Food-drug interactions and its effects on drug therapy management

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How would you tell me to take levothyroxine?
"1st thing in the morning...with a big glass of water...Nothing else for a whole hour..."
"...well 30min..."

Can I drink coffee with it?
"...good question..." "...yeah sure, why not...

Objectives

Pharmacokinetics
- Absorption
- Distribution
- Metabolism
- Elimination

Drug therapy management
- Adherence
- Tolerability
- Toxicity
- Efficacy

Levothyroxine
-a synthetic form of thyroxine (T4)

Mechanism of action
- converted to its active metabolite, L-triiodothyronine (T3)
- exert metabolic effects through control of DNA transcription and protein synthesis

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References

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- Absorption
  - ~80%
  - majority of dose absorbed from the jejunum and upper ileum

Levothyroxine
Initial Dose

- Oral: ~1.7 mcg/kg/day
  - usual doses ≤200 mcg/day
  - doses ≥300 mcg/day are rare
  - consider poor compliance, malabsorption, and/or drug interactions

Levothyroxine
Monitor

- Adults: TSH every 6-8 weeks until normalized
  - 8-12 weeks after dosage changes
- TSH (~0.5 to 5.0 mU/L)
- sx of toxicity

Levothyroxine + Dietary Fiber

TSH was determined during high-fiber intake and 2-3 months after cessation of fiber supplements.

Levothyroxine + Calcium

Subjects were instructed to take 1,200 mg/d of elemental calcium as calcium carbonate, ingested with their levothyroxine, for 3 months

Effects of dietary fiber on serum TSH and levothyroxine dose in 13 hypothyroid patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Fiber Type</th>
<th>TSH (mU/L)</th>
<th>Levothyroxine Dose (mcg/day)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Wheat bran</td>
<td>150</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>Rice bran</td>
<td>150</td>
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<tr>
<td>3</td>
<td>Oat bran</td>
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<tr>
<td>4</td>
<td>Flax bran</td>
<td>150</td>
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</tr>
<tr>
<td>5</td>
<td>Psyllium</td>
<td>150</td>
<td>0.2</td>
</tr>
<tr>
<td>6</td>
<td>Barley bran</td>
<td>150</td>
<td>0.2</td>
</tr>
<tr>
<td>7</td>
<td>Brown rice</td>
<td>150</td>
<td>0.2</td>
</tr>
<tr>
<td>8</td>
<td>White rice</td>
<td>150</td>
<td>0.2</td>
</tr>
<tr>
<td>9</td>
<td>Bran bread</td>
<td>150</td>
<td>0.2</td>
</tr>
<tr>
<td>10</td>
<td>Oat bread</td>
<td>150</td>
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</tr>
<tr>
<td>11</td>
<td>Wheat bread</td>
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</tr>
<tr>
<td>12</td>
<td>Rice bread</td>
<td>150</td>
<td>0.2</td>
</tr>
<tr>
<td>13</td>
<td>Oat bran</td>
<td>150</td>
<td>0.2</td>
</tr>
</tbody>
</table>

* Add notes: alterations on the same patient under the appropriate condition.
**Levothyroxine + Ferrous Sulfate**

All patients were instructed to ingest simultaneously, a 300-mg ferrous sulfate tablet and their usual thyroxine dose every day for 12 weeks.

Mean TSH increased from 1.6 to 5.4 mU/L.

“The mechanism of the drug interaction is probably caused by the formation of insoluble ferric-thyroxine complexes...resulting in a reduction in thyroxine absorption.”

**Levothyroxine + Coffee**

“likely that coffee physically interacts with T4, rendering the hormone less available for intestinal absorption.”

**Levothyroxine + Food Timing**

Wenzel et al. “Aspects of the absorption of oral L-thyroxine in normal man”

- Patients ingested levothyroxine under two settings:
  1. Fasting
  2. Immediately before the consumption of two buttered rolls and a boiled egg.

- Absorption was significantly better in the fasting state.

Beểnega et al. “Delayed intestinal absorption of levothyroxine.”

- After a month of separating breakfast and levothyroxine ingestion by at least 60 min, the TSH levels in these patients became adequately suppressed.

These findings form the basis of current recommendations to ingest oral levothyroxine 60 min prior to food intake.

