CONCLUSION

Iodine-123-β-CIT SPECT imaging in healthy humans demonstrates low test/retest variability and good reliability across several outcome measures. This supports the feasibility of utilizing [^{123}I]β-CIT for SPECT measurement of dopamine transporters in the evaluation of neuropsychiatric illness affecting dopamine neuronal function. Further studies of the variability of these measures in patient populations would be useful for better delineating the utility of [^{123}I]β-CIT SPECT for serial evaluations in patients groups.

ACKNOWLEDGEMENTS

This work was supported by funds from the Department of Veterans Affairs, the Public Health Service (MH30929), and a gift from Philip and Rose Hoffer. We thank Eileen Smith and Gary Wisniewski for technical support, Lynn Pantages-Torok and Quinn Ramsby for data analysis and Morgan Stratton for radiochemistry technical help.

REFERENCES

1. Neumeyer JL, Wang S, Milius RA, et al. Iodine-123-2-β-Carbomethoxy-3-β-(4-iodophenyl)-tropane (β-CIT): high affinity SPECT radiotracer of monoamine reuptake sites in brain. *J Med Chem* 1991;34:3144–3146.
2. Innis R, Seibyl J, Scanley B, et al. SPECT imaging demonstrates loss of striatal monoamine transporters in Parkinson's disease. *Proc Natl Acad Sci* 1993;90:11965–11969.
3. Laruelle M, Baldwin R, Malison R, et al. SPECT imaging of dopamine and serotonin transporters with [^{123}I]β-CIT: pharmacological characterization of brain uptake in nonhuman primates. *Synapse* 1993;13:295–309.
4. Seibyl J, Wallace E, Smith E, et al. Whole-body biodistribution, radiation absorbed dose, and brain SPECT imaging with [^{123}I]β-CIT in healthy human subjects. *J Nucl Med* 1994;35:764–770.
5. Laruelle M, Wallace E, Seibyl J, et al. Graphical, kinetic and equilibrium analyses of in vivo [^{123}I]β-CIT binding to dopamine transporters in healthy human subjects. *J Cereb Blood Flow Metab* 1994;14:982–994.
6. Baldwin R, Zea-Ponce Y, Zoghbi S, et al. Evaluation of the monoamine uptake site ligand [^{123}I]methyl 3β-(4-iodophenyl)-tropane-2β-carboxylate (^{123}I)β-CIT in nonhuman primates: pharmacokinetics, biodistribution and SPECT brain imaging coregistered with MRI. *Nucl Med Biol* 1993;20:597–606.
7. Chang LT. A method for attenuation correction in computed tomography. *IEEE Trans Nucl Sci* 1987;NS-25:638–643.
8. Gandelman MS, Baldwin RM, Zoghbi SS, Zea-Ponce Y, Innis RB. Evaluation of ultrafiltration for the free fraction determination of SPECT radiotracers: *b*-CIT, IBF and iomazenil. *J Pharm Sci* 1994;83:1014–1019.
9. Laruelle M, Baldwin RM, Rattner Z, et al. SPECT quantification of [^{123}I]iomazenil binding to benzodiazepine receptors in nonhuman primates. I. Kinetic modeling of single bolus experiments. *J Cereb Blood Flow Metab* 1994;14:439–452.
10. Levenberg K. A method for the solution of certain problems in least squares. *Quart Appl Math* 1944;2:164–168.
11. Patlak CS, Balsberg RG, Fenstermacher JD. Graphical evaluation of blood to brain transfer constants from multiple time uptake data. *J Cereb Blood Flow Metab* 1983;3:1–7.
12. Kirk R. *Experimental design: procedures for the behavioral sciences.* Pacific Grove, CA: Brooks/Cole Publishing, Co., 1982.
13. Sorensen JA, Phelps ME. *Physics in Nuclear Medicine.* Second Edition, Philadelphia: W.B. Saunders Co.; 1987.
14. Neumeyer JL, Wang S, Gao Y, Milius RA, et al. N-ω-fluoroalkyl analogs of (1*R*)-2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT): radiotracers for PET and SPECT imaging of dopamine transporters. *J Med Chem* 1994;37:1558–1561.
15. Zelnik N, Angel I, Paul SM, Kleinman JE. Decreased density of human striatal dopamine uptake sites with age. *Eur J Pharmacol* 1986;126:175–176.
16. De Keyser J, Ebinger G, Vauquelin G. Age-related changes in the human nigrostriatal dopaminergic system. *Ann Neurol* 1990;27:157–161.
17. Van Dyck C, Seibyl J, Malison R, et al. Age-related decline in dopamine transporter binding in human striatum with [^{123}I]β-CIT SPECT [Abstract]. *Soc Neurosci* 1994; 20:387.

