Effect of Ethylenediaminetetraacetic Acid on Radiostrontium Excretion in Man.* (23806)

HERTA SPENCER, JOSEPH SAMACHSON AND DANIEL LASZLO
(Introduced by L. Leiter)
Division of Neoplastic Diseases, Montefiore Hospital, N. Y. City

Certain metals which enter the animal or human body are rapidly deposited in the skeleton. This deposition can be counteracted by agents which form chelates with the metal and the metal chelate is then usually eliminated through the kidneys. The calcium salt of ethylenediaminetetraacetic acid (Ca-EDTA) is thus used as a detoxifying agent in poisoning with stable or radioactive metals, *e.g.*, lead, radioyttrium, and plutonium, since it has a higher affinity for these elements than for calcium(1-5). The sodium salt of ethylenediaminetetraacetic acid (Na-EDTA) may be even more effective for the removal of certain elements: it binds calcium and other metals in the extracellular fluid, causes demineralization and thereby inhibits the deposition of metals in bone and also promotes their removal from bone(6).

The rapid injection of Na-EDTA causes hypocalcemia and tetany(7). When this agent is infused slowly the calcium bound in plasma is replenished by calcium from bone to restore calcium homeostasis and the calcium chelate is excreted(6,8). Although EDTA binds calcium more strongly than strontium, it was of interest to study whether the demineralization caused by Na-EDTA interferes with the deposition of radiostrontium in bone, promotes the release of the already deposited isotope and thereby enhances the excretion of radiostrontium. The results of studies performed in three patients† with radioactive strontium (Sr^{85}) and Na-EDTA are reported in this communication.

Materials and methods. The investigations were divided into a control study which lasted 13, 13, and 18 days and, in an experimental study of 10, 10 and 5 days for the three patients respectively. A tracer of Sr^{85}, a γ-emitter (0.1-0.4 μc/kg) was injected intravenously on the first day of the control and experimental study in the fasting state.‡ Four grams of Na-EDTA were infused intravenously in 5% glucose in water over a 4-hour period on the first day of the experimental study and Sr^{85} was injected 30 minutes after the Na-EDTA infusion had been started. The Na-EDTA infusions were repeated on the two subsequent days in Patient 1 and on one day in Patients 2 and 3. Sr^{85} plasma levels, urinary and fecal excretions were determined during the entire study. Blood samples were obtained for Sr^{85} determinations at 1, 4, 8 and 24 hours following the injection of the tracer, daily for the next six days, and three times per week thereafter. The urine of the first day of each study was collected for radioassay in fractions at time intervals at which the blood samples were taken. Sr^{85} was then determined daily on 24-hour urine collections. The Sr^{85} content of each stool specimen was determined. The technic of the administration and of the measurement of Sr^{85} in blood and excreta has been described in previous publications(9,10). Metabolic balances of nitrogen, calcium and phosphorus were determined on six-day pools in the two phases of the study. The urinary calcium and phosphorus were determined in each urine fraction on the days of Sr^{85} administration and daily thereafter.

Results. Fig. 1 shows the results obtained in Patient 1. The rate of urinary radiostrontium excretion decreased considerably on the three days of Na-EDTA infusion and increased markedly thereafter so that the total excretion in 13 days was comparable in both studies, 39.7% versus 39.9%. The rate of urinary calcium excretion (lower half of Fig.

* This study was performed under Contract with U. S. Atomic Energy Com.

† Patient 1, 70 yr old male. Diagnosis: probable carcinoma of lung. Patient 2, 40 yr old female. Diagnosis: Hodgkins disease. Patient 3, 61 yr old male. Diagnosis: Carcinomatous polyp of colon.

‡ Produced by Nuclear and Engineering Corp., Pittsburgh, Pa.

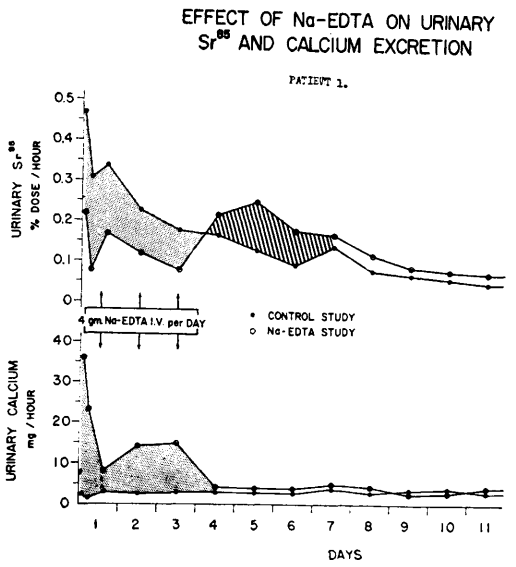

FIG. 1.

1) increased significantly on the three days of the Na-EDTA infusions, the excess calcium excretion being 70, 62 and 67% of the binding power of the chelating agent.

The effect of Na-EDTA on urinary calcium and Sr^{85} excretions of Patients 2 and 3 was similar to that of Patient 1: decrease of urinary radiostrontium and increase of urinary calcium excretion (Table I).

