EFFECT OF CHLORPROMAZINE ON GROWTH OF TRANSPLANTABLE MELANOMAS AND ON THEIR RESPONSE TO X-RAY IRRADIATION

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Repeated injection of chlorpromazine in doses of 5-20 mg/kg body weight into animals with transplantable Harding-Passy and B-16 melanomas gave a small but systematically reproducible and statistically significant inhibition of growth of the tumor nodules. Injection of chlorpromazine before x-ray irradiation potentiated the effect of inhibition of growth of the melanomas induced by irradiation by 40-50%. Delay in growth of the tumors after combined treatment continued for 2 weeks after the end of the therapeutic course. The results indicate that chlorpromazine can be used in schemes of combined treatment.

The study of the action of chlorpromazine on transplantable tumors has yielded inconsistent results. Pukhal'skaya [3], as long ago as 1957, observed an approximately twofold increase in the action of sarcolysin on Ehrlich's tumor under the influence of chlorpromazine. Reports were published that it induces regression of sarcoma 37 [7], inhibits the growth of sarcoma 45 by 45% [1], and inhibits metastasization of the Brown-Pearce tumor [2]. With respect to sarcoma 45, in another investigation inhibition of its growth by chlorpromazine was not statistically significant [4]. In experiments by other workers chlorpromazine had no effect on growth of sarcoma M-1, Crocker's sarcoma, Ehrlich's tumor, and a transplantable mammary gland tumor [1, 10, 22]. In a recent report, chlorpromazine and the closely related compound 7-hydrochlorpromazine inhibited growth of B-16 and Harding-Passy melanomas. Unfortunately the value of these investigations is limited by the fact that administration of the compounds began in the early period (2 days after transplantation of the tumors) [14].

TABLE 1. Inhibition of Growth of Melanomas by Chlorpromazine

Tumor	Number of animals in group	Interval between injections (in days)	Number of injections	Inhibition of tumor growth (in percent)	P
B-16 . . .	22	1	7	40	0,001
B-16 . . .	18	2	4	43	0,001
H-P . . .	10	1	11	46	0,025
H-p . . .	19	2	6	41	0,01

The study of the action of chlorpromazine on melanomas is particularly interesting. In this case, besides other possible mechanisms such as interference in processes taking place in the respiratory chain, in DNA synthesis, and so on [12, 14], the ability of chlorpromazine to bind itself with melanin and to accumulate in pigmented structures, which is already well known from clinical observations, post mortem material, and experimental evidence [8, 9, 15, 16, 21, 22], may be of essential importance. Complex formation is evidently involved in this process, for chlorpromazine acts as an electron donor, while melanin, with the properties of a stable free radical, may act as electron acceptor [11, 17, 18].

In the investigation described below an attempt was made to determine to what extent chlorpromazine can inhibit growth of transplantable pigmented melanomas.

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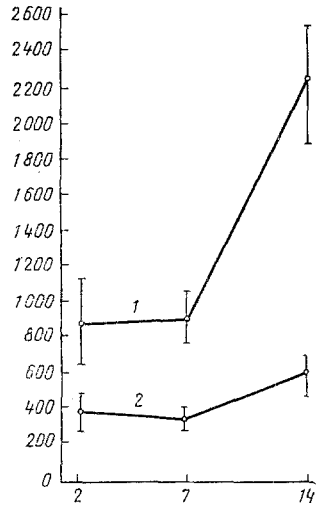

Fig. 1. Growth of Harding-Passy melanoma nodules: 1) irradiation; 2) combined treatment. Abscissa, time after end of therapeutic course (in days); ordinate, increase in volume of tumor relative to initial (in percent). Vertical lines denote probable error of mean.

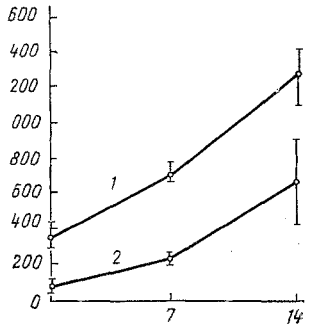

Fig. 2. Growth of B-16 melanoma nodules. Legend as in Fig. 1.

EXPERIMENTAL METHOD AND RESULTS

Harding-Passy and B-16 melanomas were transplanted into (CBA × C57BL) F_1 mice subcutaneously. Before injection of the compound began, the animals were divided into groups with an equal distribution of tumor nodules by size. Accordingly the statistical significance of differences in the weight or size of the tumor nodules during subsequent observation and at the end of the experiment was assessed by Student's criterion as applied to variances in two paired samples [5]. Chlorpromazine marketed in ampules by the L'vov Pharmaceutical Factory was used. After dilution to the required concentration it was injected intraperitoneally in a volume of 0.2 ml. The mice tolerated this compound well if the injections began with a dose of 5 mg/kg, which was subsequently increased to 10 and then 20 mg/kg. Under these conditions a small but statistically significant inhibition of growth of both melanomas was observed (Table 1).

