CHALLENGES IN NUCLEAR MEDICINE RADIATION DOSIMETRY

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Abstract

In spite of considerable progress, much remains to be done in the estimation of absorbed doses to organs and tissues in the body and in the prediction of biological effects from radiopharmaceuticals.

In *patients* undergoing *diagnostic procedures*, the biokinetics of the radionuclide has to be determined for a number of representative patients. When radiopharmaceuticals are used for *therapy*, it is essential to determine the *individual* kinetics to be able to calculate the absorbed doses to critical normal organs/tissues and to the target volume(s) with high accuracy.

There is still a lack of quantitative determinations of the organ/tissue contents of radionuclides and their variation by time. Planar gamma camera imaging is the main method for such studies. To get acceptable statistics in SPECT-images, very long acquisition times are needed. New more sensitive SPECT cameras may help. In a similar way as SPECT/CT, PET/CT is used for patient specific 3D image based internal dosimetry using the patient´s own anatomy and spatial distribution of activity as a function of time.

The transition from stylized reference phantoms to voxel phantoms, representing a broad population of patients will lead to improved dose estimates. The real challenge – at least for the therapeutic situation - is to describe the individual patient by imaging (CT, MRI) and then make individual calculations.

There is an increasing interest to combine targeting substances (antibodies, peptides, etc.) with alpha particle or Auger electron emitters. It is a challenge to develop a dosimetry that predicts the biological effects of these short-range particle emitters.

For *staff* exposure, it is important to take into account the increasing use of PET agents for imaging and to investigate the occupational exposure from a number of radiopharmaceuticals for therapy and how these affect the effective dose and the dose to fingers, hands and the lens of the eye.

Key-words: Dosimetry, nuclear medicine, radiopharmaceuticals, biokinetics

1. Introduction

In spite of considerable progress, many advances remain to be achieved in the estimation of organ absorbed doses and in the prediction of biological effects from radiopharmaceuticals.

In *patients* undergoing diagnostic procedures, the biokinetics of the radionuclide has to be determined for a limited number of representative, often normal, patients. In spite of the limited need, there is still a lack of basic biokinetic data for many of the substances used today. When radiopharmaceuticals are used for therapy, it is essential to determine the *individual* kinetics to be able to calculate the absorbed doses to critical normal organs/tissues and to the target volume with high accuracy.

For *staff* exposure, it is important to take into account the increasing use of PET agents for imaging. It is also important to investigate the occupational exposure from a number of old and new radiopharmaceuticals for therapy and how these affects both the effective dose and the dose to fingers, hands and the lens of the eye.

The aim of this paper is to draw attention to some of the remaining problems in the radiation dosimetry for radiopharmaceuticals with special reference to patient dosimetry and the dosimetry for radiopharmaceutical therapy.

2. Activity content in organs and tissues and its time variation

In patients undergoing diagnostic procedures, the biokinetics of the radionuclide has to be determined for a limited number of representative patients. In most cases however, published biokinetic data are scarce, especially with regard to quantitative measurements. The main interest for the clinician is the initial distribution and metabolism of the test substance, whereas for dosimetry, long-term retention is the most important parameter. As most published data relates to normal patients, there is a need to study variations in biokinetics due to various degrees of illness, age, etc. When radiopharmaceuticals are used for therapy, it is essential to determine the *individual* kinetics to be able to calculate the absorbed doses to critical normal organs/tissues with high accuracy.

For pharmaceuticals based on radionuclides emitting single photons, the planar conjugate view method has been the way to investigate the activity content in organs and tissues and its time variation. The accuracy of this technique is limited by the lack of knowledge of the source-organ thickness and the difficulties to correct for organ overlap. SPECT is a way to solve some of these problems, but to get acceptable statistics in the images very long acquisition times are needed. In SPECT/CT, the CT images are used, not only for identification of anatomical details but also as a basis for attenuation correction. In a similar way, PET/CT is used for patient specific 3D image based internal dosimetry using the patient´s own anatomy and spatial distribution of activity as a function of time.

3. Descriptive biokinetic models versus detailed compartment models

The ultimate goal is to construct detailed compartment models for each substance and situation. This is often not possible due to lack of data and understanding of the detailed behavior of the substance in the body. Therefore, for dosimetry, the biokinetic information is usually presented in terms of fractional uptakes and biological half-times, i.e. first-order kinetics are assumed for the different organs and tissues. Thus exponential functions are normally used to describe the retention function even if a compartment model in many cases would be physiologically more correct. In addition to the radionuclide specific models, a number of general models describing the kinetics of the excretion routes are used. Many nuclear medicine products are excreted fast into the urine. In those cases the assumption about the bladder voiding period may be a critical one. ICRP (2008) assumes a bladder voiding interval of 3.5 hours for adults, but the variations are considerable and influence the absorbed dose to the bladder wall and a number of nearby organs.