Iodine-131 Treatment of Hyperthyroidism: Significance of Effective Half-life Measurements

Gertrud E.B. Berg, Annika M.K. Michanek, Erik C.V. Holmberg and Margareta Fink

Thyroid Unit, Department of Oncology, Oncology Center and Department of Medical Physics and Medical Engineering, Sahlgrenska University Hospital, Göteborg, Sweden

Our goals were to evaluate the effect of half-life determination and differences in the half-life of ^{131}I between patients with Graves' disease and toxic nodular goiter, and the influence of antithyroid drugs on iodine uptake. **Methods:** We reviewed the records of 555 patients who had received radioiodine treatment for Graves' disease and toxic nodular goiter to analyze iodine uptake, half-life values and pretreatment with antithyroid drugs. Two different methods of dose calculation were compared: one using repeated uptake measurements at 24 and 48 hr and 4 or 6 days to define the effective half-life. The other method assumed a half-life of 5 days and uptake at 24 hr only. All patients were treated according to the first method. A follow-up questionnaire was sent to 327 patients (238 responders) to assess the treatment outcome. **Results:** After comparing the results of the two methods, we found that repeat uptake measurements and determination of effective half-life results in administered activities that differ considerably from those calculated when an assumed, fixed half-life and a single uptake measurement are used. The simpler method would lead to over- as well as undertreatment of the patient. There was a functional difference between patients with Graves' disease and toxic nodular goiter, as reflected by the shorter ^{131}I half-life in Graves' disease (mean 5.0 days) than toxic nodular goiter (mean 6.0 days) and a skewed distribution in toxic nodular goiter. Patients pretreated with antithyroid drugs had shorter ^{131}I half-lives in both categories. Ten percent of the patients required more than one treatment; 94% of the patients with Graves' disease and 45% with toxic nodular goiter had thyroxine substitution 1–5 yr after treatment. **Conclusion:** A dose calculation method that uses three uptake measurements provides sufficient data about the effective half-life of ^{131}I in the thyroid. There is considerable difference in the half-life based on the disease being treated (Graves' disease or toxic nodular goiter). The ^{131}I half-life also is shorter after pretreatment with anti-thyroid drugs. Thus, the simpler method leads to significant uncertainty, leading to over- as well undertreatment of the patient.

Key Words: hyperthyroidism; iodine-131; effective half-life; Graves' disease; toxic nodular goiter

J Nucl Med 1996; 37:228–232

Hyperthyroidism may be treated in three ways: medical therapy with antithyroid drugs, radioiodine therapy or surgery. Therapeutic strategies vary within and between different countries. In many clinics, radioiodine treatment is the most commonly used method for treating adult patients with hyperthy-

Received Oct. 5, 1994; revision accepted Jul. 5, 1995.

For correspondence or reprints contact: Dr. Gertrud Berg, Department of Oncology, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden.

roidism and is generally accepted as safe, convenient and of low cost (*1–3*).

Several years ago, much effort was made to calculate the dose of radioiodine needed to render the patient euthyroid and to avoid hypothyroism after treatment. This has proven to be difficult, however, since hypothyroidism is also the result of progressive changes in the thyroid cells of patients with Graves' disease and since hypothyroidism will eventually occur at a rate of about 3% per year regardless of the therapeutic course (*4,5*). The consequence of giving a small dose with the intention to avoid hypothyroidism is that the patient will remain toxic for a long period of time and often repeated treatments are required, resulting in larger accumulated radiation doses. In many clinics, a sufficiently high dose of radioiodine is administered to make the patient euthyroid within a reasonable time and thyroxine is substituted within a short period of time after treatment (*6–9*).

Much of the work done in the 1950s and 1960s on kinetic studies and the importance of effective half-life measurements to calculate the absorbed dose to the thyroid is still of value (*10,11*). When the intention is to give a higher absorbed dose to the thyroid to avoid retreatment, the documented formulas for calculation are now actualized with the aim of calculating the minimum activity to achieve the new goal.

At our institution, the delivered absorbed dose method (*12*) for dose calculation has been used for years. This method includes uptake measurements at three different times to calculate the absorbed dose. Therefore, our goals were:

1. To study the effect of effective half-life determination for absorbed dose calculations compared to a simpler method with a fixed effective half-life.
2. To determine whether there is a difference in effective half-life between patients with Graves' disease and toxic nodular goiter.
3. To investigate if the effective half-life of the radioisotope is influenced by the use of antithyroid drugs before radioiodine treatment.

