

Thyroid Stunning After ^{131}I Diagnostic Whole-Body Scanning

TO THE EDITOR: From their study of patients referred for radioiodine ablation, Cholewinski et al. (1) concluded that diagnostic whole-body scanning can be performed effectively with a 185-MBq (5-mCi) dose of ^{131}I 72 h before radioiodine ablation with no evidence of, and therefore no concern for, thyroid stunning.

Their study group consisted of 122 patients who were given a diagnostic dose of 185 MBq ^{131}I and who were scanned 72 h later. On the day of scanning, after its completion, the patients received an ablation dose of ^{131}I (5,550 MBq in most cases); whole-body imaging (with spot views) was undertaken 72 h later. The diagnostic and postablation scans were inspected visually, taking note of the number of foci of uptake and the intensity of uptake. Analysis of their observations led to the conclusion that no stunning had occurred and that this was a consequence of the short time interval between the diagnostic and ablation doses.

The phenomenon of stunning has been investigated using both qualitative (2,3) and quantitative methods, the latter using profile scanning (4) or an external neck probe (5). In our center we use a twin-head gamma camera in the measurement of uptake after the diagnostic dose (120 MBq) and, more recently, therapeutic dose (4,000 MBq) of radioiodine, taking into account correction for the effects of high counting rates. Uptake on the diagnostic scan is measured at 72 h and uptake of the ablation dose is measured on 1 or more occasions in the time interval 24–72 h. Shorter time intervals after the ablation dose were used to investigate the possibility of rapid turnover of the “destructive” ablation dose in the thyroid remnants.

To date, 26 patients have been investigated. Thyroid uptake after the ablation dose was reduced in 25 of the 26 patients, being $39.4\% \pm 22.9\%$ (mean \pm SD) of the diagnostic uptake (range, 10%–100%). The mean uptake (\pm SD) of the diagnostic dose was $7.6\% \pm 6.4\%$, and the mean time interval (\pm SD) between the diagnostic dose and the ablation dose was 16 ± 10 d. Within the study group, 2 patients received the ablation dose on the day of the diagnostic scan and another patient received the ablation dose 4 d after the diagnostic dose. In all 3 patients, the uptake of the ablation dose was reduced, being 86%, 59%, and 40% of the diagnostic uptake, respectively. No differences between the diagnostic and postablation scans were seen on visual inspection.

On the basis of our experience, quantitative assessment is an essential prerequisite before any conclusions are made with regard to the presence or absence of stunning. As a consequence, we believe that considerable doubts remain in relation to the authors' conclusion that there is no stunning effect using their protocol, and we are continuing to assess the magnitude of the problem in a larger pool of patients.

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REPLY: We thank McMenemin et al. for their interest in our article (1) by communicating their data, which, though preliminary, seem to suggest that quantitative parameters obtained using a dual-head gamma camera show reduced uptake of a therapeutic dose of ^{131}I administered after a diagnostic dose.

The article by McDougall (2) cited by the authors indeed looks at the phenomenon of stunning but reports only 2 of 147 patients with reduced uptake and concludes that a dose of 74 MBq ^{131}I does not adversely affect a subsequent therapeutic dose. We believe that our investigation (1) further extends this conclusion to a 185-MBq dose as used in our protocol.

Regarding various reports in the literature looking at quantitative measurements, including data on 26 patients presented by the authors, we find it intriguing that although the quantitative parameters indicate significant reductions in uptake of the therapeutic dose, usually no visual differences are found.

Considering the 3 cases described in this letter, the authors' methodology, which includes an unspecified correction for the effects of high counting rates, shows that the uptake of the therapeutic dose was reduced by 14% (100% – 86%), 41% (100% – 59%), and 60% (100% – 40%) compared with the diagnostic dose of 120 MBq. We submit that, at least in the last 2 cases, some visual effect should be apparent because a trained observer should be able to detect easily the almost halving of uptake. Indeed, evidence that 25 of 26 patients show an average reduction of about 60% (100% – 39.4%), which remains visually undetectable in a majority of cases and unsupported by adverse clinical outcomes, would lead one to at least suspect, until disproven by additional information, a systematic bias of measurement rather than a true reduction. If such a large calculated reduction (by about one half) is not apparent visually nor borne out by subsequent clinical evolution, then a worthwhile scientific inquiry must reexamine more thoroughly the process generating those numbers.

We agree that a robust methodology of quantitation should be used. However, we maintain that the numbers, particularly those presented in the literature to date, should not be regarded as being definitive proof of stunning (i.e., reduced therapeutic efficacy of the therapeutic dose) unless the following criteria are also met:

- Significant reductions (say, >33%) are apparent to an experienced observer. Experience with other imaging tests in nuclear medicine suggests that this level of reduction certainly should, and would, be visually apparent.