4. Humanlike phantoms for absorbed dose calculations

The transition from stylized reference phantoms to voxel phantoms (e.g. ICRP 2009) may lead to improved dose estimates. New phantoms, e.g. the non-uniform rational B-spline (NURBS) (Choonsik et al. 2007) can represent a broader population of nuclear medicine patients, but still the dose estimates are valid only for the phantom and not for the individual patient. Therefore, the real challenge – at least for the therapeutic situation - is to describe the patient by imaging (CT, MRI) and then make individual calculations. To check the results of the calculations, *in vivo* measurements when using photon and beta particle emitting radionuclides have been done using small TLDs, OSL dosemeters or diodes. New possibilities may be opened using quantum dot (QD) dosemeters, with physical dimensions of a few nm (Stodilka et al. 2009).

5. Diagnostic nuclear medicine

Biokinetic models designed for the purpose of dose calculations for radiopharmaceuticals are found in a number of publications also together with dose estimates. The ICRP has evaluated published data related to radiopharmaceuticals in current use during over 40 years and initiated a number of additional studies. Most of the substances used today are covered in the Publications 106 (ICRP,

2008), 80 (ICRP 1998), and 53 (ICRP, 1987). These data refers with some exceptions to normal patients. For patients with various degrees of illnesses, there is still a need to estimate biokinetics and organ/tissue doses. Further studies of age-dependent biokinetics and dosimetry are also necessary.

6. Therapeutic nuclear medicine

When radiopharmaceuticals are used for therapy, it is essential to determine the *individual* kinetics to be able to calculate the absorbed doses to critical normal organs/tissues with high accuracy. The goal of absorbed dose-guided radiation therapy is to deliver the highest possible absorbed dose to the tumour, while managing the dose to normal tissues. Due to large individual variations, models designed to be representative for the general population can *not* be used for individual dose estimations. In connection with therapy, the absorbed dose to the critical normal organs and to the tumour volume has to be estimated based on individually assessed parameters. The therapeutic effect of the radiopharmaceutical therapy can be assumed to depend on the absorbed dose to the target volume, just like in external radiation therapy. Comparing clinical observations without knowing the absorbed dose is not meaningful. If the outcome of a group of patients is to be studied, the result is of limited interest unless the absorbed dose is known for each individual patient. For the individual patient it is also important not to be exposed to unnecessary radiation, but still to get the absorbed dose needed for the treatment.

Iodide

Radionuclide treatment of hyperthyroidism and thyroid cancer with $Na^{131}I$ is the oldest radiopharmaceutical therapy method currently used and is still totally dominating with respect to number of treated patients. Fixed-activity treatments have generally been used. Recent studies have shown that an activity based criterion results in too much activity to most patients (Jönsson and Mattsson, 2004) and recent studies have shown that a dose based criterion gives a better outcome of the treatment (Kobe et al. 2008, Flux et al. 2010, Stabin et al. 2011).

Biokinetic models for iodide have been published by ICRP to be used both for occupational and environmental exposure (ICRP 1989) and for nuclear medicine investigations (ICRP 1987). Other authors have also published models designed for different purposes. For dose estimation in nuclear medicine, the MIRD model by Berman et al. (1972) is an important contribution that has been widely used. ICRP (2001) has also published a model for iodine in the pregnant woman and the foetus.
In most models intended for nuclear medicine patients the uptakes in stomach wall and salivary glands are included. This is often not the case for the models intended for dosimetry of occupationally or environmentally exposed persons. On the other hand, models for patient dosimetry may be simplified in such a way that they are unsuitable for dosimetry of the long-lived isotope ^{129}I. Due to this discrepancy a more general compartment model, which can be used for different purposes, has been developed (Johansson et al. 2003, 2004). A more elaborated physiological systems model for iodine has recently been proposed for use in radiation protection (Leggett 2010) and will be the base for the future work in ICRP.
For treatment of thyreotoxicosis, there is still no consensus on an optimal protocol. Some patients are treated to obtain a normal thyroid function. Others are treated to obtain a function somewhat under the normal and some patients are made totally hypothyroid. The situation gets more complicated by the fact that the thyroid function gradually decreases with time after treatment and that hypofunction easily can be treated with thyroid hormone substitution.
Even without consensus regarding the desirable effect of the treatment, it is important both for the individual patient and for the understanding of the radioiodine therapy and its future optimisation that the absorbed dose to the thyroid is quantified (Jönsson 2003).

