Monitoring medicines use: the role of the clinical pharmacologist

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Appreciation of the potential of newly marketed medicines to produce both benefit and harm has increased the role of the clinical pharmacologist. Pharmacoepidemiology applies epidemiological reasoning, methods and knowledge to the study of the uses and effects of drugs in human populations. Pharmacovigilance identifies and then responds to safety issues about marketed drugs. Whilst adverse drug reaction (ADR) reporting systems can identify potential problems with drugs, determination of causation requires population-based studies of adverse events (including information from large clinical trials), which attempt to link unequivocally the adverse outcome to the drug in question. Pharmacovigilance is closely linked to postmarketing surveillance and is important for determining issues such as the long-term effects of drugs, identification of low-frequency ADRs, the effectiveness of drugs for their licensed indications or in new indications and other factors which may modify the efficacy and effectiveness of the drug in question. The related field of drug utilization developed in parallel with the study of adverse drug reactions, in recognition of the dramatic increase in the marketing of new drugs, the wide variations in the patterns and extent of drug prescribing, the growing concern about ADRs and the increasing costs of drugs. With the ever increasing number of recognized adverse effects of drugs, prescribing errors, patients' expectations concerning drug safety and the need for appropriate new drug appraisal, the clinical pharmacologist will play an important role both in the introduction of new drugs and in improving the safe and effective use of established drugs.

Introduction

It was Sir William Osler who, in 1891, stated that 'A desire to take medicine is, perhaps, the great feature which distinguishes man from other animals' [1]. The speciality of clinical pharmacology lies at the interface between basic pharmacology and the drug treatment of human disease. Owing to the prominence of pharmacotherapy in modern therapeutics, clinical pharmacology has become indispensable for the development of new treatments, as well as for the proper understanding and practice of contemporary medicine. Today's clinical pharmacologist fulfils a number of roles in the current healthcare system that are closely linked to monitoring medicines use (Table 1).

A number of challenges currently face the clinical pharmacologist in monitoring medicines use. These include the rising numbers of adverse drug reactions (ADRs), medication errors and increasing concerns regarding poor prescribing [2, 3].

Monitoring medicines use

The term 'pharmacoepidemiology' first appeared in a *British Medical Journal* Editorial by Sir David Lawson in 1984 [4]. It may be defined as the application of epidemiological reasoning, methods and knowledge to the study of the uses and effects (be they beneficial or not) of drugs in

Table 1

Role of the clinical pharmacologist in the healthcare system

National
Adverse drug reaction reporting systems
National poisons information
Health technology assessment/pharmacoeconomic evaluation of new drugs
Research
Local
Drug and therapeutics committees
Formulary development
Drug information
Patient safety – investigating local drug-related incidents
Research ethics
Toxicology
Advice on use of unlicensed medicines/off-label use of medications
Undergraduate and postgraduate education – promoting evidence-based medicine and development of guidelines and shared-care protocols with primary care
Advice on clinical trials
Research

human populations. It has been traditionally subdivided into the areas of pharmacovigilance, drug utilization and prescribing quality. With the need to examine the cost-effectiveness of newly marketed medicines, pharmacoeconomics has been added as a further subdivision.

Drug utilization developed in parallel with the study of ADRs. It is defined as the marketing, distribution, prescription and use of drugs in a society with a special emphasis on the resulting medical, social and economic consequences (WHO, 2000 [5]). The increased interest in drug utilization arose as a result of a dramatic increase in the marketing of new drugs, wide variations in the patterns and extent of drug prescribing, the growing concerns around ADRs and the increasing costs of drugs.

Pharmacovigilance may be defined as the science and activities relating to the detection, assessment, understanding and prevention of any other drug-related problems [6]. Pharmacovigilance identifies and then responds to safety issues regarding marketed drugs and plays a key role in the day-to-day activities of the clinical pharmacologist. In 2008 alone, 66 medicinal products received approval from the European Medicines Agency [7], whilst 99 drugs were approved by the US Food and Drug Administration [8]. Adverse drug reaction reporting systems can identify potential problems with medicines, but determination of causation requires the careful design of population-based studies. From the first report of fetal toxicity associated with the use of thalidomide [9] to the recent drug safety concerns concerning the use of cyclooxygenase-2 inhibitors [10] and natalizumab [11], the importance of ADR reporting has been recognised. Adverse drug reactions are responsible for significant morbidity and mortality within the healthcare system, with up to 6.5% of UK admissions being associated with ADRs [12].

