Editors' view

Minimising Harm: Human Variation and Adverse Drug Reactions (ADRs)

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Do no harm?

'First, do no harm' – great advice to aspiring physicians throughout most of human history, but with the discovery of effective drugs in the twentieth century, no longer tenable as it stands. We could not get to first base in treating leukaemias, infections, cardiovascular disease, diabetes and so on if we were not prepared to accept an element of risk. It is the balance between benefit and harm that is key, rather than an unachievable ideal of absolute safety. But quantifying the probability of harm is problematic – at least for Rumsfeld's 'unknown unknowns'. The slogan 'Distaval – the safe hypnotic' adorned the drug company calendar in my father's consulting room: 'safe' in the sense that when taken in overdose it was less likely to prove fatal than barbiturates, which were the market-leading hypnotics in the nineteen fifties. Phocomelia had yet to be described, the epidemic of which jump-started drug regulation worldwide. Today's drug regulators are concerned with a far wider spectrum, including topical issues such as the licensing of generic 'biosimilar' biological treatments [1]. The concept of biosimilars has a long way to go before it achieves even the present incomplete maturity of the concept of 'bioequivalence' between different preparations of conventional low molecular weight drugs. Meanwhile, drugs continue to be prescribed during pregnancy, and may cause harm to the unborn child that is more subtle (and hence harder to recognise as drug-related) than limb defects. The report in this issue by Bakker et al of an approximate doubling in the use of selective serotonin reuptake inhibitors among pregnant women over the past ten years [2], is surely cause for concern in this regard.

Regulatory authorities appropriately remain highly sensitised to idiosyncratic drug reactions. Nevertheless, it is the less exotic but more predictable adverse effects that relate to the main pharmacological action of a drug that account for much of the harm that drugs do, and much of this should be quantifiable and predictable, and thus potentially avoidable.

The size of the problem

The total cost of medicines to the NHS was around £10.3 billion in 2005/06 – over 18% of total NHS expenditure – and drug expenditure is rising at more than 7.5% per annum. More than 5% of hospital admissions may be related to an ADR at an estimated cost of approximately £0.5 billion per annum [3]. In the present issue Wester and her colleagues report the striking observation that *fatal* ADRs are the seventh most common cause of death in Sweden, accounting for approximately 3% of all deaths in the general population [4]. Haemorrhage (especially gastrointestinal and CNS) related to antiplatelet, nonsteroidal and antithrombotic drugs, featured prominently, as it did in the Merseyside study [3]. The authors conclude that preventive measures should be taken to reduce the number of deaths caused by drugs, but this may be easier said than done.

Prevention: what is to be done?

Clearly there is no simple solution to this massive problem. Any effective strategy will necessarily involve multiple measures including population-based administrative actions (eg education, regulation, provision of information) as well as actions by individual prescribers. This is not easy: in this editors' view we consider briefly some of the difficulties, illustrated by articles from this current issue.

Education is a good place to start. Prescribing drugs is a serious responsibility, as the findings mentioned above [3, 4] confirm, and it is self evident that undergraduate education in clinical pharmacology is crucial if doctors are to be safe and effective prescribers. Yet, incredibly, many medical schools in the UK dismantled their courses in clinical pharmacology during the nineteen nineties and many ceased to examine the subject separately. There are signs that these perverse trends are beginning to be reversed, but unsurprisingly a substantial proportion of newly

qualified doctors are currently unconfident of their competence to prescribe [5]. For these individuals in particular postgraduate training in CPT will be vital.

One tactic to reduce ADRs is to prescribe a second agent to prevent an anticipated ADR associated with the primary therapeutic drug. This is sometimes justified but can escalate unacceptably (as with the old lady who swallowed the fly...). Balakrishnan and Jhaj discuss the prophylactic use of gastro-protective drugs in patients on low-dose aspirin, concluding that current practice is suboptimal [6]. Multiple drug therapy increases the likelihood of ADRs from drug interactions, which are particularly problematic in anti-HIV therapy. Back and Gibbons draw attention to interactions in this therapeutic area and, importantly, to the need to fund the provision of up to date web-based resources if harm from such drug interactions is to be minimised [7]. Mehta and colleagues [8] describe the first systematic prospective study of ADRs in the HIV/AIDS era in Sub-Saharan Africa. Many of the ADRs they documented were potentially avoidable. Antiretroviral therapy contributed substantially to community acquired ADRs, and drugs used for opportunistic infections (eg antifungals) were the commonest culprits among hospital inpatients. In this context, Damle *et al.* describe pharmacokinetic interactions between efavirenz and voriconazole [9].

