The Academy of Medical Sciences | FORUM

Safer Medicines Report

Post-marketing surveillance working group report

November 2005

Contents

Executive Summary

In spite of the substantial effort and investment expended by the pharmaceutical industry to ensure drug safety, many adverse drug reactions only become apparent following licensing of a drug and its widespread use in a real-world setting. It is therefore important to have robust procedures to detect these adverse effects, and respond to them in order to protect public health. The UK has a well-developed regulatory framework and pharmacovigilance system, but there are many inherent limitations. There is a need to improve and refine current procedures and integrate new technological developments.

The policy relevance of pharmacovigilance extends beyond safety assessment to judgements about the level of risk that drive decisions about a drug at various stages of its development and the patient and population level consequences of these decisions. Patients may be more or less risk averse than the pharmaceutical industry or doctors depending on the disease and opportunities for other therapies. The involvement of patients and the public is therefore particularly important in the development of better ways of communicating risks and benefits of drugs and taking decisions about them.

Current systems for detecting and confirming signals of adverse drug reactions include spontaneous reporting schemes and pharmaco-epidemiological studies including those that utilise databases. There is a need to strengthen all these areas through the development of new methodologies, which require objective evaluation and adequate research funding. The NHS National Programme for Information Technology (NPfIT), which is being implemented by NHS Connecting for Health, offers a unique and powerful opportunity to link drug prescribing to adverse events at a national level in England. In order to ensure that this opportunity is not lost, it is essential that this is pursued with appropriate resources in place and is designed with input from researchers with expertise in pharmaco-epidemiological and database methodologies. An ongoing dialogue between the NPfIT, the Committee on Safety of Medicines Subcommittee on Pharmacovigilance and the MHRA will be a key to part of this dialogue, which the Working Group has initiated. In parallel, concerns about the risk to privacy, which may be raised by the increasing use of information technology within the NHS, need to be addressed in the design and regulation of the systems. Links with parallel activities in the other devolved countries of the UK should are essential to ensure that UK wide pharmacovigilance is achieved.

The current systems should also be strengthened through integration with emerging technologies such as pharmacogenetics, which will require investment in collaborative and basic epidemiological research. Pharmacogenetics is now becoming routine during drug development and incorporation of pharmacogenetic studies into pharmaco epidemiology and spontaneous reporting systems should be strongly encouraged, with appropriate oversight mechanisms in place to protect patients and the public. The limiting factor will be the collection and availability of accurately phenotyped cases of adverse drug reactions. Recruitment of cases with adverse reactions and the subsequent genetic analysis will require a new partnership between the pharmaceutical industry, regulatory authorities and physicians. Pilot and feasibility studies should be set up to rapidly establish the optimal mechanisms for consent procedures and sample collection, handling and storage, using a collaborative approach and in accordance with a pragmatic ethical framework that does not act as a barrier to this research.

A theme common to all the areas discussed was the lack of expertise in the appropriate methodologies, which needs to be encouraged through development of training and availability of funding. Additionally, there are major concerns about the adequacy of training of future and current prescribers and there is an urgent need to strengthen this in undergraduate and postgraduate curricula. This should be accompanied by a strengthening of the capacity to teach therapeutics in the UK both to medical and non-medical prescribers as the numbers of the latter are likely to continue to increase.

Key recommendations

Recommendation 1:

- The implementation of the NHS National Programme for Information Technology (NPfIT) in

England should be informed by discussions with researchers to reflect the needs of drug safety monitoring. Current databases must be maintained and strengthened until the NPfIT can replicate the research capacity they offer and ideally provide the same or a higher level of data quality at a national level. Collaboration between the NPfIT and both the regulatory authorities through the Medicines and Healthcare products Regulatory Agency (MHRA) and Subcommittee on Pharmacovigilance of the Committee on Safety of Medicines (CSM) and the academic community, initiated by the Working Group should facilitate this. In parallel, communication with the other devolved countries of the UK is essential to ensure compatibility so that there can be a UK wide approach. The Working Group will work to facilitate this.

Recommendation 2:

- In order to provide more reliable estimates of Adverse Drug Reaction (ADR) rates, primary data on ADRs from all sources, including regulatory authorities academic studies and the pharmaceutical industry, should be made widely available at a realistic cost in a format that allows appropriate interpretation by those with the necessary expertise and adequate resources after independent scientific and ethical review.

Recommendation 3:

- Concerns and frustrations at the current environment surrounding the use of individual patient data in drug safety and other areas of research have been widely voiced and there is an urgent need to resolve these tensions. In the absence of changes in the law, guidelines should be developed to allow interpretation of the Data Protection Act so that drug safety data important for public health can be rapidly shared and acted upon, whilst preserving patient confidentiality.

Recommendation 4:

- New technologies such as pharmacogenetics need to be integrated with established pharmacoepidemiological approaches. Pilot and feasibility studies should be set up to rapidly establish the optimal mechanisms for consent procedures and sample collection, handling and storage. This should be facilitated by collaborations between the government, academia and the pharmaceutical industry.

Recommendation 5:

- There is an urgent need to ensure that a higher priority is given to the teaching of therapeutics to all potential prescribers including doctors at both the under- and post-graduate level and the many other groups to whom prescribing is being extended. A robust evaluation of the benefits and risks of the extension to non-medical health professionals and of patient reporting of ADRs should be undertaken

Chapter One - *Introduction*

1.1 Although many safety issues can be identified during the course of drug development through the extensive efforts and investments by the pharmaceutical industry to ensure drug safety, others cannot, either because the number or characteristics of people exposed, or the duration of exposure are insufficient. Post-marketing surveillance is therefore crucial for the identification of new adverse drug reactions (ADR) that were not identified from the development of a drug either because they are very rare or only occur after a prolonged period of exposure. Such ADRs may not have been detected during the drug development process because they cannot be predicted from knowledge of the pharmacological properties of the drug or may not be detected until many thousands individuals have taken them or have taken them for many years. Waiting for the accumulation of such large and long-term bodies of data before licensing a drug would both delay access of patients to valuable drugs and increase considerably the cost of drug development, and indeed for most drugs, it would not identify new ADRs. Post-marketing surveillance is also important for the assessment of the frequency of ADRs in populations not adequately represented during development, for example children, the elderly or those with hepatic or renal impairment. Some examples of the importance of post marketing surveillance include the identification of the lipodystrophy syndrome in patients with HIV treated with antiretroviral drugs, cough associated with ACE inhibitors and rhabdomyolysis associated with statins.