METHODS

Patients

From 1989 through 1992, 1036 patients (aged 25–89 yr) were admitted for hyperthyroidism and, after investigation, 789 patients were found to have hyperthyroidism that required radioiodine treatment. Records from 754 patients were examined, and the diagnoses of these patients were: Graves' disease (n = 456), toxic nodular goiter (n = 219) and unilateral toxic adenoma (n = 52). Twenty-seven patients had previously undergone surgery for hyperthyroidism.

The records of patients with Graves' disease and toxic nodular goiter containing complete information about uptake measurements were included in the final analysis (n = 555). Patients underwent routine laboratory testing, including pregnancy testing when appropriate, and were treated as outpatients, with the exception of a few elderly patients in need of hospital care.

Hyperthyroidism was diagnosed based upon biochemical test results, uptake measurements and thyroid scan results. The diagnosis of diffuse or nodular goiter was based upon the thyroid scan image and thyroid mass was estimated by palpation and by the thyroid scan.

After radioiodine treatment, follow-up was performed by the admitting physician. In order to register the clinical outcome of the radioiodine treated patients, a questionnaire was sent to study patients aged 70 yr and younger (n = 327). The patients were asked if they had received additional treatment for hyperthyroidism, if they had thyroxine substitution and when this therapy had started.

Biochemical Methods

For most patients, we determined serum TSH and T3 with reagents from Diagnostic Products Corp. (Los Angeles, CA; "NHS-TSH RIA Double Antibody" and "T3 RIA Double Antibody," respectively). In most patients, free T4 was determined with an analog assay.

Uptake measurements were performed with a 2-inch NaI crystal after oral administration of 0.5 MBq radioiodine. The crystal was centered at 10 cm distance from the trachea or neck phantom. The measuring time was 60 sec. Background was measured for 10 min in the room. Thyroid uptake was determined with the formula:

$$^{131}\text{I uptake} = ((\text{neck counts} - \text{background counts})/(\text{standard counts} - \text{background counts})) \times 100\%.$$

To confirm thyroid uptake ^{99m}Tc imaging was performed with a gamma camera 15 min after intravenous administration of 150 MBq [^{99m}Tc]pertechnetate.

Clinical Protocol

The patient received an oral test activity of 0.5 MBq (0.014 mCi) ^{131}I and uptake measurements were performed after 24 and 48 hr and 4 or 6 days. If antithyroid drugs were used before treatment, the patient ceased its intake 7 days before administration of the test dose. Most patients received thiamazole. Two days after the test dose, a thyroid [^{99m}Tc]pertechnetate scan was obtained. Therapeutic radioiodine was given orally in an aqueous solution.

The absorbed dose to the thyroid was defined for each patient and was in the range of 100–120 Gy. We used two methods to determine dose calculations, which are defined as follows.

Method A. The activity administered to the patient was calculated according to the following formula:

$$\text{Activity A (MBq)} = \frac{23.4 \times \text{mass (g)} \times \text{absorbed dose (Gy)}}{\text{estimated uptake at time zero (\%)} \times \text{effective half-life (days)}},$$

in which 23.4 is a physical constant describing tissue-absorbed fractions expressed in MBq/Gy. Effective half-life (days) = (Tphys × Tbiol)/(Tphys + Tbiol), in which Tbiol is the biological half-life calculated from uptake values at 24 and 48 hr and 4 or 6 days and the physical half-life of ^{131}I which is 8 days. In those cases where the retained activity increased instead of declining during the period of measurement, a fixed value of effective half-life of 7.5 days was chosen.

Method B (Simplified Method). We used the 24-hr uptake measurement and a fixed effective half-life of 5 days to recalculate the required activity to obtain the defined absorbed dose for each patient with the following formula:

$$\text{Activity B (MBq)} = \frac{23.4 \times \text{mass (g)} \times \text{absorbed dose (Gy)}}{\text{uptake at 24 hr} \times 5 \text{ (days)}}$$

Statistical Analysis

Student's t-test and a scatter diagram were used for comparison between the two methods (*13*).

