Editors' view

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Individualizing drug therapy, and 'men behaving badly'

Clinical Pharmacology is concerned with the rational, safe and effective use of drugs. Good therapeutics is about recognizing variability – 'one drug or one dose does not fit all'. Promoting the individualization of drug therapy remains the biggest challenge for the Clinical Pharmacologist.

There are many factors that mitigate against our success. While our students nod approvingly as we ply our trade – it is self evident that Jonah Lomu is different from his grandmother (Jonah's recent kidney transplant only adds to the intrigue of this notion) – the reality in practice is that complexity is irritating, recipe medicine is easier, and one dose for everyone is a much simpler message for drug companies to promote. Many drug companies have been 'hoist by their own petard' in this respect, as the recent withdrawal of rofecoxib (Vioxx) may attest (more of this later).

Multiple factors determine variability, and make up the 'patient profile' – age, weight, sex, ethnicity, smoking, alcohol, concurrent diseases, allergies, and current drug therapy. The 'drug profile' is also multifactorial, and made up of actions, pharmacokinetics, factors affecting pharmacokinetics, indications, contraindications, interactions, adverse effects, dosing regimen and monitoring. The aim of good therapeutics is to match all aspects of the drug profile with all those of the patient profile to choose the right drug, at the right dose, for the right patient. All this is set against the background of the Hippocratean dictum 'primum non nocere', or 'first do no harm'.

In this issue, Rashmi Shah (pp. 452–69) addresses the above in considerable detail in his 'search for the right dose and dosing regimen', with respect to the elderly. Other papers also reflect the theme, addressing other important notions such as compliance, accessibility, and methods of dose individualization.

The elderly provide a good starting point for discussions on dose individualization. Dr Shah says that more people in the world are getting older! (I wonder if this is true globally, with AIDs, famine and wars ravaging the third world?). Older people have more comorbidity, which means more drugs, more drug interactions, more adverse effects, more non compliance, and more for all of us to learn. It is no wonder that the elderly are often poorly served in therapeutics.

In terms of poor drug choice, Dr Shah alludes to overtreatment (i.e. without good indication) with some drugs (e.g. digoxin), and undertreatment with drugs with a good evidence basis (e.g. statins, antihypertensives, antiplatelet/anticoagulants, ACEIs and beta blockers). In terms of poor drug usage, he lists impractical directions, inappropriate dose adjustment for comorbidity (e.g. renal dysfunction), and failure to accommodate drug interactions as important factors. Non compliance of course remains a perennial issue.

Cheng *et al.* (pp. 528–35) address the issue of adherence to statin therapy and lipid control in high-risk patients with coronary heart disease. They found that compliance was actually quite good in the early period, but declined slightly over time. Weak associations were found between poor adherence and poor lipid control. Interestingly, and not surprisingly, household income was a weakly positive predictor of good adherence.

The issue of socioeconomic status and quality of prescribing was also addressed by Odubango *et al.* (pp. 496–502) again in relation to the elderly population. The relatively deprived cohort was more likely to have less evidence-based prescribing (in all of its manifestations), more polypharmacy, more potential drug interactions, and more generic drugs. The fact that this occurred in a relatively affluent country (Ireland) bodes badly for third world countries.

From my own part of the world, and in a topic of

particular personal interest, Mohan *et al.* (pp. 521–7) examined four methods of adjusting gentamicin doses within the context of extended interval dosing. They found that software packages that adjust dose based on pharmacokinetic principles were the most accurate, but that for practical purposes manual calculations and a nomogram approach were almost as good. This is probably predictable, based on the idea that ANY logical formalized approach to individualized dosing is likely to do reasonably well, and certainly better than 'one dose fits all'.

The main challenge for spreading the word about dose individualization is that just doing it is more important than whether one approach is better than another. In this respect I believe one of the greatest single tools we can advocate is the use of formulae such as that of Cockcroft and Gault, that allow the calculation of creatinine clearance that is then used for the adjustment of doses of appropriate drugs in renal impairment [1]. The basis behind such formulae is easily comprehensible, has good scientific purity, and can be readily seen to work in practice (e.g. with digoxin concentrations). If we can achieve acceptance from our colleagues outside our field that this approach is useful, it has heuristic value far in excess of its immediate impact. Such acceptance denotes at least a start in a wider acceptance of the concept of dose-individualization. From this it is a small step to individualizing in other circumstances such as hepatic dysfunction, pharmacogenetics, drug interactions, and in the elderly. It is the start of the battle to win acceptance for the principles of clinical pharmacology.

One of the drug classes that comes up repeatedly in discussions about 'the right dose, for the right patient', is NSAIDs. These drugs are amongst the most widely used groups, and particularly in the elderly. The elderly, and especially females, are at higher risk of toxicity, making this setting ideal for dose-individualization. Unfortunately, the NSAIDs are largely metabolized drugs, and therefore unable to be accommodated by use of the Cockcroft and Gault formula. Furthermore, it has been much harder to establish that drug metabolism *per se* is predictably impaired in the elderly (Shah, pp. 452–69) after obvious things such as comorbidity, drug interactions, etc. have been accounted for. The drug companies crave simplicity, so tend to advocate a one dose fits all approach.

Which brings me to Vioxx! On September 30, 2004 Merck shattered our complacency with the sudden worldwide withdrawal of rofecoxib. A longterm prospective study of rofecoxib in the prevention of colon polyps had revealed an approximately 2-fold increase in

myocardial infarction in the rofecoxib group, compared with placebo. This followed on from the suspicion of a potential prothrombotic effect shown in Merck's original VIGOR study [2].

