A COMPREHENSIVE APPROACH FOR THE EVALUATION OF COMPARATIVE DOSIMETRY OF INTERNALLY ADMINISTERED RADIOPHARMACEUTICALS

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Abstract

Recent innovations both in instrumentation and radiopharmaceuticals are helping nuclear medicine to develop as a discipline in medical practice primarily for diagnosis with an emphasis on scanning. Radiation safety of a radiopharmaceutical is based on the assessment of the radiation exposure to the critical organ from a tracer dose. It is also important to consider relative tracer doses necessary for an optimal result for selecting one of the several radiopharmaceuticals available for a similar investigation. A comprehensive formulation of an index has been attempted for the relative dosimetry integrating mainly (i) conventional method of dose calculation, (ii) physical properties of radionuclide, (iii) available nuclear instrumentation, (iv) metabolic fate of radiopharmaceutical, and (v) gross considerations for radiosensitivity of organs and dose rate. This approach has been illustrated considering the situation of brain scanning using Hg-197 chlormerodrin, Tc-99m pertechnetate, Tc-99m DTPA, short-lived In-113m DTPA and long-lived Yb-169 DTPA.

Introduction

Nuclear medicine is appearing as a discipline in medical practice which involves primarily the use of radiopharmaceuticals for diagnosis. Recently scintigraph has attained tremendous importance due to availability of advanced nuclear instruments and short-lived radiopharmaceuticals. Agents with high photon yield with low radiation dose are considered most desirable for clinical use.

Large number of radiopharmaceuticals are being developed in order to scan various organs and diseased conditions, and to improve the existing methods. Acceptance of any new product for clinical use depends on its cost, efficacy, specificity, toxicity and dosimetry. Although radiation exposure is an important consideration, it is difficult to control the medical applications by any formal method due to the fact that the primary interest lies in the immediate benifit to the patient.

The present exposition has been aimed to provide a guideline for the evaluation of relative dosimetry while choosing one of the several similar agents.

Comparative Dosimetry

Conventional method of dose calculation has been improved and standardized greatly[1]. It is based on the utilization of physical properties of radionuclides, absorbed fraction of the radiation, and the metabolic fate of the radiopharmaceutical. It provides a practical value for the concept of safety with a recommended tracer dose for a clinical study. It could be expressed by

$$D \text{ (rads/mCi)} = 1000 \text{ c/m } 1.44\ T_e \Sigma\Delta\Phi = R.A \quad \ldots\ldots\ldots(1)$$

where, R is the maximum dose rate (rads/mCi/hr) to an organ of mass m gm ($=1000\Sigma\Delta\Phi/m$), and A is the area under time-concentration curve (approximately equal to $1.44\ c\ T_e$ where c is the maximum fractional concentration and T_e is the effective half-life in hours).

Comparative dosimetry becomes important when several similar agents are available for a particular investigation. Usually the tracer dose is adjusted to keep the radiation dose within a safe limit. However, an appropriate approach should be to find out the relative amounts of tracer doses that would give similar measurable count rate at the time of study. Occasionally this method has been adopted[2]. The relative tracer dose could be expressed by

$$T \text{ (mCi)} = 1/(f.e.d) \quad \ldots\ldots\ldots\ldots\ldots(2)$$

where, f is the fractional yield of the photons used for detection, e is the detection efficiency of the instrument or at least the photo-peak interaction coefficient, and d is the activity remaining after decay or elimination by the mean time of the study. It is assumed that the target to non-target ratio for the different agents remain approximately the same.

The variations in radiosensitivity of crital and other organs have always raised questions in mind, but it is difficult to assign any quantitative value. However, it is well known that bone marrow is most radiosensitive. It would be reasonable to ascribe an emperical sensitivity factor (S_o) of 3, 2, and 1 respectively for bone marrow (and gonads during reproductive age), gastrointestines, and the rest of the organs. Further, it is also desirable to incorporate a sensitivity factor for increased dose rate (S_r). Emperically, $D/R\ (= 1.44\ T_e) = 10^{\pm n+1}$ may be used for a normalization of dose-rate sensitivity: assuming n=0 for normal condition ($S_r = 1$), one could arrive factors like $S_r = 1/(n+1)$ or $(n+1)$ for +n or -n values, the intermediate values could be obtained graphically. As an example, $S_r = 2$ if 10 rads are delivered at the rate of 10 rads/hr instead of 1 rad/hr.

$$\text{Then, } S = S_o \cdot S_r \quad \ldots\ldots\ldots\ldots\ldots(3)$$

In summary, the normalized radiation dose (NRD) for different radiopharmaceuticals used for similar investigations can be expressed by

$$NRD = R \cdot A \cdot T \cdot S \quad \ldots\ldots\ldots\ldots\ldots(4)$$

It is assumed that the radiopharmaceuticals are pure, otherwise the contributions of any radionuclide impurity and any radiochemical impurity should be taken into consideration.

Example of Brain Scanning

Mercury-197 labeled chlormerodrin has been and is being used for brain scanning[3], although technetium-99m pertechnetate has become the most preferred agent[4]. Chelates (DTPA) labeled with Tc-99m[5], In-113m[6] and Yb-169[7] can be used for brain scanning. Kidneys, upper large intestine and bladder could be taken as the critical organs for chlormerodrin, pertechnetate and chelates, respectively.

