



INTERNAL DOSIMETRY IN NUCLEAR MEDICINE

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ABSTRACT

This article reviews the current state of the art in the calculation of radiation doses for radiopharmaceuticals. Basics of dose calculations are briefly reviewed, and the sources of input data for the calculations are reviewed. Although dose calculations are needed for all kinds of radiopharmaceuticals, dose calculations in therapeutic applications are the most important for the patient; the status of dose calculations for most important therapeutic uses of radiopharmaceuticals is discussed, and the importance of performing patient-individualized dose calculations is emphasized

Keywords:

Internal Dosimetry, Dose Calculations, Nuclear Medicine

1. INTRODUCTION

Whenever patients are exposed to ionizing radiation, an estimation of radiation doses is an essential element of balancing the risks and benefits of the proposed examination. External sources of ionizing radiation in the healing arts include plain film x-rays, computed tomography (CT) examinations, positron emission tomography (PET), single photon emission tomography (SPECT), PET/CT, SPECT/CT and nuclear medicine studies. The calculation of radiation dose

estimates from internal sources of radioactivity have evolved over many decades, from the simple thyroid self-dose estimates of Marinelli and Quimby [1, 2] to three dimensional dose maps and dose-volume histograms for individual organs and tumors [3]. Methods and tools exist for the calculation of radiation dose to important tissues of the body, for dose and risk assessment, but sadly, a decades-old mentality pervades the nuclear medicine community that calculation of radiation doses and optimization of therapy for individual patients is unnecessary. Doses are calculated to permit the approval of new radiopharmaceuticals, but once approved, the compounds are administered to patients using a fixed activity (MBq) or activity per unit body weight (MBq/kg) approach, with few exceptions. For diagnostic radiopharmaceuticals, this is reasonable and safe; misadministrations occur, but doses to any individual organ are not likely to exceed 50 mSv, and effective doses are low, compared to many radiation exposures in medical imaging. In therapeutic applications, however, our goal is to maximize the radiation dose to malignant tissues while sparing as much as possible the dose to normal, healthy tissues. This can only be accomplished by characterizing the uptake and clearance of activity in the various tissues of the body, which requires serial imaging of patients and quantitative analysis of the results, an effort which nuclear medicine physicians are mostly loathe to perform. Thus, patients are generally receiving suboptimal therapy, compared to patients receiving external beam therapy for cancer, for whom, careful radiation therapy plans are made on a patient-specific basis every day. An exception is the monoclonal antibody Bexxar, for which at least 'whole body' doses (as a surrogate for red marrow doses) are calculated to estimate a patient-individualized activity administration; many in the European community are also demonstrating how patient-individualized dose calculations are necessary for managing renal toxicity for patients treated for neuroendocrine tumors, as will be discussed below. Regulatory agencies, however, are basically ignoring calls for equal use of dosimetry in the treatment of cancer patients with either external or internal sources of ionizing radiation; this issue needs to be addressed.

2. COMPONENTS OF THE CALCULATION

A ‘generic’ equation for the absorbed dose rate in an organ or tumor uniformly contaminated with radioactivity can be shown as:

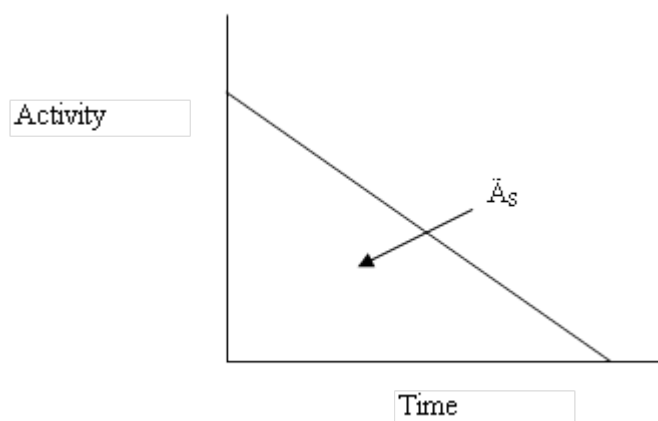
$$\dot{D}_T = \frac{k \sum_S A_S \sum_i n_i E_i \phi_i(T \leftarrow S)}{m_T} \quad (1)$$

