Comparative efficacy and the window of radioprotection for adrenergic and serotonergic agents and aminothiols in experiments with small and large animals

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This review gives a comparative evaluation of the radioprotective properties and the therapeutic index (TI) of radioprotectors from various pharmacological group in experiments on both small and large animals. It presents a hypothesis explaining the decrease in the TI of cystamine and 5-methoxytryptamine (mexamine), and the retention of that of α1-adrenomimetic indralin, and also compares the effects on large and small animals. The considerable differences in the therapeutic indices of catecholamines, serotonin and cystamine are a consequence of specific features of their mechanisms of radioprotective action. Radioprotectors acting via receptor mediation tend to provide a more expanded window of protection. The reduction in the TI of cystamine in larger animals, such as dogs, may be caused by the greater increase in toxicity of aminothiols in relation to the decrease in their optimal doses for radioprotective effect in going from mice to dogs, which is a consequence of the slower metabolic processes in larger animals. The somatogenic phase of intoxication by cystamine is significantly longer than the duration of its radioprotective effect, and increases with irradiation. The decrease in the radioprotective effect and the TI of mexamine in experiments with dogs may be caused by their lower sensitivity to the acute hypoxia induced by the mexamine. This is because of lower gradient in oxygen tension between tissue cells and blood capillaries under acute hypoxia that is determined by lower initial oxygen consumption in a large animal as compared with a small animal. Indralin likely provides optimal radioprotective effects and a higher TI for large animals via the increased specificity of its adrenergic effect on tissue respiration, which supports the development of acute hypoxia in the radiosensitive tissues of large animals. The stimulatory effect of indralin on early post-irradiation haematopoietic recovery cannot provide a high level of radioprotective action for large animals, but it may promote recovery.

Keywords: indralin; epinephrine; norepinephrine; serotonin; 5-methoxytryptamine; cystamine; therapeutic index

INTRODUCTION

The key aspects of radioprotective agents are their practicality for use in specific scenarios of radiation exposure and the corresponding tactical and technical requirements for medical preparations. At the present time, amifostine, a radioprotector from the aminothiol family, is used in clinical practice as a radioprotectant and a chemoprotectant during the radio–chemotherapy of patients with head and neck tumors, lung cancer and breast cancer, reducing the radiotoxicity and cytotoxicity of therapies [1–3]. According to clinical data reported by Trog et al. [1] (on reduction of the symptoms of postradiation mucositis during radiotherapy treatment of head and neck cancer patients), dose reduction factor (DRF) for amifostine is equal to 1.37 [4]. The first clinical investigations of the radioprotective effect of radioprotector mexamine were reported by Votkevich and Palyga [5]. Mexamine is used as a mitigator to reduce the chemotoxicity of chemotherapy [6–8]. Indralin (B-190) is used as a radioprotective agent for the medical protection of personnel during emergency situations at nuclear power plants [9, 10].

In 1951, Zenon Bacq [11] discovered the phenomenon of ‘chemical protection’ against the damaging effects of ionizing radiation via the administration of cystamine prior to lethal doses of radiation. Cystamine gave complete protection under
such conditions. Most of the known medications at the time of this discovery were screened for radioprotective properties [12, 13]. Biogenic amines including epinephrine, norepinephrine, dopamine, serotonin, tryptamine, 5-methoxytryptamine (mexamine), melatonin and histamine, i.e. essential components of the neuroendocrine regulation of vital body functions, were also subjected to such testing.

Of the above-mentioned compounds, serotonin had the highest radioprotective effect, comparable with that of cystamine [14–16]. Later, similar protective properties were found in 5-methyl derivatives of serotonin—e.g. mexamine [17]. In the first experiments with catecholamines and histamine, the radioprotective effects were slight and did not exceed 10–40% [18–22]. In later studies, however, with high-dose-rate radiation exposure and reduction of the exposure time to a few minutes, these biogenic amines exhibited a pronounced radioprotective effect [23, 24]. According to Kulinskii et al. [25], the radioprotective effectiveness of epinephrine and norepinephrine is realized through their binding to $\alpha_1$-adrenergic receptors. Later, highly protective properties were observed in the $\alpha_1$-adrenergic agonists methoxamine, phenylephrine, naphazoline and indralin [26–33].

