Thyroid Stunning Revisited

TO THE EDITOR: I read with interest the careful experimental study by Postgård et al. (*1*) and the accompanying editorial (*2*) in the *Journal*. This in vitro study suggested that thyroid stunning is a real phenomenon and is due to a decrease in iodide transport caused by the effects of radiation on thyroid cell iodine transport and not to cell death.

Although the investigators attempted to simulate the situation occurring in a thyroid cancer patient with residual functioning thyroid tissue who has been withdrawn from thyroid hormone replacement, there remain 2 issues:

First, in a patient who is to receive an imaging dose of ^{131}I for cancer surveillance, functioning thyroid cells are exposed to a progressively rising thyroid-stimulating hormone level over a period of (typically) 10–14 d before administration of radiation. The investigators used a fixed pretreatment of 1 mU/mL in the experiment. Additionally, the protocol involved administration of methimazole, which would not occur in the patient setting.

Second, based on measurements of total DNA in the preparation, the authors concluded that stunning was due to decreased iodide transport and not to cell death from radiation. However, they used a nonproliferating cell culture model. Cells are most sensitive to radiation when they are dividing. This raises the possibility that the experiment may have been biased against finding cell death from radiation as a potential cause for stunning.

REFERENCES

1. Postgård P, Himmelman J, Lindencrona U, et al. Stunning of iodide transport by ^{131}I irradiation in cultured thyroid epithelial cells. *J Nucl Med.* 2002;43:828–834.
2. Brenner W. Is thyroid stunning a real phenomenon or just fiction? *J Nucl Med.* 2002;43:835–836.

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^{131}I Versus ^{123}I for Whole-Body Scanning

TO THE EDITOR: Sarkar et al. recently reported on the relative merits of ^{123}I and ^{131}I for diagnostic whole-body scanning for thyroid tumors (*1*). Based on a limited number of patients, they claimed that in comparison with ^{123}I, ^{131}I showed superior sensitivity for identifying differentiated thyroid cancer metastases (*1*). However, we do not agree with the interpretation of several of the alleged differences between ^{131}I and ^{123}I scans in the figures shown. In addition, the authors did not include the post-therapy images, which are the optimal standard against which to judge the accuracy of diagnostic imaging.

The 96-h ^{131}I image in Figure 1 shows prominent left cervical and pulmonary metastases that the authors state are not seen in the companion ^{123}I image. However, the ^{123}I image also shows a focal increase in the same left cervical area in the neck, and a focal increase in the left posterior mid-lung field is also evident in both the 24-h ^{123}I image and the 24-h ^{131}I whole-body image shown in this figure. We agree that the target-to-background ratio for these lesions is less in the ^{123}I image than in the 96-h ^{131}I image.

In describing Figure 2A, the authors mention a right cervical focus and lung uptake that were seen in the ^{131}I images but not in the ^{123}I images. It is unclear to us how much of the cervical uptake in the ^{131}I image may be incidental esophageal activity, which is also seen in the companion ^{123}I image. Comparison of this area with the post-treatment ^{131}I images would help clarify this question. In addition, we believe that the ^{123}I images also show at least some abnormal focal uptake in the right lower lung field, even though the target-to-background activity is once again much less than that seen with ^{131}I.

In Figure 2B, we agree that the metastatic foci in the left hip, the right knee, and left axilla are identified both by ^{123}I and by ^{131}I. From the authors' arrow in the figure and description in the legend, it is not clear what is being identified in the ^{131}I image as the right iliac bone metastasis, which the authors claim is identified by ^{131}I but not by ^{123}I. If the arrow in the ^{131}I image is pointing to the focus overlying the region of the cecum in the right lower quadrant, then we would argue that a focus in the same location is evident in the companion ^{123}I scan. Similarly, we take issue with the claimed disparity between ^{123}I and ^{131}I for detection of abnormal lung uptake. Although this abnormality again shows a higher target-to-background ratio in the ^{131}I image, the soft-tissue lung activity in the ^{123}I image is clearly higher than that of the abdomen. Of all 6 ^{131}I-positive sites shown in this patient, only the left skull focus appears to have been more convincingly missed by the ^{123}I image, and by itself, this factor would not have had any significant impact on the treatment algorithm.

