

Abstracts: therapeutic challenges for 2005

ABBREVIATIONS Adverse drug reactions (ADR), gastrointestinal (GI), randomised clinical trials (RCTs), traditional non-steroidal anti-inflammatory drugs ((t)NSAIDs)

SESSION I

WHAT PRESCRIBERS DO WITH DRUGS: TOWARDS SAFER PRESCRIBING

Chairman: Sir A Breckenridge, Chairman, Medicines and Healthcare products Regulatory Agency, London

How to produce safe prescribers

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Abstract

Background Increasing complexity of available medicines, coupled with dramatic changes in undergraduate education in the last decade, have resulted in newly qualified doctors lacking sufficient knowledge to prescribe new medicines as they become junior house doctors.

Theme Reduction in working hours, demands for increasing 'clinical outputs' and the loss of the 'unit' structure in hospitals have led to reduced supervision of trainees prescribing at a time when more, not less, is needed.

Simultaneously, broadening of the prescribing base to include many new primary prescribers, has increased the chances of significant clinical errors arising from poor communication between prescribers.

Conclusions Better education to demonstrate the acquisition and maintenance of prescribing skills by doctors is urgently needed. It is proposed that the Royal Colleges develop prescribing simulation models to address this issue and, after adequate testing, require these to become part of CME and GMC registration.

References

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- 2 Holbrook J. The criminalisation of fatal medical mistakes. *BMJ* 2003; **327**:1118.
- 3 Audit Commission report on prescribing 2001.

Key words CME, doctor education, prescribing simulators, safe prescribing.

Sponsors None.

Declaration No competing interests.

Drug interactions: new mechanisms, new issues

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Abstract A drug interaction can be defined as the alteration of one drug by co-administration of another. Interactions are common: in a recent study of ADR admissions, one in six of the ADRs were due to interactions. In absolute terms, interactions leading to ADRs account for one in 100 hospital admissions. Interactions can be classified into both pharmacokinetic and pharmacodynamic; by far the commonest in the above study were aspirin-related GI bleeds where aspirin was co-administered with another drug that increased the risk of haemorrhage. Protective strategies such as co-prescription of misoprostol (a beneficial interaction) are available but were hardly ever used. In terms of pharmacokinetic interactions, the mechanisms and targets are becoming much better understood. For example, we now know that nuclear hormone receptors such as PXR are important in the induction of proteins; importantly, this not only affects the P450 enzymes (leading to the well-described interactions) but also leads to induction of transporters, whose role in drug disposition is becoming increasingly obvious. Drug transporters are now being recognised as the source of interactions, although there is need for more work in this area to fully characterise their substrate specificities and thereby their potential for interaction. Such knowledge of mechanisms is important as it allows the development of screening procedures that can be used in drug development to predict future drug interactions. However, the ultimate way of avoiding interactions will be through implementation of such knowledge by the prescriber, which is a complex and challenging area, where the large amount of information that is available from multiple sources needs to be integrated and distilled into a user-friendly format that can be understood by the prescriber.

Key words Admissions, ADR, aspirin related GI bleeds, induction of transporters, misoprostol, nuclear hormone receptors, P450 enzymes.

Sponsors None.

Declaration No conflict of interests declared.

Maximising the benefits of drugs: theory and practice of picking winners

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Abstract In 1945, Roosevelt died from untreatable hypertension. During the next half century, hypertension became a therapeutic success story, with a greater genuine choice of drugs than any other condition in medicine, and more long-term data demonstrating their efficacy in reversing the risks of stroke and myocardial infarction. Some drugs developed in the 1950s are still first-line, e.g. thiazide diuretics, whilst other subsequent drugs have become obsolete. In most classes, the initial drug was replaced by others with longer $t_{1/2}$. Winning classes have once-daily drugs with little postural hypotension, no adverse events in 80% of patients, and been demonstrably effective in outcome trials. However, these trials have also shown that the main driver of success is blood pressure reduction, and patients vary in their response to the classes. Using theoretical deduction from drugs' actions on the renin system, and empirical data from drug rotation studies, we rationalised hypertension and its treatment into two types. Type 1 are younger Caucasians who have generally high-renin hypertension, are insensitive to salt, and respond best to 'AB' drugs: Angiotensin inhibitors/blockers and Beta-blockers. Type 2 are older patients and black people who have low-renin hypertension due to salt retention, and respond best to 'CD' drugs: Calcium blockers and Diuretics. Measurement of plasma renin mass (by immunochemiluminometric assay) is now cheap and simple, and greatly facilitates choice of individual patients' winning drug. This is especially useful in resistant hypertension, predicting that low-renin patients respond to spironolactone, whilst high-renin patients require A+B combinations. Pharmacogenetics is unlikely to have a role in predicting efficacy. Even if all SNPs contributing to hypertension became known, their predictive value may be less than renin measurement, which detects non-genetic causes of salt retention. Pharmacogenetics is also unlikely to be useful in predicting short-term reversible adverse effects. We are investigating its use in predicting development of diabetes in patients receiving diuretics or blockers. It may also salvage new classes like the NEP/ACE inhibitors which have much greater efficacy than current drugs but cause angioneurotic oedema in rare patients.

