16801

Action of Furacin in Delaying Growth of a Transplanted Fibrosarcoma in Mice.*

MORRIS N. GREEN† AND CHARLES E. FRIEDGOOD.‡ (Introduced by Stuart Mudd.)

From the Departments of Bacteriology and Surgical Research, Medical School, University of Pennsylvania, Philadelphia.

Relatively little is known regarding the chemotherapy of tumors. Greenberg and Schulman[1] recently suggested that the search for new chemotherapeutic agents against neoplasms might be facilitated by using the "metabolite antagonism" approach. This concept has been extensively applied in research directed towards finding new antibacterial agents.

Furacin§ (5-nitro-2-furaldehyde semicarbazone) inhibits the growth of a large number of gram positive and gram negative bacteria.[2] Green[3] recently has shown that furacin inhibits bacterial enzymes involved in glucose and pyruvate metabolism. The following experiments were designed to test the effect of furacin on growth of a transplanted fibrosarcoma.

Materials and methods. Forty adult inbred C3H mice of the Andervont strain were used. They were all transplanted with an equal amount of mouse sarcoma S-13‖ into the right axillary space.

Furacin was prepared for injection by suspending finely powdered crystals in peanut oil, using a concentration of 200 mg per ml. The furacin was administered by subcutaneous injection in the dorsal region.

The animals were divided into 4 groups of 10 each and treated as follows:

Group I One week after transplantation, 0.1 ml of furacin suspension (containing 20 mg of furacin) was injected.

Group II Three days prior to transplantation, the animals were given 0.1 ml of the furacin suspension followed by another injection of the same dose a week after transplantation.

Group III This group were also injected with 0.1 ml of the furacin suspension 3 days prior to transplantation, again after one week and 2 weeks after transplantation.

Group IV This was the control group. The tumor was transplanted as in the other groups but no furacin was given.

All the animals were housed in wire cages and were fed Purina Fox Chow stock diet. The tumors were palpated periodically and the progress of growth recorded. At the time of death the animals were autopsied and sections of the tumor, lung, kidney and adrenal glands were prepared for microscopic examination.

Results. Table I shows the effect of furacin in prolonging the life span of the tumor-bearing mice. It will be noted in Table I that there was less than one chance in a thousand that the differences in the average survival of the furacin-treated and control groups could be due to chance alone. Although furacin exhibited a definite inhibitory effect on the growth of the tumor, eventually all the animals died as a result of the malignancy. The most effective retardation of growth was obtained with three doses of furacin (Group III). Under these conditions, the

* This work was supported by a grant from the Eaton Laboratories, Inc., Norwich, N.Y.

† Present address: School of Medicine, University of Missouri, Columbia, Mo.

‡ Present address: Mt. Sinai Hospital, New York, N.Y.

1 Greenberg, D. M., and Schulman, M. P., *Science*, 1947, **106**, 271.

§ Furacin was supplied by Dr. L. Eugene Daily of the Eaton Laboratories.

2 Dodd, M. C., *J. Pharm. Exp. Therap.*, 1946, **86**, 311; Shipley, E. R., and Dodd, M. C., *Surg., Gyn., Obst.*, 1947, **84**, 366.

3 Green, M. N., *Fed. Proc.*, 1948, **7**, 305; in press, *Arch. of Biochem.*

‖ The original tumor was supplied by Dr. Margaret R. Lewis of the Wistar Institute. It gives 100% takes on transplantation in this strain of mice.

TABLE I.
Survival Time in Days of Mice After Implantation of S-13 Tumor and Treatment with Furacin.

Group	Treatment*	Avg survival (M)	Range	Stand. Dev. (σ)	tt	P‡
I	20 mg furacin inj.	29.2	22-34	3.55	5.76	>0.001
II	40 " "	34.2	30-42	3.60	8.93	>0.001
III	60 " "	37.4	30-47	4.68	9.27	>0.001
IV	Control	20.9	18-25	2.63	—	—

* For details of treatment see under description of methods in text. Each group contained ten mice.

† $t = \dfrac{M_1 - M_2}{\sqrt{\frac{\sigma_1^2}{9} + \frac{\sigma_2^2}{9}}}$

‡ A value of $t = 4.781$ gives a chance variation (P) of 0.001.

tumor transplant was not palpable for 2 weeks, while in the control group, the tumor was palpable at the end of 5 days following transplantation. There was no evidence of metastasis in any of the animals; the fibrosarcoma growing locally was well encapsulated. In the treated animals, there was microscopic evidence of cellular degeneration with pyknotic nuclei and decreased mitotic activity of the tumors in the treated mice as distinguished from those in the untreated controls. The furacin was largely absorbed because only negligible amounts of the drug were observed at autopsy at the site of injection.

It is of interest to note that adrenal enlargement was observed in the furacin treated animals. Histologically the fascicular zone of the cortex appeared hypertrophied. The effect of furacin on the adrenal cortex will be reported in a subsequent paper. Using furacin in the doses described above, there was no evidence of parenchymal damage to the liver, kidney or lungs.

Discussion. These experiments indicate that furacin may inhibit the growth of neoplastic tissue. The histological findings in the treated tumors indicate that furacin has a selective effect on the tumor tissue. Experiments are being continued to determine which factors explain the action of furacin in inhibiting tumor growth.

Summary. Furacin inhibits the growth of mouse sarcoma S-13 in C3H mice. The average survival time of the control mice after implantation of the tumor was 21 days. The average survival time of the furacin-treated mice varied from 29 to 37 days, depending on the amount of the furacin given. Histological examination of the treated tumors reveal some cellular degeneration and a lessened mitotic activity. Hypertrophy of the adrenal cortex and symptoms of B complex vitamin deficiency were observed in the furacin-treated animals.

The authors wish to thank Dr. Margaret Reed Lewis of the Wistar Institute for her generous advice and interest in this problem as well as for cooperation in supplying the tumors and animals used in these experiments. We are also indebted to Dr. Stuart Mudd for his interest and support.