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Therapeutic challenges for 2005

D Patterson
Clinical Lecturer, The Institute of Cardiovascular Research, Ninewells Hospital and Medical School, Dundee University, Dundee, Scotland

ABSTRACT This well attended symposium, co-ordinated by Professor T Macdonald (University of Dundee), brought together leaders in Therapeutics from both the UK and USA. The 'Cox-2 saga' was the focal point of the day with presentations by Dr G Fitzgerald and Professor P Dieppe highlighting the issue and producing some lively and engaging debate.

LIST OF ABBREVIATIONS Absolute risk reduction (ARR), adverse drug reactions (ADRs), cyclo-oxigenase (Cox), gastrointestinal (GI), General Practice Research Database (GPRD), medicines monitoring unit (MEMO), National Institute of Clinical Excellence (NICE), numbers needed to treat (NNT), non-steroidal anti-inflammatory drugs (NSAIDs), prostacyclin (PGI2), relative risk reduction (RRR), thromboxane (TXA2)

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Correspondence to ***D Patterson, Institute of Cardiovascular Research, Ninewells Hospital and Medical School, Dundee University, Dundee, DD1 9SX***

tel. ***+44(0)1382 660111***

fax. ***+44 (0)1382 632333***

e-mail ***d.patterson@dundee.ac.uk***

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In the first session 'What prescribers do with drugs…' Professor D Lawson of Glasgow discussed how to produce safer prescribers. He gave a historical perspective on the development of drugs, drug licensing and the global drug industry. He highlighted the changes in under- and post-graduate education that have lead to increased prescribing errors and proposed the use of prescribing simulators on IT systems that the British Pharmacological Society and Royal Colleges could administer in both the training and appraising of tomorrows prescribers.[1]

Professor M Pirmohamed from Liverpool pointed out that although ADRs are common, only some are clinically important. Drug interactions are thought to be responsible for 1:100 of all hospital admissions and aspirin related GI bleeding the most common interaction.[2] He expanded upon induction and inhibition interactions such as occurs with cytochrome P450, P-glycoprotein and nuclear hormone receptor pregnane-X. He said drug interaction prevention strategies could be improved by providing information based on the use of receptor pharmacophores and assays of P450 to prescribers. He emphasised the crucial support role of Clinical Pharmacology in the development of computerised decision support and patient education systems that will translate knowledge into practice.

Professor M Brown from Cambridge talked about how to pick the best drugs to treat hypertension. A review of anti-hypertensive therapy was followed by a characterisation of winning drugs as well as the loser atenolol.[3] He countered the NICE recommendation of 'treatment regardless of age and ethnicity' by presentation of study findings of antihypertensive response specific to drug class in certain individuals. He reinforced this assertion by highlighting how specific drug treatments are used to treat secondary hypertension. This approach was then put forward for the treatment of the two types of essential hypertension (high-renin and low-renin) based upon the AB/CD rule.[4]

In the pre-lunch session 'Getting the evidence of what drugs do' Professor R Collins of Oxford discussed the problem of false results with many mortality and morbidity trials. He talked about how to minimise the effects of systematic and random errors and gave some examples of pitfalls in study design. He took a sober view of the EU clinical trials directive calling it a major obstacle and threat to important trials due to its increased bureaucracy, rigid approach to pharmacovigilance and burdensome authorisation and drug supply processes. He rejected the need for exhaustive policing, preferring better trial design and random data monitoring to prevent fraud.

In the British Pharmacological Society lecture and one of the highlights of the day, Dr GA Fitzgerald of Pennsylvania described his lecture as a story of 'Drugs, sex and money'. He presented a comprehensive review of the cardiovascular consequences of Cox-1 & -2 inhibition of the arachidonic acid pathway punctuated with rebuttals from various drug industry leaders blinkered by their conflict of interest. The crucial fact is that while not all 'anti-inflammatory' drugs are equal with respect to their 'aspirin' effect there is a wide spectrum of PGI2 synthesis inhibition by Cox-2 inhibitors and many traditional (and Cox-2 mimicking) NSAIDs. Data indicating the increased risk of vascular events with rofecoxcib and parecoxcib in man was already available from mechanistic studies in animals. Cox-2 inhibition increases the thrombogenic

potential of the TXA2 pathway attenuating the role of laminar shear stress induced expression of Cox-2 in the endothelium.[5, 6] Inhibition of the Cox-I pathway attenuates these effects. He presented research demonstrating the opposing effects of TXA2 and PGI2 on the initiation of atherosclerosis. He showed in his animal models how quantitative and selective suppression of Cox-2-derived prostaglandins may lead to hypertension, early atherogenesis; altered platelet and polymorpho-nuclear cell interaction with the endothelium during oxidant stress, modulation of the vascular remodeling response to hemodynamic stress, plaque destabilisation and enhanced response to thrombogenic stimuli. He stressed that the pharmacological response to Cox-2 inhibitors and NSAIDs varies significantly between individuals and that a significant interaction with aspirin occurs with ibuprofen and possibly other NSAIDs.

