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

1. AHFS drug handbook. 2nd ed. Bethesda (MD): American Society of Health-System Pharmacists, Lippincott Williams & Wilkins; 2003.
2. Thomas J, editor. Australian Prescription Products Guide 2003. 32nd ed. Hawthorn: Australian Pharmaceutical Publishing Company Limited; 2003.
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

Toft AD. Clinical practice. Subclinical hyperthyroidism. N Engl J Med 2001;345:512-6.

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.

The metabolism involves cytochrome P450 3A4 so there is a potential for interaction with other drugs, such as midazolam, metabolised by this system. Aprepitant also induces the metabolism of warfarin. The half-life of aprepitant is 9–13 hours.

Aprepitant was tested in a variety of combinations with dexamethasone, granisetron ($5HT_3$ antagonist) and a placebo in 351 patients having cisplatin for the first time. In the first 24 hours after treatment, 80% of the patients given granisetron, dexamethasone and aprepitant had no vomiting compared with 57% of those treated with granisetron and dexamethasone. Delayed emesis was prevented in 63% of the patients taking the three drugs, but in only 29% of those taking granisetron and dexamethasone.[1]

In this trial there was no extra benefit in giving aprepitant for five days. Another trial therefore compared a three-day regimen with a standard regimen of ondansetron and dexamethasone. The 530 patients had not previously been treated with cisplatin. There was no acute vomiting in 89% of the patients given aprepitant, ondansetron and dexamethasone compared with 78% of those given the standard regimen. Delayed emesis did not occur in 75% of the patients taking aprepitant and 56% of those taking the standard regimen.[2] Another randomised placebo-controlled trial produced similar results.[3]

As patients with cancer usually require several doses of chemotherapy, another trial has studied two regimens of aprepitant given during six cycles of cisplatin. All 202 patients received a standard regimen of ondansetron and dexamethasone. The prevention of emesis declined from 49% to 34% after six cycles in patients treated with the standard regimen. In patients who also took aprepitant, 64% had no vomiting after the first cycle and 59% had no vomiting after the sixth cycle.[4]

Assessing adverse events in patients who are given multiple drugs for their cancers can be difficult. Adverse events associated with regimens containing aprepitant include hiccups, asthenia, headache and altered liver function.

Although the efficacy of aprepitant has been proven, questions remain about its role in practice. As treatment guidelines often include metoclopramide for the prevention of delayed emesis, aprepitant should be compared with such regimens. There also needs to be more study of the effectiveness of aprepitant in subsequent cycles of chemotherapy. Although the results of the trial[4] look promising, few patients completed six cycles of chemotherapy. At present aprepitant can only be used with highly emetogenic chemotherapy, including high-dose cisplatin.

References †

1. Campos D, Pereira JR, Reinhardt RR, Carracedo C, Poli S, Vogel C, et al. Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. J Clin Oncol 2001;19:1759-67.
2. Hesketh PJ, Grunberg SM, Gralla RJ, Warr DG, Roila F, de Wit R, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin – the Aprepitant Protocol 052 Study Group. J Clin Oncol 2003;21:4112-9.
3. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Ma GJ, Eldridge K, Hipple A, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Cancer 2003;97:3090-8.
4. de Wit R, Herrstedt J, Rapoport B, Carides AD, Carides G, Elmer M, et al. Addition of the oral NK_1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. J Clin Oncol 2003;21:4105-11.

Iloprost

Ventavis (Schering)

Ampoules containing 20 microgram (10 microgram/mL) nebuliser solution

Approved indication: pulmonary hypertension

Australian Medicines Handbook section 6.7.3

Increased pressure in the pulmonary artery may have no obvious cause or it may be secondary to conditions such as thromboembolism and connective tissue diseases.[1] It leads to signs of right-sided heart failure, such as peripheral oedema and liver enlargement.

Some secondary causes can be treated. For example, pulmonary artery hypertension due to chronic thromboembolism may respond to pulmonary thromboendarterectomy. Some patients with advanced disease may live long enough to receive a heart-lung transplant.

Patients with pulmonary hypertension may have an imbalance of prostacyclin and thromboxane A_2. Giving an analogue of prostacyclin may therefore induce vasodilatation and reduce pressure in the pulmonary artery. Epoprostenol was approved for use in primary pulmonary hypertension in 2002, but it has to be given by continuous intravenous infusion. Treprostinil was approved in 2003, but requires continuous subcutaneous infusion. Iloprost is also an analogue of prostacyclin, but it can be given by inhalation.

Patients inhale a nebulised solution over 5–10 minutes. The serum concentration of iloprost peaks at the end of the inhalation but declines rapidly. Iloprost is extensively metabolised and none can be detected an hour after the inhalation. Some patients will need to take a dose nine times a day. Most of the metabolites are excreted in the urine, so clearance can be reduced by renal and hepatic dysfunction.

A randomised-controlled trial compared iloprost with an inhaled placebo in 203 patients with primary or secondary pulmonary hypertension. After 12 weeks, function had improved in 16.8% of the patients given iloprost, but only in 4.9% of those given a placebo.[2]

Another study enrolled 31 patients with primary pulmonary hypertension and followed them for a year. The mean

pulmonary artery pressure was reduced in the 24 people who completed the study. This was associated with an increased exercise capacity.[3]

While dyspnoea improves with iloprost, coughing is common in the first weeks of treatment. Patients may also complain of flushing and pain in the jaw. Other common adverse effects are hypotension, syncope, trismus and headache.

Although iloprost is significantly better than placebo the absolute benefits are limited. In the placebo-controlled study patients given iloprost for 12 weeks were able to walk an extra 36.4 metres in six minutes.[2] Few of the patients with secondary pulmonary hypertension gained much benefit. Iloprost has been approved for secondary pulmonary hypertension for a strictly limited range of conditions.

