Thiamazole Pretreatment Lowers the $^{131}$I Activity Needed to Cure Hyperthyroidism in Patients With Multinodular Goiter

Kyrilli Aglaia
Department of Endocrinology
Hôpital Erasme, ULB

Belgian Thyroid Club 5/12/2015
Multinodular goiter

• Prevalence
  
  Sex ratio: 1/6 for M/F

  Depending on population’s iodine sufficiency
  ✓ Framingham iodine sufficiency: 1% population
  ✓ Denmark mild iodine insufficiency: 9.8% palpation ---- 15% echo
  moderate iodine insufficiency: 14.6% palpation ----- 22.6% echo

• Complications
  
  Hyperthyroidism (22% of longstanding MNG)
  Local compression
  Malignity
## Treatment options for autonomous MNG

No official recommendations  
Guided by local practice, patients’ preferences, clinical presentation

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>$^{131}$I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient basis</strong></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Volume reduction</strong></td>
<td>+++</td>
<td>++ (40% at 1 year)</td>
</tr>
<tr>
<td><strong>Recurrent laryngeal nerve paralysis</strong></td>
<td>&lt;2%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Hypoparathyroidism</strong></td>
<td>&lt;2%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Transient hyperthyroidism</strong></td>
<td>-</td>
<td>~ 3%</td>
</tr>
<tr>
<td><strong>Permanent hypothyroidism</strong></td>
<td>+++</td>
<td>++ (15-20% at 1 year)</td>
</tr>
<tr>
<td><strong>Autoimmunity induction</strong></td>
<td>-</td>
<td>~ 5%</td>
</tr>
</tbody>
</table>
Radioiodine therapy

**Efficiency:**
depends on the thyroid **absorbed dose**

\[
\text{Prescribed Dose (\mu Ci)} = \frac{\text{Mass of Gland (g)} \times \text{Desired Dose (\mu Ci/g)}}{\text{Uptake at 24 hours}} \times 100\%
\]

Max legal threshold for outpatient $^{131}$I administration in Belgium: **15mCi**

- **Low** radioiodine uptake (RAIU)
- **Heterogeneity** of $^{131}$I uptake
- **Large goiter volume**

Can hamper $^{131}$I treatment efficacy
Requiring **very high activities** of $^{131}$I
Iodine uptake by thyrocyte

1. Increase TSH levels
   - Injection of rhTSH

2. Depletion of intrathyroid iodine pool
   - Endogenous TSH by AT drugs

**Apical Pole**
- H$_2$O$_2$ - generating System DUOX 1/2
- NIS (iodide symporter)
- I$^-$ channel
- Tg (thyroglobulin)
- TPC (iodothyroglobulin peroxidase)
- RTSH (reverse thyroid-stimulating hormone)
- T4 + T3 (thyroid hormones)

**Basal Pole**
- TSH (thyroid-stimulating hormone)
- thiamazole

++

- **H$_2$O$_2$**
- **I$^-$**
- **Na$^+$**
- **TgI**

++
rh TSH in MNG treatment

- 0.01-0.9mg rh TSH
- 24-76h prior to $^{131}$I
- 2-4 fold increase in RAIU
- Baseline RAIU dependent

Inter individual variations
Off label use

rh TSH in MNG treatment

- 0.01-0.9mg rh TSH
- **35-56% gain** in goiter volume reduction
dose dependent

Inter individual variations
Off label use

Nielsen VE et al Arch Intern Med 2006
Objective of the study

Determine
Whether
✓ pretreatment with thiamazole (MTZ) could enhance 24h RAIU
And
✓ So decrease the $^{131}$I activity needed to treat patients with subclinical hyperthyroidism and MNG
Patients and methods

Prospective, randomized controlled
patients referred for $^{131}$I treatment
2006 -2013

Inclusion criteria:
✓ subclinical hyperthyroidism: TSH< 0.4mU/L , N FT3, FT4
✓ 24hRAIU< 50%

Exclusion criteria:
✓ thyroid surgery
✓ thiamazole within 6 months prior to enrollment
✓ past $^{131}$I treatment
✓ Solitary autonomous nodule
Patients and methods

Day 0:
Thyroid $^{99m}$Tc scintigraphy
SPECT CT/MRI (volume estimation)
Administration 10µCi for 24h RAIU

Day 1:
Low iodine diet, LID
Or
MTZ 30mg/d 42d

Day 01:
24h RAIU
If <50%
Serum TSH, FT4, FT3, Tg-Ab, TPO-Ab, UIC
Randomisation
Day 43:
Stop MTZ

Day 47:
Serum TSH, FT4, FT3, UIC
Thyroid $^{99m}$Tc scintigraphy
SPECT CT/ MRI
Administration 10µCi for RAIU

Day 48:
24h RAIU
Therapeutic $^{131}$I activity calculation
Administration on outpatient basis
Patients and Methods