- Where:
- \dot{D} = absorbed dose rate in target region T (rad/hr or Gy/sec)
 - A_S = activity (μCi or MBq) in source region S
 - n_i = number of radiations with energy E_i emitted per nuclear transition
 - E_i = energy for the i th radiation emitted by the nuclide (MeV)
 - $\phi_i(T \leftarrow S)$ = fraction of energy emitted that is absorbed in the target region T originating in source region S
 - m_T = mass of target region T (g or kg)
 - k = proportionality constant (rad-g/ μCi -hr-MeV or Gy-kg/MBq-sec-MeV)

The proportionality constant must be properly calculated and applied for the unit system of choice. One may also apply radiation weighting factors (once called “quality factors”) to the result of this equation to calculate the equivalent dose rate. For many years, this was not an important issue, when nuclear medicine involved only beta and gamma emitters; now the introduction of some alpha emitters makes this an important consideration. The value recommended by the International Commission on Radiological Protection (ICRP) for the radiation weighting factor for alpha emitters is 20, but this is believed to be too high for use in calculating doses from nuclear medicine therapy agents [4].

We are usually interested in an estimate of total absorbed dose from an administration, rather than an initial dose rate. In equation 1 the quantity activity (nuclear transitions per unit time) causes the outcome of the equation to have time dependence. To calculate cumulative dose, the time integral of the dose equation must be calculated. In most cases, the only term which has time dependence is activity, so the integral is just the product of all of the factors in the above equation except for activity by the integral of the time-activity curve.

Figure 1: Activity x time



Regardless of the shape of the time-activity curve, its integral, however obtained, *will have units of the number of total nuclear transitions* (activity, which is transitions per unit time, multiplied by time). Therefore, the equation for cumulative dose would be shown as:

$$D_T = \frac{k \sum_S \tilde{A}_S \sum_i n_i E_i \phi_i(T \leftarrow S)}{m_T} \quad (2)$$

Where: D_T is the absorbed dose in target region T (rad or Gy) and \tilde{A}_S is the cumulated activity in source region S ($\mu\text{Ci-hr}$ or MBq-sec).

2.1. Input Data

Some consider equation 2 to consist of two general parts, (1) a 'biological' component, involving \tilde{A} , and (2) a 'physical' part, involving all of the other terms. Indeed part (2) is often characterized by 'Dose Factors' for specified source and target regions for a particular radionuclide [5]. These Dose Factors are typically tabulated for retrieval, and/or integrated in software programs to facilitate dose calculations, e.g. OLINDA/EXM [6]. The values for the 'absorbed fractions' come from modeling assumptions or Monte Carlo calculations in anthropomorphic 'phantoms' (mathematical models of the human body). These phantoms for many years were based on geometrical constructs to represent the body and its organs [7, 8], but more recently have been replaced with more realistic models based on medical image data [9]. Thus calculation of radiation dose for a given radiopharmaceutical usually involves acquiring data to calculate the \tilde{A}_S values, which involve the biological distribution and retention of activity in the body. Data are obtained in animals or in human volunteers or patients. In the former case, the animals are given the radiopharmaceutical and may be sacrificed, and individual organs harvested and assayed for their radioactivity content, or they may be imaged using small animal PET or SPECT imaging systems. Human data may be gathered in anterior/posterior projection mode in SPECT systems, or using PET or SPECT imaging systems. Animal data need to be extrapolated for use in calculating dose estimates for humans [10]. For either human or animal data, gathering the correct number of data points at appropriate time intervals is essential to a successful analysis. Most kinetic data are characterized by one or more exponential terms. To characterize any one phase of uptake or clearance with an exponential function, one needs a minimum of two data points [11]; for example, if an organ has an early, fast clearance phase and a later, slow clearance phase, a minimum of four data points are needed, with two during the early phase and two during the late phase. Careful design of a study to collect biokinetic data, with these considerations, is essential to obtain the necessary data.