1.2 The UK has much strength in pharmacovigilance, including a well established regulatory framework, highly developed spontaneous reporting systems and novel analytical methods, such as Proportional Reporting Ratios (PRR)[1]. Furthermore, in the General Practice Research Database (GPRD), it has one of the most powerful and extensively used databases in the world[2]. The responsibility for post-marketing surveillance lies with regulatory authorities and the pharmaceutical industry but it depends crucially on the prescriber to ensure it functions effectively. The involvement of patients is currently also being explored in the UK.

1.3 There is also a large multidisciplinary body of expertise from basic science through clinical medicine to epidemiology, statistics and public health, which has made major contributions to the estimation of hazards and understanding of drug safety. There is an appreciation of the importance of safety issues by the editors of the key medical journals and active consumer and media engagement in the issues[3]. However, there are several limitations of the current systems which are discussed in this document. There are many opportunities for improving the process of post marketing surveillance through wider collaborations between the many disciplines and agencies involved to improve the quality and completeness of the information that need to be supported and encouraged. In parallel, the development of better means of communicating risks and benefits in collaboration with patients and the public would ensure that medicines are used safely and effectively to improve public health.

Chapter Two - *Current sources of data*

Spontaneous reporting

Situation – the issues

2.1 Spontaneous ADR reporting schemes depend on individual reports from healthcare professionals of their clinical suspicion that a drug may have been responsible for an adverse event. In most countries, such reports are centrally collated in a database, for example the ADROIT database in the UK, which can be used to detect signals of unrecognised toxicity that require confirmation or refutation using other sources of data[4]. In recent years, there have been major advances in the use of mathematical approaches to assess whether or not reports of a particular drug/reaction combination is in excess of expectations but which do not depend on drug exposure data which are rarely available[1 5–8]. The methods yield similar results unless the number of cases is small, but it is important to note that their aim is to separate a signal from background noise and provide an indication of the strength of the signal. However they do not prove that an association is causal. The methodology is summarised in the paper by Waller and Evans[9]. There are several limitations to spontaneous reporting, the most important of which are under-reporting and the lack of denominator data so that it is impossible to assess the frequency of the ADRs. There is also the so-called "Weber effect" which refers to the observation that reporting is much more frequent for newly licensed drugs and declines over time. Comparisons of new drugs with older drugs of the same class are thus complicated by the time factor. Additionally, if the ADR is rare, then there may be a considerable lag time in the detection of the reaction which relies on the accumulation of a sufficient number of cases to provide a signal.

2.2 Once a signal has been detected which is considered to be sufficiently strong and is potentially important clinically, detailed evaluation is necessary. This involves assessing the clinical data and any other relevant data including pre-clinical data, mechanistic studies, clinical trials and post-marketing studies. The key issues to be considered in the assessment are causality, frequency, clinical implications and preventability with a particular focus on identifying the information required to confirm or refute the signal. If existing data are inadequate, new research from basic science through clinical investigation to pharmacoepidemiological studies may be required.

Challenges, opportunities and solutions

2.3 In recent years, there have been a number of improvements in the methods used to identify and evaluate signals[9]. A new quantitative tool known as impact analysis is under development based on the ADR data giving rise to the signal, an assessment of plausibility and some exposure data. However, these are dependent on the reporting of the events, and equally (if not more) important are measures to ensure the events are reported. In the UK, the reporting of adverse reactions has been extended to pharmacists[10] and nurses[11] and patient reporting has recently been introduced on a pilot basis. This is one of the recommendations of the recent review of the UK Yellow card system for ADR reporting[12]. However, there is considerable concern that the reduced emphasis on the teaching of clinical pharmacology in both undergraduate and post graduate medical education will threaten the ADR reporting systems. Furthermore, with the increase in the prescriber base, for example through extension of prescribing powers to nurses and pharmacists, there is a danger that if the training is not carefully developed and monitored ADRs may increase due to the lack of knowledge and inexperience of the prescribers. Moreover, ADRs may remain unreported unless appropriate training in ADR identification and reporting is also provided (see chapter 5). Despite these measures, there may be inadequate power in detecting signals of new ADRs if there is heavy reliance on one data source. To this end, there needs to be openness

in relation to reporting of serious ADRs by the industry, academia and clinicians as soon as possible after completion of studies in order to allow independent and timely collation of the data into systematic reviews[13].

Recommendations

- Fundamental to the contribution of spontaneous reporting to pharmacovigilance is the need to maintain and strengthen spontaneous reporting systems.
- Key issues are the evaluation of the patient reporting initiative and education of all groups who report.
- Prompt sharing of data between regulatory authorities, the pharmaceutical industry and researchers is essential. It will be key to collation of data into systematic reviews that are regularly up-dated in order to allow the rapid detection and evaluation of signals.
- Further methodological work should be supported on signal detection and analysis. This should include further development of methods to optimise the use of the various data sources of data and bring them together to enable robust decision making once the body of evidence is established is of equal importance as these decision will have major public health implications (I'm not sure what we are trying to say here – what is of equal importance?)

