Study of the effect of repeated potassium iodide prophylaxis in an adult rat model

ConRad Munich

May 9th 2017

French Institute for Radiological Protection and Nuclear Safety

General Context: Nuclear accident & Risk management

Physical approach:
Sheltering - confinement - food restriction - evacuation...

Pharmacological approach:
Single dose of stable iodide 130 mg

\[ \text{Radioactive iodide (}^{131}\text{I)} \]

- 0.44 TBq
- 1,800,000 TBq
- 130,000 TBq

(Adapted from Becker, 1998)

Wolff-Chaikoff effect
(Mechanism of regulation of the thyroid hormone synthesis)

(Adapted from Jacob et al., 2005; Schlumberger et le Guen, 2012; Le Guen et Schlumberger, 2016)
Lesson from Fukushima NPP accident?

- How to proceed in case of repeated release of radioiodine is an open, very important question which came up again recently during the Fukushima accident.
- Many episodes of discontinuous radioelements release, over several days.
- More than one dose of potassium iodide could be necessary.

Toxicological impact

- Clinical biochemistry and immunological profile?
- Thyroid hormone status?
- Mechanisms involve in thyroid hormone synthesis (Wolff-Chaikoff effect)?
1. Thyroid hormone synthesis

- Thyroid hormone synthesis & Wolff-Chaikoff effect

- 150 µg/day

- NIS: \(\text{Na}^+/\text{I}^-\) symporter
- PDS: pendrine
- TPO: thyroid peroxidase
- Tg: thyroglobulin
- DUOX: dual oxidase
- MCT8: monocarboxylate transporter 8
- T4: thyroxine
- T3: triiodothyronine

Adapted from Pesce & Kopp., 2014
Thyroid hormone synthesis & Wolff-Chaikoff effect

2. Wolff-Chaikoff effect

Acute KI prophylaxis

Wolff and chaikoff, 1948; Wolff, 1968; Calil-Silveira et al., 2016; De Souza et al., 2015; Leung & Braverman, 2014; Corvilain, et al., 1988; Arriagada et al., 2015; Juan C Solis-S et al., 2011

NIS: Na⁺/I⁻ symporter
PDS: pendrine
TPO: thyroid peroxidase
Tg: thyroglobuline
DUOX: dual oxidase
MCT8: monocarboxylate transporter 8
T4: thyroxine
T3: triiodothyronine
3. Escape from Wolff-Chaikoff effect

**Thyroid hormone synthesis & Wolff-Chaikoff effect**

- NIS: Na⁺/I⁻ symporter
- PDS: pendrine
- TPO: thyroid peroxidase
- Tg: thyroglobulin
- DUOX: dual oxidase
- MCT8: monocarboxylate transporter 8
- T4: thyroxine
- T3: triiodothyronine
Assess the toxicological effects of repeated administration of KI (target dose 1 mg/kg/24h, over 8 days)

The target dose 1 mg/kg: an optimal and efficient dose recently determined at IRSN (pharmacokinetics study)

Input data for the French central pharmacy of the armed forces (GLP and MA)

GLP: good laboratory practice, MA: marketing authorization
KI 1mg/kg/24h
Saline solution (SS) pH 7.4

Adult wistar rat (3 months)

