Nonuniform Absorbed Dose Distribution in the Kidney: The Influence of Organ Architecture

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ABSTRACT

The development of novel, systemically administered radionuclide therapies (such as radioimmunotherapy) relies on the ability to predict dose-limiting toxicity to normal tissue. Where the kidney is the principal route of excretion of the radionuclide preparation and/or breakdown of products, nephrotoxicity may be the dose-limiting factor. Until recently, conventional (MIRD) dosimetry assumed the distribution in the kidney to be uniform. A new MIRD phantom of the kidney models it as a set of uniform suborgans. In the work described here, the assumption of uniformity of distribution and of heterogeneity of dose rate (and, thus, absorbed dose) was tested in the mouse model. In this paper, we examine the nonuniformity of distribution and the subsequent dose rate for 4 antibody preparations (IgG (150 kD), F(ab')2 (100 kD), Fab (50 kD) and sFv (27 kD)) labeled with 4 radionuclides (125I, 131I, 186Re, and 90Y) of interest in radioimmunotherapy (RIT). The kidney was considered as a whole and as two suborgans (cortex and medulla), and the nonuniformity of the dose-rate distribution was measured by a correlation of modeled dose-rate distribution with the dose-rate distribution obtained for an equivalent uniform radionuclide distribution. The heterogeneity of distribution, the inter- and intra-suborgan, was seen to increase as the molecular weight of the antibodies decreased. The assumption of uniform activity distribution for the whole kidney gives a poor estimation of the distribution of the dose rate. In the cortex, the longer-range β emitters smooth out the effect of heterogeneous distribution and, in mice, an assumption of uniform cortex self-dose distribution may be sufficient for simple calculations. It is unclear how much this smoothing would be relevant in the human kidney.

Key words: radionuclide dosimetry, kidney, antibody, radioimmunotherapy

INTRODUCTION

In systemically administered radionuclide therapy, the estimation of a radiation-absorbed dose is needed for two functions: the absorbed dose to the target tissue (generally, a tumor) is required to estimate the probability of a cure; the absorbed dose to normal (nontarget) tissue is required to estimate the rate of complications. In this paper, we examine the problems that can arise in the second case, where the organ of interest is the kidney. The interest in the absorbed dose to the kidney arises in systemically administered radionuclide therapy, as normal-tissue dosimetry is often used to determine the maximum safe administered activity; one frequently proposed method of achieving a high therapeutic ratio is the use of rapidly cleared agents. Where the route of clearance is by way of the urine, the absorbed dose to the kidney may be the dose-limiting factor, especially when autologous stem cells are used to protect against the radiation-absorbed dose to bone marrow.
This paper is concerned with the delivery of radionuclides by antitumor antibodies (radioimmunotherapy (RIT)). In this therapy, the bone marrow–absorbed dose is generally the dose-limiting factor. This may not be the case where autologous bone marrow rescue is feasible or with some rapidly cleared antibody preparations; the kidney-absorbed dose is likely to be dose limiting for patients undergoing such treatments.

Until the publication of MIRD 19,1 each kidney was taken to be a single region (source and target); MIRD 19 has improved this situation by considering the kidney as a set of 4 “suborgan” components. In this paper, we examine the nonuniformity of the distribution and subsequent dose rate for 4 antibody preparations (IgG, F(ab)\(_2\), Fab, and sFv), labeled with 4 radionuclides (\(^{125}\)I, \(^{131}\)I, \(^{166}\)Re, and \(^{90}\)Y) of interest in RIT.

Requirements for Meaningful Dosimetry

In general, within the MIRD schema, the absorbed dose is calculated from the residence time (\(t\)), which is the time integral of the time-activity curve (the “cumulated activity”) normalized for administered activity:

\[ \tau = \frac{\int A(t) dt}{A_0}. \]

The absorbed dose to a region \(k\) is then calculated as the sum of the absorbed dose to region \(k\) from activity deposited in all regions \(h\):

\[ D_k = \sum_h \tau_h S_{kh}. \]

where \(A(t)\) is the time-activity curve in the organ of interest, \(A_0\) is the administered activity, \(D_k/A_0\) is the mean absorbed dose to region \(k\) per unit of administered activity, and \(S_{kh}\) is the mean dose to region \(k\) per unit of cumulated activity in region \(h\).

