Editors' view

Uncertain risks of drug related harms, the precautionary principle and limitations of meta-analysis

JM Ritter, Editor-in-Chief British Journal of Clinical Pharmacology

Department of Clinical Pharmacology, King's College London, School of Medicine at Guy's, King's College & St Thomas' Hospitals, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH UK

Quantifying uncertainty

Even something as precise as the mathematics of risk quantification can cause controversy. For example, the risk of progressive multifocal leukoencephalopathy (PML) in patients taking natalizumab – see a recent FDA warning letter <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm182667.htm> which points out that the risk for developing PML appears to increase with the number of infusions received; the current rate of PML in patients who have received at least 24 infusions ranges from 0.4 to 1.3 per 1,000 patients. This can be presented as absolute risk (number of events/number of patients exposed) or as an actuarial risk that takes account of duration of exposure. Biogen idec (manufacturers of natalizumab) prefer the former and the Wall Street Journal (supported by a Harvard School of Public Health biostatistician) prefer the latter, leading Keith Winstein (see <http://online.wsj.com/article/sb125245536076594245.html>) to comment that 'different methods of weighing the risks and benefits of medical treatments lead to varying conclusions about their safety.' Thus, quantifying a known risk is difficult enough. Unquantifiable risk can be even more of a headache! In this editors' view we touch on two different potential causes of drug-related harm where identifying and quantifying a risk is both topical and problematic. Until this can be rectified, prescribers faced with individual patients with varying clinical needs and cardiovascular risks and who must try to weigh the risk/ benefit of their therapeutic advice, are in a quandary.

Insulin glargine and carcinogenicity

Insulin glargine is one instance where potential risk has proved controversial. Insulin is mitogenic, stimulating DNA synthesis and cell division. Insulin glargine is 6-8-fold more mitogenic than human insulin, and cultured breast cancer cells proliferate in response to near-therapeutic concentrations of this analogue *in vitro*. The controversy surrounds recent cohort and longitudinal observational registry studies and their interpretation [1–7]. While it is agreed that important scientific questions have been raised that require further investigation [6], it has been argued that such concerns should not be aired on the basis of incomplete evidence, for fear of provoking unnecessary alarms and anxieties [7] – what the late distinguished Jim Petrie deprecated as 'shroud waving'. This is a difficult and emotive issue. Evidence that new variant Creutzfeldt Jacob disease (nvCJD) could cross between species, unsupported by quantitative knowledge of the relevant risks, was enough to justify the policy of mass culling of UK cattle. This policy was based on the precautionary principle via a worst case scenario – an approach based on the Hippocratic principle to first do no harm ('primum non nocere'). From the viewpoint of a clinician (or perhaps a farmer), the precautionary principle seems akin to constructing aero planes from reinforced concrete to minimize injury to the passengers in the event of a crash: unfortunately such 100% safe planes will not fly. What is needed before taking a plane or a medication is to be informed as to the benefit risk balance. But how can the prescriber or patient judge risk/ benefit when risk is so

uncertain? This is where pharmaceutical regulators have a role to play, since the principle applies to European pharmaceutical regulation [8], and may be used to leverage more information (see below). It is therefore surely reasonable to bring *a priori* concerns to public attention even when more work is needed to define the nature and magnitude of a possible risk.

Myocardial infarction and non-steroidal anti-inflammatory drugs (NSAIDs)