RESULTS

Treatment Outcome

Of the 555 patients, 389 were classified as having Graves' disease and 166 as having toxic nodular goiter. Five hundred two patients (90.5%) were treated for the first time, 51 (9.2%) were retreated and 2 (0.4%) received a third treatment. Eight

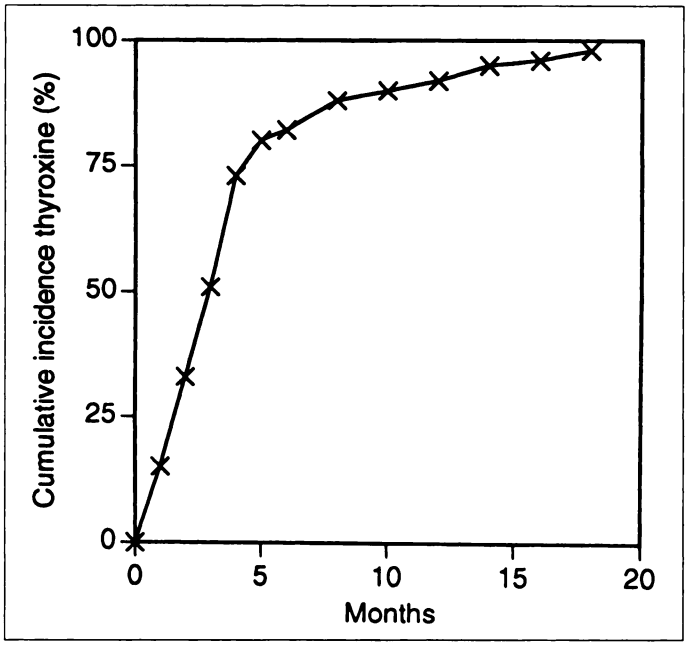

FIGURE 1. Cumulative time to thyroxine onset in 114 patients with Graves' disease who had thyroxine substitution after radioiodine treatment.

percent of the patients with Graves' disease and 13% of the patients with toxic nodular goiter required more than one treatment. Overall, the frequency of retreatment was 10%.

There were 238 (76%) responders to the follow-up questionnaire: 193 had Graves' disease and 45 had toxic nodular goiter. Thyroxine substitution after therapy was prescribed to 179 (94%) in the Graves' disease group and to 21 (45%) in the toxic nodular goiter group 1–5 yr after treatment. Mean time between radioiodine therapy and onset of thyroxine supplementation was 4.7 mo. The cumulative time to thyroxine onset for 114 Graves' disease patients with thyroxine substitution is shown in Figure 1.

Grave's Disease versus Toxic Nodular Goiter: Affect on Effective Half-life

There is a clear difference in ^{131}I half-life distribution for Graves' disease and toxic nodular goiter (Figs. 2 and 3). The mean effective ^{131}I half-life for Graves' disease is 5.0 days (s.d. = 1.3) and 6.0 days (s.d. = 1.2) for toxic nodular goiter. The mean Tbiol is 16 days for Graves' disease and 30 days for toxic nodular goiter, range 2.0–120 days. Two-tailed t-testing was performed to compare ^{131}I effective half-life values from Graves' disease and toxic nodular goiter to evaluate the hypothesis that these parameters are applicable to the same population. We found that $t = 8.456$ and $p < 0.001$, the implication being that the effective half-life of ^{131}I in patients with Graves' disease is significantly lower than that of toxic nodular goiter patients.

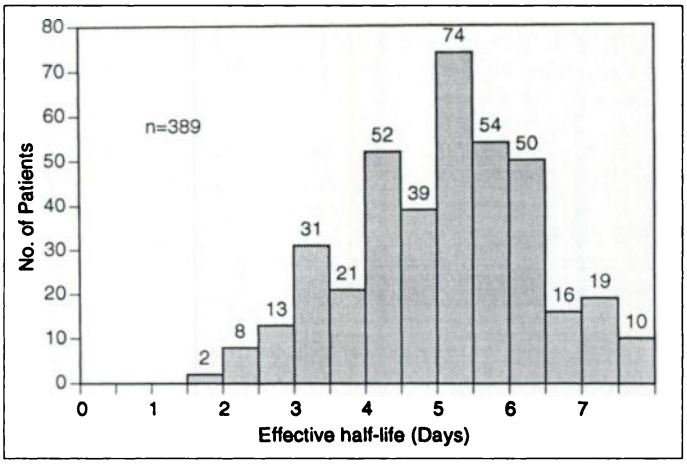

FIGURE 2. Distribution of effective half-life values from patients with Graves' disease.

