Thyroxine:
When do we need to assess an overdose?

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Disclosures: None

36th EAPCCT Congress, Madrid, May 2016
Outline

★ Background
★ Thyroxine overdose
  □ clinical manifestations
  □ toxic dose and concentration
★ Why acute thyroxine overdoses are associated with low toxicity?
★ Evaluation of thyroxine overdose
★ When do we need to assess thyroxine overdose?
★ Conclusion
Definitions

★ Hyperthyroidism
  ▪ ↑ production of thyroid hormones; overactive thyroid

★ Thyrotoxicosis
  ▪ pattern of manifestations due to excess hormone
  ▪ ↑ production, ▪ T₄ → T₃, diseases, ↑ hormone intake

★ Thyroid storm (thyrotoxic crisis)
  ▪ life-threatening condition of untreated thyrotoxicosis

★ Thyroxicosis factitia
  ▪ thyrotoxicosis due to excessive intake of thyroxine
Possible scenarios of thyroxine overdose

★ Unintentional:
- pediatric “general” (usually single incident)
- medication error (short- or long-term)

★ Intentional:
- acute deliberate self harm
- thyroxicosis factitia
  - Munchausen syndrome
  - misuse; e.g., weight loss, athletes (stimulants)
Epidemiology of thyroxine poisoning

- Among the top 5 prescription count in the USA

  - 13,623 exposures; 0.63% of all exposures reported
  - 65% unintentional
  - 33% < 6 year old
  - moderate-major toxicity 0.41%
  - no fatality cases
Thyroxine overdose: Problem statement

★ Thyroid hormones essential for proper body function
★ Thyroxine (levothyroxine) is a common drug
★ Thyroxine overdoses:
  - large number of cases
  - delayed symptoms, but may present early < 24 h
  - low morbidity in most cases; severe toxicity is rare
★ Question:
  - When or should thyroxine overdose be assessed?
★ Relevance: Assessment may alter management
Thyroid hormones function

- Regulate normal growth and development
- Maintain normal metabolic homeostasis
  - stimulate metabolic activity and $O_2$ consumption
- Used for treating thyroid disorders
- Excessive exposure: hyperadrenergic state affecting C-V, G-I and central nervous systems
<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>Hyperactivity, insomnia</td>
</tr>
<tr>
<td>Atrial fibrillation, SVT</td>
<td>Irritability</td>
</tr>
<tr>
<td>Wide pulse pressure</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Tremor</td>
<td>Dysphoria</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>Palpitations</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>Heat intolerance</td>
</tr>
<tr>
<td>Warm moist skin</td>
<td>Diaphoresis</td>
</tr>
<tr>
<td>Hair loss</td>
<td>Fatigue and weakness</td>
</tr>
<tr>
<td>Lid retraction or lag</td>
<td>Weight loss + ↑ appetite</td>
</tr>
<tr>
<td>Muscle weakness, myopathy</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Polyuria</td>
</tr>
<tr>
<td>High output congestive heart failure</td>
<td>Oligomenorrhea</td>
</tr>
</tbody>
</table>
### Clinical manifestations of acute overdose

*BCPT 2015, 117:250; AJDC 1987, 141:1025; AJEM 1985, 3:297*

<table>
<thead>
<tr>
<th>Serious</th>
<th>Non-serious</th>
</tr>
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<tbody>
<tr>
<td>Blood pressure ↑ or ↓</td>
<td>Tachycardia &lt; 120/min</td>
</tr>
<tr>
<td>Heart rate ↑ or ↓</td>
<td>Hyperactivity, restlessness</td>
</tr>
<tr>
<td>SVT</td>
<td>Tremor</td>
</tr>
<tr>
<td>↑ QT</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Agitation</td>
<td>Headache</td>
</tr>
<tr>
<td>Confusion</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Coma</td>
<td>Hot flushes, diaphoresis</td>
</tr>
<tr>
<td>Seizures</td>
<td>↑ Temperature</td>
</tr>
</tbody>
</table>

Onset ≤ 7-11 d, rarely early (12 h); resolution within 14 d
### Thyroxine toxic dose


<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>≤ 5-6 year</th>
<th>Dose (mg)</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| 2015 | 181| 60%        | 0.01-9    | 16%: 41% adults, 3% children  
No difference in dose between:  
symptomatics and asymptomatics children and adults |
| 2003 | 30 | 100%       | 0.08-9.5  | 27%, mild; most also ingested T₃ |
| 1995 | 92 | 100%       | 0.05-5    | 9%, mild; no toxicity if < 2 mg |
| 1987 | 41 | 100%       | 0.05-13   | 27%, mild: 2.99±2.37 mg  
asymptomatics: 1.75±2.83 mg |
| 1985 | 78 | 96%        | <0.05-3   | 5%, mild: no toxicity if < 1.5 mg  
2 patients, > 10 mg: no effect |

No correlation between ac. thyroxine dose and toxicity
Thyroxine (TT₄) concentration in overdose
(normal range: 51-154 nmol/L)

★ 91-1,219 nmol/L, 2-6 h post ingestion
  *Eur J Pediatr* 2003;162:639 (n=7/30)

★ 157-705 nmol/L, 1-5 h post ingestion
  *Am J Dis child* 1987;141:1025 (n=11/41)

★ 254-1079 nmol/L, < 24 h post ingestion
  *Ped Emerg Care* 1986;2:14 (n=9/9)

★ 337, 382 nmol/L; 3, 18 h post ingestion
  418 nmol/L, 48 h post; mild

Early T₄ measurement is unlikely to affect management

No correlation between early concentration and toxicity
Why acute thyroxine overdose is associated with mild toxicity?