2.2. Diagnostic Radiopharmaceuticals

There are many diverse radiopharmaceuticals employed in diagnostic imaging of nuclear medicine patients. The number and type of agents is constantly changing, so it is a challenge to maintain organized lists of the radiation dose estimates for all agents that may be in use. Dose estimates for diagnostic radiopharmaceuticals are not generally needed on a daily basis. When a new radiopharmaceutical is being considered for approval, part of the approval process involves characterization of the dosimetry for the agent, ultimately being based on data gathered in humans. These dose estimates are included in the standard information distributed with the agent (often referred to as the 'package insert'). Consideration of radiation dose is not an important issue in routine administrations for diagnostic imaging; the doses are generally low, and the main concern is to give the best amount of activity that will produce a good quality image. Radiation dose becomes a concern with a radiopharmaceutical misadministration occurs, when an administration occurs accidentally or intentionally to a pregnant woman, and in a few other limited circumstances. Dose estimate tables in 'package inserts' are not always the most reliable or up to date; compendia published by an ICRP Task Group on Radiopharmaceutical Dosimetry are generally considered to be the most reliable and up to date. They are currently contained in three publications that have been produced since 1983 [12].

For diagnostic, but not therapeutic, applications of radiopharmaceuticals, The ICRP also defines a quantity effective dose (E); certain organs or organ systems were assigned dimensionless 'tissue weighting factors', which are assumed to relate to their differing radiosensitivity for expressing fatal cancers or genetic defects. Summing the products of each organs actual equivalent dose and the assigned tissue weighting factors gives a single number, which is the 'effective dose' The most recent weighting factors (Table 1) were given in ICRP Publication 103 [13]. Effective dose values for a number of diagnostic radiopharmaceuticals given in these ICRP publications are shown in Table 2.

Table 1. Weighting Factors Recommended by the ICRP for Calculation of Effective Dose [13]

Organ	Tissue Weighting Factor
Gonads	0.08
Red Marrow	0.12
Colon	0.12
Lungs	0.12
Stomach	0.12
Bladder	0.04
Breasts	0.12
Liver	0.04
Esophagus	0.04
Thyroid	0.04
Skin	0.01
Bone Surfaces	0.01
Brain	0.01
Salivary glands	0.01
Remainder	0.12

2.3. Therapeutic Radiopharmaceuticals

Standardized dose estimates may be given for therapeutic radiopharmaceuticals (note the values in Table 2 for $^{131}\text{I-NaI}$, which may be given in tracer or therapeutic amounts, and for $^{153}\text{Sm-EDTMP}$), for general interest. When therapeutic radiopharmaceuticals are used, however, it is more appropriate to gather biokinetic data for each individual subject, using a diagnostic level of the therapeutic agent or surrogate (e.g. use of $^{111}\text{In-Zevalin}$ to determine the probable biodistribution of $^{90}\text{Y-Zevalin}$), and performing a predictive dosimetry study to determine the maximum amount of the therapeutic agent that can be given while not exceeding undesirable radiation doses to healthy tissues. Such optimization of therapy is performed for every patient receiving external beam therapy for cancer, but unfortunately, is not often done to plan nuclear medicine therapy. Typically, standard amounts of activity or activity per unit body weight of the subjects is given, with no pre- or post-therapy evaluation of the radiation doses received.

Table 2. Standardized Dose Estimates for Selected Radiopharmaceuticals [12].

