The radioiodine turnover rate as a determinant of radioiodine treatment outcome in Graves' disease

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Abstract

For individual iodine-131 (^{131}I) treatment dosage calculations, most physicians use the 'standard dosage formula', which requires measurements of thyroid volume and thyroidal ^{131}I uptake. The effective half-life of ^{131}I (T_{eff}) is then unjustifiably ignored. Evidence is presented that the 5/24h ^{131}I uptake ratio can be used as a surrogate parameter for T_{eff}, and that it is a determinant of the ^{131}I therapy outcome for patients with Graves' disease. A correction factor based on the thyroidal ^{131}I metabolism in individual patients could provide a means to increase the success rate of radioiodine treatment.

Introduction

It is the current opinion of a majority of internists and nuclear physicians in Europe that patients with Graves' hyperthyroidism are best treated with anti-thyroid drugs (ATD), such as thiamazole or propylthiouracil (PTU). In the Netherlands this regimen is formalized in the Guideline for thyroid disorders, with specific reference to the "as low as reasonably achievable" (ALARA) principle as a motivation [1]. After 12-18 months medical treatment, about 50% of all patients are cured of hyperthyroid symptoms. Radioiodine treatment (RIT) is generally preserved for ATD-refractory patients. Only for patients with very large goiters, or when immediate results are desired, surgery (total thyroidectomy) is the treatment of choice. Radioidine treatment is a safe and effective treatment modality [2]. The goal of RIT in Graves' disease is euthyroidism with or without L-thyroxine medication. This goal can be achieved by different dosage regimens. Controversies over the preferred ^{131}I dosage regimen for Graves' hyperthyroidism have existed ever since the first therapeutic dose, notwithstanding the wealth of publications over more than six decades [3-4]. In the USA the administration of relatively high fixed dosages of ^{131}I is the treatment of choice, with the aim of fast elimination of hyperthyroidism. Two arguments are often proposed in favour of this approach: a) the natural course of Graves' disease results in late hypothyroidism in more than half of all patients during their life-time with an annual incidence of 2%-5%, [5] and b) an individualized approach involves additional cost and effort, *viz.* measurements of thyroid volume and ^{131}I uptake. However, there is an advantage of dose calculation over the use of a fixed dosage, as the only factor influencing the outcome is the radiation dose delivered to a certain thyroid volume [4]. An individualized calculated dosage approach is a legal requirement in some European countries e.g. in Germany, because of radiation safety concerns. Most physicians in Europe and in Japan favour this approach, with a view to minimizing the risk of iatrogenic hypothyroidism - a view that was reinforced by the finding that an adequate supply or endogenous production of triiodothyronine, substantially enhances patients' well-being [6].

Individualized RIT dosage schemes

For individualized dosage calculations most physicians use the standard dosage formula also called becquerel-per-gram formula: $D=V*100/U*C$, where D is the treatment dosage in MBq, V equals the thyroid volume in ml, U represents the ^{131}I uptake percentage, usually at 24h after a test dose, and C is a constant (usually 3.7MBq/ml) [7]. The standard dosage formula harbours one important flaw: the residence time of ^{131}I, which has great bearing on the radiation dose delivered to the thyroid, is considered to be constant. In actual fact the biological half-life of thyroidal ^{131}I in patients with Graves' disease varies considerably, roughly between 1 and 8 days. A short biological half-life is associated with a reduced thyroidal iodine pool [8, 9]. In individual patients with Graves' hyperthyroidism substantial changes in ^{131}I uptake are observed over relatively short periods of time. Moreover, the metabolic rate of thyroidal ^{131}I (radioiodine turnover rate) isn't constant [10]. The common practice of a single ^{131}I uptake measurement (at 24h) doesn't provide information about the ^{131}I turnover rate [11, 12]. It is often argued that measurements of T_{eff} are tedious; it has been suggested that up to 10 measurements over a 7-day period are required. Some years ago Aktay et al. (1996) demonstrated that a two-point measuring scheme at 4h and 24h after a ^{131}I test dose can serve as an alternative to traditional measurements of T_{eff} [12]. This very interesting study, however, did not provide practicable adjustments to current dosage methods.

The ^{131}I turnover rate as a determinant of the clinical outcome of RIT

At the University Medical Center Utrecht we established a strong association between the ^{131}I turnover rate measured before RIT and the clinical outcome (Fig. 1) [13]. In patients treated with 3.7MBq/ml and using the standard dosage formula, only a small overlap was observed between hypothyroid, euthyroid, and recurrent hyperthyroid outcome groups. In other words the ^{131}I turnover rate, defined as the 5/24h uptake ratio, is an important determinant of the clinical outcome.

