

## Letters

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### Fenofibrate–warfarin interaction

Editor, –The 'Medicinal mishap' about the fenofibrate–warfarin interaction (Aust Prescr 2006;29:166) perpetuates the myth that protein binding interactions are clinically relevant. Unless the clearance of unbound drug is saturable (not the case with fenofibrate), protein binding displacement interactions do not lead to sustained increases in steady-state concentrations of unbound drug if the drug has a low clearance (as is the case with warfarin).<sup>1,2</sup> It is the unbound concentrations of drug that correlate with the pharmacological effect. The only determinant of steady-state unbound concentration of drug, apart from the dose rate, is its clearance. This is generally dependent on hepatic metabolism or, in some cases, renal clearance or a combination of both.

Fenofibrate is an analogue of clofibrate, so information about clofibrate is relevant to the fenofibrate–warfarin interaction. Clofibrate potentiates the anticoagulant activity of warfarin but not because of displacement from plasma proteins. It causes a very small increase in the free fraction of warfarin but 'this pharmacokinetic interaction does not account for the clinical interaction between the two drugs, since free warfarin concentrations are unchanged'.<sup>3</sup> The mechanism of the interaction is unknown but is likely to be related to warfarin's effect on the synthesis of clotting factors. The metabolism of clofibrate is also a significant consideration. Clofibrate is hydrolysed to the active metabolite, clofibric acid, which is largely metabolised to its ester glucuronide. In a process known as 'futile cycling', ester glucuronides of clofibric acid and several other active drugs are retained in renal impairment. Their resultant hydrolysis yields higher than average plasma concentrations of the active drug. This futile cycling in renal failure with marked retention of clofibric acid has been reported in animal studies.<sup>4</sup>

The patient in the case had a very low creatinine clearance (17 mL/min). We suggest that there was 'futile cycling' of fenofibric acid, the active metabolite of fenofibrate, leading to high plasma concentrations and a substantial interaction with warfarin. Five other cases of a marked potentiation of warfarin by fenofibrate have been reported.<sup>5,6</sup> Unfortunately, the patients' renal function was not recorded but three were elderly with multiple diseases so they may have had substantial renal impairment.

The important point is that protein binding displacement interactions between any pair of highly bound drugs do

not alter their unbound concentrations and, consequently, increased effects are most unlikely. This applies particularly to drugs with low clearances, such as warfarin.

We agree with the advice that closer monitoring of patients on warfarin is needed when starting fenofibrate to avoid excessive anticoagulation. Particular care is necessary if the patient has renal impairment.

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*Dr RA Ghiculescu, author of the case, comments:*

I concur that protein binding is usually of little clinical importance. Many so-called protein binding displacement interactions are reported but the weight of evidence shows this is not the mechanism to explain clinically relevant drug interactions. However, the reference I cited does report such a

phenomenon with fenofibrate itself and was therefore quoted as one of two possible mechanisms for this interaction. Apart from protein binding displacement the other mechanism was the probable inhibition of the CYP450 2C9 by fenofibrate.<sup>1</sup>

#### Reference

1. Kim KY, Mancano MA. Fenofibrate potentiates warfarin effects. *Ann Pharmacother* 2003;37:212-5.

#### Brand substitution was not the problem

Editor, –The title of the Medicinal mishap 'Brand confusion with digoxin' (*Aust Prescr* 2006;29:153) was misleading. It unfairly blames the 'proliferation of new brands' for the error that was made.

The patient's usual medications included warfarin and digoxin 62.5 microgram (Lanoxin PG) but he was given 250 microgram tablets (Sigmaxin). He consequently suffered digoxin toxicity.

Brand proliferation is a fact of life and is not new. It is the basis of substantial cost-savings for individuals and for governments. All of the brands must be of good quality and must be interchangeable. In Australia, the Therapeutic Goods Administration undertakes checks during the registration process. Given that Lanoxin PG and Sigmaxin PG are marked as interchangeable brands of digoxin in the Schedule of Pharmaceutical Benefits, there was no error in dispensing a different brand, provided that the patient had consented and the prescriber had not checked the box on the prescription that reads 'Brand substitution not permitted'. The error in this case was selection of the wrong strength: Sigmaxin rather than Lanoxin PG.

A better target for our wrath is the case of the Coumadin and Marevan brands of warfarin. The product information for the two brands states 'Do not interchange Coumadin and Marevan. Bioequivalence between these two brands of warfarin has not been established'. Clinical reports suggest these brands are not bioequivalent.<sup>1,2,3,4</sup> A pharmacoeconomic analysis concluded that use of one brand only is 'economically attractive'<sup>5</sup> given the costs of morbid events.

The argument that 'to withdraw one brand would seriously disadvantage those patients who are stabilised on it'<sup>6</sup> has been advanced for years and serves to perpetuate the current unsatisfactory situation. It's time to bite the bullet and withdraw one of these inequivalent brands of warfarin, even if short-term inconvenience results for some patients and their prescribers in the form of monitoring the changeover.

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#### Injunction impedes independent information

Editor, –The editorial about the injunction (*Aust Prescr* 2006;29:120) noted that the judge felt the public interest would be best served by the regulatory authorities examining the evidence supporting the efficacy of *Ginkgo biloba*.