**Outline**

- Objectives
- Levothyroxine
- Isoniazid
- Atripla
- Additional food/drug interactions
- Resources
- References

**Isoniazid**
Isoniazid

- antitubercular agent used in treatment of latent tuberculosis

Absorption
- Very water soluble. Practically insoluble in lipid solvents
- Absorbed in upper small intestine. Stomach does not play a significant role. Hence gastric emptying rate becomes important.

Mechanism of Action
- Inhibits synthesis of mycolic acids (essential components of mycobacterial cell walls)
- Kills only dividing bacteria
- Bacteriostatic in first 24hrs. Bactericidal thereafter.

Guidelines for the treatment of Latent Tuberculosis

"...The initial approach to gastrointestinal intolerance, not associated with hepatic toxicity, is to change the hour of drug administration."

"...if patients have epigastric distress or nausea with the first-line drugs, dosing with food is recommended."

Table: Study Intervention w/isoniazid

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Amax</th>
<th>ACmax</th>
<th>ABDC</th>
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<tbody>
<tr>
<td>Peloquin et al.</td>
<td>High-fat meal</td>
<td>↑50%</td>
<td>↑11%</td>
<td>↑12%</td>
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<td>Melander et al.</td>
<td>Carb based</td>
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<td>↓3%</td>
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<td>Mannisto et al.</td>
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<td>Joshi et al.</td>
<td>Carb based</td>
<td>↑35%</td>
<td>↓22%</td>
<td>↓20%</td>
</tr>
<tr>
<td>Carb based lunch</td>
<td>↑144%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study Intervention w/isoniazid

Graph: Absorption: Amax

Time
Isoniazid + Food
Does it make a difference?

...so what?

Figure 1: Time-averaged INH serum concentrations for 14 subjects across the four treatments.

Isoniazid
Mechanism of Action... revisited

Post Antibiotic Effect
- the continued suppression of bacterial growth following limited exposure of organisms to an antimicrobial agent

Time-dependent vs. concentration-dependent killing
- it is better to keep the time of serum concentration above the MIC longer (AUC/MIC larger)
- the higher the serum concentration, the greater the postantibiotic effect

Cmax and AUC of INH were significantly reduced by food.

The UC Public Health Service TB Trial 22 results:
- lower level of AUC of INH in the first 12hrs significantly associated with treatment failure or relapse.

Mechanism of Action... revisited


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Atripla

### Atripla

**Drugs**
- tenofovir
- emtricitabine
- efavirenz

**Class**
- NRTI
- NRTI
- Non-NRTI

**Side effects**
- Renal insufficiency
- Osteomalacia
- Hyperpigmentation
- Rash
- Neuropsychiatric
- Transaminase levels

**High-fat meal**
- AUC ↑40%
- Cmax ↑14%
- no Δ from fasting
- AUC ↑28%
- Cmax ↑19%

**Light meal**
- no Δ from fasting
- ---

Patient Case...
32yo male diagnosed with HIV
MEDS: Atripla one tablet daily (started 5/2012)
Abilify 2mg daily
LABS: lipids, comprehensive metabolic panel are all WNL.

Treatment Options:
1) Complera
2) Truvada + Viramune
3) Strivid

Remember...
1) Adherence
2) Tolerability
3) Toxicity
4) Efficacy
Objectives

- Absorption
- Distribution
- Metabolism
- Elimination

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- Tolerability
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Levothyroxine/isoniazid/Atripla
- What they interact with?
- Interaction/timing
  - pharmacokinetics
    - adherence, tolerability, toxicity, efficacy

Drug-therapy management
- Applying evidence-based data/guidelines
- Working with patient to design a regimen that fits their needs (financially, culturally, socially, etc.)

References

1. Lexicomp and UpToDate searches on "levothyroxine", accessed 9/2012
2. UpToDate search term "Levothyroxine", accessed 8/2012
5. Norman R. “Ferrous Sulfate Reduces Thyroxine Efficacy in Patients with Hypothyroidism” 15 December 1992 • Annals of Internal Medicine • Volume 117 • Number 12
10. C. A. Peloquin, “Pharmacokinetics of isoniazid under fasting condition, with food, and with antacid” INT J TUBERC LUNG DIS 3(8):703–710