P-2b-72

APPLICATION OF RADIOPROTECTORS IN RADIATION PROTECTION

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INTRODUCTION

Possibility of protection from ionizing radiation when an organism, as a unit, absorbs radiated energy practically does not exist. In the previous investigations no medicine has been invented that could successfully be applied in therapy of radiation diseases. Today, in the cases of accidental irradiation with high doses of ion radiation and developing of radiation syndrome, today it is possible to apply only conservative and symptomatic therapy with poor prospects that results of treatment will be positive (1, 2).

Therefore, the activity of numerous investigators is directed towards finding an effective radioprotective mean that would successfully prevent development of radiation syndrome and protect cells and tissue from free radicals that appear as a consequence of interaction between radiation energy and the matter (3-6).

For this purpose several hundred thousands of different compounds, that had been considered potential chemical radioprotectors, have been tested. Out of total, 50.000 have shown greater or lesser radioprotective effect, and only some of them have shown such characteristics that could be used in protection of people. Among the investigated compounds certain number of them, under specific circumstances, have shown a considerably protective effect in the experiments with the animals (7, 8, 9)).

However, the fact is that nothing has been discovered that could have low toxicity, and high protective effect together with prolonged performance in the case of later radiation. Therefore, the aim of this work is to point out all the achieved results in the field of radioprotection on the base of information from literature and the results obtained form the experiments, and to stimulate an international collaboration and exchange of experience in this field.

DEVELOPMENT AND APPLICATION OF RADIOPROTECTORS IN RADIATION PROTECTION

Considering the results of investigating great number of radioprotective compounds, it can be stated that those containing sulphur have the most protective effect. That are aminothiols, aminodisulphides, tiourei derivatives, thiosulphur and thiophosphoric acid, dithiocarbamates, thiazole, some biogen amines and their derivatives (7).

Among the large number of tested compounds, the most examined were cisteamine derivatives, i.e. compounds known as aminothiol radioprotectors (8).

These radioprotectors synthesize in a form of ester with phosphor acid for achieving better stability, lower toxicity and for better penetration and distribution into the tissue. Carriers of radioprotective effect are free thiols that appear after taking radioprotector into the organism.

Radioprotective effect of these boundings is based on their ability to provoke hypocrisy, hypothermia, to form mixed disulphide with biological important macromolecules, to give exchangeable oxygen to the damaged molecules, to heighten the level of endogen glutathione, to neutralize free radicals, by which they support reparation of damages caused by radiation (9, 10, 11).

In Table 1 is given an overview of toxicity, protective doses and dose reproductive factors for some aminothiols.

Table 1. Toxic and protective doses and dose-reduction factor of some aminothiols

Radioprotector*	**Toxicity** LD_{50}(mg/kg)**	**Protective doses** (mg/kg)**	**DRF****
Cistein	1700	1200	1,7
MEA	200	150	1,7
Cistamin	220	150	1,7
AET	480	400	2,1
WR-638	1120	500	2,0
WR-2721	950	500	2,7
WR-36899	1120	450	2,2
WR-77913	3574	2200	2,0
WR-151327****	785	315	1,9
Merkaptoprophinonilglycin*****	2100	20	1,4
Glutathione	4000	4000	1,3

* Results from the research for $LD_{50/30}$ on mice radiated with X or gamma radiation.

