The Importance of Patient-Specific Dosimetry to Minimize the Risk of Red Marrow Toxicity from $^{131}$I-mIBG Therapies

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Abstract

$^{131}$I-Meta-iodobenzylguanidine ($^{131}$I-mIBG) is a radiopharmaceutical used in the diagnostic and therapeutic application for neuroendocrine tumors. The similarity of mIBG structure to guanethidine and the neurotransmitter norepinephrine provides a means of specific tumor localization. Treatment of $^{131}$I-mIBG is generally limited by the maximum tolerated absorbed doses to red marrow that should not exceed 2 Gray. The principal side effect, hematological toxicity, has proven to be the therapy-limiting toxicity. Pre-therapeutic patient-specific dosimetry is essential to ensure that a treatment dose has high degree of safety and efficacy. The purpose of this article was to review the methods applied for red marrow dosimetry to minimize the risk of toxicity. Focus is given on data concerning the therapeutic application of neuroendocrine tumors patient treated with $^{131}$I-mIBG.

INTRODUCTION

Meta-iodobenzylguanidine (mIBG) is a guanethidine derivative structurally resembling norepinephrine, providing a means of specific tumor localization for radiopharmaceutical delivery to neuroendocrine tumors [1-3]. Its structure consists of a combination of the benzyl portion of bretylium and the guanidine group of guanethidine. It is radio iodinated at position 3 of the aromatic ring (Figure 1). The uptake of mIBG in adrenomedullary tissue occurs by a type I amine uptake mechanism [4,5]. The first clinical applications of $^{131}$I-mIBG have been developed at the University of Michigan since 1980. A variable response to treatment has been reported, and although the treatment is usually given with palliative intent, complete responses have occasionally been reported [6-8]. $^{131}$I emits beta particle with a maximum energy of 0.61 MeV and a gamma ray of 364 keV. It has a physical half-life of 8.05 days (Table 1). Approximately 80% of beta particles transmit through the cells within a radius of about 0.8 millimeters [9]. The beta particles emitted by $^{131}$I taken up into neighboring cells while gamma emission is used for imaging.

Damage to living tissues from radiation-absorbed dose is then a limitation of $^{131}$I-mIBG treatments. The critical organ of this radiopharmaceutical is the red marrow. The principal side effect is hematological toxicity, especially thrombocytopenia and leukopenia [7,10]. The contribution of radiation-absorbed dose to red marrow should not exceed 2 Gray [11-13]. Howman-Giles et al., [14] had reported the side effects with $^{131}$I-mIBG in 12 patients of malignant pheochromocytoma. Grade 3 thrombocytopenia was observed in 79 % of the cases and grade 3 and 4 granulocytopenia in 53% and 19 %, respectively. Additionally, the long-term effects are hypothyroidism as a consequence of inadequate thyroid blockade. The thyroid blockade drugs are likely to interfere with the uptake or retention of $^{131}$I-mIBG, which should be withdrawn before treatment. Radiation-induced leukemiamay be developed after treatment with $^{131}$I-mIBG, but this is a rare possibility [10]. Leukemia is a stochastic effect that has no threshold dose. The incidence of secondary leukaemia is proportional with radiation dose. However, leukaemia appears earlier after treatment than do other cancers that reach a peak incidence within 5 to 10 years and decline slowly thereafter.

Internal Dosimetry Concept

The most widely used method of calculating internal dosimetry for a patient treated with unsealed sources has been developed by the Medical Internal Radiation Dose (MIRD) Committee of the American Society of Nuclear Medicine. The concepts of MIRD for internal dose calculation are a set of source organs (i.e., those that have a significant uptake of the radiopharmaceutical) and a
set of target organs (i.e., those that are being irradiated by the source organs) [15-18]. The MIRD schema makes the assumption that activity is uniformly distributed in the source organ. It also assumes that the shape, size, and position of the organs are represented by the mathematic anthropomorphic models (Figure 3) [19]. The basic MIRD expression of absorbed dose in the target organ can be calculated by the simple formula in equation 1 and 2 [19-21]. This method arises in calculating the absorbed dose to the target organ from radioactivity in a source organ as shown in Figure (2) [22].

\[ D_{rk} = A_0 S(r_k \leftarrow r_h) = A_0 \tau S(r_k \leftarrow r_h) \]  

where \( D_{rk} \) is absorbed dose to a target organ (\( \mu Ci/hr \) or \( mGy/MBq/sec \)),

\( A_0 \) is the cumulated activity in the source organ (\( \mu Ci-hr \) or \( MBq-sec \)),

\( \tau \) is the residence time of radioactivity (hr),

\( A_0 \) is the administered dose (\( \mu Ci \) or \( MBq \)), and

\( S(r_k \leftarrow r_h) = \frac{k \sum n_i E \varphi_i \rho_i}{m} \)  

where \( S(r_k \leftarrow r_h) \) is absorbed dose per unit activity (rad/\( \mu Ci-hr \) or \( mGy/MBq-sec \)),

\( k \) is the MIRD schema provide a proportionality constant that is 2.13 (rad-g/\( \mu Ci-hr-MeV \) or \( Gy-kg/MBq-sec-MeV \)),

\( n_i \) is the number of radiations with energy \( E \) emitted per nuclear transition,

\( E \) is the energy per radiation (MeV),

\( \varphi \) is the fraction of energy absorbed in the target, and

\( m \) is the mass of the target region (g or kg).

