Possible Parathyroid Imaging Using Ga-67 and Other Aluminum Analogs

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Aluminum has been found to localize in parathyroid adenomas, but it has no isotopes suitable for imaging. Chemical analogs of aluminum were therefore evaluated as potential parathyroid seekers. Uptakes of gallium-67, scandium-46 and lutetium-177 were measured in rat parathyroid, thyroid, cervical muscle, and whole blood, over the time period 30 min to 8 days. Both differential and absolute uptakes of Ga-67 and Sc-46 in the parathyroids are greater than that reported for Se-75 selenomethionine. Uptake of Ga-67 is about 2% of the injected dose per gram of parathyroid tissue at 3–4 days, with a parathyroid-to-thyroid uptake ratio of about 6. Studies indicate possible imaging of adenomas at least as small as those now detected only with invasive methods.

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The precise preoperative determination of parathyroid adenoma location is desirable. While some success has been achieved with venous catheterization coupled to parathyroid hormone (PTH) radioimmunoassay and with arteriography (*1–4*), these techniques are invasive and painful to the patient. The use of radiolabeled compounds for imaging (*5–9*) has not proved of value in cases where the parathyroid adenoma is small (less than 1 g), and is not useful in most cases of large, aberrantly located adenomas. From a series of elemental analyses of human adenomas and tracer studies in rats, parathyroid adenomas and normal glands were found to take up aluminum to a greater extent than surrounding tissues in patients taking aluminum-containing drugs and in test animals given a dietary loading of aluminum (*10*). These observations indicated that aluminum might be an element that could be used for parathyroid imaging if a suitable emitting isotope could be found. Unfortunately there are no such isotopes of aluminum. The elements gallium, scandium, and lutetium would be expected to imitate the chemical behavior of aluminum based on periodic and charge-density properties, and each of these elements has at least one isotope suitable for imaging studies. Tests were done to evaluate the potential of these elemental analogs of aluminum for parathyroid imaging.

METHODS AND RESULTS

Male Sprague–Dawley rats, 100–200 g, were maintained (a) on standard laboratory rat chow or (b) on a low-calcium diet to enlarge the size and increase the activity of the parathyroid glands (*11*). In some cases, thyroid suppression, effected by 7-μg sodium levothyroxine daily in the diet, was used to determine its effect on radionuclide uptake in various tissues. Each animal was injected in a lateral tail vein with 150 μCi of gallium-67, scandium-46, or lutetium-177. Animals were killed at times ranging from 30 min to 8 days after tracer administration, and the parathyroids, thyroid, cervical muscles, and whole blood were sampled for counting with a shielded 35-cm^3 Ge(Li) detector coupled to a 4096-channel pulse-height analyzer. The tissue concentrations in each of four rats were averaged to determine each data point. In the case of the animals on the low-calcium diet, differences were noted between 14 and 29 days on the diet. Data from each set of two animals were therefore averaged and results expressed separately