Polycytemia

Polycytemia is a chronic disease characterized by an increase in red blood cell mass. Many new agents for haematological proliferations have been introduced successfully. Today there remains a distinct subgroup of elderly patients with *polycythaemia vera* and essential thrombocythaemia for whom ^{32}P-orthophosphate is the most optimal treatment option. The phosphate ion is a bone-seeker this makes

the radionuclide suitable for radiotherapy of the bone marrow. The radiopharmaceutical is used to suppress hyperproliferative cell lines rather than to eradicate them. ^{32}P is, however, also distributed into proliferating and protein-synthesizing cells, resulting in an enhanced absorbed dose, besides in bone tissue, also in liver and spleen (Thomas 2002). Usually the substance is administered orally, but may also be given intravenously. The activity is generally given as a fixed activity per unit body surface alternatively a fixed activity per unit body weight (Tennvall et al. 2007).

Bone palliation

Bone pain arising from skeletal metastases from prostate or breast tumours may be treated with radiation from bone-seeking substances. Those are preferentially taken up in the metastases since the proliferation rate is higher here. Usually substances used for this purpose are pure beta-emitters, such as ^{89}Sr-chloride, or they may emit a minor amount of gamma radiation, such as ^{153}Sm-EDTMP (ethylene diamine tetramethylene phosphonate), which also allows visualizing the distribution of the substance using an ordinary gamma camera. Another beta emitting substance that has been used for bone palliation is ^{186}Re-EHDP (hydroxyethylidine diphosphonate). Alpha emitters may also be advantageous, due to the short range and high energy of the alpha-particles, a bone seeking substance of special interest is ^{223}Ra-chloride. The treatment is merely palliative, and the absorbed dose that may be obtained in the tumour tissues is limited by the dose to the red marrow. A more careful doseplanning than has been done up to now is a prerequisite for the ongoing work on absorbed dose escalation (also using a mixture of short- and long-lived radionuclides) and the development of integrated therapies, combining chemotherapy or biphosphonate therapy with radiopharmaceutical therapy or combining external and radiopharmaceutical therapy.

Monoclonal antibodies and peptide receptor specific substances

By labeling tumour specific monoclonal antibodies with radionuclides a potential tool for a treatment, and hopefully an eradication of micro metastases and disseminated tumours, is obtained. Such substances have been subject for research for a long period, and presently two commercially available labeled antibodies are ibritumomab tiuxetan labeled with ^{90}Y (Zevalin®) and tositumomab labeled with ^{131}I (Bexxar®) for the treatment of non-Hodgkins lymphoma. The antibody binds to the CD20 antigen found on the surface of normal and malignant B cells, allowing radiation from the attached radionuclide to kill them and some nearby cells. In addition, the antibody itself may trigger cell death via antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis. Together, these actions eliminate B cells from the body, allowing a new population of healthy B cells to develop from lymphoid stem cells. As an example, the ibritumomab regimen takes 7–9 days, with two administrations of ibritumomab. The first uses ^{111}In- ibritumomab for imaging. A scan is done to assess biodistribution of the drug. This test activity is used to determine that no excess amounts go to the marrow, liver, etc. in this particular patient. Then ^{90}Y- ibritumomab is administered by i.v. infusion as the actual treatment.

For clinical research, various other antibodies are also labeled with a number of radionuclides emitting beta-radiation, ^{90}Y, ^{131}I, ^{177}Lu etc., and also alpha emitters, such as ^{211}At, which show advantageous properties, since they will deliver a highly localized radiation dose to micro metastases. Often today in clinical routine the dosage of the radioisotope in these cases are based on clinical studies of therapeutic effect and effect on normal tissues, like red bone marrow or kidneys. As a result of these studies a fixed activity per body weight has been established, that spares normal tissues from acute effects of the irradiation, but still has a therapeutic effect on the tumour. This is a simple but suboptimized way of treatment. In reality since a large margin is needed to the threshold for severe damage of the critical organ, the tumour dose may be too low to reach curative effect. An accurate dosimetry will therefore increase the probability for a successful treatment.

