The accelerating need for pharmacovigilance

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ABSTRACT – The search for new drugs takes on greater complexity with increasing knowledge, allowing more sophisticated therapeutic interventions. At the same time there is increasing commercial pressure for the pharmaceutical industry to find 'blockbuster' drugs which will be marketed globally to maximise profit in the shortest possible time. Other changes in the industry – shortened times for drug development and increasing outsourcing of functions – make for an environment where some pre-marketing safety issues may go unnoticed. The increasing challenge to pharmacovigilance is not only to be able to find early signals of drug problems, but to rapidly determine the true benefits and risks. We may not have adequate systems to prevent unnecessary harm from globally marketed drugs.

Commercial trends in the pharmaceutical industry

At the 'Pharma Summit 99' (Institute for International Research, Amsterdam, 26–28 January), the audience was told by Drs David Webber and Stephen Allport (of Glaxo Wellcome) of the challenges facing the pharmaceutical industry in strategic and project planning.

Product life cycles are getting shorter, influenced by regulatory price control and the economics of the industry. It costs about three times the annual sales income to get a successful product on the market, with a development time of 10–12 years. In order to reach sales growth targets for this industry, costs need to be cut by 20–40% or sales increased by that amount. Advances in technology should allow for a shorter time to market. It was also proposed that time to peak sales, rather than the level of the peak *per se*, was most important for market success. From 1991 to 1998, so-called 'blockbusters' have doubled their share of the top twenty products in the global market (from 7 to 13.3%).

To maintain commercial success, companies must evaluate and re-evaluate market potential: a company cannot afford to sustain problematic or unprofitable products.

Another aspect touched on by many speakers at the meeting was the importance of genomic research, combinatorial chemistry and rapid test systems. These approaches should yield a number of novel products with specific physiological effects. Many similar entities might suddenly become available in different companies further exacerbating the need to be first to market.

There was much discussion in the conference about mergers/takeovers and outsourcing in the industry. A general picture arises of a major pharmaceutical company which will contain within its central structure only one or two functions, such as vast marketing and research and development strength. Every other activity will be outsourced.

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Possible implications for drug safety

Mergers and takeovers greatly stress the management of companies. In the safety area there is a need to coordinate activity across the new company. The outsourcing of clinical trials and other work to contract research organisations adds to the complexity of who should report what safety information to whom and with what priority. Who is responsible for data concatenation and analysis? How is safety information translated into information and action?

Reducing the time to market will put further stress on the pre-marketing staff to manage safety data, which are not usually as clear cut and manageable as the efficacy data. That shortcuts may occur, and subtle but important signals be overlooked, must be considered more possible than in the past.

There is at least a risk that the direction the industry is taking may lead to some safety issues being overlooked, however carefully companies try to manage in the volatile commercial climate.

Regulatory authorities

Drug regulatory authorities have the responsibility to check what the industry is proposing to market, but they have been drawn into the industry's cycle of shortening time to market by reducing their own evaluation time more and more. In some instances the authority's own income is related to its turnover of approvals. Will this mean that the checks will be less thorough? Moreover, there is an increasing move for one major country's approval to be taken as valid for other countries.

The challenge to safety does not stop there. The aim of the industry is to get the widest market as fast as possible. Drugs will be marketed simultaneously in as many countries as possible and as aggressively as possible. If a safety problem does occur it is quite clear that many more people could be exposed to the drug than hitherto before recognition and before action is taken.

Post-marketing monitoring

Post-marketing drug safety still depends heavily on clinical concern reports (somewhat misleadingly called 'spontaneous reports'). Information technology has vastly improved

the ability to transmit information between industry and national authorities, between national authorities themselves, and to the WHO. Strict regulatory conditions have also been applied to the timeliness of reports of serious adverse reactions. Case control studies have been increasingly used to investigate signals further and patient/prescription databases are more often used as a source of information. Other methods used in pharmacovigilance are cohort studies such as in the Intensive Medicines Monitoring Programme in New Zealand and the Prescription Event Monitoring in the UK, but these have not been widely used. The question then is: will the current systems be adequate to ensure drug safety in the future?