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TABLE 1. TRACER CONCENTRATIONS IN RAT TISSUES AT TIMES INDICATED*

Tracer	Time	Parathyroid	Thyroid	Muscle†	Blood†
Ga-67					
control	1–2 days (n = 7)	3.4(1.7–5.5)	2.9(1.4–4.2)	0.6(0.5–0.9)	0.6(0.3–1.0)
	3–6 days(n = 8)	2.8(2.6–5.0)	1.6(1.3–2.5)	0.5(0.4–0.6)	0.14(0.08–0.25)
lo-Ca diet (a)	1–2 days(n = 4)	1.4(0.9–1.8)	1.1(0.7–1.3)	0.5(0.3–0.6)	0.6(0.4–0.9)
	3–6 days (n = 6)	2.1(1.4–2.7)	1.3(0.7–1.9)	0.5(0.4–0.6)	0.3(0.2–0.4)
lo-Ca diet (b)	1–2 days(n = 4)	2.4(1.9–2.9)	1.1(1.0–1.3)	0.5(0.3–0.7)	0.7(0.4–1.0)
	3–6 days(n = 6)	5.3(3.0–7.1)	0.9(0.6–1.2)	0.2(0.2–0.4)	0.14(0.04–0.23)
thyroid-suppressed	1–2 days(n = 6)	2.4(1.0–3.8)	1.4(0.4–2.7)	0.6(0.5–0.8)	0.6(0.2–1.2)
	3–6 days(n = 8)	3.7(2.3–5.4)	1.4(0.8–2.4)	0.5(0.4–0.8)	0.15(0.08–0.23)
Sc-46					
control	1–2 days(n = 7)	4.4(3.8–6.2)	4.2(3.3–5.3)	1.2(1.0–1.3)	1.2(0.3–2.7)
	3–6 days(n = 8)	3.9(2.4–6.0)	2.8(2.0–4.2)	0.9(0.6–1.3)	0.19(0.06–0.50)
lo-Ca diet (a)	1–2 days(n = 4)	3.4(2.4–4.5)	2.6(2.2–2.8)	1.2(0.8–1.5)	1.4(0.5–2.5)
	3–6 days(n = 6)	3.8(3.1–4.4)	2.2(2.0–2.3)	0.9(0.8–1.0)	0.16(0.09–0.23)
lo-Ca diet (b)	1–2 days(n = 4)	6.3(4.7–7.6)	2.8(2.4–3.4)	1.1(0.8–1.3)	1.5(0.7–2.3)
	3–6 days (n = 6)	7.8(4.8–11.0)	2.7(2.2–3.6)	0.8(0.6–1.1)	0.22(0.12–0.39)
thyroid-suppressed	1–2 days(n = 7)	3.7(1.7–5.0)	2.3(1.2–2.9)	1.0(0.5–1.2)	1.1(0.4–2.3)
	3–6 days(n = 9)	4.3(3.1–5.8)	3.0(2.1–5.6)	1.1(0.9–1.5)	0.17(0.06–0.52)

* Conditions: control, low-calcium diet (a: 14 days, b: 29 days), and thyroid-suppressed. Uptake is percentage dose per gram of dry tissue, normalized to 180-g body wt. Data averaged over period indicated: mean and (range).

† Large range due to time variation of uptake over the averaging period

for each of the two durations. Table 1 summarizes the results obtained with Ga-67 and Sc-46. The variations of tissue radionuclide concentration with time are shown in Figs. 1A and B. Ratios of Lu-177 uptake in these studies were similar to those found with Ga-67, but absolute uptake was lower by factors of 5 to 10. Because of this low uptake, Lu-177 is not considered useful for imaging, and data for this nuclide are not shown.

For all three radionuclides studied, parathyroid uptake was greater than that in any of the other tissues. For Ga-67 the ratio of uptake in parathyroid to that in thyroid was about 6 at 3–4 days in the case most resembling a parathyroid adenoma: animals fed the low-calcium diet for 29 days to induce secondary hyperparathyroidism. Other researchers, using a comparable rat model, have reported parathyroid-to-thyroid uptake ratios for [^{75}Se] selenomethionine of 2.5 at 15 min and 2.1 at 60 min after tracer administration (*12*). The comparable ratio for I-125 toluidine blue at 15 min was 0.9, and by 60 min toluidine blue was unmeasurable. In a study of 14 patients, the average parathyroid-to-thyroid uptake for selenomethionine was 2.7 (*8*). From these data we can conclude that this rat model is a useful one for the study of radionuclide uptake by human parathyroid tissue.

In the rat model used, Ga-67 uptake at 3–4 days in the parathyroids was 20 times that in muscle and 40 times the blood level. For Sc-46, comparable ratios were 10 and 30, and for [^{75}Se] selenomethionine, 4.3 and 2.4 (*8*). Absolute uptake averaged 7.5–10.0% per gram of dry tissue for Ga-67 and Sc-46. Maximum values found with selenomethionine were about 1.0% per gram, and about 3.0% per gram with toluidine blue (*9*).