Table 2

Examples of healthcare automated databases

Group Care Cooperative
Kaiser Permanente Medical Care
HMO Research Network
United Health Group
Medicaid
Health Services Databases in Saskatchewan
Automated pharmacy record linkage in The Netherlands
Tayside Medicines Monitoring Unit (MEMO)
UK General Practice Research Database (GPRD)
Irish Health Service Executive Primary Care Reimbursement Service (HSE-PCRS) pharmacy claims database

The economic impact of hospital admissions due to ADRs is significant, and it has been estimated that up to seven 800-bed hospitals in the UK are occupied at any one time by patients admitted with a suspected ADR [12]. Furthermore, up to 70% of these ADRs were deemed avoidable, 17% of which were due to drug interactions [9]. Within the inpatient hospital setting, up to 15% of patients have been reported to suffer one or more ADR, half of which were definitely or possibly avoidable, with an associated length of stay of 0.25 days per patient episode [13].

A number of surveillance systems exist to signal possible ADRs. These include voluntary reporting systems, prescription event monitoring, record linkage schemes and electronic databases. One of the difficulties with voluntary reporting systems is that less than 10% of all serious ADRs are ever reported [14]. There are a number of reasons for this, including uncertainty that the reaction is definitely caused by the drug, the ADR being previously considered too trivial or well known to report, or a lack of knowledge on how to report an ADR [15].

Whilst clinical trials are rarely designed/powered to detect uncommon or unexpected adverse events [16, 17], the clinical pharmacologist is still perhaps best placed to predict ADRs prior to the registration process. A study by Aagard *et al.* of phase 2/3 trials analysed the data used to support the registration for three scenarios (trovafloxacin/alatrofloxacin and risk of hepatotoxicity; tolcapone and risk of hepatotoxicity and neuroleptic malignant syndrome; and rituximab and risk of cytokine release syndrome). They suggested that it would have been possible to foresee these important ADRs at the time when the drug was licensed [18]. The worldwide withdrawal of rofecoxib in 2004 stimulated an international review of how best to measure and monitor drug safety with the use of large-scale patient databases. A number of international automated databases now exist, which allow the development of large-scale population studies to assess drug safety (Table 2).

An ideal research database should include records from inpatient and outpatient care, emergency care and mental

Table 3

Strengths and weaknesses of automated prescription databases

Strengths	Weaknesses
Large sample size	Uncertain diagnosis
Relatively inexpensive	Lack of information on confounding variables (e.g. smoking status)
Relatively complete data	Lack of information on over-the-counter/nonprescription items
Population/'real world' based	Unstable population due to economic factors
No recall and interviewer bias	Only include medical illnesses severe enough to come to medical attention Results may not be generalizable to the wider population

health care. It should include all laboratory and radiological tests and all prescribed and over-the-counter medications. Furthermore, the population should be stable over time and large enough to enable the discovery of rare drug events, and all parts of the database should be linked using a unique patient identifier. Current prescription databases, however, have a number of strengths and weaknesses (Table 3).

The effectiveness of large-scale drug-safety monitoring using a number of databases is, however, reduced as a result of the diversity and isolation of some healthcare databases which stem from the differences in the language, coding and structure of these healthcare systems, as well as issues regarding patient confidentiality and data protection. In the USA, the Sentinel system was developed with the aim of capturing data on over 100 million subjects for prospective drug safety surveillance by July 2012 [19]. The combination of an active surveillance system (which proactively questions diverse automated healthcare databases) and the traditional passive safety surveillance system will allow the provision of a comprehensive means of monitoring drug safety. In Europe, the EU-ADR Project ('Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge') was launched in 2008, and aims to exploit information from various electronic healthcare record databases in Europe to produce a computerized, integrated system for the early detection of drug safety signals [20]. Using the age-adjusted incidence rates of upper gastrointestinal bleeding, drug utilization patterns and the confirmation of an increased risk of upper gastrointestinal bleeding, this project has demonstrated the feasibility of combining a number of European databases using a distributed network approach, which will allow for large-scale drug-safety monitoring [21].

