Indigenous preparation of therapeutic doses of $^{131}\text{I}$-MIBG (Metaiodobenzylguanidine) injection for treatment of Pheochromocytoma /Neuroblastoma - Indian Experience

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$^{131}$I-MIBG (Metaiodobenzylguanidine)

Proven radiopharmaceutical for the diagnosis and therapy of Neuroendocrine tumors in particular, Adrenal medullae tumours (Phaeochromocytoma, Neuroblastoma) and their metastasis

**Mechanism of uptake**

Structural similarity to adrenaline and noradrenaline responsible for uptake and storage in cells of the sympathetic nerve endings or neuroendocrine tumors
Aim

Indigenous synthesis of therapeutic doses of $^{131}$I-MIBG injection for the regular supply to various Nuclear Medicine Centers in India

$^{131}$I-MIBG injection, diagnostic doses are available from BRIT, India since 1999
Present work

✓ MIBG Ligand

✓ Radiolabeling

✓ Purification

✓ Formulation, Sterilization and Aseptic dispensing

✓ Quantification of purity/stability
Synthesis

m-Iodobenzylamine + NH₂CN → 100-135°C → 4 h → Cyanamide

Characterization: mp, IR & ¹H-NMR

Presently it is being procured from ABX chemicals, Germany
Radiolabeling*

(I) NH NH

(2-4 mg)  \( \text{(500-1000mCi)} \)

(0.4-0.5 ml)

Sodium Acetate solution is added to reaction vial after cooling (pH 5)

Characterization by Electrophoresis and chromatographic techniques

Purification

Ion-exchange chromatography using Dowex-1 (8%, 200-400)

Pure $^{131}$I-MIBG obtained in acetate buffer at pH 5
Formulation

- Pure product formulated in isotonic saline (Radioactive conc. ~15 mCi/ml on the day of preparation)
- Benzyl alcohol (0.9%) as radioprotectant

Sterilization

- Membrane filtration using pre-sterilized 0.22µM filter assembly
- Aseptic dispensing in multi dose vials & sealing
Quality Assurance Control
(Good Manufacturing Practices)

Aseptic Requirements - Production

- Sterile Glass wares
- Sterile Filters
- Fumigation of the production plant
- UV lamp
- Exposing media plate in working environment

Quality Control

Physicochemical control:
- Clarity
- pH
- Radioactive Concentration
- Radionuclidic Purity
- Radiochemical Purity

Micro biological control:
- Sterility test
- BET test

Environmental control
- Spore strip/ Biological indicator
- Biological media
Characterization

Electrophoresis (0.05 M NaOAc solution, 300 V, 30 min)

Radiolabelled reaction mixture

Pure product

Chromatographic techniques

PC: PrOH:NH₃ (3:1)

TLC: Solvent - EtoAc:EtOH (1:1)
Results

Quality Parameters of $^{131}$I-mIBG injection **

<table>
<thead>
<tr>
<th>No of Batches</th>
<th>Radioactive concentration (mCi/ml)</th>
<th>Specific Activity (mCi/mg)</th>
<th>% Radiochemical Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>11 – 15</td>
<td>60-150</td>
<td>97.2-99.1</td>
</tr>
</tbody>
</table>

** Therapeutic doses : 40 x 100 mCi each
**Typical batch stability data of Therapeutic $^{131}$I-MIBG**

<table>
<thead>
<tr>
<th>Room temperature stability</th>
<th>Stability at -70°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>(RAC: ~15 mCi/ml)</td>
<td>(RAC: ~15 mCi/ml)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Time</th>
<th>$%^{131}$I (free I⁻)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45 min</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>2 h</td>
<td>2.3</td>
</tr>
<tr>
<td>3</td>
<td>3 h</td>
<td>3.5</td>
</tr>
<tr>
<td>4</td>
<td>24 h</td>
<td>17.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Time</th>
<th>$%^{131}$I (free I⁻)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 day</td>
<td>1.4</td>
</tr>
<tr>
<td>2</td>
<td>3 day</td>
<td>2.8</td>
</tr>
<tr>
<td>3</td>
<td>5 day</td>
<td>3.5</td>
</tr>
<tr>
<td>4</td>
<td>7 day</td>
<td>4.3</td>
</tr>
</tbody>
</table>

* with radioprotectant
## Recovery yields

<table>
<thead>
<tr>
<th>Source of Raw material $^{131}$I</th>
<th>RAC of $^{131}$I (mCi/ml)</th>
<th>% pure product recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhruva Reactor, BARC</td>
<td>700-1500</td>
<td>35-45</td>
</tr>
<tr>
<td>Fission Produced (Imported)</td>
<td>2000-3000</td>
<td>50-60</td>
</tr>
</tbody>
</table>
$^{131}$I-MIBG - Therapeutic challenges???

Handling of higher radioactivities
Rapid radiolytic damage at room temperature

Full/semi automated gadgets/techniques—minimize exposure (ALARA) and time

Operation protocol—By modules
# Standard Operating Protocol (Three Modules)

## First Module

<table>
<thead>
<tr>
<th>Module</th>
<th>Process</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry heat bath</td>
<td>Radiolabelling</td>
<td>50</td>
</tr>
</tbody>
</table>
## Second Module

<table>
<thead>
<tr>
<th>Module</th>
<th>Process</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vacuum in line assembly</td>
<td>Purification, Formulation &amp; Sterilization</td>
<td>10</td>
</tr>
</tbody>
</table>

Pure product after ion exchange purification is sent for storage at -70°C within 30 min preventing less radiolytic damage.
<table>
<thead>
<tr>
<th>Module</th>
<th>Process</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma sterilized Combination seals and Pneumatic capping device</td>
<td>Aseptic dispensing &amp; sealing</td>
<td>10</td>
</tr>
</tbody>
</table>
Product Specifications

\(^{131}\text{I} -\text{Meta iodobengyl guanidine} \ [\text{MIBG}] \text{ injection} \)  
(therapeutic doses)

- **Appearance**: Clear Colorless solution
- **pH**: 3.5 – 8
- **Radiochemical Purity**: Not less than 94%
- **Radioactive Concentration**: 5-15mCi/ml on the date of preparation
- **Specific activity**: >10 mCi/mg on expiry date
- **Date of Expiry**: 5 days from the date of preparation
- **Sterility**: Sterile
- **Endotoxin**: as per RPC monograph
- **Storage**: Deep freezer, below -20°C
- **Shipping**: In dry ice with adequate lead shielding (Type-A package)
Conclusions

✓ Regular production of Therapeutic $^{131}$I-MIBG injection for 3-5 patient doses (100 mCi each) is prepared and supplied every month

✓ Product complies with the specifications of British Pharmacopoeia product

✓ Overall batch recoveries of $^{131}$I-MIBG are between 40-60%

✓ Stability of the product is “not less than 94%” for a period of 7 days, when stored below -20°C

✓ Approved by Radiopharmaceutical Committee (RPC), India for regular production & supply

✓ Regular supplies from January 2008
Thankyou for your kind attention!