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EDITORIAL

Optimization of Radioiodine Therapy of Thyrotoxicosis: What Have We Learned After 50 Years?

In nuclear medicine, the treatment of thyrotoxicosis with radioactive iodine is considered the quintessential therapeutic intervention (*1,2*). None would doubt that this therapy can be effective; nevertheless, after half a century and treatment of hundreds of thousands of patients, the indications, patient selection, goals of therapy and dose selection remain highly controversial, varying greatly from country to country and institution to institution (*1–12*).

Bockisch et al. (*13*) bring a number of these points into striking relief. Their study population differs greatly from that usually encountered in the United States, in that there was a relative paucity of Graves' disease and a high frequency of unifocal, multifocal or diffuse autonomy as the cause of hyperthyroidism. In addition, a significant number of euthyroid patients who were not candidates for surgery were treated with radioiodine to shrink goiters.

Thyrotoxicosis due to a wide range of etiologies is potentially treatable by radioiodine, but it is necessary to exclude, by quantitative or qualitative tracer studies, patients for whom this would be inappropriate (e.g., those with factitious thyrotoxicosis, destructive thyroiditis and markedly expanded iodine pool leading to low uptake) (*1,2,7*).

Radioiodine therapy is remarkably safe, as it must be for radiotherapeutic intervention in a benign condition for which alternative therapies exist (*1,2,10,14–16*). With the exception of hypothyroidism, side effects are uncommon, but may include radiation thyroiditis, temporary exacerbation of thyrotoxicosis, nausea, vomiting and anorexia (*1,2,15,17,18*). Radioiodine treatment of Graves' disease may result in an exacerbation of ophthalmopathy although the data are by no means consistent (*19,20*). There has been a disproportionate concern for radiation-induced carcinogenesis, leukemogenesis, mutagenesis and teratogenesis. The risk of thyroid cancer following radioiodine therapy is reduced (*1,2,14*). The risks of leukemia and other malignancy are either no greater than in appropriate control populations, or they are marginally increased. Little or no convincing data exist for radioiodine therapy causing increases in infertility or mutagenesis and teratogenesis in subsequent pregnancies above the relatively high background incidence of these phenomena (*1,2,7,10,15,16*), with the exception of risk of intrauterine thyroid ablation when radioiodine is administered during pregnancy (when the ability of fetal thyroidal iodine concentration has developed) (*21*). While risk cannot be said to be nonexistent, failure to convincingly demonstrate these effects contrasts with the small, but by no means trivial, morbidity and even mortality that may result from untreated thyrotoxicosis, untoward reactions to antithyroid drugs and anesthetic and surgical complications and catastrophes (*1,2*). There is a growing recognition, particularly in the U.S., that younger patients, including women in the reproductive age group and even children, may be suitable candidates for radioiodine therapy (*1–3,5,10,16*).

The goal of therapy when treating thyrotoxicosis is prompt, predictable elimination of the hypersecretory endocrine state with a single dose of radioiodine (*1,2,7*). Controversy arises about whether hypothyroidism following radioiodine therapy is a complication or otherwise negative endpoint (*1,2,8,12,15,17,18,22*). Because modern thyroid stimulating hormone (TSH) assays are a highly sensitive and specific means to diagnose post-^{131}I hypothyroidism at an early phase and physiologically adjust thyroid hormone replacement, hypothyroidism cannot be considered a serious negative outcome. The general availability of cheap, predictively bioavailable synthetic thyroid hormone also contributes acceptability of hypothyroidism as an endpoint. While supraphysiological hormone replacement may increase the risk of osteoporosis, synthetic thyroid hormone is among the cheapest and safest drugs available when administered in appropriate doses and with appropriate TSH monitoring. Once the dose has been titrated, it is usually stable and requires only infrequent biochemical monitoring.

