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DECORPORATION OF POLONIUM FROM RATS BY NEW CHELATING AGENTS

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Abstract — The effectiveness of newly synthesised thiol chelating agents has been studied to reduce ^{210}Po in organs and tissues of rats. From four derivatives of meso-2,3-dimercaptosuccinic acid (DMSA) only the ethoxyethyl diester (DEEDMS) was efficient in decreasing total activity in the analysed tissues (to 80% of control animals) when repeated subcutaneous treatment started 1 h after intravenous injection of ^{210}Po. The most pronounced effect was achieved with three derivatives of dithiocarbamate: N,N′-dimethyl-(MeTTC), N,N′-diethyl-(EtTTC), N,N′-di(2-hydroxyethyl)ethylenediamine-N,N′-bisdithiocarbamate (HOEtTTC). When treatment started immediately after ^{210}Po administration, the total content of ^{210}Po in analysed tissues was reduced to 74–41% of control values. These bis-dithiocarbamates were further used in combination with 2,3-dimercaptopropane-1-sulphonate (DMPS) for removal of intramuscularly injected ^{210}Po, simulating contaminated wounds. When DMPS was injected locally and diethyldithiocarbamate (DDTC) derivates repeatedly subcutaneously, the total amount of ^{210}Po retained (including the injection site and inner organs) was reduced by 40–50% of control values.

INTRODUCTION

Polonium, like several heavy metals, reacts with thiol groups and thus chelating agents containing these groups seem to be the most suitable for its decorporation. In the present study with rats, derivatives of dimercaptosuccinic acid and diethyldithiocarbamate, which were originally designed for decorporation of cadmium, were investigated for decorporation of ^{210}Po. Screening experiments revealed that both classes of chelators might be effective agents for polonium decorporation[1].

METHODS

Young female Wistar or Sprague-Dawley rats (90–110 g) were used. ^{210}Po was injected intravenously (i.v.) in 0.05 M nitric acid (75 kBq.kg^{-1}) or intramuscularly (i.m.) in 0.3 M nitric acid (100 kBq.kg^{-1}) to simulate contaminated wounds from which ^{210}Po penetrates the body more slowly than with i.v. administration. First, the effect of several diesters of meso-2,3-dimercaptosuccinic acid (DMSA) soluble in peanut oil was investigated: diethyl-(DEDMS), dimethoxyethyl-(DMEDMS), diethoxyethyl-(DEEDMS) and diphenethyl-DMSA (DPhEDMS) (Figure 1). 2,3-Dimercaptopropanol (BAL) served as reference substance. Second, three derivatives of diethyldithiocarbamate (DDTC), soluble in water, were tested: N,N′-dimethyl-(MeTTC), N,N′-diethyl-(EtTTC), N,N′-dihydroxyethylethylenediamine-N,N′-bis-dithiocarbamate (HOEtTTC (Figure 2). Third, a combination of 2,3-dimercaptopropane-1-sulphonate (DMPS) and DDTC derivatives was used. The chelators were injected intraperitoneally (i.p.) or subcutaneously (s.c.) or, in the case of simulated wounds, locally (i.m.) (for treatment schedule see tables). Dissected tissues were digested and radioactivity of ^{210}Po was measured by alpha scintillation counting[1].

RESULTS AND DISCUSSION

After i.v. injection of ^{210}Po and treatment with DMSA derivatives, only DEEDMS was efficient (Table 1). It decreased total ^{210}Po in the analysed tissues as

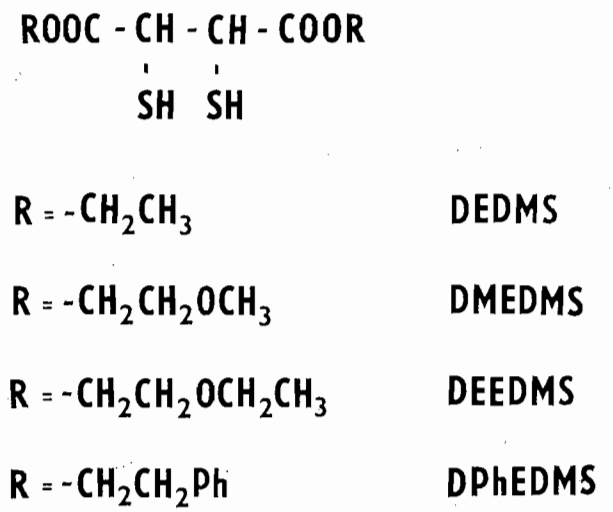

Figure 1. Structure of diesters of meso-2,3-dimercaptosuccinic acid as chelators for ^{210}Po. For explanation of abbreviations see Methods section.

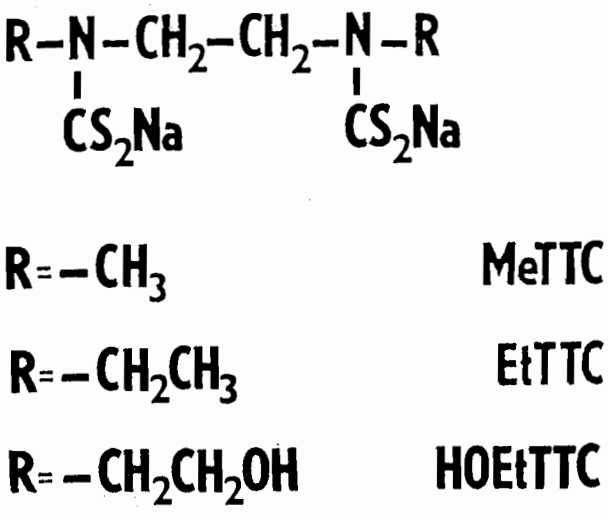

Figure 2. Structure of bis-dithiocarbamates as chelators for ^{210}Po. For explanation of abbreviations see Methods section.