In June 2006 a complaint about the promotion of Tebonin brand of *Ginkgo biloba* was sent to the:

- Therapeutic Goods Administration (TGA) which has jurisdiction over the pack and package insert
- Complaints Resolution Panel which deals with advertisements in printed media and the internet
- Complaints Resolution Committee of the Complementary Healthcare Council of Australia which investigates complaints about pharmacy posters, leaflets, fax and direct mail.

The TGA response was classified 'commercial-in-confidence'. However, the TGA did note that the indications for Tebonin changed in July 2006 from 'For the symptomatic relief of tinnitus' to 'May assist in the management of tinnitus'.

In October 2006 the Complaints Resolution Committee suggested that issues relating to the product's efficacy should be referred to the TGA.

In November 2006 the Complaints Resolution Panel determined that promotional statements about Tebonin made in print media and the internet breached the Therapeutic Goods Advertising Code. Schwabe Pharma Australia was requested to withdraw the advertisements from further publication and not use similar representations in the future.<sup>1</sup>

In December 2006 the Tebonin pack and insert continued to state that Tebonin was 'an effective treatment' for tinnitus. Print advertisements, although slightly changed, still claimed the product offered 'relief' from tinnitus without the TGA qualifier 'may'.<sup>2</sup> A number of Australian internet pharmacy sites also continued to promote Tebonin as an 'effective treatment' for tinnitus.

The Tebonin case suggests that confidence in Australian regulatory authorities may be misplaced.

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## References

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2. Phytomedicine offers relief for the misery of vertigo, tinnitus [advertisement]. Natural Health Products Pty Ltd. Canberra SundayTimes. 2006 Dec 3;21.

## Drug dosing adjustment in people with reduced GFR

Editor, –The article 'Prescribing in renal disease' (Aust Prescr 2007;30:17–20) is a useful contribution to the complex issues currently facing prescribers. There is wide agreement that determining kidney function by measurement or assessment of glomerular filtration rate (GFR) is preferable to using the serum creatinine alone, for all clinical purposes (including drug dosing).

The vast majority of prescribing in Australian general practice occurs without knowledge of the patient's kidney function. When an assessment of kidney function is available it is now usually in the form of an automatically generated eGFR (estimated GFR) derived from the Modification of Diet in Renal Disease (MDRD) study. Few, if any, practitioners routinely calculate GFR by using the Cockcroft-Gault equation or measure creatinine clearance on all patients.

After considering these matters, a meeting of the Australian Creatinine Consensus Working Group agreed that the following recommendation should be promoted to Australian prescribers:

Decision making in drug dose adjustment in people with chronic kidney disease is enhanced by an assessment of kidney function based on GFR rather than a serum creatinine concentration alone. In most out-of-hospital settings (particularly general practice) where an eGFR (MDRD) is on hand and no other measure of GFR is known or readily accessible, it is clinically appropriate to use eGFR to assist drug dosing decision making.

However, for critical dose drugs, particularly in a hospital setting, it remains important to adhere to the published recommendations that usually involve the use of the Cockcroft-Gault equation to estimate GFR, or to measure creatinine clearance in order to amend dosing for renal function.

The product information guiding dose adjustment in patients with reduced GFR is often permeated with imprecise and

undefined terminology (such as renal impairment, mild/moderate renal insufficiency) and is in need of a major overhaul with an emphasis on the recently introduced staging of chronic kidney disease by GFR reduction. There is also variability in the recommended use of the Cockcroft-Gault equation with regard to use of estimated ideal body weight from height and build, and there has been no update to the formula to account for re-standardisation of creatinine assays.

Automatically generated eGFR using the MDRD formula more closely correlates with true GFR than an estimate based on Cockcroft-Gault (particularly in the key clinical area of GFR reduction between 15 and 60 mL/min/1.73m<sup>2</sup>) and both are better than a timed clearance. At the very least the eGFR alerts treating doctors to the possibility of reduced renal function prompting the use of other estimates if desired. In the future it is likely that eGFR will be the major basis for adjusting doses for people with reduced GFR. At present it appears reasonable and indeed preferable, in the absence of any other measure of kidney function, to use the eGFR (recognising its limitations) as a guide to prescribing particularly with non-critical dose drugs.

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*Dr Randall Faull and Ms Lisa Lee, authors of the article, comment:*

We are pleased there is agreement that prescribing of critical dose drugs should continue to follow published recommendations which usually use the Cockcroft-Gault equation to estimate GFR. We are however concerned about the message that body size is unimportant when considering the dosage of drugs. The automatically reported eGFR does not consider body size in its calculation, and so while it functions very well as a screening (and alert) device for renal impairment, it fails to differentiate between large and small people who will have markedly different absolute GFRs. From first principles it is the absolute GFR upon which the drug dosage should be based. The Cockcroft-Gault equation is accessible to general practitioners. Along with a calculator for ideal body weight, it is readily available on Medical Director, a computer program which is widely used by Australian general practitioners. The eGFR is an evolving tool and the MDRD equation can be adapted to consider body weight. In the future that may become the appropriate standard recommendation for calculating drug doses.