Once selection criteria and therapeutic goals are defined, the appropriate choice of radioiodine dose is most controversial. Bockisch et al. define

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TABLE 1
Some Factors Ideally Required for the Choice and Dispensing of an Appropriate Dose of ^{131}I

Accurately and easily ascertainable	Ascertainable only with relative difficulty and/or poor accuracy	Currently not readily ascertainable
Size of tracer and therapy doses dispensed.	Thyroid volume—palpation (highly inaccurate), ultrasound, MRI.	Microdosimetry.
Thyroid uptake measurements (single or multiple).	Metabolically active volume of the thyroid—planar scintigraphy, ^{123}I SPECT, ^{124}I PET.	Individual biological sensitivity of the thyroid to irradiation.

and set forth clearly dosimetric principles underlying thyroid radioiodine therapy at a macrodosimetric level, which depend on two principal factors: the radioiodine-avid component of the thyroid mass and the cumulated activity which is dependent on maximal thyroid uptake and the $T_{1/2}$ of thyroidal radioiodine retention. Bockisch et al. are to be complimented on the meticulous determination of cumulated activity from multiple radioiodine uptake measurements following tracer and therapeutic radioiodine doses in a large number of patients. They were able to show that a single delayed (96 or 192 hr) uptake measurement predicted the cumulated activity with great accuracy. A 24-hr or earlier, uptake is generally more convenient and widely employed, but later measurements might be more appropriate. They also demonstrate that when uptake and therapy were performed under conditions of constant thyroid drug dosage and near euthyroidism, the therapeutic dose delivered a consistently smaller (by approximately 15%) radiation dose than would be predicted from the tracer study. This is a particularly clear-cut demonstration of a previously observed phenomenon that goes to the heart of the dosimetry of radionuclide therapy. Tracer doses of radiopharmaceuticals of high specific activity, should act as true tracers and exert no pharmacological effect. Their use to predict behavior of therapeutic doses of radiopharmaceuticals may be impaired by early effects of the therapeutic intervention itself. Bockisch et al. demonstrate a small reduction in uptake and $T_{1/2}$ which was consistent and predictable. Where very large tracer activities are used (e.g., 5–10 mCi ^{131}I in thyroid cancer) the tracer dose itself may exert a negative effect on the subsequent uptake of a therapeutic dose, an example of a failure of the true tracer principle leading to so-called "thyroid stunning."

The other necessary parameter for dosimetry is thyroid volume which can be as cheap, simple and potentially inaccurate as an estimate from palpation or as complex and expensive as MRI. Ultrasound is often advocated for this purpose. Total thyroid volume, however, may be inadequate when there are unifocal or multifocal areas of autonomy within the gland (*23,24*). This raises the question whether thyroid imaging, in addition to uptake measurements, is a necessary prerequisite to radioiodine therapy. When Graves' disease is the most common etiology of hyperthyroidism and the patient has evidence of ophthalmopathy or dermopathy with a uniformly enlarged thyroid gland on palpation, many would hold imaging to be unnecessary. In the presence of an asymmetrical or irregular gland and absence of features of Graves' disease, such imaging may well be indicated. Perhaps the ultimate in absolute quantitative thyroidal iodine uptake and the depiction of metabolically active thyroid tissue has been achieved by ^{124}I thyroid PET (*25,26*). In addition to these factors, the final unpredictability of therapeutic response to radioiodine therapy results from difficult to establish microdosimetric and target tissue sensitivity factors (See Table 1). These may be accommodated for in a crude fashion using empirical experience. It is well-recognized that solitary nodules and multinodular goiters are more radioresistant than Graves' disease, that large glands are less sensitive than small glands, all other factors being equal and that prior treatment with antithyroid drugs reduces responsiveness to radioiodine therapy. Beyond these broad generalizations the individual target tissue sensitivity remains unknown (*1,2,6,17,18,22*).

The choice of radioiodine dose is also influenced by a host of regulatory, legal, cultural and logistical factors that may vary greatly. Thus, in addition to the theoretically generally desirable goal of reducing whole-body irradiation, another aim of Bockisch et al. was to shorten the duration of hospitalization required for ^{131}I therapy, which was a consequence of stringent restrictions governing such therapies in Germany. At a time when the NRC is perceived by many as excessively constraining and adversarial toward nuclear medicine, it would be well to consider the current relatively enlightened NRC policies that permit thyrotoxic patients with doses of ^{131}I as high as 30 mCi. In some countries far more restrictive limits (as low as 2 mCi) require inpatient ^{131}I therapy for almost all thyrotoxic patients. This eliminates a major advantage of the technique because in the U.S. the duration of hospitalization for surgical thyroidectomy may now be as short as 24 hr to 48 hr. Another major advantage is the NRC regulation exempting ^{131}I excreted by patients from many of the usual regulations relating to the disposal of radionuclides. This eliminates the need for enormously expensive holding tanks, pumps, venting systems and monitors required to perform ^{131}I therapy in certain countries. In terms of practical risk reduction, the massive dilution and radioactive decay during sewage processing make