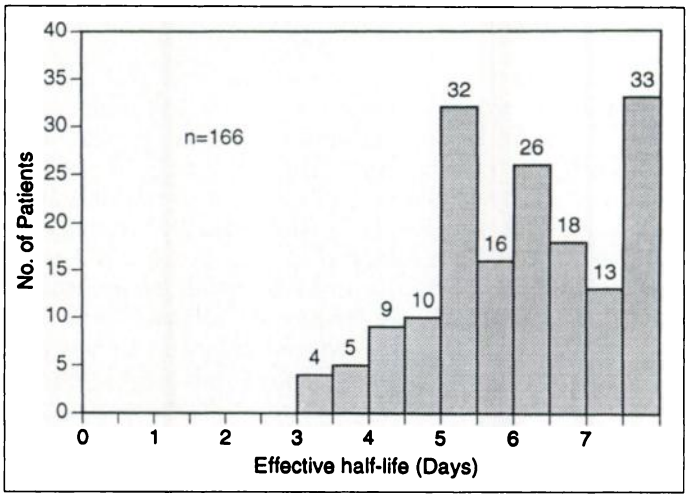

FIGURE 3. Distribution of effective half-life values from patients with toxic nodular goiter.

Antithyroid Medication: Affect on Effective Half-life

The values of effective half-lives in the relation to prior antithyroid medication are shown in Table 1. A two-tailed t-test comparing ^{131}I effective half-lives in patients with Graves' disease with and without prior antithyroid drugs resulted in $t = 6.63$ and $p < 0.001$. Similarly, for toxic nodular goiter, $t = 3.65$ and $p < 0.001$. Thus, patients pretreated with antithyroid drugs will have significantly shorter effective ^{131}I half-lives than nonpretreated patients even if the treatment is discontinued 1 wk before testing.

Absorbed Dose Administered Activity

The mean values of absorbed doses chosen were 111 Gy (s.d. = 10.4) and 119 Gy (s.d. = 13.6) for Graves' disease and toxic nodular goiter patients, respectively. Mean administered activities were 375 MBq (s.d. = 142.4) and 501 (s.d. = 222.4) for Graves' disease and toxic nodular goiter patients, respectively.

Comparison of Dose Calculation Methods A and B

The activity given to each patient according to Method A was compared to the corresponding activity calculated using Method B. For patients with Graves' disease, both under- and overtreatment would occur with Method B, whereas the majority of patients with toxic nodular goiter would be given too high an activity. The result expressed as the percent difference in activity is shown in the histograms in Figures 4 and 5 for Graves' disease and toxic nodular goiter, respectively.

We evaluated the agreement between the two methods by plotting the difference against the means of both methods (*12*) (Fig. 6). The plots display a considerable lack of agreement and

TABLE 1
Effective Half-lives of Iodine-131 in Patients with Graves' Disease and Toxic Nodular Goiter in Relation to Antithyroid Medication

	With medication		Without medication	
	No. of patients	$T_{1/2}$ (s.d.)	No. of patients	$T_{1/2}$ (s.d.)
Graves' disease	124	4,4 (1,4)	251	5,3 (1,1)
Toxic nodular goiter	30	5,3 (1,2)	129	6,1 (1,1)

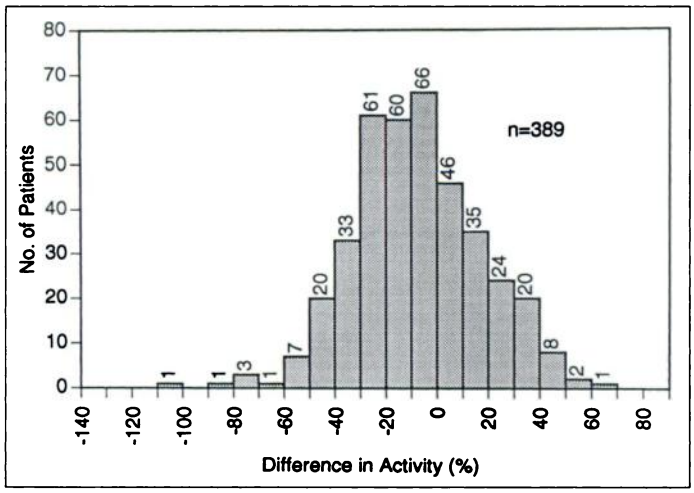

FIGURE 4. Difference in administered activity (%) between Methods A and B in patients with Graves' disease. A = activity (MBq). Calculation is based on 24-hr, 48-hr and 4 or 6 days uptake measurements to determine the effective half-life. B = activity (MBq). Calculation is based on a fixed value of effective half-life of 5 days.