The answer lies in understanding the physiology and pharmacokinetics of thyroid hormones.
**Regulation of the thyroid axis**

**TSH:** 31-kDa hormone, α and β subunits; t½=50 min
- stimulates thyroid hormones (T₄, T₃) synthesis and secretion
- via G protein-coupled receptor; activates adenylyl cyclase → ↑cAMP

**T₄:** prohormone of the more potent triiodothyronine (T₃)
Thyroid hormones synthesis

Tyrosyl residue

TPO

Organification

Coupling

MIT DIT

Source: DOI:10.15347/wjm/2014.008. ISSN 20018762 (modified)
Thyroid hormone transport

★ Secretion from the gland: $T_4 >> T_3$ (x20)
★ Protein binding:
  thyroxine binding globulin (TBG) 80%,
  transthyretin (TTR) 15-20%, albumin 5-10%
  binding proteins increase circulating hormone pool,
  delay clearance, modulate delivery to tissues
★ ↑ serum $T_4$ increases TBG saturation (normal ~ 25%)
Deiodination of thyroid hormones

ID: iodothyronine deiodinase; selenocysteine containing enzymes
ID2: ↓ by hyperthyroidism, fasting, medications (propranolol, PTU)
ID3: inactivates T4 and T3 by producing rT3 and T2, respectively
Deiodination of thyroid hormones

- **ID**: iodothyronine deiodinase; selenocysteine containing enzymes
- **ID2**: ↓ by hyperthyroidism, fasting, medications (propranolol, PTU)
- **ID3**: inactivates $T_4$ and $T_3$ by producing $rT_3$ and $T_2$, respectively
- **$T_4$ inactivates ID2 (↑ ubiquitination); $T_3$ activates ID3 (↑ expression)**
Thyroid hormone action

MCT = monocarboxylate transporter
OATP = organic anion transporting polypeptide
TR = thyroid hormone receptor, RXR = retinoic acid x receptor
TRE = thyroid response element, CoR = co-repressor, CoA = co-activator

Down-regulation
Reduce T₃ binding

T₄, T₃ passively diffuse into the cell
T₃, T₄ into deiodinase 2
T₃, T₄ into deiodinase 2
T₃ binds TR
TR binds RXR
TR complex binds TRE
Gene transcription
mRNA
Protein
rT₃
T₃
T₃ reduces T₃ binding
Pharmacokinetics of levothyroxine

- **Absorption**: duodenum and ileum
  - $F=80\%$ ($T_3 - 95\%$); $T_{max}=4\ h$ ($T_3 - 2\ h$)

- **Protein binding**: 99.96% ($T_3 - 99.6\%$)
  - Protein binding saturation increases in overdose

- **Volume of distribution**: 10 L/kg ($T_3 - 40\ L/kg$)

- **Metabolism**: deiodination (2/3), liver (1/3)

- **Elimination half life**: 7 days ($T_3 - 1\ day$)

- **Early sampling in thyroxine treated patients**:
  - + 8-13% in $TT_4$ and $FT_4$ levels within 5-9 h post dose
  - reflecting distribution phase, not steady state

*(Thyroid 1993;3:81-85)*
Possible reasons for low thyroxine toxicity after acute single overdose

- High protein binding
- ↑ protein binding in overdose (↑ TBG saturation)
- Relative rapid clearance of $T_3$
- Slower $T_4 \rightarrow T_3$ (↑ ubiquitination of ID2 by $T_4$)
- Increased $T_4 \rightarrow rT_3$ and $T_3 \rightarrow T_2$ (induction of ID3 by $T_3$)
- Down-regulation of nuclear thyroid receptors by $T_3$
- Reduced binding of $T_3$ to thyroid receptors by rT3
- Time required for action (conversion, transcription)

More binding, less production, more inactivation, slow action
Evaluation of thyrotoxicosis

- TSH: suppressed in hyperthyroidism (< 0.01 mIU/L)
- Total and free T₄ and T₃ (↑ FT₄ in most thyrotoxicosis)
- Thyroglobulin (Tg): low in thyrotoxicosis factitia
- Radioidine uptake: low in thyrotoxicosis factitia

- Thyroid hormone binding ratio, free T₄ or T₃ index
- Thyroxine binding globulin (TBG)
- Thyroid peroxidase and Tg antibodies:
  ↑ in autoimmune thyroid disease
- Thyroid scanning and ultrasound: for nodular disease
How should thyroxine overdose be assessed?