In light of the above considerations, we believe that the authors have exaggerated the differences in sensitivity between ^{123}I and ^{131}I for detection of distant metastases, even though ^{131}I did show some of them better. In contrast, other authors have reported competitive or superior sensitivity for ^{123}I, compared with ^{131}I, for diagnostic thyroid tumor scanning, including identification of distant metastases (*2*,*3*). In a study by Siddiqi et al. (*3*), diagnostic scanning with ^{123}I correctly identified thyroid metastases in 9 of 12 patients (confirmed in post-therapy scans) in whom ^{131}I diagnostic scanning had negative findings. In a perhaps related observation, we note that the quality of the whole-body ^{123}I images shown by Sarkar et al. (*1*) does not appear as good as that found by others (*2*,*4*), possibly contributing to suboptimal sensitivity in their experience.

The ability to image ^{131}I later after dosing than is possible with ^{123}I, afforded by the longer half-life of the former, no doubt contributes to the improved target-to-background uptake ratio and thereby the sensitivity for detecting potential lower-avidity sites of thyroid metastases. Gerard and Cavalieri recently reported that using a larger 185-MBq ^{123}I dose in combination with a later 48-h imaging time can improve the target-to-background ratio and, thereby, the sensitivity for detecting less-iodine-avid sites of differentiated thyroid tissue (*4*). Use of this approach in the patients shown by Sarkar et al. (*1*) would likely have improved the conspicuity of the ^{123}I foci corresponding to the thyroid metastases in question.

A final important consideration is the potential adverse influence of stunning by diagnostic doses of ^{131}I. Given that the evidence of

such potential is now compelling (*4*,*5*), it is all the more important to optimize the sensitivity of ^{123}I diagnostic imaging to avoid the use of ^{131}I for this purpose, which may compromise subsequent therapeutic efficacy.

REFERENCES

1. Sarkar SD, Kalapparambath TP, Palestro CJ. Comparison of ^{123}I and ^{131}I for whole body imaging in thyroid cancer. *J Nucl Med.* 2002;43:632–634.
2. Shankar LK, Yamamoto AJ, Alavi A, Mandel SJ. Comparison of ^{123}I scintigraphy at 5 and 24 hours in patients with differentiated thyroid cancer. *J Nucl Med.* 2002;43:72–76.
3. Siddiqi A, Foley RR, Britton KE, et al. The role of ^{123}I-diagnostic imaging in the follow-up of patients with differentiated thyroid carcinoma as compared to ^{131}I-scanning: avoidance of negative therapeutic uptake due to stunning. *Clin Endocrinol.* 2001;55:515–521.
4. Gerard SK, Cavalieri RR. I-123 diagnostic thyroid tumor whole-body scanning with imaging at 6, 24, and 48 hours. *Clin Nucl Med.* 2002;27:1–8.
5. Park HM. The stunning effect in radioiodine therapy of thyroid cancer. In: Freeman L, ed. *Nuclear Medicine Annals.* Philadelphia, PA: Lippincott, Williams, & Wilkins; 2001:49–67.

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REPLY: We appreciate the comments by Drs. Gerard and Mandel and are pleased to have a second opportunity to clarify the common misperception that ^{123}I is better than ^{131}I at detecting thyroid cancer metastases.

First, we want to reiterate the purpose of our study (*1*). It was not our intent to assess the efficacy of diagnostic (pretherapy) ^{123}I imaging in comparison with post-therapy imaging, a subject addressed in other publications. Instead, we compared ^{123}I imaging directly with diagnostic ^{131}I imaging using comparable (74–185 MBq) amounts of radiotracer. To our knowledge, this has been the only study with a head-to-head comparison of ^{123}I and ^{131}I in patients with thyroid cancer, including those with distant metastases.

