Letter to editor

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Approximation of time-uptake curve to a modified Bateman equation based on three uptake tests — potential value for dosimetry of corpuscular radiation

Cyprian Świętaszczyk, Stanisław E. Pilecki
Department of Nuclear Medicine, The Dr. Władysław Bieganski Specialist Hospital in Grudziadz, Poland
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Abstract

BACKGROUND: Many models of assessing radiopharmaceutical kinetics for dosimetry have been developed, starting from the formula of Marinelli. They are either inaccurate or require taking multiple patient uptake measurements.
MATERIAL AND METHODS: Radiotracer behavior is approached to a modified Bateman equation ("biphasic model"). The calculated effective half time, maximum uptake and the cumulated uptake according to the biphasic model is compared to the values obtained with the most popular Marinelli's method ("simplified model"). The calculations can be performed by free online-accessible software on the site: www.nuk.bieganski.org ("Calculator").
RESULTS: Using of the software allows a direct comparison of the obtained effective half times according to both, the simplified and the biphasic, models. Further errors can come from imprecise measure of the maximum uptake value (especially, when the time of the measurement differs from the true point of the maximum uptake) and from neglecting of the ascending branch of the time-uptake curve. It is possible to compare the cumulated uptake values according to both models ("correction factor"). The results can be combined with the widely known formula of Marinelli. The operations require only one additional uptake measurement, which could be performed shortly after the i.v. administration of the radiotracer, i.e., during the same visit of the patient.
CONCLUSION: The proposed theoretic model could be verified practically for some i.v.-administered radiopharmaceuticals.
KEY words: effective half time, radiotracer uptake, radionuclide therapy, computation

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Correspondence to: Cyprian Świętaszczyk
Department of Nuclear Medicine
The Dr. Władysław Bieganski Specialist Hospital
15–17 Rydygiera St., 86–300 Grudziadz
Phone/Fax: +48 56 641 46 21
E-mail: c.swietaszczyk@bieganski.org

Background

The calculation of radioiodine activity for treatment of thyroid disorders according to Leonidas D. Marinelli (1906–1974) [1, 2] was the first attempt to optimize radionuclide therapy. Therapy of thyroid disorders with iodine-131, as the most common one, frequently serves as the paradigm of radionuclide therapy.

The dose of corpuscular radiation delivered to a target during radionuclide therapy can be expressed as:

$$D = \frac{E_{mean}}{m} A \int_0^\infty U(t)dt, \text{ where:}$$

D: focal radiation dose,
E_{mean}: mean energy of particles emitted per one radioactive disintegration,
m: target mass,
A: administered activity of the nuclide,
$U(t)$: uptake of the radionuclide in the target as a function of time.
The integral of the function multiplied by A equals the total number of radioactive disintegrations occurring in the organ (also referred to as "cumulated activity" or "time integrated activity"). It is assumed that:

— the range of the particles released by the decaying nuclei is much shorter than the diameters of the target structure;

— there is no radiation delivered to the target from outside;
— there is no significant influence of the radiation emitted on the kinetics of the radiotracer and on the target's mass.

Precise determination of the target activity/uptake in function of time is frequently a challenge. The primary model [1, 2], further referred to as "simplified model", takes into consideration only the maximum uptake of the radionuclide and the effective half time; only few (even two) uptake tests are necessary for calculation of the function which can be mathematically expressed as:

$$U_{t(sim)} = U_{mm} 2^{-t/T_{ef}}, \text{ where:}$$

U_{mm}: the measured maximum uptake value (i.e., the highest obtained value of uptake, frequently lower than the true maximum),
t: the time elapsed,
T_{ef}: the effective half-time of the radiotracer in the organ,
$U_{t(sim)}$: the uptake in the time t according to the simplified model.

The procedure of the simplified model can be further modified with either:
— determination of some typical (mean) parameters for a given kind of radionuclide therapy [3, 4], or
— more accurate determination of these parameters in a given patient [5, 6].

In the former methods, some kinetic parameters have been determined experimentally, what allows additional reducing of the number of the measurement procedures even to one. Although the results reflect a statistical mean, not each patient equals such a standard. In the author's experience, there is known a female patient suffering from Graves disease with the measured radioiodine effective half time in the thyroid of less than 1 day; if a "standard effective half time" had been used for the calculation of the administered activity (above 4 days [4]), the method would have underestimated this activity more than four-fold. The latter methods are more personalized, but need numerous tests to be performed, what in turn causes logistic problems.