TABLE 2
A Comparison of a Number of ^{131}I Dosing Schemes for Treatment of Thyrotoxicosis

Dosage scheme	Goals of therapy	Comments
1. Small fixed doses (2–3 mCi) administered repeatedly if necessary.	To minimize total radiation dose and incidence of hypothyroidism. Accept need for frequent retreatment.	May require multiple doses and many months before thyrotoxicosis is controlled.
2. Largest possible outpatient dose (30 mCi in U.S.)	To achieve control of hyperthyroidism as quickly as possible and minimize need for retreatment. Accept very high incidence of hypothyroidism.	Most patients rapidly become hypothyroid and are often on replacement within 12 wk.
3. "A Sliding scale"* 3–5 mCi for small glands/mild thyrotoxicosis; 7–12 mCi for moderate size glands/moderate thyrotoxicosis; and 20–30 mCi for large glands/severe thyrotoxicosis/thyrocardiac patients.	To achieve prompt control of hyperthyroidism in the majority of cases with a single dose while minimizing incidence of hypothyroidism.	Some degree of dose individualization achieved with minimal effort.
4. First approximation dosimetry*. Thyroid volume from palpation or U/S and single ^{131}I thyroid uptake. (e.g., 100–200 μCi ^{131}I/g retained in the gland at 24 hr.)	To achieve prompt control of hyperthyroidism in the majority of cases with a single dose while minimizing incidence of hypothyroidism.	Dose individualization achieved with modest commitment of resources.
5. Higher precision dosimetry* (e.g., use of multiple uptake measurements, ^{124}I PET, ^{123}I-SPECT, precision thyroid volume measurements).	To achieve prompt control of hyperthyroidism in the majority of cases with a single dose while minimizing incidence of hypothyroidism.	A greater degree of dose individualization achieved with major commitment of resources.

*Additional "fudge factors" may be assigned for age, presence of cardiac disease, prior antithyroid drug therapy, or nature of the pathology (e.g., toxic nodule or toxic multinodular goiter, presence of concomitant Hashimoto's thyroiditis).

this means of disposal safe, practical and cost effective. A major factor favoring the choice of ^{131}I therapy in the U.S. is the relative ease with which the majority of thyrotoxic patients may be treated as outpatients. It would appear that the patients of Bockisch et al. who required some period of hospitalization could have been treated as outpatients under prevailing conditions in the U.S.

As with much in modern, routine clinical practice, it is not so much "how much can we do" as "how much should we do," given limited and shrinking resources and a growing need to justify the cost-effectiveness of all diagnostic investigations and therapeutic interventions. This does not minimize the importance of complex and sophisticated research protocols for radioiodine therapy, particularly if they result in new insights or provide rational guides to simpler practice protocols. Bockisch et al. illustrate that a single late uptake measurement could accurately predict cumulated activity in the thyroid gland derived from a complex series of multiple uptake measurements, interpolations and extrapolations.

Despite all this, it is not unequivocally clear that any particular radioiodine dosage schema is superior over another in all circumstances. Clearly, there is more than one way to skin a cat, but after 50 yr the ideal method remains elusive (See Table 2). Regulatory, logistical, cultural and philosophical factors play as large a role as objective dosimetric criteria (*1–3,5*). For example, patient acceptability, health care costs and the logistical inconvenience of retreatment may be different between countries or between practice settings within a country. There is a reciprocal relationship between the incidence of hypothyroidism and the failure of initial therapy resulting in the need for retreatment (*1,2,4,6,8,11,12,17,18,22*). The population in the Bockisch et al. study is remarkable for the relatively low incidence of hypothyroidism and the high frequency of failed initial therapy. Moreover, within their planned dosage scheme, patients who were believed to have been undertreated had an even higher frequency of therapeutic failure, while the opposite was true in those believed to have been overtreated. Consequently, Bockisch et al. increased the radiation dose for each group of patients by 50 Gy. Relatively little has been done to compare the efficacy of a simple fixed dose (low or high) against a sophisticated, individualized dosimetry protocol with respect to the incidence of early and subsequent hypothyroidism and the need for retreatment.

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