Pharmaco-epidemiological studies

Situation – the issues

2.4 Pharmaco-epidemiology encompasses many observational aspects of pharmacotherapy including utilisation, safety, clinical outcomes and economics of the use of medicines. Observational research allows the study of drug safety issues that cannot be pursued by experimental methods for the reasons discussed earlier but without the benifits of randomisation. This report is focusing on safety and the role of such studies in the post-marketing phase. The whole process of drug development is designed to establish the balance of benefits and risks of a new drug so that decision can be made whether it should be licensed and used in clinical practice. Whereas the benefits of a drug (defined as its efficacy) can be measured relatively simply for most drugs within a realistic timescale, and every effort is made to define the risks (defined as harm, side effects, adverse reactions or toxicity), some of these cannot be detected until very large numbers have been studied or sufficient patients have been exposed for long enough periods of time. There is therefore a need to continue to monitor the potential risks of new drugs after they are licensed. Several different study designs are employed to explore signals identified from spontaneous reporting with analytical methods dependent on the design adopted. These are summarised by Strom[14]. In addition to further evaluation of rare events detected by spontaneous reporting by appropriate study designs, pharmaco-epidemiological studies can be used to quantify the risks from commonly used drugs using a variety of methodologies. Equally important is the use of multiple studies of exposure and outcome using different methods and populations to evaluate contentious issues such as the recent MMR claims in the UK. Although it is impossible to demonstrate absolute safety, the failure of a range of studies employing different methodologies and in different populations to demonstrate adverse effects has been crucial to the continued use of the vaccine to preserve public health.

Challenges, opportunities and solutions

2.5 Issues of inconsistency and credibility are in part an inherent risk of observational methodology and may cause difficulties and differences in interpretation. Using different data sets and different methodologies to address the same questions will help to narrow the range of uncertainties and provide more convincing data. There is limited expertise in this type of research in the academic community which is undoubtedly linked to the lack of adequate resource from funding bodies to undertake it.

2.6 A major threat to observational studies has been posed in the UK by recent legislation related to confidentiality (see chapter 4). It is often impossible to obtain individual consent, and

indeed is not necessary if the data are analysed with appropriate safeguards to ensure anonymization. However, the NPfIT in England offers a unique opportunity to improve the detection and evaluation of ADRs, provided the data are made available to the relevant people including the regulatory authorities, the pharmaceutical industry and academic groups. The involvement of the public and their understanding of, and support for, the importance of such research is crucial. Furthermore, the Pharmacovigilance Plan that is recommended in ICH Guideline E2E[15] represents a major advance in the detection of important adverse reactions post-marketing.

Recommendations

- In order to provide the expertise and resources to undertake pharmacoepidemiological studies, training at the undergraduate and postgraduate levels need to be strengthened, and an appropriate level of resources made available.
- Adoption of the ICH Pharmacovigilance Plan should be welcomed and widely implemented
- The essential role of the NHS National Programme for Information Technology (NPfIT) must be recognised and the opportunity seized early during its development to ensure that it can be utilised in the future for evaluation of drug safety issues. Links with parallel activities in the other devolved countries of the UK should be facilitated to ensure that UK wide pharmacovigilance is achieved

Databases

Situation – the issues

2.7 The UK NHS provides an infrastructure that supports pharmaco-epidemiological research and several UK databases are used internationally. There are currently four main categories of databases in the UK:

- Prescription event monitoring (PEM) is operated by the Drug Safety Research Unit (www.dsru.org/main.html) which collects data prospectively from GPs on events experienced by patients taking a selection of newly marketed drugs[16].
- Population-based primary care research databases that comprise computerised anonymised longitudinal patient records from the major GP software systems. These include Mediplus and DIN-link (both commercially run; www.imshealth.com), the General Practice Research Database (GPRD; run by the MHRA on a non-profit basis; www.gprd.com) and Q research (run by the University of Nottingham; www.nottingham.ac.uk/~mczqres/).
- MEMO (the Tayside Medicines Monitoring Unit) which is a record-linkage database (www.dundee.ac.uk/memo/). This incorporates data on dispensed medication from general practice, inpatient data and information from other national data sets for patients in the Tayside region of Scotland[17].
- Disease registries, with over 100 databases listed in the directory of clinical databases at www.docdat.org.

2.8 The strengths of the databases are that they are population based reflecting routine usage in a general population and provide denominator data. The disadvantages are that most are prescription based and compliance is unknown. Furthermore, they are mainly based in primary care with little information on secondary care. The data quality is variable and data on confounding factors may not be collected. There is often a considerable lag time in data collection and even for the largest, the power to explore rare events is low. Finally, there is limited expertise and resource to maximise their use.

2.9 In North America, claims databases (e.g. Puget Sound, Kaiser Permanente, United Health, MediCaid, Saskatchewan) are used for pharmacoepidemiology but as they were designed for administrative purposes the quality of medical information is variable, and the specific information needed to assess a safety issues may not be available. There are a number of other databases in Europe. The strength of the UK databases is indicated by their frequent use by North American academics[14].

Challenges, opportunities and solutions

2.10 The implementation of the NHS National Programme for Information Technology (NPfIT) in which it is planned to implement a single system linking NHS patient records from any source in an electronic Health Record offers a unique opportunity to link drug prescribing to adverse events at all levels of care to allow an analysis of drug safety at a national level in England. However, there is a risk that if this is not pursued with sufficient resource and appropriate measures put in place, the existing systems may no longer be available without an adequate replacement.

2.11 The NPfIT is limited to England, while other systems are being developed in parallel in the devolved countries. It is important that the different systems are compatible; otherwise, a UK-wide approach will not be feasible and will limit the opportunities for major advances in pharmacovigilance.

2.12 There are in addition opportunities within the existing databases which could be exploited. Whereas PEM is used principally for signal detection, MEMO and the GP research databases have been used to strengthen and refute signals, to quantify absolute and relative risks and to identify sub-populations at risk. Important issues which are particularly difficult to assess during drug development such as the impact of maternal drug exposure on pregnancy outcome, neonatal and early childhood health and the use of medicines in children could be addressed with appropriate ethical review and approval. Although the current initiatives in relation to medicines in children will ultimately improve the quality of data available on such medicines, the relative lack at present makes the uses of such data crucial to assessments of drug safety in children

2.13 As discussed later, the delivery of training in therapeutics within an integrated curriculum is crucial for improved pharmacovigilance. Opportunities also exist, for example in relation to the UK Biobank to undertake pharmacogenetic studies in collaboration with the databases.

