DISTRIBUTION OF ^{99m}TC-Sn DIPHOSPHONATE AND FREE ^{99m}Tc-PERTECHNETATE IN SELECTED SOFT AND HARD TISSUES

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Because increased uptake of ^{99m}Tc-diphosphonate (ethane-hydroxy-1, 1-diphosphonate) occasionally occurs in the anterior neck region, the possible increased affinity of the diphosphonate bone-scanning agent for cartilage was investigated. In vivo scintigraphic studies and organ analyses from rats and rabbits injected with this bone scintigraphic agent were performed.

Trachea-to-muscle uptake ratios were a high 45:1 in adult Sprague-Dawley rats and approached the femur-to-muscle ratio of 93:1. Technetium-99m-diphosphonate uptake was also increased, but to a lesser extent, in xiphoid cartilage, tendon, and ear cartilage; this was proportional to the calcium content of the organ. The thyroid showed a high affinity for free pertechnetate but not ^{99m}Tc-diphosphonate, providing further evidence that the increased neck uptake of this ^{99m}Tc-diphosphonate is due to tracheal, not thyroid activity. In addition, premedication of three patients with 200 mg of potassium-perchlorate did not block this neck uptake.

Interpretation of scintigraphs performed with ^{99m}Tc-diphosphonate that show lesions in the cervical spine should take into account the potential for false-positive readings caused by this increased tracheal uptake.

In our initial studies with a new diphosphonate bone scintigraphic agent (Osteoscan, Miami Valley Laboratories, Procter & Gamble) labeled with ^{99m}Tc (*1,2*), an increased concentration of radioactivity in the anterior neck was frequently observed in the scintiscans. An interpretation of abnormal concentration of the bone-scanning agent in the cervical spine region was untenable in light of bone scintiscans performed with a dual-probe rectilinear scanner that showed greater concentrations of radioactivity in the anterior neck view than in the posterior view (Fig. 1). Since increased soft-tissue uptake, e.g., salivary glands, stomach, and thyroid, would occur when tagging efficiency of diphosphonate by pertechnetate was poor, the observed uptake in the cervical spine region could result from free, unreduced pertechnetate. However, a high tagging efficiency of diphosphonate with ^{99m}Tc was obtained (greater than 98% by thin-layer chromatography). In these studies, therefore, the uptake seen in the neck region should not be due to injected free $^{99m}TcO_4^-$; but the possibility of in vivo dissociation from Sn-diphosphonate could not be completely excluded.

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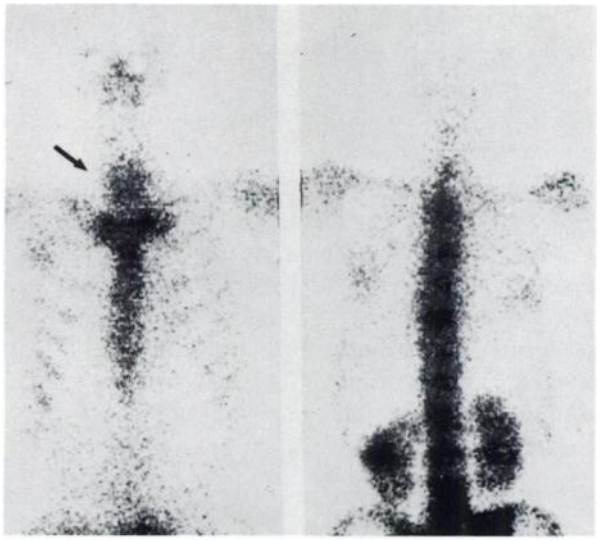

FIG. 1. Anterior (left) and posterior (right) scintiscans from dual-probe rectilinear scanner show greater concentration of radioactivity in anterior neck view indicating increased uptake not in cervical spine.

Similar observations of an increased uptake in the anterior neck have been made with ^{18}F, suggesting a possible association with calcified tissue.

Additional support for nonthyroid uptake of bone-seeking agents came from a study in one patient who had received ^{131}I 1 week prior to the bone scan so that the position of the thyroid gland could be accurately located (Fig. 2A). By employing the appropriate window of lower energy, the diphosphonate distribution in the same patient is shown (Fig. 2B), with the thyroid position located by ^{131}I (area enclosed by black line). The increased area of activity appears to be in the tracheal cartilage region, not in the thyroid gland.

In this study we undertook an evaluation of the extent of connective tissue, soft tissue, and osseous uptake of technetium administered either in free pertechnetate form ($^{99m}TcO_4^-$) or as technetium-tin-diphosphonate. Since this bone-scanning radiopharmaceutical chemisorbs to hydroxyapatite (*3*), we sought to relate ^{99m}Tc-diphosphonate uptake to the calcium content of the tissues and the age of the animal.

