EFFECT OF MODE AND SCHEDULE OF ADMINISTRATION ON CARCINOGENIC EFFECT OF N-METHYL-N'-NITRO-N-NITROSO-GUANIDINE IN RATS

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The method of long-term administration of N-methyl-N'-nitro-N-nitroso-guanidine (MNNG) with the drinking water is usually used to induce gastric tumors in rats [1, 3, 8]. A drawback of this method is the long time required for the experiments. The latent period of development of tumors of the gastrointestinal tract can be shortened if high single doses of MNNG are given perorally through a tube [5, 9]. The powerful carcinogenic effect of a mixture of two nitrosamines (MNNG and methylnitrosourea) dissolved in dimethylformamide is given as a single injection into the antral-pyloric part of the stomach [2]. However, even with this experimental schedule, with its unnatural and complicated method of administration of the carcinogens, necessitating a surgical operation, the latent period of tumor development remains long. By interrupted administration of MNNG through a tube [10] the process of carcinogenesis can be significantly accelerated, but because of death of the animals in the early period of the experiment, this method has not achieved widespread popularity.

We have modified this method, reducing the size of the single dose and lengthening the intervals between injections of MNNG, and used it to study carcinogenesis in rats and its dependence on the mode and schedule of its administration.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats initially weighing 200-250 g and receiving a standard diet. The rats were weighed weekly. The experimental rats (30) each received 1-2 ml of an aqueous solution of MNNG (the MNNG was synthesized by É. M. Osipova, Senior Engineer of the Laboratory of Chemical Synthesis, All-Union Oncologic Scientific Center, Academy of Medical Sciences of the USSR) in a concentration of 5 mg/ml via gastric tube daily for 2-3 days. The doses were repeated after 4-10 days. The size of the dose and the duration of the interval between doses of the carcinogen varied depending on the animals' state. The total dose of MNNG received by each rat was 250 mg. Ten intact rats served as the control. The experiment ended 25 weeks after it began. Rats which were still alive were killed with ether vapor. All the rats underwent autopsy. All the tumors found, and also organs with signs of pathological changes, were studied histologically. Paraffin sections were stained with hematoxylin and eosin.

EXPERIMENTAL RESULTS

The mean values of the body weight of the rats in the experimental group were distinctly lower than the corresponding values in the control. At the end of the experiment the mean body weight of animals in the experimental group was 368 ± 8.6 g compared with 425.0 ± 16.0 g in the control. Of the 30 rats used in the experiment, by the time of appearance of the first tumor 26 animals remained alive. The number of rats remaining alive after 25 weeks in the experimental group was 64.5% of their number in the control. The causes of death of the animals were intestinal atony, diarrhea, and pneumonia. The experimental rats showed degenerative changes in the mucous membrane of the gastrointestinal tract in the form of multiple erosions and (or) acute

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ulcers. These were most marked in the first 2-3 days after administration of MNNG. During the next 5-7 days, when no MNNG was given, epithelization of the damaged areas was observed. Alternation of injury and repair of the mucous membrane of the gastrointestinal tract was observed throughout the experiment.

Tumors were found in 26 rats, i.e., in all rats surviving until the appearance of the first tumor. All tumors were located in the gastrointestinal tract: stomach, small intestine, and liver. Tumors of the forestomach were found in 26 (100%) rats, tumors of the glandular part of the stomach in five (19.2%), and tumors of the small intestine in seven (26.9%) of the 26 rats. Lesions of the gastrointestinal tract were multiple in half of the cases. The first tumor of the forestomach was found on the 84th day, in the glandular part of the stomach on the 168th day, and in the small intestine on the 163rd day of the experiment. The average time of discovery of tumors was: 91.3 ± 3.8 days for the forestomach, 168.6 ± 0.2 days for the glandular part of the stomach, and 166.3 ± 1.2 days for the small intestine. Histologically the tumors of the forestomach were multiple papillomas, squamous-cell keratinizing carcinoma, and sarcoma; tumors of the glandular part of the stomach were adenomas and adenocarcinomas; tumors of the small intestine were adenocarcinomas and sarcomas. Metastases of a squamous-cell carcinoma were found in the lung and peritoneum of two rats. One rat developed carcinoma of the liver. No changes were found in the mucous membrane of the gastrointestinal tract of rats of the control group. Under our experimental conditions, a high proportion of animals of the experimental group developed tumors in different parts of the gastrointestinal tract. An advantage of this method is the rapid development of the induced tumors, whose frequency was already quite high by the 25th week, whereas when MNNG is administered with drinking water, the average latent period of development of gastric tumors was 61.4 ± 8.2 weeks, and of tumors of the small intestine 49.2 ± 4.9 weeks [4]. The total dose of MNNG at the 7th month of administration with drinking water also was much greater, and was almost twice that which we used in our experiments. The fact that gastric carcinogenesis is stimulated by exposure of the regenerating epithelium to MNNG also has been described in the literature [10]. Our own results are in agreement with the published data. The use of lower doses and longer intervals between doses of the carcinogen, in our investigation, reduced the mortality of the animals in the early stages of the experiment. Cases of simultaneous development of tumors in different parts of the gastrointestinal tract are known in clinical oncology [6, 7]. It can be concluded from the results of the present investigation that this method of tumor induction is an effective model which can be used with advantage in experimental oncology to study the morphogenesis of multiple tumor development in organs of the gastrointestinal tract, and also in the search for inhibitors of carcinogenesis and the study of the therapeutic and prophylactic action of chemical preparations.

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