So-called spontaneous reporting has the advantage of being cheap and continuous for the lifetime of the drug but is acknowledged to have problems of under-reporting, incomplete reporting and delay. The current improvements in IT and regulation mean that serious, and particularly unexpected, adverse reaction reports will be transmitted from industry to national regulatory authorities and *vice versa*. International industry will have a huge amount of information on their own products, which they will summarise as periodic safety updates for regulators. Most national authorities will have a large amount of information but not the same as industry. There is no arrangement continuously to transfer information about problems seen between most national authorities, apart from 'rapid alerts'. On the other hand, the national authorities have information on all drugs causing (serious and otherwise) adverse reactions in their country; they also have access to the WHO database into which all countries deposit all (serious and otherwise) case information, and have done for 30 years.

The above situation for report transfer and management is complex, governing the exchange and entry of large amounts of data. Pertinent questions are whether this will continue to work efficiently in the future, and who will be able to analyse these large amounts of data: we may have a large amount of data, but little information. The observations of the Uppsala Monitoring Centre, in managing the download of data from 55 countries to the WHO database, are that changes in staff, software and hardware, plus other breakdowns, constitute many practical obstacles to data exchange; but these can be reduced.

Serious adverse reactions

These are variously defined as involving death, being life-threatening, disabling/incapacitating, or resulting in or prolonging hospitalisation, but many clinically important issues do not reach these criteria for seriousness. This was exemplified by the 'practolol syndrome' being presaged by reports of 'dry eye'; and by elevations of some laboratory tests (eg creatine phosphokinase elevations may predict myopathy). In future, with the rapid exposure of large populations to a blockbuster drug, it will be necessary to institute prospective studies (post-marketing surveillance would be one appropriate method) when surrogate markers of serious disease are affected such as liver and renal function tests.

Medical information from adverse reaction reports is reduced to hierarchically ordered terms for storage and search. The current trend is to attempt to add a large number of terms, with the aim of being as close to the reporter's free text as possible. However, medical decision-making is needed on both the data input and search. Wrong decisions in choice of terms or search strategies may result in considerable biases in results of searches.

Response to warning signals

What happens if an adverse reaction signal is found? Information on exposed populations is available from IMS and sometimes in national statistical repositories, but how often is it used rapidly in signal analysis? Case control studies are often instigated to investigate signals. Many efforts are made to speed up the process by using medical information databases. Such studies are not always easy, are expensive and may not be translatable to other populations. More important, they take time – sometimes years – when the data are not readily available. During this time many people (tens of thousands for a 'blockbuster' drug) may have been exposed whilst waiting for an answer. We are often content with an 'answer' such as that a drug may be causal, plus an idea of frequency. This information is of limited clinical value. We need to know the range of severity of the reaction, at-risk groups, what action should be taken if the reaction occurs, and to consider the relative benefits and risks of alternative therapies (or indeed of doing nothing). Sophisticated populations expect the medical profession to have more knowledge of therapy than it possesses. Patients'

Key Points

The pharmaceutical industry aims are: shorter times to market; shorter time to peak sales; increased profitability

Spontaneous reporting remains the main post-marketing tool for pharmacovigilance signal generation, and therefore the main failsafe system

Very large numbers of patients will be exposed to a 'blockbuster' drug, and to any possible harm, very rapidly, whilst analysis of safety signals is occurring

Are the current systems for data capture, analysis, and communication of key safety information fast enough to cope with the challenges of blockbuster drugs?

A continuous global pool of data relevant to safety may help: analysis should be rapid and transparent, and communications to health professionals and the public should be more informative and should acknowledge uncertainty

demands will increase as new drugs are strongly promoted and their use accelerated.

Sildenafil (Viagra) as an example of a challenge

This blockbuster drug is being taken by men, many apparently healthy. However, impotence may be an early feature of vascular disease[1,2].

The current controversy is whether the drug may cause myocardial infarction or other vascular events. Does sexual intercourse cause myocardial infarction, or stroke, etc.? How often? In which patient groups? Does Viagra worsen a risk from sexual activity if such risk exists? The questions are many, but the current advice is to avoid the use of the drug 'in men for whom sexual activity is inadvisable because of their cardiac status' (Pfizer, summary of product characteristics). There are also warnings on the risks of interactions, which may modify responses. There are therefore dilemmas for the prescriber and patient such as: is diabetes a contraindication? How often is impotence a marker of vascular disease[3]? How much should one investigate the patient before prescribing[4]? Other broader questions such as misuse and non-prescription availability of the drug are also important social questions.

