Managing Drug Interactions That Can Reduce Levothyroxine Efficacy

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Key words: Drug interactions, Levothyroxine, Hypothyroidism

Levothyroxine is one of the most commonly prescribed medications for the treatment of persons with hypothyroidism and the suppression of thyroid neoplasms. Most persons with hypothyroidism require lifelong therapy with levothyroxine. The absorption of levothyroxine after oral administration is about 80%. Certain drugs and dietary components can interfere with the bioavailability of levothyroxine. Drugs include calcium carbonate, iron salts, and aluminum and magnesium-containing antacids.
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Drug Interactions

**Calcium carbonate.** Schneyer\(^4\) first reported in 1998 that calcium carbonate reduced the efficacy of levothyroxine and proposed that calcium carbonate, excipients, or contaminants in the preparation may form insoluble chelates with levothyroxine, resulting in decreased absorption. A cohort study of 20 patients who were receiving long-term levothyroxine therapy and calcium carbonate showed reduced levothyroxine absorption and significant increases in thyroid-stimulating hormone (TSH) levels.\(^1\) In vitro data collected by the same investigators revealed that levothyroxine adsorbs to calcium carbonate at a pH of 2.0, which simulates a gastric pH. In a pharmacokinetic study of 7 healthy volunteers, Singh and colleagues\(^5\) demonstrated that coadministration of calcium carbonate with levothyroxine reduces total thyroxine absorption over 6 hours. Four case reports have confirmed the significance of this interaction.\(^6-9\)

**Ferrous salts and chromium.** Campbell and colleagues\(^10\) first studied the interaction of levothyroxine and ferrous sulfate in 1992. For 12 weeks, ferrous sulfate was added daily to the

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### Table 1. Signs and Symptoms of Hypothyroidism

<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Bradycardia</td>
<td>Cold intolerance</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>Constipation</td>
</tr>
<tr>
<td>Coarse, brittle hair</td>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Dry skin</td>
<td>Decreased hearing</td>
</tr>
<tr>
<td>Goiter</td>
<td>Depression</td>
</tr>
<tr>
<td>Hyporeflexia</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Myxedema (puffy face, hands, and feet)</td>
<td>Fatigue, lethargy</td>
</tr>
<tr>
<td>Pallor</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>Impaired memory</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>Menstrual disturbances</td>
</tr>
<tr>
<td>Muscle/joint pain</td>
<td>Weight gain</td>
</tr>
</tbody>
</table>

Adapted from Jameson J, Weetman A. In: Kasper DL et al, eds. Harrison’s Principles of Internal Medicine. 2005.\(^18\)
Regimen of 14 patients who were receiving stable levothyroxine replacement therapy. Eleven patients had an increase in TSH levels; 9 patients experienced an increase in signs and symptoms of hypothyroidism. In vitro data verified the formation of insoluble complexes of the iron molecule with levothyroxine. A case report of a pregnant woman showed the clinical relevance of the interaction of ferrous sulfate and levothyroxine. The patient developed hypothyroidism with the addition of ferrous sulfate, necessitating an increase in the levothyroxine dose; she developed hyperthyroidism when the iron supplement was discontinued. Another case report also showed an increase in TSH levels in a patient who took daily ferrous fumarate supplements. Chromium is similar to iron in molecular size and charge. It is available OTC as a dietary supplement and is most often used for glucose control and weight loss. In a pharmacokinetic study of 7 healthy volunteers, chromium decreased levothyroxine absorption.

**Aluminum- and magnesium-containing antacids.** An increase in TSH levels with aluminum hydroxide was first reported in 1992 in a euthyroid patient (patient with a normally functioning thyroid) who was taking a stable dose of levothyroxine. The patient’s TSH level returned to baseline after the aluminum hydroxide-containing antacid was discontinued; it increased again with rechallenge. The investigators confirmed this observation in 5 additional patients and in in vitro experiments that showed complexing of levothyroxine to aluminum hydroxide. (Note that sucralfate is a complex of aluminum hydroxide and can interfere with levothyroxine absorption.) Another case series confirmed the aluminum interaction by in vitro experiments and resulted in decreased absorption with magnesium oxide. In vitro experiments with various magnesium salts showed that magnesium carbonate may be more likely than magnesium oxide to adsorb to levothyroxine.

### Management of Interactions

Frequent screening for drug interactions is prudent in persons who are receiving levothyroxine therapy. Consider the possibility of a drug interaction when patients present with worsening signs and symptoms of hypothyroidism (**Table 1**). A thorough medication history should include questions about use of OTC medications, such as antacids and laxatives, and dietary supplements, in order to identify divalent and trivalent cations. These products may be used by patients to treat symptoms of hypothyroidism, such as constipation. In addition, many postmenopausal women receive levothyroxine therapy; therefore, concurrent use of calcium supplements is likely. Management of these interactions can be resolved by discontinuing the interacting drug or supplement; if this is not possible, advise patients to separate the doses of the 2 agents (**Table 2**). For patients who are receiving long-term supplementation with iron or calcium, more frequent monitoring or adjustment of the levothyroxine dose may be required.

### References


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