The purpose of the study is to discuss a model which potentially combines a higher accuracy in determination of the parameters of the time-uptake function with a lower number of patient uptake tests. Self-designed, free-accessible programs for the calculations are accessible on the web-site of the Department of Nuclear Medicine in Grudziądz, Poland: http://www.nuk.bieganski.org/ (the tool was described earlier in the reference [7]). The programs are accessible in two languages: Polish and English; unless one's native is Polish, the User should first click the English flag (right upper corner) and then proceed to CALCULATOR (the last green button, left side). This study concentrates on two algorithms: "Kinetic modeling I" and "Kinetic modeling II" (option 4 and 5, respectively) in "Calculations related to nuclear medicine".

Materials and methods

A biphasic model of radiotracer behavior was developed. It was assumed that:
— the radiotracer is injected i.v. as a bolus;
— its concentration in blood decreases exponentially in function of time;
— its influx rate into the target is proportional to its concentration in blood, and
— its efflux rate from the target is proportional to its concentration in the target (follows the rules of the first order kinetics).

In such a case, the uptake of the radiotracer in the target in function of time may be approached by the Bateman [8] equation describing the quantity of the second nuclide in the radioactive chain [9]. After appropriate modification, this formula is:

$$U_{t(biph)} = F(2^{-t/T_{ef}} - 2^{-t/T_a}), \text{ where:}$$

$U_{t(biph)}$: the uptake of the radiotracer according to the biphasic model,
T_{ef}: the effective half-time of the radiotracer in the target,
T_a: the half time of the influx of the radiotracer into the target,
F: a proportionality factor. It is also assumed that
$T_a < T_{ef}$.

Integration of the uptake functions according to both (simplified and biphasic) models allows to get the formulas for "time-integrated uptake" or "cumulated uptake". Thus, one gets:

$$\int U_{t(sim)} dt = -U_{mm} \frac{T_{ef}}{\ln(2) 2^{t/T_{ef}}} \text{ and hence}$$

$$\int_0^\infty U_{t(sim)} dt = U_{mm} \frac{T_{ef}}{\ln(2)},$$

and

$$\int U_{t(biph)} dt = F \frac{(T_a 2^{t/T_{ef}} - T_{ef} 2^{t/T_a})}{\ln(2) \cdot 2^{\frac{(T_a + T_{ef})t}{T_a T_{ef}}}} \text{ and hence}$$

$$\int_0^\infty U_{t(biph)} dt = F \frac{(T_{ef} - T_a)}{\ln(2)}$$

for the simplified and biphasic model, respectively. After division of the cumulated uptake according to the biphasic model by the cumulated uptake according to the simplified model, one receives the ratio, by which the cumulated activity in the biphasic model exceeds the cumulated activity in the simplified one:

$$C_f = \frac{F(T_{ef} - T_a)}{U_{mm} T_{ef}}.$$

This parameter is further referred to as correction factor, C_f.

The next issue one needs to address is to find the parameters of the equations for both models, particularly for the biphasic one, i.e., T_{ef}, T_a and F. The program "Kinetic modeling I" allows to determine the effective half time according to the earlier known procedure. Logarithmized uptake values are plotted on a chart against the time values, then a straight line is created with the method of least squares:

$$\log_{10} U_t = a \cdot t + b,$$

where a and b are the calculated parameters of the straight line. Optimally, the two points should lie far one from another and far after the peak of the curve. The slope a of the generated line is related to the T_{ef}:

$$T_{ef} = \frac{-\log_{10} 2}{a}.$$

An innovation of the program offers an additional possibility to successively approximate the T_a and F for the biphasic model; the mathematical details are discussed in the Appendix.

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The program "Kinetic modeling II" allows determining of all three parameters in a semi-automated manner by numerical analysis. Three measurement points are necessary for proper functioning of the program; optimally: the first — before the expected peak (shortly after the activity administration), the second one in a time close to the expected peak, and the third one well after the peak. The mathematical details are discussed in the Appendix.

Knowledge of the correction factor allows introducing suitable modifications to the Marinelli's formula and thus using the most common and the simplest existing algorithm for calculation of the therapeutic activity; there is no necessity to introduce a completely new formula:

$$A[MBq] = \frac{24.67 \cdot D[Gy] \cdot m[g]}{U_{mm}[\%] \cdot T_{ef}[d]} \cdot \left(\frac{181.9}{E_{mean}[keV]} \right) \cdot \left(\frac{1}{C_f} \right)$$, where:

A: the activity of a radionuclide required for a therapy,
D: the intended focal radiation dose,
m: the target mass,
U_{mm}: the measured maximum uptake of the radiopharmaceutical,
T_{ef}: the effective half time,
E_{mean}: the mean kinetic energy of the emitted particles per one radioactive disintegration (for I-131: 181.9 keV),
C_f: correction factor (this part of the formula is important, when the correction factor is different from one).