The radioprotective activity of biogenic amines is associated with a partial neutralization of the radiobiological ‘oxygen effect’ phenomenon: i.e. the fact that an increase in cellular oxygen tension permits more radiation damage to occur. Evidence for the hypoxic mechanism of the radioprotective effect of biogenic amines was first obtained by van der Meer and van Bekkum [23, 34], and confirmed by Konstantinova and Graevskii [22]. A close relationship between the radioprotective efficacy of biogenic amines and the local tissue hypoxia induced by their vasoactive actions has been established [35–41].

A similar correlation for sympathomimetics was not always quite so explicit [42]. Application of pharmacological antagonists eliminated the radioprotective effect of serotonin, histamine, epinephrine, norepinephrine, phenylephrine and indralin [25, 32, 35, 43, 44]. The same effect was observed with animal radiation exposure in an atmosphere of increased oxygen pressure [32, 45–47].

**REVIEW**

The window of radioprotection for biogenic amines and aminothiols: a comparative investigation

The therapeutic window for drugs, including radioprotectors, is their most important characteristic [13], and is closely associated with the selectivity and affinity of the drug in relation to the expressed cellular receptors responsible for its pharmacological action. The therapeutic window for radioprotectors can be estimated from the therapeutic index (TI), which is defined as the ratio of the drug LD50 (lethal dose, 50%) to the drug ED50 (effective dose, 50%). The LD50 and the ED50 is based on a probit analysis, typically using at least three drug doses that do not result in all-or-none mortality or drug effect [48]. The ED50/30 of a radioprotector is its average effective dose for 30-day survival when the animals are exposed to radiation LD90–100/30. The LD50/3 is the average lethal toxic dose of the radioprotector for 3-day survival.

Figure 1 and Table 1 present comparative data for the dose–response of the radioprotectors and the TI of the following biogenic amines: epinephrine, norepinephrine, tryptamine, serotonin and mexamine; and the aminothiol cystamine, following intraperitoneal (IP) administration in mice. In small laboratory animals exposed to 9-Gy $\gamma$-radiation at a high dose rate (>1 Gy/min), epinephrine, norepinephrine, serotonin, mexamine and cystamine have been observed to have remarkable radioprotective properties [40, 49].

![Figure 1](https://academic.oup.com/jrr/article-abstract/56/1/1/2580731)

**Table 1.** The therapeutic index for the radioprotective effect of epinephrine, norepinephrine, serotonin, mexamine, tryptamine and cystamine injected IP to mice 5 min before 9 Gy (LD90–100) and >1 Gy/min $\gamma$-irradiation [41, 49].

| Compound     | ED50/30 (mg/kg) | LD50/3 (mg/kg) | Therapeutic index |
|--------------|-----------------|----------------|------------------|
| Epinephrine  | 0.23            | 6.28           | 27.3 (14.6–52.0) |
| Norepinephrine| 0.90            | 29.2           | 32.4 (17.0–61.9) |
| Serotonin    | 3.16            | 435.3          | 137.7 (91.8–206.6)|
| Mexamine     | 3.46            | 186.4          | 53.9 (43.5–60.8) |
| Tryptamine   | 90.4            | 288.8          | 3.08 (1.98–4.79) |
| Cystamine    | 87.5            | 285.1          | 3.26 (2.82–3.7)  |

Data shown are therapeutic index with confidence limits for the interval 95%.
The window of radioprotection defined by the LD50/ED50 for epinephrine (27.3) and norepinephrine (32.4) in mice was very similar (Table 1). The TI of serotonin was 137.7, more than 2–3-fold higher than that of mexamine and the sympathomimetics (Table 1). The significantly lower radioprotective effectiveness of tryptamine resulted in its low TI. The tryptamine molecule differs from the serotonin molecule by the lack of a hydroxyl group in the fifth position of the indole ring, which predetermines a high binding affinity for the serotonin receptor. Therefore, there is a marked decrease in selectivity of the pharmacological and radioprotective action of tryptamine. As seen in Fig. 1, an ED50/30 decrease in selectivity of the pharmacological and radioprotective effectiveness of tryptamine resulted in its low TI. The TI of aminothiols, such as cystamine, was 10-fold lower than that of the biogenic amines (Table 1); this was also noted in early research [50–52]. The largest TI for sulphur-containing radioprotectors is 9–12 (for phosphorothioates) [13, 53–55], 10-fold lower than for serotonin. This distinction is caused by the different mechanism of action in the sulphur-containing radioprotectors compared with the biogenic amines. Biogenic amines exert their effect via specific cell receptors that initiate an amplification cascade and produce a vasoconstrictive reaction, inducing acute hypoxia in radiosensitive tissues and thus increasing body radioreistance. The dose–response effect of biogenic amines can be described by the Clark–Ariëns relation. Sulphur-containing radioprotectors produce their effect via immediate participation in the primary radiochemical and biochemical processes that develop in the cell during irradiation.