The major issue is that whilst information is being assembled to answer the questions, the company must market the drug extensively to meet commercial goals. The Internet also draws the attention of doctors and patients to the availability of Viagra so that there is a degree of consumer peer promotion as well[5].

Some possible improvements

National analysis concentrates mainly on serious adverse reactions, but this is inadequate. Professional expertise should focus more on the analysis and interpretation of data, which could be managed in one place. The need to get useful information from the pharmacovigilance experts to health care practitioners and the public as fast as possible is paramount: information known only within the pharmacovigilance circle is nearly useless. The information needed by the patient and clinician does not have to be in the form of a final answer, but both groups need to know about all risks in terms of probability, approximate frequency and severity.

Commercial viability is essential to the pharmaceutical company and to the community if we wish to benefit from advances in drug therapy. We cannot expect industry to fly in the face of commercial reality. Pharmacovigilance is a truly global matter: we must assemble, much more reliably and quickly, *all* records of clinical concerns around the world as well as drug use, clinical and demographic details.

At another meeting (the Uppsala Monitoring Centre/WHO Anniversary Symposium, Stockholm, December 1998) some proposals were made which will add strength to the current pharmacovigilance procedures. The international development of Large Automated Multipurpose Population based Databases (LAMPS) has a special potential to 'permit rapid, accurate, affordable identification of important new drug safety issues', but such work must be coordinated and the information collated and analysed transparently by an independent body. Access to information must be wide, if not open, and it seems that this could be most easily achieved under WHO auspices. The Uppsala Monitoring Centre, as the WHO Collaborating Centre for International Drug Monitoring, has developed a new database which can receive case information on drug use and patient demographics as well as adverse reaction reports containing much more detail than in the past.

One approach could be to assemble as complete a global cohort of drug users as possible, together with suspected adverse reaction information, categorised according to the type and source of information (multinational medical data – for example from IMS, individual case reports, complete continuous data from databases, etc.). It should be possible to transfer such information to one place for continuous global analysis, done transparently and with an agreed expert panel to advise. Many will point out the pitfalls of data obtained from heterogeneous and overlapping sources, but to have current global data in an accessible and standard format both allows powerful data-mining tools to be used to generate signals, and facilitates finding artefacts and duplications in the data.

Other important suggestions made at the Stockholm meeting were:

- to link phenotype, genotype, allergy and congenital malformation information and adverse reaction information in order to identify genetic and pregnancy risk groups
- to expand work on the science of benefit risk analysis and communicating risk
- to do much more consequence analysis and to find objective and quantitative measures of the effectiveness of pharmacovigilance.

Acknowledgement and disclaimer

We have created pharmacovigilance and pharmacoepidemiological approaches that are complementary and have worked well, but it is almost certainly wrong to assume that our current approach to pharmacovigilance is adequate for the future because it lacks a true global vision and cooperation, in spite of the efforts of the WHO and ICH.

The use of sildenafil as an example is not to imply that there is a problem with the drug *per se* nor with the efforts of those who are involved in managing safety issues. I simply wish to show that there is a potential for a problem, based on a sample of current literature, which may not be elucidated for some time. This delay in clarifying potential risk is a fact of life with any drug, but for those with huge, rapid market penetration the possibility for morbidity and mortality is clearly great.

The aim of this paper, which gives a personal view, is not

to find fault with the huge efforts and advances that have been made in the past, but to highlight the challenges ahead and to try to see how we can develop in the future. If this paper provokes discussion it will have succeeded.

References

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5 Viagra effective treatment for diabetes-related impotence (1999) Doctor's Guide (0300h, 3 Mar 99) http://www.pslgroup.com

Addendum

Confidentiality: Access to the database is closely guarded by username and password. No retrospective tracing of a case is possible without reference to the reporting centre. We do not store any personal information regarding the patient.

In thirty years of operation there has been no breach of patient confidentiality. There have been a few cases of third-party misuse of the data, which resulted in debarring from further use.

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