Recommendations

- The implementation of the NPfIT for England should be informed by discussion with researchers and the regulatory authorities.
- Current databases need to be maintained and strengthened until the NPfIT can replicate the research capacity and provide the same or a higher level of data quality at a national level.
- This exciting development should be linked to similar activities in the other devolved countries to ensure there is a UK-wide approach to pharmaco vigilance
- Training opportunities and resources for research based on the use of databases need to be identified.
- The use of databases for pharmacogenetic studies should be explored through funding streams made available by the Departments of Health and Research Councils in the UK

Other sources: Clinical trials and systematic reviews

2.14 The Phase III randomised controlled trials which are pivotal to the development and licensing of a new drug or the extension of the indications for its use are largely undertaken by the pharmaceutical industry. By contrast, trials to evaluate the optimal use of the drugs are often undertaken subsequent to licensing by academic groups funded by non-commercial sources. An important aspect of all trials is the assessment of the safety of the drug and the risk/benefit profile. The most important feature is that they provide an unbiased estimate of the frequency of the event by comparison with a group that is not receiving the drug (but may be receiving standard therapy). The trials provide reliable information on common ADRs but have a number of limitations. First, the number of individuals exposed is likely to be relatively small and therefore rare events may not be detected. Secondly, the eligibility criteria may exclude individuals who are more likely to develop ADRs such as children, the elderly or those with co-morbidity or impaired liver or renal function. Therefore, the generalisability of the results is limited. Thirdly, the duration of the

trial may be short, particularly for drugs that may need to be given for long periods and may have delayed onset ADRs. There may be under-reporting that may be biased by knowledge of the treatment participants are receiving. Finally, the trials are costly to mount which often means that they are relatively small and therefore have limited power for ADR detection.

2.15 Systematic reviews and evidence synopses could address this issue but unfortunately the reviews (and indeed the trials on which they are based) largely focus on efficacy[18]. Furthermore, there are often difficulties in accessing the trial data with limited sharing of relevant data. The combination of data from different trials is also complicated by the lack of standard systems for reporting adverse reactions. The collation of data from different types of studies is limited by the methodology currently available.

Challenges, opportunities and solutions

2.16 Many of the issues can be addressed by designing trials with adequate power and duration and broad eligibility criteria. Such trials, if not already undertaken at the time of licensing, could be part of the requirement conditional on the granting of the marketing authorisation. Reporting and collation of ADRs will, in theory, be improved by the EU Clinical Trials Directive, which requires the establishment of a European Pharmacovigilance Database. However, it is still unclear how this will function for non-commercial trials which are covered by the Directive. Standardisation of definitions and QA and QC to improve the quality of the data are also an important part of the process. The recent publication of the updated CONSORT guidelines[19] should highlight both to authors and editors the importance of adequate and standardised reporting of ADRs, as well as efficacy data in publication of trial results. This will enable data to be more reliably combined in systematic reviews. Methodology to combine data from different types of pharmacoepidemiological studies also needs to be developed.

Recommendations

- Standardised adverse event reporting criteria should be developed and the new CONSORT guidelines should be universally adopted.
- Primary data on adverse events from all sources should be more widely available in a format that allows appropriate interpretation by those with necessary expertise in secondary research in order to produce more reliable estimates of ADR rates.

Chapter three - *Potential new approaches*

New Technologies

Situation – the issues

3.1 Pharmacogenetics, the study of DNA sequence variation as it relates to differential drug response, is distinct from the other 'omics' technologies because it is an unchanging characteristic about a person, whereas the other technologies (gene expression profiling, proteomics, and metabonomics) measure more dynamic variables.

3.2 Such technologies can generate scientific insights into the variability of patients response to medicine. These insights are being applied to all areas of medicine development and use, and are increasingly a core aspect of medicine development. The ability to understand the basis of variable patient response allows significant benefit to patients in terms of greater likelihood of beneficial response, and enhanced delivery of medicines through the drug development process.

3.3 As these technologies are still relatively new, much of their use has been applied in exploratory clinical research; nevertheless they are increasingly being applied to the study of the biological mechanisms underlying ADRs, both in the pharmaceutical industry and in academia. There are increasing examples of these technologies impacting medicine labelling (e.g. atomoxetine, trastuzumab, imatinib, 6-mercaptopurine) showing that this is not a future possibility, but a use applicable today, driven by regulatory agencies and healthcare systems, as well by industry.

Challenges and opportunities

3.4 The new technologies may offer an unprecedented opportunity to better understand ADRs, and develop preventive strategies, in cases where there is a genetic component[20]. This will be important for existing medicines, but the lessons learnt from this will feedback into the development of new drugs.

3.5 Profiling for expression of genes and proteins is now technologically possible but is hampered by lack of access to the appropriate tissues, which is related to the invasive nature of tissue collection, lack of tissue storage facilities, and the difficulty of introducing it into large-scale studies. Metabonomics, the analysis of endogenous metabolites in biofluids such as urine or plasma, is a much newer technology, where little is presently known about how to interpret and validate the data. A common factor for all these profiling technologies is that they produce large amounts of data that pose challenges in data management, statistical analysis and interpretation. There is no consensus on the most appropriate way to generate or analyse such data and these approaches have mainly been applied to exploratory research at this time.