As is known, the damage to body tissues by radiation is induced by the development of free radical processes in cells, resulting in DNA radical among other radical molecules. Aminothiols can take part in competitive radical oxidation/reduction reactions via OH scavenging and by ‘chemical repair’ (H donation from SH groups). Radical scavenging by aminothiols is a first-order reaction. The mechanism of their radioprotective action is first of all to prevent interactions between DNA radicals and oxygen (which lead to DNA strand breakage and chromosome aberrations). The induction of increased cellular reducing equivalents [56, 57] and the change in tertiary DNA structure [58] by aminothiols contributes significantly to this process.

Finally, a common feature of the radioprotective action of biogenic amines and aminothiols is the neutralization of the ‘oxygen effect’, although the mechanisms differ for these compounds. Biogenic amines exert their effect through the neurohormonal receptor system, but sulphur-containing radioprotectors act directly on tissues. Biogenic amine molecules have some anti-radical activity, but compared with aminothiols, their contribution to cell redox potential is limited due to the extremely low drug doses used for radioprotection (Fig. 1).

As a result of these different mechanisms, there is a distinction in the dose–response function in terms of DRF: a linear relationship for sulphur-containing radioprotectors [49, 59–61] and a logarithmic relationship for biogenic amines [62]. This translates to the larger protective effect of low doses of biogenic amines, compared with sulphur-containing radioprotectors, increasing the therapeutic window of the former. In Fig. 1, the higher specificity of the radioprotective action of biogenic amines compared with cystamine is seen by the 100-fold lower requirement in concentration. This scheme explaining the radioprotective effect of biogenic amines and aminothiols rather oversimplifies the true situation [13, 63], but as noted above, the character of their dose–response curves confirms the basic mechanisms of their modes of action.

The window of radioprotection for indralin, mexamine and cystamine in small and large animals: a comparative analysis

To compare the windows of radioprotection for radioprotectors in small and large animals, the following drugs were chosen: indralin (α1-adrenomimetic), mexamine (serotonin derivative) and cystamine (a sulphur-containing radioprotector). This choice was based on the availability of published data from experiments with large animals (dogs and monkeys). Figure 2 shows the dose–response relationship of indralin in experiments with mice, rats, hamsters and dogs [64]. As seen, optimal radioprotective doses of indralin for dogs are appreciably lower than those for small animals. Table 2 presents the comparative radioprotective efficacies of indralin and mexamine in experiments with dogs. A 5–30 mg/kg dose of indralin protects 90–100% of dogs exposed to lethal doses of γ-radiation. Mexamine at doses that are effective in small animals is ineffective at similar doses in dogs under similar irradiation conditions.

This striking difference between indralin and mexamine provides evidence of the fact that the same decrease in blood flow in hematopoietic tissues (owing to the vasoconstrictor
The radioprotective effect of indralin and mexamine injected IM into dogs 5 min before γ-irradiation (47)

| Groups   | Dose (Gy) | Dose rate (Gy/min) | Dose (mg/ kg) | n | 60-day Survival (%) | MLS, (days) |
|----------|-----------|--------------------|---------------|---|---------------------|-------------|
| Control  | 3.8       | 2.3–2.8            | –             | 14| 14.3                | 17.0        |
| Indralin | 3.8       | 2.3–2.8            | 30.0          | 12| 100.0*              | –           |
|          |           |                    | 10.0          | 15| 86.7*               | 18.0        |
|          |           |                    | 5.0           | 11| 90.9*               | 20.0        |
| Mexamine | 3.8       | 2.3–2.8            | 30.0          | 7 | 14.3                | 17.2        |
|          |           |                    | 10.0          | 7 | 0                   | 16.4        |
|          |           |                    | 5.0           | 5 | 20.0                | 17.3        |
| Control  | 4.0       | 0.1–0.11           | –             | 27| 14.8                | 17.3        |
| Indralin | 4.0       | 0.1–0.11           | 30.0          | 11| 90.9*               | 16.0        |
| Mexamine | 4.0       | 0.1–0.11           | 30.0          | 8 | 12.5                | 17.6        |

Statistically significant (P < 0.05 by two-tail Fisher exact test) difference between indralin and mexamine groups is indicated with an asterisk. MLS = mean of life span of deceased animals, n = number of animals.

