DOSIMETRY OF INTERNAL EMITTERS IN NUCLEAR MEDICINE AND RADIATION PROTECTION : AT WHAT LEVEL

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Abstract

The inadequacy of conventional dosimetry at the organ level assuming a uniform activity distribution has been brought out in specific examples. In each case dosimetry at different anatomical levels is presented bringing out the probable understanding and lacuna in the radiobiological consequences of such dosimetry. Bone dosimetry of alpha and beta emitters is presented. Dose to whole kidney and differential doses to medulla and cortex from ^{203}Hg-neohydrin are described. The mean dose to lung from ^{131}I-MAA, the mean local dose to capillary bed and to capillary epithelium adjacent to an MAA particle are reviewed. The importance of Auger electron emission and the consequent transmutational effects is discussed with the examples of ^{125}I in thyroid, ^{125}I-UdR in proliferating cells, ^{55}Fe in erythrocytes. High doses to limited portions of fingers while handling ^{113m}In and ^{99m}Tc labelled pharmaceuticals is presented.

Introduction

In nuclear medicine the clinician wants to know what are the potential hazards to a patient if he undergoes a particular investigative procedure which is expected to yield diagnostic information of clinical value. In the case of radiation protection the similar question is: what are the potential hazards to the worker under given exposure situation. The focus of interest is the biological effect which is the end-point in a complicated chain of events at the physical, chemical and physiological levels. Conventional dosimetry is mainly concerned with the primary event, viz. physical step, and the absorbed dose is an indicator only of physical events that happen at the macroscopic level. But we are far from understanding the biological significance of the absorbed dose. Partial consideration to the secondary events is attempted to be given by assigning a somewhat arbitrary value for the RBE or QF and quoting a rem dose.

For a proper evaluation of the biological effect, we should know the microscopic spatial and temporal distribution of the primary and secondary events. This leads to a detailed consideration of several factors, some associated with the radiation alone like radiation quantity and dose rate, others associated with the target as well, like location of radionuclide in the cell, the biochemistry of the labelled compound, bond rupture resulting from nuclear recoil after beta emission, chemical effect of nuclear transmutation on functional integrity of molecule, effect of sudden changes of charge on daughter nuclide (particularly important for isotopes decaying by electron capture), oxygen tension, cells at risk, radiosensitivity of cells in question, etc.

Further, concepts like LET and absorbed dose are macroscopic quantities or 'expectation values'. As the volume over which the absorbed energy is computed is reduced, the fluctuations associated with the stochastic nature of the interaction process assume increasing importance; concepts like 'event size', 'local energy density' and 'event size spectrum' have then to be introduced. This approach has not yet been made in practical situations of concern in internal dosimetry.

Very often we are not quite clear as to what is the biological end-point that is of relevance, although it is generally accepted that for comparatively

low doses as are encountered in routine occupational exposure or diagnostic nuclear medicine procedures, the effects may be classified into two categories, viz (i) those leading to the impairment of the functional integrity of the organ (this may be due to reduction in number of functioning cells or fibrosis with scarring) and (ii) induction of malignancies[1].

With all these complications, the question arises: At what level should dosimetry be done? Can we be satisfied with the conventional calculation of absorbed dose at the organ level assuming a uniform concentration of radionuclide? Or should we go down to the tissue, cell and even subcellular level? Should we consider the stochastic nature of the interaction process and enter into details of the microdosimetric concepts? What degree of sophistication is necessary and what degree sufficient?

The problem is discussed in terms of some well-known examples of practical interest.