Drs. Gerard and Mandel cite several studies to bolster their case for ^{123}I imaging. The study by Shankar et al. (*2*) compared diagnostic (pretherapy) ^{123}I imaging with post-therapy ^{131}I imaging; that is, there was no comparison with diagnostic ^{131}I studies. Also, was the "medium energy" collimator used in that study optimal for ^{131}I? Gerard and Cavalieri assessed the sensitivity of ^{123}I in a similar fashion (*3*). That ^{123}I provides "acceptable levels of sensitivity" when compared with post-therapy imaging, as claimed in their article, does not necessarily imply it is as good as, let alone better than, ^{131}I. Another limitation of their study was that it focused on detection of cervical tissue including thyroid remnants, not extracervical metastases. The last study cited, by Siddiqui et al., had a similar theme (*4*). The main thrust of this study was the comparison of pretherapy ^{123}I imaging to post-therapy ^{131}I scans. The authors also appear to suggest that ^{123}I is superior to ^{131}I, but the data provided are far from convincing. The diagnostic ^{131}I and ^{123}I studies were not done (sequentially) at the same time. Although details are lacking, it appears that they were done up to 5 mo apart, rendering any comparison moot. Furthermore, neither the amounts of ^{131}I used for diagnostic imaging nor the imaging times or counts were included, and the only figure in the entire article has a very count-poor ^{131}I image. Thus, none of the 3 studies cited as showing the superiority of ^{123}I directly compared the 2 agents at the same sitting using comparable amounts of tracer.

Needless to say, we do not agree with Drs. Gerard and Mandel's interpretation of the images. However, we do applaud their painstaking attempts to find abnormalities on the ^{123}I images corresponding to obvious lesions on the ^{131}I studies because it proves our point that metastases are better visualized with ^{131}I. In our view, many of the lesions that were seen on the ^{123}I images would not have been appreciated without the benefit of the accompanying ^{131}I scans. We also concur with their statement that "target-to-background activity [for ^{123}I] is. . . much less than that seen with ^{131}I."

Our study did not address such other issues as stunning or the need for routine pretherapy whole-body imaging in the first place (*5*). But we do emphasize that development of an appropriate diagnostic algorithm must take into account the relative insensitivity of ^{123}I for thyroid cancer metastases in the 74- to 185-MBq range.

In conclusion, it is misleading to claim that ^{123}I is superior to ^{131}I for the detection of thyroid cancer metastases before therapy without actually comparing the 2 tracers. Having made a direct comparison, we have found just the opposite—that ^{131}I is the better imaging agent. Although editorial constraints limited the number of figures in our article, the images that we provided adequately proved this point. We realize that a direct comparison of diagnostic ^{123}I and ^{131}I images is difficult and that patients with distant metastases are few, but we hope that studies similar to ours will be done by others.

REFERENCES

1. Sarkar SD, Kalapparambath TP, Palestro CJ. Comparison of ^{123}I and ^{131}I for whole body imaging in thyroid cancer. *J Nucl Med.* 2002;43:632–634.
2. Shankar LK, Yamamoto AJ, Alavi A, Mandel SJ. Comparison of ^{123}I scintigraphy at 5 and 24 hours in patients with differentiated thyroid cancer. *J Nucl Med.* 2002;43:72–76.
3. Gerard SK, Cavalieri RR. I-123 diagnostic thyroid tumor whole-body scanning with imaging at 6, 24, and 48 hours. *Clin Nucl Med.* 2002;27:1–8.
4. Siddiqi A, Foley RR, Britton KE, et al. The role of ^{123}I-diagnostic imaging in the follow-up of patients with differentiated thyroid carcinoma as compared to ^{131}I-scanning: avoidance of negative therapeutic uptake due to stunning. *Clin Endocrinol.* 2001;55:515–521.
5. Sarkar SD, Palestro CJ, Love C. Utility of whole body radioiodine scintigraphy prior to the initial ^{131}I treatment for differentiated thyroid carcinoma [abstract]. *Endocrinol Jpn.* 2000;47(suppl):P-121.

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