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.

Cytochrome P450 drug interactions

Editor, – We are writing with respect to the article 'Cytochrome P450 drug interactions: are they clinically relevant?' by J. Martin and M. Fay (Aust Prescr 2001;24:10–2).

In this article, the authors state 'Some selective serotonin reuptake inhibitors (SSRIs) (e.g. fluoxetine, paroxetine and fluvoxamine) inhibit CYP2D6… The addition of fluoxetine, paroxetine or fluvoxamine (CYP2D6 inhibitors)…'.

These statements are not accurate in that fluvoxamine maleate has, to date, not been shown to be a significant inhibitor of CYP2D6 – *in vitro* or clinically.[1–7] The product information clearly states that 'Fluvoxamine has only a weak effect on CYP2D6, and it is therefore not likely that it will increase plasma concentrations of drugs metabolised by CYP2D6 to a clinically relevant effect'.

Pamela Noble
Manager, Scientific Affairs & Medical Marketing
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Dr J. Martin and Dr M. Fay, authors of 'Cytochrome P450 drug interactions: are they clinically relevant?', comment:

It is prudent to be aware of the safety issues when prescribing fluvoxamine with other drugs that are metabolised by the cytochrome P450 system. Fluvoxamine, however, has only a weak inhibitory effect on CYP2D6 and we agree with Solvay Pharmaceuticals that this is unlikely to be as clinically significant as fluvoxamine's other well-documented drug interactions.

Editor, – It may be useful for readers to have some additional information about psychotropic drugs and cytochrome P450 enzymes (Aust Prescr 2001;24:10–2).

Fluvoxamine seems not to significantly inhibit 2D6 as it has no effect on the O-demethylation ratio of dextromethorphan at a steady state dose of 100 mg/day. However, fluvoxamine potently inhibits cytochrome P450 1A2 and most patients treated with even low doses of 100 mg/day will reach population minimums for CYP1A2 activity (i.e. become poor metabolisers). Other potent inhibitors of 1A2 are mexiletine, lidocaine, and (weaker) tocainide, and also flavones – a class of dietary phytochemicals found at high concentrations in tofu.

Cytochrome P450 1A2 metabolises many structurally related psychotropic drugs – for instance all the quaternary tricyclic antidepressants (clomipramine, amitriptyline, doxepin, dothiepin, but not nortriptyline) and also many neuroleptics like clozapine, olanzapine, chlorpromazine and structurally related drugs. Their metabolism is also induced by cigarette smoking which may have significant clinical consequences.

Besides nefazodone, fluoxetine (via its metabolite norfluoxetine, which can have a half-life of up to 14 days) is also an inhibitor of cytochrome P450 3A4 and may thus, *inter alia*, inhibit ergotamine metabolism and precipitate ergotism.

It is incorrectly stated in the article that serotonin syndrome can be precipitated by combining tricyclic antidepressants and selective serotonin reuptake inhibitors.

Ken Gillman
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Dr J. Martin and Dr M. Fay, authors of 'Cytochrome P450 drug interactions: are they clinically relevant?', comment:

The letter from Dr Gillman gives some interesting information on potential cytochrome P450 interactions with psychotropic drugs. However our brief was to focus on clinically significant drug interactions only, and we tried to use only reports from the literature that indicated clinical significance. The aim of the article was to provide a few general rules to help clinicians identify potential drug interactions, rather than provide an exhaustive list.

However, there are several points in this letter which we would like to comment on. Firstly fluoxetine, although having an active and long half-life metabolite, is unlikely to have much clinically relevant inhibition of CYP3A4. The evidence comes from *in vivo* studies with terfenadine and midazolam (CYP3A4 substrates) which showed no increase in plasma concentrations of these with the addition of fluoxetine, and no change in cognitive state when added to midazolam. *In vitro*, fluoxetine has one hundred times less CYP3A4 inhibition than ketoconazole.

Secondly, serotonin syndrome can be precipitated by giving a selective serotonin reuptake inhibitor to a patient already on a tricyclic antidepressant. Concentrations of amitriptyline, clomipramine, imipramine and maprotoline have been shown to increase up to five fold with the addition of both fluoxetine

and fluvoxamine. This is associated with anticholinergic, serotonergic and adrenergic adverse effects.