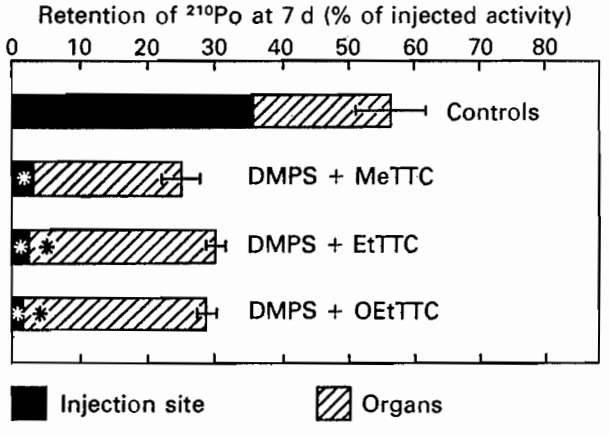

Figure 3. Effect of combined treatment on i.m. injected ^{210}Po. Five rats per group, treatment 1 mmol DMPS.kg^{-1} body mass, i.m., at 2 h and 3 d; 0.5 mmol.kg^{-1} of other chelators, s.c., at 2 h and 1–4 d. Asterisk (*) indicates statistically significant difference between treated and control animals ($p<0.05$) at 7 d. Control values (% of injected activity): injection site 35.7 ± 5.7; total 56.5 ± 5.5.

efficiently as BAL but, in contrast to BAL, it did not increase the activity in the brain. All three derivatives of DDTC substantially decreased ^{210}Po in tissues when injected s.c., beginning immediately after i.v. injection of ^{210}Po. As seen in Table 2, total retention of ^{210}Po was reduced by MeTTC, EtTTC and HOEtTTC to 74, 65 and 41% of control values, respectively. However, after administration of MeTTC and EtTTC the contents of ^{210}Po in the liver increased up to 150% of controls. No such increase was observed after injection of HOEtTTC, which further decreased retention of ^{210}Po in kidneys and bones more than the two other derivatives.

As to simulated wounds, an efficient treatment should reduce ^{210}Po at the injection site without increasing its accumulation in other body tissues, which may be difficult. Oxathiol, a water soluble derivative of BAL, has been shown to enhance translocation of ^{210}Po from the wound site but also to stimulate its accumulation in the kidneys[2]. Similar results were obtained with low doses of DMPS. Only when large doses of DMPS were injected, was nearly all ^{210}Po removed from the injection site without increasing its deposition in the kidneys. Such dosage, however, caused severe irritation of tissues at sites of DMPS administration (unpublished own observation).

Increased accumulation of i.v. injected ^{210}Po in the kidneys, after administration of DMPS, can be counteracted by DDTC[3]. Therefore, we tested the efficiency of DMPS administered into simulated wounds in combination with s.c. injected derivatives of DDTC. As shown in Figure 3, about 90% of ^{210}Po was removed from its i.m. injection site by two local injections of DMPS. At the same time, retention of ^{210}Po translocated into analysed tissues increased after treatment with two derivatives of DDTC, to about 130% of control values. Most of the increased accumulation of ^{210}Po was in liver and kidneys. In spite of this, overall retention of ^{210}Po (at the injection site plus in the organs) was reduced by about one half.

CONCLUSION

From the new chelators tested, the HOEtTTC, a derivative of DDTC, seems to be the most effective one

Table 1. Retention of ^{210}Po after treatment with diesters of DMSA.

Chelator	Retention of ^{210}Po in % of control values at 11 d*				
	Brain	Liver	Kidneys	Bones	Total
BAL	414**	93	89**	63**	82**
DEDMS	157**	100	135**	94	100
DEEDMS	100	109	101	67**	81**

*Five rats per group: treatment 0.4 mmol.kg^{-1} body mass, i.p., 5 times (every second or third day).
**Statistically significant difference between treated and control animals ($p < 0.05$). Control values (% of injected activity): brain 0.07 ± 0.015; liver 7.2 ± 2.0; kidneys 6.8 ± 0.3; bones 6.3 ± 0.7; total 53.0 ± 2.0.

Table 2. Retention of ^{210}Po after treatment with derivatives of DDTC.

Chelator	Retention of ^{210}Po in % of control values at 7 d*				
	Brain	Liver	Kidneys	Bones	Total
MeTTC	94	139**	46**	57**	74**
EtTTC	75**	151**	41**	42**	65**
HOEtTTC	74**	104	25**	19**	41**

*Five rats per group: treatment 0.4 mmol.kg^{-1} body mass, s.c., starting immediately after ^{210}Po i.v. injection and continuing once daily for 5 consecutive days.
**Statistically significant difference between treated and control animals ($p < 0.05$). Control values (% of injected activity): brain 0.11 ± 0.01; liver 8.5 ± 0.30; kidney 7.6 ± 0.2; bones 10.5 ± 0.9; total 63.2 ± 1.3.

for removal of ^{210}Po from the body. The effect of this substance will therefore be further investigated in more detail.

ACKNOWLEDGEMENT

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