Taking care of thyroxine

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Summary

Some of the pharmaceutical properties of thyroxine have important implications for the quality use of medicines. The stability of thyroxine tablets is limited and they may reach the expiry date before the bottle is finished. Administration should preferably be on an empty stomach and be consistent with respect to food and other drugs. The long half-life of thyroxine enables longer dosing intervals of up to a week if required. The two Australian brands of thyroxine are identical and patients can swap brands safely, but this should not be assumed for overseas brands.

Key words: hypothyroidism, hyperthyroidism, pharmacokinetics.

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Introduction

Thyroxine tablets are important in managing hypothyroidism, but treatment may be sub-optimal if they are used incorrectly. The tablets have pharmaceutical properties which can impair the patient's management. Discussing the correct use and storage of the tablets is an important part of prescribing thyroxine.

Availability

Synthetic preparations of thyroxine contain the *laevo* isomer of thyroxine, usually as the sodium salt. There are two brands of thyroxine available in Australia, each as 50 microgram, 100 microgram and 200 microgram tablets (pack size 200) with five repeats on the Pharmaceutical Benefits Scheme. Parenteral preparations of thyroid hormone have little use in Australia, outside of specialist centres.

The two Australian brands are marketed by Sigma and one of its subsidiaries. They are identical products so patients can swap them safely, but this assumption should **not** be extended to overseas brands.

Stability

Thyroxine is stable in dry air, but unstable in the presence of light, heat and humidity. In some cases overseas, thyroxine tablets have been unstable even at room temperature, and storage temperatures of 8°C to 15°C were required to maintain potency. In the USA, the Food and Drug Administration has determined that stability and potency problems with oral thyroxine preparations could potentially have adverse effects on health. It is therefore very important that thyroxine tablets should be kept in their original container and stored out of sunlight in a cool dry place.[1]

The expiry date for Australian manufactured thyroxine tablets is one year from the date of manufacture. There are 200 tablets in a bottle, so it is possible that patients on half tablet doses will not finish the bottle before the stock expires. The expiry date should be emphasised to the patient to ensure they do not continue taking a thyroxine preparation that may be waning in potency. However, stock with a shelf-life of 18 months will soon be available. This formulation will require refrigeration at all times.

Absorption

Thyroxine is variably absorbed from the gut following oral administration. It has a bioavailability of 40–80%. Absorption may decrease with age.[1,2]

The extent of thyroxine absorption is increased in the fasting state and is influenced by the content of the gastrointestinal tract. Some substances bind the thyroxine, making it unavailable for diffusion across the gut wall. Concurrent administration with iron salts, antacids, calcium carbonate (including milk), sucralfate, cholestyramine and soy-based formulas may therefore decrease absorption of thyroxine.

Administration

Patients should be instructed to take thyroxine 30–60 minutes before breakfast in order to maximise absorption. If this is too difficult or threatens compliance, the patient may try taking the thyroxine last thing at night on an empty stomach. Patients who still decide to take their tablets with, rather than before, breakfast need to do this consistently, to avoid fluctuating thyroxine concentrations. Depending on the fibre and milk content of the meal, taking thyroxine with food may require a larger dose to maintain euthyroidism, because of the decreased bioavailability.

While most patients take a daily dose, the long half-life of thyroxine lends itself to longer dosing intervals, such as alternate daily dosing. Once-weekly dosing is also possible although a slightly larger dose than seven times the normal daily dose may be required. This regimen may be suitable for poorly compliant patients who require supervised dosing.[3]

For patients, particularly children, who cannot swallow tablets, the tablets may be crushed in 10–20 mL of water, breast milk or non-soybean formula. The resulting mixture should be used immediately and any remainder discarded.[2] Breast milk contains

only 20–30% of the calcium concentration of cows milk, making the likelihood of decreased thyroxine bioavailability less likely. Nonetheless, if breast milk is used to deliver the thyroxine, it should be used consistently, in order to minimise any variation in absorption.

Onset and duration of action

The half-life of thyroxine in euthyroidism is 6–7 days. This is reduced to 3–4 days in hyperthyroidism and prolonged to 9–10 days in hypothyroidism. Thyroxine has a full therapeutic effect 3–4 weeks after starting treatment and will continue to have a therapeutic action for 1–3 weeks after treatment stops. In view of the long half-life, dose changes should only be made every 3–4 weeks. Despite undergoing both hepatic and renal clearance, there is no evidence that dose adjustment is required for patients with liver or kidney disease.[1,2]

Monitoring

The dosage is adjusted according to thyroxine and thyroid stimulating hormone plasma concentrations, which should always be interpreted in conjunction with each other and the patient's condition.[4] Monitoring is suggested at six-weekly intervals when starting therapy until the patient has stabilised, then six monthly thereafter, or earlier if symptoms suggestive of hyper- or hypothyroidism occur.

Drug interactions

Most drug interactions are seen during shifts to and from the euthyroid state and rarely have any clinical significance during periods of thyroid stability. The hyperthyroid state increases clearance of some hepatically cleared drugs, notably propranolol, metoprolol and theophylline. Antacids, iron salts, calcium carbonate (milk), sucralfate, cholestyramine and soy-based formulas reduce the absorption of thyroxine.

Conclusion

There are significant stability, absorption and drug interaction issues surrounding the use of thyroxine. It is essential that prescribers and pharmacists convey this information to patients in order that therapeutic efficacy may be maximised.

References

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3. Grebe SK, Cooke RR, Ford HC, Fagerstrom JN, Cordwell DP, Lever NA, et al. Treatment of hypothyroidism with once weekly thyroxine. J Clin Endocrinol Metab 1997;82:870-5.
4. Australian Medicines Handbook 2004. Adelaide: Australian Medicines Handbook Pty Ltd; 2004.

Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 79)

9. The dose of thyroxine should be decreased in patients with renal failure.
10. Food increases the absorption of thyroxine tablets.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Aprepitant

Emend (Merck Sharp and Dohme)

80 mg and 125 mg capsules

Approved indication: emetogenic cancer chemotherapy

Australian Medicines Handbook section 12.3

Many anticancer drugs induce nausea and vomiting. Cisplatin is particularly toxic and induces vomiting which can last for days. Although anti-emetic regimens can control some of the symptoms, possibly half the patients treated with highly emetogenic chemotherapy continue to suffer nausea and vomiting.

To address the problem, researchers have looked at the role of substance P in vomiting. This peptide is found in the brain and the gut and its actions are mediated through the neurokinin-1 receptor. Blocking this receptor may prevent vomiting.

Aprepitant is a selective antagonist of the neurokinin-1 receptor which can cross the blood-brain barrier. It has no affinity for serotonin ($5HT_3$) or dopamine (D_2) receptors.

Patients take aprepitant orally once a day for three days, starting one hour before chemotherapy. The drug is slowly absorbed and extensively metabolised. As it has non-linear pharmacokinetics increasing the dose reduces bioavailability and clearance.