Effects of mexamine and indralin) when used in experiments with dogs [47] does not exert a highly radioprotective effect, and that indralin has another mechanism of action for its protective properties.

Table 3 displays the windows of radioprotective action for indralin, mexamine and cystamine in various laboratory animals, including dogs. There is a fundamental difference between indralin versus mexamine or cystamine in the TI value for smaller and larger animals. Indralin, an α1-adrenergic agent [32, 44], had a TI typical for epinephrine and norepinephrine (Tables 1 and 3) and this TI remained the same for both smaller and larger animals. For example, the TI for indralin in mice, rats, hamsters, guinea pigs and dogs following an intramuscular (IM) injection of the drug was equal to 23.7, 16.9, 17.8, 25.6 and 31.1, respectively (Table 3). It is very important to have an expanded window of radiation protection for indralin when orally administered in large animals (when sulphur-containing radioprotectors are weak or ineffective) [54, 65]. TI for indralin given per os in dogs corresponds to 23.7 (Table 3). The large window of radioprotection for indralin is maintained for both dogs and non-human monkeys [66]. In contrast, the window of protection for cystamine was decreased in going from mice to rats and dogs, i.e. with increased size of animal. The TI of cystamine following parenteral injection of the drug in mice, rats and dogs was 3.3, 2.1 and 1.2, respectively (Table 3). A similar picture was observed for amifostine, whose window of protection was reduced in terms of TI from 12 to 3 in going from mice to dogs [53–55, 67–69].

The above fact may be explained by the more pronounced increase in aminothiol toxicity in going from mice to dogs compared with the change in the radioprotective effect of the doses. It is known that the somatogenic stage of cystamine toxicity is much longer than the duration of its radioprotective effect, and this toxicity is prolonged by radiation exposure [70]. One might expect aggravation of the above situation in dogs as a result of the slower metabolism of aminothiols in irradiated animals. Accumulation of the toxic effects of aminothiols decreases their radioprotective action [71–73]. The increase in the radioprotective effectiveness of cystamine with increasing drug dosage is limited by the maximum tolerated dose [49], which does not exceed the ED50 in dogs [66, 74]. The decrease in the toxicity of aminothiols by vitamins and other agents permits a possible increase in their radioprotective effect [13, 75–82].

Similar trends in reducing the window of protection were observed for mexamine, where TI decreased from 53.9 (43.5–60.8) for mice to 23.6 (14.1–37.9) for rats (Table 3); the radioprotective effect of mexamine did not exceed 50% in experiments with dogs [83]. In contrast to cystamine, a reduction in mexamine toxicity was observed following radiation exposure, a result of receptor desensitization under these conditions [84]. The decrease in the radioprotective effectiveness of mexamine is likely attributed to the weaker hypoxic response caused by this agent in larger animals. This effect is associated with the initial cellular oxygen consumption rate. If there is sufficient time for the cell to adapt to the lack of oxygen supply by reducing oxygen consumption, acute low cellular oxygen tension is averted. The reduced reactivity of dogs to acute hypoxia may be explained by the 2–5-fold lower initial oxygen consumption per unit body weight in large animals as compared with mice and rats. The acute stress reaction to hypoxia caused by inhalation of a hypoxic gas mixture that contains 5–7% oxygen, reflected by an increase in the succinate dehydrogenase activity in lymphocytes, has been shown to be lower in dogs than in rats [64, 85]. In contrast to the effects seen in small animals, the acute hypoxic hypoxia noted above protects less than 50% of dogs [64, 86].

Therefore, the decrease in blood flow in the dog’s spleen and bone marrow (by up to 25% and 50% respectively) induced by mexamine [47] is not adequate for radioprotection. The low radioprotective effectiveness of acute hypoxia and mexamine has previously been shown in experiments in dogs and monkeys [81, 87–91].

### A hypothesis for the difference in the protective effectiveness between indralin and mexamine or cystamine in large animals

