THE USE OF DTPA TO INHIBIT THE EXTRAPULMONARY DEPOSITION OF CURIUM-244 IN THE RAT FOLLOWING THE BRONCHIAL INTUBATION OF OXIDE SUSPENSIONS

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INTRODUCTION

Much experimental evidence has accumulated on the use of the calcium or zinc salts of diethylenetriaminepenta-acetic acid (Na_3Ca DTPA and Na_3Zn DTPA) for removing actinides from animals (1). However, such studies are based on experiments in which the actinides have been administered as the citrate or nitrate complexes. The present work looks at the efficacy of Na_3Ca DTPA and Na_3Zn DTPA for enhancing the excretion of curium after pulmonary intubation of curium-244 dioxide (CmO_2).

MATERIALS AND METHODS

High fired CmO_2 was supplied by the Radiochemical Centre (Amersham, Bucks, U.K) and was fractionated by ultrafiltration as described previously (2).

In the animal experiments Na_3Zn DTPA or Na_3Ca DTPA were administered intravenously in isotonic saline. The diuretic Lasix, frusemide B.P., (0.2 ml, 8.9 mg kg^{-1}) was injected intravenously at intervals to promote a high urine flow to allow the collection of adequate volumes of urine for analysis by gel permeation chromatography.

The methods of pulmonary intubation, gel permeation chromatographic separation and radioactivity determinations are given by Stradling *et al.*, (2).

RESULTS AND DISCUSSION

After intubation into the lung, 0.22-1.2 μm diameter curium dioxide particles rapidly form particles of 0.001 μm in diameter (2). These particles, believed to be of the hydroxide, then diffuse passively to the blood probably through pores in the alveolar epithelium (3). In the blood intact 0.001 μm particles of CmO_2 combine with serum proteins. The protein-bound CmO_2 rises from 45% of the circulating radioactivity at 35 minutes after pulmonary intubation to >90% at 24 hours; the remaining activity is 0.001 μm particles.

0.001 μm particles will also combine with serum proteins *in vitro*. For example, when serum labelled for 24 hours was chromatographed on Sephadex G-200, Cm eluted with the α and γ globulins, and the transferrin and albumin fractions in about equal amounts. Negligible activity (< 1%) was recovered in the low molecular weight fractions where unbound particles or curium would elute. However,

if Na_3Ca DTPA or Na_3Zn DTPA is added at a concentration of 0.02 mg. ml^{-1} to the serum 6 minutes before the 0.001 μm particles the reaction between particles and proteins is inhibited and even after 24 hours 99% of the radioactivity eluted as intact particles. Similarly, intact 0.001 μm particles could be regenerated from protein-bound Cm by addition of Na_3Ca DTPA (2.5 $mg.ml^{-1}$). It is suggested that DTPA blocks receptor sites for the particles on the protein by a preferential binding process.

Previous work has shown that a major factor infuencing the urinary excretion of Cm following the intake CmO_2 into the lungs is the renal dialysis of 0.001 μm particles (2). The binding of particles to serum proteins may compete with this process. The above studies in vitro suggest that either Na_3Ca DTPA or Na_3Zn DTPA could maintain these 0.001 μm particles in the blood for long enough to permit the quantitative urinary excretion of Cm. The effect of administering Na_3Ca DTPA or Na_3Zn DTPA to rats exposed to CmO_2 suspensions is shown in Table 1. If the concentration of Na_3Ca DTPA or Na_3Zn DTPA in the blood is maintained above 0.002 $mg.ml^{-1}$ (Expt. 2), by administering 0.28 $mg.kg^{-1}$ body weight initially followed by injections of 0.14 $mg.kg^{-1}$ at 30 minute intervals, then deposition of Cm in the skeleton and liver is markedly reduced. The interval between successive injections corresponds to the half time of DTPA in the blood (4). At higher concentrations (Expt. 3) Na_3Ca DTPA is still effective in minimising tissue deposition even when administered 2 hours after small particle suspension. In all of the experiments where Na_3Ca DTPA or Na_3Zn DTPA and Lasix were administered before the oxide suspension the Cm was excreted as 0.001 μm particles. When the oxide suspension was administered before the DTPA and Lasix the Cm was present in the urine as 0.001 μm particles and Cm citrate. The Cm citrate is probably formed from particles and citrate in the renal tubular fluid (2).

The experiments outlined above demonstrate that (i) DTPA is not chelating Cm but inhibiting a reaction between 0.001 μm CmO_2 particles and serum proteins (ii) Na_3Ca DTPA and the less toxic Na_3Zn DTPA are equally effective and (iii) to obtain efficient urinary excretion of Cm the concentration of DTPA in the blood must be maintained above about 0.004 $mg.ml^{-1}$. Animal experiments indicate that following an accidental intake of $^{244}CmO_2$ by man, about 90% of that fraction destined to translocate to blood would do so during the next month (5). Therefore, for DTPA therapy to be most effective it should be administered continually over this period at a constant rate of 14 $mg.kg^{-1}.day^{-1}$. This is within the dose range normally used in clinical practice (6).

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Table 1. Injection schedules, tissue distribution and excretion of ^{244}Cm after administering ^{244}Cm oxide

Expt. No.	Injections	Injection schedule[a]		Tissue distribution and excretion[b] (%)			
		mg.kg^{-1} body wt	t min	Lungs	Liver	Skeleton	Urine
1	Lasix	8.9	-5 ; 120, 210	11.1	15.6	33.5	32.4
2	$Na_3ZnDTPA$	0.28;0.14[c]	-5;25,55,85..235	13.1	0.5	1.5	79.8
3	$Na_3CaDTPA$	14;7[c]	120;140,180...360	12.2	0.3	1.5	83.5

[a] Suspension of 0.001 μm diameter particles 100 μl, 500 Bq administered by tracheal intubation at zero time. The injection times shown for DTPA are relative to this labelling. The amount of DTPA administered in the first injection is twice that administered in subsequent injections. Lasix 0.2 ml, 8.9 mg. kg^{-1} administered intravenously at -5, 120 and 210 minutes except experiment 3 where these times are relative to the first injection of DTPA.

[b] Values expressed as a percentage of initial lung burden; animals killed 240 min after initial injection. Remainder of ^{244}Cm present in blood, kidneys and gastro-intestinal tract and contents. No faeces were passed during the course of the experiments.

[c] To convert to mg.ml^{-1} of blood divide by 70 (7).

The metabolic data were closely similar when Na_3 CaDTPA or $Na_3ZnDTPA$ were administered by the same injection schedule.

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