The MIRD Schema: From Organ to Cellular Dimensions

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Nuclear medicine procedures provide valuable diagnostic information and noninvasive approaches to therapy. As with any medical procedure, however, the risks and benefits must be weighed. The absorbed dose is an essential part of assessing the risk from diagnostic radiological procedures and predicting efficacy in radiation therapy. The generalized MIRD Schema was formulated to facilitate the calculation of mean absorbed dose from distributed sources of radioactivity (*1*). Although the basic MIRD formalism is general in that it can be employed with any model representing distributed sources, its ultimate utility depends on its application to a biologically relevant model. As a practical solution to the complex nature of internal dosimetry, the MIRD Committee adopted a simple anthropomorphic model of the human body (*2*). The organs modeled within the phantom were assumed to conform to the uniform isotropic model, that is, they are regions within a homogeneous material that is sufficiently large so that edge effects are negligible, and the activity is uniformly distributed within each of the source organs (*1,2*). This approach provides useful estimates of the mean absorbed dose to model organs from incorporated radionuclides by using information on the tracer distribution and biokinetics in the various organs, radiations emitted by the radionuclide, and the physical characteristics of energy deposition of the radiations.

Although the use of simple models to represent the human body is adequate for many purposes, the mean organ absorbed dose alone may not always reliably correlate with the biologic response. For instance, much attention has been devoted to the potential biologic implications of nonuniform activity distributions at the macroscopic (*3–5*), multicellular (*6–8*) and cellular (*9–11*) levels in both organs and tumors. In addition, there is considerable evidence that the mean organ dose alone does not consistently correlate with the biologic effects of Auger electron emitters, which deposit their energy in a highly localized fashion (*12*). These observations raise questions regarding the usefulness of mean organ doses in these situations (*13–15*). As pointed out by Kassis (*13*), however, the MIRD Schema is intrinsically able to accommodate most of these complex dosimetric problems provided that appropriate biologic data are available. The purpose of this report is to review the MIRD Schema and briefly outline its capacity to address these issues.

MIRD FORMALISM

The MIRD Schema itself is a logical and concise mathematical dosimetry formalism consisting of several basic equations (*1*) that can be briefly summarized as follows. The mean absorbed dose $\bar{D}(r_k \leftarrow r_h)$ to target region r_k from activity in the source region r_h is given by

$$\bar{D}(r_k \leftarrow r_h) = \tilde{A}_h \sum_i \frac{\Delta_i \phi_i(r_k \leftarrow r_h)}{m_k}, \qquad \text{Eq. 1}$$

where $\tilde{A}_h$ is the cumulated activity in the source region (h), m_k is the mass of the target region (k), Δ_i is the mean energy emitted per nuclear transition and $\phi_i(r_k \leftarrow r_h)$ is the fraction of energy emitted from the source region that is absorbed in the target region for the ith radiation component. Equation 1 may be simplified to:

$$\bar{D}(r_k \leftarrow r_h) = \tilde{A}_h S(r_k \leftarrow r_h), \qquad \text{Eq. 2}$$

where S is defined by

$$S(r_k \leftarrow r_h) = \sum_i \frac{\Delta_i \phi_i(r_k \leftarrow r_h)}{m_k}. \qquad \text{Eq. 3}$$

The utility of this formalism lies in its simplicity and generality. No assumptions are made regarding the composition and geometry of the source and target regions, or the distribution of activity within the source regions. The S-values can be calculated for any geometric model of sources and targets. Accordingly, given an appropriate model and set of biologic data, the basic MIRD Schema is

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capable of accommodating nonuniformities in activity distribution even down to subcellular levels.

DOSIMETRY MODELS

Organ/Suborgan

In principle, a variety of models of varying complexity can be employed with the MIRD Schema. As indicated above, it has been traditional to use the uniform isotropic model for the various organs in the body. This model, used in conjunction with the anthropomorphic phantom, has allowed tabulation of the organ S-values for numerous radionuclides (*16*). The S-value tables provide a simple and convenient way to calculate mean organ doses within the MIRD approach. Development of dosimetry models suitable for nonuniform activity distributions of radionuclides does not require that the uniform isotropic model or the concept of S-values be abandoned (*13*). Rather, new model geometries need to be developed to describe the biological system (*13,15*). For instance, it has recently been shown that the distribution of ^{111}In-labeled radiopharmaceuticals is highly nonuniform in rat tissues (*14*). Perhaps most striking was the distribution of ^{111}In-oxine in the kidney. The cortex accumulated nearly all of the organ's activity, with only a small amount of activity being taken up in the medulla. In principle, S-values could be readily tabulated for a multicompartment kidney model as well as for a variety of like geometries. In fact, this technique has already been used in modeling the compartments of the heart (*17*), and a similar method was adopted in constructing a tumor model for macroscopic nonuniformities in activity distribution (*3*). In essence, these macroscopic models make use of the uniform isotropic model, although, the "organ" is divided into a number of subregions. All of these geometric configurations are amenable to calculating appropriate S-values, and the corresponding absorbed dose estimates may be calculated using the MIRD Schema, provided the uptake and clearance patterns of the radioactivity are known for each subregion.