The saga of the COX 2 inhibitors has not been a happy one. The COX 2 gut protection hypothesis arrived with a hiss and a roar in 1999 [3], and was adopted with vigour [!] because of its biological plausibility and because of our entrenched fear of the gastrointestinal toxicity of conventional NSAIDs. Just as we were all ready for Prozac (fluoxetine), so the time was right for the COX 2s.

To say the COX2 agents have done well is an understatement. They have been blockbusters! Sales of rofecoxib have topped 80 million and \$2.5 billion annually [4]. Yet the evidence for their superiority has never been great, even with respect to their better gastrointestinal tolerability. Despite over 8000 patients enrolled in the CLASS study [5], a statistical decrease in GI events with celecoxib compared to diclofenac and ibuprofen was only achieved (just) at 6 months by combining end points rather than reporting results related to the originally defined primary endpoint [6]. Furthermore, CLASS was not a single study, but a combination of 2 studies that ran for 12 and 15 months. The results of the longer study periods were available at the time the study was published, and showed that the benefits seen at 6 months were no longer evident [6]. Thus, at best, the improvement in GI events could be considered marginal. This contrasts markedly with Pharmacia's claims in a piece of promotional material in New Zealand that 'Celebrex has the advantage of being 92% less likely to cause upper GI events compared to conventional NSAIDs' [7]. The reference supporting this was 'Data on file, Pharmacia Corporation (SUCCESS-1), 2001'. Scarcely a good evidence basis, I say.

The VIGOR study was slightly more convincing in terms of improvement in GI events compared with naproxen, showing a relative risk reduction with 95% confidence interval of 0.3–0.6 [2]. However, there was also an unexpected 4-fold increase in myocardial infarction in the rofecoxib group. Overall mortality was 0.5% in the rofecoxib group *vs* 0.4% in the naproxen group, which did not quite reach significance. Thus in terms of the solid end point of mortality, there was no signal of any advantage with rofecoxib. Interestingly another study does not even show rofecoxib to have any advantage in GI toxicity compared with diclofenac and ibuprofen [8].

Merck went into damage control mode, claiming that the difference in cardiac toxicity was due to a protective effect of naproxen, not any prothrombotic tendency of

rofecoxib. The FDA sent Merck a warning letter in September 2001 saying 'You have engaged in a promotional campaign for Vioxx that minimizes the potentially serious cardiovascular finding observed in the VIGOR study. . . . They also stated that 'the DDMAC has reviewed your promotional activities and materials and has concluded that they are false, lacking in fair balance, or otherwise misleading in violation of the Federal Food, Drug and Cosmetic Act . . . ' [9]. Reviewing this saga after the withdrawal of rofecoxib, Topol stated 'Sadly, . . . Merck's commercial interest in rofecoxib sales exceeded its concern about the drug's potential cardiovascular toxicity' [4].

Whether rofecoxib is actually prothrombotic or merely lacking antithrombotic activity remains in question. Whether this is a COX 2 class effect, a dose effect, or merely an idiosyncrasy of rofecoxib remains in question. Pfizer are certainly making hay while the sun shines by actively claiming in their promotional material safety with celecoxib. It is doubtful they have the evidence for their strongly positive assertions of safety.

An alternative explanation for the adverse cardiovascular effects of rofecoxib could relate to greater renal antiprostaglandin effects. Evidence has accrued, including from VIGOR itself, that rofecoxib is associated with more oedema, congestive heart failure and increase in BP than conventional NSAIDs [4, 10]. Such effects could well over time result in increased cardiovascular events. Sadly this obvious question has never been answered, and now will not be.

A tantalizing further question is whether Merck just got the dose wrong (too high, therefore more type A adverse reactions) or did not advocate enough dose individualization (reduction) in the elderly. Shah states in his paper 'Despite often conducting adequate dose-finding studies, the sponsors in their attempt to maximize efficacy take forward the highest effective dose (from their dose-ranging studies) for investigation in pivotal studies'. If this applied to Merck and rofecoxib, they may well have been hoist by their own petard.

Paradoxically, it could be argued that Merck have acted (albeit too late) excessively to the latest evidence. Had they taken the early cues about possible cardiovascular effects more seriously, and organized appropriate prospective trials in patients with cardiovascular disease, with sensible dose adjustment in the elderly, we would have a better perspective of the goods and bads of the COX 2 inhibitors. Having a class of anti-inflammatory agents *without* antiplatelet effects could be desirable for such things as the operative period, the periparturient period and during dental extractions. Instead,

a pall now hovers over the whole COX 2 class, and we may be the worse for it.

The COX 2 saga is an example of men behaving badly. Unfortunately it is also a product of our times. 'Short on the truth, but contains few lies', said a prominent medical director of a drug company at a recent symposium I attended. Sadly this is the crux of marketing. Joel Bakan recently wrote in his book 'The Corporation' – 'The corporation's legally defined mandate is to pursue relentlessly and without exception its own economic self-interest, regardless of the harmful consequences it might cause to others' [11].

It is not surprising that deception is part of Big Pharma's persona. Our leaders George Bush, Tony Blair and John Howard have raised lies and deception to an art form. Sadly the population does not seem to care (John Howard has just been reelected as Prime Minister in Australia with an increased majority, and I fear the results of the next elections in both the UK and the USA). This sort of behaviour, both at a political level and specifically in relation to drug companies, can only occur if we allow it to. We must all be more proactive in the interests of the greater good (our patients) by recognizing and not tolerating bias, both in others and in ourselves.

But meanwhile, remember and laud the Cockcroft and Gault equation!

References

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