PREVENTION OF ACUTE PULMONARY EDEMA IN IRRADIATED RATS

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Experiments on rats showed that preparations with a marked prophylactic action against the development of pulmonary edema in unirradiated animals are in some cases ineffective (or may even aggravate the development of edema) in irradiated (650 R) rats. Conversely, substances ineffective or detrimental in unirradiated animals may have a marked prophylactic action in irradiated rats.

KEY WORDS: *pulmonary edema; prophylaxis; x-ray irradiation.*

Irradiation has a marked effect on the development of pulmonary edema [2-4, 9]. A considerable increase in resistance of rats to the factors producing pulmonary edema is observed on the fourth day after x-ray [3, 4] or γ-ray irradiation [2] in doses of 650-800 R. The prevention and treatment of acute pulmonary edema in irradiated animals have not previously been studied.

Accordingly, various agents used for the prevention and treatment of hemodynamic, neurogenic, and toxic forms of pulmonary edema were tested during radiation sickness.

EXPERIMENTAL METHOD

Experiments were carried out on 212 albino rats (males and females). The animals were irradiated on the RUM-11 apparatus in a dose of 650 R (180 kV, 15 A, 0.5 mm copper filter, focus—skin distance 40 cm, dose rate 30 R/min). Hemodynamic pulmonary edema was induced by injecting adrenalin intravenously in a dose of 0.03 mg/100 g. To prevent adrenalin pulmonary edema, dihydroergotoxin (DHET) [13] was injected intravenously in a dose of 0.2 mg/100 g over a period of 10 min, and papaverine [1] was injected intraperitoneally in a dose of 5 mg/100 g 20-25 min before the injection of adrenalin. Neurogenic pulmonary edema was produced by bilateral vagotomy in the neck after tracheotomy. To accelerate and intensify the pulmonary edema, 5 min after vagotomy the animals were given an intravenous injection of 0.85% NaCl solution in a dose of 2 ml/100 g. To prevent neurogenic pulmonary edema, insulin [6, 10] was injected intravenously in a dose of 4 units/100 g 60 min before vagotomy after the animals had starved for 24 h, or a 30% solution of ε-aminocaproic acid (ε-ACA) [6] was injected in a dose of 75 ml/100 g 20-25 min before vagotomy. Toxic pulmonary edema was produced by intravenous infusion of a 14% solution of chloramine B in a dose of 21 mg/100 g. To prevent chloramine pulmonary edema hydrocortisone [12] was injected intravenously in a dose of 5 mg/100 g 5 min before, or in two doses, each of 2.5 mg/100 g, 40 min and 20 min before the injection of chloramine. Hypothermia [5, 7] with or without premedication also was used. The premedication consisted of diphenhydramine (10 mg/kg), trimeperidine (0.1 mg/kg), amidopyrine (20 mg/kg), and hexobarbital (50 mg/kg). All these substances were injected intraperitoneally. The development of pulmonary edema was judged from the duration of survival of the animals after the edema-inducing procedure, the lung index (LI), and the dry residue of the lungs (DRL). In addition, in the experiments with chloramine the increase in weight of the fluid in the lungs (IFL) and the increase in the blood volume in the lungs (IVL) [11] were determined.

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TABLE 1. Effect of Intravenous Injection of Insulin (4 units/100 g) and ε-ACA (75 mg/100 g) on Development of Postvagotomy Pulmonary Edema in Irradiated and Unirradiated Rats