** Received through i.p. injection, except for cistein that is applicated i.v.

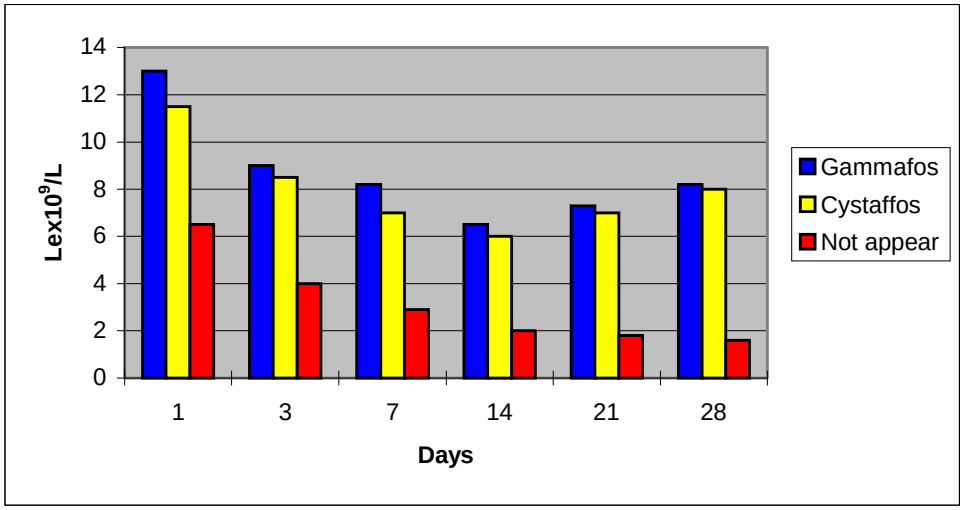
*** DRF (doze-reduction factor) = LD-50 radiation with protector / LD-50 radiation without protector

**** Achieves high protectiveness from neutron radiation

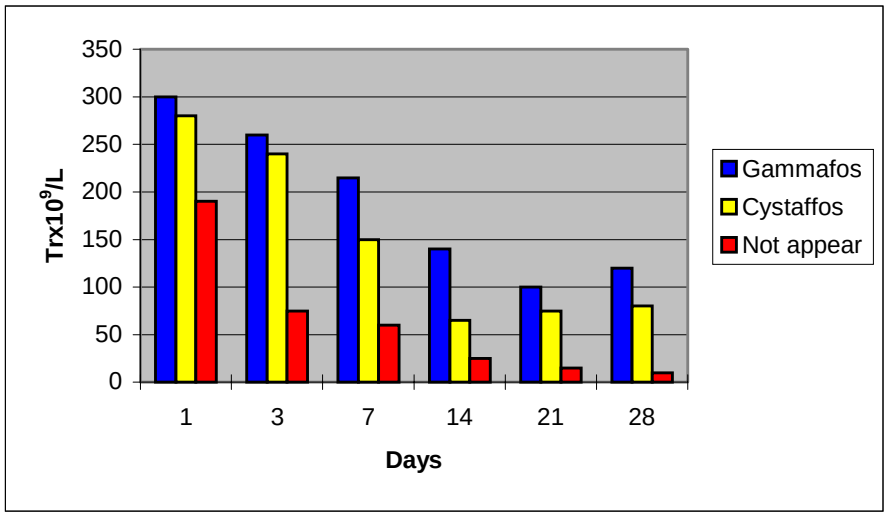
***** Achieves considerable protection applied after radiation

