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TOXICITY OF SOME NEW CHELATING AGENTS FOR RADIOSTRONTIUM REMOVAL

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The following chelating compounds were compared with respect to their acute intraperitoneal LD_{50}: EDTA (ethylenediamine tetra-acetic acid), DTPA (diethylenetriamine penta-acetic acid), DIMEDTA (dimethylethylenediamine tetra-acetic acid), PDTA (propylenediamine tetra-acetic acid), HEDTA (N-hydroxyethyl ethylenediamine tri-acetic acid).

The toxicity of the newly synthetised compound DIMEDTA is almost equal to the toxicity of DTPA, both substances being less toxic than the other three complexing agents tested. LD_{50} values for PDTA are within the values found for EDTA. The influence of the new chelating substances on radiostrontium elimination will be evaluated in the near future.

The objective of this work was to evaluate the mammalian toxicity of some newly sinthesized chelating compounds as compared to the toxicity of substances already in use in treatment of radioelement poisoning such as EDTA (ethylenediamine tetra-acetic acid), DTPA (diethylenetriamine penta-acetic acid) etc.

Chelating therapy with the polyamino acids such as EDTA has not proved to be very useful in removing radiostrontium from the body since stability constants of these chelating agents with Ca are higher than those with strontium (1). In order to find a chelating agent more effective for radiostrontium removal attempts have been made to synthesise chelating agents with a higher relative complexing power for strontium than those already in use. As a part of a broadly conceived endeavour dimethylethylenediamine tetra-acetic acid and propylenediamine tetra-acetic acid have been synthesized. The dissociation constants of the respective acids and the stability constants of their chelates with some metal ions have also been measured (2).

CC′-dimethylethylenediamine tetra-acetic acid (DIMEDTA) was synthesized from pure *meso*-2,3-diaminobutane and sodium chloro-acetate by condensing them in alkaline solution at 95° C (2). Propylenediamine

tetra-acetic acid (PDTA) was made by a similar approach from pure racemic propylenediamine (C-methylethylenediamine) which in turn was prepared by the method advocated by *Dwyer* (3).

Although one can make predictions of chelating efficiency from the knowledge of chemical structure, relative formation constants, chelate diffusion rates etc., the final answer as to the effectiveness of a chelating agent must come from appropriate testing in animals (4). Since low toxicity is one of the qualities desirable in new compounds meant for

Table 1.

Mortality following single intraperitoneal injection of EDTA, DIMEDTA, DTPA, PDTA and HEDTA

Complexing agent	Dose mg/kg	Mortality ratio	LD_{50}		95% confidence limits	
			mg/kg	mM/kg	mg/kg	mM/kg
EDTA	250	0/6				
	315	0/6				
	397	4/6	396,9	1,06	350,5 – 449,4	0,96 – 1,20
	500	4/6				
	690	6/6				
DIMEDTA	247	0/4				
	356	0/4				
	513	0/4	675,5	1,89	562,5 – 811,2	1,58 – 2,27
	742	3/4				
	1070	4/4				
DTPA	400	0/6				
	474	2/6				
	562	1/6	665,6	1,69	607,5 – 729,2	1,54 – 1,85
	666	0/6				
	789	6/6				
PDTA	200	0/6				
	240	0/6				
	285	1/6	356,6	1,10	337,0 – 377,3	1,04 – 1,16
	337	6/6				
	400	0/6				
HEDTA	200	1/6				
	240	0/6				
	285	0/6	337,0	1,21	299,6 – 379,1	1,14 – 1,28
	337	3/6				
	400	5/6				

EDTA = ethylenediamine tetra-acetic acid
DIMEDTA = dimethylethylenediamine tetra-acetic acid
DTPA = diethylenetriamine penta-acetic acid
PDTA = propylenediamine tetra-acetic acid
HEDTA = N-hydroxyethylethylenediamine tri-acetic acid

therapeutic use, the first part of our investigation was mainly concerned with testing of comparative toxicities of new chelating agents.

The following chelating compounds were compared by determination of their acute intraperitoneal LD_{50}: ethylenediamine tetra-acetic acid (EDTA), diethylenetriamine penta-acetic acid (DTPA), dimethylethylenediamine tetra-acetic acid (DIMEDTA), propylenediamine tetra-acetic acid (PDTA) and N-Hydroxyethyl ethylenediamine tri-acetic acid (HEDTA).

Female rats 5–6 months old (150–220 g) were given intraperitoneal injections. The compounds were applied in a volume of 1 ml per 100 g of body weight, the dilutions of the complexing agent being freshly made on the day of the testing. The pH was adjusted to 7 by addition of the necessary amount of 10 N sodium hydroxide. Groups of 4–6 animals were used for each dose level tested. Five dose levels were used with each compound. The intraperitoneal injection of the complexing agent was followed by 24 hour observation period for pharmacologic effects and evidence of toxicity.

LD_{50} values and their 95% confidence limits were calculated by the method of moving averages (5). The results of the acute intraperitoneal toxicity in rats are shown in Table 1. Mortality ratio for a given dose of a compound is tabulated in column 2. In column 3 and 4 LD_{50} values and their confidence limits are expressed both in milligrams and millimoles per kg of body weight.

All of the tested chelating agents caused similar symptoms, which were rapid in onset and became severe within approximately 10 minutes with signs of distress and hypocalcemic convulsions. Death usually supervened within the first 2 hours.

The toxicity of the newly synthesized compound DIMEDTA is almost equal to the toxicity of DTPA, both substances being less toxic than the other three complexing agents tested. LD_{50} values for PDTA are however within the values found for EDTA.

Whether this difference, although statistically significant, increases the chances of DIMEDTA being superior chelating agent to those which are already in use, depends, of course, on other properties some of which are going to be evaluated in the near future.

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Sadržaj

TOKSIČNOST NEKIH NOVIH KOMPLEKSONA ZA ODSTRANJIVANJE STRONCIJA IZ ORGANIZMA

Izvršeno je određivanje komparativne toksičnosti kompleksona određivanjem akutne LD_{50} nakon intraperitonealne aplikacije. Uspoređena je toksičnost: EDTA (etilendiamin tetra-octena kiselina), DTPA (dietilentriamin penta-octena kiselina), DIMEDTA (dimetil etilendiamin tetra-octena kiselina), PDTA (propilendiamin tetra-octena kiselina) i HEDTA (N-hidroksietil etilendiamin trioctena kiselina).

Toksičnost novosintetiziranog spoja DIMEDTA gotovo je jednaka toksičnosti DTPA. Oba su ta kompleksona manje toksična od ostalih testiranih spojeva. LD_{50} vrijednosti za PDTA su otprilike jednake kao za EDTA. Istraživanja o djelovanju novih kompleksona na eliminaciju stroncija iz organizma su u toku.

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