The European Surveillance of Antimicrobial Consumption is a European project with 34 participating countries and collects data on the consumption of antimicrobials,

antiviral and antifungal agents [22]. It is another example of how drug utilization data can be used to inform future drug policy. Importantly, antimicrobial resistance data are also being collected by the European Antimicrobial Resistance Surveillance System (EARSS), and it is hoped that this joint approach will provide an overall picture of current and emerging trends in antimicrobial use and resistance in Europe. Given the diversity of prescription databases available, it is therefore important for the modern clinical pharmacologist to be able to identify the particular strengths and weakness of a particular database in order to identify the most appropriate data source when a particular research study is planned and to avoid bias which may arise from the use of heterogeneous sources of information. This would help to permit a balanced view on the benefits and safety of drugs.

All nations are currently facing an irreconcilable gap between the cost of medicines and the scarce resources available to pay for them. Therefore, the rational and cost-effective use of medicines will become an ever more important role for the clinical pharmacologist and the general public.

The clinical pharmacologist and medication errors

Medication errors are one of the most preventable causes of patient harm. The majority of these errors occur, not as a result of reckless behaviour on the part of health care providers, but as a result of the speed and complexity of the medication use cycle. A number of definitions exist for a medication error. One definition proposed by the National Co-ordinating Council for Medication error reporting and prevention is 'any preventable event that can cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer' [23]. According to this definition, medication errors also include prescribing errors, which may be defined as the incorrect drug selection for a patient and can include the dose, quantity and indication, or prescription of a contraindicated drug. The incidence of medication errors varies between 2 and 14% among patients admitted to hospital, with between 1 and 2% of patients in the USA being harmed as a result of medication errors, the majority of which are due to poor prescribing. Medication error has been estimated to result in 7000 deaths per annum and accounts for nearly 1 in 20 hospital admissions in the USA [24]. Medication errors (7%) were the second most common incidents reported (after patient falls) in the National Audit Commission report on patient safety [25]. One of the reasons for the wide variation in medication error rates is due to the differing definitions and methodologies used for studying medication errors [26, 27]. Medication errors may be classified according to their place (prescribing, dispensing or drug administration) in the medication use cycle. A more recent classification has been proposed that is based on human error theory. In this

classification, errors may be subdivided into either mistakes (knowledge or rule-based errors) or skill-based errors [action-based errors (slips) or memory-based errors (lapses)] [26]. One advantage of this classification is that it applies human error theory to medication errors, allowing root-cause analysis to be applied to provide solutions to particular errors. Reason's Model of Accident Causation suggests that there are latent conditions (organizational processes and management decisions) leading to error-producing conditions (environmental, team, individual or task factors that affect performance), which lead to active failures (errors such as slips, lapses or mistakes or violation of particular rules) and ultimately an accident [28]. The fatal intrathecal administration of vincristine illustrates this latent failure model of complex system failure. In one such case, the coroner remarked, 'We can put a man on the moon but why can't we find a safe method to prevent these deaths?' [29]. A similar systematic approach to examining the causes of prescribing errors revealed that most mistakes were made by junior medical staff as a result of slips in attention or because prescribers did not apply the relevant rules [30].

As discussed earlier, prescribing errors may be defined as the incorrect drug selection for a patient and include the dose, quantity and indication, or prescription of a contraindicated drug. Lack of knowledge of the prescribed drug, its recommended dose and the patient details contributes to prescribing errors. Other contributory factors to prescribing errors include illegible writing, poor medicine reconciliation, confusion over the drug names, the inappropriate use of decimal points and the use of abbreviations or verbal orders [27]. The recent EQUIP study, which was an in-depth investigation into causes of prescribing errors by foundation trainees (within 2 years of graduation) in relation to their medical education, examined 124 260 medication orders across 19 hospitals, 11 077 of which contained errors, producing an error rate of 8.9%. There were 50 016 medication orders written by foundation year 1 doctors, in which 4190 errors were detected, producing an error rate of 8.4%. Almost all errors were intercepted by pharmacists before they could affect patient care. Potentially lethal errors were found in less than 2% of prescriptions. One of the recommendations of this report was that prescribing errors could be reduced if a standardized prescription chart were to be introduced into all UK hospitals [31]. A universal prescription chart currently exists in Wales, which is supported by nationally agreed prescription-writing standards and is accompanied by an e-learning program, which is updated annually [32].

