STIMULATING ACTION OF ESTRADIOL DIPROPIONATE ON INDUCTION OF SARCOMAS OF THE UTERUS BY 1,2-DIMETHYLHYDRAZINE IN MICE

V. S. Turusov, A. B. Linnik, and O. V. Morozova

UDC 618.14-006.3.04-092:577.175.642

KEY WORDS: 1,2-dimethylhydrazine; sarcomas of the uterus; estrogens.

Sarcomas of the uterus arise in a high percentage of cases in CBA mice through the action of 1,2-dimethylhydrazine (DMH) [3]. Pregnancy has been shown to inhibit [1, 2], and administration of estradiol dipropionate (EDP) to accelerate [1], the appearance and growth of these tumors.

In the present investigation the effect of the duration of administration of EDP on the development of sarcomas of the uterus induced by a much smaller total dose of DMH than in the previous work [1] was studied.

EXPERIMENTAL METHOD

Female CBA mice aged 2-3 months, obtained from the "Stolbovaya" Nursery (30 mice per group) were used. DMH was injected subcutaneously in distilled water in a dose of 8 mg/kg weekly for 10 weeks. EDP in olive oil was injected subcutaneously once a week in a dose of 10 μg per mouse on the day before injection of DMH, and its administration continued for 10 weeks (group 2), 20 weeks (group 3), or 25 weeks (group 4). The experiment ended 50 weeks after the beginning of injection of DMH. The mice remained under observation until they died naturally, or were killed when their condition was poor, or if tumors of the uterus more than 2 cm in diameter could be palpated in them. The material was treated histologically and stained with hematoxylin–eosin.

EXPERIMENTAL RESULTS

During the first weeks of the experiment some of the mice receiving EDP died in all groups (Table 1). After the 20th week, the mortality among the mice in groups 2, 3, and 4 was due almost entirely to the development of uterine tumors.

The first sarcomas of the uterus were found 17-18 weeks after the beginning of the experiment in groups 3 and 4. The increase in their frequency with time is illustrated in Fig. 1 and their final frequency shown in Table 1. In group 1 (DMH) only one sarcoma of the uterus (3.3%) was noted during the period of observation, at the 49th week of the experiment. In the animals of groups 2, 3, and 4, receiving both DMH and EDP, the frequeny of sarcomas of the uterus was much higher: 25, 65.4, and 73%, respectively; the differences from group 1 are statistically significant (Table 1). In the mice of group 5, receiving EDP only, no tumors of the uterus developed throughout the period of observation. Microscopically and according to their histological structure the sarcomas of the uterus which developed after the combined action of DMH and EDP did not differ from the analogous tumors induced by DMH alone, which were described in detail previously [3].

In the animals of all groups receiving DMH a few tumors were observed in other locations also (anal region, intestine, and if a combination of DMH and EDP was given, single cases of leukemia), but no differences were found between the frequency of these tumors in different groups.

Laboratory of Carcinogenic Substances, Department of Carcinogenic Agents, Oncologic Scientific Center, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR L. M. Shabad.) Translated from Byulleten' Éksperimental'noi Biologii, Vol. 90, No. 11, pp. 599-600, November, 1980. Original article submitted February 4, 1980.

 0007-4888/80/9011-1586$07.50

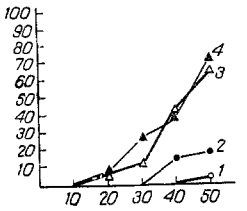

Fig. 1. Increase in frequency of appearance of sarcomas of the uterus under the influence of EDP. Abscissa, time after beginning of administration of DMH (in weeks); ordinate, number of animals with sarcomas of the uterus (in %). 1) DMH (group 1); 2) DMH + EDP, 10 weeks (group 2); 3) DMH + EDP, 20 weeks (group 3); 4) DMH + EDP, 25 weeks (group 4).

TABLE 1. Frequency of Development of Sarcomas of the Uterus 50 Days after Beginning of Experiment

Group	Treatment	Duration of injection of EDP, weeks	Number of mice			χ^2, P†
			total †	with sarcomas of uterus		
				abs.	%	
1	1,2-DMH	—	30	1	3,3	
2	1,2-DMH+ EDP	10	28	7	25	4,04, <0,05
3	1,2-DMH+ EDP	20	26	17	65,4	22, <0,001
4	1,2-DMH+ EDP	25	26	19	73	23, 0,001
5	EDP	25	27	—	—	—

*Survived until detection of first uterine sarcoma (17 weeks).
†Compared with group 1; P calculated with Yates' correction for the small number of animals.