Results

Theoretical uptake-curves which fulfill the considered conditions of radiopharmaceutical behavior have been created. They served for examining of the possible values of the correction factor.

If the measured maximum uptake (U_{mm}) is equal to the peak (i.e., the test is performed exactly in the time of peak), the correction factor (C_f) increases along with the increasing ratio T_a/T_{ef}. The increase is more pronounced for low T_a/T_{ef}-ratios, then the trend slows down and reaches as much as e (~2.7183) for T_a equal to T_{ef}. For instance, if the T_a equals half of the T_{ef}, the C_f is 2.0; it indicates that the cumulated uptake is underestimated two-fold in the simplified model as compared to the biphasic one. If additionally U_{mm} is lower than the true peak, the cumulative error increases proportionally. The issue is illustrated in Figure 1.

Discussion

Because of its logistic advantages, application of the simplified model is the most popular approach to personalized dosimetry. In its simplest version, only two uptake tests are necessary: the first around the expected peak and the second some time thereafter.

Such approach, although very convenient, is prone to at least three sources of error:

1. Overestimation of the effective half time; this inaccuracy is particularly pronounced, when the first measured value is placed too early on the time-uptake curve. It may result in an overestimation of the cumulated uptake.
2. Underestimation of the maximum uptake, when the measured maximum value does not correspond to the true peak of the curve; it may result in an underestimation of the cumulated uptake.
3. Neglecting of the ascending branch of the time-uptake curve; it results in an underestimation of the cumulated uptake.

The effective half time could be theoretically better approached (but never perfectly calculated) by the simplified method with increasing number of the measurements; however, such a calculation would never be perfect. The fact is an implication of the mathematical algorithm itself. Using the biphasic function should theoretically give the effective half time, whose value is not biased in such a way. Separate performing of the calculations with both programs (i.e., "Kinetic modeling I" and "Kinetic modeling II") allows a direct comparison of the effective half times calculated by each of these models.

The program "Kinetic modeling II" tries to combine a low number of patient tests with a higher precision of the results. The first test should be performed preferably in a time point between the administration of the radiopharmaceutical and the peak; in most cases, it could take place even during the same visit of the patient as the administration. The second and third uptake value should be preferably measured near the expected peak and some time after the peak, respectively. Thus, the procedure of uptake tests would not be much more engaging than in the simplified model.

Both the programs give also additional information about the theoretically calculated peak, i.e., the time and the percentage of the maximum uptake of the radiotracer. This could be useful for some purposes, possibly also for a further optimization of the administration-measurement procedure.

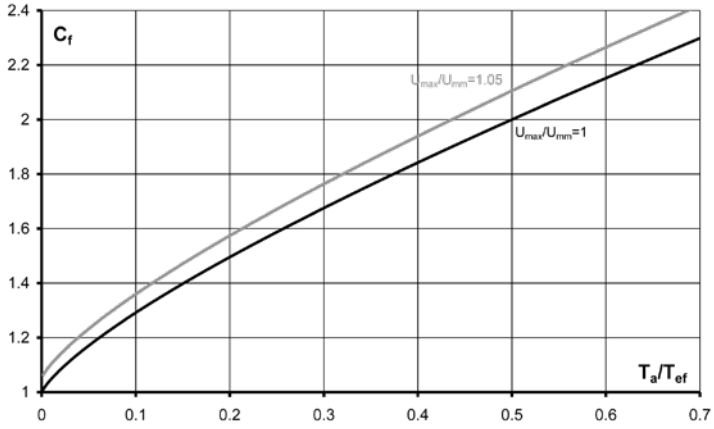

Figure 1. Correction factor (C_f, abscissa) as a function of the quotient of the half-time of the radiotracer influx and the effective half time (T_a/T_{ef}, ordinate). It is assumed that the measured maximum uptake equals the true peak of the curve (black line). For comparison, the grey line reflects the C_f in a case, if the measured maximum uptake is lower by a factor of 5% than the true one (for example: 28.5% instead of 30%)

The biphasic model comes from pure mathematical considerations. Actually, biologic processes differ from the ideal mathematical ones to some extent. The biphasic model could reflect the uptake of a radiotracer in a target organ, when some kinetic criteria are fulfilled (listed at the beginning of "Material and methods"). Radioiodine therapy of the thyroid disorders and palliative therapy of bone metastatic lesions after i.v. injection of radiopharmaceuticals are candidates which probably well approach to these criteria. Some types of receptor radionuclide therapy, despite frequently occurring saturation effects, also could be regarded as approaching the model to a satisfactory degree. A therapy after oral administration of a radiotracer could approach this model to a degree less than satisfactory.