Inhaled iloprost is likely to be cheaper than intravenous epoprostenol, but epoprostenol is proven to increase survival in patients with primary pulmonary hypertension. In contrast to the other prostacyclin analogues, iloprost is given intermittently. It is uncertain whether there could be a rebound in the pulmonary artery pressure between inhalations.

In addition to the prostacyclin analogues bosentan, an oral endothelin receptor antagonist, is also available to treat primary pulmonary hypertension. Comparative studies are therefore needed to determine the best medical therapy.

References

1. Keogh AM, McNeil KD, Williams T, Gabbay E, Cleland LG. Pulmonary arterial hypertension: a new era in management. Med J Aust 2003;178:564-7.
2. Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002;347:322-9.
3. Hoeper MM, Schwarze M, Ehlerding S, Adler-Schuermeyer A, Spiekerkoetter E, Niedermeyer J, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. N Engl J Med 2000;342:1866-70.

Methyl-5-aminolevulinate

Metvix (Galderma)

2 g tubes of cream containing 160 mg/g

Approved indications: actinic keratoses, basal cell carcinoma

Australian Medicines Handbook section 14.3

Squamous cell carcinomas can develop from actinic keratoses. While some keratoses will resolve with reduced exposure to sunlight others need to be removed. As an alternative to surgical treatments, severe cases can be treated with topical fluorouracil. Methyl-5-aminolevulinate, which is a porphyrin precursor, is another antineoplastic drug that can be applied directly to the lesions.

After applying methyl-5-aminolevulinate, the lesion is covered with an occlusive dressing for three hours. This results in the accumulation of the porphyrins which are produced by the enzymatic conversion of methyl-5-aminolevulinate. The lesion is then exposed to a dose of red light. This light activates the intracellular porphyrins causing damage to the cells. The treatment is repeated one week after the first application. If there is no response after three months the patient can be re-treated once.

In an Australian study there was a complete response in 71 of 88 patients with solar keratoses. A placebo cream resulted in only three of 23 patients responding. The complete response rate of 81% was greater than the 60% who responded to one treatment of cryotherapy. A European study also compared the two treatments, but found that the response rate to cryotherapy was higher (75%) than the response to methyl-5-aminolevulinate (69%).[1]

Methyl-5-aminolevulinate can also be used to treat basal cell carcinoma. Although a few more patients will respond to photodynamic therapy than cryotherapy (95% v 91%), the response rate is less than that of surgical excision (90% v 98%). Recurrences are also less likely after surgical excision, but photodynamic therapy may give a better cosmetic outcome. Methyl-5-aminolevulinate can therefore be considered for superficial or nodular basal cell carcinomas where surgery is inappropriate.

As methyl-5-aminolevulinate is a photosensitiser it can cause phototoxic reactions. Patients should not expose the treated areas and surrounding skin to sunlight for two days after treatment. Burning, pain, redness and oedema are very common adverse effects. Some patients develop blisters or skin ulcers. In the European study more of the patients had a reaction to methyl-5-aminolevulinate than to cryotherapy (43% v 26%).[1]

Methyl-5-aminolevulinate works best on keratoses which are not hyperkeratotic. If treatment is successful it gives a good cosmetic result. It can therefore be considered for thin lesions on the face or scalp when other treatments are unsuitable.

Reference

1. Szeimies RM, Karrer S, Radakovic-Fijan S, Tanew A, Calzavara-Pinton PG, Zane C, et al. Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. J Am Acad Dermatol 2002;47:258-62.

NEW FORMULATIONS

Amisulpride

Solian solution (Sanofi-Synthelabo)

100 mg/mL oral solution

Metoprolol succinate

Toprol-XL (AstraZeneca)

23.75 mg, 47.5 mg, 95 mg and 190 mg controlled-release tablets

Approved indication: chronic heart failure

Australian Medicines Handbook section 6.4.3

Beta blockers used to be contraindicated in heart failure, but they can benefit some patients with chronic stable heart failure.[1]

A placebo-controlled study of 3991 patients who were already on optimum therapy, such as a diuretic and an ACE inhibitor, found that metoprolol significantly reduced deaths. After a year the mortality rate was 7.2% in the metoprolol group and 11% in the placebo group.[2]

The preparation used in the clinical trial was an extended-release formulation. This contained metoprolol succinate as opposed to metoprolol tartrate which is used in the treatment of angina and hypertension.

The two salts of metoprolol have been compared in a haemodynamic study. This found that both salts had similar effects.[3] The extended-release formulation is given once a day. Its peak plasma concentrations are only 25% or 50% of those of the conventional formulation, but they produce comparable beta blockade over 24 hours.

When the extended-release tablets are prescribed for heart failure, the dose must be slowly increased over several weeks. If the heart failure gets worse during this titration metoprolol succinate may need to be discontinued.

References

1. Fletcher P. Beta blockers in heart failure. Aust Prescr 2000;23:120-3.
2. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-7.
3. Kukin ML, Mannino MM, Freudenberger RS, Kalman J, Buchholz-Varley C, Ocampo O. Hemodynamic comparison of twice daily metoprolol tartrate with once daily metoprolol succinate in congestive heart failure. J Am Coll Cardiol 2000;35:45-50.

Further reading

http://www.npsradar.org.au/articles/metoprolol.php

† At the time the comment was prepared, a scientific discussion about this drug was available on the web site of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int).

Answers to self-test questions

1. False
2. False
3. False
4. False
5. False
6. True
7. True
8. False
9. False
10. False

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