RADIOPROTECTIVE DRUGS IN THE SYSTEM OF RADIATION PROTECTION OF EXPOSED RADIATION WORKERS AND POPULATION IN THE CASE OF NUCLEAR ACCIDENTS

LA Ilyin [1], IB Ushakov [2], MV Vasin [3]

[1]Burnasyan Federal Medical Biophysical Center of Federal Biomedical Agency, Moscow, Russia; [2]State Scientific Center – Institute of Biomedical Problems of Russian Academy of Science, Moscow, Russia; [3] Medicine of Catastrophe Department of Russian Medical Academy of Post-Graduate Education, St Polikarpova 10, Moscow 125284, Russia

e-mail: mikhail-v-vasin@yandex.ru

Abstract

Radiation workers can be exposed to most significant radiation risks during the early stage of radiation accidents at nuclear power plants. Radioprotector indralin has been developed as a mandatory standard agent for prevention of the acute radiation injuries. Indralin (B-190), being a radioprotective drug of emergency action, is designed to prevent the acute radiation damage at exposures to a high dose rate of ionizing radiation (>1 Gy/hour) and particularly to reduce the risk of mortality from emergency exposures at the doses that cause severe and extremely severe forms of acute radiation illness. According to the dose reduction factor, the expected radiation protective effect of the radioprotector for humans is up to 1.5. The drug betaleukin (recombinant human IL-1β) proposed as agent of early urgent anti-radiation therapy applying within two hours after irradiation. The antiemetic drug latran (ondansetron) has included in first-aid kit of personnel for prevention and arrest of primary radiation syndrome, potassium iodide tablets − for protection of thyroid gland from its injury by iodine radionuclides. To prevent resorption in the gastrointestinal tract (due to the retrograde intake from the respiratory system) of cesium and strontium radionuclides, ferrocene and adsobar or algisorb are administered, correspondingly. Sodium-calcium and zinc salts of pentetic acid (pentacin and zinkacin) are applied to fight against the incorporation of plutonium, TUE, alkaline-earth and rare-earth radionuclides. Key radiation protection measures of the exposed population at the areas of radioactive fallouts from the accidents at nuclear power plants are primarily defined by organizational measures of a sanitary nature.

Keyword: *indralin, iodide potassium, ferracene, algisorb, pentacin, zincacin, riboxin*

Out of the analysis of space and time parameters, and sequence of events in large radiation accidents, the overall affected area can be segmented into the zones of highly probable people's deaths and acute effects of exposure [1]; probable non-lethal sub-acute and chronic exposure to gamma-beta-radiations from radionuclides on- and off-site in the accident elimination activity [2]; where normal life is impossible or difficult [3], and less contaminated by radioactivity and yet to be cleaned up [4].

Radiation damage to the reactor personnel can occur due to external γ- and β-radiation from radioactive material released into environment, contact γ- and β -radiation, i.e. depositing on clothes, body and visible mucous, and internal irradiation through inhalation of radioactive substances.

The history of this kind of situations shows that external γ-radiation is the primary and determining factor in development of the acute radiation syndrome of local personnel and emergency workers (liquidators) at the onset and ensuing stages of major accident. Within this timeframe, the main source of internal (thyroid) irradiation is short-lived radioisotopes of iodine and iodine-131.

In the Russian Federation, the adopted radiation protective agent is indralin (B-190) [1-6]. This is an emergency radioprotector to be consumed for prevention of acute radiation damage from exposure to gamma

radiation, gamma-neutron radiation of a high dose rate (>1 Gy/h), and high-energy protons. The preventive peroral dose is 0.45 g (three 0.15 g tablets). The radioprotector takes effect in 5 minutes reaching the maximum action in 10-15 minutes. Duration of the protective effect is approximately an hour. If necessary (for example, continuing exposure) the indralin dose should be repeated in one hour [5]. In terms of the dose reduction factor (DRF), the anticipated anti-radiation effect of the protector for human is 1.5 [6].