the scatter of difference increases as the activity increases. The mean difference was −7.4 (s.d. = 111.1) for patients with Graves' disease and −135.6 (s.d. = 153.4) for toxic nodular goiter patients. The following two examples emphasize the importance of the effective half-life in dose calculation:

Example 1. A patient with Graves' disease with a thyroid mass of 50 g and uptake measurements of 43%, 27% and 18% at 24 and 48 hr and 4 days will have an estimated uptake at time zero of 64% and an effective ^{131}I half-life of 1.6 days. The selection of 100 Gy as the absorbed dose to the thyroid for treatment will result in the patient receiving 1143 MBq (30.9 mCi) using method A and 539 MBq (14.6 mCi) with method B.

Example 2. A patient with toxic nodular goiter with a thyroid mass of 40 g and uptake values of 34%, 41% and 40% after 24 and 48 hr and 4 days, respectively, will have an estimated uptake at time zero of 42% and a ^{131}I half-life of 7.5 days. If 120 Gy are chosen for treatment, Method A results in 356 MBq (9.6 mCi) while Method B will give as much as 660 MBq (17.8 mCi).

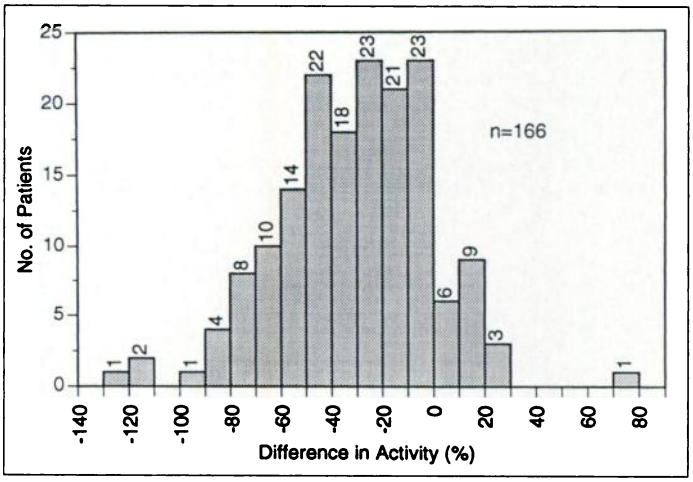

FIGURE 5. Difference in administered activity (%) between Methods A and B in patients with toxic nodular goiter. A = activity (MBq). Calculation is based on 24-hr, 48-hr and 4 or 6 day uptake measurements for determination of effective half-life. B = activity (MBq). Calculation is based on a fixed value of effective half-life of 5 days.

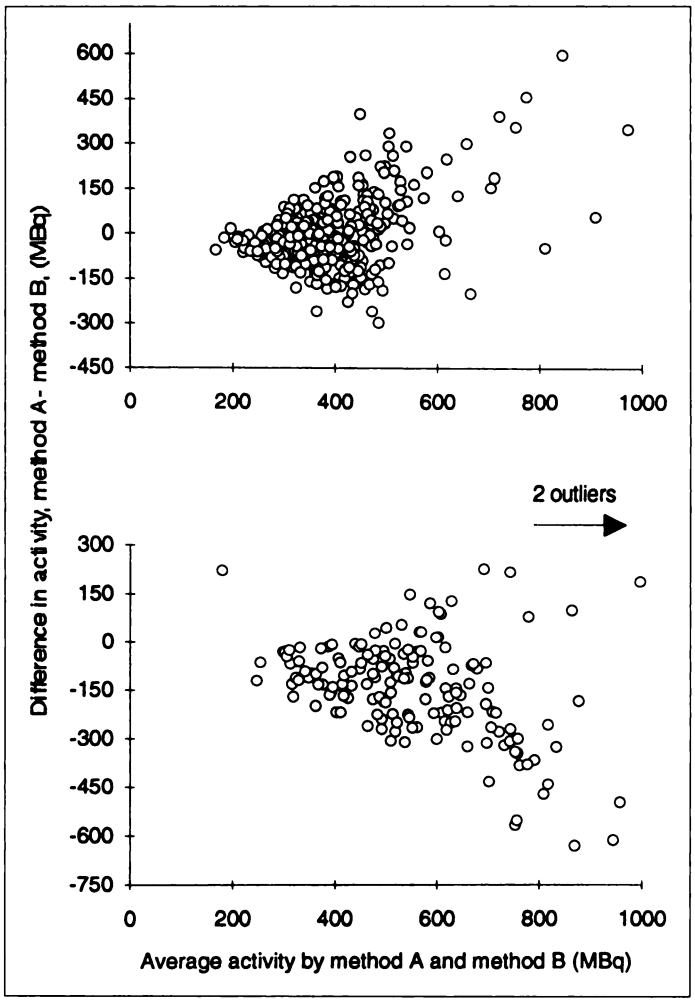

FIGURE 6. Difference against mean for patients with Graves' disease (above) and toxic nodular goiter (below).

