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Synthesis and radioprotective study of novel amino-alkyldithiocarbamic acid derivatives against γ-irradiation in mice

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Background: The aim of this study was to evaluate the radioprotective capacity of some novel aminoalkylated dithiocarbamic acid potassium salts against γ-irradiation in mice. ***Materials and Methods:*** Eight compounds containing 2-aminoethyl-, 3-aminopropyl-, 4-aminobutyl-, 5-aminopentyl-, 6-aminohexyl-, 7-aminoheptyl-, 8-aminooctyl and 9-aminononyl of dithiocarbamate derivatives were prepared. Male NMRI mice were injected intraperitoneally (IP) with a geometric progression of doses (300 -1000 mg/kg), through the dose response range for lethal toxicity. To evaluate the radioprotecive activity, one-half of the toxic LD_{50} of each compound were injected IP to groups of twenty mice, 30 minutes prior to γ-irradiation. The treated animals were kept for 30 days, and the lethality was recorded each day. ***Results:*** Among Eight compounds of alkyl dithiocarbamic acid derivatives, 5-aminopentyl, 7-aminoheptyl, 8-aminooctyl and 9-aminononyl dithiocarbamic acid mono potassium salts are new compounds. All evaluated compounds showed a concentration-dependent effect on the survival in mice. The LD_{50} values were found to be more than 599 mg/kg. The percentages of 30-day survival of mice for 2-aminoethyl, 7-aminoheptyl and 8-aminooctyl dithiocarbamic acid derivatives were 7%, 40% and 13.5%, respectively, when injected 30 minutes before γ-irradiation. Other compounds had no radioprotective effects. Statistical analysis showed a significant difference between the treated and control groups for the 7-aminoheptyl derivative ($p<0.05$). ***Conclusion:*** Among the compounds investigated in this study, 7-aminoheptyl dithiocarbamate derivative showed more radioprotective effects in comparison with the others. Although it seems that the radioprotective effects in these derivatives correlate with the size of the alkyl chain, more experiments are required to support this hypothesis. **Iran. J. Radiat. Res., 2009; 7 (2): 91-96**

Keywords: *Radioprotective effect, aminoalkyl dithicarbamic acid, γ-irradiation.*

INTRODUCTION

With respect to radiation damage to humans, it is important to look for possible radioprotective agents to modify the normal response of biological systems to radiation-induced toxicity or lethality [(1)]. Early developments of such agents focused on thiol synthetic compounds, such as amifostine. This compound reduced mortality; however, there were difficulties in administering aminothiols which led to adverse effects. Hence, the development of radioprotective agents with lower toxicity and an extended window of protection have attracted much attention [(1)]. Free radical scavenging is based on the consumption of free radicals produced by ionizing irradiation in biological system to be most important mechanism of radioprotective effects [(2)]. For radioprotective effects of compounds with thiol functional group, the presence of free thiol group or a thiol derivative that can be converted to a free thiol in vivo is essential for radioprotecive effects [(3)]. Dithiocarbamic acids and their salts are sulfur containing derivatives have been reported to have antiviral, bactericidal, antimicrobial, and antitumor effects, and they have been used for

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prophylaxis and therapy of metal toxicity [4]. It has been demonstrated that certain dithiocarbamates are effective radioprotective agents [4-6]. The aim of this study was to evaluate the radioprotective capacity of some novel aminoalkylated dithiocarbamic acid derivatives against γ-irradiation in mice.

MATERIALS AND METHODS

All chemicals were purchased from Merck (Darmstadt-Germany) and Sigma-Aldrich (Steinhaim-Germany). Melting points were determined, using a Reichert-Jung hot plate apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VNMR-400 instrument. All spectra were recorded in D_2O and Sodium 3-trimethyl-silylpropane sulfonate was used as an internal standard. Infrared spectra were acquired on a Nicolet Magna–IR 550 spectrometer. Mass spectra were measured with a Finnigan TSQ-70 spectrometer (70 eV). The purity of all compounds was confirmed by TLC.

General procedure for the preparation of aminoalkyl dithiocarbamic acid mono potassium salt [7].