Radiopharmaceutical	Effective Dose (mSv/MBq)
O-15 Water	9.30E-04
F-18 Fluoro-deoxyglucose	1.90E-02
Ga-67 Citrate	1.00E-01
I-123 Hippuran	1.20E-02
I-123 Sodium Iodide (25% Uptake)	1.70E-01
I-125 Albumin	2.20E-01
I-131 Hippuran	5.20E-02
I-131 MIBG	1.40E-01
I-131 Sodium Iodide (25% Uptake)	1.70E+01
In-111 DTPA - normal renal function	2.10E-02
In-111 Pentetreotide also known as Octreoscan	5.40E-02
Sm-153 Lexidronam also know as Quadramet	1.97E-01
Tc-99m Disofenin also know as HIDA (iminodiacetic acid)	1.70E-02
Tc-99m Exametazime also known as Ceretec and HMPAO	9.30E-03
Tc-99m Macro aggregated albumin (MAA)	1.10E-02
Tc-99m Medronate also know as Tc-99m Methyenedi-phosphonate (MDP)	5.70E-03
Tc-99m Mertiatide also know as MAG3	7.00E-03
Tc-99m Neurolite also known as ECD and Bicisate	1.10E-02
Tc-99m Pentetate also know as Tc-99m DTPA	4.90E-03
Tc-99m Pyrophosphate	5.70E-03
Tc-99m Red Blood Cells	7.00E-03
Tc-99 Sestamibi also know as Cardiolite (rest)	9.00E-03
Tc-99 Sestamibi also know as Cardiolite (stress)	7.90E-03
Tc-99m Sodium Pertechnetate	1.30E-02
Tc-99m Sulfur Colloid	9.40E-03
Tc-99m Tetrofosmin also know as Myoview (rest)	7.60E-03
Tc-99m Tetrofosmin also know as Myoview (stress)	7.00E-03
Tl-201 Thallous Chloride	1.40E-01
Xe-133 Xenon Gas (rebreathing for 5 minutes)	7.30E-04

While it is known that thyroid uptake of radioiodine varies considerably from patient to patient [14], that the rate of hypothyroidism resulting from the treatment of Graves disease with

radioiodine is correlated with the absorbed dose [15], and that first treatment efficacy is significantly enhanced with pretherapy planning to achieve a prescribed radiation dose [16], the debate continues over dose-based versus fixed-activity-based approaches to treatment of hyperthyroidism [17]. Treatment of thyroid cancer with ^{131}I NaI has been a common therapeutic use of radiopharmaceuticals for many decades. Treatment regimens are generally based on a fixed-activity approach, although there have been exceptions [18, 19]. ^{131}I metaiodobenzylguanidine (mIBG) has been used for more than 20 years for the treatment of adult and paediatric neuroendocrine tumours, including pheochromocytoma, paraganglioma and neuroblastoma. Standard protocols involve administrations of around 7 GBq to values over 30 GBq (for adults) [20, 21, 22]. In studies in which dosimetry has been evaluated, it has been seen that absorbed doses to tumor, marrow and other organs vary considerably when fixed administered activities are administered [23, 24].

Two products, 'Bexxar' (^{131}I -labeled tositumomab) and 'Zevalin' (^{90}Y -labeled Ibritumomab tiuxetan) are approved by the US FDA for treatment of relapsed or refractory B-cell non-Hodgkins lymphoma. Both agents employ the anti-CD20 antibody. Bexxar is administered after a tracer amount of the agent is given and a simple dosimetric analysis is performed that targets a whole-body dose of 0.75 Gy [25], whereas for Zevalin, dosimetry was not recommended during the approval process [26], and this agent is administered on an activity per unit body weight basis.