The experimental results revealed the very strong stimulating action of EDP on the development of uterine sarcomas induced by DMH. In previous experiments [1-3], in which DMH was given for 30-40 weeks, the frequency of development of uterine sarcomas was 48.3-65%; the first tumors were found 29-35 weeks after the beginning of the experiment. In the present experiments, administration of DMH for 10 weeks combined with injection of EDP for 20-25 weeks thus induced tumors with the same or even a higher frequency than after administration of DMH alone for 30-40 weeks. Furthermore, the time of appearance of the first tumors was shortened by at least 10 weeks.

The marked potentiating effect of EDP on the induction of sarcomas in the uterus by DMH resembles to some extent the results of the combined action of carcinogens and croton oil (or its active principle, phorbol myristate acetate, in both cases the carcinogen induces the appearance of tumors (in small numbers) after a long latent period, but the action of the stimulating agent (EDP in the present experiments or phorbol myristate acetate in the experiments with the cutaneous carcinogen) significantly increases the frequency of tumor development and considerably shortens the time of their appearance. Considering that EDP in the present experiments did not induce sarcomas of the uterus during the period of observation, this new model can be regarded as a convenient one with which to study the stimulating (cocarcinogenic) action of estrogens on chemical carcinogenesis. This model has two distinctive features. First, it uses a carcinogen (DMH) close in the mechanism of its action to nitroso compounds, whereas until recently usually polycyclic aromatic hydrocarbons have been used in such experiments, such as those to study the effect of hormones

on induction of tumors of the mammary gland or uterus. Second, the estrogen in this case stimulated growth of an induced connective-tissue malignant tumor, whereas previously the objects on which estrogens acted were as a rule tumors of epithelial origin.

As regards the mechanisms of the stimulating action of the estrogen on sarcoma development in the uterus, the possibility that the estrogen may affect binding of metabolites of DMH with cell macromolecules or stimulation of proliferation of the mesenchymal elements of the uterus must be borne in mind. The latter suggestion seems more important, considering the great increase in the frequency of tumors in the animals of groups 3 and 4 compared with group 2, in which EDP was given simultaneously with DMH and, consequently, it could affect interaction between carcinogenic metabolites and the cells. In groups 3 and 4, in which the highest frequency of development of uterine sarcomas was observed, EDP was given during the last 10 weeks (group 3) or 15 weeks (group 4), after exposure to DMH had ceased. Allowing for the very rapid excretion of DMH from the body (under 24 h) and the fact that its carcinogenic metabolites are short-lived compounds, the effect of EDP on interaction between metabolites and target cells under these conditions can be completely ruled out. Consequently, the difference in the frequency of appearance of tumors in the animals of group 2, on the one hand, and in the mice of groups 3 and 4, on the other hand, can be ascribed on reasonably solid grounds to the intensified proliferation of cells transformed by DMH, induced by EDP.

LITERATURE CITED

1. E. A. Ird and I. O. Smirnova, Éksp. Onkol., No. 1, 69 (1979).
2. V. S. Turusov, L. S. Bazlova, and V. A. Krutovskikh, Byull. Éksp. Biol. Med., No. 5, 458 (1979).
3. V. S. Turusov, L. S. Bazlova, and N. S. Lanko, Cancer Lett., 3, 37 (1977).

EFFECT OF *Brucella abortus* ON GROWTH OF GRANULOSA-CELL CARCINOMA OF THE OVARY

N. P. Litvinikova, L. P. Trubcheninova, and A. Yu. Baryshnikov

UDC 618.11-006.6-092:576.851.42

KEY WORDS: *Brucella abortus*; adoptive transfer; carcinoma of the ovary.

In recent years, besides systematic adjuvants such as *C. parvum* and BCG, the antitumor action of *Brucella abortus* has been intensively studied. An inhibitory action of *B. abortus* has been demonstrated on the development of Rauscher and Graffi virus leukemias and on the growth of ascites and solid tumors [1-5, 12].

The object of this investigation was to study the effect of *B. abortus* (strain 19-BA) on growth of granulosa-cell carcinoma OC-1-72 of the ovary. Optimal doses, ways, and methods of administration of *B. abortus* and the possibility of adoptive transfer of inhibition of tumor growth by peritoneal exudate (PEC) and spleen cells were studied.

EXPERIMENTAL METHOD

Living brucellosis vaccine from Omsk Research Institute of Natural Food Infections, prepared from vaccine strain 19-BA of batches 19-72 and 13-2, was used in the experiments. The vaccine was diluted with physiological saline and injected intraperitoneally, intravenously subcutaneously, or into the tumor nodule. The vaccine was killed by heating to 60°C for 1 h.

Oncologic Scientific Center, Academy of Medical Sciences of the USSR, Moscow.

(Presented by Academician of the Academy of Medical Sciences of the USSR L. M. Shabad.) Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 90, No. 11, pp. 600-602, November, 1980. Original article submitted July 10, 1979.

0007-4888/80/9011-1588$07.50