In one experimental local irradiation of the tumor nodules by the RUM-7 x-ray apparatus, with a voltage of 30 kV, giving a total dose of 2400 R in 6 sessions, was given to the animals of the experimental group immediately before the injection of chlorpromazine. Under these conditions no significant potentiation of the irradiation effect was found under the influence of chlorpromazine. Inhibition of growth of the tumor nodules was 70% compared with 60% after irradiation alone ($P > 0.05$). In another experiment two groups of 19 mice with melanoma B-16 were compared. They were sacrificed after 7 sessions of irradiation given at intervals of 2 days. Inhibition of tumor growth induced by x-ray irradiation (total dose 2800 R) was potentiated in this case by 43% ($P < 0.001$) by the action of chlorpromazine injected approximately 30 min before irradiation.

In two other experiments the dimensions of the tumor nodules were measured repeatedly during life and various times after the end of the therapeutic course in small groups consisting of 9-10 animals each. Potentiation of the irradiation effect by preliminary injection of chlorpromazine was observed to the extent of 42% in the case of melanoma B-16 (7 sessions at intervals of 2 days, total dose 2800 R) and of 50% in the case of Harding-Passy melanoma (total dose 2900 R, 8 sessions at intervals of 2 days). The results of observations on these animals are given in Figs. 1 and 2. In both cases, for 2 weeks after the end of the therapeutic course, the delay in growth of the tumors receiving combined treatment was still observed. Later, however, the differences in the life span of the animals were small for Harding-Passy melanomas (average 26 and 33.5 days after the end of treatment) and absent altogether in the case of the melanoma B-16 (39.2 and 39.6 days respectively). Since in parallel experiments carried out at the same time and under the same conditions irradiation inhibited growth of the tumor nodules by approximately 60% it must be concluded that the resultant effect of combined treatment is inhibition of tumor growth of the order of 85-90%.

Chlorpromazine thus gives systematically reproducible and statistically significant inhibition of growth of transplantable B-16 and Harding-Passy melanomas. However, this inhibition is not so great as would be expected from the use of this compound alone in the treatment of even experimental melanomas. Nevertheless, the results of combined treatment obtained in these experiments suggest that chlorpromazine could be incorporated into the therapeutic plan. The ability of chlorpromazine to accumulate in pigmented structures, by forming a complex with melanin, suggests that it may be used as a carrier of a radioactive isotope and conductor into the tissues of pigmented tumors.

LITERATURE CITED

1. A. P. Vorona, Vopr. Onkol., No. 8, 78 (1966).
2. V. I. Pudov, Farmakol. i Toksicol., No. 4, 454 (1971).
3. E. Ch. Pikhal'skaya, Abstracts of Proceedings of the 2nd Scientific Conference to Review Work of the Institute of Experimental Pathology and Therapy of Cancer [in Russian], Moscow (1958), p. 9.
4. A. B. Syrkin, Vopr. Onkol., No. 3, 34 (1960).
5. Yu. V. Urbakh, Biometric Methods [in Russian], Moscow (1967).
6. V. A. Chernov, Cytostatic Substances in the Chemotherapy of Malignant Neoplasms [in Russian], Moscow (1964).
7. M. Belkin and W. G. Hardy, cited in [10].
8. H. Bernstein et al., Invest. Ophthalm., 2, 384 (1963).
9. S. H. Carry et al., Proc. Soc. Exp. Biol. (New York), 134, 314 (1970).
10. M. Chorazy, Nature, 184, 200 (1959).
11. B. Commoner et al., Nature, 174, 689 (1954).
12. G. Correman et al., Science, 130, 191 (1959).
13. E. M. Craustone, Cancer Res., 18, 897 (1958).
14. M. J. Dowkins et al., Biochem. J., 73, 16 (1959).
15. J. S. Forrest et al., Agressologie, 4, 259 (1963).
16. J. S. Forrest et al., Agressologie, 7, 147 (1966).
17. H. C. Longnet-Higgins, Agressologie, 7, 231 (1966).
18. H. S. Masson, Arch. Biochem., 86, 225 (1960).
19. J. Nielsen et al., Brit. Med. J., 3, 634 (1969).
20. A. Potts, Invest. Ophthalm., 1, 523 (1964).
21. A. Potts, Ophthalmologica (Basel), 3, 399 (1964).
22. M. H. Wan Woert and S. H. Palmer, Cancer Res., 29, 1952 (1969).