Promotion of Radioisotope Excretion¹ ²

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INTRODUCTION

Nuclear medicine would be greatly aided if compounds were available to promote the excretion of unwanted radioisotopes from biological systems. Such preparations would make possible greater use of long-lived radionuclides in medicine and would reduce some of the environmental hazards associated with nuclear energy. The biochemistry of radioisotope excretion is complicated because there are so many radioelements and each has its own metabolic pathway. Since study of the compounds that do promote the excretion of a few specific radionuclides has provided much information about body pools and spaces, further developments will increase the scope of nuclear medicine.

Considerable progress has been made in relatively few years in developing compounds to protect against the radioisotopes present in fallout or formed during nuclear accidents (1,2). Isotope dilution with stable iodine seems to be a very satisfactory protection against iodine-131. Effective chelators have been developed for the removal of plutonium-239 and zinc-65. Norwood (1) has shown

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Fig. 1. Effect of delay in administration of ca. 0.5 millimol of manganese disodium EDTA on the excretion of manganese-54 from rats, expressed as per cent of control rats. When the chelate is administered immediately after the radioisotope, 95 per cent of the radioactivity is eliminated in six days and 96 per cent in nine days. A 72-hour delay in injection of the manganese chelate reduces the elimination of zinc-65 to 80 per cent in six days.
that intravenous rather than oral administration of calcium trisodium DTPA is the more effective method of removing plutonium-239 from man. Spencer et al (3) have demonstrated that zinc-65 is mobilized to a measurable degree clinically by intravenous administration of either calcium disodium EDTA or calcium trisodium DTPA.

We became interested some years ago in chelates of the stable form of elements as a means of promoting the removal of the corresponding radioisotope. We have now studied a number of these stable chelates in rats, the animal usually used for the experimental evaluation of agents to promote the excretion of radioisotopes and have obtained excellent results. Studies illustrating the effectiveness of this type of chelate have been made with manganese disodium EDTA\(^1\) to increase the rate of excretion of manganese-54 and with zinc disodium EDTA\(^1\) to promote the excretion of zinc-65. Both chelates are available in quantity as agricultural chemicals (4).

MATERIALS AND METHODS

The experimental studies were all conducted with young male rats. The unanesthetized rats were injected in a tail vein with 1 ml of normal saline solution containing approximately 5 \(\mu\)C of carrier-free manganese-54 or zinc-65 chloride.\(^2\) A saline solution of manganese disodium EDTA or zinc disodium EDTA was administered intravenously after the injection of the radioisotope. Usually 160 mg (ca. 0.5 millimols) of the appropriate chelate was given immediately after the radioisotope, but in some instances the injection was delayed for 4, 24, or 72 hours, so that the influence of late injection on the promotion of excretion of the radioisotopes could be studied. In other experiments, the dosage of the chelates was halved or quartered to examine dosage relationships on the rate of excretion.

Promotion of excretion of each radioisotope was measured by periodic determinations of the body burden of experimental compared to control rats. Groups of four animals were used for each variation in procedure, and body burden measurements were made at intervals up to nine days in an ARMAC scintillation detector designed for small animals. To reduce instrument contamination, the rats were placed in quart milk cartons which, in turn, were enclosed in plastic bags before insertion into the chamber of the scintillation detector. A false back was placed in the chamber so that the milk cartons were positioned in the same portion of the instrument for each measurement. Motion was minimized in critical experiments by anesthetizing each rat with 50 percent carbon dioxide: oxygen prior to placing in the milk carton and by maintaining the anesthesia through the addition of ca. 1 g of dry ice to each milk carton.

RESULTS

The results on the promotion of excretion of radioisotopes for the experimental rats are expressed as percent of body burden of the control rats. Signifi-
Fig. 2. Effect of delay in administering ca. 0.5 millimol of zinc disodium EDTA on the elimination of zinc-65 from rats, expressed as per cent of control rats. If the zinc chelate is administered immediately after the radioisotope, then 84 per cent of the radioactivity is eliminated in three days. A delay of four hours in injection of the metal chelate reduces the per cent elimination to 42, of 24 hours to 25, and of 72 hours to 14.
cant data of the studies are shown graphically in Figs. 1-3. Administration of the manganese or zinc chelate was effective in varying degrees in promoting the excretion of the corresponding radioisotopes, depending on the conditions.

As brought out in Fig. 1, administration of 0.5 millimols of manganese disodium EDTA causes excretion of 96 percent of manganese-54 over the nine days recorded if it is given immediately after injection of the radioisotope. Over 92 percent of the manganese-54 was eliminated during the first two days and 95 per cent, in six days. A delay of three days in the administration of the manganese disodium EDTA reduced the amount of radioisotope eliminated to 80 percent in six days.

The excretion studies with zinc disodium EDTA are contrasted in Fig. 2. If the chelating agent is administered immediately after injection of the radioisotope, 84 percent of the zinc-65 is eliminated in the first three days. After this time the rate of elimination is the same as that for controls. Delays in injecting the chelating agent have a profound effect: delay of 4 hours reduces the per cent elimination to 42, of 24 hours to 25, and of 72 hours to 14.

Use of smaller amounts of the chelating agent reduces the effectiveness of excretion. As shown in Fig. 3, administration of zinc disodium chelate causes elimination of the following amounts of the radioisotope in three days: 40 mg - 60 percent; 80 mg - 75 percent; and 160 mg - 84 percent.

**Discussion**

The results of the studies show how very effective manganese disodium EDTA and zinc disodium EDTA are in promoting the excretion of manganese-54 and zinc-65, respectively. These metal chelates presumably exchange the stable for the radioisotopic form of the corresponding element, and the new combination is eliminated. The principle is broad and many additional radioisotopes and metal chelates should be investigated.

If there is a time delay in the administration of the metal chelate, promotion of the excretion of each radioisotope is greatly reduced. This suggests that the zone of action is outside bone in the exchangeable pool since both manganese-54 and zinc-65 are bone seekers. We (5-7), among others (1,2), have studied the retention and translocation of radioisotopes from the alimentary tract and circulation to the bone, and believe we (7) have evidence that the mucopolysaccharides are biological compounds which are important to the metabolism of radioisotopes.

It is difficult at present to define with any precision the compartments, pools, and spaces that are involved in the metabolism of radioisotopes. The schematic compartment model for mineral metabolism given in Fig. 4 summarizes current concepts, but shows also the lack of exactness in defining the metabolic pathways. More definite understanding of the biochemistry governing the retention, translocation, and excretion of radioisotopes will bring new opportunities to nuclear medicine. Much of the same information will be useful in developing procedures for promoting the excretion of radioisotopes that may accumulate in human beings as a result of nuclear accidents.
Fig. 3. Effect of the reduction of zinc disodium EDTA dose on the elimination of zinc-65 from rats, expressed as per cent of control rats. When varying amounts of zinc disodium EDTA are administered immediately after injection of zinc-65, three days later the following levels of radioactivity are present: 40 mg - 60 per cent; 80 mg - 75 per cent; and 160 mg - 84 per cent.
Manganese disodium EDTA and zinc disodium EDTA, two metal chelates widely used as agricultural products, have been shown to promote the excretion from rats of the corresponding radioisotopes manganese-54 and zinc-65. The effect is greatest the sooner the metal chelates are administered after injection of the radioisotopes. The principle of administering metal chelates to promote the excretion of radioisotopes corresponding to the metal of the chelate is broad. Further work will give greater understanding of the biological factors governing the metabolism of radioisotopes. This work will both increase the scope of nuclear medicine and provide treatments for nuclear accidents.

REFERENCES