3.6 Under clinical trial conditions, DNA variation has been shown to be an important determinant of variable drug response[21]. However, there is currently very much less evidence available upon which to assess the impact of DNA variation on adverse events in the post-marketing setting (as opposed to the controlled clinical trial environment)[22]. Poor patient compliance, incorrect diagnosis or prescribing, and inappropriate drug combinations are all quoted as environmental variables that will reduce or confound our ability to measure the impact of DNA variation on adverse events post-marketing. There is a shortage of data looking at the impact of DNA variation in a real world setting and more research is needed in this area. In particular, funding is needed to investigate genetic variability in response to established compounds, which are unlikely to be sponsored by pharmaceutical companies. Most studies to date have been retrospective and have looked at one or a few genetic determinants without any consideration of environmental factors. This may result in an incomplete phenotype, and may be one of the major reasons for the lack of replicability between different studies. Prospective studies and utilisation of databases is needed in the

investigation of common adverse events. However, this is unlikely to be possible with rare events, where the scarcity of cases poses challenges to any research methodology. The following issues further compound the situation:

- Following up a report of an ADR to obtain a DNA sample presents major logistical and consent issues and it may be difficult to obtain the necessary phenotype (clinical) data in sufficient detail.
- Serious ADRs to marketed drugs are uncommon and so it may be difficult to obtain sufficient numbers to permit a meaningful analysis in a short period of time.
- A plausible biological hypothesis may be difficult to define in the case of safety issues, so pharmacogenetics may require a whole genome approach, a technology that is still evolving and is not yet being applied routinely.
- Ethical issues may prevent collection of DNA from patients identified in databases as having had a serious, but rare, adverse event.

3.7 An issue that also needs to be addressed concerns validation or replication of a preliminary pharmacogenetic association. Ideally hypotheses concerning the basis of adverse events and how they could be managed would first be generated from preliminary studies and then confirmed by prospective studies. However, performing prospective studies of rare ADRs poses significant logistic and ethical problems. The scale of studies required to establish superiority of an intervention compared to normal therapy is unachievable for the rare, serious adverse events that can be identified in the post-marketing arena. However, there are precedents in drug safety for validating an intervention in real-time i.e. introducing a procedure to manage the adverse reaction, and monitoring the event rate after implementation. This of course requires an accurate system for measuring these event rates, and one that is independent of subjective bias (for example, ADR reports may increase after publicity, which could significantly affect measured rates). Therefore, implementation of pharmacogenetic/genomic derived safety management will critically depend on the ability to measure adverse event rates before and after an intervention to investigate the effect of the intervention. This improved signal quantification will require both a more accurate – and less subjective – numerator value, and a consistent method to measure the denominator.

3.8 Establishing the predictive value of pharmacogenetic results will be key to their future utility in affecting prescribing decisions. There is a shortage of pharmacogenetic/genomic data in the post-marketing arena, and much greater emphasis needs to be placed on generating these critical data on the following:

- The contribution of DNA variation to adverse events in the post marketing arena
- Ability of prospective use of genetic information) to impact health outcomes in clinical practice.
- The ability of proteomic, transcriptomic and metabonomic data to provide scientific insights into the mechanistic basis of adverse events.

3.9 Generating these data in an efficient and timely manner will inevitably require collaboration between industry, academic groups, regulatory authorities & healthcare providers. Opportunities also exist to undertake pharmacogenetic studies in collaboration with the databases, for example in relation to the UK Biobank.

Recommendations

- Pilot and feasibility studies should be set up to rapidly establish the optimal mechanisms for consent procedures and collection, handling and storage issues. This will require collaboration between industry, academic groups, regulatory authorities and healthcare providers.
- A pragmatic and less bureaucratic ethical framework needs to be established so that perceived ethical concerns do not act as a barrier to this research. An important role for regulatory authorities will be in supporting such research and establishing the validity of the research objectives

such that ethics committees and patients can understand the value of pharmacogenetic research in this area

- The new technologies should be integrated into planned pharmacovigilance studies, and the use of yellow card data for genetic studies should be encouraged with the appropriate oversight mechanisms in place.
- Expertise and techniques in the appropriate interpretation of data generated through the use of the new technologies needs to be urgently developed.

Regulatory approaches

Situation – the issues

3.10 In the UK and many other developed countries, spontaneous reporting systems such as the yellow card scheme remain the bed-rock of pharmacovigilance. However, all other available data relating to the benefits and risk of licensed medicines needs to be considered. In this context, randomised controlled trials and pharmacoepidemiological studies are gaining greater importance in both the detection of new safety issues and in their evaluation.

3.11 In the EU, legislation sets out the responsibilities of pharmaceutical companies with regard to pharmacovigilance. Pharmaceutical companies have to have a qualified person responsible for a system of pharmacovigilance within their organisation. This system has to be able to collect and manage relevant pharmacovigilance data and information, detect safety problems and report both data and issues to the regulatory authorities (the MHRA in the UK).

Challenges and opportunities

3.12 Decisions have to be made at a number of levels in the assessment of drug safety. Many of these are made at an early stage of drug development and may lead to the discontinuation of a development programme if the risks are thought likely to outweigh the benefits. This decision will be influenced by factors such as the severity of the disease in which the drug will be used and its likely efficacy, the availability of alternative treatments and the severity and reversibility of the adverse events and last but not least the reliability of the evidence of toxicity. Once a drug is licensed, the same factors will influence the decision making process about the action to be taken when a new safety issue is identified, perhaps the most important being the robustness of the evidence. In view of the inherent difficulties in determining causality from observational data, some of the most difficult decisions will be whether the available data justify withdrawal of the drug or its careful continued use with appropriate communication with doctors, patients and the public.

3.13 Over the last 20 years there have been a number of international initiatives to strengthen safety monitoring of drugs and to harmonise regulatory requirements in the area of pharmacovigilance. The Council of International Organisations of Medical Science (CIOMS) guidelines have covered various aspects of pharmacovigilance and a working group is currently developing guidance on pre-licensing safety data management and assessment. The International Conference on Harmonisation (ICH) is a forum for the harmonisation of guidelines between the US, Europe and Japan and a new guideline (ICH E2E)[15] currently under development relating to the planning of pharmacovigilance activities by companies and regulatory authorities, especially for the early post licensing phase of a new drug. It provides a structure for summarising the risk associated with a drug and presenting a pharmacovigilance plan based on a specification which sets out the identified risks, the potential from important unidentified risks and potentially at-risk populations and situations that have not been studied pre-licensing. Pharmacovigilance specification and plans will likely be required by some regulatory authorities at the time of application for marketing authorisation and for major changes. They will represent a major advance in highlighting the importance of post-marketing surveillance. A second major initiative which could also bring major benefits to pharmacovigilance is the European Pharmacovigilance database (EUDRAvigilance) which is being set up to

improve reporting of ADRs in the EU. If access to the data on this database was widened beyond that currently planned, after appropriate independent scientific and ethical review, for example to allow access to academic groups, this would provide another valuable data source.