2. A lesion showing a significant level of stunning by quantitation shows clinical behavior consistent with reduced efficacy of treatment. This may include demonstration of a requirement for additional therapeutic doses compared with lesions not showing stunning; an increase in size or intensity (or both), either on nuclear medicine imaging or a correlative imaging modality such as CT; or an adverse clinical outcome attributable to failure of radioiodine therapy because of stunning.

We are encouraged by the fact that several groups continue to study the phenomenon further, and we look forward to their additions to the literature. Our article (1) was not intended to decide the issue conclusively but, more, to present a clinically oriented view. We hope that other groups, including the authors of this letter, do not lose sight of clinical correlation based on quantitative techniques that may not be totally robust. As we maintain above (and in other replies), any conclusion of stunning must be regarded as hypothesis and not proven fact, until and unless additional criteria as described above are met.

The interest generated by our study (1) and other previous articles seems to suggest that an appropriately designed multicenter study of ^{131}I therapy with 2 groups of patients—1 group receiving a diagnostic dose and the other group not receiving a diagnostic dose—before radioiodine therapy would provide additional insight. Such a study would provide evidence whether efficacy of the therapeutic dose is (or is not) affected significantly by a diagnostic dose. Otherwise, clinical points of view (e.g., such as ours and that of McDougall (2)) and quantitative approaches (e.g., such as by McMenemin et al. and others) will remain limited by not encompassing the entire issue.

We look forward to further publications on this issue, including by the authors of this letter, hopefully considering the criteria raised by us.

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The Endogenous Mammary Gland Na^+/I^- Symporter May Mediate Effective Radioiodide Therapy in Breast Cancer

TO THE EDITOR: We agree with Nakamoto et al. (1) that targeting breast cancer cells with ^{131}I , by use of the Na^+/I^- symporter (NIS), would represent a powerful and much needed method of directed therapy in breast cancer. To evaluate this concept, Nakamoto et al. transfected the rat NIS complementary DNA into a human breast cancer cell line and measured iodide accumulation under various conditions, both in cell culture and in a mouse xenograft model. As they point out, a major limitation of

this approach is the absence of an effective method of selective transfection in vivo. Because mammary gland NIS (mgNIS) is upregulated in proliferating breast, we hypothesized and subsequently proved that it is also endogenously expressed in malignant breast tissue (2). mgNIS expression was shown in 20 of 23 biopsy specimens of invasive breast carcinoma compared with none of 8 normal samples from reductive mammoplasties. Furthermore, in 2 transgenic mouse models of breast cancer, significant uptake of the iodide analog $^{99\text{m}}\text{Tc}$ -pertechnetate was shown within the tumor by scintigraphic imaging, and this uptake was abolished by coinjection of perchlorate. The absence of iodide uptake by the nontransfected breast cancer line in Nakamoto's work is consistent with findings that NIS is not constitutively expressed by MCF-7 cells in culture (3). The authors apparently assumed that human breast cancer does not express NIS in vivo.

We concur with Nakamoto et al. (1) that ^{131}I iodide therapy may have a promising role to play in breast cancer. However, use of endogenous mgNIS may represent a more readily attainable means of delivery, as is being examined in our laboratory. Furthermore, because thyroid NIS and mgNIS are differentially regulated, it should be possible to adequately decrease thyroid iodide uptake without affecting breast cancer uptake through suppression of pituitary thyroid-stimulating hormone release. Therefore, when treating breast carcinoma using endogenous mgNIS, there may be no need for thyroidectomy, as suggested by Nakamoto et al.

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REPLY: We thank Dr. Zuckier and his colleagues for their thoughtful comments about our work (1). Their finding that the mammary gland Na^+/I^- symporter (mgNIS) is expressed during lactation and in breast cancer is a timely and important discovery (2). We believe that this is extremely significant and has direct implications for the diagnosis and therapeutic management of patients with breast cancer. It is also good news for these patients because it obviates the need for thyroidectomy. As was pointed out by Dr. Zuckier et al., we assumed that breast cancer cells did not take up iodide. When we began our work in 1999 our purpose was to investigate whether it would be possible to ablate transfected cells with radioiodide by increasing the accumulation of iodide in them. Although it turns out that most breast cancer tissue has its own mgNIS, we believe our approach has potential in various kinds of cancers that do not have their own NIS. Other researchers have used the same strategy for various cancers that do not accumulate iodide, and successful selective introduction and expression of the symporter gene have been reported (3,4). Although investigation by Dr. Zuckier's group indicates that a major hurdle

has been overcome for breast cancer, we have found few articles describing whether this strategy is really effective for treatment in vivo. It is encouraging that we have found several articles describing successful therapeutic effects assessed in vitro by clonogenic assay. Our preliminary biodistribution data showed that the estimated radiation dose from ^{131}I was insufficient for xenografted tumors because of the rapid excretion of iodide from the transfected cells, although a clear scintigraphic image was obtained. We believe that the next important problem to resolve to make the technique applicable to treating many kinds of cancer is to devise a way to retain sufficient ^{131}I within the cells to produce a therapeutic effect.

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