

medicines. An interesting example is the potential interaction between thyroxine and celery seed tablets.

### Case reports

Our first case involved a 55-year-old woman who, after considerable monitoring, had finally been stabilised on a daily dose of thyroxine 100 microgram. A month later, her doctor found that her  $T_4$  levels were low again and her dose was doubled. The patient then remembered that in the past month she had also started taking celery seed tablets for osteoarthritis. Suspecting a potential interaction, she ceased the celery seed tablets without increasing the thyroxine dose as the doctor had advised. Next time her thyroxine levels were checked they had increased to within the normal range. She tried recommencing celery seed a month later but after a week she felt lethargic, bloated and had dry skin. When she stopped the celery seed tablets, she reported that her 'general energy levels improved'.

A second report was received from a 49-year-old woman who had taken thyroxine for many years. When her  $T_4$  became extremely low her doctor suspected that she had not been taking her tablets. The patient argued that she had taken her thyroxine, but she had recently commenced taking celery seed tablets to treat arthritis. She ceased the celery seed tablets and one month later her thyroxine levels had returned to within the normal range.

### Evidence

Celery seed extracts (*Apium graveolens*) are a popular herbal remedy for the treatment of arthritis, gout, fluid retention and cystitis. Celery seed/fruit should not be confused with the edible celery stem.<sup>1</sup> Studies have shown that celery plant extracts have anti-inflammatory activity against carrageenan-induced rat paw oedema.<sup>2</sup> Hypotensive and hypoglycemic activities have also been reported.<sup>1</sup> In preliminary research, five of 23 celery-based preparations showed antiarthritic

effects, but no anti-inflammatory or antipyretic effects. The celery seed activity was thought to be dependent on processing at low temperatures.<sup>3</sup>

An extensive literature search did not find other reports of an interaction between celery seed extracts and thyroxine. However, when reference was made to these case studies in an article in a Queensland newspaper, the Queensland Medication Helpline received a flood of calls about similar experiences. A total of 10 cases are now on file. Although the validity of these anecdotal reports needs to be tested, as their number accumulates so too does the suspicion that the interaction is real. A pharmacokinetic study of the  $T_4$ -celery interaction is under consideration by the Mater Hospital Pharmacy Services' Therapeutic Advisory Service.

### Conclusion

Anecdotal evidence indicates a potential interaction between thyroxine and celery seed tablets. Since consumers often fail to volunteer details of self-medication with complementary medicines, prescribers and pharmacists should ask directly what herbal/nutritional medicines consumers are taking. If celery seed tablets are being co-administered with thyroxine, it is strongly recommended that thyroid function tests are closely monitored and any suspected interaction reported.

### REFERENCES

1. Newall CA, Anderson LA, Phillipson JD. Herbal medicines – a guide for health-care professionals. London: Pharmaceutical Press; 1996.
2. Lewis DA, Tharib SM, Veitch GBA. The anti-inflammatory activity of celery *Apium graveolens* L. (Fam. Umbelliferae). Int J Crude Drug Res 1985;23:27-32.
3. Turmeric has anti-inflammatory effects. Reuters Health eLine [serial online] 2000 June 8. <http://www.reutershealth.com/frame/eline.html>

E-mail: geraldinemoses@hotmail.com

## Your questions to the PBAC

### Celecoxib

The listing of celecoxib as a general benefit on the Pharmaceutical Benefits Scheme (PBS) from 1 August 2000 was welcomed by arthritis sufferers Australia-wide. However, the decision to list the 200 mg capsules with an issue quantity of 60 rather than 30 has surprised many pharmacists. This exceeds the 30 day supply rule, taking into account the manufacturer's recommended one capsule a day dosage.

A more serious problem is the number of potential adverse sulfonamide-type reactions that may occur around Australia, and the subsequent waste of Commonwealth funds when celecoxib is discontinued by the patients. In our town of 5000 there has been a high demand for celecoxib and within one week of listing we had six adverse sulfonamide-type reactions, with swelling of the throat, body rash and fever. One patient ended up in Moruya Hospital and the rest were referred to their general practitioner.

As a medication review pharmacist, I am concerned about the incidence and severity of these reactions. They usually occur within a few days of commencing celecoxib and the patient has to cease the medication. As celecoxib 200 mg is the most commonly prescribed dose, I believe that the decision by the Pharmaceutical Benefits Advisory Committee to list the 200 mg capsules in a quantity of 60 was a poor one, and will result in a significant waste of PBS funds.