Conclusion

The proposed model of calculation of the correction for the dosimetry seems to deliver the results in a relatively simple way. Its practical testing can be considered.

Appendix. Mathematical operations used in these programs

A. Kinetic modeling I

First, user-selected logarithmized uptake values are approached to a straight line by linear regression:

$$\log_{10} U_t = a \cdot t + b,$$

hence the effective half time is calculated (see the text for details).

For additional approximation of the T_a and F (biphasic model), an uptake test value (time and uptake) made chronologically before the maximum measured uptake is chosen (t_1 and U_1). A combined formula is constructed:

$$U_1 = \frac{10^{(a \cdot t_{last} + b)}}{(2^{-t_{last}/T_{ef}} - 2^{-t_{last}/T_a})}(2^{-t_1/T_{ef}} - 2^{-t_1/T_a}),$$

where t_{last} and U_{last} are uptake values of the (chronologically) last test. In the combined formula, the T_a-value is iteratively so modified that the obtained uptake-value gradually approximates the true (measured) one (U_1). The User may then optionally modify the values obtained by a trial and error method.

B. Kinetic modeling II

Three uptake tests are entered. Thus, one receives three pairs of uptake values (time and uptake): t_1, U_1, t_2, U_2, t_3, U_3. For each pair, an equation time-uptake (according to the biphasic model) is constructed; hence, one obtains a system of three equations with three unknowns (T_{ef}, T_a and F):

$$1.: U_1 = F(2^{-t_1/T_{ef}} - 2^{-t_1/T_a})$$
$$2.: U_2 = F(2^{-t_2/T_{ef}} - 2^{-t_2/T_a})$$
$$3.: U_3 = F(2^{-t_3/T_{ef}} - 2^{-t_3/T_a})$$

Since there are exponential equations, it is impossible to solve the system using a simple analytical method. An iterative method must be applied instead.

At the beginning, the second equation is solved for F. This F is substituted into the first equation forming a combined one:

$$U_1 = \frac{U_2}{(2^{-t_2/T_{ef}} - 2^{-t_2/T_a})}(2^{-t_1/T_{ef}} - 2^{-t_1/T_a}).$$

Then, a user-defined range of T_{ef}, in which the true T_{ef} is sought, is divided by 400; in this way, the T_{ef}-progression is set. From the upper limit of T_{ef}, the T_{ef}-progression is successively subtracted till the T_{ef} reaches the lower limit. Thus, the temporary T_{ef}-value is defined each time (i.e., $T_{ef(i)}$, where the i ranges from 1 to 400).

Then, for each $T_{ef(i)}$, the $T_{a(i)}$ value (within a range lower than $T_{ef(i)}$) solving the combined equation is iteratively sought; sometimes, it is possible to find the $T_{a(i)}$ only for some $T_{ef(i)}$. Thus, a series of till 400 pairs $T_{ef(i)}$ and $T_{a(i)}$ is obtained. Within this series, there is one pair, which approaches the sought solution.

Afterwards, all the equations in the system are solved for F, delivering till 400 sets of $F_{1(i)}$, $F_{2(i)}$ and $F_{3(i)}$:

$$1.: F_{1(i)} = \frac{U_1}{(2^{-t_1/T_{ef(i)}} - 2^{-t_1/T_{a(i)}})}$$

$$2.: F_{2(i)} = \frac{U_2}{(2^{-t_2/T_{ef(i)}} - 2^{-t_2/T_{a(i)}})}$$

$$3.: F_{3(i)} = \frac{U_3}{(2^{-t_3/T_{ef(i)}} - 2^{-t_3/T_{a(i)}})}$$

Thus, for each $T_{ef(i)}$ and $T_{a(i)}$ pair found, three F-values ($F_{1(i)}$, $F_{2(i)}$ and $F_{3(i)}$) are calculated. The sought solution (the set of values: F, T_{ef} and T_a) is this one, for which all F ($F_{1(i)}$, $F_{2(i)}$ and $F_{3(i)}$) are the same (ideally), or for which the differences are minimal. The expected error of T_{ef} arises from the T_{ef}-progression. By further narrowing of the user-defined T_{ef}-range, one is able to receive a set of solutions with a lower expected error.

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