A solution of diamine (0.025 mole) in 6.5 ml methanol was added drop wise over a period of 40 minutes to a stirred solution of carbon disulfide (0.03 mole) in a solution of potassium hydroxide in methanol (2%, 6.25 ml) cooled by an ice-salt bath. The reaction medium was stirred at room temperature for additional 4 hours. The precipitated product was then filtered, washed with methanol and diethyl ether, vacuum dried and stored in a desiccator.

2. Aminoethyl dithiocarbamic acid mono potassium salt:
Yield (85%), Melting point: 198ºC.
IR (KBr), ν (cm^{-1}) 3242, 2934, 1577, 1470, 1255, 1157, 917. ^{1}H NMR (D_2O), δ (ppm): 3.61 (t, 2H, J=6Hz), 2.98 (t, 2H, J=6Hz). Mass: 136 (M^+)

3. Aminopropyl dithiocarbamic acid mono potassium salt:
Yield (76%), Melting point: 130ºC.
IR (KBr), ν (cm^{-1}) 3250, 2975, 1465, 1383, 1147, 1050. ^{1}H NMR (D_2O), δ (ppm): 3.50(t, 2H, J=6Hz), 2.85 (t, 2H, J=6Hz), 1.78 (t, 2H, J=6Hz). Mass: 150 (M^+)

4. Aminobutyl dithiocarbamic acid mono potassium salt:
Yield (89%), Melting point: 219ºC.
IR (KBr), ν (cm^{-1}) 3365, 2970, 1511, 1316, 1061, 994. ^{1}H NMR (D_2O), δ (ppm): 3.22-3.29 (m,4H), 1.31-1.40 (m,4H). Mass: 164 (M^+)

5. Aminopentyl dithiocarbamic acid mono potassium salt:
Yield (58%). Paste
IR (KBr), ν (cm^{-1}) 3314, 2951, 1491, 1307, 1022, 913. ^{1}H NMR (D_2O), δ (ppm): 3.19-3.26 (m ,4H), 1.32-1.46 (m,2H), 1.09-1.15 (m, 4H). Mass: 178 (M^+)

6. Aminohexyl dithiocarbamic acid mono potassium salt:
Yield (75%), Melting point: 155ºC.
IR (KBr), ν (cm^{-1}) 3230, 2929, 1475, 1296, 1086, 942. ^{1}H NMR (D_2O), δ (ppm): 3.22-3.27 (m,4H), 1.33-1.42 (m,2H), 1.09-1.15 (m,6H). Mass: 192 (M^+)

7. Aminoheptyl Dithiocarbamic acid mono potassium salt:
Yield (82%), Melting point: 138ºC.
IR (KBr), ν (cm^{-1}) 3380, 3196, 2929, 2858, 1490, 1296, 1157, 937. ^{1}H NMR (D_2O), δ (ppm): 3.80 (m, 2H), 3.23-3.30 (m, 2H), 1.30-1.40 (m, 2H), 1.05-1.14 (m, 2H), 0.89-0.93 (m, 6H). ^{13}C NMR (D_2O), δ(ppm): 57.36, 48.11, 28.61, 28.39, 27.62, 26.08, 16.10. Mass: 206 (M^+)

8. Aminooctyl dithiocarbamic acid mono potassium salt:
Yield (69%), Melting point: 132ºC.
IR (KBr), ν (cm^{-1}) 3126, 2929, 1485, 1284, 1101, 937. ^{1}H NMR (D_2O), δ (ppm): 3.35-3.40 (m,3H), 3.23 (m, 1H), 1.34(m,1H), 1.04-1.12 (m,3H), 0.85-0.93 (m, 8H). Mass: 220 (M^+)

9. Aminononyl dithiocarbamic acid mono potassium salt:
Yield (75%), Melting point: 135ºC.
IR (KBr), ν (cm^{-1}) 3185, 2924, 1501, 1296, 1157, 933. ^{1}H NMR (D_2O), δ (ppm): 3.38-3.43 (m,3H), 3.25 (t, 2H, J=7.6Hz) 1.31-1.42 (m,

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2H), 1.05-1.16 (m, 4H), 0.91-0.96 (m, 8H). Mass: 234 (M^+)

Animals

Eight-week old male NMRI mice (Pasteur Institute of Iran), weighting 28 ± 3 g were used. A standardized pelleted diet was given and tap water was *ad libitum*. The animals were housed in groups of seven for one week in a quarantine facility. All the mice were kept under controlled lighting conditions (light: dark, 12:12h) and temperature (22±1°C) in the university's animal house. Experiments were conducted according to principles outlined in "The guide for the care and use of laboratory animals" prepared by Tehran University of Medical Sciences.