In the general formulation, regions can be any constituent of the body (from the whole body to single cells); the cumulated activity and the resultant doses are considered to be uniformly distributed within any region. The factors \(S_{kh}\) are calculated from the geometry of the regions, the nature of the intervening tissues, and the emissions from the particular radionuclide of interest. The use of the MIRD formulation requires the identification of relevant uniform regions (source and target) and the measurement of \(A(t)\) for those regions. In clinical studies, we may have biopsy data (often from a single time point) and serial external imaging data (Single-photon emission computed tomography (SPECT) or positron emission tomography (PET)); the temporal and spatial resolution of this data will be limited by the constraints of clinical trials. A combination of models can compensate for the limitation of clinical data; MIRD standard phantoms and distribution models derived from clinical and preclinical data can be used to determine the maximum activity to be administered. For this to be meaningful where the kidney is the limiting factor, the relevance of the MIRD phantom of the kidney must be assessed.

The Kidney

The kidney is a highly structured organ, both organizationally and anatomically. Its main functions are the excretion of water-soluble waste products, the retention of required products, and the regulation of the body’s water and electrolyte balance. Between 20% and 25% of the cardiac output passes through the kidney, where the blood is filtered, with molecules of molecular weight in the order of 30–70 kD experiencing an increasing restriction to passage out of the blood; proteins of higher molecular mass but cylindrical shape may present with a cross-section similar to a globular protein of lower molecular mass and, thus, pass into the collection tubules. The filtrate then undergoes selective and passive reabsorption, with waste products allowed to pass through to the urine, while the homeostasis of the body is maintained. The gross anatomy of the kidney can be divided into two parts: the outer cortex, where most of the filtration and reabsorption takes place, and the central medullar, where the tubules come together to pass urine to the renal pelvis and ureter.

Antibodies and Fragments

Antibodies directed against tumor-associated antigens have been investigated as targeting agents for radionuclide therapy by a number of groups.2-3 Whole IgG antibody and various-sized fragments have been proposed as delivery agents:

- Whole IgG
  - 150 kD
- Kidney excretion of breakdown products
• $\text{F(ab')}_2$
  - 100 kD
  - Cylindrical molecule
  - Can exhibit the radius of smaller globular protein, leading to significant renal uptake
• Fab
  - 50 kD
  - Significant filtration
• sFv
  - 27 kD
  - Freely filtered

METHODS

Distribution Studies
• In the studies described here antibodies and fragments directed against CEA were used (IgG (A5B7),6 Fab$^{'2}$,7 Fab,$^{'2}$ and sFv (MFE)).8 The studies are described fully in Flynn et al.9 Briefly, the antibodies and fragments were labeled with $^{125}$I and administered through i.v. to nude mice bearing human colorectal tumor xenografts. Groups of mice were killed and the kidneys excised at 1 hour (sFv and Fab groups only), 3 hours (all groups), 24 hours (all groups), 48 hours (not sFv group), and 72 hours (not sFv group) time points. One kidney from each mouse was weighed, solubilized in 7 M KOH and total radioactivity was measured in a well counter; the other kidney was fixed in 10% formalin, processed to paraffin wax, and sectioned at 5 μm. Sections were dewaxed and imaged by phosphor storage plate technology (“radioluminography”—RL) with a pixel size of 50 μm, then stained with hematoxylin and eosin (H&E) and digitally imaged by visible light, with the pixel size set to 50 μm. The H&E and the RL images were coregistered by cross correlation.10 Regions of interest (ROI) were defined for whole kidney, cortex, and medulla on the H&E images; these ROI were transferred to the RL images.

Homogeneous Distribution Models
A model of a homogeneous kidney was constructed by taking the whole kidney ROI from the H&E image on the RL image. This whole kidney ROI was populated with a randomly distributed

![Figure 1](image-url)
Gaussian distribution containing the same mean number of counts per pixel as the RL image. A model of uniform uptake in the cortex was constructed in a similar way: total counts in each ROI were measured and redistributed, as above. A “homogeneous component” kidney was constructed by combining the uniform cortex and the uniform medulla images.

Dose-Rate Calculations
Dose-rate distribution images were generated from uniform and actual distribution images by convolution with beta point-dose kernels. Dose–rate distributions were estimated for 125I, 131I, 186Re, and 90Y. To compare the dose rate from the uniform model with actual distributions, the inhomogeneity of dose–rate distribution was measured using the Pearson Correlation Coefficient; this coefficient will approach 1, as the correlation between the distributions improves (in this case, as the actual distribution becomes more homogeneous). Whole-kidney homogeneity was assessed for all antibody preparations, and cortex for the preparations that showed filtration through the kidney.