To estimate the size of a human parathyroid adenoma that might be imaged, a simple neck phantom was constructed and models of various-sized adenomas were tested with several Ga-67 uptake ratios. A bottle 9 cm in diameter was used to simulate a human neck. It was filled with a solution of Ga-67 at a concentration representing, by volume, 50% soft tissue, 25% blood, and 25% bone and cartilage. The thyroid gland was simulated with two 17.5-ml "lobes" filled with a Ga-67 solution. The parathyroids were simulated with sealed filter-paper discs of varying cross-sectional area placed behind the "thyroid." Human Ga-67 distribution values for blood, muscle, and bone (*13*) and scaled factors from the rat studies for thyroid and parathyroid, were used to define emitter concentrations. Human thyroid uptake estimated by this method is the same as that measured—0.9% per kg of organ weight (*13*). The phantom was imaged using an assumed dose of 3 mCi of Ga-67, 10-min imaging time on a dual-energy camera with a 6-mm pinhole collimator, and with uptake ratios for normal and thyroid-suppressed conditions at 4 days after injection. With this model, a 300-mg adenoma is at the limit of visual-

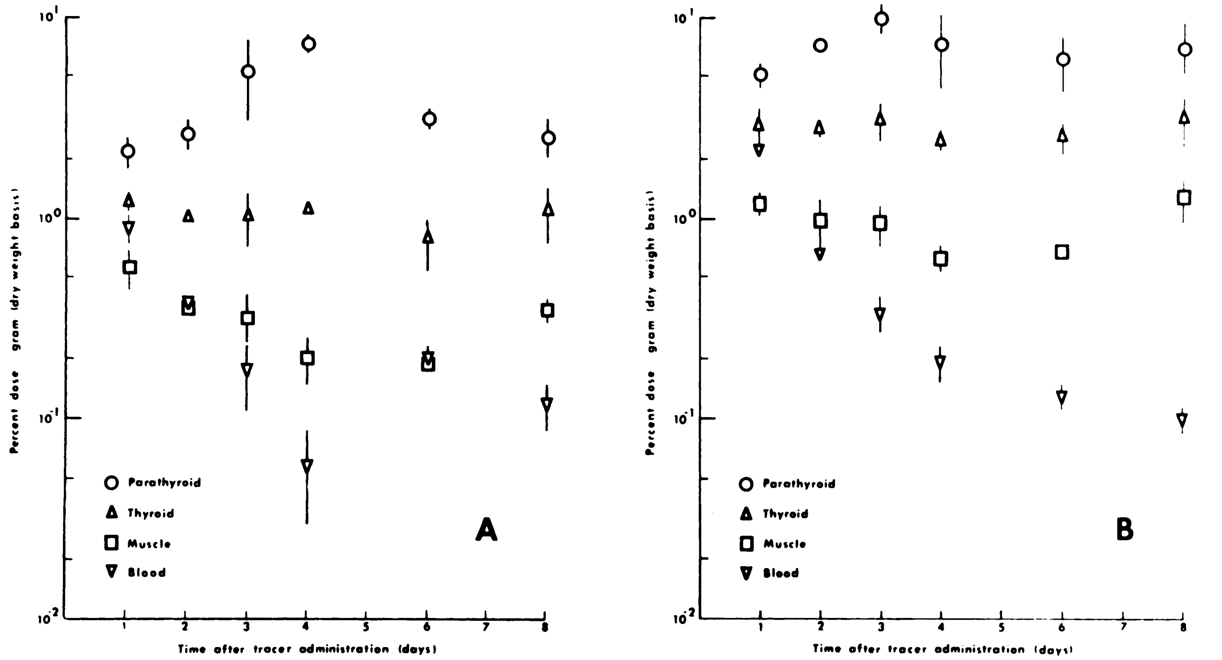

FIG. 1. Tracer concentration in tissues of rats with diet-induced secondary hyperparathyroidism. Each point represents data averaged from two animals; errors include variation between animals and counting errors. Dry weight to wet weight ratio is 0.2. (A) Ga-67; (B) Sc-46.

ization (Fig. 2A). The model of a 1-g adenoma, the nominal limit with [^{75}Se] selenomethionine, is easily visualized under the same conditions (Fig. 2B).