Toxicity studies

For toxicity studies the compounds were dissolved in sterile distilled water or suspended in sterile distilled water containing 0.2% polysorbate 80 (Tween 80). Male NMRI mice were injected intraperitoneally (IP) with a geometric progression of doses (300-1000 mg/kg), through the dose response range for lethal toxicity. Ten animals were used for each subgroup, and four doses were used for to determine each LD_{50}. Animals were observed for 72 h. For determination of the toxic LD_{50} numbers of the observed deaths were analyzed by Probit analysis [8].

Radioprotective effect studies

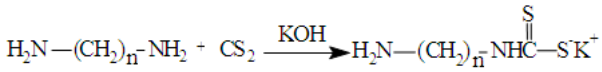
Whole-body irradiation was performed by a cobalt-60 γ-radiation source (Theratron 780, Canada). The mice were placed in ventilated plexiglass cages and irradiated in groups of 10 simultaneously. The source to skin distance was 82 cm and the dose rate was 96 cGy/min at room temperature (23±2°C). To evaluate the radioprotecive activity, one half of the toxic LD_{50} of each compound were injected IP to groups of twenty mice 30 minutes prior to γ-irradiation [9]. The mice were irradiated with a dose equal to the $LD_{100/30}$ (Lethal dose for mice in 30 days) of the control mice (800 cGy). This dose was obtained in preliminary study with respect to 14 mice that irradiated with 800 cGy of gamma irradiation. The treated animals were kept for 30 days and the lethality was recorded each day.

Statistical analysis

The data were analyzed and LD_{50} values were determined using Probit statistical analysis test [8], and were expressed as the mean ± SE. The percentages of survivals of various derivatives were compared using two-sample test for proportions [10].

RESULTS AND DISCUSSION

Several dithiocarbamate derivatives have been prepared, some of them which containing chelating groups additional to dithiocarbamyl moiety. Synthesis of dithiocarbamates is relatively simple and these compounds are usually prepared either by the reaction of amines with carbon disulfide in aqueous media in the presence of a base [7], or by the same reaction in an organic solvent [11] (formula 1). It has been previously shown that the most potent basic thiol radioprotective compounds strongly contain basic amine functions [12]. The same patterns of antiradiation activity have been observed for dithiocarbamates [13].



Formula 1. Preparation of aminoalkyl dithiocarbamic acid mono potassium salts.

Among the alkyl dithiocarbamic acid derivatives, which their radioprotective effects were evaluated in this study some derivatives had been previously prepared, but 5-aminopentyl, 7-aminoheptyl, 8-aminooctyl and 9-aminononyl dithiocarbamic acid mono potassium salts were new compounds. The toxicity of compounds was determined *in vivo* against male NMRI mice, and after IP injection all compounds showed a concentration-dependent effect on

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the survival in mice. The results of this study showed that the percentage of survival of male NMRI mice at 30 days were 7%, 40% and 13.5% for 2-aminoethyl, 7-aminoheptyl and 8-aminooctyl dithiocarbamic acid derivatives, respectively, when injected 30 minutes before γ-irradiation (table 1 and figure 1). Statistical analysis showed a significant difference between the treated and control group for the 7-aminoheptyl derivative ($p<0.05$) (table 1). Dithiocarbamates are well known as metal chelating agents, and this property could be a possible mechanism for their radioprotective effects [4]. We, previously, have reported that kojic acid and chromone derivatives with metal complex showed radioprotective effects with the possible mechanism of superoxide dismutase activity [14, 15]. Free radical scavenging is one of the main mechanisms of natural and chemical compounds. Thiol group can react with free and toxic substance induced by gamma irradiation and reduced damage in tissue [16]. In the present study, the synthesized compounds contained dithiocarbamic acids which were potentially converted to the thiol group as an antioxidant agent. When compared with the other compounds, the 7-aminoheptyl dithiocarbamic acid derivative showed more radioprotective effects probably due to its easy conversion to the active compounds with free thiol groups *in-vivo*. Due to poor absorption of 9-aminononyl dithiocarbamic acid derivative after IP injection, it is difficult to attribute the lack of radioprotective property to its chain length. Although it seems that the radioprotective effects correlate with the size of the alkyl chain, more experiments are required to support this hypothesis.