Rather than add a 'protective' agent, perhaps it would be better to substitute another drug with a similar therapeutic effect but different mechanism and different secondary pharmacology (clopidogrel for aspirin, say)? This is generally sounder territory, but again there may be unpleasant surprises in store for the unwary: tramadol is sometimes substituted for an NSAID as an analgesic in patients at risk of peptic ulceration, but Tørring and her colleagues report that among patients hospitalised for perforated peptic ulcer, tramadol appears to increase mortality similarly to NSAIDs [10]. Whether this will prove to be a causal relationship and if so, what is its mechanism remain to be elucidated.

What of the possibility of identifying patients at increased risk of an ADR by genotyping for key components of drug action (eg the receptor) or elimination (eg CYP450s) – the fashionable strategy of 'personalised medicine'? This has yet to prove itself, but is a tantalising holy grail. In the present issue, Hirt *et al* report that the rate of metabolism of nelfinavir to the active metabolite M8 is approximately halved in $*1/*2$ or $*2/*2$ genotypes of CYP2C19 compared with $*1/*1$ [11]. Conversely, low-dose aspirin inhibits platelets similarly in patients carrying or not carrying the P2Y₁₂H2 haplotype and/or the 34T allele. So these genetic polymorphisms of the platelet ADP receptor (P2Y₁₂) do not appear to contribute to the putative phenomenon of 'aspirin resistance' [12] – an important negative if such a phenomenon exists as a true entity (a controversial issue to which we may return in a future article). Such complexities mean that progress to a clinically useful therapeutic strategy in routine clinical service

remains a long way off, not least because of the necessary but severe hurdle of clinical trial before such strategies are introduced into clinical practice. Exciting times, with many a mountain still to climb!

REFERENCES

- 1 Prugnaud J-L. Similarity of biotechnology-derived medicinal products: specific problems and new regulatory framework. *Br J Clin Pharmacol* 2008; 65: 619–20.
- 2 Bakker MK, Kölling P, van den Berg PB, De Walle HEK, De Jong van den Berg LTW. Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. *Br J Clin Pharmacol* 2008; 65: 600–6.
- 3 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK, Breckenridge AM. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients *Br Med J* 2004; 329: 15–19.
- 4 Wester K, Jönsson AK, Spigset O, Druid H, Hägg S. Incidence of fatal adverse drug reactions: a population based study. *Br J Clin Pharmacol* 2008; 65: 573–9.
- 5 Tobaiqy M, Mclay J, Ross S. Foundation year 1 doctors and clinical pharmacology and therapeutics teaching. A retrospective view in light of experience. *Br J Clin Pharmacol* 2007; 64: 363–372.
- 6 Balakrishnan S, Jhaj R. Letter to the Editor: Prophylactic use of gastro-protective agents in patients on low-dose aspirin. *Br J Clin Pharmacol* 2008; 65: 621–2.
- 7 Back DJ, Gibbons SE. Letter to the Editor: Response to 'Communicating Information about Drug Interactions'. *Br J Clin Pharmacol* 2008; 65: 617–18.
- 8 Mehta U, Durrheim DN, Blockman M, Kredo T, Gounden R, Barnes KI. Adverse drug reactions in adult medical inpatients in a South African hospital serving a community with a high HIV/AIDS prevalence: prospective observational study. *Br J Clin Pharmacol* 2008; 65: 396–406.
- 9 Damle B, LaBadie R, Crownover P, Glue P. Pharmacokinetic interactions of efavirenz and voriconazole in healthy volunteers. *Br J Clin Pharmacol* 2008; 65: 523–30.
- 10 Tørring ML, Riis A, Christensen S, Thomsen RW, Jepsen P, Søndergaard J, Sørensen HT. Perforated peptic ulcer and short-term mortality among tramadol users. *Br J Clin Pharmacol* 2008; 65: 565–72.
- 11 Hirt D, Mentré F, Tran A, Rey E, Auleley S, Salmon D, Duval X, Tréluyer J-M, COPHAR2-ANRS Study Group. Effect of CYP2C19 polymorphism on nelfinavir to M8 biotransformation in HIV patients. *Br J Clin Pharmacol* 2008; 65: 548–57.
- 12 Bierend A, Rau T, Maas R, Schwedhelm E, Böger RH. P2Y₁₂ polymorphisms and antiplatelet effects of aspirin in patients with coronary artery disease. *Br J Clin Pharmacol* 2008; 65: 540–7.