Cardiovascular harm from COX-2 inhibitors is well documented but hard to quantify. We have written before both here and elsewhere [9, 10] on this fraught topic and return to it now. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit COX-1 and COX-2 to varying extents. NSAIDs (notably aspirin) which inhibit COX-1 mediated platelet thromboxane (TX) production in whole blood by >95%, inhibit platelet aggregation and are anti-thrombotic. But there is also a pharmacological rationale to anticipate a *pro-thrombotic* effect of COX-2 inhibition, namely reduced prostacyclin synthesis through inhibition of COX-2. In the event, COX-2 inhibition is indeed *pro-thrombotic* unless accompanied by profound inhibition of platelet thromboxane biosynthesis (measured as TXB₂ formed in whole blood allowed to clot in a glass tube) [11]. Rofecoxib ('Vioxx') was compared with naproxen (an NSAID that potently inhibits COX-1) in the VIGOR study, in an attempt to differentiate these drugs on the basis of gastro-toxicity; an observed excess of myocardial events in patients treated with rofecoxib was attributed initially to cardioprotection by naproxen (see [9–11] for the original references). Subsequently a randomised controlled trial (RCT) of rofecoxib versus placebo was performed to test the hypothesis that rofecoxib would prevent adenomatous colonic polyps from enlarging and/or becoming malignant (chemoprophylaxis), and an excess of cardiovascular events occurred in rofecoxib-treated patients. Rofecoxib was withdrawn voluntarily, and the question whether its cardiovascular toxicity was a class effect was debated. Further evidence of cardiovascular harm led to the withdrawal of valdecoxib and parecoxib. Additional toxicities contributed to the withdrawal of lumiracoxib (liver failure) and valdecoxib (Stevens-Johnson syndrome, as well as an excess of myocardial infarctions and strokes). RCT data further demonstrated a dose-related increase in cardiovascular risk for celecoxib, which remains on the market at lower doses [12].

RCTs of NSAIDs were not designed with primary cardiovascular end points: cardiovascular toxicity has emerged during studies designed to look for possible benefits as regards chemoprophylaxis for colon cancer or gastro-toxicity. Consequently, the precision with which such risks are quantified is poor, reflected by wide confidence inter-

vals. For example, a trial with parecoxib/valdecoxib after cardiac surgery noted a relative risk of myocardial infarction of 3.7-fold (95% CI 1.0 to 13.5) [13]. Surely this should be a situation where meta-analysis can ride to the rescue? Indeed it has, but only up to a point. In one meta-analysis [14] allocation to rofecoxib, celecoxib, valdecoxib, etoricoxib or lumiracoxib was found to be associated with a significant 42% increase in serious vascular events relative to placebo. High doses of ibuprofen or diclofenac (but not naproxen) were also associated with a similarly increased relative risk. The late John Swales jested that meta-analysis is a bit like combining a case of Chateau Palmer with a thimbleful of vinegar – one is left with a case of vinegar. Presentation of the NSAID trial data that identifies cardiovascular risk is commercially highly sensitive, and some of it has been questioned [15–18] as the hazard ratios were sensitive to reintroduction of missing data – rather more than a thimbleful of vinegar we fear. A further problem with the RCT data is that apart from the RCT with parecoxib/valdecoxib after cardiac surgery mentioned above [13] most RCTs excluded high cardiovascular risk patients, who are nevertheless exposed to NSAIDs during ordinary clinical practice and in whom relative as well as absolute risk may be disproportionately increased by COX-2 inhibition compared with low risk individuals. Thus, while confirming a risk of COX-2 inhibition, the meta-analysis might underestimate its magnitude when NSAIDs are administered to older patients with cardiovascular risk factors and who were excluded from the RCTs on which the meta-analysis was based. That such analysis is indeed a blunt instrument in this context is suggested by its failure to discriminate between the excess risks caused by any of the above individual drugs, since pharmacologically it is unlikely that they are equally potent in this regard [14].