Table 1. LD_{50} and radioprotective activity of aminoalkyl dithiocarbamic acid derivatives following intraperitoneal injection of compounds 30 min prior to exposure to an acute whole-body gamma dose of 800 cGy ($LD_{100/30}$).

Compound	LD_{50} (mg/kg)[a]	Dose injected (mg/Kg)	%Survival of mice at 30 days
Distilled water	---	---	0
2-Aminoethyl dithiocarbamate derivative	1068 ± 13	534	7
3-Aminopropyl dithiocarbamate derivative	1155 ± 133	550	0
4-Aminobutyl dithiocarbamate derivative	396 ± 31	180	0
5-Aminopentyl dithiocarbamate derivative	681 ± 52	315	0
6-Aminohexyl dithiocarbamate derivative	599 ± 74	200	0
7-Aminoheptyl dithiocarbamate derivative	855 ± 21	440	40*
8-Aminooctyl dithiocarbamate derivative [b]	800 ± 50	370	13.5
9-Aminononyl dithiocarbamate derivative [b]	740 ± 46	350	0

[a] 95% confidence limits
[b] Suspension injected
*Significant difference compared to control, ($P< 0.05$)

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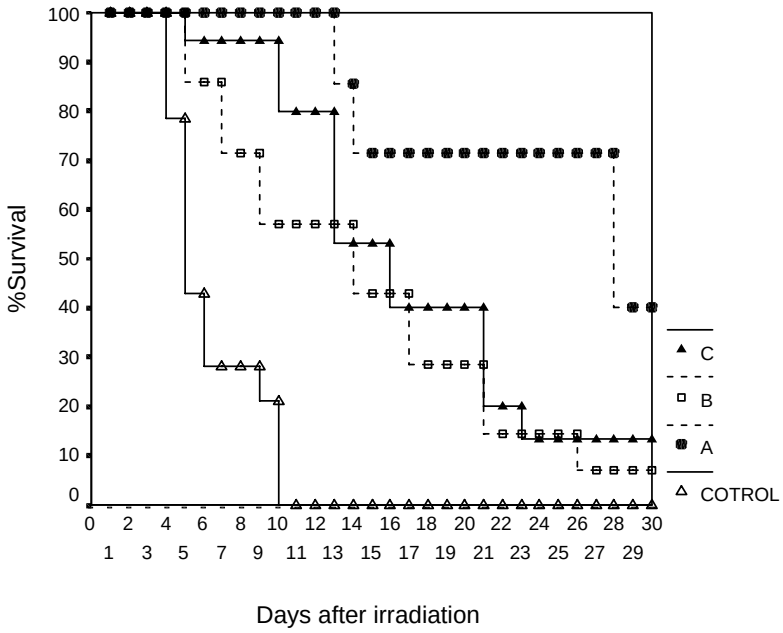

Figure 1. Effects of gamma radiation (800 cGy) on lethality in control, 7-aminoheptyl dithiocarnbamic acid monopotassium salt (A), 2 -aminoethyl dithiocarbamic acid monopotassium salt (B) and 8-aminooctyl dithiocarbamic acid monopotassium salt (C). Irradiation was after 30 min treatment. Survival was followed for 30 days. Each group was consisted of 20 mice.

CONCLUSION

Among the aminoalkyl dithicarbamic acid derivatives investigated in this study, 7 -aminoheptyl dithiocarbamic derivative showed the best radioprotective effect. Because of unreliable absorption of derivatives with longer alkyl chain after intraperitoneal injection it is not possible to evaluate their radioprotective capacity and assign a structure activity relationship for these derivatives.

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