Increased retention of ^{99m}Tc-diphosphonate noted in cartilage relative to soft tissue could be explained by either of two mechanisms. First, true chemisorption on the hydroxyapatite could have occurred as a result of calcification of the tissue (an age-related effect). Alternatively, since the cartilage is a less vascular tissue than muscle (*4*), cartilage could have retained the diphosphonate because of a delay in removal of the radiopharmaceutical by the draining blood supply. Therefore, a comparison was made between the distribution of $^{99m}TcO_4^-$ and ^{99m}Tc-diphosphonate to differentiate between tissue-binding specificity and disappearance of radiopharmaceutical solely as a function of vascular supply.

MATERIALS AND METHODS

The tissue and cartilaginous retention was determined in four young (160 gm) and four adult (250 gm) Sprague-Dawley rats and twenty young (1.6–2.5 kg) and young adult (2.9–3.7 kg) New Zealand white rabbits. The rats were injected intravenously with 500 μCi of ^{99m}Tc-diphosphonate or free ^{99m}Tc-pertechnetate. The rats were sacrificed at 3 hr postinjection, the time of our human bone scintiscans. Tracheal and xiphoid cartilage, tendon, muscle, thyroid, and bone (femur and iliac crest) were removed and the percent of dose per gram of organ determined. The concentration of calcium and phosphorus was also quantitated for each tissue (*5*).

In order to determine the relationship of uptake of ^{99m}Tc-diphosphonate and $^{99m}TcO_4^-$ to time postinjection, twenty adult rabbits were injected intravenously with 3 mCi of either radiopharmaceutical. Groups of two or three rabbits were sacrificed at 1, 3, 7, and 24 hr postinjection and muscle, cartilage, bone, and thyroid tissues radioassayed. The radioactivity in percent of dose per gram sample was then plotted as a function of time, after correction for radioactive decay.

Three patients were given 200 mg potassium perchlorate 2 hr prior to injection of the bone-imaging agent on the assumption that $KClO_4$ would block thyroid trapping of TcO_4^- but not cartilage uptake (*6*).

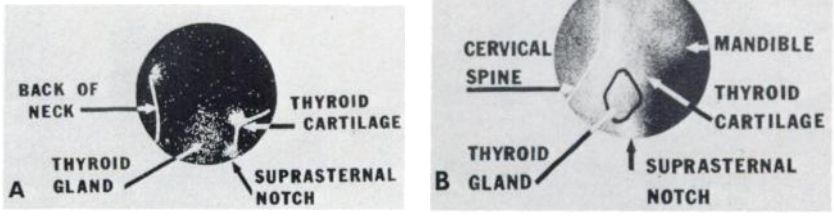

FIG. 2. (A) Thyroid region of neck located by ^{131}I scintigraph obtained 1 week previously. (B) Black outline of thyroid superimposed on neck image using ^{99m}Tc window. Cervical spine region and other areas of increased uptake are identified as mandible, thyroid cartilage, and suprasternal notch.

RESULTS

Because of the specificity of ^{99m}Tc-diphosphonate for hydroxyapatite, the highest uptake and retention appeared in femur ends with a mean femur shaft-to-muscle ratio of 93:1 in adult rats and 215:1 in young rats. The rat tracheal cartilage-to-muscle ^{99m}Tc-diphosphonate ratio was 45:1 in adults and 60:1 in young animals. The retention of ^{99m}Tc-diphosphonate in thyroid tissue was only three to four times that of muscle. As expected, the thyroid-to-muscle ratio for free pertechnetate was very high: 215:1 in the adult and 64:1 in the young rat. Trachea-to-thyroid ratios for diphosphonate at 3 hr were 13:1 in the adult and 20:1 in the immature animal. Figure 3 shows the selective retention ratios of ^{99m}Tc-diphosphonate : pertechnetate at 3 hr. Subsequent timed clearance studies (1, 3, 7, 24 hr) in rabbits with ^{99m}Tc-diphosphonate or pertechnetate showed that free pertechnetate was cleared more rapidly from both the femur and trachea than ^{99m}Tc-diphosphonate; the femur retained the diphosphonate completely over the 24-hr postinjection period.