RESULTS
Antibody Distribution
The 125I RL image of the sFv distribution at 1 hour (A) and the coregistered H&E stained image (B) are shown as Fig. 1. The ROI for the whole kidney and the division between the cortex and medulla (defined on the H&E image) are shown on both images. This RL image demonstrates inter- and intra-component inhomogeneity.

Dose Distribution
The calculated $\beta$ dose–rate distribution for 90Y (A) and 131I (B) for sFv is shown as Fig. 4. The contour map indicated that the longer $\beta$ particle path length of 90Y gives a more homogeneous dose–rate distribution.

Whole-kidney inhomogeneity is shown in Table 1. No significant differences were seen between the distributions for Fab and (Fab)$_2$ preparations, and these are shown in a single column. The nuclide with the shortest-range electron

![Figure 2](image-url)
emissions (\(^{125}\text{I}\)) shows the most inhomogeneity. The dose rate from antibody preparation that has the highest cortex:medulla ratio (sFv) remains highly inhomogeneous, with all radionuclides studied. The most homogeneous whole-kidney dose rate is given by IgG with \(^{90}\text{Y}\).

The inhomogeneity in cortex dose rate is shown in Table 2. IgG is not filtered and is not

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**Figure 3.** Intercomponent homogeneity (expressed as Cortex:Medulla ratio) as a function of time after injection for the four antibodies.

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**Figure 4.** Contour maps showing the actual dose rate in the cortex (C) and medulla (M) as a percentage of the dose rate obtained from a uniform distribution. These maps show the dose rate distribution from sFv antibody labelled with \(^{90}\text{Y}\) (panel A) and \(^{131}\text{I}\) (panel B). Reproduced from ref. 9, page 186 with permission.
included—again, there was no difference between Fab and F(ab)/H110322 preparations, and these are shown in a single column. The smoothing effect for the longer-range electrons is again evident by the increase in the correlation between the estimated true dose rate and the estimated dose rate for an equivalent uniform distribution.

**DISCUSSION**

The prediction of radiation nephrotoxicity is crucial for the development of systematically delivered radionuclide therapy; it is expected to be the dose-limiting factor where bone marrow toxicity is controlled. Dose distribution within the kidney is a major factor in the prediction of nephrotoxicity. Current models of the kidney assume a uniform distribution (and, thus, of dose rate and absorbed dose) either at the level of the whole kidney or at the suborgan level, including the cortex. We have investigated this assumption in the mouse kidney and indicated where it does not hold. It is important to discuss the relevance of this for dosimetry in humans.

The first problem that arises when trying to extend this work to humans is that the human kidney is considerably bigger than that of the mouse. The prediction of radiation nephrotoxicity is crucial for dosimetry in humans. Where more accurate distribution can be determined, by measurement or model, voxel-based methods (using point-dose kernels or Monte Carlo methods) will provide a more accurate estimate of dose distribution.

**CONCLUSIONS**

The distribution of radionuclides and, hence, of the regional dose rate and absorbed dose in the mouse is dependent on the molecular size of the antibody; this is a function of the extent to which the antibody is filtered, and of retention by the kidney subsequent to filtration. The smallest antibodies moved rapidly into the kidney but showed some retention in the cortex. The whole antibody was not filtered, and the level of activity seen in the kidney was the result of its presence in the blood pool. For those antibodies which were filtered, the distribution of radionuclide in the kidney was heterogeneous both inter- and intraregion.

<table>
<thead>
<tr>
<th>Table 1. Inhomogeneity in Whole-Kidney Dose Rate</th>
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<tbody>
<tr>
<td>radionuclide</td>
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<td>125I</td>
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<td>131I</td>
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<td>186Re</td>
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<td>90Y</td>
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Whole-kidney Mean Pearson Correlation Coefficient between the dose-rate distribution calculated from the actual distribution and the distribution calculated from an equivalent uniform distribution.

<table>
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<th>Table 2. Inhomogeneity in Cortex Dose Rate</th>
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<tr>
<td>radionuclide</td>
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<td>131I</td>
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<td>186Re</td>
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<td>90Y</td>
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Cortex Mean Pearson Correlation Coefficient between the dose-rate distribution calculated from the actual distribution and the distribution calculated from an equivalent uniform distribution for antibodies filtered by the kidney.
The assumption of uniform activity distribution for the whole kidney gives a poor estimation of the distribution of the dose rate. In the cortex, the longer-range $\beta$ emitters smooth out the effect of heterogeneous distribution and, in mice, an assumption of uniform cortex self-dose distribution may be sufficient for simple calculations.

REFERENCES


