

wider curriculum. The skills of the doctors providing training should also meet minimum standards. The doctors should be centrally funded for this role (at present in the UK nurses and pharmacists sometimes have to pay for themselves, or defer training until one of the small number of bursaries becomes available). In some states in the USA, pharmacists are certified by the same board as physicians, which aids local acceptability. Overall, there is a clear rationale to extend prescribing rights. While it needs continued evaluation, where it has been introduced it seems to have improved access, been liked and, on the evidence of a small number of case studies, been effective. Extending prescribing rights is also logical. The burden of knowledge associated with medicines is vast and expanding, so it makes sense to share the task of prescribing while retaining an integrated system of care.

The role of the doctor is in a transition akin to that which theatre went through in the last century. The doctor's role has been like that of the great Victorian 'actor-managers' – controlling the whole show, making all the key decisions and being centre stage in the action. Medicine is getting too complex for that

model to survive. Doctors should move to the equivalent of the theatre director of today. They can set direction, strategy and priorities, working with teams of colleagues, including non-medical prescribers.

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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.

Warfarin pharmacogenetics

Editor, – Dr Martin has comprehensively reviewed the genetic and environmental factors contributing to the large inter-individual variability in warfarin requirements (Aust Prescr 2009;32:76–80). These factors explain about 50% of such variability which is quite impressive considering that for most drugs, 100% of the dose variability cannot be explained. It is very unlikely that additional genetic factors will be uncovered, as whole genome association studies have clearly identified CYP2C9 and VKORC1 genotype as the major genetic contributors to dosage requirements with a very small contribution by CYP4F2.¹ Other factors that need to be considered are drug-drug interactions, medication adherence, psychosocial factors and the less than optimal system of care for people prescribed warfarin.²

The Food and Drug Administration in the US refers to the genetic factors (CYP2C9 and VKORC1) which influence dosage requirements in the product information for warfarin, but Medicare and Medicaid will not pay for the genetic test (except as part of clinical trials) because of insufficient evidence of benefit. There is clearly a need for large scale prospective studies, including pharmaco-economic studies, before any decisions are made to incorporate genetic testing into best practice guidelines.³

In Australia, the situation is complex as some pathology services already advertise the test, but there are no known large prospective multicentre trials being conducted to determine feasibility, interpretation, dosage recommendations and cost-benefit. It is timely that this be done so that Australia, with its different spread of ethnicities and diets, can contribute to the evidence and importantly, that Australian-based cost-benefit analyses and dosage recommendations can be made to determine whether or not warfarin genetic testing should become part of treatment guidelines.

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Prescribing in liver disease

Editor, – Tailoring treatment to the individual is the art of therapeutics and is supported by an increasing understanding of inter- and intra-individual variability (the science). Dose adjustment in liver impairment is difficult because a reliable predictor of hepatic drug clearance is lacking.¹ Drs Sloss and Kubler recently discussed the use of the Child-Pugh classification to guide dose adjustment in liver impairment (*Aust Prescr* 2009;32:32–5). This is a tool of last resort and there are several other factors that can and should be used to guide dosing.

If measures of clinical effects (desired and adverse) are available, these can be used to guide dosing. Firstly, many drugs have validated biomarkers of drug effect (for example INR for warfarin) or surrogate markers of clinical outcome (for example HIV viral load for antiretroviral treatment).² Similarly many drugs have concentration-related symptoms, for example pain for analgesics, or dry mouth and constipation for anticholinergics. Secondly, the concentration of some drugs can be easily measured. This is particularly valuable as therapeutic drug monitoring is available for many drugs with narrow therapeutic ranges, the drugs that prescribers are most concerned about in hepatic impairment. Immunosuppressants and anticonvulsants are examples of these.

We also recommend that prescribers consider the potential effect of liver impairment on the active drug moiety by changes in clearance (potentially decreased) and oral bioavailability (potentially increased). Pharmacokinetic variability due to hepatic impairment can be managed by considering clearance of the active moiety and first-pass metabolism in conjunction with monitoring drug effects, biomarkers, or concentrations.

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Editor, – Drs Sloss and Kubler discuss hepatic metabolism in a recent article (*Aust Prescr* 2009;32:32–5). They point out that, in phase I reactions, hydrolysis is very common. They go on to state that hydrolysis involves the addition of molecular oxygen. This sounds more like oxidation.

The term 'hydrolysis' refers to water and involves cleavage of a molecule with the addition of water, whether it is mediated by acid or base or by a hydrolase enzyme. Hydrolases are, in fact, like a particular type of transferase enzyme where water accepts the transferred group. So water is actually utilised and not created as stated in the article.