★ History:
   - dose, circumstances, time elapsed, duration
   - preexisting cardiac disease, chronic thyroxine Tx.

★ Clinical manifestations:
   - note: delayed presentation
   - clinical follow up is recommended

★ Laboratory and ancillary tests:
   - to be considered
Should thyroxine dose be assessed?

★ Paracelsus: "The Dose Makes the Poison"
★ Defining exposure as non/minimally toxic requires:
  - unintentional, asymptomatic, dose estimate
★ Thyroxine overdose may be severe (rarely)
★ Dose should be assessed in all overdose scenarios

Should assessment include laboratory evaluation?

★ May guide need for monitoring and management

When do we need to get laboratory evaluation?

★ According to the overdose scenario
When do we need laboratory evaluation?
Unintentional thyroxine overdose (1)

☆ Pediatric “general”
- single dose, variable amount
- ↓ toxicity as: ↑ PB, ↓ $T_4 \rightarrow T_3$, ↑ $T_4 \rightarrow rT_3$, rapid $T_3$ Cl
- early high $T_4$ levels do not correlate with toxicity
- most patients are asymptomatic or mildly affected
- laboratory evaluation: if patient symptomatic
When do we need laboratory evaluation?
Unintentional thyroxine overdose (2)

★ Medication error – short term
- single (e.g., double dose) or very few extra doses
- new higher steady state has not been reached
- toxicity is usually not expected; could be mild
- laboratory evaluation: if patient symptomatic

★ Medication error – long term
- new higher steady state reached; toxicity expected
- questions: reduce dose? discontinue? renewal?
- laboratory evaluation: even if patient asymptomatic
When do we need laboratory evaluation?
**Intentional thyroxine overdose**

- **Deliberate self harm**
  - single dose, variable amount (usually high)
  - acute (↓ toxicity), acute on chronic (↑ toxicity)
  - early high $T_4$ levels may not correlate with toxicity
  - lab. evaluation: if symptoms, OR acute on chronic

- **Thyrotoxicosis factitia**
  - refer to as unintentional long term medication error
  - tests to differentiate from endogenous disease
  - laboratory evaluation: in all patients
Conclusions

★ All thyroxine overdoses require assessment of: dose, duration, circumstances, symptoms

★ All thyroxine overdoses require clinical follow up

★ Laboratory evaluation is suggested if:
  □ patient symptomatic, regardless of circumstances
  □ long term medication error
  □ intentional (misuse, self harm - sympt. or ac. on ch.)

★ Laboratory evaluation should include:
  □ TSH, total and free $T_4$ and $T_3$
  □ consider tests to distinguish from endogenous dis. (e.g., Tg, antibodies, uptake, scan, sonography)
THANK YOU
## Characteristics of circulating T₄ and T₃

<table>
<thead>
<tr>
<th>Hormone property</th>
<th>T₄</th>
<th>T₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production rate</td>
<td>90 µg/d</td>
<td>32 µg/d</td>
</tr>
<tr>
<td>Fraction directly from thyroid</td>
<td>100%</td>
<td>20%</td>
</tr>
<tr>
<td>Total hormone concentration</td>
<td>8 µg/dL</td>
<td>0.14 µg/dL</td>
</tr>
<tr>
<td>Fraction unbound</td>
<td>0.02%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Unbound hormone concentration</td>
<td>21·10⁻¹² M</td>
<td>6·10⁻¹² M</td>
</tr>
<tr>
<td>Intracellular hormone fraction</td>
<td>~ 20%</td>
<td>~ 70%</td>
</tr>
<tr>
<td>Relative metabolic potency</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>---------------------------</td>
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</tr>
<tr>
<td><strong>TSH</strong></td>
<td>dopamine, steroids,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>levodopa, somatostatin</td>
<td></td>
</tr>
<tr>
<td><strong>PB of T\textsubscript{4},T\textsubscript{3}</strong></td>
<td>salicylates, furosemide</td>
<td></td>
</tr>
<tr>
<td><strong>TBG</strong></td>
<td>androgens, steroids</td>
<td>estrogens, tamoxifem</td>
</tr>
<tr>
<td><strong>I uptake</strong></td>
<td>perchlorate, thiocyanate, ↑ I</td>
<td>↓ I</td>
</tr>
<tr>
<td><strong>Thyroid peroxidase</strong></td>
<td>methimazole, PTU</td>
<td></td>
</tr>
<tr>
<td><strong>ID2</strong> ((T\textsubscript{4} \rightarrow T\textsubscript{3}))</td>
<td>contraceptives, PTU, propranolol, amiodarone, steroids, iopanoic acid</td>
<td></td>
</tr>
<tr>
<td><strong>T\textsubscript{4} synthesis</strong></td>
<td>Li, I (Wolff–Chaikoff)</td>
<td>I (Jod-Basedow)</td>
</tr>
</tbody>
</table>

**TR\textsubscript{α} receptors:** in brain, kidneys, gonads, heart

**TR\textsubscript{β} receptors:** in pituitary gland, liver