Eur J Nucl Med Mol Imaging (2007) 34:1129–1130
DOI 10.1007/s00259-007-0419-0

LETTER TO THE EDITOR

Radioiodine treatment of hyperthyroidism: fixed or calculated doses; intelligent design or science?

James C. Sisson · Anca M. Avram · Domenico Rubello · Milton D. Gross

Received: 22 February 2007 / Accepted: 26 February 2007 / Published online: 25 April 2007

Dear Sir,
All agree that radioiodine therapy will remove hyperthyroidism caused by Graves' and toxic nodular diseases. However, therapeutic dosing of radioioidine remains controversial. Recent reports have promulgated the virtues of prescribing fixed doses of ^{131}I [1–3]. Others have delineated the value of calculating doses based on thyroid volume and fractional concentration of the radionuclide [4–6].

Among those prescribing radioiodine therapies, there has been agreement on two principles. First, following elimination of hyperthyroidism, hypothyroidism is an almost inevitable consequence of radioiodine treatment [7]. Thus, few, if any, therapists now seek to produce euthyroidism. Second, hyperthyroidism impairs health, creates disability, and, occasionally, poses a risk to life; the disorder should be eliminated as soon as possible. A third principle has frequently been neglected in the arguments for one or the other method of therapy: radiation to the patients can have harmful effects, and therefore the dose to normal tissues should be *a*s *l*ow *a*s *r*easonably *a*chievable, a standard tenet of radionuclide use in diagnosis and therapy, abbreviated ALARA [8].

Investigators have published results demonstrating no significant difference in the fraction of patients whose hyperthyroidism persists after an initial dose of ^{131}I, whether derived by fixed or by calculated methods, but frequently these therapies eliminated hyperthyroidism in less than 80% of patients [2, 3]. Moreover, repeated administrations of ^{131}I mean that hyperthyroidism has been prolonged, and that the patient has received an extra burden of radiation. Based on the second principle above, this mode of therapy was less than optimal.

After a year of observation, one group described an 85% cure rate (defined as euthyroid plus hypothyroid patients) from a fixed dose of 370 MBq, but only 67% of their patients had this outcome with 185 MBq [1]. Although disappearance of hyperthyroidism in 85% of patients is impressive, the result with the lower dose implies that two-thirds of the patients receiving 370 MBq were over-treated and, thereby, the third principle, ALARA, was violated. In fact, if the therapist chooses a sufficiently large fixed dose in MBq, more than 90% of patients will lose their hyperthyroidism, but is this optimal treatment? Treatments of hyperthyroidism by ^{131}I have not been followed by demonstrable increases in the incidences of cancer [9], but this should not be *carte blanche* for all methods of prescribing. After ^{131}I therapy, radiation to the urinary bladder will approach 0.3 Gy in some patients [10]; this is a level of particular concern for induction of cancer [11] and a hazard to be minimized. Indeed, for their own well-being, health care workers are restricted to exposures of no more than 5 rem (approximately 0.05 Gy) each year.

Larger glands do not regularly exhibit proportionally higher uptakes of ^{131}I. Since two factors that contribute to absorbed radiation, gland volume and radioiodine concentration, are frequently not correlated, it seems sensible to make the measurements to attain the appropriate amount of therapy. When dosimetry was based on relative concentration of radioactivity in an established volume of thyroid, the

J. C. Sisson · A. M. Avram · M. D. Gross
Division of Nuclear Medicine, Department of Radiology,
University of Michigan and Department
of Veterans Affairs Health Systems,
Ann Arbor, MI, USA

D. Rubello (✉)
Nuclear Medicine Service, S. Maria della Misercordia Hospital,
Viale Tre Martiri, 140,
45100 Rovigo, Italy
e-mail: domenico.rubello@libero.it

proportions of patients requiring further treatment was reduced to 14% [6] and ≤10% [4, 5]. Since rates of cure above 90% are difficult to achieve with any dose [4], despite a report of 100% elimination [12], failure rates of 5–10% will probably reflect the upper level of the dose-response curve.

Geographical factors may influence the target of a calculated dose. Absorbed radiation of 200–300 Gy was followed, in Germany, by cure rates of 90% [4, 5] and 100% [12]. In the United States, 0.175 mCi per milliliter of thyroid (probably 160 Gy) led to an 86% disappearance of hyperthyroidism [6], and ≤100 Gy induced cure in 81% of patients in Hungary [13]. Dose adjustments must also be made for possible radioresistance in some patients, especially that induced by prior treatment with propylthiouracil or thiamazole, a condition found in most studies. It is possible that discontinuing antithyroid drugs for 4 months or more may restore sensitivity of tissue to radioiodine and, *pari passu*, account for the beneficial responses to relatively lower levels of Gy seen in Hungary [13].