The high radioprotective effect of indralin was validated in experiments with seven animal species including dogs and primates [1,6,8]. Unlike the sulfur-contained radioprotectors (cystamine and amifostine), indralin is tolerated well by humans when administered in preventive doses [2]. The window of its therapeutic action is broader as compared with the sulfur-contained radioprotectors [7]. The anti-radiation action remains in force during combined exposure to radiation and professional environments with extreme emotional and physical stresses, vibration, etc. [2,6,9].

Indralin is classed with radioprotectors acting through cell receptors mechanism. It belongs to the group of derived biogenic amines. Pharmacological properties of the agent refer it to direct α1-adrenergic agonists. Pharmacological, including anti-radiation action, is blocked by α-adrenoceptor blocking drugs such as tropaphen, prazosin, terazosin and promazine [1,2.6,10,11]. The radioprotector induces acute hypoxia in radiosensitive tissues disturbing microcirculation by abrupt contraction of pre-capillary smooth muscles with simultaneous enhancement of oxygen intake by cells as a result of the direct α(1)-adrenergic effect [1,2,6,7,12].

The peroral indralin dose of 0.45 g produces in human a typical adrenergic effect increasing blood pressure (BP) over 90 minutes; maximum BP rise (15-22%) is observed within the interval of 15-55 minutes following the dose. The effect comes about, first of all, by way of diastolic pressure rise conditioned by strengthening of peripheral resistance to circulation during vasoconstriction on the pre-capillary level and a reflex heart rate reduction to 50-60 beats/min without episodes of arrhythmia. A minor hypertension effect (diastolic BP rise to 90 mmHg) is tolerated well by normal people. Moderate thermal (40^{o} C) and physical stresses were found to provoke a trend to a less pronounced bradycardia and a more frequent rise of diastolic BP. The agent does not affect renal, hepatic and hemopoietic functions significantly. In contrast to sulfur-contained radioprotectors cystamine and amifostine [2,6,13], this agent does not cause dyspeptic complications. Indralin does not permeate through the hematoencephalic barrier; it also does not deteriorate human performance assessed by shifts in the neuromotor functioning (ability to perform dynamic work, statistical endurance, static and dynamic tremor, sensorimotor reaction). The radioprotector does not lower tolerance of thermal loads up to 40^{o} C during moderate physical work and of aviation labor factors (longitudinal and latitudinal G-forces, hypoxic hypoxia, vibration and vestibular loads) [2, 6]. Based on the results of ergonomic testing, indralin impacted neither operator's performance of compensator tracking nor piloting precision and quality as judged by dispersion of controlling motions along the latitudinal and longitudinal control channels [2,6,14].

Primary radiation reaction may develops in the hours immediate after acute intensive gamma-irradiation. To arrest or relieve radiation vomiting, antiemetics are applied for emergency medical aid. In the Russian Federation, latran (ondansetron) is the approved animetic for radiation emergency [2,6,15].

Betaleukin, recombinant human IL-1β [16,17], is recommended as agent for early emergency radiation therapy. It potentiates the radioprotective action of indralin [18]. Betaleukin is an anti-inflammatory cytokine which is administered immediately after exposure with the purpose to stimulate cell proliferation and differentiation in affected hemopoiesis system, to reduce leucopenia and to mitigate clinical manifestation of the bone marrow radiation syndrome [16,17]. Betaleukin is injected subcutaneously at a dose of 1 μg (ampoule content is deluted by 1 ml of sterile isotonic 0.9% NaCl solution) within 2 hours after exposure. The injection side effects can be shiver and body temperature rise over 2-3 hours, infiltrate and redness of the puncture place in 4-6 hours after injection. Allergic reactions are very rear. To avoid exacerbation of affection, betaleukin must not

be injected to people in febrile state, with significant hypotension, in a state of shock or with combined damages (radiation exposure plus wound and thermal burns) [16].