Recommendations

- Data on ADRs from all sources should be made more widely available in a format that preserves confidentiality but allows appropriate interpretation and analysis by those with the necessary expertise.
- The ICH guidance on pharmacovigilance planning should be welcomed and universally adopted.
- The outcomes of regulatory decisions should be monitored and audited in order to determine whether they have had a beneficial public health outcome.
- Sometimes regulatory decisions have to be made on data which may not be robust. The reasons for these decisions need to be communicated clearly to all the relevant stakeholders.

Chapter four - *Implications of new approaches*

Legal

Situation – the issues

4.1 Clinical research that includes clinical trials and pharmaco-epidemiological studies inevitably entails the collection and analysis of confidential personal data on human subjects. In general, personal information on patients is held under legal and ethical legislation on confidentiality, and it is reasonable to expect that the information will be held in confidence. Personal data are now primarily governed by the Data Protection Act 1998 (DPA 1998) which transposes European Directive 95/46/EEC into UK law. The recently adopted European Clinical Trials Directive 2001/20/EC (implemented in the UK under the medicines for Human Use (Clinical Trials) regulation 2004/1031) makes specific reference to the duty to observe the rights of the trial subjects to "protection of data concerning him in accordance with Directive 95/46 are safeguarded" Similarly, the data protection requirement is written into Directive 2004/23/EC, which governs the quality standards and safety of human tissues and cells.

4.2 Such information should not be used or disclosed in a form that might identify the patient without consent. However, there are exceptions to this, such as section 60 of the Health and Social Care Act 2001, which provides interim power to ensure that patients' identifiable information necessary to support activities such as clinical audit, record validation and research can be used without the consent of patients. This legislation supports medical research where obtaining consent is not practicable and where anonymised data will not suffice. This regulation is overseen by the Patient Information Advisory Group (PIAG).

4.3 There is however a great deal of concern and frustration from researchers with these pieces of legislation which have increased bureaucracy, and led to confusion and difficulties in interpretation. There is a real danger that this may in the long run hamper medical research of all types in the UK.

Challenges, opportunities and solutions

4.4 The ability to undertake pharmaco-epidemiological research in the UK should be facilitated by the integrated healthcare system represented by the NHS. However, this potentially advantageous position is being severely compromised, as has been pointed out by a number of reports[23–25] because of difficulties in obtaining access to patient data. The Academy in its recent report on 'Strengthening Clinical Research' stated[24]:

> *It is the Academy's view that the UK should attempt to avoid an overly bureaucratic system where privacy concerns represent a growing barrier to participation in research'.*

4.5 Although there is provision within the legislation to obtain patient data without consent where there is *overriding public interest* (and medical research might legitimately considered to fulfil this requirement), variation in interpretation has led to a great deal of confusion, with many ethics committees misunderstanding population research. Indeed, it has been proposed that access to personal records for medical research should not require informed consent in certain circumstances, and these should be specifically and permanently exempted[26].

4.6 Furthermore, differing interpretations of the Data Protection Act by local officials may have various consequences: it may delay the start of a research programme adding to the bureaucracy faced by the researcher. Worse still, it may actually prevent the research from starting altogether. Guidance from professional bodies such as the GMC, MRC and BMA has not been consistent, and rather than clarifying the situation, has in fact added to the problem. Although it may not be possible in the short-term to alter primary EU and secondary UK legislation, it should be possible for professional regulatory bodies to issue joint and clear

guidelines that could be used to inform those responsible for data protection and correct any misapprehensions/ misinterpretation.

4.7 The situation is further compounded by the fact that researchers may have to go through several approval processes starting with the funding body, a NHS ethics committee, an independent scientific panel (for example when using databases such as GPRD), a University (where the investigator is a University employee), Data Protection Officers and the R & D Departments within each hospital Trust. There is therefore a need for a more streamlined process of ethical review, which could be achieved by developing standardised guidelines.

Recommendations

- Clear guidelines must be developed to allow appropriate interpretation of the Data Protection Act so that drug safety data important for public health can be shared and acted upon rapidly and without undue bureaucracy.
- The stifling bureaucracy involved in undertaking clinical research needs to be reduced through streamlining of the ethical and NHS Trust review processes.

Ethical issues

Current situation – the issues

4.8 Assessment of the safety of medicines is an increasingly important part of public health protection and as such is an ethical activity. Patients benefit from ADR monitoring both directly in relation to their own clinical care and indirectly in improvements in medicines prescribing. However, pharmacovigilance is subject to certain ethical constraints that need to be balanced carefully with the acknowledged benefits. Reporting of ADRs is usually initiated by doctors or other health professionals but this is being extended to patients[12].

Challenges, opportunities and solutions

4.9 Reporting by health professionals needs to be consistent with the law and ethical requirements of confidentiality. Concerns about confidentiality, and regulations to protect it, need to be proportionate to the harm a breach of confidentiality could cause, but also to the benefits of data sharing in the interests of public health and safety. In almost all cases, patients will be willing to give their consent to this information being passed to the relevant authority, if the purpose is clearly explained. In some cases, the patient may not be competent to consent and it is arguable that reporting would be in the best interests of the patient. A stronger justification could be made by arguing that disclosure is in the public interest, provided that such disclosure is to a specific authority and confidentiality of the patient is respected.

4.10 An approach to the issue of consent, particularly in circumstances where it is impossible or very difficult to obtain consent from all the individuals and, as in pharmacovigilance where it is crucial that all individuals are included, is to suggest that completely anonymised data are provided. There are serious limitations to such data in many circumstances, for example, where follow up is essential. Clear explanations of the methods of ensuring confidentiality by linked anonymous data need to be provided to the relevant populations.

