EXPERIMENTAL STUDY OF THE ANTITUMOR PROPERTIES OF NORDOPAN GLUCOSIDES

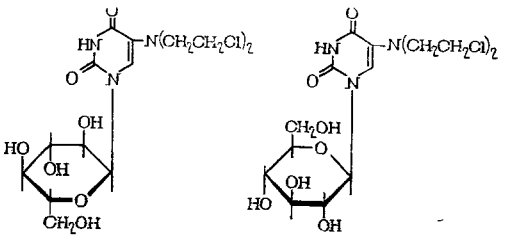
D. V. Popov, G. N. Platonova,
E. P. Studentsov, and L. F. Larionov

UDC 615.277.3:547.918].015.

The action of two anomers of glucopyranosylnordopan on experimental tumors and leukemias of mice was studied. The α glucoside of nordopan was shown to have marked antitumor and antileukemic activity. The β glucoside had weak antitumor properties and moderate antileukemic action.

The search for substances with antitumor activity among the chloroethylamine derivatives of pyrimidine has led to the development of compounds such as dopan [1, 4-6], nordopan [2, 3, 12-14], and ipenyl [8, 9], which are used for the treatment of leukemias and some forms of malignant tumors. The next step toward the production of alkylating metabolites of nucleic acid metabolism is the synthesis of haloalkylamine derivatives of the nucleosides. In the 1960s the chloroethylamine analogues of uridine and cytidine were synthesized in Czechoslovakia [10, 11, 15]. In their experimental study on AK leukemia only 5-di(2-chloroethyl) aminomethyluridine (ipenyl riboside) was found to possess antileukemic activity.

Glucose derivates of 5-di(2-chloroethyl)aminouracil (nordopan) were obtained in 1970 at the Lensovet Leningrad Technological Institute, namely: the hydrochlorides of N_1-[α-D-glucopyranosyl]-5-di(2-chloroethyl)aminouracil and N_1-[β-D-glucopyranosyl]-5-di(2-chloroethyl)aminouracil.



In the investigation described below the antitumor and antileukemic action of the α and β anomers of glucopyranosylnordopan was studied.

EXPERIMENTAL METHOD

The action of the α and β forms of N_1-D-glucopyranosylnordopan was studied in mice with subcutaneously implanted solid tumors (sarcoma-298 and adenocarcinoma-755) and leukemias La, L1210, and Nk/Li. Altogehter 650 C57BL, DBA/2, C3HA, and noninbred mice were used. The compounds were injected intraperitoneally in all experiments, both with subcutaneous tumors and with intraperitoneally transplanted leukemias. In the latter case the action of the compounds was directed against generalized leukemia. Injections of solutions of the compounds began at times when the tumors could just be palpated, but considering the rapid generalized development of the leukemias, in these animals injections began 24 h after transplantation. Treatment continued for 5-10 days in the experiments with the solid tumors and 6-10 days in the

Institute of Experimental and Clinical Oncology, Academy of Medical Sciences of the USSR, Moscow.
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 75, No. 5, pp. 73-75, May, 1973. Original article submitted May 5, 1972.

TABLE 1. Action of α and β Anomers of Glucopyranosylnordopan on Transplanted Mouse Tumors and Leukemias

Compound	Sarcoma 298				Adenocarcinoma 755				Hemocytoblastosis				Lymphoblastosis				Lymphatic leukemia			
	dose (mg/kg)	no. of animals	wt. of tumor (g)	inhibition, %	dose (mg/kg)	no. of animals	wt. of tumor (g)	inhibition, %	dose (mg/kg)	no. of animals	lifespan (days)	increase in lifespan (%)	no. of animals	lifespan (days)	increase in lifespan (%)	dose (mg/kg)	no. of animals	lifespan (days)	increase in lifespan (%)
Dopan	0,3	10/9	6,87/4,11	40	0,2	10/10	9,1/6,3	35	0,4	30/30	7,2/12,6	75	20/20	8,0/10,4	30	20/20	16,7/28,8	72
α-Glucoside	30	10/9	2,14/0,27	87	13	10/10	10,2/4,16	59	12	30/30	7,1/12,3	73	20/20	8,5/12,2	44	10/10	16,7/30,5	86
β Glucoside	10	10/10	5,49/3,97	27	18	10/10	9,12/6,98	35	15/20	40/40	7,8/12,4	59	20/20	7,8/9,6	24	—	—	—

Note. Only results significant for $P \leq 0.005$ are included in the Table. Numerator gives indices of control group; denominator those of experimental group.

leukemias. The results were assessed by the weight of the tumors of the lifespan (for the leukemias) and expressed as percentages of inhibition of tumor growth or of increase in the mean lifespan of the leukemic mice. Statistical analysis of the numerical results was carried out by Student's method. All the experimental results were compared with the action of dopan, the antitumor activity of which, as has been shown in the writers' laboratory [2, 3], is the same as that of nordopan.