In order to accelerate the process of post-radiation reparation of organism, anti-oxidant therapy is provided to clean-up workers subject to prolonged exposure to low-intensity γ-radiation in contaminated area who are likely, based on calculations, to receive absorbed doses of 150-250 mSv. The list of therapeutic agents includes riboxine, aminotetravit, tetrafolevit, glutamevit, undevit, etc. containing such vitamin antioxidants as ascorbic acid, rutin, vitamin E, β-carotine, and B vitamins. In this situation, adequate and rich in vitamins and animal proteins diet is of utmost criticality. The ample positive effect of medication therapy and prophylaxis is achieved within seven days and persists the next two weeks following the course of therapy [2,6,13,19,20].

It has already been said that iodine radioisotopes present the outmost risk amongst all fallout elements in the early and intermediate stages of a nuclear plant accident. These isotopes are inhaled with air and incorporate eventually in the thyroid of personnel and clean-up teams. This is why part and parcel of the radiation protection system is prompt rendering of so-called iodine prophylaxis to local personnel and arriving clean-up teams [3,4,6, 21, 22]. It is well known, that proper dosage of stable iodine blocks synthesis of thyroxin in the thyroid (Wolff–Chaikoff effect). High iodine concentration closes thyroid cell channel for iodine anion and bars radioactive iodine from participation in iodination in the process of thyroxin synthesis [13,23, 24]. One tablet with 125 mg of potassium iodide once and timely took by an adult blocks incorporation of radioactive iodine in the thyroid up to 99% and retains the protective effect over 24 hours [21, 22]. Potassium iodide effectiveness in reducing the radiation dose to the thyroid is the highest provided the tablet is taken 2 hours in advance (emergency notification) or promptly after anticipated fallout. Potassium iodide intake within one or two hours after the inhalation of radioactive iodine reduces thyroid exposure by 75%; its intake in 5 hours has a 50% effect at best. Delayed administration of stable iodine preparations (8 or more hours since exposure) will be of no use, as the larger portion of inhaled radioactive iodine has already been absorbed by the thyroid and the stable analog will be helpless in radionuclide decorporation from this critical organ [21, 22].

Our experience from the Chernobyl disaster [25] and results of the onsite survey of more than 300 clean-up workers pointed out explicitly that, aside from iodine radioisotopes, exposure to other radionuclides, i.e. fission isotopes, neutron activation products, plutonium isotopes and transplutonium elements, through inhalation was largely within the emergency limits. Based on measurements of airborne and inhaled radioactivity, actual doses to the workers did not exceed the admissible annual limits [26]. These data provide support for the fact that inhaled iodine radionuclides are the most hazardous component of internal exposure to fallouts in consequence of radiation emergency on a stationary and transport nuclear reactor. Yet, in exquisite emergency, e.g. at a radiochemical plant, radioactive waste storage or any other object when fallout intensity and isotope composition are unknown or differ from “ordinary” fallouts of nuclear accident, after evacuation and radiometry, including with the use of whole-body counters (WBC), in specialized hospitals the affected can be, if necessary, treated against incorporation of radionuclides in organism. Methods of treatment include so-called complexones, i.e. chemical compounds that form soluble nondissociated complex chelates with numerous metal rings and are eliminated from organism by excretion. The most widespread compounds are polyamine-polyacetic acids, Na-Ca and Zn salts of diethylene triamine pentaacetic acid (DTPA), pentacinum and zincacin, specifically [27]. These compounds form stable complexes with radioactive isotopes of alkali-earth and rare-earth elements, transurane and transplutonium elements, etc. To control incorporation of plutonium, transplutonium and fission radionuclides, with the exception of cesium and strontium, pentacin and zincacin are prescribed as highly dispersed aerosol inhalations or a regimen of intravenous injections [15, 27].

