TOXICITY DECREASING AND PROTECTIVE EFFICACY INCREASING OF SULFUR CONTAINING RADIOPROTECTORS WITH AID OF UNITHIOL

S. A. Grachev, A. G. Sverdlov, E. V. Kropachev, I. K. Koroleva, N. G. Nikanorova

It is known that the best radioprotectors are sulfur containing preparations such as cysteamine, cystamine, AET, WR-2721 etc. The searches for new radioprotectors for forty years show that there is a very low probability to find new compounds that would be more effective protectors than the listed above ones. Maybe it is impossible in principle. However all these preparations have high toxicity. Mechanism of the toxicity is still unknown but its presence essentially limits the possibility to use such compounds.

For a few last years we tried to decrease toxicity of the sulfur containing protectors without decreasing their protective efficacy. The attempts to overcome these effects by the way of combination of the compounds with other radioprotectors have not been very successful. Our last experiments show that the progress can be achieved in the case of a combination of aminothiols or their derivatives with the unithiol which is untoxic and is used in medicine as an antidot.

For example, high radioprotective effect of cysteamine is known. This preparation is widely used in radiobiological and medicinal practice in the West and in our country. But this preparation is rather toxic. We tried to decrease the negative property of cysteamine by substitution of H-atom of SH-group by a dithiol rest, that is we synthezied mixed disulfide of cysteamine and unithiol. The essential decreasing cysteamine toxicity at the full preservation of its high protective activity in the content of mixed disulfide named MDCU was found. LD_{50} of MDCU is equal to 750 mg/kg (a share of cysteamine in this compound is 460 mg/kg). LD_{50} of pure cysteamine hydrochloride is 244 mg/kg. As matter of fact it means that in the content of MDCU cysteamine toxicity has decreased 2 times. Table 1 showes the toxicity of cysteamine in content of different cysteamine derivatives calculated in mg and in mmoles to 1 kg of mice weight.

Table 1

Toxicity of cysteamine in contents of its different derivatives

Compound	Mol.weight	LD_{50} mg/kg	LD_{50} mM cysteamine/kg
Cysteamine HCI	113.6	244	2.15
Cystamine 2HCI	226.2	233	2.06
AET 2HBr	281.0	491	1.75
Buntle salt	157.2	450	2.86
MDCU (our comp.)	375.0	750	4.00

The decreasing cysteamine toxicity in content of MDCU gives an opportunity to enhance its protective ability because it is possible to increase the administration dose of cysteamine (in content of MDCU) (see Table 2).

Table 2

Survival (%) of irradiated mice with use of the drug dose equal to 642 mg/kg

Time between I.P. administration of prep. and X-Ray irradiation	Dose of irradiation, Gy				
	6.0	7.0	8.0	9.0	10.0
15 min	100	100	95	90	71
1 hour	100	100	95	70	11
2 hour	100	81	41	41	0
Without drug	100	36	0	0	0

In the following studies it was shown that the same effect is obtained at simultaneous administration of cystamine and unithiol and there is no necessary to make complicated synthesis of mixed disulfide. Moreover, unithiol addition to such radioprotectors as cystamine, AET, WR-2721 has decreased sharply their toxicity. The found effect of unithiol gives the opportunity to increase their protective efficacy. So if Dose Reduction Factor (DRF) for cystamine is 1,4 then in the combination with unithiol it is more than 1,7. Table 3 showes the unithiol influence on radioprotective efficacy of cystamine.

Table 3

Survival (%) of irradiated mice protected by combination

Compound	Dose of irradiation, Gy					
	7.0	8.0	9.0	10.0	11.0	12.0
Cystamine, 150 mg/kg	86	86	33	33	18	3
Cystamine, 350 mg/kg	100	100	90	69	64	53
+Unithiol, 170 mg/kg						
Control	33	6	0	0	0	0