The radiation doses for the different agents were calculated by taking values of nuclear parameters (except for ytterbium-169[8]) and absorbed fractions of energy for different organs from MIRD pamphlets[1]. Biological factors (such as, concentrations in organs, biological half-lives, time of study after administration of tracer dose, and usual tracer doses) were assumed. However, these assumptions were based on various publications (such as the summary in a text book[9]). Estimation of relative tracer dose was based on the useful photon yield, photo-peak interaction coefficient of useful photon energy in 2-inch NaI crystal (thickness), and the fractional activity remaining after effective loss by the mean time of study. Relative tracer doses were then normalized to 10 mCi of Tc-99m pertechnetate. Further, it was assumed that a 100% of the dose was initially uniformly distributed in the total body and remained uniform although the fractional concentrations in different organs were different. The emperical sensitivity factor for dose rate was obtained using a semi-log plot of $10^{\pm n+1}$ (for 1.44 T_e values) against $\pm n$.

Table 1 and Table 2 represent the basic physical and biological data. Table 3 shows the aspects of dosimetry for the total body. Table 4 summarizes the results for the critical organs.

Table 1: Basic physical data for the radiopharmaceutical

Labeling nuclide	Chemical agent	Physical half-life (hr)	Useful photon energy (keV)	Useful photon yield (%)	Usual tracer dose (mCi)
Hg-197	Chlormerodrin	65.0	67-81	90.8	0.75
Tc-99m	Pertechnetate	6.0	140.5	88.3	10.0
Tc-99m	Chelate (DTPA)	6.0	140.5	88.3	10.0
In-113m	Chelate (DTPA)	1.67	393.0	65.4	15.0
Yb-169	Chelate (DTPA)	763.2	177 & 198.0	55.3	10.0

Table 2: Basic biological data for the radiopharmaceutical

Agent	Photo-peak interaction coefficient (2-in NaI)	Biological half-life (hr)	Time gap of study (hr)	Relative tracer dose (mCi)	$\Sigma\Delta\phi$ for total body
Hg-197 Chlor.	1.00	6	3.0	13.6	0.225
Tc-99m Pert.	0.98	48	1.0	10.0	0.130
Tc-99m DTPA	0.98	2	0.5	11.6	0.130
In-113m DTPA	0.77	2	0.5	24.7	0.474
Yb-169 DTPA	0.97	2	0.5	17.2	0.554

Table 3: Calculation of dosimetry for the total body

Agent	Dose rate rads/mCi/hr	Area under conc.-time curve (1.44 cT_e)	Radiation dose (rads/mCi)	Rads per usual tracer dose	Normalized rads/test
Hg-197 Chlor.	0.0032	7.91	0.0253	0.018	0.38
Tc-99m Pert.	0.0019	7.68	0.0146	0.146	0.16
Tc-99m DTPA	0.0019	2.16	0.0041	0.041	0.08
In-113m DTPA	0.0068	1.31	0.0089	0.089	0.41
Yb-169 DTPA	0.0079	2.87	0.0227	0.227	0.60

Table 4: Calculation of dosimetry for the critical organ

Agent	Concerned organ	Fractional conc. (c)	Biological half-life (hr)	Rads per usual tracer dose	Normalized rads/test
Hg-197 Chlor.	Kidneys	0.2	1704	8.2	75.9
Tc-99m Pert.	UL intest.	0.1	12	0.8	2.0
Tc-99m DTPA	Bladder	0.5	2	1.5	2.8
In-113m DTPA	Bladder	0.5	2	4.5	20.8
Yb-169 DTPA	Bladder	0.5	2	10.6	28.1

Discussion

Radiation dose rate (R) can be calculated with a high degree of accuracy except when the mass of the concerned organ is variable or uncertain (such as bladder with urine[10]). Considerable uncertainity could be inherent with 'A' due to difficulties in obtaining distribution patterns of the radiopharmaceuticals in human organs under normal and diseased conditions. Relative tracer doses could be calculated with sufficient accuracy if instrumental sensitivity for different agents (radionuclides) are determined experimentally. Quantitative assessment for radiosensitivity would remain a radiobiological problem particularly with reference to dose rate. However, it does not seem very unreasonable, at present, if a factor of 2 is used to increase the index of radiation dose when 10 rads are delivered at the rate of 10 rads/hr instead of 1 rad/hr.

Reduction of radiation doses in diagnostic uses of radioisotopes has remained an important consideration from the point of view of exposure to patient and population. In earlier days, usually low level counting techniques have been considered to reduce the tracer dose[11]. In recent days, it appears that the diagnostic values are being enhanced by quantitation of scans with computors in studies with multi-millicuries of short-lived radiopharmaceuticals[12]. In practice, one has to compromise to certain extent the radiation dose with the specificity, efficacy or the cost of the radiopharmaceutical. In the growing phase of the development of radiopharmaceuticals, it is hoped that the present consideration would help in the selection of the agent to reduce the radiation dose in an investigation under optimal condition.

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