Days

24h:
- KI 1mg/kg: 4 rats
- SS: 4 rats

4d/d5:
- KI 1mg/kg: 8 rats
- SS: 8 rats

8d/d9:
- KI 1mg/kg: 8 rats
- SS: 8 rats

8d/d10:
- KI 1mg/kg: 4 rats
- SS: 4 rats

8d/d30:
- KI 1mg/kg: 13 rats
- SS: 13 rats

Euthanasia

Blood Thyroid

Adult model: Experimental design

ConRad Munich 2017
### Adult model results: clinical biochemistry

#### Plasma parameters

<table>
<thead>
<tr>
<th>prophylaxis</th>
<th>KI mg</th>
<th>Creatinine µM</th>
<th>Urea mM</th>
<th>Proteins g/L</th>
<th>ALAT U/L</th>
<th>ASAT U/L</th>
<th>Uric acid µM/24h</th>
<th>Creatinine µM/24h</th>
<th>Urea mM/24h</th>
<th>Proteins mg/24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1d</td>
<td>0</td>
<td>47.71±2.11</td>
<td>5.59±0.04</td>
<td>55.20±0.71</td>
<td>31.44±1.21</td>
<td>80.90±1.47</td>
<td>17.21±1.56</td>
<td>95.36±10.26</td>
<td>5.5±1.82</td>
<td>11.18±3.6</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>49.34±2.53</td>
<td>6.11±0.16</td>
<td>56.33±1.24</td>
<td>32.68±0.28</td>
<td>80.57±1.62</td>
<td>17.10±1.69</td>
<td>92.08±1.02</td>
<td>8.31±0.59</td>
<td>7.08±1.17</td>
</tr>
<tr>
<td>4d</td>
<td>0</td>
<td>43.04±0.92</td>
<td>4.73±0.14</td>
<td>52.73±1.25</td>
<td>26.15±1.43</td>
<td>80.49±6.35</td>
<td>12.34±0.88</td>
<td>96.07±3.28</td>
<td>8.28±0.27</td>
<td>6.11±2.22</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>42.59±0.56</td>
<td>4.80±0.29</td>
<td>53.17±1.03</td>
<td>25.82±1.56</td>
<td>74.99±5.51</td>
<td>16.39±2.71</td>
<td>115.82±15.13</td>
<td>10.41±1.42</td>
<td>4.36±2.26</td>
</tr>
<tr>
<td>8d/d9</td>
<td>0</td>
<td>43.36±0.69</td>
<td>5.20±0.23</td>
<td>53.56±1.00</td>
<td>29.59±1.60</td>
<td>84.25±6.07</td>
<td>12.17±1.28</td>
<td>97.73±4.52</td>
<td>9.73±0.76</td>
<td>5.00±2.57</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>41.92±0.83</td>
<td>4.98±0.26</td>
<td>52.31±0.40</td>
<td>23.70±1.34*</td>
<td>68.48±4.62</td>
<td>12.38±0.90</td>
<td>91.22±3.11</td>
<td>8.98±0.50</td>
<td>6.54±2.95</td>
</tr>
<tr>
<td>8d/d10</td>
<td>0</td>
<td>42.48±0.50</td>
<td>4.89±0.33</td>
<td>54.83±1.71</td>
<td>25.86±3.17</td>
<td>78.59±1.53</td>
<td>14.63±0.82</td>
<td>105.56±11.32</td>
<td>9.14±1.32</td>
<td>13.69±1.38</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>42.54±0.74</td>
<td>5.04±0.18</td>
<td>53.36±0.99</td>
<td>25.10±0.70</td>
<td>65.08±3.07*</td>
<td>13.50±0.56</td>
<td>108.89±5.43</td>
<td>11.11±0.39</td>
<td>15.06±6.30</td>
</tr>
<tr>
<td>8d/d30</td>
<td>0</td>
<td>44.54±3.93</td>
<td>5.46±0.72</td>
<td>57.25±1.67</td>
<td>30.63±1.46</td>
<td>124.51±12.69</td>
<td>17.05±0.82</td>
<td>126.27±8.76</td>
<td>11.22±0.55</td>
<td>11.99±3.32</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>44.99±1.99</td>
<td>5.62±0.83</td>
<td>56.10±2.09</td>
<td>30.58±1.35</td>
<td>112.18±8.29</td>
<td>17.28±1.08</td>
<td>129.94±6.18</td>
<td>10.40±0.49</td>
<td>10.16±2.26</td>
</tr>
</tbody>
</table>

Results are expressed as Mean ± SEM, * p<0.05
Adult model results: hormonal status

TSH: thyroid stimulating hormone
T4: thyroxine
T3: triiodothyronine

Results are expressed as Mean ± SEM
Adult model results: immunological parameters

Anti-Tg : Anti-thyroglobulin antibody
Anti-TPO : Anti-thyroperoxidase antibody

Results are expressed as Mean ± SEM
Adult model results: histological profile

1: follicle
2: colloid

positive cells
Adult model results: thyroid genes expression

Results are expressed as Mean ± SEM

* p<0.05, **p<0.01, ***p<0.001 KI vs SS
Conclusions

Lack of toxicity, no pathological effect (clinical biochemistry – hormonal – histological and immunological results)

Safety of KI repeated administration at 1mg/kg/24h over 8 days in an adult model

- Data transmitted to central pharmacy of armed forces

Thyroid genes expression

Reversible transient Wolff-Chaikoff effect

- State of equilibrium

- 1 to 8 days of KI prophylaxis/Wolff-Chaikoff effect:
  - A: Early Wolff-Chaikoff effect
  - B: late Wolff-Chaikoff effect

- 2 days after KI withdrawal/ the escape from Wolff-Chaikoff effect

- 30 days post-prophylaxis
Ongoing activities

- What effects could repeated intake of KI have on the development of central nervous system (CNS) of the progeny?

Ongoing studies (hormonal and mechanistic) in the CNS and Thyroid gland, will improve our understanding of this motor effect.

- In utero model: indirect exposure to KI (mother treatment: KI 1 mg/kg/24h over 8 days of gestation)
Perspectives

Link between behavioral effects and Omic variation
- Thyroid
- CNS

Deleterious effects
- Behavior
- Hormonal status

Evolve the MA Updated guideline

Adjust the prophylactic design for in utero model

Solutions

ConRad Munich 2017
Acknowledgements

PRIODAC Project Funding

Toxicology team
SOUIDI Maâmar
MANENS Line
LESTAEVEL Philippe
GRISON Stephane
EBRAHIMIAN Teni
KERESELIDZE Dimitri
GUEMRI Julien

Pharmacology team
SUHARD David
PHAN Guillaume

Animal care team
VOYER Frederic
SACHE Amandine
GRANGER Romain
THANK YOU FOR YOUR ATTENTION!

QUESTIONS?