### Assessment of Red Marrow Dosimetry

The activity and concentration of the \(^{131}I\)-mIBG in all major organs are given by equation 2:

\[ S(r_k \leftarrow r_h) = \frac{k \sum n_i E \varphi_i \rho_i}{m} \]  

<table>
<thead>
<tr>
<th>Table 1:</th>
<th>The physical data of iodine-131 [9].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma energies</td>
<td>364 kilo electron volt (82 % abundance)</td>
</tr>
<tr>
<td></td>
<td>637 kilo electron volt (7 % abundance)</td>
</tr>
<tr>
<td></td>
<td>284 kilo electron volt (6 % abundance)</td>
</tr>
<tr>
<td>Beta energies</td>
<td>192 kilo electron volt (89 % abundance/average)</td>
</tr>
<tr>
<td></td>
<td>610 kilo electron volt (89 % abundance/maximum)</td>
</tr>
<tr>
<td>Half-life</td>
<td>8.05 days</td>
</tr>
<tr>
<td>Physical half-life</td>
<td>1.35 days</td>
</tr>
<tr>
<td>Biological half-life</td>
<td>1.35 days</td>
</tr>
<tr>
<td>Effective half-life</td>
<td>7.60 days</td>
</tr>
<tr>
<td>Specific gamma constant (( \Gamma ))</td>
<td>0.22 milliroentgen per hour at 1 meter per millicurie</td>
</tr>
</tbody>
</table>
source organs and spaces in the body must be determined for the dose calculation step (Figure 4) [23]. The red marrow is the critical organ for most $^{131}$I-mIBG therapies. Mostly, red marrow doses cannot be determined directly. Calculation of the internal radiation absorbed dose to red marrow using a standard blood model and patient-specific data by measuring the total body clearance of the $^{131}$I-mIBG and the retained activity in peripheral blood will reduce these radiation effects and improve the quality of life of the patients after treatment. The activity in the blood is determined from periodic heparinised blood samples. The activity in the total body could be monitored redundantly using independent techniques: total body counting with a probe using fixed geometry and conjugate views of whole body scans obtained by a dual headed gamma camera [24]. Following the MIRD schema, the absorbed dose to red marrow ($D_{rm}$) is calculated as the sum of self-absorbed dose in red marrow ($D_{rm\rightarrow rm}$), and the absorbed dose to red marrow from activity in the remainder of the total body ($D_{rm\rightarrow rb}$) [11,25].

$$D_{rm} = D_{rm\rightarrow rm} + D_{rm\rightarrow rb} \quad (3)$$

$$D_{rm} = \bar{A}_{rm} \times S_{rm\rightarrow rm} + \bar{A}_{rb} \times S_{rb} \quad (4),$$

Where $\bar{A}$ is the cumulated activity and $S_{target\rightarrow source}$ is the $S$ value for a source irradiating a target. The cumulated activity represents the time integral of the activity in the source region over the time interval of interest.

**Blood Activity:** Changing activities concentration in blood can be determined from serial blood samples acquired at various time after the administration of $^{131}$I-mIBG. Usually, 3 to 5 ml of blood is collected at 1, 4, 24, 48,72 and 96 hours from a vein in the limb opposite to that in which the 37 MBq of $^{131}$I-mIBG was administered. The radioactivity of each sample is measured with a calibrated gamma counter. The activity concentration in red marrow ($\bar{A}_{rm}$) is determined from the serial of blood activity. The principal equation is Equation 5.

$$\bar{A}_{rm} = [\bar{A}_{bl}] \times m_{rm} \times RMBLR \quad (5),$$

where $[\bar{A}_{bl}]$ is the cumulated activity concentration in blood $m_{rm}$ is the patient-specific red marrow mass and $RMBLR$ is the red marrow to blood activity concentration ratio.

The values of $m_{rm}$ are generally difficult to assess. They may be scaled from the reference man value of 1.5 kg for 70 kg man by using the patient’s total body mass ($m_{tb}$), as $m_{rm} = (1.5 \text{ kg}/70 \text{ kg}) \times m_{tb}$ [26,27]. As regards RMBLR, specific values have been suggested for different therapies. In case of radioimmunotherapy with monoclonal antibodies the well-known equation by Sgouros [28] is generally applied in equation 6.

$$RMBLR = \frac{RMECFF}{(1 - HCT)} \quad (6),$$

where $RMECFF$ is the patient-specific Red Marrow Extra Cellular Fluid Fraction $HCT$ is the haematocrit.