In session 3, 'What drugs do to patients', Sir A Breckenridge described the MRHA's role in protecting the public health and providing information to prescribers and patients without placing obstacles in the path of the development of innovative products. The increased relative risk of thrombotic events attributable to Cox-2 inhibitors (2·3–3·4) must be put into perspective and compared with cigarette smoking (2·9), lipo Apo B/Apo A (3·3), hypertension (1·9) and diabetes (2·4). He explained how 6·5% of hospital admissions related to ADRs had a total cost to the NHS of £466 M/year.[2] He summarised the strengths and weaknesses of the available methods of pharmacovigilance such as the Yellow Card Scheme (provides signals of clinical toxicity and rare ADRs but nothing on frequency); the GPRD with 3 million patients (cradle to grave but no hospitalisation or dispensing data) and MEMO from Dundee (only 400,000 patients but includes dispensed prescribing, hospitalisation, death certificate and laboratory data). He criticised the poor performance of prescription event monitoring with more than two-thirds of all projects never started or completed but said matters should improve after the introduction in 2005 of legislation requiring drug licensing applicants to describe in advance their pharmacovigilance systems. In closing he stated the need to focus less on finding harm and more on extending knowledge of drug safety by level of exposure.

Professor P Dieppe from the MRC used his experience with NSAIDs and osteoarthritis to explore whether ADRs were inevitable or preventable.[7] He demonstrated concern for the loss of trust in pharmacotherapeutics subsequent to the Cox-2 debacle. Interestingly he pointed out that early communication by pharmacologists may have prevented the debacle and more importantly pre clinical studies had focussed on low risk subjects and ignored those who are high risk, most likely to take the drug over long periods and suffer ADRs. He contentiously stated that licensing authorities are compromised by links with the pharmaceutical industry. Using benoxyprofen and celecoxib, as examples, he demonstrated how profits had been placed before patient safety and how prescribers had allowed themselves to be controlled by the pharmaceutical industry. He called for the full disclosure of all trial and ADR data immediately they occurred and the phased introduction of new drugs in large simple randomised controlled trials, with financial firewalls between companies and those involved in the licensing and assessment. Equally, he said healthcare providers need to align themselves with patient preferences and understanding of risk/benefit ratios.[8]

In the final session 'What patients do with drugs?', J Avorn from Harvard, describing the semantic battle between the terms 'compliance', 'adherence', 'persistence' and 'concordance'. His review of the data available revealed a huge problem with most patients on chronic drug therapy taking medication for < 50% of the time leading to significant failures in costly public health strategies. He described a spectrum of causal factors including doctors' training that focuses on getting the right diagnosis but under-emphasised behavioral issues, growing diagnostic and therapeutic options that crowd out talking with the patient, falling 'professional sovereignty', increasing cultural differences, problems of 'risk state management', polypharmacy and, in the USA, drug costs. He touched upon some unanswered questions, including whether computers could help by providing automated prompts, medication lists and pharmacy dispensing data or whether a 'non-doctor' would be better as patient medication educator.

Dr M Denvir from Edinburgh introduced one of his patients Margo MacDonald (MSP) to discuss patients' preferences when it comes to treatment. He put forward the role of the doctor in explaining complex choices between treatments by using the example of the RRR versus ARR of preventing stroke in patients with lone atrial fibrillation treated with aspirin (RRR 20% vs ARR 1·6%) compared to warfarin (RRR 66% vs ARR 3–4%). An alternative way to describe risks and benefits to patients is to use NNT: for aspirin we need to treat 62 to prevent one stroke with a bleeding risk of 1% per year (placebo 1%/year) while for warfarin we need to treat 25–30 to prevent one stroke with a 1·3% risk of bleeding (a 30% increase). Margo MacDonald gave her perspective on factors affecting a patient's desire to be involved in choosing including attitudes to risk, educational status, experience and socio-economic status and factors that improve communication including transparency, accountability, and the availability of statistics that can be readily understood by the patient. In closing she said that perhaps if patient groups were involved earlier, in the prioritisation of healthcare treatments, then understanding of the differences between the available treatment options could be improved.

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