A similar analysis was done in a group of patients with
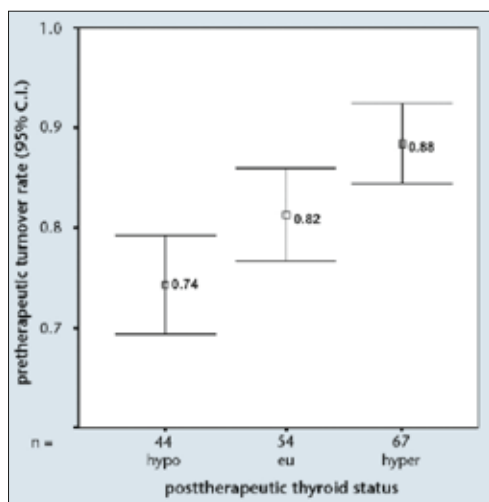
Figure 1. The clinical outcome (ordinate) as a function of the pre-therapeutic ^{131}I turnover rate (abscissa) after treatment with 3.7MBq ^{131}I/ml. Means are presented for each of the three outcome groups; bars indicate 95% confidence intervals.
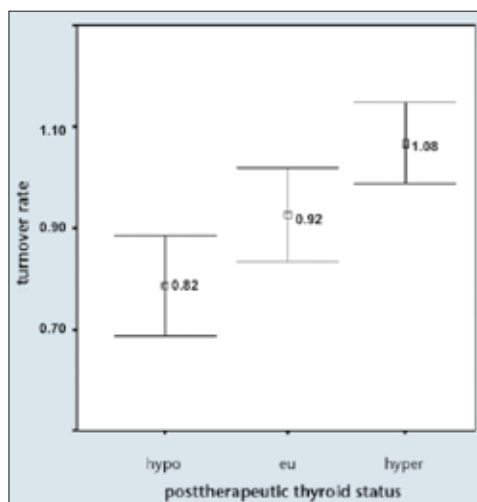

Figure 2. The clinical outcome (ordinate) as a function of the pre-treatment ^{131}I turnover rate (abscissa) after treatment with 7.4MBq ^{131}I/ml.
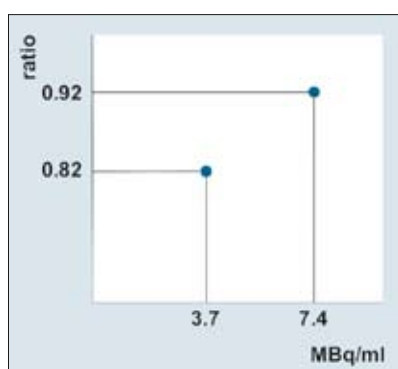
Figure 3. Diagrammatic representation of the mean turnover rate versus the administered dosage (MBq/ml) in patients with a euthyroid outcome after RIT.
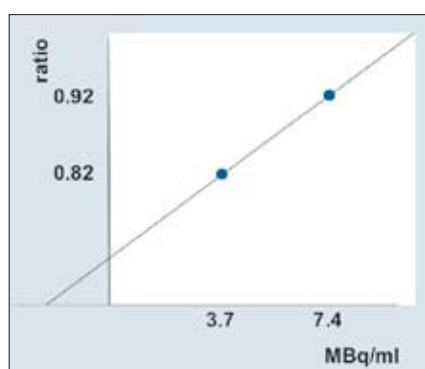
Figure 4. A linear relation between the two measuring points would yield impossible results (negative ^{131}I treatment dosage for ratios below 0.70).
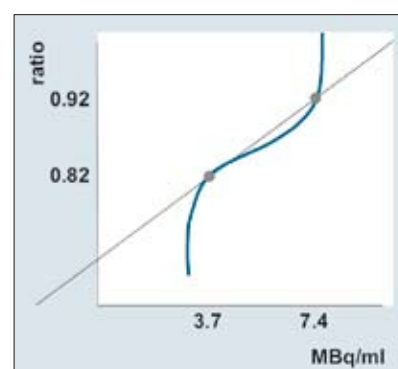
Figure 5. Proposed S-shaped dose-effect relationship.

Graves' hyperhyroidism who had been administered a double ^{131}I dosage (i.e., 7.4MBq ^{131}I/ml). Again the correlation between the clinical outcome and the pre-treatment turnover rate was evident (Fig. 2).

An analysis in the euthyroid outcome patient groups of the administered dosage vs. the mean turnover rate for each of the two dosage groups (Fig. 3) leads to an interesting perspective.

A linear relation between the two points can be ruled out, as this would result in negative ^{131}I treatment dosages for patients with turnover rates below about 0.70 (Fig. 4).