Reducing errors

A systematic approach to medication errors and learning from other industries, such as the aviation or oil industry, should be adopted to reduce medication errors. One of the difficulties with medication errors is the low level of reporting [33]. One of the reasons for such a low level of reporting

is a poor safety culture that exists within the healthcare setting [34]. The development of a supportive safety culture that encourages the reporting of medication errors will allow one to put in place processes to avoid future medication errors. However, a safety culture does not develop overnight, but evolves over a period of time. In some instances, it may begin at a pathological level, where the attitude is one of 'who cares as long as we are not caught'. However, with increasing trust and knowledge, a safety culture within an organization can evolve to a generative level, where the attitude is one of 'safety is how we do business around here' [35].

Prescribing errors often occur because the prescriber has no immediate access to the relevant information relating to the drug or patient. Electronic prescribing can therefore support the prescribing process and help reduce prescribing errors. Computerized systems containing rules to prevent incorrect or inappropriate prescribing can help to increase the appropriateness of drug treatment and reduce errors [36–38]. However, the effects of computerized physician order entry systems on patient outcome remain understudied and, when examined, provide variable results.

An alternative approach to reducing medication errors is to target high-alert drugs and procedures. The implementation of carefully planned series of low-cost interventions focused on high-risk medications, driven by information derived largely from internal event reporting and designed to improve a hospital's medication safety have been shown significantly to reduce patient harm as a result of medication errors [39]. Drugs that have been identified as having a high potential for error include potassium chloride, high-strength narcotic agents, cancer chemotherapy, insulin, heparin and epidural drug infusions. The restricted supply of strong potassium chloride to reduce medication errors has long been recommended, and stocking only one strength of morphine ampoules on paediatric wards has been successful in preventing errors involving the selection of the incorrect ampoule. The complex design of infusion pumps and the design of ampoules which look similar place the onus on manufacturers to supply products that can be administered safely.

In the field of education, concerns have been raised regarding the readiness of medical undergraduates for their future roles in prescribing [40]. Evidence exists that education will lead to safer prescribing, although such educational initiatives are often short lived [41]. The development of the Prescribe initiative, based on the belief that a thorough understanding of the basic principles of clinical pharmacology will translate into safe prescribing will help to support and improve prescribing in the undergraduate medical curriculum [42]. The practical application of pharmacology to the prevention, treatment and alleviation of disease, which is therapeutics, should become part of all doctors' undergraduate education and continuing professional development.

In conclusion, medication errors are one of the most preventable causes of patient injury, although the incidence of such errors varies widely as a result of the differing definitions and methodologies. The majority of medication errors occur as a result of poor prescribing, which emphasizes the need to improve prescribing skills. The problems, sources and methods of avoiding medication errors are multifactorial and multidisciplinary, and it is important to adopt a supportive safety culture to improve the rate of reporting of medication errors, allowing further investigation of these important causes of preventable harm. The clinical pharmacologist has a unique insight into the many causes of medication errors, particularly in the field of prescribing, and therefore has a particular role in preventing these particular types of preventable patient harm.

Conclusion

A number of influences act on the prescriber when deciding to prescribe. The prescriber will already have their own knowledge, values, attitudes, experiences and habits concerning the treatment of a particular condition. The prescriber will also be influenced by the patient, academia, colleagues, cost of therapy and the pharmaceutical industry that markets the product. These influences also act on the patient's attitude to their treatments, because the patient has access to numerous sources of information regarding their treatment. One of the important roles of the clinical pharmacologist is therefore to provide unbiased advice on the most cost-effective and rational use of medicines in society to improve patient outcome. Clinical Pharmacologists already fulfil these roles within organizations such as the National Institute for Clinical Excellence (NICE), the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) in the UK.

The progressive loss of specialists with the specific attributes of clinical pharmacologists has already been highlighted in the medical literature [43]. However, the clinical pharmacologist retains an important role in monitoring medicine use in today's healthcare system. Opportunities exist to improve pharmacovigilance systems through improved ADR-reporting rates, the development of hypothesis-led pharmacoepidemiological studies and the increased use of prescription databases. We currently face an irreconcilable gulf between the cost of drugs and the available resources to pay for them, which leaves the clinical pharmacologist in the key role of promoting the rational and cost-effective use of medicines. With the ever increasing number of adverse effects of drugs, prescribing errors, patients' expectations concerning drug safety and the need for appropriate new drug appraisal, the clinical pharmacologist will play an important role in reducing medication errors and in educating new prescribers and patients about their medicines.

Competing Interests

There are no competing interests to declare.

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