DISCUSSION

When radioiodine therapy was introduced more than 50 years ago, it was first given to elderly patients since it was suspected to induce cancer and genetic damage (*12*). These hazards, however, have proven to be negligible and younger adult patients are being prescribed this treatment (*14,15*).

In Sweden, most centers choose 35 yr as the lower age limit for radioiodine treatment. This policy is supported by recently published Swedish multicenter studies (*16,17*), in which 10,552 patients aged 50–75 receiving radioiodine therapy were studied to determine later incidences of cancer. With the exception of a possible small risk for stomach cancer, no indications of radiation-related cancer risk were found. The study supports the view that radioiodine therapy is a safe method for adult patients, but it also stresses the importance of choosing the lowest possible administered activity to achieve the desired clinical effect. This is especially important given the fact that younger and younger adults are admitted for radioiodine treatment (*2*).

Determining the half-life is an important factor in dose calculation, in that the effective half-life may differ, with a range from 1.6 to 7.5 days, giving a possible difference in the formula by a factor of 4.6. This contributes to a greater error in the formula than that expected from thyroid volume determination, which is estimated to be a factor of about 1.5 and is considered a significant source of error (*18*).

The use of the delivered absorbed dose method results in low frequency of repeat treatments (10% in our patient population),

although the mean accumulated administered activity is lower than that from fixed ablative doses (*6–8*).

We compared our results to those of other investigators who have used the delivered absorbed dose method to determine the half-life and found a correlation between clinical outcome and the absorbed dose. Thus, our chosen absorbed dose is 100–120 Gy, which results in repeat treatment rates of 8% in our Graves' disease patients and 13% in our toxic nodular goiter patients. These measures are comparable to values reported by Holm et al. (*4*) and Kung et al. (*19*): 44% repeat treatments when using 60–100 Gy (*4*) and 40% of the patients still toxic 1 yr after therapy after an 80-Gy dose (*19*).

The prevalence of nodular goiter is higher in iodine-poor areas such as central Europe than in iodine-rich areas such as the U.S. In Sweden, the iodine supply has become sufficient during the last decades, but we still find a high proportion of nodular goiter (30%) in our population compared to the U.S. (*20*). The difference in ^{131}I half-lives for nodular and diffuse goiter in this study stresses the importance of using scintigraphy to differentiate between the two conditions, which is not always easy by palpation alone (*21*). The higher rate of treatment failure among toxic nodular goiter patients may be explained by the fact that new hot nodules may develop in the thyroid after treatment in areas that did not take up radioiodine primarily.

In our study, we found that patients taking antithyroid drugs before treatment have a significantly shorter effective half-life and, therefore, a faster turnover of radioisotope than untreated patients. The reason for this may be the behavior of the antithyroid drug per se, which decreases the protein-bound iodine fraction in the gland. Another possible explanation is that the illness might have been considered more serious among the pretreated patients and a shorter half-life would therefore be suspected in this category. Regardless of the reason, a short effective half-life could result in undertreatment if it is not considered in the dose-calculation. This perhaps explains why pretreated patients have been shown to have a higher frequency of radioiodine therapy failure (*22,23*).

CONCLUSION

We have shown that measuring the effective half-life is important to determining the administered activity. The delivered absorbed dose methodology for dose calculation can be optimized for individual patients. Therefore, differences in iodine intake, thyroid hyperactivity and prior treatment with antithyroid drugs will be considered. Use of this method of calculation means that the patient will have to come to the hospital four times within a week for the dose calculation and treatment. Although this procedure is not laborious for the physician, especially when using computerized calculation, it does require extra effort from the patient. We are sure, however, that any inconvenience will be readily accepted by the patient once they know that the method results in more accurate treatment.

ACKNOWLEDGMENTS

The authors thank Dr. Sture Lindberg, former head of the Department of Nuclear Medicine, Sahlgrenska Hospital, who introduced us to the dose calculation method.