The uptake of ^{99m}Tc-diphosphonate in growing bone (of young rats and rabbits) was greater than in adult bone by a factor of 1.5–2.7. Elemental calcium and phosphorus analyses showed that the increased uptake of ^{99m}Tc-diphosphonate in growing and mature bone was not a direct function of the concentration of calcium or phosphorus per gram of bone since these were identical in the two age groups. In contrast the older rats did have more calcium in all cartilage samples than the younger rats. Tracheal cartilage contained 47.5 mg calcium per gram of tissue in the adult compared with 28.3 mg calcium per tissue in the trachea of the younger animals. Soft tissues with higher calcium content had increased ^{99m}Tc-diphosphonate retention (Fig. 4). Also, there appeared to be a correlation between higher calcium-to-phosphorus ratios (approaching that of hydroxyapatite) and increased retention.

Premedication of three patients with 200 mg of potassium perchlorate did not block the neck uptake as this chemical would if the thyroid were concentrating ^{99m}Tc-diphosphonate or pertechnetate.

DISCUSSION

Scintigraphic and animal organ analysis data indicate that cartilage, especially from the trachea, had increased retention of ^{99m}Tc-diphosphonate compared with muscle and thyroid. Furthermore, this increased ^{99m}Tc-diphosphonate retention in trachea cannot be attributed to delayed clearance from cartilage since free pertechnetate cleared at an equal rate from all tissues except thyroid, suggesting equivalence of vasculature. There was also a low retention of ^{99m}Tc-diphosphonate in the thyroid when compared with $^{99m}TcO_4^-$ (1:500 at 3 hr) making it most unlikely that the area of increased activity we have seen in the anterior neck in bone scintigraphy is due to thyroid uptake of free pertechnetate from the bone-scanning agent. The animal data further confirm the marked affinity of cartilage for diphosphonate, especially in the trachea.

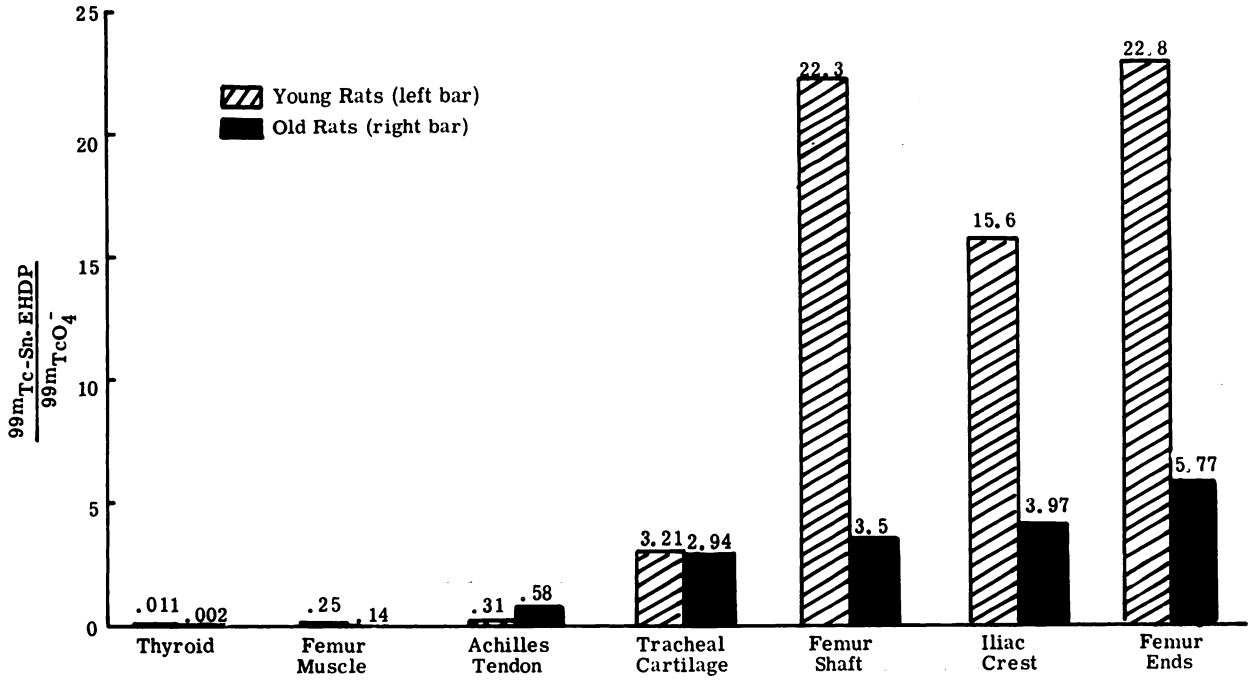

FIG. 3. Histogram comparing tissue retention ratio of ^{99m}Tc-diphosphonate to $^{99m}TcO_4^-$ in young and old rats 3 hr postinjection.

