomach OZh-5	17.0	–	0.890
Lymphosarcoma LI0-1	–	–	
Crocker's sarcoma	Stimulation by 19-64%	–	0.958 for 64%

The effect of asazol on hemopoiesis was also studied in cats receiving eight daily doses of 20, 30 and 40 mg/kg body weight of the preparation by mouth. With a dose of 20 mg/kg of asazol the morphological picture of the cats' blood was unchanged. Under the influence of doses of 30 and 40 mg/kg body weight, 50-100% greater than the therapeutic dose for rats, a moderate leukopenia developed in the period of administration of the drug. After cessation of administration of asazol in a dose of 30 mg/kg the fall in the white cell count persisted, but not for so long or to such an extent as after the dose of 40 mg/kg. The leukopenia developing after 30 mg/kg was reversible, whereas after a dose of 40 mg/kg a very profound and persistent leukopenia developed. The differential white cell count showed that the fall in the total white cell count was mainly attributable to a decrease in the absolute number of neutrophils, and to a lesser degree to a decrease in lymphocytes.

Hence, if overdosage is avoided, the depressing action of asazol on leukopoiesis is moderate and reversible. No effect of asazol on the red cell count was observed.

SUMMARY

The authors studied antiblastic properties of a new preparation (thiazolyl-2) amide N-acetylsarcolysin (asazol). Asazol possesses a marked antiblastic effect with respect to a number of transplantable tumors. However, the action of asazol exerted on various tumor strains differed: in some cases complete regression of the tumors and their considerable inhibition occurred whereas in others – antiblastic action was absent and the tumor growth was even stimulated. The range of antiblastic effect of asazol differed from that of sarcolysin. Asazol produces a moderate depressive effect on hemopoiesis. Clinical tests of the drug are recommended.

LITERATURE CITED

1. A. Ya. Berlin and V. P. Bronovitskaya, Zhur. Obshchei Khimii 30, 1, 324 (1960).
2. L. F. Larionov, Vestnik Akad. Med. Nauk SSSR 2, 8 (1958).
3. L. F. Larionov, Vestnik Akad. Med. Nauk SSSR 6, 25 (1959).
4. L. F. Larionov and Z. P. Sof'ina, Doklady Akad. Nauk SSSR 114, 5, 1070 (1957).
5. V. I. Trusheikina, in: Annotations of Scientific Researches of the AMN SSSR during 1955 [in Russian] (Moscow, 1956) p. 437.