RAIU estimation

\[
\frac{\text{Thyroid cpm (t) } - \text{ Leg cpm (t)}}{\text{Standard cpm (t) } - \text{ background (t)}}
\]

cpm: counts per minute

\[\mu\text{Ci activity} = \frac{\text{R activity } \mu\text{Ci} \times \text{thyroid size (gr)}}{24 \text{ h uptake } (%)}\]

\[\text{R (required) activity varied from 90-200 } \mu\text{Ci/gr according to thyroid size}\]

Roudebush C et al., Ann Intern Med. 1977
Results

Baseline clinical characteristics of LID and MTZ groups

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>LID</th>
<th>MTZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Age</td>
<td>70.7±7</td>
<td>66.5±14</td>
</tr>
<tr>
<td>Sexe ratio (F:H)</td>
<td>8:2</td>
<td>10:2</td>
</tr>
<tr>
<td>TPO-Ab+/Tg-Ab+</td>
<td>0/0</td>
<td>0/0</td>
</tr>
</tbody>
</table>
## Results

Thyroid function and thyroid volume before and after 42 days of LID or MTZ treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After treatment</th>
</tr>
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<tbody>
<tr>
<td>Nº patients</td>
<td>LID 10</td>
<td>MTZ 12</td>
</tr>
<tr>
<td>TSH (N:0.4-4.0 mIU/l)</td>
<td>0.09 (0.04-0.17)</td>
<td>0.13 (0.04-0.30)</td>
</tr>
<tr>
<td>FT4 (N: 0.8-1.7 ng/dl)</td>
<td>1.27 ± 0.20</td>
<td>1.25 ± 0.20</td>
</tr>
<tr>
<td>FT3 (N:1.8-4.6 pg/ml)</td>
<td>3.60 ± 0.50</td>
<td>3.30 ± 0.60</td>
</tr>
<tr>
<td>Volume ml MRI</td>
<td>LID [87 (45.7-184.5) [4]</td>
<td>MTZ [55 (29-63) [7]</td>
</tr>
<tr>
<td></td>
<td>LID 39 (31-56) [6]</td>
<td>MTZ 44 (31.5-61) [5]</td>
</tr>
</tbody>
</table>

Data are expressed as median (25th-75th percentile) [number of cases] ± SEM

* different from baseline, p<0.5, ** different from LID group after treatment, p<0.5
MTZ modified regional thyroid $^{99m}$Tc uptake

Previously ‘resting’ tissue surrounding hyper functioning areas ----- **REACTIVATED**
as a result of the MTZ induced TSH increase
Results

Change in mean RAIU after 42 days of LID, MTZ treatment

Data are expressed as mean ± SEM

24h RAIU increased by **2 fold** after $^{131}$I treatment preceded by MTZ
Results
Changes in calculated $^{131}$I activity after LID, MTZ

MTZ enhanced RAIU led to **31% decrease** in $^{131}$I activity needed to treat the patients.

Data are expressed as median (25th-75th percentile)

Exceeding 15mCi outpatient $^{131}$I threshold

- LID
- MTZ
Subclinical hyperthyroidism was ‘cured’ in all patients

30% hypothyroidism post MTZ enhanced RAIU

12 months follow up

Serum TSH (mIU/L)
## In comparison

<table>
<thead>
<tr>
<th>MTZ</th>
<th>rh TSH</th>
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<tbody>
<tr>
<td>• Gradual and <strong>slight TSH</strong> increase</td>
<td>• Acute <strong>supra normal TSH</strong> peak</td>
</tr>
<tr>
<td>• <strong>No</strong> thyroid swelling</td>
<td>• Thyroid gland <strong>swelling</strong></td>
</tr>
<tr>
<td>• <strong>FT3, FT4 normalized</strong> or reduced</td>
<td>• Transient hyperthyroidism <strong>high FT3, FT4</strong></td>
</tr>
<tr>
<td>• <strong>Volume</strong> long term?</td>
<td>• <strong>Volume reduction</strong> gain 30-65% after 1 year</td>
</tr>
<tr>
<td>• <strong>30%</strong> hypothyroidism after 1 year ---- long term?</td>
<td>• <strong>50%</strong> hypothyroidism after 5 years</td>
</tr>
<tr>
<td>• <strong>Modifies</strong> regional $^{99m}$Tc uptake</td>
<td>• <strong>Cost</strong></td>
</tr>
<tr>
<td></td>
<td>• <strong>Modifies</strong> regional $^{131}$I uptake</td>
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Conclusions

- Thiamazole (MTZ) pretreatment induced an average 2 fold increase in 24h RAIU.
- MTZ lowered the $^{131}I$ activity needed to treat subclinical hyperthyroidism in MNG patients.
- MTZ is easy, low cost with few secondary effects.
- MTZ did not modify $^{131}I$ efficacy.
- MTZ enhanced $^{131}I$ treatment resulted in 30% hypothyroidism (further reduction of $^{131}I$ activity possible).
- Thyroid volume reduction needs to be evaluated.
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- Didier Blocklet
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