Animals	Procedure	Number of rats	Number of rats dying, in %, during 3 h after vagotomy; length of survival, in min, in parentheses	LI	DRL	IFL	IVL
Unirradiated	Control	8	0	6,3±0,30	20,97±0,28	0,00±0,06	0.00±0.27
	Vagotomy	8	100 (20,2±4,6)	15,7±1,42	12,81±0,70	6,21±1,24	3,25±0,55
	Insulin + vagotomy	8	87,5 (38,1±14,7)	12,3±2,07	16,97±1,60	3,36±1,50	2,63±0,66
	ε-ACA + vagotomy	8	87,5 (56,2±18,9)	12,6±0,86	15,35±0,85	3,48±0,68	2,78±0,51
Irradiated	Control	8	0	6,9±0,31	20,22±0,27	0,36±0,10	0,23±0,30
	Vagotomy	8	63,8 (75,2±18,7)	10,8±1,17	14,79±0,78	4,12±1,17	0,41±0,78
	Insulin + vagotomy	8	63,8 (89,8±12,0)	7,3±0,57	20,72±1,04	0,25±0,49	0,08±0,46
	ε-ACA + vagotomy	8	87,5 (25,1±7,0)	15,7±1,62	14,19±0,86	5,36±1,00	4,03±0,95

EXPERIMENTAL RESULTS AND DISCUSSION

After injection of adrenalin all the unirradiated animals died within 5-6 min with evidence of severe pulmonary edema (LI = 19.7 ± 0.37, DRL = 15.91 ± 0.96). In the intact rats LI was 5.6 ± 0.33 and DRL 20.87 ± 0.18. If DHET was given, all the animals survived after injection of adrenalin. The pulmonary edema in these animals was less severe (LI = 10.37 ± 1.27, $P < 0.001$; DRL = 18.92 ± 0.84; $P < 0.05$). Papaverine not only had no prophylactic action on the unirradiated animals, but actually aggravated edema development. These animals died 2-3 min after the administration of adrenalin, with a high value of LI (21.7 ± 1.4, $P < 0.02$) and a low value of DRL (13.95 ± 0.52, $P < 0.02$). In the irradiated animals hemodynamic pulmonary edema developed less intensively, as shown by the lower value of LI (11.97 ± 1.49, $P < 0.001$) and the higher value of DRL (16.03 ± 1.58, $P < 0.05$). Under these circumstances 87.5% of the rats survived. Papaverine had a marked prophylactic action on the irradiated animals (LI = 8.5 ± 0.9, $P < 0.05$; DRL = 18.98 ± 0.23, $P < 0.05$), whereas DHET completely prevented the development of pulmonary edema (LI = 6.2 ± 0.5, DRL = 20.25 ± 0.42).

Injection of insulin and ε-ACA into unirradiated rats increased their survival period after vagotomy and reduced the water content in the lungs (Table 1). Injection of insulin into the irradiated animals also prolonged their survival after vagotomy and completely prevented the development of pulmonary edema. However, injection of ε-ACA into the irradiated rats reduced their survival period after vagotomy; under these circumstances LI increased as a result of a sharp increase in the pulmonary blood volume.

All the unirradiated animals receiving chloramine died within 14.2 ± 1.3 min after its injection, with signs of very acute pulmonary edema (LI = 22.3 ± 2.23, DRL = 13.29 ± 0.59, IFL = 8.4 ± 1.28, IVL = 8.46 ± 0.87). Injection of hydrocortisone 5 min before the injection of chloramine did not affect the survival period of these rats or the degree of edema. Giving hydrocortisone in two separate doses shortened the survival period of the unirradiated animals to 9.1 ± 1.2 min ($P < 0.02$). Under these circumstances their DRL was lower than that of the animals receiving chloramine alone (11.67 ± 1.02, $P < 0.05$). The irradiated animals lived longer (20.2 ± 2.3 min, $P < 0.05$) than the unirradiated after injection of chloramine. All the indices of edema development were much lower in these animals (LI = 15.4 ± 2.3, $P < 0.05$; DRL = 16.8 ± 1.2, $P < 0.05$; IFL = 3.84 ± 1.83, $P < 0.05$; IVL = 5.47 ± 1.51, $P < 0.05$). Injection of hydrocortisone into the irradiated rats 5 min before injection of chloramine prolonged their survival a little (24.3 ± 1.66 min, $P < 0.05$) but caused virtually no change in the severity of their pulmonary edema. Administration of hydrocortisone in two doses likewise did not affect the development of chloramine edema in the irradiated albino rats, although it shortened their survival (14.6 ± 1.17 min, $P < 0.05$).

