Levothyroxine in Psychiatry: Issues Related to Absorption After Oral Dosing

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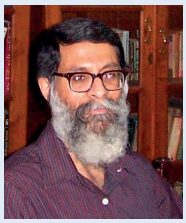

Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to *JCP* readers in psychiatric and general medical settings.

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The prevalence of hypothyroidism is about 0.3%; the disorder is more common with increasing age and in women relative to men.[1] Subclinical hypothyroidism occurs in 4%–20% of adults, depending on the population studied and the disease definition applied.[2] Clinical and subclinical hypothyroidism are sometimes observed in psychiatric disorders. For example, these endocrine states may be associated with developmental delay or mental retardation,[3] mood or cognitive disturbance in the elderly,[4] dementia,[5] psychosis,[6] depression,[7] bipolar disorder,[8] rapid-cycling mood disorder,[9] and other conditions. Hypothyroidism may also be an adverse outcome of lithium therapy.[10] Levothyroxine (T_4) supplementation is commonly considered in such situations and when depressed patients are medication refractory.[11]

Once patients have been stabilized on T_4 therapy, the dose tends to remain constant for years.[12] However, problems could arise from situations that affect T_4 absorption, and psychiatrists may not be familiar with these pharmacokinetic matters. This article therefore examines clinically significant food and drug interactions, with specific focus on T_4 absorption after oral dosing.

The Stomach and Absorption of T_4

Most of an orally administered dose of T_4 is absorbed within 20–30 minutes, and maximal absorption occurs by 3 hours in the jejunum and ileum.[12] This implies that if nothing else is ingested within 3 hours of an oral T_4 dose, then there will be no interference with T_4 absorption.

Gastric acidity is important for the absorption of T_4; physiologic states associated with diminished gastric acidity and drugs that diminish gastric acidity both decrease T_4 absorption.[12] The absorption of T_4 will therefore be lower in the presence of alcoholism, atrophic gastritis, small bowel disease, or malabsorption states associated with any cause, including bariatric surgery.[12,13] Absorption of T_4 would also be diminished by proton pump inhibitors[14] and antacids.[12,13] In theory, anticholinergic drugs, which decrease gastric acidity,[15] may also decrease T_4 absorption, although this has not yet been studied or reported. It is best, therefore, to avoid administering T_4 in proximity with drugs that reduce gastric acidity.

Food and Absorption of T_4

It is recommended that T_4 be taken on an empty stomach, at least half an hour before breakfast, because food interferes with the absorption of T_4.[12,13] Coffee has been specially described to diminish T_4 absorption,[16] as have grapefruit juice (but not orange juice),[17,18] papaya fruit,[19] and dietary fiber, including bran.[16] Milk and other dairy products, and perhaps other foods that are rich in calcium, may impair the bioavailability of T_4 (see the next section), although there is no formal study of the interaction.

Soy milk[20] and soy protein[21] can also substantially interfere with T_4 absorption. Administering T_4 in soft gel capsule form has been suggested as a possible way of reducing the effect of coffee on the absorption of T_4.[22]

- Circumstances that result in decreased absorption of orally administered levothyroxine (T_4) include drugs and disorders that reduce gastric acidity; constituents of food such as fiber; items of consumption such as soy, coffee, and grapefruit juice; and drugs and supplements such as calcium, iron, sucralfate, orlistat, and phosphate binders.
- Patients should therefore take T_4 on an empty stomach, at a time as distant as possible from intake of food, beverages, and other medications.
- If this is not feasible, possible impairment in absorption can be accepted and the dose of T_4 titrated to target hormonal levels.

Medications and Absorption of T_4

Besides agents that reduce gastric acidity, many drugs have been reported to decrease T_4 absorption. The commonest are calcium and iron supplements.[12,13,23] All formulations of calcium—carbonate, acetate, and citrate—reduce T_4 absorption by about 20%–25%.[24] It has therefore been suggested that if patients receiving T_4 also need calcium supplementation, the calcium should be dosed at least 4 hours distant from the T_4.[25]

Others drugs that can impair T_4 absorption include raloxifene,[26,27] imatinib,[28] orlistat,[29] phosphate binders such as sevelamer[30,31] and lanthanum carbonate,[32] nutritional supplements such as chromium picolinate,[30] sucralfate, ion exchange resins, bile acid sequestrants,[12,13] and possibly ciprofloxacin.[33] Waiting 4 hours after ingestion of T_4 before giving bile acid sequestrants such as colesevelam may suffice to prevent the latter from interfering with the absorption of the former.[34] Ezetimibe does not interfere with T_4 absorption.[30]

This list is not comprehensive. There have been many stray reports of interactions in which the interaction was minor or the mechanism was unknown. This article preferentially emphasizes the important interactions and provides guidance that could be expected to cover all contingencies, regardless of the interacting drug.