RESULTS AND DISCUSION

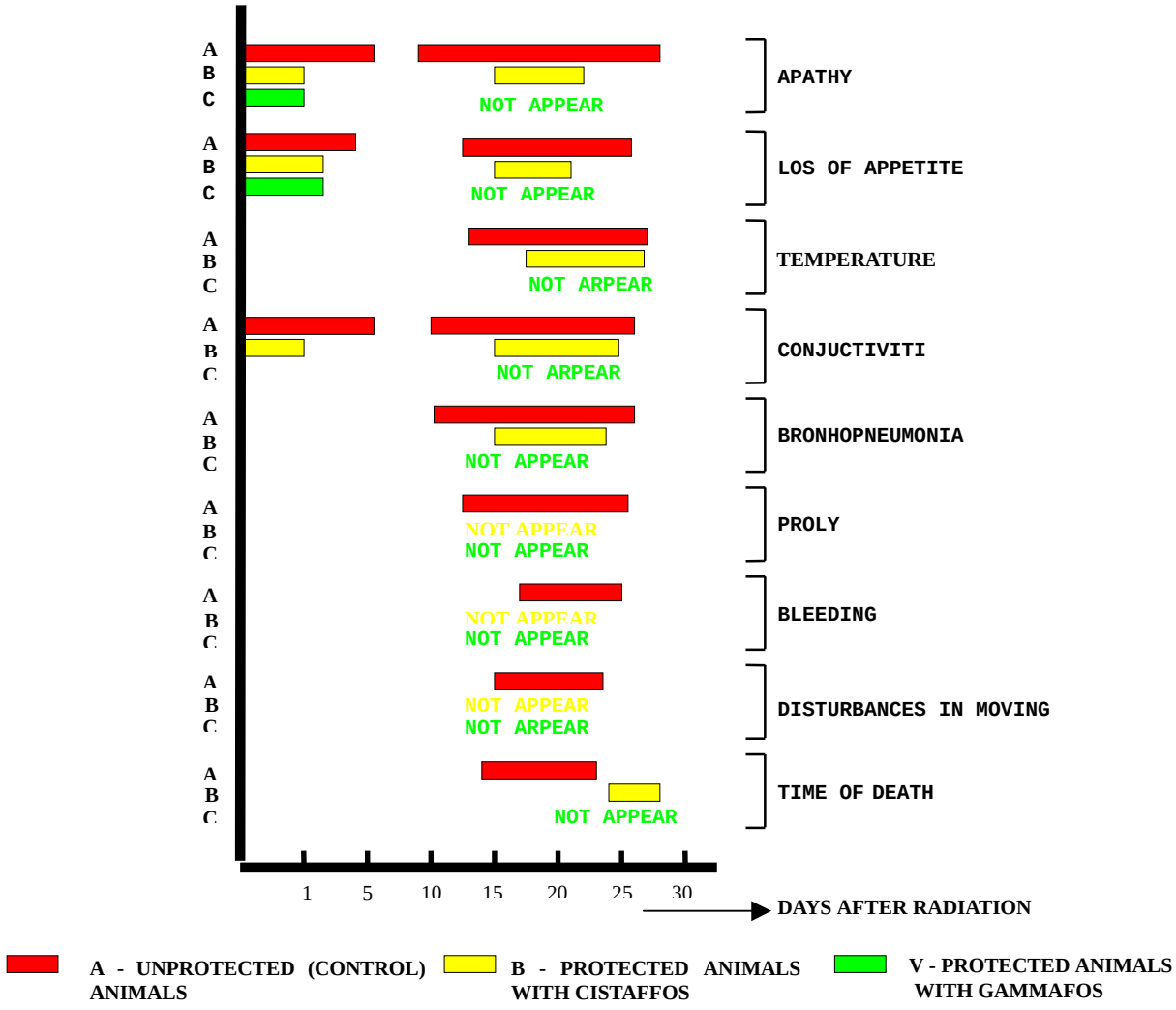
Comparative investigation of protective effects of castoffos (WR-638) and gammafos (WR-2721) in experiment with big aanimals (sheep, goats, pigs) have been performed at the end of 80s at the Institute for radiology at the Veterinary University in Sarajevo, where the first author conducted the experimental part of the investigation (8, 12-14). The experimental animals were radiated with polyletal doses of highly energized X-radiation on linear accelerator of 4 MeV and the protectors were applied 20 minutes before radiation. It has been found out that good protective effect is present in both radioprotectors (Graph 1 and 2, Picture I).



Graph 1. Changes in the number of leukocytes in protected and unprotected animals.



Graph 2. Change in the number of thrombocyte in protected and unprotected animals.



Picture 1. Frequency and appearing of clinical symptoms of acute radiation in protected and unprotected animals

Mechanisms that describe the phenomenon of radioprotection are complex and are still not enough well explained. However, it is known that radioprotective activity is accomplished through different mechanisms on three special levels of cell organization:

- molecular level
- physiological-biochemical level and
- organic level (9).