Survival curves for cells treated with external beam irradiation characteristically are sigmoidal (S-shaped) curves [14, 15]. We propose that the same applies for thyrocyte populations after RIT (Fig. 5).

An S-shaped curve can be described mathematically if four points on the curve are known. With the two measuring points obtained from the earlier studies, we only need to know the (asymptotic) minimum and maximum to define the curve. Even though these asymptotic limits cannot be actually measured, reasonable values can be chosen on the basis of clinical experience. We know from the literature that few physicians have ever considered therapeutic dosages below 2MBq/ml. Likewise, dosages over 9MBq/ml are considered inappropriate by a vast majority. When we use these values as

limits for the curve, and plot the dependent variable on the ordinate, the following result is obtained (Fig. 6).

For practical purposes the actual values for the limits aren't of decisive importance. Mathematical excercises show that even a 2MBq extension of the limits results in significantly different treatment dosages *only* in cases of extreme turnover rates, such as were encountered in less than 3% of all patients.

The individually required ^{131}I dosage can now be read from the curve. If for instance the measured 5/24h ratio in a given patient is 0.87, it follows from the curve that the required dosage equals 5.6MBq/ml (Fig. 7).

With regard to the standard dosage formula this implies that the constant "C" is replaced by a correction factor "F". For practical purposes the mathematical data representing the sigmoidal curve can be fed into a spread sheet; after entering the individually observed turnover ratio, the correction factor F is automatically calculated and displayed in MBq/ml (Fig. 8).

In this spread sheet cells B1 and B2 represent the lower and upper limits of the curve (2 and 9MBq/ml, respectively). Cells B3 and B4 contain the uptake ratio (0.82) and dosage (3.7MBq/ml) as observed in the patients who became euthyroid after single-dosage RIT; cells B5 and B6 contain the corresponding data from double-dosage patients. When the actual, individually observed 5/24h ^{131}I uptake ratio (in this exam-
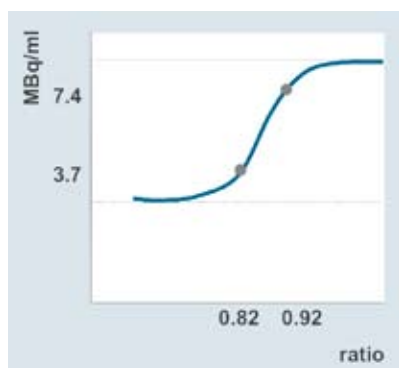
Figure 6. The dependent variable is plotted on the ordinate, and lower and upper dosage limits 2 and 9MBq/ml, respectively are introduced.
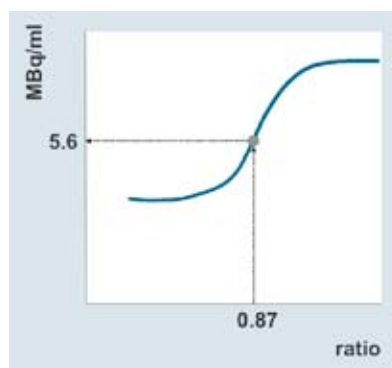
Figure 7. Any observed turnover rate corresponds with the required dosage per ml.

ple: 0.87) is entered in cell B9, the factor F (in this example: 5.7MBq/ml) is displayed in cell B10. The mathematical expression of cell B10 is: fx = B1+(B2-B1)/(1+EXP((B8-B9)/B7)).

The factor F is then entered in the 'revised standard dosage formula': $D=V*100/U*F$, where D is the treatment dosage (MBq), V equals the thyroid volume (ml), U represents the 24h ^{131}I uptake percentage, and F is a correction factor (for the patient in our example: 5.7MBq/ml).

Cells B7 and B8 contain the mathematical data for the definition of the sigmoidal curve:
B7: fx = 1/(10*(LN((B2-B4)/B4-B1))-LN((B2-B6)/(B6-B1))));
B8: fx = 0.82+B7*LN((B2-B4)/(B4-B1)).

Discussion

After 65 years of experience with RIT for Graves' disease, clinical research has been able to identify most parameters that influence the clinical outcome. However, even today there is no dosage formula that covers all these parameters. The frequently used standard dosage formula doesn't account for differences in T_{eff} of thyroidal ^{131}I in individual patients. The 5/24h uptake ratio (^{131}I turnover rate) is a strong indicator of the outcome, and it can be used as a surrogate parameter for T_{eff}. Practicable correction factors are now available for a temptative revision of the standard dosage formula.

For optimal RIT dosage calculation in patients with Graves' hyperthyroidism, other issues must also be observed.