References

- 1 Dickerson JE, Hingorani AD, Ashby MJ *et al.* Optimisation of antihypertensive treatment by crossover rotation of four major classes. *Lancet* 1999; **353**:2008–13.

Key words Angiotensin inhibitors/blockers, beta-blockers, calcium blockers, diuretics, hypertension, NEP/ACE inhibitors, renin system, spironolactone.

Sponsors None.

Declaration No conflict of interest declared.

SESSION 2

GETTING THE EVIDENCE OF WHAT DRUGS DO: THE KEY TO EFFECTIVE PRESCRIBING

Chairman: Professor D Webb, Professor of Clinical Pharmacology & Therapeutics, University of Edinburgh, Edinburgh, Scotland

Reliably assessing the efficacy and safety of drug treatment

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Abstract Although there are a few striking examples of treatments for serious disease that really do work extremely well, most claims for big improvements turn out to be evanescent. Unrealistic expectations about the chances of discovering large treatment effects could misleadingly suggest that evidence from small randomised trials or from non-randomised studies will suffice. By contrast, the reliable assessment of any more moderate effects of treatment on major outcomes – which are usually all that can realistically be expected from most treatments for most common serious conditions – requires studies that guarantee both strict control of bias (which, in general, requires proper randomisation and appropriate analysis, with no undue data-dependent emphasis on specific parts of the overall evidence) and strict control of random error (which, in general, requires large numbers of deaths or of some other relevant major outcome). Past failures to produce such evidence, and to interpret it appropriately, have already led to many premature deaths and much unnecessary suffering (and the obstacles caused by the EU Directive on Clinical Trials are likely to exacerbate this situation).

References

- 1 Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. *Lancet* 2001; **357**:373–80.
- 2 MacMahon S, Collins R. Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. *Lancet* 2001; **357**:455–62.

Key words Control of bias, non-randomised studies, small randomised trials, strict control of random error.

Sponsors None.

Declaration No conflict of interest declared.

BPS LECTURE**COX-2 INHIBITORS: LESSONS IN DRUG DEVELOPMENT FROM THE ARACHIDONIC ACID CASCADE**

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Abstract

Background Concern has been expressed about the cardiovascular safety of selective inhibitors of COX-2 tNSAIDs. Some of these drugs exhibit superior safety to tNSAIDs. None have been shown to exhibit superior efficacy.

Methods or Theme Integration of information from studies of mechanism in mice, clinical pharmacology, observational studies and placebo-controlled RCTs.

Studies in mice and humans establish a biologically plausible mechanism whereby drugs selective for COX-2 inhibition may predispose to an elevation in blood pressure, initiation and acceleration of atherogenesis, modulation of vascular remodelling, plaque destabilisation and an exaggerated response to such a thrombogenic stimulus.

This is consistent with 5 RCTs involving 3 members of the class – celecoxib, rofecoxib and valdecoxib. Data consistent with this mechanism also exist for etoricoxib and lumiracoxib.

Some tNSAIDs, such as diclofenac and meloxicam exhibit selectivity for COX-2 which resembles celecoxib, but RCTs to address this hypothesis have not been performed.

Ibuprofen appears neutral in epidemiological analyses, but may undermine the cardioprotective effects of aspirin.

Naproxen appears somewhat protective in epidemiological studies, consistent with an extended half-life and an 'aspirin effect' in some, but not all subjects. An ibuprofen-like interaction with aspirin may have implications for those in whom this does not pertain.

Conclusions Selectivity for inhibition of COX-2 is a continuum and detection of a mechanism based effect is conditioned by dose, duration of action, duration of dosing and concomitant therapy, such as low dose aspirin. There is also considerable interindividual variability in the selectivity actually attained *in vivo* by drugs like celecoxib and valdecoxib. Nonetheless, a small but absolute and biologically plausible cardiovascular hazard has been

established for rofecoxib, celecoxib and valdecoxib, suggesting that this risk is likely to extend to more selective drugs such as etoricoxib and lumiracoxib and perhaps embrace some tNSAIDs, such as meloxicam, diclofenac and nimesulide. Low dose aspirin would be expected to mitigate, but not abolish the risk. This occurred in the only RCT prestratified for aspirin use, where the GI benefit of the coxib compared to the tNSAID was also attenuated.