In a patient with borderline hyperparathyroidism from a 150-mg adenoma (serum calcium 10.0 mg%, TRP 83–90%, and measurable but low serum PTH), tissue uptake of Ga-67 at 13 days after injection showed ratios of 13.2 for parathyroid-to-thyroid and 32.4 for parathyroid-to-muscle. Aluminum concentration ratios in these same tissues were 9.3 and 9.8, respectively, indicating a reasonable modeling of aluminum behavior by the Ga-67. In one obvious case of hyperparathyroidism (palpable cervical mass, serum calcium 13.7 mg%, bone pain, and visible radiographic demineralization), Ga-67

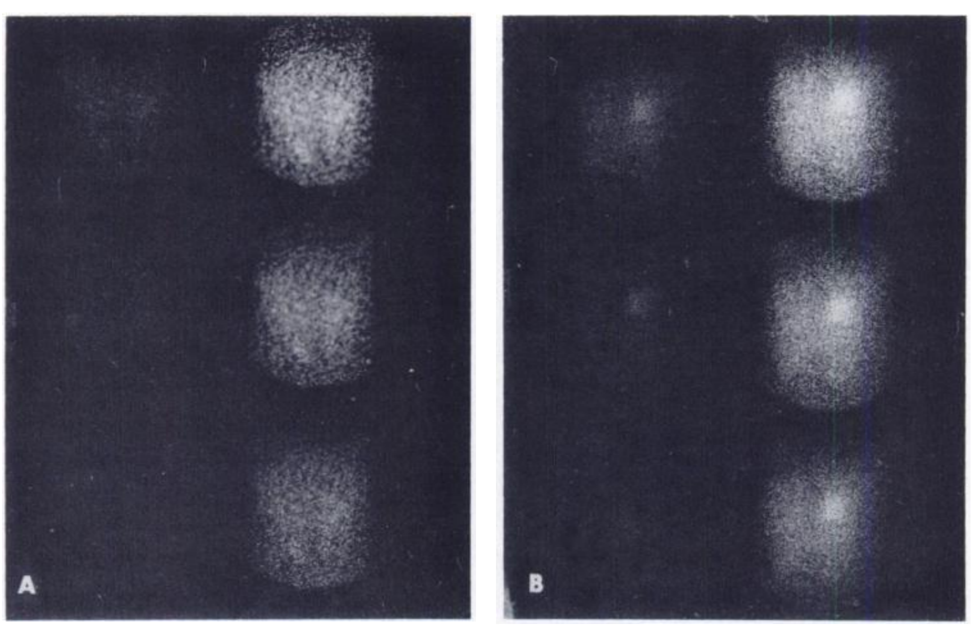

FIG. 2. Image of human neck phantom used to imitate parathyroid uptake of Ga-67. (A) Model of 300-mg adenoma, right inferior position. (B) Model of 1-g adenoma, left superior position.

given during a clinical evaluation was taken up well enough to provide a scintiscan of a 15.6-g adenoma (*14*).

DISCUSSION

Gallium-67 is currently used for tumor detection, and Sc-47 has also been shown to behave in essentially the same manner as Ga-67 (*15*). The preferential uptake of these elements by parathyroid adenomas may be due in part to "tumor-like" characteristics of these glands. In vitro tests with bovine and human PTH have shown that Ga-67 and Sc-46 are not bound to the hormone (*16*), indicating that factors other than hormone synthesis are involved in the uptake of aluminum and its chemical analogs by parathyroid tissue.

In our studies, the parathyroid uptakes of Ga-67 and Sc-46 were found to be higher than the reported uptake of Se-75 selenomethionine, and the background was also lower. With Ga-67, the standard clinical dose is 12 times that for selenomethionine, and with uptake ratios found to be best at 3-4 days after tracer administration, there may be no need for early serial scans to visualize a parathyroid adenoma against a changing background. Mild thyroid suppression did not significantly reduce thyroid uptake in these experiments, but trends in the data suggest that it may be useful in specific cases. Image enhancement using pertechnetate for background subtraction and multiplane tomographic scanning may increase sensitivity, possibly to the point of visualizing small adenomas as well as the larger ones. Scandium-47 with a 160-keV gamma photon (73%) and a 3.4-day half-life may also be a useful agent for imaging, although its 440-keV β^- may limit the allowable tracer dose.

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