EDITORIAL

It's natural so it must be safe

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(Aust Prescr 2002;25:50–1)

Background

In her recent book 'The Poison Principle'[1], Gail Bell makes a discursive commentary on poisons and poisoners through the ages. After reading the book I realised that almost all the deadly substances she discusses could be classified as 'natural'. Gail Bell clearly separates common poisons from medicines but Paracelsus in the 16th century would not make this distinction. He contended, with some justification, that it was all a question of dose!

Many complementary medicines have a long history of traditional use, and are generally regarded as safe. That is why they are sold through a range of outlets, often without the need for the advice of a health professional. Does this mean that we can make a clear distinction between poisons and medicines, and uncritically accept the mantra 'natural = safe'? Recent examples of previously unsuspected toxicity tell us of the need for continuing vigilance.

Aristolochic acids (found in the plant genus *Aristolochia*) have recently been shown to cause nephropathy and, probably, renal (urothelial) cancer.[2] They should not be, but occasionally are, adulterants in traditional Chinese and other medicines available in Australia. As a safety precaution, the analytical laboratories of the Therapeutic Goods Administration (TGA) reviewed the chemical composition of around 100 herbal products which might have been contaminated by aristolochic acids. The results for the majority of these products were reassuringly negative. However, a small number of products were urgently recalled. Even stricter controls around these 100 herbal medicines have now been put in place.

Immediate toxicity is relatively easy to detect but linking natural substances with outcomes such as cancer is more difficult because of the time between exposure and the onset of symptoms. Without being alarmist, it is perfectly possible to claim that some so-called 'idiopathic' diseases could be the unrecognised results of taking complementary, or prescription, medicines.

Another recent concern is St John's wort (*Hypericum perforatum*) which some people take for depression.[3] The plant contains substance(s) which increase the production of drug metabolising enzymes found in the gut and liver (in particular cytochrome P450 3A4[4]). This may increase the metabolism of some prescription medicines, leading to interactions which result in organ rejection (cyclosporin), worsening of HIV-AIDS (indinavir), inadequate anticoagulation (warfarin) and breakthrough bleeding (combined oral contraceptives).[5]

Concealment of known potential toxicity is rare, but the requirement for complementary medicines containing guarana to declare their caffeine content on the label has only recently become mandatory. Guarana's 'energising' effects relate to its caffeine content. You probably would not buy a product for yourself or your children with 'added caffeine', but without this important labelling you might not realise that caffeine is what you get with guarana – a 'natural' product.

Reviewing the quality and safety of complementary medicines is the responsibility of the TGA. It is advised by the Complementary Medicines Evaluation Committee (CMEC), a Commonwealth Government committee established in 1997. All complementary medicines included on the Australian Register of Therapeutic Goods (ARTG) are evaluated for quality and safety. Manufacturers and sponsors are only required to 'hold the evidence' for preparations for which minor therapeutic claims are being made. These claims are not routinely evaluated for a listable preparation (a preparation carrying the symbol AustL, with a number,

In this issue...

Many people believe that complementary medicines are safe. Tony Smith explores this myth, while Stephen Myers alerts us to some of the interactions between complementary medicines and warfarin.

Warfarin can interact with alcohol. This may complicate the management of some of the heavy drinkers discussed by Greg Whelan.

Thrombosis is a known complication of oestrogen therapy. While Edith Weisberg discusses this risk, Paul Neeskens questions whether hormone replacement therapy has any benefit beyond symptom relief.

The benefits of some of the drugs mentioned in the article by Daniel O'Brien and Beverly Biggs may be limited in the prevention of malaria. When designing a regimen for a traveller to a malarious area, the adverse effects of chemoprophylaxis need to be considered. Rohan Jayasinghe and Pramesh Kovoor remind us that some of these antimalarial drugs can prolong the QT interval on the ECG.

on its packaging). Compounds which make more serious claims (disease prevention, modification or management) are evaluated for efficacy in addition to the mandatory review of safety and quality. If these claims are accepted a registered compound will have AustR, with a number, on its packaging and label.

Good manufacturing practice is comparatively easy to assess and ensure; safety on the other hand is often dependent on the **absence** of data in any of the worldwide databases. The Adverse Drug Reactions Advisory Committee has a close link to CMEC, and wants to increase reporting of suspected adverse responses to complementary medicines. In Australia, we rely on voluntary reporting from health professionals, many of whom do not yet ask about what patients are taking apart from their prescription drugs.

There is little readily available and reliable information on complementary medicines for health professionals. Free information lines such as the Therapeutic Advisory Information Service* of the National Prescribing Service are helpful, and the recommendations of CMEC are accessible on the TGA web site.†

* Freecall 1300 138 677, e-mail tais@nps.org.au

† http://www.health.gov.au/tga/cm/cm.htm

If 50% of our patients are taking complementary medicines, neither patients nor prescribers can afford to be ignorant. Unbiased education is required for health professionals and consumers alike. Who is to collate and provide it? Perhaps this is a future task for the National Prescribing Service in conjunction with its member organisations?

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Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Hypertension in diabetes

Editor, – I refer to the article 'Hypertension in diabetes' (Aust Prescr 2002;25:8-10).

The author suggests that while AT_1 receptor antagonists may have the same benefits as ACE inhibitors, this has yet to be shown in clinical trials. I would draw your attention to the recently published PRIME program[1,2], which evaluated the effects of irbesartan on morbidity and/or mortality in patients with hypertension and type 2 diabetes across the continuum of early and advanced stages of diabetic renal disease.

The PRIME program consisted of two trials, IRMA 2 and IDNT.

In IRMA 2, the irbesartan 300 mg group demonstrated a 70% relative risk reduction in the primary end-point of progression to overt proteinuria, compared with a control group (placebo in addition to other non-excluded antihypertensive therapies), $p = 0.0004$.[1]

In IDNT, the primary end-point was the time until the first occurrence of doubling of serum creatinine, or end-stage renal disease, or all-cause mortality. The irbesartan group demonstrated:

- a 20% relative risk reduction in the primary end-point compared with the control group (placebo in addition to other non-excluded and antihypertensive therapies), $p = 0.02$
- a 23% relative risk reduction versus the amlodipine group, $p = 0.006$.[2]

In a recently updated position statement by the American Diabetes Association on diabetic nephropathy[3], the recommendation is that in treatment of albuminuria/nephropathy both ACE inhibitors and the AT_1 receptor antagonists can be used. The recommendations are as follows:

- in hypertensive and non-hypertensive type 1 diabetic patients with microalbuminuria or clinical albuminuria, ACE inhibitors are the initial treatment of choice
- in hypertensive type 2 diabetic patients with microalbuminuria or clinical albuminuria, AT_1 receptor antagonists are the initial drugs of choice.

While the AT_1 receptor antagonists are a newer class of drug, and data in the past have been limited, there is certainly a growing body of evidence such as PRIME on their use in hypertensive diabetic patients.

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