An attempt was made to estimate the ionized calcium excreted on the days of Na-EDTA administration by comparing the ratio of urinary Sr^{85}/Ca^{++} of the control to that of the experimental study:

$$Ca^{++}\ exp. = \frac{\%\ Sr^{85}\ exp.}{\%\ Sr^{85}\ control} \times Ca^{++}\ control,$$

assuming that the Sr^{85}/Ca^{++} ratio remains unaltered when Na-EDTA is infused. These calculations reveal that most of the calcium excreted on the days of Na-EDTA administration was chelated and that the urinary excretion of ionized calcium of each patient was lower than in the control study (Table I).

The plasma curve of each of the three patients was only slightly higher in the experimental than in the control phase and did not reflect the major changes of urinary Sr^{85} excretion. The clearances of calcium and Sr^{85} were calculated. The data of Patient 1 are illustrated in Fig. 2. In the control study, the clearance of Sr^{85} was approximately five times higher than that of calcium. In the Na-EDTA study, the Sr^{85} clearance decreased by a factor of 2-2.5 while the clearance of total calcium (Ca^{++} + chelated calcium) increased considerably. Following the discontinuation of Na-EDTA, the Sr^{85} and calcium clearances returned rapidly toward control levels, the Sr^{85} clearance being slightly higher than in the control phase.

The fecal Sr^{85} excretions did not signifi-

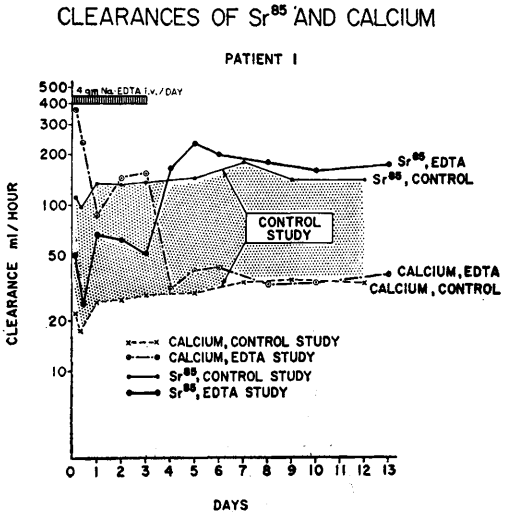

FIG. 2.

TABLE I. Effect of Na-EDTA upon Urinary Sr^{85} and Calcium Excretion.

Patient No.	Type of study	Urinary Sr^{85}, % dose Day 1	Urinary Sr^{85}, % dose Day 2	Urinary calcium, mg/day Day 1	Urinary calcium, mg/day Day 2
1	Control	8.5	5.6	58	65
	Na-EDTA	3.9	2.8	383 (27)*	346 (33)*
2	Control	21.4	10.4	202	172
	Na-EDTA	9.4	8.1	469 (89)*	463 (134)*
3	Control	7.8	3.6	71	45
	Na-EDTA	2.7	1.6	318 (25)*	341 (20)*

* mg Ca^{++} estimated by Sr^{85}/Ca ratios (see text).

cantly differ in the control and experimental phase.

Discussion. Since the binding capacity of EDTA is higher for calcium than for strontium (Log $K_{Ca} = 10.6$ and Log $K_{Sr} = 8.6$), strontium will not be appreciably chelated by Na-EDTA in the presence of the large excess of calcium in the serum. Thus, the serum ionic calcium is lowered by the infusion of Na-EDTA while the serum ionic strontium level is not decreased. Increased tubular reabsorption of ionic calcium may aid in restoring calcium homeostasis, and may be accompanied by a parallel increase in tubular reabsorption of ionic strontium. This explains the decrease of urinary radiostrontium excretion during the excretion of *chelated* calcium, in contrast with the enhancement of urinary radiostrontium excretion when an excess of *ionized* calcium is excreted(11).

The increased tubular reabsorption may be the cause of the slight rise in the plasma level of radiostrontium. It is possible, however, that another factor may also be contributory: demineralization induced by the chelating agent may retard the entry of radiostrontium into bone and may promote the removal of the already deposited isotope. Bauer *et al.* have shown that half of the dose of Sr^{90} present in the skeleton of rats four hours after intraperitoneal injection of the isotope is already fixed in the non-exchangeable fraction of the bone salt(12). Studies carried out with Sr^{85} in man have revealed that approximately one-third of the injected Sr^{85} is deposited in the skeleton three hours after the intravenous injection of the tracer. The infusion of Na-EDTA may, therefore, increase the strontium content of plasma and of "soft tissues" due to demineralization and increased tubular reabsorption of strontium. Strontium can then be released from these sites upon termination of the EDTA infusion. The rebound Sr^{85} excretion compensates for the inhibition in the Na-EDTA phase so that the cumulative radiostrontium excretion in the experimental study is comparable to, but not in excess of that of the control study.

Summary. The effect of sodium salt of ethylenediaminetetraacetic acid, Na-EDTA, upon radiostrontium (Sr^{85}) metabolism in man was investigated under controlled metabolic conditions. Urinary radiostrontium excretion was inhibited in each of 3 patients when Na-EDTA was infused. This depression was followed by excess excretion of the isotope after discontinuation of Na-EDTA. The mechanism of action responsible for this metabolic shift is discussed.

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