As part of the first aid, ion-exchange sorbent ferrocene (a Russian ferrocyanide agent) is prescribed to bind cesium and strontium isotopes that ingressed the gastrointestinal tract from the respiration organs

retrogradely. Adsobar (activated barium sulfate), algisorb (an alginic acid compound) or polysurmin (silicon-antimonide cation) are used to bind strontium isotopes [27]. Natural pectic substances are of limited utility as first aid agents. It should be kept in mind that unlike the population of contaminated areas, on-site personnel and clean-up teams are not imperiled by the alimentary path of internal exposure.

One of the mandatory methods of protecting the reactor personnel from external contact contamination is sanitization (deactivation of radiation) of clothes and bodies implemented, as a rule, after evacuation from the site. In addition to the conventional washing with soap, body radioactivity is removed with the help of detergent "Zaschita" consisting of fine mesh ion-exchange resins and surfactant species. This is the most active remedy for integument contaminated by fission radioisotopes (uranium and plutonium products) and transuranium elements [28, 29].

To put a line under the issue, it should be said that personnel of Russian nuclear objects are provided with personal emergency first aid kits containing tableted B-190, potassium iodide, latran, ferrocene, adsorbar and packs with powder "Zaschita" [13,19].

As it is known, drawn up from the lessons of protecting people during the massive Chernobyl accident, the current radiation emergency roster includes sheltering, iodine prophylaxis and evacuation [30, 31]. All aspects of iodine prophylaxis with reference to the Chernobyl experience and WHO guidelines (update 1999) are recounted in the recent official Guidelines for iodine prophylaxis in the event of radiation accident published in the Russian Federation in 2010 [22]. In our paper we draw attention to only several general statements. While exposure to radionuclides through inhalation is a dominating permanent factor for local personnel and clean-up teams, implications of the breathing pathway for population are determined by the period people stay in the radioactive cloud before it drifts away. Therefore, clearly the principle of emergency iodine prophylaxis should be applied to the population, too. At the same time, the alimentary pathway, i.e. iodine-131 ingestion with milk and other local foods (by country population in particular), becomes the major contributor to total absorbed dose to the thyroid as was evidenced by numerous Chernobyl monitoring and control works [22]. Consequently, the most effective and preferable option of preventing internal exposure to radioactive iodine and other radionuclides through diet is banning contaminated products, milk specifically. If there is no possibility to supply the population with "pure" foodstuffs, milk products for younger children in particular, iodine prophylaxis is applied over the period of 3-5 days till actions have been taken to provide delivery of healthy food to affected areas. On the lapse of two to three months, iodine-131, one of the major components of local food contamination, ceases to be a problem because of the short (8.1 days) half-lived period.

On this background, long-lived fission radionuclides, cesium-139 in the first place, grow in significance. The Chernobyl accident urged on the establishment of emergency limits in compliance with generally accepted practice. For instance, 100 mSv were defined as the dose limit in a year since accident (50 mSv from external gamma-radiation and 50 mSv from incorporated cesium-137) [30. 31]. As a rule, sanitization and organizational arrangements resulted in actual doses received by population of the most heavily contaminated and tightly controlled areas to be 3-4 times smaller than the existing emergency limits. Till recently, there have been two antipodal views on practicality of providing populations chronically exposed to low-intensity radiation with radioprotective or gastrointestinal sorbent agents to eliminate long-lived radionuclides (Sr-90 and Cs-137). The author of monograph "The foundations of organism protection from exposure to radioactive substances" made a close scrutiny of the issue and substantiated his negative attitude [27].

In conclusion we should remind it that after the Fukushima-1 disaster Japan's health ministry ordered to stop sale of all foods contaminated by radioactivity at the top of or slightly beyond the routine safety limits, i.e. admissible induced radioactivity in the vicinity of accident-free operating nuclear object. You will recall that these radiation safety limits for food products were calculated with regard to the effective dose for humans equal

to 1 mSv per a year when no protection except radiation monitoring is required. This approach is questionable. The point is that, if for no other reason but from formal considerations, people have to be evacuated from areas where predicted annual dose rate is slightly above 1 mSv.

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