

CHANGES IN THE ANTITUMOR ACTIVITY  
OF THIOPHOSPHAMIDE (THIO-TEPA) DUE  
TO ADRENALIN IN EXPERIMENTAL CONDITIONS

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We have previously shown that thiophosphamide (triethylenimide of triphosphoric acid, thio-TEPA), in tolerable therapeutic doses, causes distinct changes in the glands of internal secretion and that, by means of various factors acting on the endocrine system, it is possible to modify both the toxic properties of these preparations and their anti-tumor activity [5]. These observations suggest that thiophosphamide and analogous preparations may act indirectly (through the endocrine system) on tumors.

In recent years the probability of an indirect action of alkylating agents on tumors has become more evident as a result of the discovery of new facts [1, 6, 8]. It is not yet certain, however, whether only the endocrine system takes part in the indirect action of these substances or whether other systems of the body, regulating tissue growth and differentiation, such as, for example, the nervous system, are also involved. In this connection, it was of interest to study the antitumor activity of ethylenimine derivatives and, in particular, thiophosphamide when their administration was accompanied by that of hormones and preceded by interference with nervous processes. The need for such an investigation is also demonstrated by facts previously established by us: the antitumor activity of ethylenimine derivatives is enhanced to some extent if they are given in conjunction with chlorpromazine or with ganglion-blocking substances [3]. In this paper we describe the results of a study of the general toxic and antitumor action of thiophosphamide when administered together with adrenalin.

EXPERIMENTAL METHOD

Eleven experiments were carried out on 303 male rats weighing 130-140 g with a transplantable sarcoma 45. Each experiment was conducted on 4 groups of animals: 1 control and 3 experimental groups (the experimental rats received thiophosphamide, adrenalin, and a combination of both preparations). Administration of the preparations began on the 7th day after transplantation of the tumor. Thiophosphamide was injected intraperitoneally and adrenalin subcutaneously, and both drugs were given at the same time. On the 17th day after inoculation of the tumor suspension, the animals were sacrificed by decapitation and weighed, and the weight of the tumor, the spleen, and the endocrine organs was determined. The influence of the preparations on growth of the tumor was assessed by the coefficient of activity ( $K_a$ ) [2, 4]. When the general action of the preparation was assessed, consideration was paid to the animals' condition, the change in weight of the spleen and endocrine organs, and also the coefficient of growth ( $K_g$ ) [2, 4]. The numerical data in all cases were analyzed by statistical methods.

The thiophosphamide used in the experiments was synthesized in our Institute by A. A. Kropacheva and co-workers, and the adrenalin was a commercial 0.1% solution in ampules. Thiophosphamide solution of the required concentration was made up before use.

## EXPERIMENTAL RESULTS

In 9 experiments thiophosphamide, in the doses used (1.0 and 0.5 mg/kg) exhibited a clear antitumor effect [ $K_a = (+49) - (+76)\%$ ]. The action of the preparation on the organism was shown by a smaller increase in body weight of the animals by comparison with the controls, and by a significant decrease in the weight of the thymus (by 68%;  $\alpha > 0.95$ ) and spleen (by 32%;  $\alpha > 0.95$ ). Any action on the pituitary, thyroid, adrenals, and testes and appendages was ill defined.

Administration of adrenalin in doses of 1 and 2 mg/kg also was accompanied by a slowing of the rate of growth of the transplanted sarcoma 45 of rats [ $K_a = (+36) - (+62)\%$ ], although this effect was weaker than in the animals receiving thiophosphamide. A dose of adrenalin of 0.25 mg/kg proved ineffective against growth of the tumors. The action of adrenalin on the animals in these doses varied with the dose. In a dose of 2 mg/kg considerable emaciation of the animals was observed, with loss of weight of the appendages (by 34%,  $\alpha > 0.95$ ), the thyroid (by 27%,  $\alpha > 0.99$ ), the hypophysis (by 19%,  $\alpha > 0.9$ ) and an increase in weight of the adrenals (by 15%,  $\alpha > 0.9$ ). A reduction of the dose to 1 and 0.25 mg/kg led to appreciable weakening of the action of adrenalin, both on the organism as a whole ( $K_g$  was close to zero) and on its endocrine system.

When thiophosphamide and adrenalin were administered together, in the 9 experiments in which adrenalin was given in doses of 1 and 2 mg/kg a more marked antitumor effect was found than when these substances were given separately in the same doses. The inhibition of growth of the tumors was 12-52% greater when the drugs were given together than when thiophosphamide alone was used.

The effect of a combination of these drugs on the animals was not constant. In some cases their combined administration led to a more marked emaciation of the animals, while in others, on the contrary, the manifestations of the general toxic effect were less marked than when thiophosphamide and adrenalin were given separately. No direct relationship was observed between this effect and the dose of adrenalin. The action of a combination of these substances on the spleen and endocrine organs was similar to the action of either adrenalin (pituitary, thyroid, adrenals, pancreas) or thiophosphamide (spleen, thymus) alone, while the decrease in weight of the testes and appendages was more marked than when the 2 drugs were given separately.

Since thiophosphamide and adrenalin, in the above doses in most experiments, each showed distinct antitumor activity, it was important to elucidate the character of the increase in their antitumor effect when administered simultaneously. Comparison of the values of  $K_a$  in the 3 experimental groups showed that in 6 experiments the increase in the antitumor effect observed after combined administration of thiophosphamide and adrenalin could be attributed to the simple summation of the effects of each, while in 5 experiments the sum of the  $K_a$  values of thiophosphamide and adrenalin, when given separately, was significantly greater than  $K_a$  for a combination of these drugs. Meanwhile, the results of 2 experiments indicated a potentiating effect of adrenalin on the antitumor activity of thiophosphamide. Whatever the character of the potentiation of the antitumor effect by simultaneous administration of thiophosphamide and adrenalin, the practical value of this combination is obvious.

No conclusion can be drawn from these experiments regarding which of the pharmacological properties of adrenalin is mainly responsible for its inhibitory action on tumor growth and, in consequence of this, responsible for the increased antitumor effect of a combination of thiophosphamide and adrenalin. However, in face of reports in the literature showing that adrenalin acts on the endocrine system and, in particular, on the function of the anterior lobe of the pituitary [7], and of the results of the present experiments, it cannot be wholly denied that the changes caused by adrenalin in the endocrine system are concerned in this effect.

## SUMMARY

The antineoplastic activity of thiophosphamide, administered simultaneously with adrenalin was studied in rats with transplanted sarcoma 45.

Thiophosphamide was administered intraperitoneally in a dose of 0.5-1.0 mg/kg body weight, whereas adrenalin was given subcutaneously in 3 doses: 2 mg/kg, 1 mg/kg and 0.25 mg/kg. Administration of the preparations was started on the 7th day after tumor transplantation and continued for 8 days. Thiophosphamide and adrenalin administered simultaneously produced a more marked antineoplastic effect than when given separately in the same doses.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

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