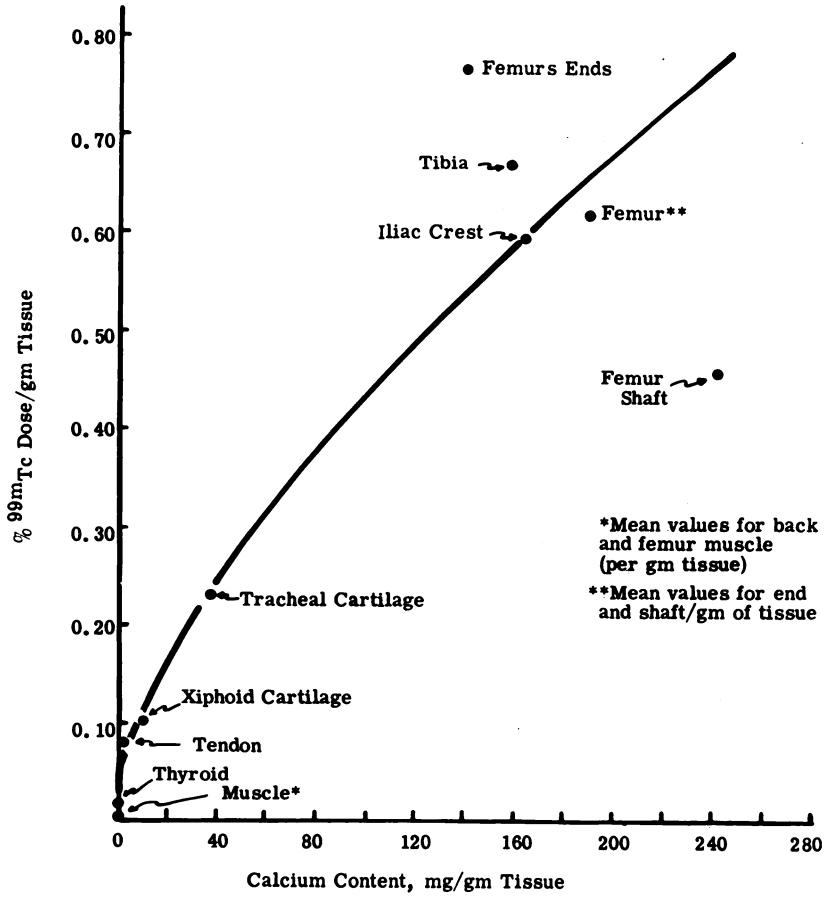

FIG. 4. Tissue retention of bone-scanning agent ^{99m}Tc-diphosphonate at 3 hr postadministration in adult rat as function of calcium content of tissues.

The relationship of tissue calcium content to diphosphonate uptake is apparent from Fig. 4. It is not uncommon to observe some tracheal calcification in older age groups of rodents and humans. Although increased localization of ^{99m}Tc-diphosphonate in the neck region is not constant from patient to patient, it is not generally observed in patients under age 40. Since thyroid preloaded with perchlorate should have little uptake of ^{99m}Tc-pertechnetate (*6*), the high uptake in the neck even in the presence of perchlorate strongly reinforces our conclusion that thyroid cartilage calcification leads to uptake of the bone-scanning agent in these patients.

REFERENCES

1. SILBERSTEIN EB, SAENGER EL, TOFE AJ, et al: Imaging of bone metastases with ^{99m}Tc-Sn-EHDP (Diphosphonate), ^{18}F, and skeletal radiography. *Radiology* 107: 551–555, 1973

2. SILBERSTEIN EB, FRANCIS MD, TOFE AJ, et al: Studies on the distribution of a technetium-99m diphosphonate in cartilaginous and osseous tissues and the effect of age on this process. *J Nucl Med* 14: 637–638, 1973

3. TOFE AJ, FRANCIS MD: Optimization of the ratio of stannous tin: ethane-1-hydroxy-1, 1-diphosphonate for bone scanning with ^{99m}Tc-pertechnetate. *J Nucl Med* 15: 69–74, 1974

4. BREAZILA JE, ed: *Textbook of Veterinary Physiology*, Philadelphia, Lea and Febiger, 1971, pp 560–561

5. JOHN MK: Automated digestion system for safe use of perchloric acid. *Anal Chem* 44: 429–430, 1972

6. WERNER SC, INGBAR SM: *The Thyroid*, 3rd ed, New York, Harper & Row, 1971, p 42