Bone Dosimetry

Bone dosimetry is a classical example of the inadequacy of the conventional organ dose computation for an assessment of the potential risks. The inhomogenous structure of bone and bone cavities(where the linear dimensions of the inhomogeneities are frequently of the same order as the range of the ionizing particles), the varieties of cells at risk and the non-uniformity of distribution of the radioisotope make the situation complex. A good deal of effort and ingenuity have gone into the solution of the problem from both the theoretical and experimental sides. From a consideration of the critical tissues for radiation damage, it is usual to calculate the following separately[2]:

i) Dose to a very small tissue-filled cavity in the bone matrix, D_o (to evaluate risk to osteocytes, cells lining Haversian canals and blood vessels in Haversian systems which are concerned with maintaining the functional integrity of bone as a living tissue).
ii) Mean dose to endosteal cells near the surface of bone trabeculae in the marrow cavities, D_s (osteogenic sarcoma risk).
iii) Mean dose to active marrow in trabecular cavity $\bar{D}_m$(leukaemogenesis risk).

Typical results for radium and strontium-90 are shown in Table 1[2].

Table 1

Dose rates in rad/year from skeletal burden of 1 uCi

	Radiation	D_o	$\bar{D}_m$	$\bar{D}_s/\bar{D}_m$
^{226}Ra series	α	36	10.5	7
$^{90}Sr + ^{90}Y$	β	2.7	1.1	0.5

It is only by a detailed consideration of the cells at risk that we are able to perceive a major difference between the alpha and beta emitters. In view of the limited range of alpha rays, the bone marrow dose is only a small fraction of the endosteal dose in the case of alpha emitters. This is borne out by experience where we find that the incidence of leukaemia in radium

poisoning cases has been negligibly low and osteogenic sarcomas(and cancers of paranasal sinuses) are more common. With ^{90}Sr both leukaemia and osteogenic sarcomas have been induced in animals.

We shall next consider the question of non-uniformity of distribution of radium(and strontium) in bone. In addition to a diffuse distribution in the bone matrix, hot spots also occur where the local concentration may be 30-40 times the average concentration[3]. For ^{226}Ra, the range of variation of concentration is faithfully reflected in a corresponding range of variation of dose rates between the different concentration sites (factor of 16). Due to the longer range of beta rays from ^{90}Sr, the local dose rate variations are not that marked(factor of 3). We still do not know whether the hot spots play a role in radiation damage to bone and what the biological significance of the non-uniformity of damage is.

Neohydrin Dosimetry

Controversy was intense a few years ago whether ^{203}Hg-neohydrin should not be banned as a radiopharmaceutical for kidney and brain scanning in view of the high kidney doses. Neohydrin concentrates primarily in the cortex from where it is eliminated only very slowly. Since the cortical mass is about half that of the kidney, the dose to cortex would be twice that to the kidney as a whole had the isotope been uniformly concentrated. The cortex dose can be taken as 146 rads and the medulla dose as 77 rads per millicurie of ^{203}Hg-neohydrin[4].

We may discuss the question a little further. Is there firm evidence to show that 100 rads to the cortex is necessarily more harmful than 50 rads to the kidney as a whole? What is the biological end-point we are looking for? The natural incidence of malignant tumours of the kidney is quite small; also there is as yet no established case of radiation-induced kidney tumour. If malignancy is not the critical end effect, we have next to consider impairment of functional integrity. At the levels used in diagnostic procedures, gross impairment like acute or chronic nephritis is ruled out and much milder damage, which cannot be unambiguously pinpointed, must be considered. It appears that the fine vasculature is the histological site of damage of primary importance in the pathogenesis of radiation induced nephrosclerosis; the renal epithelium is relatively resistant but it may degenerate as a result of damage to the fine vasculature[5]. Since the proximal and distal parts of the tubules lie mainly in the cortex, it is not inconceivable that secondary tubular damage may be somewhat more intense from 100 rads to cortex than 50 rads to total kidney. On the other hand, it has been pointed out[6] that the effective surface area of the renal cortex is about 4 times larger than the surface area of the kidney. Hence the escape of the beta radiations from the cortex will reduce this dose variation factor of 2 by an amount which has not yet been computed. The uncertainty remains.