$RMECFF$ varies among patients. In the absence of specific knowledge, a value of 0.19 is generally assumed. However, the most importance of $RMBLR$ is the actual patient haematocrit. The value of $RMBLR$ is in the range of 0.2-0.4, depending on haematocrit. The normal values of haematocrit are of the order of 0.41-0.50 for males and 0.36-0.44 for females [29,30].

**Total Body Retention:** This information can be measured most conveniently with a probe placed at 2 to 6 meters from the surface of the patient as shown in Figure (5) [23]. Here, one obtains a reading for the count rate from the patient about 10 to 20 minutes after the activity is administered and prior to any excretion via urine or feces. This initial value is used to normalize all subsequent measurements made in the same geometry. The assumption of this approach is that the sensitivity of the probe or dosimeter used to measure the various readings is reasonably independent of where the activity is located within the patient. As in the probe case, positioning of the patient for repeat scans will require a localization method. One technique is the use of wall-mounted lasers to make reposition of the patient serially.

A second method for measuring total body retention is a sequence of whole body images taken with a gamma camera in scanning mode. Generally, these images will include regions from the top of the head to the toes with the arms being visible at the sides of smaller patients. This method has the advantage that distributions within patient organs can be acquired at the same time as the whole body image.
In general, the biodistribution of 131I-mIBG in the total body includes the activity in the red marrow, in identified source organs and in the remainder of the body. The cumulated activity in the remainder of the body ($A_{rb}$) is determined from Equation 7.

Remainder of the body equals the total body minus by the red marrow.

$$A_{rb} = A_{tb} - A_{m} = A_{tb} - \left[ A_{tb}\right] \times m_{tb} \times RMBLR \quad (7)$$

Where $A_{tb}$ is the cumulated activity in the remainder of the body $A_{rb}$ is the cumulated activity in the total body

**Patient-specific dosimetry calculation:** The equation for red marrow dose calculation is rewritten as in equation 8 [29-31], which represents the data of each patient. The patient-specific parameters are expressed in lower case letters (e.g., $m_{tb}$ is the total body mass of the patient), while the standard man/woman parameters are expressed in capital letters (e.g., $m_{TB}$ is the total body mass of the standard man/woman).

$$D_{rm} = \left[A_{tb}\right] \times m_{RM} \times RMBLR \times S_{RM-\epsilon-RM} +$$

$$\left(A_{tb} - A_{m}\right) \times m_{tb} \times m_{TB} \times RMBLR \times S_{RM-\epsilon-TR} \times$$

$$m_{TB} \times S_{RM-\epsilon-RM} \times m_{MB} \times m_{TB} \times m_{TB} \times m_{TB}$$

$$D_{bm} = \left[A_{tb}\right] \times m_{RM} \times RMBLR \times S_{RM-\epsilon-RM} +$$

$$\left(A_{tb} - A_{m}\right) \times m_{tb} \times S_{RM-\epsilon-RM} \times$$

$$m_{TB} \times S_{RM-\epsilon-RM} \times m_{MB} \times m_{TB} \times m_{TB}$$

Generally, the administered dose of 131I-mIBG is in terms of total activity (GBq), activity per unit of body weight (GBq/kg), or activity per unit of body surface (GBq/m²) whichever is convenient, but the relationship between radiation dose from 131I-mIBG and toxicity may be uncertain [32,33]. However, the publication of O’Donoghue et al., showed [34] that the red marrow dose predicted with patient-specific data was better than administered activity or administered activity per meter square with respect to hematological toxicity. Certainly, biodistribution and retention time of 131I-mIBG in the body of each patient has a different pattern. It may occur from the previous treatment of patients such as external radiation therapy and chemotherapy issues. Changmuang et al., [35] showed the interested results of Thai-neuroendocrine tumor patients treated with 131I-mIBG. The maximum administered dose calculated from tracer dose (37 MBq) delivered to each patient did not exceed the red marrow dose limit 2 Gray. The toxicity for each patient was observed every 2 weeks. It showed only a few numbers of patients with significant hematological toxicity.

**DISCUSSION & CONCLUSION**

Biodistribution and retention activity of 131I-mIBG in the body of each patient has a different pattern. The administration activities with traditional methods should be considered. Therefore, assessment of red marrow dose using patient-specific dosimetry technique before 131I-mIBG treatments with a diagnostic dose of 131I-mIBG is a good predictor for red marrow toxicity, as shown the step in Figure (4). If this method is used for the future planning of 131I-mIBG treatments to maximize the treatment potential with acceptable toxicity, it is believed that, the morbidity will decrease and the quality of life of the patients will be improved.

Patient-specific dosimetry technique is comparatively easy to perform before and during therapy. Moreover, this method can be applied to the treatment of thyroid cancer with 131I-Na in renal dysfunction patients [36,37] non-Hodgkin B-cell lymphoma with 131I-Rituximab Radioimmunotherapy [38-40] and neuroendocrine tumors with 177Lu-DOTATATE peptide receptor radionuclide therapy [41] that has been published.

**REFERENCES**


