Drug Safety - Does It Work?

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Summary

People working in Pharmacovigilance strive to implement the regulations - but can they be confident that the output of their activity is translated into more informative and useful product information for the prescriber or patients? How have things improved over recent years? Has the increase in information sources and case report numbers had a positive effect? What could be the way forward to improve provision of accurate and helpful safety information?

Introduction

The regulations for those working in Pharmacovigilance are complex and continuing demands from regulatory bodies for companies to give ever more detailed information about adverse events has only served to make the task more complicated.

But is the production of more information the answer to the problem? Perhaps we are inadvertently creating 'a wood and trees' problem where too much data is obscuring the useful information? It is well recognised that making the haystack bigger does not help find the needle!

Detection

It seems that the quantity of safety data produced may not now deliver the required results. When the Thalidomide tragedy of the late 1950s and early 1960s triggered the realisation that Pharmacovigilance was needed, there followed many good examples of how spontaneous reports from the marketplace could signal new and previously unsuspected side effects. In recent years, signals have increasingly been found not from any series of single case reports, but from publication of an academic paper, whose significance becomes apparent only in retrospect, suggesting a return to the mechanisms of the 1960s.

The neuropathic side effects of thalidomide were first reported in a British Medical Journal article in 1960, followed by case reports of phocomelia which were largely ignored and it was not until the link was recognised following a paediatric meeting in Dusseldorf in 1961 that the drug was withdrawn.

There may be similarities with the recognition that the early oral contraceptive pills containing large doses of oestrogen had an association with thrombosis. The difference in risk associated with the 'third generation' progestogens however was raised in 1995 by targeted epidemiological studies and not from spontaneous ADR reporting.

More recently, the Vioxx issue five years ago of cardiovascular complications that subsequently resulted in a record compensation payout of $5 billion by Merck, gradually emerged through the results of various studies such as 'VIGOR' and finally 'APPROVe', again not through analysis of spontaneous case reports.

It appears that there are few, if any, recent good examples of safety signals from single case reports. Companies are unlikely nowadays to change their product information based on spontaneous reports seen as a signal where the causalities and underlying pathology may be poorly documented and incompletely understood.

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The MHRA Good Pharmacovigilance Practice Guide agrees: "A single report of a suspected adverse reaction can only rarely be considered as a signal in itself. New reports should be routinely and systematically reviewed in the context of the existing cumulative data to see if they represent a potential new signal".

Having said that, there are definitely other but less visible advantages to using large numbers of spontaneous ADR reports to update the risk/benefit information. The exposure to a greater patient population and larger numbers from the marketplace allow an improved understanding of the recognised adverse effects associated with a product use, providing a current picture of the state of knowledge on the use of the medicine.

The fact remains that companies spend huge amounts of time and resources on producing this information when perhaps it doesn't make the difference we had hoped for.

Sharper Focus

Things have undoubtedly improved immeasurably over the last 40 years and even more recently since Vioxx five years

ago. Companies are more conscious of the need to focus on risk/benefit and the credibility that a company gains by promptly and scrupulously updating its product information. The consequent understanding of the benefit/risk profile in line with the emerging safety profile fed back from the marketplace should be seen as a real commercial advantage. Thus the necessity of regulatory obligation can be considered also a virtue.

So could it happen again? Does the ongoing level of regulatory scrutiny mean that from now on we are safe from any future recurrence of catastrophic adverse drug reactions? With all the work put in by PV specialists, have we provided a foolproof way to detect new problems early on?

Sadly it seems not. It could happen again. Despite the haystack of adverse events growing larger and probably the best we can expect is a low visibility of increasing quality of risk assessment for a product but still no guarantee that the iceberg will be identified by its tip. Going through the prescribed method is no watertight guarantee that we are safe, although it is always useful to look at updating the information and adding to the body of knowledge about the medicine's use. Right now there are no good recent exoamples where early detection has prevented later difficulties.

Other Sources

It may be that early indications come from different directions. A Marketing Authorisation Holder (MAH) will have access to other sources of safety information that should be considered for inclusion in the signal detection process. Information from new non-clinical research, post-authorisation studies, continuing clinical trials to develop additional indications and initiatives such as registries and surveys must all be assessed.

Faster Information

In terms of where prescribers obtain their information, the last ten years has seen a huge change with the internet being used to provide immediate access to epidemiological data, as well as the speed with which it can be updated and communicated to pharmacists and clinicians. While the collation and interpretation of any new information needs to be done with the same degree of diligence, its dissemination to prescribers and pharmacists has been dramatically improved which is beneficial in terms of providing the latest available risk/benefit information.

However the immediacy of the internet can cause inconsistencies in terms of the currency of information provided. For example, in-date medicines on the pharmacy shelf may contain a patient information leaflet which was correct at the time of manufacture but has now been superceded by internet updates. This can lead to confusion for both prescribers and for patients.

Risk Management

What has happened over recent years is a rebalancing of the risk/benefit equation, with more emphasis being given to the risk side of the equation and robust and specific Risk Management Plans becoming a condition of licensing. These are product specific and require a safety related programme which may demand either more work to be done through further safety studies or by the enhanced monitoring of suspected safety issues and evaluating risks.

So how can things be improved? In my view, companies should be more willing to update their product information within a faster timeframe, especially as the internet provides an easy and effective means of making information public and the availability of an updated SmPC to the prescriber and dispensing pharmacist is now instantaneous. Sometimes this may not happen as companies may be cautious about communicating current information on risk/benefit for commercial reasons. However, for the long-term benefit of the patient population, the sooner this information can be made available the better.

Regulators, as the custodians of public health, are quite rightly cautious in their scrutiny of adverse event data. Perhaps they now recognise that many Periodic Safety Update Reports are unwieldy and difficult to utilise effectively. The sheer volume of information produced can be unusable as a source of easy to access facts and these reports have gone beyond being helpful.

What prescribers need is a concise assessment of the risk, in the form of distilled and accurate information that can be accessed easily and put into clinical practice at the point of prescribing. The problem remains of how to consistently provide it.