Neuroendocrine tumours

Neuroendocrine tumours may be treated with ^{131}I-mIBG or somatostatin receptors labeled with ^{90}Y or ^{177}Lu. Treatment with ^{177}Lu-octreotate is a relatively new modality, which has increased significantly in frequency during the last years. For these treatments the kidneys are critical organs. Therefore good kidney dosimetry is necessary. By using the absorbed dose to the kidneys as a limiting factor,

treatment with ^{177}Lu-octreotate can be individualized, e.g., overtreatment can be avoided and patients with the potential to receive additional treatment can be identified. Further studies are needed to define tolerance doses to the kidneys so that treatment can be optimized. (Garkavij et al. 2010, Swärd et al. 2010)

Treatment of liver tumours with microspheres
Selective internal radiation treatment (SIRT) is a treatment modality that is rapidly growing (Ahmadzadehfar et al. 2010). Microspheres labeled with ^{90}Y are injected into the intrahepatic artery. The administered activity is calculated from planned dosimetry is based on body surface (calculated from length and weight) and specific risk factors based on quantitative determinations of the tumour and liver volumes. The planned dose in the liver is 4 Gy to normal liver tissues and 4 times more is expected to the tumours, but without individual dosimetry, the resulting doses can vary very much (at least a factor of four. A methodology for a more accurate dosimetry in this case has been described by Gulec et al. (2010).

Tab. 1 Typical activity and absorbed dose per administration for some common therapy agents (excluding ^{131}I-iodide) (Nosske et al. 2012)

Substance	**Typical adm. activity (MBq)**	**Tumor dose Gy**	**Critical organ 1 Gy**	**Critical organ 2 Gy**
^{32}P- phosphate	185		Red marrow: 2.0	Bone surfaces: 2.0
^{89}Sr - chloride	150		Bone surfaces: 2.6	Red marrow: 1.7
^{153}Sm- EDTMP	2500		Bone surfaces: 17	Red marrow: 3.8
^{90}Y-Zevalin®	1000		Kidneys: 2.4	Red marrow: 2.7
^{131}I-Bexxar®	3000		Thyroid: 8.1	Kidneys: 5.9
^{177}Lu - octreotate	7400	200	Kidneys: 23	

Non-uniform distribution of activity in an organ or tissue
Data on suborgan activity distributions is especially important in radionuclide therapy as “cold spots,” or regions receiving inadequate absorbed dose, can lead to reduced tumor control probabilities and failure to cure or control disease. In such cases, the evaluation of the absorbed doses to tissue regions with submillimeter dimensions ranging up to dimensions of only a few centimeters is of interest.

Biologically effective dose (BED)
Uptake nonuniformity and associated absorbed dose non-uniformity may significantly affect the outcome. Another factor is that the time of tumor volume changes is comparable to the time of maximal uptake and radiopharmaceutical effective half-time, affecting the dose estimates because of volume changes during dose delivery. The efficacy of targeted radionuclide therapy is thus dependent on the uniformity of the radionuclide uptake distribution, volume changes during treatment and also on radiosensitivity of the tissues. The biologically effective dose (BED) might be a relevant quantity in terms of establishing response or toxicity relationships (Prideaux 2007). It also normalizes differing dose rates of multiple modalities so that various treatment modalities can be combined.

7. Challenges related to exposure of staff

For *staff* exposure, it is important to take into account the increasing use of PET agents for imaging and to investigate the occupational exposure from a number of radiopharmaceuticals for therapy and

how these affects both the effective dose and the dose to fingers, hands and the lens of the eye (ICRP, 2008, Carnicer et al. 2011, Kopec et al. 2011).

8. Summary and conclusions

There is continuously a need to collect biokinetic data from patients/volunteers related to the clinically used radiopharmaceuticals. When radiopharmaceuticals are used for therapy, it is essential to determine the *individual* kinetics to be able to calculate the absorbed doses to critical normal organs/tissues with high accuracy. In recent years, there has been an increasing interest in combining biologically specific targeting agents (antibodies, peptides, etc.) with short-range alpha particle or Auger electron emitters. It is a challenge to develop a dosimetry that predicts the biological effects of these particle emitters.
We don´t fully know what scale of dosimetry is needed to understand and predict radiation effects; mean absorbed doses to whole organs, sub organ regions, voxel regions, single cells. The current research to use radiobiological modeling to convert the temporal and spatial distribution of absorbed dose to a biologically effective dose (BED) for tumour tissue and for normal tissues might be a way forward.

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