The question arises about whether the radioprotective properties of indralin in experiments in dogs and monkeys [64, 92] are high compared with those of mexamine, with the same reduction of blood flow in hematopoietic tissues [47]. The mechanism for the high level of effectiveness of indralin remains elusive. We propose a hypothesis based on the scientific concept that metabolic activation in hypoxic tissues is...
initiated and sustained by the sympathetic nervous system, for which an adaptation–trophic role was discovered by Orbeli [93]; and excessive adrenergic stimulation may sharply increase cellular oxygen consumption. This can lead to acute ischemia in tissues both small and large animals, with a concomitant increase in radiosensitivity if tissues lack an adequate oxygen supply. The vasoconstrictive effect of sympathomimetic drugs is inevitably associated with increased tissue oxygen consumption, in contrast to serotonin [94–101]. An increase in adrenaline leads to an increase in succinate-dependent ATP synthesis and Ca2+ accumulation in mitochondria, which is due to the known activation of succinate-dependent ATP synthesis and oxygen consumption [102–105]. Adrenaline activates oxidative phosphorylation through α1-adrenergic receptors [106]. Indralin increases oxygen consumption in bone marrow cells in vitro by up to 50% when tissue oxygen tension is lower than 10 µmol [107]. Myeloid multipotent progenitors and pluripotent stem cells [108] have α1-adrenergic receptors that realize a similar scenario.

The lack of blood flow in radiosensitive tissues caused by the vasoconstrictive effect of the α1-adrenergic agonist indralin, with its simultaneous stimulation of tissue respiration, may lead to more acute tissue hypoxia, which would be sufficient to explain the observed increase in tissue radiosensitivity.

The increase in cell radioreistance owing to acute low oxygen tension is a result of the considerable increase in cellular oxygen consumption previously discussed [64, 109]. The radioprotective effect of uncouplers of oxidative phosphorylation confirms such a possibility [110–112].

However, there is hitherto no direct proof of our proposed hypothesis. It is necessary to examine the other pharmacological properties of adrenergic agents that could potentially mitigate radiation damage and possibly influence their radioprotective effects.

Catecholaminergic neurotransmitters are known to be able to regulate the migration and repopulation of immature human CD34+ cells [113–116]. Norepinephrine increases DNA synthesis in bone marrow mesenchymal stem cells through α1-adrenergic receptors [117], which plays a significant part in early post-irradiation haematopoietic recovery [118]. This stimulatory effect is very likely accomplished via MAP kinase signaling cascades (MEK > ERK) as intracellular transducers of noradrenergic signals [119, 120]. Besides, acute adrenergic stimulation inhibits the proliferation of haematopoietic progenitor cells via p38/MAPK signalling [121], which could provide an opportunity for an extension of post-irradiation repair time and mitigation of radiation damage to myelopoiesis. Proinflammatory cytokine IL-6 gene expression, induced by α1-adrenergic agents through involving p38 MAPK and NF-κB pathways [122, 123], could potentially contribute to early processes of post-irradiation hematopoietic recovery [124–127]. ROS play a critical role in mediating the response to alpha1-adrenergic stimulation [128].

The importance of these effects of adrenomimetics for their complete protective action may be observed if radioprotectors are applied after radiation exposure. In such a situation, they fail to exert a protective effect as antagonists of the ‘oxygen effect’. Radioprotectors, such as serotonin, adrenaline, cystamine and 2-aminoethylisothiouanium bromide hydrobromide (AET) are known to have a small radioprotective effect if applied within 10 min after irradiation [129–132]. Under conditions of liver shielding in rats, Maisin et al. [133, 134] has

Table 3. The window for the radioprotective effect of indralin, mexamine and cystamine administrated by various routes to small and large animals 5 min before LD90–100/30 and >1 Gy/min γ-irradiation [66]

| Radioprotectors | Animal species | Administration | n  | ED50/30 (mg/kg) | Therapeutic index |
|-----------------|----------------|----------------|----|----------------|------------------|
| Indralin        | mice           | IP             | 480| 17.4 (13.5–22.4) | 19.3 (14.0–25.1) |
|                 |                | IM             | 240| 21.9 (16.2–29.4) | 23.7 (15.3–36.5) |
|                 |                | PO             | 180| 14.8 (12.4–17.6) | 59.6 (41.4–85.9) |
|                 | rats           | IP             | 210| 32.1 (25.8–38.5) | 8.4 (6.3–11.3)   |
|                 |                | IM             | 310| 61.5 (39.2–96.6) | 16.9 (9.6–29.8)  |
|                 |                | PO             | 110| 70.0            | 18.2             |
|                 | hamsters       | IM             | 522| 50.7 (42.9–59.8) | 17.8 (14.8–24.1) |
|                 |                | PO             | 90 | 124.4 (95.7–161.8)| 8.9 (5.5–14.5)   |
|                 | guinea pigs    | IM             | 35 | 28.8 (17.0–49.0) | 25.6 (13.7–47.4) |
|                 |                | IM             | 96 | 6.0 (4.3–8.3)   | 31.1 (20.6–47.3) |
| Mexamine        | mice           | PO             | 78 | 23.2 (20.7–25.9) | 23.7             |
|                 |                | IP             | 320| 4.1 (3.0–5.5)   | 53.9 (43.5–60.8) |
|                 | rats           | IP             | 90 | 5.7 (4.3–7.6)   | 23.6 (14.1–37.9) |
|                 |                | IM             | 35 | 8.3 (6.5–10.1)  | No               |
|                 | dogs           | IM             | 20 | 30.0< ED50      | No               |
| Cystamine       | mice           | IP             | 400| 87.5 (77.0–98.0) | 3.3 (2.8–3.7)    |
|                 | rats           | IP             | 100| 57.7 (45.1–73.9) | 2.1 (1.6–2.8)    |
|                 | dogs           | IV             | 35 | 60.0           | 1.2              |

