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Yosoji Ito, Susumu Tsurufuji, (the Late) Eiichi Murai, Sadahiko Ishibashi, Morizo Ishidate, and Zenzo Tamura : Detoxication and Excretion of Radioactive Strontium. II.[1] Effect of Several Organic Acids having Chelating Ability.

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Very rapid deposition of radioactive strontium into the skeletal tissues is exclusively attributable to the physicochemical exchange of strontium ion in the body fluid with calcium in the bone mineral.[2] In order to inhibit this physicochemical processes and to delay skeletal accumulation of radioactive strontium it would be greatly effective to bind strontium ion into undissociated form with a chelating agent. However, almost all of the known chelating agents bind much more readily with calcium than with strontium. In fact it has been clearly recognized that EDTA is ineffective in activating the excretion of radiostrontium.[3~5]

If a chelating agent is able to combine with radiostrontium *in vivo* and to decrease effectively the concentration of its ion, it would decrease skeletal deposition of radiostrontium.

In the present experiment several organic acids were examined under this criterion in order to find an effective chelating agent. Since the difference in chelate formation constants of these organic acids between those with strontium and with calcium is relatively small, these acids were expected to be effective, though the constants are not so high.

Litter mates of male albino rats about 2 months old were divided into groups (control and treatment). The rats were injected subcutaneously with 0.2 cc. of 10^{-5} mole/L. solution of strontium chloride containing about 3 μc of $^{90}Sr + ^{90}Y$. Immediately after radiostrontium injection a solution of experimental materials (Table I) was given by intraperitoneal injection. Control groups of rats were injected with equal volume of 0.9% NaCl solution. Sixty minutes later the rats were sacrificed by cutting the carotid artery under anesthesia of sodium pentobarbital and the blood was drawn from each rat. Radioactivity assay was performed on the liver, kidneys, spleen, serum, and a part of the skull bone (a part of combined frontal and parietal bones). Percentage recovery of injected dose of radiostrontium in these organs was calculated and is summarized in Table I. Total serum radiostrontium was estimated by assuming the total volume of the serum to be 2.5 cc./100 g. body weight of a rat.[6] Marked decrease of radiostrontium deposition into the skull bone was observed in all the groups of rats treated with the experimental materials. On the other hand, soft tissues, i.e., the liver, the kidneys, and the serum took up much more radioactive strontium in experimental groups of rats with the exception of the citrate group. The decrease in deposition of radiostrontium into the bone and the increase of remaining activity in the soft tissues, above all in the serum, would indicate inhibition of physicochemical exchange of radiostrontium between a solid phase (bone mineral crystals) and a liquid phase (circulating body fluids). Much attention should be paid to the data on the citrate group, since it is known that sodium and zirconium citrates are effective in activating the excretion of radiostrontium.[7] Nevertheless, the effect of citrate, which inhibits skeletal deposition of radiostrontium and retains it in the body fluid (soft tissues) was less distinct than with other materials examined.

Strontium chelate, if it is formed, would decrease skeletal deposition of radiostrontium and retain it in the body fluids, but urinary excretion of radioactivity would not increase unless the strontium

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1) Part I : Yakugaku Zasshi, **78**, 76(1958).
2) W.F. Neuman, M.W. Neuman : Chem. Revs., **53**, 1(1953).
3) S.H. Cohn,, J.K. Gong : Proc. Soc. Exptl. Biol. Med., **83**, 550(1953).
4) J.K. Gong, W.L. Milne, S.H. Cohn : U.S. AEC Documents NRDL-426(1953).
5) T. Fukuda : Nippon Acta Radiologica, **15**, 845(1955).
6) N.I. Berlin, D.C. VanDyke, W.E. Siri, C.P. Williams : Endocrinology, **47**, 429(1950).
7) J. Schubert, H. Wallace : J. Biol. Chem., **183**, 157(1950).

TABLE I. Distribution of Injected Radioactive Strontium

Compound (Na Salt)		Citrate		Tricarballylate		Citraconate		Tartrate		Lactate	
Dose		2 mM/kg.		8.5 mM/kg.		15 mM/kg.		8.5 mM/kg.		18 mM/kg.	
Tissue		Sr recovery[b]	p[c]	Sr recovery[b]	p[c]	Sr recovery[b]	p[c]	Sr recovery[b]	p[c]	Sr recovery[b]	p[c]
Serum	C[a]	2.43	0.10	2.43	0.005	1.94	0.005	1.92	0.05	1.92	0.005
	T[a]	2.62 slight increase		3.51 marked increase		3.48 marked increase		2.40 moderate increase		2.98 marked increase	
Liver	C[a]	1.16	0.05	1.16	0.005	0.95	0.005	0.48	0.005	0.48	0.005
	T[a]	1.57 slight increase		2.01 marked increase		1.87 marked increase		1.34 marked increase		3.68 marked increase	
Kidneys	C[a]	0.51	—	0.51	0.005	0.34	0.01	0.37	0.005	0.37	0.01
	T[a]	0.59 unchanged		1.95 marked increase		0.89 marked increase		0.96 marked increase		0.68 moderate increase	
Spleen	C[a]	0.11	—	0.11	—	0.08	0.005	0.06	—	0.06	0.01
	T[a]	0.10		0.19		0.13		0.07		0.07	
Skull	C[a]	0.48	0.005	0.48	0.005	0.58	0.005	0.48	0.005	0.48	0.005
	T[a]	0.38 moderate decrease		0.22 marked decrease		0.37 marked decrease		0.31 marked decrease		0.29 marked decrease	

a) C : Control group T : Treated group
b) The values indicate per cent of dose injected.
c) Probability of F calculated for testing the significance for the difference between control and treated groups.

chelate could pass easily through the kidneys. The fact that the radioactivity of the kidneys showed marked increase in the groups treated with tricarballylate, citraconate, tartrate, and lactate compared to citrate group appears to be a phenomenon worthy of great notice. Further investigation has already solved the question, at least in the case of tricarballylate, i. e. the marked accumulation of radioactivity in the kidneys of the rats treated with tricarballylate is taken as the phase of very activated excretion of radiostrontium through the kidneys by this chemical. Details of this result will be described in the following paper.[8]

Summary

Effect of tricarballylate, citraconate, tartrate, lactate, and citrate, which are able to form chelating complex with strontium, on the distribution of parenterally administered radioactive strontium was examined, and it was indicated that all of these organic acids markedly decreased skeletal depostion of radiostrontium and four acids other than citrate markedly increased radiostrontium in the blood serum and soft tissues.

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8) Y. Ito, S. Tsurufuji, S. Ishibashi, M Ishidate, Z. Tamura, H. Takita : This Bulletin, **6**, 34 (1958).