Cellular and Multicellular

The MIRD Schema is not limited to organ or sub-organ dosimetry. The Schema is also relevant for dosimetry at the cellular and multicellular levels. Since the inception of radioimmunotherapy, there has been interest in dosimetry for multicellular clusters. Unlike external beam radiotherapy, where all of the cells in the tumor are irradiated fairly uniformly, tumor therapy with incorporated radionuclides results in nonuniform irradiation of the tumor cell population. This is a result of nonuniform cellular uptake of the radionuclide and the limited range of particulate radiations in tissue. If the tumor is to be eradicated, the reproductively viable cells in the tumor must receive doses in the sterilization range. Therefore, knowledge of the dose profile across the cells of the cluster is needed. Aside from the biokinetic data, the dose profiles can depend on the radiation properties of the nuclide, the fraction of cells labeled, location of the radiochemical within the cell (i.e., cell surface, cytoplasm, nucleus) and physical dimensions of the cells and the cluster (*6*). However, despite these complexities, this dosimetric problem can be addressed by the MIRD Schema with the individual cells serving as "organs" and the uniform isotropic model still appropriate, albeit at a cellular level. S-values can be calculated for subcellular, cellular and multicellular geometries, thereby facilitating absorbed dose calculations at these levels. The utility of the calculations is limited by the uncertainties in the biologic input data with respect to cellular dimensions, uptake and clearance patterns for each cell in the cluster, etc. In general, such data are obtained using invasive procedures and cannot presently be acquired for individual patients. Consequently, absorbed doses calculated for small-scale geometries, based on past experience from a limited number of patients, must be used to project future outcome in other patients (*18*).

Cellular and subcellular dosimetry have applications beyond multicellular clusters. There are a number of instances where knowledge of the self-absorbed dose to individual cells and their nuclei is required. Examples include radiolabeled blood cells, ascites, isolated cells in an organ that preferentially incorporate the radiochemical (*19*), as well as cultured cells in the laboratory. Here, S-values for subcellular and cellular dosimetry would facilitate calculation of absorbed doses to the cytoplasm, nucleus, and cell as a whole, from activity distributed on the cell membrane or in the cytoplasm or nucleus (*20*).

CONCLUSIONS

Although the examples outlined above for organ, suborgan, multicellular, cellular and subcellular dosimetry may not be an exhaustive list of the possibilities, they clearly point out the flexibility of the MIRD Schema for calculating absorbed doses from incorporated radionuclides. It should be noted, however, that, even for tissues of known radiosensitivity, there are instances where the mean absorbed dose alone is of limited utility in terms of predicting biologic outcome whether calculated at the organ or cellular level. In vivo experiments in mouse testis have demonstrated that, while the dose-response curves based on mean organ doses for emitters of low linear-energy-transfer (LET) radiations (i.e., beta particles, gamma rays, x-rays) are all very similar (*21*), strikingly different dose-response curves have been observed for emitters of low-energy Auger electrons (*21*). Similar observations have been made in studies with cultured mammalian cells even when the mean absorbed dose to the cell nucleus is calculated (*22,23*). In fact, both in vivo and in vitro studies have shown that the relative biological effectiveness (RBE) of Auger emitters varies from as low as unity when the emitter is localized in the cytoplasm (*21,24,25*) to values as high as those observed for alpha particles of high LET when the emitter is covalently bound to DNA in the cell nucleus (*26*). Hence, the absorbed dose, calculated at the organ or cellular level, cannot alone be

used to explain the complex variety of biologic responses elicited by Auger emitters. This is, however, not necessarily a deficiency in the MIRD Schema that was used to calculate the doses. It may be that we need to define more accurately the location and spatial dimensions of the primary radiosensitive targets in the cell to allow a direct correlation between the absorbed dose from Auger emitters and the biologic effect. This problem is unlikely to be surmounted in the near future, given that not only the radiosensitive targets, but also the location of the radionuclides relative to the targets must be identified (*24*). These considerations led to the proposal that the mean organ absorbed dose for Auger emitters be corrected with a factor that depends on the fraction of activity in the organ that is bound to DNA (*27*).

In summary, the MIRD Schema is a general approach for the dosimetry of incorporated radionuclides that is applicable at the organ, multicellular, cellular and subcellular levels. The MIRD Committee recognizes, however, that at any one of these levels, under some circumstances, absorbed dose by itself may not be the appropriate quantity to use for predicting biologic response. Other quantities such as radiosensitivity of the tissue, radiation quality, subcellular distribution and dose rate must be taken into account. Despite this, calculation of absorbed dose at the required biologic level remains a critical first step in risk/benefit analysis.

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