Other ways of assessing risk are also problematic. Epidemiological associations between NSAID use and myocardial infarction are not reassuring, but can operate in either direction as pointed out recently by Nicholas Moore [19]: taking an NSAID painkiller might cause a heart attack but anginal pain might equally prompt consumption of an NSAID painkiller ('reverse causation'). It is, however, noteworthy that risk of myocardial infarction associated with different NSAIDs in the general population correlates strongly with the potency of usual therapeutic doses of each NSAID in inhibiting COX-2 [20], excepting only naproxen which inhibits platelet thromboxane synthesis by >95% as noted above [11, 20]. This correlation with pharmacological potency would not be expected on the basis of reverse causation (why should the angina sufferer reach for the most potent COX-2 inhibitor?) and is consistent with, but short of proof of, causality. We are left with a strong *a priori* case for believing that any NSAID that does not also cause substantial inhibition of platelet thromboxane synthesis will increase cardiovascular risk, but uncertainty as to the magnitude of the effect. The 42% increase risk relative to placebo identified by meta-analysis of RCTs

[14] may be an underestimate for the reasons given above. Even if it is not, the magnitude of the effect is striking when compared to relative risk reductions of approximately 25–33% achieved by antihypertensive therapy [21] or simvastatin [22] which have been (rightly, in our view) hailed as major advances in cardiovascular disease prevention.

It has been argued elsewhere that since NSAIDs are the most widely prescribed group of therapeutic drugs worldwide, they could represent a serious public health risk [10]. In the present issue of the Journal, Benedict Wheeler and colleagues report on the population impact of regulatory restrictions to prescribing COX-2 inhibitors, and conclude that withdrawal/regulation of such drugs has been associated with a favourable reversal of hospital MI admission trends in people aged ≥ 65 years but not in younger people [23], so it does seem possible that even the limited withdrawals of NSAIDs applied to date may have had a beneficial effect detectable at the population level. More education and more discriminating use of NSAIDs by patients (old as well as young) might have an even bigger impact.

This begs the question of what should a clinician recommend when faced with a high cardiovascular risk patient with a painful chronic condition? We do not have the answer (one rational but inadequately evidence-based strategy would be the use of a drug such as naproxen with potent COX-1 as well as COX-2 inhibitory activity $\pm$ acid suppression if needed), but suspect that currently many physicians recommend regular high dose paracetamol (acetaminophen). Before following this latter route it is worth reflecting that paracetamol is a COX-2 selective inhibitor, albeit not a very potent one [24–26]. In the Nurses' Health Study (>70,000 women studied over 12 years) self-reported paracetamol use was associated with dose-dependent increased cardiovascular risk (relative risk 1.41, 95% CI 1.26–1.93) in contrast to aspirin which was associated with reduced risk [27]. Would labeling of NSAIDs, including over-the-counter remedies containing paracetamol, warning of the class effect of increased cardiovascular risk associated with COX-2 inhibition, help consumers and their doctors to make sensible choices, as argued elsewhere [10], or is this suggestion akin to 'shroud waving'? Either way, RCTs powered for cardiovascular endpoints are sorely needed. One such study (SCOT: <http://clinicaltrials.gov/ct2/show/NCT00447759>) of celecoxib (academically planned and Pfizer-funded) has attracted comment (<http://www.bmj.com/cgi/content/full/bmj.b3443?ijkey=7i5Ml4z59SOg1yz&keytype>); two of the investigators who designed the trial (Christopher Hawkey and Ian Ford) explained in a response (http://www.bmj.com/cgi/eletters/339/sep02_1/b3443#220504) that the European Medicines Agency (EMA) obliged Pfizer to fund such a trial if feasible, and that they had responded by designing with Tom MacDonald a study that EMA regarded as feasible and required Pfizer to fund, so it appears that regulatory authorities do indeed have lever-

age to get these questions addressed. The precautionary principle provides a justification to the regulators for exerting such leverage, and new knowledge could lead to major health benefits: for some patient groups avoiding NSAIDs could have a larger impact on cardiovascular events than prescribing well validated therapies such as antihypertensive drugs [22], simvastatin [23] or aspirin [28].