4.11 Direct reporting by patients may allow a more rapid detection of signals and capture of events that are more "personal" experiences of pain, suffering or emotional disturbance. However there are concerns that patient reporting may be "captured" by organised interest groups that could jeopardise its value. The value of pharmacoepidemiology depends on it being robust and informative and not subject to the vagaries of private interest. The fundamental issue is to ensure that the system is sensitive and specific to safety issues rather than other considerations. The key to ensuring informed consent of individuals in the process of pharmacovigilance is the provision of good quality information which is widely available on key issues such as the role of the various agencies and the uses to which information will and will not be put.

4.12 Although it is widely acknowledged that the principal new technology of value in pharmaco-vigilance is large-scale pharmacogenetics,

routine collection of DNA is unlikely to take place outside of specific research studies in the near future. The collection of DNA samples for research is relatively sensitive to changes in public opinion and ethical views are divided even among experts. Pharmacovigilance without genetic information may properly be considered as public health research but it may be that such research with genetic data will not . Currently, the collection of DNA samples requires relatively specific consent to future uses of the samples and re-consent where a novel use is proposed outside the scope of the original consent. The breadth of the scope of consent is a difficult issue and is in part related to the research strategy used.

4.13 The feedback of data and research results also requires consideration; the current consensus is that feedback of general population results is good practice, as is feeding back individual results which make a contribution to an individual's care. Feeding back results of uncertain interpretation or which can make no difference to care is however not recommended. Particular consideration needs to be given to the predictive value of the information and to different perceptions of the utility of imperfectly predictive information.

4.14 The policy relevance of pharmacovigilance extends beyond safety assessment to judgements about the level of safety that drive decisions about a drug at various stages of its development and the patient and population level consequences of these decisions. Patients may be more or less risk averse than the pharmaceutical industry or doctors depending on the disease and opportunities for other therapies[27–29]. The possibility of population segmentation by response to drugs and possible creation of orphan populations or drugs by increasing knowledge of genetic links is also likely to become increasingly important. We know relatively little about how this information is or should be used in clinical practice and in doctor-patient communication and informed decision-making, and research is needed here.

4.15 As well as addressing concerns about the availability of data from patients and their doctors, the pharmaceutical industry has a crucial role to play in developing an open and transparent system of data generation and information sharing, which has to be weighed against companies' interests in the need for commercial confidentiality.

4.16 The increasing use of information technology within the NHS is likely to make data capture, transfer and automated analysis more efficient and informative but may raise concerns about the risk to privacy. This concern needs to be addressed in the system design and regulation of the systems.

Recommendations

- A consistent concern of the public in the area of medical research and specifically drug development is the protection of the public interest. The ethical requirements of honesty in reporting, replicability of results, independent scrutiny of data, avoidance of publication bias and justice in the distribution of risks and benefits of research suggest that ground rules for public/private collaboration in drug safety monitoring and drug safety research need to be strengthened and widely publicised.
- Further research is needed on how patients and doctors use the kind of risk information generated by pharmacovigilance.

Chapter Five - *Other issues*

Education and training

5.1 There are major concerns that the current undergraduate medical education may not prepare doctors adequately for their role in preventing ADRs through safe prescribing and in detecting and reporting ADRs. Many medical schools have adopted a problem-based approach but often with no subject base identifiable in the course. To address this problem, the British Pharmacological Society has developed a curriculum which could be used in problem based learning approaches[30]. With regard to postgraduate education, there is some emphasis on ADRs in examinations, but less formal CPD education on generic issues, or even on adverse reactions from new therapies, is rare.

5.2 Non-medical prescribers now include nurses, both as independent and as supplementary prescribers, and pharmacists as supplementary prescribers. Extension to other professions is also under consideration. Each profession brings different skills; nurses have experience in diagnosis and clinical management but know relatively little about drugs and their adverse reactions, whereas pharmacists are well versed in the latter but much less in the clinical areas. An essential element of the extension of prescribing to other health care professional is the need for training not just in prescribing but in the detection and reporting of ADRs.

5.3 The most recent version of "Tomorrow's doctors" increases the prominence of clinical pharmacology and therapeutics although not supporting its re-emergence as a specific discipline. The challenge is now for medical schools to deliver the learning objectives within a revised and integrated curriculum. There are equal if not greater challenges to the extension of prescribing to other health professionals and concerns about the availability of adequate infrastructure and personnel to ensure this is satisfactory. The Royal Pharmaceutical Society specifies learning outcomes for undergraduate programmes and recently consulted on the future pharmacy workforce. The National Council for Pharmacy Postgraduate Education provides courses for pharmacists and has produced a distance learning pack on ADR detection and reporting. Training for nurses is governed by the Nursing and Midwifery Council, which oversees courses on nurse prescribing. However, there is a concern as to the quality of individual courses given the lack of adequate clinical pharmacological expertise in the UK. There may be additional safety issues arising from prescribing by non-medical groups and this needs to be carefully monitored and evaluated.

Recommendations

- The key objective must be that medical graduates should be competent to prescribe safely and effectively. In addition, they should be able to assimilate information about new drug developments throughout their professional career.
- There is an urgent need to ensure that medical education is strengthened and a higher priority is given to the teaching of therapeutics.
- Drug safety needs to be incorporated more effectively into post-graduate curricula and the role of continuing education in such issues should be clearly identified in physician revalidation and should be an essential part of the portfolio of any prescribing doctor
- The extension of prescribing to other non-medical professionals requires a similar programme of initial and continuing education. To ensure that the benefits of such an extension outweigh any potential risks, a careful evaluation of the benefits and risks of prescribing by non-medical health professionals needs to be undertaken.
- There is a need to increase the capacity for teaching of therapeutics to all potential prescribers in the UK.