Cures appear to be attained with lesser Gy in glands of smaller volume [4–6, 13]. It may be that larger amounts of tissue are associated with greater variability in the distribution radioiodine. Although many physicians have estimated gland volume by palpation, ultrasound assessments will almost certainly provide more accuracy [14]. Volumes of functioning tissue in nodular glands are determined with difficulty, but with experience consistency should be attained. Adjustments in the prescribed dose must also take into account the different sensitivities to absorbed radiation in glands manifesting different volumes and in those with heterogeneous function.

Determinations of the effective half-life of ^{131}I in hyperthyroid glands have been reasonably consistent at 5–5.5 days [15] despite observations of occasional greater disparity [13]. For the large majority of patients, measurements of ^{131}I concentrations in the glands beyond 1 day will likely aid in the care of only a small minority of recipients.

For most patients, measurements of thyroid volume and fractional uptake of ^{131}I in the gland at 1 day and adjustments for the effects of known factors will suffice for prescriptions of initial doses that will result in about a 90% cure rate of hyperthyroidism while minimizing over-treatments that encumber unnecessary exposure to radiation. The calculations may be in terms of Gy or simply of the main variables determining Gy: MBq/ml (or mCi/ml).

Treatments with radioiodine should be based on principles leading to the highest quality of patient care. Science is the basis for the principles and for the advances we seek in medicine.

References

1. Allahabadia A, Daykin J, Sheppard MC, Gough SCL, Franklyn JA. Radiodiodine treatment of hyperthyroidism—prognostic factors for outcome. J Clin Endocrinol Metab 2001;86:3611–7.
2. Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA. A randomized comparison of radioiodine doses in Graves' hyperthyroidism. J Clin Endocrinol Metab 2003;88:978–83.
3. Metso S, Jaatinen P, Huhtala H, Luukkaala T, Oksala H, Saimi J. Long-term follow-up study of radioiodine treatment of hyperthyroidism. Clin Endocrinol 2004;61:641–8.
4. Peters H, Fischer C, Bogner U, Reiners C, Schleusener H. Treatment of Graves' hyperthyroidism with radioioidine; results of a prospective study. Thyroid 1997;2:247–51.
5. Reinhardt MJ, Brink I, Joe AY, von Mallek D, Ezziddin S, Palmedo H, et al. Radioiodine therapy of Graves' disease based on tissue-absorbed dose calculations: effect of pre-treatment thyroid volume on clinical outcome. Eur J Nucl Med 2002;29:1118–24.
6. Alexander EK, Larsen PR. High dose ^{131}I therapy for the treatment of hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab 2002;87:1073–7.
7. Kendall-Taylor P, Keir MJ, Ross WM. Ablative radioiodine therapy for hyperthyroidism: long term follow up study. Brit Med J 1984;289:361–3.
8. IRCP. Protection of the patient in medicine. IRCP publication 52. Ann IRCP 1987;17 4:5. New York: Pergamon Press.
9. Ron E, Doody MM, Becker DV, Brill AB, Curtis RE, Goldman MB, et al. Cancer mortality following treatment for adult hyperthyroidism. JAMA 1998;280:347–55.
10. Pollycove M, Feinendegen LE. Biologic responses to low doses of ionizing radiation: detrement versus hormesis. Part 2. Dose responses in organisms. J Nucl Med 2001;42:26N–37N.
11. IRCP. Radiation dose to patients from radiopharmaceuticals. ICRP publication 53. Ann IRCP 1994;278. New York: Pergamon Press.
12. Willemsen UF, Knewewitsch P, Kreisig T, Pickardt CR, Kirsch CM. Functional results of radioiodine therapy with 300-Gy absorbed dose in Graves' disease. Eur J Nucl Med 1993;20:1051–5.
13. Bajnok L, Mezosi E, Nagy E, Szabo J, Sztojka I, Varga J, et al. Calculation of the radioiodine dose for the treatment of Graves' hyperthyroidism: is more than seven-thousand rad target dose necessary? Thyroid 1999;9:865–9.
14. Lucas KJ. Use of ultrasound volume in calculating radioactive iodine dose in hyperthyroidism. Thyroid 2000;10:151–5.
15. Peters H, Fischer C, Bogner U, Reiners C, Schleusener H. Radioiodine therapy of Graves' hyperthyroidism: standard vs. calculated ^{131}iodine activity. Results from a prospective, randomized, multicentre study. Eur J Clin Invest 1995;25:186–93.