Richard Lord  
Pharmacist  
Narooma, NSW

### PBAC response:

The Pharmaceutical Benefits Advisory Committee (PBAC) recommends the maximum quantity and the number of repeats that should apply to the prescribing of a particular medication. The maximum quantity recommended for listing by the PBAC

usually corresponds to the pack size produced by the manufacturer.

For drugs which are intended for use in chronic conditions, the PBAC recommends a maximum quantity and number of repeats which will provide sufficient supply of the drug for six months' therapy at normal dosage levels.

The current dosage of celecoxib for the treatment of osteoarthritis is 200 mg once daily or 100 mg twice daily, with some patients requiring 200 mg twice daily. The dosage for rheumatoid arthritis is 100 mg or 200 mg twice daily. The PBAC therefore recommended a maximum quantity of 60 capsules for both the 100 mg and 200 mg strengths of celecoxib in an attempt to encompass the complete dosage range required by patients. The maximum quantity listed in the Pharmaceutical Benefits Scheme (PBS) Schedule for celecoxib 200 mg provides for one month's therapy at maximum dosage levels and for two months' therapy at minimum dosage levels. The maximum number of repeats (three, for consistency with the listings of the non-steroidal anti-inflammatory drugs) provides for a supply of four months or eight months of medication depending on the patient's dose.

Doctors are under no obligation to prescribe the full maximum quantity specified in the Schedule for a particular drug. They may, at their discretion, prescribe smaller quantities than those listed in the Schedule.

The mechanism via which adverse drug reactions are monitored in Australia is administered by the Adverse Drug Reactions Advisory Committee (ADRAC) of the Therapeutic Goods Administration. Pharmacists who see unexpected reactions can notify the ADRAC Secretariat by filling out the blue report card which is enclosed in every copy of the PBS Schedule.

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## Medications which may lower seizure threshold

*Neil Buchanan, Emeritus Professor, University of Sydney, Sydney*

Most people who have epilepsy are warned that certain substances, especially other medications and alcohol, 'do not mix with their pills'. This is partly correct and is more valid with the older, enzyme-inducing drugs (phenytoin, phenobarbitone and carbamazepine) than with the newer antiepileptic drugs.

What people with epilepsy are not sufficiently informed about are the factors which lower the seizure threshold and make them more liable to have seizures. Such factors include stress, sleep deprivation, alcohol, menstruation and, especially in children, intercurrent infection and fever. Antiepileptic drugs may occasionally make seizures worse, either idiosyncratically when being introduced, or if the dose is excessive. Table 1 shows some medications which may provoke seizures by lowering the seizure threshold, rather than by interacting with antiepileptic drugs.

We do not know how often seizures occur because a drug has altered the seizure threshold. Many reports are anecdotal. In the past two years of specialist practice I have seen 25 patients where clinical judgement would suggest a particular medication has provoked a seizure. The commonest seizure-provoking drug was pethidine. With hindsight, 19 of the 25 patients might have avoided this problem if they had known that it could have occurred. The severity of the seizures varied, but three patients were admitted to intensive care units.

The list of potential seizure-provoking medications shown in Table 1 is probably incomplete. The list has been compiled from personal observations, discussions with colleagues, data from the Adverse Drug Reactions Advisory Committee (ADRAC) and published product information. The purpose of compiling such a list does not imply the use of these drugs is prohibited. Rather it aims to alert doctors and people with epilepsy to medications that could provoke seizures. Attention to the mention of epilepsy in the precautions section of published product information would identify most potential problems.

With regard to anaesthetic agents, there are reports of seizures post-anaesthesia. Whether this relates to the anaesthetic agent itself or withdrawal seizures after an anaesthetic is not clear. While propofol is effectively used in the management of status epilepticus, there are definite reports of seizures after its use as an anaesthetic. From the patient's point of view, the reason why is not of great concern.

The implications are:

- medical practitioners should be aware of the possibility of a change in seizure threshold
- people with epilepsy should be aware of the possibility that medicines may lower their seizure threshold
- medications which may alter the seizure threshold should only be used if really necessary and no safer alternative exists.