T_4 Supplementation and the Risk of an Unexpected Hyperthyroid State

A patient who is started on T_4 may regularly take it under circumstances of diminished absorption (eg, proximal to breakfast), and if the clinician does not know this when titrating the T_4 dose to clinical efficacy, the patient will receive a higher T_4 dose than would otherwise have been necessary. If the patient's dosing behavior later changes (eg, the patient regularly delays breakfast), resulting in improved absorption of T_4, there is a risk that the T_4 dose will become supraphysiologic, leading to an unexpected hyperthyroid state. Proper patient education, regular inquiry about dosing behavior, and regular monitoring of cardiovascular and hormonal parameters could help clinicians remain alert to such changes.

Clinical Guidance

1. Patients are generally advised to take T_4 early in the morning, at least 30 minutes before breakfast. It is necessary for them to understand that coffee, food, and many medications impair the absorption of T_4 and therefore they should take T_4 on an empty stomach, with a glass of water (but not coffee), at a time as distant as possible from when they take their comedications and eat their next meal.
2. Proper advice is easy to give but not necessarily easy to follow. Some patients may rise, complete their morning rituals and routines, and leave for work, all within the span of half an hour. Others may have medication scheduling problems related to shift work. Still others may have difficulty in remembering to take their psychotropic or general medications unless these medications are taken with breakfast. T_4 absorption will probably be diminished in all of these patients. These patients should nevertheless be advised to adhere to the usual guidance as far as possible. Beyond this, the clinician should recognize that the compromised absorption of T_4 can usually be compensated for by an increase in the T_4 dose and that the appropriate dose can be discovered by titrating to target thyroid-stimulating hormone (TSH) levels. Importantly, in such situations, patients should not later change their dietary or dosing habits (eg, delay or skip breakfast or shift other morning medications to the afternoon or night) lest the change result in normalization of T_4 absorption and thence to a hyperthyroid state. Or, if a change in dietary or dosing habits is inevitable, the patient should be instructed to inform the clinician, who can then down-titrate the T_4 dose on the basis of reestimation of hormonal levels.
3. In a 6-month, randomized, double-blind, crossover trial in 105 patients with primary hypothyroidism (all of whom were on a stable dose of T_4), Bolk et al[35] showed that T_4 administered at bedtime was associated with lower TSH and higher free T_4 and total triiodothyronine levels relative to the same dose administered in the morning. An earlier pilot study[36] by the same team suggested that bedtime dosing of T_4 does not alter the TSH circadian rhythm. This is logical, given that T_4 has a half-life of about a week (longer, in patients with hypothyroidism). Therefore, in unusual circumstances, some thought must be given to the possibility of dosing T_4 just before bedtime, with dosing as distant from the last meal (and the last comedications) as possible.
4. Proton pump inhibitor (PPI) use may pose a special problem. The half-life of PPIs is typically short, about an hour. However, their duration of action is considerably longer, about a day, because new H+/K+ pumps must be synthesized for fresh acid

production.[37] An additional matter is that PPIs are best dosed about 20 minutes before breakfast, when they could be expected to maximally interfere with T_4 absorption as T_4 is conventionally dosed. Clinicians should be aware that in patients who go on or off PPI therapy, fluctuations in T_4 absorption could occur, with associated fluctuations in thyroid status. There may therefore be a case for bedtime dosing of T_4 in patients receiving PPI therapy.

5. Clinicians should be aware that any sustained changes in the absorption of T_4 would result in changes in thyroid status only after a time lag of a few weeks. This is because, as already stated, T_4 has a long half-life.

Parting Notes

There are patients in whom hormonal levels show wide fluctuations in the context of a stable T_4 dose. Before suspecting issues related to absorption, clinicians must rule out poor medication adherence. Because T_4 has a long half-life, occasional missed doses (or occasional poor absorption for any reason) will not have a significant clinical impact; however, frequent nonadherence would raise TSH levels. Becoming pregnant or gaining weight could also increase T_4 need.[12] Finally, patients who switch formulations of T_4 may experience changes in the degree of adequacy of dose related to differences in bioavailability.

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