Communication

5.4 The involvement of patients and the public, often referred to as consumers, in all areas of

health care and research has become increasingly important in recent years and its value is now well recognised (www.invo.org.uk). In parallel with this, there has been an increased lack of trust in medical experts and the government from events such as Bristol and Alder Hey. There are several areas where increased consumer involvement could be valuable in improving pharmacovigilance, some of which are described here. First, consumers could assist in the design and planning of formal pharmaco-epidemiological studies in particular the acceptability of procedures to individuals and the quality of the information provided to participants. Ongoing involvement could assist in the smooth running of the studies and the dissemination of the results.

5.5 A second area is the interpretation and communication of risks of drugs to the general population. Certainly, journalists and editors in the mass media need a better understanding of epidemiology. However, despite this there is no doubt that the media may overplay the risks of a drug to increase readership but such tactics may discourage people from taking a drug with large benefits which has rare but serious risks. The establishment of pressure groups with specific agendas and often little expert input has led to major threats to public health often fuelled by lawyers. The development of better ways of communicating risks and benefits of drugs, for example by relating them to common situations and by giving absolute as well as relative risks, is urgently needed and would benefit from the involvement of consumers.

5.6 The third area is patient reporting which is likely to become increasingly important as more drugs are available over the counter and GP records may therefore not contain all of the drugs taken by an individual. However, there is a genuine concern that patient reporting may lead to a disproportionate public response, which whilst increasing the number of reports may make it more difficult to recognise signals by increasing the "noise". It is crucial that the pilot system is adequately evaluated before extending it widely. Education of the public, which may need to start as early as the first school, with a broader and more informed understanding of the relative importance of the risks and benefits of drugs is essential if we are to benefit as a society from the introduction of new drugs. Consumers can play a key role in ensuring that the risks and benefits of new drugs are adequately assessed and that the public understands that it is rare, if not impossible, to have an effective drug without some potentially serious adverse effects.

5.7 A further area where consumers could play a role is in the communication of the need for confidential individual patient data to be made available (with and without consent) with appropriate safeguards to improve public health. Recent initiatives developed by the CSM to involve patients and the public in issues such as reporting of ADRs and the provision of information on drugs to patients is a major step forward and should be encouraged and expanded.

Recommendations

- Increased involvement of patients and the public particularly in the area of communication of risks should be encouraged and facilitated.
- The role of patients in the reporting of adverse events should be robustly evaluated to ensure that any increase in the number of reports does not make the interpretation of signals more difficult and therefore may jeopardise the recognition of new hazards.
- Work with the media to ensure better communication and more balanced reporting of potential drug safety issues is essential to ensure that drugs and vaccines which can improve public health are not rejected by the population.

Biological medicines

5.8 There has been an increase in the number of biological medicines (i.e. those produced from biological systems such as human and animal tissues or laboratory-cultured cells) in recent years and this is likely to continue. There are several special issues that need to be considered in relation to pharmacovigilance with such agents that are related to their special

characteristics. The complex starting material from which many of the medicines are prepared poses an immediate problem as tissues from living creatures are inherently variable and may contain adventitious agents that could pose a threat to the safety of the final product. Although this risk can largely be controlled by the methods used, this may not be possible for agents such as transmissible spongiform encephalopathies (TSEs) which cannot be measured accurately, or where the hazard is completely unknown, so that the residual risk cannot be eliminated. Another difficult area is in the development of bioassays to standardise the efficacy and safety of different batches. It may be very difficult to control the manufacturing processes for a complex material, which may lead to subtle differences in the final product or variation in potency. They may represent a substantial safety issue. Pharmacovigilance is therefore crucial for biological medicines, both those produced by recombinant technologies and more importantly those which are prepared from tissues from living creatures. It is unlikely that spontaneous reporting will be effective for these medicines, and novel methodologies will need to be developed.

Recommendation

- Research into more effective methodologies for post-marketing surveillance of biological medicines needs to be undertaken.

Vaccines

5.9 Whilst vaccines have been addressed by another Working Group there are a number of specific issues related to pharmacovigilance that should be highlighted. First, vaccines are given prophylactically to healthy individuals, primarily young children. The population exposure is high and often ideally universal. Vaccines are highly effective at disease reduction in the population, and in addition may provide indirect protection for the unvaccinated. However, for the individual the risk/benefit ratio may change over time. Serious ADRs are likely to be rare and therefore better systems for their detection such as record linkage are crucial. In addition, novel epidemiological methodologies involving only cases such as ecological methods, case-coverage methods, case-crossover and self-controlled case series methods need to be explored further since the may represent powerful tools meriting the same attention as more traditional cohort and case-control methods[31]. Individuals and particularly parents have a lower tolerance of adverse effects for vaccines than for drugs, and therefore, vaccine safety issues result in intense media interest which may threaten national vaccination strategies.

Recommendations

- Novel methodologies for the detection of ADRs to vaccines need to be developed given that serious vaccine-related ADRs are likely to be rare, and may take many years to manifest themselves.
- Research on methods of communicating the risks and benefits of vaccines in factual and non-alarmist ways that are meaningful and easily understood by the general public needs to be undertaken to maximise the public health benefits of vaccines.

Chapter Six - *Measures of success*

- More rapid and complete reporting of serious adverse reactions leading to the earlier detection of the risk associated with drugs so that appropriate action can be taken rapidly to estimate the risk to patients.
- National level data with increased power and reliability from the NPfIT in England and linked initiatives in the other devolved countries of the UK to enable new safety issues to be recognised and quantified more rapidly and accurately so that action can be taken to minimise the risks to patients.
- Incorporation of pharmacogenetics into clinical practice and drug safety assessment with the aim of identifying individuals susceptible to ADRs and defining those patients who are at greatest risk of harm.
- Improved assessment of impact of regulatory procedures undertaken in response to ADRs, specifically the identification of those patients who are at greatest risk and the size of that risk or in extreme circumstances the removal of a drug from the market to prevent further harm to patients of its continuing availability.
- Better understanding of and more measured media and public response to drug safety issues so that drugs or vaccines which have genuine benefits but also predictable and quantifiable risk are used appropriately and their use is not threatened by uninformed or biased reporting in the media with important public health consequences.

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