EXPERIMENTAL DEVELOPMENT OF COMBINED TREATMENT FOR ACUTE RADIATION SICKNESS

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INTRODUCTION

A wide application of nuclear energy in various areas of human activity and a growing number of workers occupationally exposed to radiation increase the risk of emergency (1-3). The most severe impact results from nuclear power plant accidents, especially those with a reactor core damage, as in the case of Chernobyl accident, the largest one, when many persons received doses which caused acute radiation sickness. Complicated and varied pathogenetic mechanisms of acute radiation sickness as well as the fact that there are certain stages in its course suggest that a combined treatment is required. Our studies aimed at mitigating the cardinal symptoms of acute bone-marrow radiation syndrome were carried out for years along several lines:

- development of drugs and procedures for early treatment to be effective within the first 24 h postirradiation;
- search for drugs to intensify hemopoietic recovery when used in the latent period;
- investigation of drugs for prophylaxis or incidence reduction of infectious syndrome
- in the agranulocytosis period.

The practical results of the studies are presented in this paper.

MATERIALS AND METHODS

Animals: Male and female mongrel dogs, 1 to 5 years old, weighing 10-20 kg and maintained under the vivarium conditions on a standard diet.

Irradiation: A single uniform total-body exposure to ^{60}Co gamma-rays from the experimental generator EGO-2 at a dose rate >0.6 Gy/min and doses of 3.46 Gy (LD_{90}) and 3.65 Gy (LD_{95}). In special series of experiments to assess the preventive agents for early radiation syndrome, radiation doses were 8 Gy and 20 Gy.

Remedies investigated for modification of radiation damage manifestations: Dimetcarb and dixaphen, complex drugs comprising dimetpramide - an antiemetic, and sydnocarb or caffeine with ephedrine - central nervous system stimulators; prodigiosan, a lipopolysaccharide obtained from *Bacterium prodigiosum*; proteus vaccine; derinate, a DNA-based drug; estradiol dipropionate; hemosorption, a detoxication procedure; and an anti-infectious complex including broad-spectrum antibiotics and vitamins.

Efficiency criteria: The severity of acute radiation sickness and its symptoms, changes in the peripheral blood (erythrocytes, hemoglobin, reticulocytes, ESR, thrombocytes, leukocytes, differential blood count), 45-day dog survival.

Statistical processing: ^{2} test, Student's t-test, Wilcoxon-Mann-Whitney test.

RESULTS AND DISCUSSION

Early radiation responce shows as nausea, vomiting, hypodynamia,asthenia, undue fatiguability. To prevent these symptoms, dimetcarb and dixaphen were used. In the dog experiments, at a dose of 8 Gy which causes 91% nausea, dimetcarb orally administered 1.5 h before or immediately after irradiation led to a 40% reduction, with less pronounced hypodynamia. The other drug, dixaphen, was injected intramuscularly. It is more efficient, having the ability not only to prevent but also to stop actual vomiting in 50-60% of animals at a dose of 20 Gy.

To decrease the early postradiation intoxication symptoms and to mitigate the subsequent acute radiation sickness course, the hemosorption efficiency was studied, with optimal application conditions specified. The results clearly demonstrate the procedure to be appropriate within the first 24 h postirradiation. Hemosorption makes the damage far less severe and increases the dog survival by 50% at LD_{95} (3.65 Gy).

The detoxicating effect of hemosorption manifested itself, in particular, in removal from the exposed dogs' blood of potential radiotoxins, medium-molecular compounds of peptide nature, their amount growing substantially in the early postradiation period. Special experiments showed that isolated polypeptides suppress the hemopoietic precursor cell pool at the level of granulocyte-macrophage committed cells. Hemosorption treatment resulted in a significant increase of these cells in the bone marrow and peripheral blood at the acute stage of radiation sickness as compared with the control.

Acute bone marrow syndrome was treated for with the drugs we combined into a group called "early therapy agents". These can stimulate cytokine production, step up repairing the initial radiation injuries, intensify restoration of the hemopoietic stem cell count and microenvironment. The drugs are efficient when used in the first 24 h postradiation. The dog experiments demonstrated that the drugs which belong to high-molecular compounds (derinate) or proteolypopolysaccharides (proteus vaccine, prodigiosan) mitigate distinctly the radiation sickness course and promote the peripheral blood reconstitution following a single subcutaneous or intramuscular injection in 24 h after irradiation. At a dose of 3.46 Gy (LD_{90}), the survival rate exceeded that of the control by 31-60% ($p<0.05$). In addition to higher survival, the treated dogs exhibited a much lower incidence of severe forms of acute radiation sickness (40-50%, with 96% in the control), less pronounced hemorrhagic syndrome and a less profound drop in some peripheral blood parameters than the control did. The best results were obtained for proteus vaccine: it was also efficient at a higher radiation dose (3.65 Gy), close to the lowest absolute lethal one, with a survival rate of 50-60% (5% in the control).

