LETTERS

Letters to the Editor

Warfarin and beetroot

I was interested to read your article 'How to manage warfarin therapy' (Aust Prescr 2015;38:44-8). In the article and subsequent online quiz, it mentions beetroot as being one of the foods that can affect INR, which I found rather unusual. After having worked as a senior pharmacist on a cardiothoracic ward for a number of years, I have counselled countless patients on warfarin and factors that can influence INR and I have never heard of beetroot being one of them. After doing some of my own research, I came across the vitamin K contents of beetroot, which was listed to be approximately 0.3 micrograms per 100 g in comparison with spinach 540 micrograms per 100 g.

Consequently, I believe that consuming beetroot while taking warfarin would have an insignificant effect on INR compared to other foods. I also noted in the quiz that vitamin C was listed as not affecting INR and, although there is limited evidence, there are a number of case reports of vitamin C at high doses affecting INR. Vitamin C is also listed in the Western Australian Department of Health's Living with Warfarin: Information for Patients,[1] so I believe that it is worth mentioning as something that could possibly affect INR.

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REFERENCE

1. WA Medication Safety Group. Living with warfarin: information for patients. Perth: Western Australian Department of Health; 2015. www.watag.org.au/wamsg/docs/Living_with_Warfarin.pdf [cited 2015 Sep 7]

Philip A Tideman, Rosy Tirimacco, Andrew St John and Gregory W Roberts, authors of the article, comment:

Louise Vanpraag rightly points out that the beetroot bulb is a negligible source of vitamin K. It was our oversight in not explicitly naming the beetroot leaves as the rich source of vitamin K rather than the bulb.

While there have been two separate case reports of a possible interaction between high doses of vitamin C and warfarin causing an elevated INR, three separate crossover trials using daily vitamin C doses of 1–10 g for periods of one week to six months have failed to reveal an interaction.

Warfarin brands

Although a comprehensive guide to managing warfarin, the article in the April 2015 issue (Aust Prescr 2015;38:44-8) did not mention the problem of brand confusion with warfarin. Transition of care, such as hospital admission, is a time when warfarin management may be compromised. In Australia we have two brands – Coumadin and Marevan. Both are manufactured by Aspen Pharmaceuticals, and are available in different strengths and tablet colours. Recently reported incidents involving warfarin brand confusion at our hospital resulted in dose omissions due to Marevan not being available on the ward and inadvertent switching from Marevan to Coumadin. Although no patient harm resulted, time was spent in sourcing the 'right' brand and managing the incidents.

The Pharmaceutical Benefits Scheme notes that the brands have not been shown to be bioequivalent and should not be interchanged.[1] However, a systematic review comparing the bioequivalence of six international warfarin brands found that switching brands was relatively safe.[2] In 44 years of reporting adverse drug reactions in Australia, only three reports, all from 1977, implicate brand switching.[3]

The manufacturer has previously been approached to phase out one brand, with a recommendation that Coumadin be primarily used.[4] We call for either bioequivalence testing of Coumadin and Marevan by the manufacturer or, in the interests of medication safety, for only one brand of warfarin to be available.

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2. Dentali F, Donadini MP, Clark N, Crowther MA, Garcia D, Hylek E, et al. Brand name versus generic warfarin: a systematic review of the literature. Pharmacotherapy 2011;31:386-93.
3. Therapeutic Goods Administration. Database of Adverse Event Notifications (DAEN). Canberra: Department of Health; 2013. www.tga.gov.au/database-adverse-event-notifications-daen [cited 2015 Sep 7]
4. Dooley M. Recommendations for warfarin in Victorian public hospitals [letter]. Aust Prescr 2003;26:27-9.

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Philip A Tideman, Rosy Tirimacco, Andrew St John and Gregory W Roberts, authors of the article, comment:

We agree that brand continuity for warfarin is preferred. While it seems unlikely there would be clinically significant differences in the two brands, which vary by a single excipient, there has been no formal bioequivalence testing. The availability of a single brand in Australia would simplify warfarin management and remove any confusion about brand swapping for both patients and clinicians.

Naltrexone and liver disease

In the good review on long-term drug treatment of patients with alcohol dependence (Aust Prescr 2015;38:41-3), the important issue of underuse of pharmacotherapy for alcohol dependence is identified and an outline of treatment is given. However, the article states that naltrexone is contraindicated in acute hepatitis or liver failure. In my clinical practice, varying degrees of chronic liver disease are commonly encountered when treating an alcohol-dependent population. Continued heavy drinking is much more likely to pose a greater risk to liver function than naltrexone. Arguably, the risk–benefit assessment likely favours naltrexone treatment. Naltrexone can be prescribed in patients with stable or compensated cirrhosis but is not recommended in acute liver failure. It carries a low risk of hepatotoxicity. However, in my experience, many potentially suitable patients are not given the drug because of concerns about hepatotoxicity.

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REFERENCE

1. Yen MH, Ko HC, Tang FI, Lu RB, Hong JS. Study of hepatotoxicity of naltrexone in the treatment of alcoholism. Alcohol 2006;38:117-20.

Philip Crowley, the author of the article, comments:

Precautions listed in naltrexone's product information include saying it may cause hepatocellular injury when given in excessive doses, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects. The product information also states that naltrexone is contraindicated in acute hepatitis or liver failure. This is based on a study in which 300 mg/day naltrexone was administered to obese patients. Five of 26 naltrexone recipients, and none of the placebo group, developed elevated serum transaminases after 3–8 weeks of treatment.[1]

Data on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) have been used as an indicator of hepatotoxicity, with concentrations indicating both the effects of medication on hepatotoxicity, and reduced hepatotoxicity due to reduced alcohol consumption. Twelve of 1383 participants (0.9%) in the COMBINE study[2] had elevated liver enzymes greater than five times the upper levels of normal. (Most cases were in the naltrexone group.) These effects resolved following discontinuation of the drug. This is the one study large enough to detect an adverse effect at this low level of incidence.

The study that Dr Mike McDonough refers to supports other smaller studies[3,4] indicating that naltrexone was not hepatotoxic at the recommended dose in a trial of 74 participants.

I agree that often patients do better in a risk–benefit assessment when taking naltrexone compared to not taking it (because of concerns about minor liver enzyme changes).

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2. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, et al.; COMBINE Study Research Group. Combined pharmacotherapies and behavioural interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA 2006;295:2003-17.
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