Molecular level:

- cleansing of free radicals
- donation of H-atom
- bounding to critical biological targets
- forming mixed disulphide formations

Physiological-biochemical level:

- hypoxsy
- loosening unproteined disulphide
- biochemical stroke
- Hypothermia.

Organic level:

- stimulating reparation of cells

Good radioprotector should have the following characteristics:

- possibility of acting after administration in the organism
- ability of fast resorbtion and distribution in tissue and organs
- great therapeutic application
- absence of unwanted accompanying effects
- absence of cumulative effect in repeated administration
- efficacy in the first hour after radiation
- efficacy for different types of radiation (X, gamma, neutrons)
- efficacy in joined and fraction radiation.

In other words, the ideal mean would be the one that can provide continual protection over several days, that could reduce the doses of radiation for factor 10 without appearing of accompanying and toxic effects (8).

Certain information, received from volunteers, tell us about the applying of WR-2721 as a possible radioprotector for people despite the presence of certain unwanted accompanied effect (9, 10, 11). As a potential mean for protecting people, this radioprotector is interesting for two reasons:

- As a protective mean in the conditions of mass radiation
  - accidents at the nuclear equipment
  - war
- Possibilities of using radiotherapy in cancer diseases
  - selective protection of healthy tissue in relation to the sick one
  - anticancerogen and antimutagen features.

In relation to the different protection of the healthy tissue in contrast to the tumor tissue, there are three assumptions (9):

- deficit vascularisation of tumor
- considerably slow process of concentrating protectors in the tissue of tumor
- often hypocrisy in the tissue of tumor, that can be an obstacle for activating of protectors that demand normal oxygenation.

Besides the appliance in radiotherapy, this protector may find its place in adjuvant in citostatic therapy of the

malignant diseases (10, 11), because it lessens unwanted effects of antineoplastic medicament (lessens hematotoxicity of ciklophosphamide and cis-platine).

In the 80'ss in our country the investigation on the field of radioprotection followed the trends in the world. This cannot be said for the 90's. Until the time when there will be better conditions for continuing of investigations in the field of radiobiology and radioprotection, we will have to apply recommendations given by international organizations in the field of radioprotection and should apply law regulations that demand applying of the means of protection:

- justified appliance of the source
- optimal protection from harm effects
- the limits of equivalent and effective doses
    - applying sources is justified if it gives positive neto-advantage

10. *exposure is as low as possible (ALARA- principal)*

When talking about any group or single radioprotectors, one has to have in mind that they cannot prevent damages of critical macromolecular and apply molecular cellular water in the case of extremely fast direct application of radiation energy. Radioprotective effect, indeed, is an ability of radioprotector to inhibit indirect radiation, to repair direct and indirect damages - if they occur - and to enable a spontaneous reparation of the cells damaged by radiation.

CONCSLUSION

Protection of people and animals from ioning radiation with chemical matters is certainly possible. However, before the concrete applying, we have to wait for a while and solve the problems concerning the unwanted effects and invent pharmaceutics formulation of radioprotectors for oral application.

In contemporary circumstances and with the available means of radioprotection, the basic problem can be summarized in estimating the risk from radiation, on one hand, and determining tolerant doses of radioprotectors and accompanying of the unwanted effects, on the other side. Yet, there are many situations where the advantages of radioprotectors may be used. Primarily, this can be applied in the situations when short stay in radiation zone is necessary and there ise no possibility of other protection (accidental situation with the sources of ion radiation, fixing the damage or the result of larger damages in nuclear plant and extraordinary situation when a danger of massive radiation is predictable.

For the moment it can be concluded that applying appropriate radioprotective mean in protection from the ioning radiation is possible only if the protector is used before exposure to radiation and if the protection lasts about 60 minutes after application.

GRATITUDE

The authors want to express gratitude to the investigation team at the Institute for radiology, Veterinary University in Sarajevo, especially to prof. dr Zdravko Milisevic and dr Emilija Horsic that gave a considerable contribution in the field of radioprotectors in FR Yugoslavia during the 80's.

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