EXPERIMENTAL RESULTS

It is clear from Table 1, which summarizes the results obtained in a series of experiments, that in antitumor and antileukemic activity the α anomer was the more active of the two glucosides studied. Nordopan α-glucoside inhibited growth of sarcoma-298, which is sensitive to alkylating agents, by 87%, and at the same time it considerably (by 59%) inhibited growth of adenocarcinoma-755, sensitive to antimetabolites. In its antitumor activity α glucoside was slightly superior to dopan, which inhibits the growth of these same tumors by only 40 and 35%, respectively.

Dopan and the α glucoside had equal activity against acute La hemocytoblastosis and prolonged the survival of mice with this leukemia by 73-75%. The two compounds had a less marked effect on subacute lymphatic leukemia L1210 (30 and 44%, respectively) and prolonged the survival of mice with Nk/Li ascites lymphatic leukemia by 72% (dopan) and 86% (α glucoside).

Nordopan β glucoside had a less marked antileukemic action. The lifespan of mice with La leukemia treated with the β anomer was greater than that of the untreated control mice by only 59%. This compound had virtually no action on L1210 leukemia. The β glucoside had a very weak antitumor activity both when acting on sarcoma-298 and on adencarcinoma-755.

In their toxicity these compounds differed sharply from dopan. The sessional therapeutic doses of the α and β glucosides of nordopan are some tens of times greater than the therapeutic dose of dopan.

Nordopan glucosides are thus less toxic than dopan, they are similar to dopan in their antileukemic activity, but in their antitumor activity they differ somewhat from each other and also from dopan.

The appreciable differences between the antitumor activity of the α and β glucosides, despite the very slight difference in their structure, can be explained by the difference in the metabolism of these compounds in animals with tumors and in the neoplasms themselves.

LITERATURE CITED

1. E. G. Vishnyakova, Vopr. Oncol., No. 5, 568 (1958).
2. O. V. Zubova, in: Annotations of Scientific Work of the Academy of Medical Sciences of the USSR for 1955 [in Russian], Moscow, (1955), p. 385.
3. O. V. Subova, in: Problems in the Chemotherapy of Malignant Tumors [in Russian], (1960), p. 75.
4. E. M. Ivanova, Abstracts of Proceedings of the 3rd Scientific Conference to Review Work of the Institute of Experimental and Clinical Oncology, Academy of Medical Sciences of the USSR [in Russian] (1959), p. 29.

5. L. F. Larionov and G. N. Platonova, Vopr. Onkol., No. 5, 36 (1955).
6. L. F. Larionov, Brit. J. Cancer, 10, 26 (1956).
7. G. N. Platonova, Byull. Éksperim. Biol. i Med., No. 6, 53 (1957).
8. O. Dvorak, J. Elis, F. Perlik, et al., Neoplasma, 18, 365 (1971).
9. J. Farkas and F. Sorm, Collect. Czechosl. Chem. Commun., 26, 893 (1961).
10. J. Farkas and F. Sorm, Collect. Czechosl. Chem. Commun., 28, 1620 (1963).
11. J. Farkas and F. Sorm, Collect. Czechosl. Chem. Commun., 34, 1696 (1969).
12. B. Y. Kennedy and A. Theologides, Cancer Chemother. Rep., 11, 77 (1961).
13. D. A. Lyttle and H. I. Petering, J. Nat. Cancer Inst. (Washington), 23, 153 (1959).
14. E. Shanbron, S. Miller, and H. Haar, Clin. Res., 7, 57 (1959).
15. Y. Zemlicka, Y. Smrt, and F. Sorm, Collect. Czechosl. Chem. Commun., 29, 635 (1964).