Skeletal Targeted Therapy (STR), mostly for palliation of pain involving bone metastases, is carried out with a number of agents, including ^{89}Sr -chloride, ^{153}Sm -EDTMP, (ethylenediamine tetramethylene phosphoric acid), ^{186}Re and ^{188}Re -HEDP (hydroxyethylene diphosphonate), ^{177}Lu -177-MDP (methylene diphosphonate) and EDTMP. The number of metastases is usually high, and dosimetry is generally not performed for use of these agents. As noted above, the introduction of alpha emitters in radiopharmaceutical therapy has caused a re-evaluation of the use of appropriate radiation weighting factors to be used in internal emitter therapy. ^{223}Ra chloride has a natural affinity for metabolically active bone. It decays by the emission of 4 α -particles via progeny isotopes to stable ^{207}Pb , with a total decay energy is 28 MeV. Hindorf et al. [27] evaluated the biodistribution and dosimetry ^{223}Ra -chloride (Alpharadin) in patients with osteoblastic skeletal metastases secondary to hormone refractory prostate cancer.

They found that the self absorbed dose to the kidneys was less than 0.2 Gy per injection for all patients and that the calculated absorbed doses to normal tissues following intravenous injections of ^{223}Ra chloride injections of 100 kBq/kg were very low and are unlikely to be a limiting factor in this patient population. A comprehensive evaluation of the dosimetry of ^{223}Ra chloride was recently published by Lassmann and Nosske (4). Other alpha emitters that have been or are being evaluated for radiopharmaceutical therapy (not necessarily for STR) include ^{211}At , ^{212}Bi , ^{213}Bi , and ^{225}Ac .

The use of radiolabeled peptides for treatment of neuroendocrine tumours has been under active evaluation, using somatostatin analogues such as DOTA-DPhe(1)-Tyr(3)-octreotide (DOTATOC). Barone et al. [28] estimated kidney doses from administrations of 8 – 23 GBq of ^{90}Y DOTATOC and found a strong correlation between radiation dose (expressed as 'biologically effective dose', a quantity that takes into account the rate at which dose is delivered and tissue radiosensitivity parameters and repair kinetics) and measured values of creatinine clearance in individual patients. Hindorf et al. [29] found that interpatient variability to whole body, kidneys, and tumor was quite significant, but larger than the intrapatient variability, suggesting that data obtained during a subject's first therapy may be used to guide future therapies. Forrer et al. [30] compared the biodistribution and dosimetry of ^{111}In -DOTATOC and ^{111}In -DOTATATE in five patients with known metastatic neuroendocrine tumors, with multiple administrations of about 200 MBq. Their analyses showed small differences between the radiopeptides, but a significantly higher mean absorbed dose to the liver was found for ^{111}In -DOTATATE, and a favorable tumour-to-kidney ratio ($P=0.065$) was calculated for ^{111}In -DOTATOC. A high interpatient absorbed tumor dose variability was found, which is not unexpected as receptor densities vary markedly among patients and tumors. Bodei et al. [31] evaluated long term renal toxicity after peptide radiotherapy with ^{90}Y -DOTATOC and ^{177}Lu -DOTATATE in 23 and 5 patients, respectively. Their results showed the high importance of the importance of clinical screening and individualized dosimetry. For patients who enter therapy with renal toxicity-associated risk factors, patients should not receive a BED higher than 28 Gy, and noted that fractionation of activity in multiple cycles is also helpful in managing renal toxicity. Barone et al. [32] evaluated kidney toxicity in the administration of ^{90}Y -DOTATOC in nine male and nine female subjects. Estimation of renal dose to observe and control possible

toxicity were significantly influenced by distribution of the radionuclide, size of the target organ (i.e., the kidney), the absorbed dose rate and fractionation.

3. CONCLUSIONS

The science of internal dosimetry in nuclear medicine is in a very mature state. Many resources for facilitating dose calculations are available, and internet and software tools have allowed many users to perform dosimetry calculations, once appropriate biokinetic data are gathered in animal or human experiments. A considerable number of diagnostic and therapeutic radiopharmaceuticals are widely available; the number and type of agents is frequently changing, so new dosimetry calculations are always being needed. A most interesting recent development is the appearance of alpha emitters for use in radiopharmaceutical therapy, and many promising new therapeutic agents are being tested and introduced to the worldwide market.

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