When patients are scheduled for RIT, thyroid medication should be withheld during ^{131}I treatment and during ^{131}I up-

take measurements alike. The efficacy of RIT under continued ATD medication is reduced: not only by a lower uptake and shorter half-life of radioiodine, but by a heterogeneous energy dose distribution within the thyroid also. Discontinuation of combination treatment (ATD and levothyroxine) for 3-5 days before RIT through 3-5 days after RIT is advised, in order to restore the efficacy of radioiodine treatment [1, 16-20]. A recommendation in conformity with the Dutch guideline to preserve RIT for patients who are not cured after 12-18 months ATD medication constitutes a negative selection, because both for ATD and for RIT the success rate decreases with increasing thyroid volumes [1, 21, 22].

When more sophisticated individual dosage calculations are being applied, the standardization of thyroid volume measurements and ^{131}I uptake measurements becomes more pertinent. Also the accuracy of the measurements must be optimized. Thyroid scintigraphy is used to differentiate between different causes of thyrotoxicosis, and it facilitates the choice of the preferred therapeutic intervention. Scintigraphic volume measurements have been used ever since the introduction of the so-called Himanka formula [23]. However, scintigraphic volume estimates are off by 30% on average, [23,24] which is only slightly better than for volume estimates by palpation. Therefore, they are simply not suitable for this purpose. An easy, practical, and accurate alternative is ultrasound; the mean error with this modality is less than 5% [24, 25].

Radioiodine uptake measurements serve a single purpose, *viz.*, to facilitate the calculation of the required therapeutic ^{131}I activity for patients who are scheduled for RIT. Consequently ^{131}I is the only suitable tracer for thyroidal iodine uptake measurements. A very small tracer amount (4MBq) suffices for use with a dedicated thyroid probe. A ^{131}I source, placed in an anthropomorphic neck phantom, is used as a reference for the in vivo measurements. Measurements should be done under strictly standardized conditions, which include regular calibration and quality controls of the thyroid probe, proper patient preparation (no excess iodine intake), and standardized measuring conditions such as geometry and background radiation levels. Iodine-131 uptake measurements should be performed under identical conditions as RIT; most importantly, thyroid medication should be withheld for identical periods. Recent scintigraphic procedures, especially involving ^{131}I radiopharmaceuticals, lead to falsely increased uptake percentages [26].

At many institutions the ^{131}I uptake is measured only at one time-point (usually 24h) after ingestion of the tracer activity. However, a single measurement is not indicative of the residence time of thyroidal ^{131}I, which is proportional to the absorbed radiation dose and thus to the clinical effect of the treatment. Measurements at dual time points (e.g., at 5 and 24h) allow an estimation of the radioiodine turnover rate, which may lead to more accurate calculation of the required ^{131}I dosage.

Figure 8. Spread sheet for individual dosage calculation (for mathematical data: see text).

	A	B
		Bladen	Grafieken	5m
1	phi1:	2
2	phi2:	9
3	x1:	0,82
4	y1:	3,7
5	x2:	0,92
6	y2:	7,4
7	phi4:	0,04249
8	phi3:	0,868315
9	5-/24-h I-131-uptake ratio	0,87
10	I-131 ther dosage (MBq/ml)	5,569393

The ^{131}I uptake percentage is variable over time. Especially in patients with Graves' hyperthyroidism, the variations in disease activity result in widely varying measurements within days or weeks. Therefore it is mandatory to do the uptake measurements shortly before RIT; the optimal interval is 2 days or less. A secondary advantage of this regimen is that thyroid medications have to be withheld only once.

One final issue should be addressed, i.e., the inverse relation between radiation sensitivity and goiter size. Already in 1975 DeGroot reported that larger thyroid volumes need to be treated with higher dosages per volume unit (MBq/ml) [27]. This was confirmed by others [22, 28, 29]. It seems fair to assume that the dose-effect relationship also for this parameter is best represented by an S-shaped curve. Further study is warranted to approve or to disapprove this assumption.

The volume data used in our study groups were obtained from scintigraphic measurements. As we have shown, such measurements are inaccurate [23, 24]. Secondly, no allowances were made for the decreased radiation sensitivity of larger goiters. In spite of these confounders, the pre-therapeutic 5/24h uptake ratio was a strong predictor of the outcome of ^{131}I treatment. The number of euthyroid outcomes after one ^{131}I treatment could possibly be increased when a compensation factor, based on the uptake ratio, is included in the standard dosage formula. Only through large prospective, and preferably multi-center studies it can be determined whether the promise of further dosage optimization can indeed be fulfilled.

Acknowledgement

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