Commentary

An agenda for UK clinical pharmacology

Adverse drug reactions

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Our ability to understand fully the characteristics of clinically important adverse drug reactions is hindered by a lack of emphasis on biological mechanisms, patient susceptibility factors and long-term outcomes. Assessment of drug safety needs to move beyond industry and regulatory perspectives, towards a greater focus on evidence-based preventive and management strategies that will allow patients and physicians to deal with adverse drug reactions at the bedside. This would ideally involve close collaboration between clinical pharmacologists and pharmacoepidemiologists skilled at interrogating the increasingly sophisticated electronic healthcare databases. In light of the myriad safety scares that are constantly emerging, patients and physicians would be best served by a centrally funded independent network of rapid-response drug safety researchers who can use techniques of teleanalysis to describe fully the magnitude of risk, the potential biological mechanisms and patients' susceptibility factors.

Introduction

As a researcher involved in the study of adverse drug reactions, I often ponder the exact nature of the beast. Some may consider 'an elephant' to be an apt description, not only because of connotations surrounding an unwanted beast in the room, but because of the fabled six blind men and the elephant. Readers conversant with Asian literature will recall that when the blind men reached out for the elephant, they gave varying accounts of what they were identifying, including a pillar, a rope and a brick wall, depending on which part of the elephant's anatomy they had examined. So it is with research into adverse drug reactions, in which a combination of narrow priorities and restricted access to information can hinder awareness of the big picture, resulting in a failure to define all the key characteristics of the elephant.

There are undeniably myriads of workers toiling away at a diverse range of tasks, from preclinical animal toxicology to pharmacovigilance and randomized controlled trials in humans. However, while some aspects of adverse drug reactions are thoroughly researched, other equally important areas are often left unexplored (Table 1). Pre-clinical testing and spontaneous reporting systems (within the domains of pharmaceutical companies and regulatory authorities) have become the mainstay of our current system, and there is woefully little emphasis on elucidating the biological mechanisms [1], examining susceptibility

Table 1

Neglected areas in adverse drug reactions research

Generally well covered in adverse drug reactions research	Only occasionally covered in adverse drug reactions research
Preclinical animal toxicology	Characteristics and natural history of the adverse reaction
Early-phase human studies	• intensity and outcomes
Dose-ranging studies	• DoTS (Dose-relatedness, Timing, Susceptibility factors)
Randomized controlled trials to evaluate efficacy	Underlying biological mechanisms Prevention (including role of monitoring; e.g. what method of monitoring, how frequently and the predictive value) Management of patients with the adverse drug reaction
Pharmacovigilance Pharmacoepidemiology in certain centres	

factors and developing preventive strategies [2] and management strategies [3].

Systematic reviews

Much of what we currently have in drug safety stems from the birth of pharmacovigilance, which was aimed at

protecting the public from serious, unusual adverse reactions (thalidomide and practolol come to mind). Hence, regulatory action typically involves suspending the drug (in serious cases) or adding a caution in the product information about the possibility of a new adverse reaction and the need for closer monitoring of the patient. While this current scheme offers protection for the pharmaceutical company and the regulatory authorities, it offers little comfort for physicians and patients involved in managing chronic conditions, in which drug therapy needs to be continued with appropriate risk-mitigation strategies, such as the use of lower dosages, shorter durations of treatment or simultaneous use of other healthcare interventions that can prevent or mitigate harm. Moreover, the strength of current signal detection systems is in detecting new or unexpected findings, often relating to more extreme phenotypes of adverse reactions that have low background

incidences. This gives us only a small snapshot of the beast, and we are seldom able to derive clinically important measures, such as the relative risk and its confidence intervals, or absolute estimates of risk, such as the likely number of patients affected or the number needed to treat for harm.

Equally, while a great deal of drug safety information comes from clinical trials, the limited generalizability of trial populations is a major issue, as are concerns regarding inadequate sample sizes and limited durations of follow-up. There are also inescapable concerns surrounding the key objectives of the study, because most trials are designed to demonstrate efficacy and safety, rather than detecting harm, a fine distinction that influences how thoroughly adverse events are studied. To be fair, randomized controlled trials probably represent the best method for evaluating pharmacologically predictable adverse reactions, for which prospective monitoring can be incorpo-

Figure 1

A meta-analysis of the risk of gastrointestinal bleeding in patients taking aspirin (redrawn based on data from Derry and Loke [4])

Figure 2

A meta-analysis of the risk of fractures in patients taking thiazolidinediones, highlighting sex as a susceptibility factor (redrawn based on data from Loke *et al.* [5])

rated, particularly with regards to events that have high background incidences (say, for instance, events with a greater than 5% frequency, which would be at the upper end of what European regulators judge as common). Again, the trials are reaching out for a different, although equally important, part of the elephant.

Some of the methodological problems related to limited sample sizes and inadequate power can of course be overcome by techniques of systematic review and meta-analysis. In the era of evidence-based medicine, these techniques are used to help us arrive at more precise and less biased estimates of risk. Examples of the use of meta-analysis in studying adverse drug reactions are shown in Figures 1 and 2 [4, 5].

However, while there are many examples that have addressed clinically important adverse reactions, systematic reviews have a fundamental weakness in their absolute reliance on the availability and quality of primary data. The lack of research activity in several areas of drug safety (as illustrated in Table 1) limits the scope of systematic reviews and hinders the development of comprehensive assessments of specific adverse reactions in a technique described as teleoanalysis [6], which is an exploration that uses data from all available sources, including randomized

trials, observational studies and even case series and case reports.

Teleoanalysis

If we return to the fable of the blind men and the elephant, we can hope that the teleoanalyst would be able to work out the nature of the beast simply by gathering the separate reports from the blind men and putting the pieces of the jigsaw together. A specific adverse reaction could be characterized fully, with precise estimates of the risk, information on dose relatedness, time course and which patients were susceptible [7]. Examples of such teleoanalysis can be found with regard to congestive heart failure associated with thiazolidinedione therapy [8] and gastrointestinal damage from nonsteroidal anti-inflammatory drugs [9], in which data from randomized controlled trials, pharmacoepidemiological studies and spontaneous case reports were systematically reviewed. Despite covering such a broad range data sources, the first of these teleoanalyses was still unable to address key clinical questions concerning the prognosis of patients affected by the adverse reaction, the role of natriuretic peptide or

echocardiographic monitoring for early detection, or the value (if any) of long-term diuretics in resolving the heart failure.

Conclusions

It should be clear from this that the study of adverse drug reactions has to move beyond licensing or regulatory driven concepts that are currently focused mainly on signal detection and clinical trials. The scope of the work is simply too big to rely simply on pharmaceutical companies or regulatory authorities. There are encouraging developments in Canada, where Drug Safety and Effectiveness Networks are planned, involving rapid-response pharmacoepidemiology personnel (with access to large prescription databases), working in tandem with experts in meta-analysis, and using a wide range of models, such as indirect comparisons and network methods. It remains to be seen whether UK clinical pharmacology will be left behind by these developments in Canada.

Many important adverse events are rare or unexpected or unpredictable, and no single methodological approach can successfully capture the problem in its entirety. I believe that multiple analytical techniques and close co-operation between different drug safety research groups are required to help recognize the exact nature of the elephant and eventually provide information to patients and clinicians on how to manage problems. On a final parting note, perhaps it would be timely to remind readers of the large beast of adverse drug–drug interactions, which will undoubtedly need to be tackled with the same energy and methodological rigour as proposed here.

Competing Interests

There are no competing interests to declare.

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