Editor, – In the article on cytochrome P450 drug interactions (Aust Prescr 2001;24:10–2) there is mention of the inductive capacity of St John's wort on the CYP3A4 enzyme. In view of the high first-pass effect on oestradiol and the intermediate effect on ethinyloestradiol, is it possible for pill failure, breakthrough bleeding and postmenopausal bleeding to occur when St John's wort is used by women on the oral contraceptive or hormone replacement therapy?

James Brodribb

Obstetrician and Gynaecologist

Hobart

Dr J. Martin and Dr M. Fay, authors of 'Cytochrome P450 drug interactions: are they clinically relevant?', comment:

We agree with Dr Brodribb that there is likely to be quite a significant drug interaction with St John's wort (CYP3A4 inducer) and oestrogen/progesterone (CYP3A4 substrates) combinations. However, we were unable to find case reports of this in the literature, unlike the interactions with St John's wort and other 3A4 substrates. However, because of the likelihood of a significant interaction we would discourage St John's wort from being used by patients taking the contraceptive pill or hormone replacement therapy. We would also encourage the reporting of any suspected drug interaction.

Activities to improve hospital prescribing

Editor, – As a director of pharmacy in an Australian public hospital, it was naturally with some interest that I read the recent discussion of activities to improve hospital prescribing (Aust Prescr 2001;24:29–31). Jonathan Dartnell correctly points out that much prescribing in hospitals is undertaken for acutely unwell patients by relatively inexperienced prescribers, and that factors such as rapid staff turnover and poor information systems can exacerbate the problems caused by these factors. It was particularly disappointing, therefore, to discover that the discussion fails to address the important roles played by hospital-based pharmacists in advancing the quality of prescribing.

Advanced clinical pharmacy services are widely established in our hospitals, and make a substantial contribution to the quality of prescribing in these institutions (and the wider community). A properly resourced clinical pharmacy service allows experienced pharmacists with specialist expertise to work alongside hospital-based prescribers to improve outcomes for patients through activities such as drug therapy monitoring, or screening for adverse drug reactions and interactions. Despite Dr Dartnell's assertion that there is little information available about drug use in our hospitals, pharmacy departments around Australia maintain active drug utilisation evaluation programs, providing a sound basis for locally targeted educational strategies, and underpinning audit and feedback activity that can make a real difference to prescribing patterns. In contrast to confrontational approaches such as the enforcement of prescribing restrictions, a co-operative approach that brings together doctors, nurses and pharmacists in a multidisciplinary effort to improve prescribing has a durable and positive effect upon prescribing practices.

Neglecting recognition of the role of skilled clinical pharmacy practitioners in influencing prescribing is a curious omission from a discussion focused upon ways to improve drug use in hospitals. Simply providing information (such as prescribing guidelines) is not enough. Without the sustained contribution of clinical pharmacists as a way to influence prescribing in hospitals, and the substantial contribution that these practitioners make to averting drug-related harm, health care in Australia would be a great deal less safe, and in all probability, much more expensive. Appropriate recognition of this contribution by funding agencies and hospital administrators is long overdue.

Chris Alderman

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Quality Use of Medicines and Pharmacy Research Centre

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Dr Jonathan Dartnell, author of 'Activities to improve hospital prescribing', comments:

I agree that pharmacists are essential contributors in improving hospital drug use, as are patients, doctors, nurses, quality improvement teams, clinical pharmacologists, clinical epidemiologists, behavioural scientists and administrators. I deliberately avoided defining the roles of any of the players apart from doctors as their contributions can, and do, change depending on the availability of personnel and resources in any given setting. While we would wish otherwise, clinical pharmacy services are variably established, implemented and supported. In some hospitals advanced clinical pharmacy services are routine, in other hospitals basic clinical pharmacy is not available.

In the examples cited in my article, pharmacists were key players providing academic detailing, developing and implementing guidelines, auditing and providing feedback. This was in the context of multidisciplinary programs, such as drug usage evaluation (DUE) programs. I recognise their importance and strongly support them, but most hospitals do not have DUE programs and those that exist are not necessarily based in pharmacy departments.

A major constraint in conducting DUE is the limited drug use data that are available without resorting to manually intensive methods. The few electronic data that are available are not linked to prescribers, patients and indications, and as these data are not standardised, inter-hospital aggregations and comparisons are difficult. Community prescribing data has its own limitations but national data are available.

Electronic prescribing in hospitals

Editor, – Hugo Stephenson makes some very good points in his editorial, 'Electronic prescribing in hospitals: the road ahead' (Aust Prescr 2001;24:2–3). There is clearly a need for hospitals to implement electronic strategies to reduce adverse events, improve the quality of patient care through decision-support tools and facilitate the continuum of care between hospitals and the community.

