EFFECT OF ANTI-INFLAMMATORY AND ANTIPROTEOLYTIC PREPARATIONS ON VASCULAR DISORDERS IN THE INTESTINE OF ANIMALS IRRADIATED IN SUPERLETHAL DOSES

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Rats were irradiated with superlethal doses of Co^{60} γ rays (900 and 1000 R) and then were given intraperitoneal injections of antiphlogistic (butadione 5 mg/kg, paracetamol 15 mg/kg, rheopyrine 3 mg/kg) and antiproteolytic (trasylol 7.5 c. i. u./kg combined with ε-aminocaproic acid 200 mg/kg) preparations. The states of the vessel walls of the small and large intestine of the rats were assessed 72 h after irradiation by the migration of Evans' blue dye into the tissues of the intestine. Butadione proved to be the most effective drug and considerably reduced the quantity of dye in the tissue. It increased the survival time of the irradiated animals, from which it can be concluded that vascular disorders play an important role in the pathogenesis of the intestinal form of radiation sickness.

After exposure to radiation, stasis of blood develops in the intestinal mucous membrane [6, 7], extensive hemorrhages and foci of necrosis in the capillary walls appear [4, 5, 9], and the lumen of the arterioles of the submucosa becomes constricted and becomes occluded [9] by edema and by local constriction bands [2].

Attempts were made to overcome the vascular disorders in irradiated animals with the aid of trasylol [1] in conjunction with ε-aminocaproic acid and also with a series of antiphlogistic drugs (butadione, rheopyrine, paracetamol), in the mechanism of whose action an important role is played by their vasoconstrictor properties and their ability to increase the resistance of blood vessel walls [3, 8, 13].

EXPERIMENTAL METHOD

Experiments were carried out on 250 Wistar rats of both sexes weighing 150-180 g. An intestinal form of acute radiation sickness was induced by whole-body γ-ray irradiation on a "Gamma-Cell" apparatus in doses of 900 and 1000 R, in a dose rate of 34 R/sec.

Injury to the blood vessels of the small and large intestine was assessed by the quantity of Evans' blue dye contained in the tissues of the intestine after intravenous injection (20 mg/kg); the dye was estimated colorimetrically 3 days after irradiation. This time corresponds to the severest clinical manifestations of the intestinal form of radiation sickness. Trasylol (7500 c. i. u./kg body weight six times a day), ε-aminocaproic acid (200 mg/kg four times a day) butadione (5 mg/kg four times a day), paracetamol (15 mg/kg four times a day), and rheopyrine (3 mg/kg twice a day) were injected intraperitoneally daily for 3 days after irradiation

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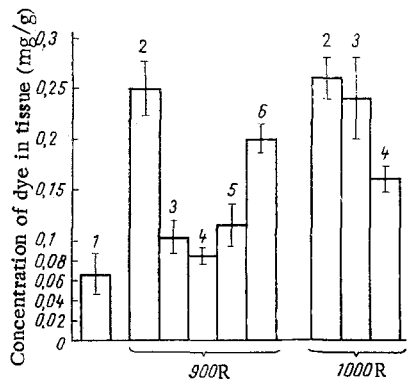

Fig. 1. Change in concentration of Evans' blue dye in tissues of small intestine of rats 72 h after irradiation in doses of 900 and 1000 R: 1) intact animals; 2) irradiated; 3) irradiated, then receiving trasylol with ε-aminocaproic acid; 4) the same, but receiving butadione; 5) the same, but receiving paracetamol; 6) the same, but receiving rheopyrine.

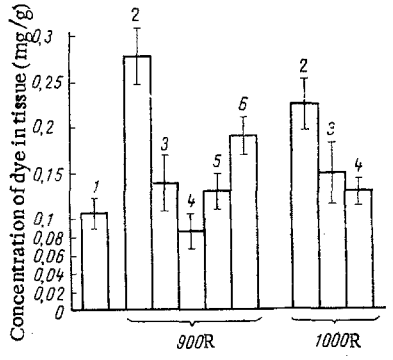

Fig. 2. Change in concentration of Evans' blue dye in tissues of large intestine of rats 72 h after irradiation in doses of 900 and 1000 R. Legend as in Fig. 1.

At the end of the experiment, under superficial anesthesia, the retro-orbital sinus of the rats was punctured to obtain blood for determining the cell counts.

EXPERIMENTAL RESULTS

In the irradiated, untreated rats the cell counts in the peripheral blood fell sharply. Marked diarrhea developed after 2.5-3 days. After irradiation in a dose of 900 R there was a marked increase in the concentration of dye in the tissues of the small (0.25 ± 0.026 compared with 0.07 ± 0.0025 mg/g in the control) and large (0.28 ± 0.029 compared with 0.007 ± 0.028 mg/g in the control) intestine.

In rats treated with antiproteolytic drugs (Fig. 1) the quantity of Evans' blue dye migrating into the tissue of the small intestine was reduced by more than half the amount migrating in the irradiated control animals. Of the antiphlogistic drugs used, butadione had the strongest action on migration of the dye into the tissue of the small intestine. Paracetamol reduced migration of the dye rather more weakly, and rheopyrine had no such action whatever ($P > 0.05$). The drugs used had a similar action on the state of the blood vessels of the rats' large intestine. In this case also butadione was the most effective drug, reducing the migration of Evans' blue dye.

After irradiation in a dose of 1000 R, approximately the same quantity of dye migrated into the tissue of the small and large intestine as in rats irradiated in a dose of 900 R. The drugs had a much less marked action in this case than in animals irradiated in a dose of 900 R. Butadione, for instance, reduced migration of the dye by only 1.6 times, while trasylol in conjunction with ε-aminocaproic acid had no effect whatever on the vascular permeability of the small intestine.

The effects of both drugs on the permeability of the vessels of the large intestine was stronger (Figs. 1 and 2).

With the smaller dose (900 R) of irradiation the vessels of the small and large intestine were damaged to an equal degree, whereas after irradiation in the larger dose (1000 R) the vessels of the small intestine were more severely damaged than those of the large, and this accounted for differences in their response to the drugs.

In special series of experiments butadione and trasylol with ε-aminocaproic acid were given to the irradiated animals for 3-5 days. In some rats the mortality by this time was 88% after irradiation in a dose of 900 R and 100% after a dose of 1000 R.

The clinical picture of radiation sickness in the rats receiving butadione was the same as in the untreated animals, although somewhat more marked motor activity and less marked diarrhea were present. This difference became particularly conspicuous by the 5th day after irradiation. Administration of butadione reduced the mortality among the rats on the 3rd-5th day after irradiation in a dose of 900 R by 28%, and after irradiation in a dose of 1000 R by 15%. Rats receiving butadione survived on the average 2.5 days longer than the untreated rats.

Administration of trasylol with ε-aminocaproic acid had no appreciable action on the time of death of the animals irradiated in doses of 900 and 1000 R.

These results suggest that the vascular disorders in the intestine produced by irradiation of rats in superlethal doses can be partly reversed by the use of antiphlogistic drugs. It can also be postulated that the vascular disorders play an important role in the pathogenesis of the intestinal form of radiation sickness.

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