This study was supported by the King Gustav V Jubilee Clinic Cancer Research Foundation, Gothenburg, Sweden.

REFERENCES

1. Glinoer D, Hesch D, Lagasse R, Laurberg P. The management of hyperthyroidism due to Graves' disease in Europe in 1986. Results of an international survey. *Acta Endocrinol* 1987;285(suppl):6–23.
2. Solomon B, Glinoer D, Lagasse R, Wartofsky L. Current trends in the management of Graves' disease. *J Clin Endocrinol Metab* 1990;70:1518–1524.
3. Wartofsky L, Glinoer D, Solomon B, et al. Differences and similarities in the diagnosis and treatment of Graves' disease in Europe, Japan and the United States. *Thyroid* 1991;1:129–132.
4. Holm L-E, Lundell G, Israelsson A, Dahlqvist I. Incidence of hypothyroidism occurring long after iodine-131 therapy for hyperthyroidism. *J Nucl Med* 1982;23: 103–107.
5. Kinser JA, Roesler H, Furrer T, Grutter D, Zimmermann H. Nonimmunogenic hyperthyroidism: cumulative hypothyroidism incidence after radioiodine and surgical treatment. *J Nucl Med* 1989;30:1960–1965.
6. Eriksson E, Eriksson K, Wahlberg P. Treatment of hyperthyroidism with standard doses of radioiodine aiming at ablation. *Acta Med Scand* 1985;217:55–60.
7. Kendall-Taylor P, Keir MJ, Ross WM. Ablative radioiodine therapy for hyperthyroidism: long-term follow-up study. *Br Med J* 1984;289:361–363.
8. Nordyke RA, Gilbert FI. Optimal iodine-131 dose for eliminating hyperthyroidism in Graves' disease. *J Nucl Med* 1991;32:411–416.
9. Shapiro B. Optimization of radioiodine therapy of thyrotoxicosis: what have we learned after 50 years? *J Nucl Med* 1993;34:1638–1641.
10. Halnan KE. Radioactive isotopes in radiotherapy. *Clin Radiol* 1961;12:232–240, 311–323.
11. Chapman EM. Treatment of hyperthyroidism with radioactive iodine. In: Blahd WH, ed. *Nuclear medicine*. New York: McGraw Hill; 1971:711–734.
12. Blomfield GW, Jones JC, MacGregor AG, Miller H, Wayne EJ, Weetch RS. Treatment of thyrotoxicosis with radioactive iodine. *Br Med J* 1955;2:1223–1229.
13. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307–310.
14. Cooper DS. Treatment of thyrotoxicosis. In: Braverman LE, Utiger RD, eds. *The thyroid. A fundamental and clinical text*, 6th ed. Philadelphia: J.B. Lippincott; 1991:887–916.
15. Brill AB. *Safety of ^{131}I treatment of hyperthyroidism*. Boca Raton: Year Book Medical Publishers; 1986:347–361.
16. Holm LE, Hall P, Wiklund K, et al. Cancer risk after iodine-131 therapy for hyperthyroidism. *JNCI* 1991;83:1072–1077.
17. Hall P, Boice JD, Berg G, et al. Leukemia incidence after iodine-131 exposure. *Lancet* 1992;340:1–4.
18. Clerc J, Izembart M, Dagousset F, et al. Influence of dose selection on absorbed dose profiles in radioiodine treatment of diffuse toxic goiters in patients receiving or not receiving carbimazole. *J Nucl Med* 1993;34:387–393.
19. Kung AWC, Choi P, Lam KSL, Pun KK, Wang C, Yeung RTT. Discriminant factors affecting early outcome of radioiodine treatment of Graves' disease. *Clin Radiology* 1990;42:52–54.
20. Orgiazzi JJ, Mornex R. Hyperthyroidism. In: Greer AM, ed. *The thyroid gland*. New York: Raven Press; 1990:405–495.
21. Ripley SD, Freitas E, Nagle CE. Is thyroid scintigraphy necessary before I-131 therapy for hyperthyroidism? Concise communication. *J Nucl Med* 1984;25:664–667.
22. Velkeniers B, Cytryn R, Vanhaelst L, Jonckheer MH. Treatment of hyperthyroidism with radioiodine: adjunctive therapy with antithyroid drugs reconsidered. *Lancet* 1988;1:1127–1129.
23. Bockisch A, Jamitzky T, Derwanz R, Biersack HJ. Optimized dose planning of radioiodine therapy of benign thyroidal diseases. *J Nucl Med* 1993;34:1632–1638.