In the example given, acetylsalicylic acid (aspirin) reacts with water to form acetate (acetic acid) and the free phenolic salicylate, salicylic acid.

The aqueous nature of the body makes hydrolysis very probable. In fact, it is by confining easily hydrolysed intermediates within a hydrophobic enzyme active site that unique reactions can occur enzymatically that would be impossible in aqueous solution.

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Pitfalls in interpreting laboratory results

Editor, – I have read Dr Pat Phillips' article (*Aust Prescr* 2009;32:43–6) with interest. He points out that an individual's laboratory result may be abnormal for them, but still lie within the reference interval. This can occur when the individual's biological or 'intra-individual' variance is small compared with the 'inter-individual' or group variance. The 'index of individuality' – which is the ratio of the intra-individual coefficient of variation (CV_i) to the group CV (CV_g) – is used to estimate this variance. If the index is less than 0.6, the population-derived reference interval will not be of great use and the variable is said to show high individuality. If it is greater than 1.4 it should be useful.

The example used in the article on alkaline phosphatase is unfortunate, as this variable shows high individuality and the population reference interval is of limited value. For a variable such as ionised calcium, where the intra-individual variation is close to the inter-individual variation and therefore has a high index of individuality, it will be useful.

Another detail worth mentioning is that the appropriate CV for calculating the least significant difference is the combined intra-individual and analytical CV. This is obtained by squaring the respective CVs to obtain the variances, adding them and taking the square root to obtain the combined CV.

There is much published information on these sources of variation.^{1,2} The possibility that individuals vary significantly in their intra-individual variances is recognised. Nevertheless

taking these combined values into consideration can be helpful, as Dr Phillips shows, in interpreting successive laboratory results in patients on treatment.

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Dr Pat Phillips, author of the article, comments:

I appreciate Dr Masarei identifying the 'index of individuality' as an objective way to tell when a test result may be within the relevant reference range (based on a group of people) but outside the individual's healthy range (which may be much narrower). This distinction can be clinically important. For example, a free T4 may be within the laboratory range (that is, normal) but be biologically high for the individual and

associated with a suppressed or increased thyroid stimulating hormone. This is the pathophysiology of the real clinical syndromes 'subclinical' hyper- and hypothyroidism.

Unfortunately, the only measure of result variability given by most laboratories is the laboratory reference range, which includes many components of variability as well as that occurring within one individual. In these situations, one has little choice and must interpret the individual result in the context of the general laboratory range.

However, when interpreting sequential results in one individual, one does not consider the laboratory reference range but the total variability within that individual (CV_i). I suggested that the least significant change should be considered a true signal of biological change over and above the background 'noise' of variability and is approximately $2CV_i$. The major point was that when interpreting laboratory results, one is trying to identify a clinical signal against the background variability. For single results the only information about the background variability is the laboratory reference range, but for sequential results the appropriate measure of variability is the variability within the individual and the least significant change.

Subsidised medicines for Aboriginal and Torres Strait Islander people

Since August 2006, the Pharmaceutical Benefits Scheme (PBS) has been including new listings specifically for the treatment of common conditions in Aboriginal and Torres Strait Islander people. Some listings are medicines new to the PBS, while others vary the restrictions for prescribing existing PBS items. For the most up-to-date information on relevant PBS-subsidised items, and their conditions for prescribing, see the current list in the fact sheet at www.pbs.gov.au.

A new listing is nicotine replacement therapy for nicotine dependence.

The items in the box are available as 'Authority PBS prescriptions'. For more information about PBS access by Aboriginal and Torres Strait Islander people, send an email to pbs-indigenous@health.gov.au

For changes to this list and other listings, readers can subscribe to news alerts from the PBS at www.pbs.gov.au/html/healthpro/subscription/manage

Authority PBS listings as at 1 August 2009

Treatment of a fungal or a yeast infection

1. Bifonazole cream (1%)
2. Clotrimazole lotion (1%)
3. Ketoconazole cream (2%) and shampoo (1%, 2%)
4. Miconazole nitrate (2%) as cream, powder, lotion and tincture
5. Nystatin cream (100 000 units per g)
6. Terbinafine cream (1%)

Prophylaxis of thiamine deficiency

7. Thiamine tablet (100 mg)

Treatment of whipworm infestation

8. Albendazole tablet (200 mg)

Treatment of chronic suppurative otitis media

9. Ciprofloxacin ear drops (0.3%)

Treatment of a dermatophyte infection where topical treatment has failed

10. Terbinafine tablet (250 mg)

Nicotine replacement therapy

11. Nicotine transdermal patch (releasing approximately 15 mg over 16 hours)