The Austin and Repatriation Medical Centre (A&RMC), Melbourne, is in the process of implementing a fully integrated, web-based electronic health system, including electronic prescribing and administration. Features of the system will include use of mobile computing for bedside prescribing/recording and clinical decision support. We plan to pilot the electronic prescribing and administration software in November 2001 with roll-out to the Medical Centre during 2002.

Our impression from evaluation of prescribing software used in general practice is that the software would require significant modification for the hospital environment. In addition, there are scalability issues that would need to be overcome for general practice software to perform well over a hospital network.

Initial funding for implementation of the electronic health system at the A&RMC was provided by the Department of Human Services, Victoria. However, further funding will be required to complete the project.

If hospitals are to implement electronic prescribing and administration and realise the benefits of such a system, funding must be provided, as it has been for general practice.

Rosie McKew

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Team Leader, Electronic Prescribing and Administration Project Team

Austin & Repatriation Medical Centre

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Electronic prescribing in general practice

Editor, – I am writing to express my concern over the amount of errors I have seen with computer-generated prescriptions. The most alarming example I saw recently was a prescription for fluvastatin which was meant to be Fluvax [influenza vaccine]. Aside from this I have also encountered numerous prescriptions with incorrect dosages (e.g. 14 nocte for Rulide [roxithromycin] 300 mg) and many examples of incorrect strengths (e.g. Adalat [nifedipine] 60 mg instead of 30 mg). There are also a huge number of prescriptions printed out as private when they clearly are not.

Nearly all of these mistakes can easily be picked up by the doctor with a quick check of the script they have just printed out and simply require a quick handwritten correction. Computer-generated prescriptions are certainly an enormous improvement over their handwritten counterparts, however improvements can still be made with a tiny amount of effort.

Chris Morris

Pharmacist

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Rh D immunoglobulin

Editor, – Further to my article on the shortage of Rhesus D immunoglobulin (Aust Prescr 2000;23:36–8), a mini-dose of Rh D was marketed in May 2001. This has the dosage of 250 IU and should be offered to every Rh D negative woman with no preformed anti-D antibodies, for problems in the first twelve weeks of gestation. The indications usually include miscarriage, termination of pregnancy, ectopic pregnancy and chorionic villous sampling. The 250 IU dose is sufficient to prevent immunisation by a fetomaternal haemorrhage of 2.5 mL of red blood cells (5 mL of whole blood).

The introduction of the mini-dose is a significant achievement as currently a larger than necessary dose is being used for these first trimester indications. This will therefore allow a more efficient usage of the limited amount of anti-D. A communication plan is being developed.

Mark Dean

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Direct to consumer advertising

Editor, – It has become apparent in the last couple of years that many pharmaceutical companies are providing a broader spectrum of services to general practitioners and their patients. Examples include educational activities, clinical audits and patient education services.

One large multinational company states on its advertising material that it has two current databases of patient-based information containing (as at December 2000) over 22 000 and 9000 entries. These patients have been enrolled, usually by their general practitioners, often via the software utilised by the general practitioner, to receive patient educational material from the company. This material relates to particular diagnoses where the company's product has been prescribed.

Direct to consumer advertising would appear to be looming on the horizon. This would provide far easier access for the marketing and sale of pharmaceutical products, bypassing the current appropriate systems that are in place – systems such as advertising in professional journals, and distribution of pharmaceuticals through appropriate outlets.

In this case, the consumer is usually a patient. A patient often has an illness. This illness may be physical, emotional, spiritual, mental, or a combination of some or all. Consequently, it is not unreasonable to assume that the patient is vulnerable, due to disability, fear, anxiety, lack of appropriate information, etc.

Pharmaceutical companies are primarily businesses, and not benevolent societies. To succeed in today's environment a business usually has to be profit-driven, and responsible to its shareholders. Advertising plays a major role in this successful profile.

If my crystal ball gazing is correct, and direct to consumer advertising is in the pipeline, then pharmaceutical companies would be wise to prepare themselves in advance. This would make commercial sense. Data collection would have to be part of this strategy. If this does occur, then the normal gatekeeping provided by general practitioners and pharmacists will be bypassed to a large degree, and the costs of pharmaceuticals to society would presumably increase considerably.

Scott Bell

Rural and Remote Locum

Tas.