It is known that the principal critical point in the bone marrow of acute radiation sickness is the hemopoietic system and its status determines the outcome. Investigated as a stimulator of postradiation hemopoietic recovery was estradiol dipropionate, a steroid hormone involved in the regulation of hemopoiesis. It was injected intramuscularly every other day starting from the midlatent period, i.e. from 5 to day 19 postradiation. With this scheme, estradiol raised the survival rate up to 47% at LD_{95} ($p<0.05$), slowed down a drop of leukocytes and promoted their clear-cut earlier restoration compared to the control, thus shortening the agranulocytosis period. At the height of disease, 20 days postradiation, the leukocyte count was 0,5 10^9 and 1,0 10^9/l blood ($p<0.05$) in the control and treated animals, respectively.

The leukopoiesis-stimulating effect of estradiol is associated with increased number of myeloid series cells in the bone marrow, due to mature and young divisible cells, and of granulocyte-macrophage precursor cells in the bone marrow and peripheral blood.

To prevent agranulocytosis-related infectious complications, we developed rational complexes by combining antibiotics of different classes to be used in cycles. The application of these complexes of systemic-action antibiotics or poorly absorbed aminoglycosides with delayed administration (starting from day 6-7, twice a day) for microbial decontamination of the intestine alongside with vitamins increases the dog survival up to 60-100% at LD_{50}-LD_{90}. At the absolute lethal dose the effect drops down to 30-40% (Fig.). The antibiotic therapy significantly reduced the severity of clinical symptoms, successfully prevented infections and mitigated the course of complications developed. However, the treatment produced little or no beneficial effect on the damaged hemopoiesis.

With one of the drugs under investigation (derinate, proteus vaccine, estradiol) or hemosorption included into the antibacterial complex, the efficiency grew from 30-40% to 70-90% at a near-absolute lethal dose and the length of antibiotic therapy was shortened (Fig.).

This is of great importance since the therapeutic agents applied together with antibiotics reduce an adverse effect of the latter on hemopoiesis and immunity by shortening their use. Our data indicate that a combined application of the remedies studied and an antibiotic complex not only mitigated the damage but also enhanced hemopoiesis. The difference was most prominent for estradiol used in combination with antibiotics.

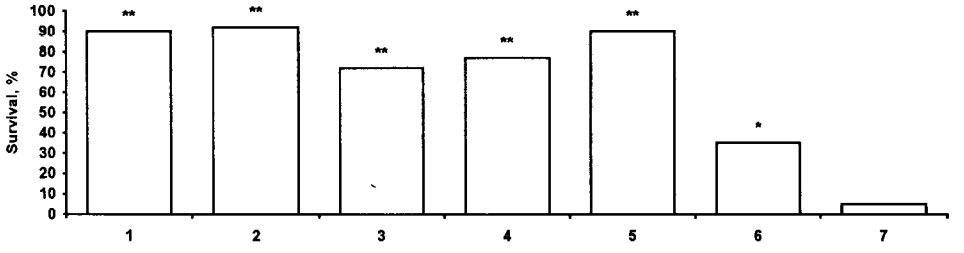

Figure. Efficiency of different remedies used in combination with antibiotics in dogs irradiated at a dose of 3.65 Gy (LD_{95}): 1 - hemosorption; 2 - proteus vaccine; 3 -prodigiosan; 4 - derinate; 5 - estradiol; 6 - antibiotics; 7 - control. Each group includes at least 10-12 dogs.
* significant difference from the control ($p < 0.05$);
** significant difference from antibiotics ($p < 0.05$).

Thus, the studies have demonstrated the efficiency of various remedies which should be included into the antibacterial complex to make it more effective in the treatment of acute radiation sickness. The results obtained conform with the evidence (4) that multiple administration of a cytokine (CSF) to exposed dogs adds to the antibiotic efficiency. The early therapy agents capable of stimulating the endogenic cytokine production and of enhancing the natural body resistance have the advantage of a single intake which facilitates essentially their practical application.

If the early therapy agents or hemosorption cannot be used within the first 24 h postradiation, we would recommend, as an alternative, that a hemopoietic stimulator (estradiol) should be included into the antibiotic complex starting from the midlatent period. The symptomatic drugs (dimetcarb or dixaphen) are also shown to be appropriate for prophylaxis and cure of early radiation response manifestation.

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