References

- 1 FitzGerald GA. Coxibs and Cardiovascular disease. *N Engl J Med* 2004; **351**(17):1709–11.
- 2 Wong D, Wang M, Cheng Y *et al.* Cardiovascular hazard and non-steroidal anti-inflammatory drugs. *Curr Opin Pharmacol* 2005; **5**(2):204–10.

Key words Cardiovascular, cyclooxygenase, prostacyclin, thromboxane.

Sponsors None.

Declaration College declaration of interest form completed and filed.

SESSION 3**WHAT DRUGS DO TO PATIENTS: EXAMINING THE REAL WORLD**

Chairman: Professor AD Struthers, Professor of Cardiovascular Medicine & Therapeutics, Ninewells Hospital & Medical School, Dundee, Scotland

Detecting and preventing drug toxicity, the role of the MHRA

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Abstract The responsibilities of the medicines regulator are first, to protect the public health by allowing only medicines with an appropriate risk-benefit balance on to the market, second, to provide appropriate information so that the prescriber of medicines and the patient who takes them can both do so in the full knowledge of their properties, and third, not to put unnecessary regulatory hurdles in the way of those who wish to introduce innovative products.

At the centre of medicines regulation is the concept of risk–benefit balance, which is very relevant in the overall assessment of medicines. This concept is poorly understood by the press and the public in our increasingly risk averse society.

The tools available to the regulator to manage this balance are the prelicensing assessment of quality,

efficacy and safety of a medicine. Since the amount of clinical data on safety at this stage is usually limited, the acquisition of post licensing information is most important. Safety signals generated from spontaneous adverse reaction reports are further investigated in studies using clinical data bases and in clinical trials. The delivery of commitments given at the time of licensing by the sponsors of new drugs within an agreed time frame are an important part of any risk-management strategy.

Key words Adverse reaction reports, medicines regulator, prelicensing assessment, risk–benefit balance.

Sponsors None.

Declaration No conflict of interest declared.

Adverse reactions: inevitable or preventable?

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Abstract

Background Recent problems due to adverse reactions to drugs such as Cox-2 inhibitors have resulted in renewed interest in the issue.

Methods or Theme We have examined trials of NSAIDs (both traditional ones and coxibs) to examine their reporting of adverse events. We have also examined the gap between the types of patient included in trials with those who subsequently use the drugs, and the potential effects of the discrepancy on adverse events.

Some of the recent literature on ways of reducing the problem of adverse events has also been examined.

Problems in trial inclusion and reporting have been uncovered. These have affected the perception of adverse events arising from NSAIDs.

Some interesting new initiatives to try to reduce the problem have been reported.

Conclusions There will always be a problem with adverse events. We can reduce the risk by altering aspects of trial practice and post-marketing surveillance.

References

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Key words Adverse events, NSAIDs, trials.

Sponsors MRC and NHS R&D.

Declaration No interests to declare.

SESSION 4

WHAT PATIENTS DO WITH DRUGS

Chairman: Professor N Douglas, President of the Royal College of Physicians of Edinburgh, Edinburgh, Scotland

THE DAVIDSON LECTURE

CONCORDANCE WITH TREATMENT. HOW TO GET PATIENTS TO KEEP TAKING THE MEDICINE?

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Abstract

Background There is growing data documenting the extent to which patients frequently fail to take their drug regimens as directed, particularly for chronically administered medications.

Methods or Theme This talk will review that evidence as well as the reasons that have been identified for such non-compliance. It will also propose concrete strategies for reducing non-adherence to prescribed therapy.

Conclusions Non-adherence is a large concern in primary care, and is probably increasing in light of the growing number of risk–state management drugs prescribed. It can undercut the effectiveness of even the best-conceived medical regimen. However, a better understanding of the causes of poor compliance can yield practical approaches to overcome this common and important clinical problem.

Key words Compliance, concordance, drug utilisation, patient behavior.

Sponsors None.

Declaration I have no conflicts of interest related to this presentation.

Do patients have treatment preferences when it comes to drug treatment?

Chairman: Dr M Denvir, Consultant Cardiologist,
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Patient: Margo MacDonald MSP, Edinburgh, Scotland

CME