Data shown are the means and confidence limits for the means interval 95%. PO = oral administration, IV = intravenous injection.
detected a protective effect from cysteamine applied after exposure to lethal doses of whole-body radiation in cases where the radioprotector alone was not sufficient. The therapeutic effect of indralin saves up to 55% when it is applied to rats after whole-body irradiation with partial shielding of the upper quadrant of the abdomen [63]. Indralin used after carboplatin injection also reduces its hematoxicity [135, 136].

It is clear that the therapeutic action of indralin and other radioprotectors noted above is essentially lower than its preventive protective effect. Thus, neutralization of the ‘oxygen effect’ by these drugs is a key aspect of their radioprotective action. It is important to note that pharmacological modulation of gene expression by radioprotector action can’t of itself achieve significant ‘chemical’ protection. Therefore, the favourable effects of indralin on early post-irradiation hematopoietic recovery do not in themselves constitute a high radioprotective action.

In summary, indralin is likely to provide a high therapeutic index in large animals via the specificity of its adrenergic action of gene expression by radioprotector action can’t of itself achieve significant ‘chemical’ protection. Therefore, the favourable effects of indralin on early post-irradiation hematopoietic recovery do not in themselves constitute a high radioprotective action.

CONCLUSION

The radioprotective properties of biogenic amines and aminothiols have attracted investigators’ attention for more than six decades. This review provides a comparative study of the window of radioprotection for biogenic amines and aminothiols based on personal and literary databases. Comparative analysis of the window of radioprotection for biogenic amines and their derivatives and the aminothiol cystamine indicates that catecholamines, serotonin and mexamine have a more than 10-fold greater TI relative to cystamine in experiments with small animals. The TI of tryptamine, which lacks a hydroxyl-group in the fifth position of the indole ring, is deprived of serotonin selectivity and does not differ from that of cystamine. The considerable differences in TI between catecholamines, serotonin and cystamine are caused by the differences in the pharmacology, toxicology of radioprotectors and mechanisms of their radioprotective action. Receptor-mediated radioprotective agents have greater preferences over aminothiols and thus provide an expanded window of protection.

We propose a hypothesis explaining why the window of radioprotection for cystamine and mexamine is reduced, and that for the α1-adrenomimetic indralin is not essentially changed in moving from small to large animals. The reduction in the TI of cystamine in larger animals, such as dogs, may be caused by the greater increase in toxicity of aminothiols in relation to the decrease in their optimal doses for radioprotective effect in going from mice to dogs, which is a consequence of the slower metabolic processes in larger animals.

The somatogenic phase of intoxication by cystamine is significantly longer than the duration of its radioprotective effect, and increases with irradiation [70]. The protective action of cystamine is limited by the maximum tolerated dose. Antioxidants lower the toxicity of aminothiols and increase the maximum tolerated dose and thus the corresponding radioprotective effect.

The decrease in the radioprotective effect and TI of mexamine in experiments with dogs may be caused by their lower sensitivity to the acute hypoxia induced by mexamine (because of a decrease in the oxygen tension gradient in tissues under conditions of lower initial oxygen consumption in a large animal as compared with a small animal).

Indralin, owing to its high radiation protective effect as observed in experiments on dogs and monkeys, would not provide that via only a vasoconstrictor action for reasons similar to that noted above for mexamine. The stimulatory effect of indralin on early post-irradiation haematopoietic recovery cannot provide high radioprotective action, but may only promote recovery. Thus, indralin is likely to provide optimal radioprotective effects and a high TI in large animals because of the specificity of its adrenergic effect on tissue respiration, promoting acute hypoxia in radiosensitive tissues when the tissues lack an adequate oxygen supply because of the development of pharmacological vasoconstriction.

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