Hypothermia in the unirradiated rats (without premedication) increased their survival after injection of chloramine (from 12.3 ± 0.94 to 40.0 ± 2.56 min; $P < 0.001$) and reduced the severity of the pulmonary edema (LI = 9.7 ± 0.73, $P < 0.001$; DRL = 16.98 ± 0.78, $P < 0.01$; IFL = 2.09 ± 0.43, $P < 0.01$; IVL = 1.48 ± 0.34, $P < 0.001$). In the irradiated rats, hypothermia without premedication also prolonged the survival of the rats after injection of chloramine (34.2 ± 7.28 min, $P < 0.001$) but it had no effect on the severity of the chloramine pulmonary edema.

After premedication and hypothermia, the irradiated and unirradiated animals died within 1-2 min after chloramine poisoning. Premedication which, combined with hypothermia, is an effective preventive measure against adrenalin pulmonary edema [8], thus had an unfavorable action in the same combination on animals receiving chloramine.

The results of these investigations show that substances with a marked prophylactic action against the development of pulmonary edema in unirradiated animals, in some cases had no significant effect on the formation of pulmonary edema (or may even aggravate its development) in irradiated animals. Conversely, substances ineffective or actually harmful when given to unirradiated animals have a marked prophylactic action on irradiated animals. In many cases, different preventive measures should be taken against the development of pulmonary edema in irradiated and unirradiated animals.

LITERATURE CITED

1. V. M. Volkov and V. V. Kurnosov, Abstracts of Proceedings of the 22nd Students' Scientific Conference of Yaroslavl' Medical Institute [in Russian], Yaroslavl' (1968), pp. 16-17.
2. E. F. Girs, in: Current Problems in the Biochemistry and Clinical Aspects of Respiration (Proceedings of the 2nd All-Union Conference) [in Russian], Vol. 1, Ivanova (1972), p. 320.
3. V. M. Kopylov, in: Hypoxia and Narcosis [in Russian], Vol. 2, Yaroslavl' (1971), pp. 116-121.
4. V. M. Kopylov, in: Hypoxia and Narcosis [in Russian], Vol. 2, Yaroslavl' (1971), pp. 125-129.
5. G. V. Kurygin, M. L. Fafurina, G. M. Nikolaev, et al., in: The Toxicology and Hygiene of Petrochemical Products and Petrochemical Production Processes (2nd All-Union Conference) [in Russian], Yaroslavl' (1972), pp. 129-139.
6. V. P. Mikhailov, in: Hypoxia and Narcosis [in Russian], Vol. 2, Yaroslavl' (1971), pp. 134-135.
7. M. L. Fafurina, in: Problems in the Pathology of the Cardiovascular System [in Russian], Yaroslavl' (1970), pp. 26-30.
8. M. L. Fafurina and V. M. Lobanovskii, in: Hypoxia and Narcosis [in Russian], Vol. 2, Yaroslavl' (1971), pp. 122-123.
9. P. A. Chizhov, "Ways of increasing the resistance of the organism to pulmonary edema," Author's Abstract of Candidate's Dissertation, Yaroslavl' (1975).
10. B. Fischetti and E. Paroli, Boll. Soc. Ital. Biol. Sper., 39, 457 (1963).
11. K. A. Gaar and L. D. Seager, Proc. Soc. Exp. Biol. (New York), 118, 287 (1965).
12. D. Henschler and E. Reich, Klin. Wschr., 37, 716 (1959).
13. E. M. MacKay and E. F. Pecka, Proc. Soc. Exp. Biol. (New York), 73, 568 (1950).