^{131}I-Human Serum Albumin Macroaggregates for Lung Scanning

Uncertainty in the effective tissue mass to be considered in the dose computation can be illustrated by ^{131}I HSA macroaggregates in lung scanning. If a homogenous distribution of MAA in lungs is assumed, average dose to lung is about 1.5 rads for 30 uCi[7]. If a more realistic volume distribution is assumed, viz. the capillary bed of the lungs with a mean diameter of 10 um, the average local absorbed dose is nearly 5.5 rad. At the cellular level, absorbed dose to capillary epithelium adjacent to an MAA particle is several orders of magnitude higher than the average local absorbed dose, although this extreme dose is received only over a distance of one or two cell thicknesses. The problem is the anatomical level at which the dose is to be evaluated. If the induction of malignancy is the end-point of interest, the integral dose is

probably a valid indicator of the potential hazard. We do not yet know the biological significance of the very high level of local absorbed dose.

A somewhat similar situation exists in the field of radiation protection for assessing hazards from plutonium inhalation.

Significance of Auger Effect

Radionuclides decaying by electron capture and isomeric transitions are attractive in in vivo applications since they do not emit particulate radiations which give a radiation dose to the organ but do not contribute any diagnostic information. Several such radionuclides are now in common use, e.g. ^{51}Cr, ^{55}Fe, ^{57}Co, ^{58}Co, ^{67}Ga, ^{75}Se, ^{85}Sr, ^{123}I, ^{197}Hg and ^{99m}Tc, ^{113m}In. Certain special features of the electron capture process and the process of internal conversion consequent on gamma photon emission are of great relevance. After these two processes, the K or L shell vacancy initiates orbital excitation and electrons fall down from outer orbits successively into the vacancies in inner orbits. Excess energy is lost by X-ray emission in part but a large part of de-excitation occurs through the emission by the Auger effect of several electrons of low energy with a range in tissue of less than a micron. They, therefore, give a very high local dose to the tissue over a micron length. In addition their LET is very high and hence a correspondingly high RBE/QF will have to be postulated, leading to an intense local rem dose. We are still far from understanding the precise biological significance of this peculiar feature but some indications are available in the case of ^{125}I dosimetry which we shall touch upon subsequently.

Another consequence of Auger electron emission needs attention. As a result of the release of several Auger electrons, the daughter atom is left with a strong positive charge. If this charged nuclide is bound within a molecule it attracts electrons from various molecular positions and the positive charges are distributed throughout the molecule. The various positively charged atoms within the molecule strongly repel each other, which may lead to a virtual 'Coulombic explosion' of the molecule.

^{125}I Dosimetry

Conventional macroscopic dosimetry of ^{125}I in thyroid has been shown to be entirely inadequate in view of the special characteristics of the radiations from the radionuclide, and one has to go down to subcellular microdosimetry for obtaining a better understanding of the possible biological effects of ^{125}I. Since the range of Auger electrons is small compared to the dimensions of the thyroid cell, the cell-colloid interface or the apical membrane, which is the seat of thyroid hormone biosynthesis, receives a high dose. On the other hand the nucleus which is farther away gets only about one-fourth the dose to apical membrane. The variation between the nuclear and apical membrane doses is accentuated in thyrotoxic conditions in view of the greater distance of the nucleus from the apical membrane of the columnar cell of the thyrotoxic gland. The clinical significance of these observations has led to intense interest in the use of ^{125}I for therapy of thyrotoxicosis in preference to ^{131}I. However the clinical experience as well as the follow-up periods are as yet too small for an unambiguous conclusion to be drawn[8].

The biological significance of the high LET of the Auger electrons and the possibility of Coulombic explosion mechanisms have not yet been clarified. Perhaps since the ^{125}I decay takes place mainly in the colloidal gel outside the apical membrane the latter effect may not be critical[9].