REFERENCES

- 1 Hemkens LG *et al.* Risk of malignancies in patients with diabetes treated with human insulin or insulin analogue: a cohort study. *Diabetologia* 2009; 52: 1732–44.
- 2 Jonasson JM *et al.* Insulin glargine use and short-term incidence of malignancies – a population-based follow-up study in Sweden. *Diabetologia* 2009; 52: 1745–54.
- 3 Colhoun HM & SDRN epidemiology group. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network epidemiology group. *Diabetologia* 2009; 52: 1755–65.
- 4 Curry CJ, Poole CD, Gale EAM. The influence of glucose-lowering therapies on cancer risk in type II diabetes. *Diabetologia* 2009; 54: 1766–77.
- 5 Smith U, Gale EAM. Does diabetes therapy influence the risk of cancer? *Diabetologica* 2009; 52: 1699–1708.
- 6 Gale EAM. Insulin glargine and cancer: another side to the story? *Lancet* 2009; 374: 521.
- 7 Pocock SJ, Sneeth L. Insulin glargine and malignancy: an unwarranted alarm. *Lancet* 2009; 374: 511–3.
- 8 Asif J. General product safety law in The law and regulation of medicines (Feldschreiber P ed) 2008 Oxford University Press.
- 9 Aronson JK. The NSAID rollercoaster – more about rofecoxib. *Br J Clin Pharmacol* 2006; 62: 257–9.
- 10 Ritter JM, Harding I, Warren JB. Precaution, cyclooxygenase inhibition, and cardiovascular risk. *Trends in Pharmacological Sciences* 2009; 30: 503–8.
- 11 Patrono C, Baigent C. Low dose aspirin, coxibs and other NSAIDs: a clinical mosaic emerges. *Mol Interv* 2009; 9: 31–9.
- 12 Solomon SD *et al.* Cardiovascular risk of celecoxib in six randomised placebo-controlled trials: the cross trial safety analysis. *Circulation* 2008; 117: 2104–13.
- 13 Nussmeier, NA *et al.* Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005; 352: 1081–91.
- 14 Kearney PM *et al.* Do selective cyclooxygenase-2 inhibitors and traditional nonsteroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials *BMJ* 2006; 332: 1302–8.
- 15 Curfman GD *et al.* Expression of concern. *N Engl J Med* 2005; 353: 2813–4.

- 16** Bresalier RS *et al.* The Adenomatous Polyp Prevention on Vioxx (APPROVe). Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005; 352: 1092–102.
- 17** Nissen SE. Adverse events of rofecoxib. *N Engl J Med* 2006; 355: 203–4.
- 18** Furberg C. Adverse effects of rofecoxib. *N Engl J Med* 2006; 355: 204.
- 19** Moore N. No obvious extra cardiovascular risk associated with low-dose NSAIDs. *Clin Pharm Therap* 2009 advance online publication 6 May doi:10.1038/clpt2009.66.
- 20** Garcia Rodriguez LA *et al.* Role of dose potency in the prediction of risk of myocardial infarction associated with non-steroidal anti-inflammatory drugs in the general population. *JACC* 2008; 52: 1628–36.
- 21** Blood pressure lowering treatment trialists' collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomized trials. *BMJ* 2008; 336: 1121–7.
- 22** Heart Protection Study Collaboration. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; 361: 2005–16.
- 23** Wheeler BW, Metcalfe C, Gunnell D, Stephens P, Martin RM. Population impact of regulatory activity restricting prescribing of COX-2 inhibitors: ecological study. *Br J Clin Pharmacol* 2009; 68: 752–64.
- 24** Aronoff DM *et al.* New insights into the mechanism of action of acetaminophen: its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthetases. *Clin Pharmacol Therap* 2006; 79: 9.
- 25** Hinz B *et al.* Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB J* 2008; 22: 383–90.
- 26** Li S *et al.* Acetaminophen: antipyretic or hypothermic in mice? In either case, PGHS-1b (COX-3) is irrelevant. Prostaglandin and other lipid mediators 2008; 85: 89–99.
- 27** Chan AT *et al.* Nonsteroidal anti-inflammatory drugs, acetaminophen and the risk of cardiovascular events. *Circulation* 2006; 113: 1578–87.
- 28** Collins R *et al.* Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials *Lancet* 2009; 373: 1749–60.