On the contrary if ^{125}I is attached to essential structures such as DNA the influence of the charge transfer processes and the associated Coulombic explosion effects may be comparable to if not outweigh the radiation effects in producing the biological effect. This has been demonstrated[10,11] while studying the relative effect of varying doses of ^{125}I-UdR, ^{131}I-UdR and ^{3}H-TdR on proliferating mouse cells in vivo. The toxicity of ^{125}I-UdR was reported to be 10 times greater than that with ^{3}H-TdR when these specific precoursors of DNA were utilised by either bone marrow cells, or proliferating cells in the whole body in general. A similar finding was reported with ascites tumor cells also. The greater radiotoxicity of ^{125}I-UdR has been explained as due to a variety of factors including (i) differences in energy deposition in the cell nucleus per disintegrating atom (ii) greater inhomogeneity in the distribution of energy around the site of decay in the case of ^{125}I(iii) transmutational effects of ^{125}I, specially the consequences of molecular explosion.

^{55}Fe Dosimetry[12]

^{55}Fe, an electron capture radionuclide, is an important neutron activation product found in fallout. Levels as high as 3 pCi/mg blood have been recorded in New York residents. It has been computed that the dose to erythrocytes is about 10 times that to whole blood since the Auger electrons deposit their energy entirely within the erythrocyte itself where the ^{55}Fe is tagged. Dose to aggregates of ferritin molecules in which highest concentration of iron is found has been calculated to be about 200 times that to erythrocyte. However, the critical tissue in this case is perhaps the erythrocyte precursor cells in the bone marrow wherein a concentration around one-third of that in erythrocytes has been found, leading to a dose around 3 times the blood dose.

Skin Dosimetry

Skin dosimetry has acquired some urgency in view of the increasing use of short-lived isotopes like ^{113m}In and ^{99m}Tc in nuclear medicine. In the milking of the generator, the preparation of the radiopharmaceuticals and injection to the patient, levels of several tens of millicuries have to be handled at a time. The tips of two or three fingers, in particular, get exposed to significantly high doses(around 10 mrem/mCi-min). If the ICRP dose limit of 75 rem/year to hands is not to be exceeded, we would be severely curtailed in the scope of work; not more than two or three brain scanning preparations can be handled per person per week.

In this connection the health physicist turns to ICRP for guidance. A report of an ICRP Task Group[1] has something to say on skin dosimetry. The report recognises that the end-point of relevance here is not carcinogenesis, since the skin is relatively highly radioresistant, but radiation dermatitis. According to the report, in the case of irradiation of part of a tissue, the significant parameter is the mean dose to the entire tissue. If only a fraction/of tissue is exposed, the dose allowed can be 1/f of dose limit for the whole organ. On this basis, if the dose limit for entire skin with an area of about 2 square meters is 30 rem/year, the dose to 1 cm^2(of the order of high exposure areas of finger tips) could go as high as 60 kilorems. So why need we worry?

But the situation is not that simple. There is a limit beyond which the above concept cannot be extended. A vital consideration is the range of dose rate over which effective linearity of dose response can be assumed to hold. The point at which departure from linearity occurs will depend on the precise cellular mechanisms involved and the extent to which abscopal effects come into play. It may happen that at high doses the response may be higher than

would be predicted from a linear hypothesis since a number of contiguous cells are affected and irrepairable physiological damage occurs. The Report says that linear response can be assumed up to hundred rems per year and possibly several hundred rems per year, and recommends that 'the present limit of 30 rem/year averaged over 1 cm^2 of skin be increased to at least 100 rems in a year with a proviso that irradiation of the same area year after year should be avoided if possible'. The health physicist wishes that the ICRP Task Group had categorically set a specific limit, say 500 rems per year, instead of vaguely leaving it at,'at least 100 rems per year', so that he could ask the technicians, with some authoritative sanction behind him, to accept a higher work load with the generators. Note again the words,'if possible'. In the present case of working with generators the irradiation is going to be received by the same area year after year unless a right handed person could be persuaded to become left-handed. Of course there is no sanctity about the limit of 1 cm^2 which is taken as the 'significant area' for averaging and the Report says '1 cm^2 seems reasonable on grounds of operational convenience'.

Conclusion

In this present paper dosimetry at different anatomical levels has been presented with the help of specific examples. In each case probable biological significance of such dose estimation also has been brought out. However, still there are several uncertainties in the biological significance of such detailed dose estimates and the importance of the possible transmutational effects with electron capture radionuclides.

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