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What is Pharmacovigilance and How Has it Developed?

Origins and Definition of Pharmacovigilance

In the beginning, there was thalidomide. The history of drug safety goes back further but, for practical purposes, the story of modern pharmacovigilance begins there.

In the late 1950s there was little, if any, regulation of medicines outside the USA (where thalidomide was not allowed on to the market), and their testing and development was almost entirely in the hands of pharmaceutical companies. In the case of thalidomide, unjustified claims of safety in pregnancy were made, and its use as a sedative and treatment for nausea and vomiting was targeted at pregnant women. The drug turned out to be a teratogen, producing a variety of birth defects but particularly limb defects known as phocomelia (Figure 1.1). Worldwide, about 10 000 babies were affected, particularly in Germany where the drug was first marketed. As phocomelia was otherwise a very rare congenital abnormality, a major increase in its incidence did not go unnoticed in Germany, but the cause was initially thought to be environmental. In 1961, a series of just three cases of congenital anomalies associated with thalidomide use in Australia was reported in *The Lancet*, the problem was finally recognised and the drug withdrawn from sale.

At the beginning of the 1960s, publication of possible adverse effects of drugs in the medical literature was effectively the only mechanism for drawing attention to them. Thalidomide produced a non-lethal but visible and shocking adverse effect, leading people to ask why so many damaged babies had been born before anything had been done? This question is central to subsequent developments. It is unlikely that we

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Figure 1.1 Child affected by thalidomide-induced phocomelia.

will ever be able to predict and prevent all the harms that may be caused by medicines, but limiting the damage to much smaller numbers is now achievable. Today we would expect to be able to identify an association between drug and outcome analogous to thalidomide and phocomelia after the occurrence of less than 10 cases, so at least three orders of magnitude more effectively than six decades ago.

The overriding lesson learnt from thalidomide was that we cannot just wait until a drug safety problem hits us. The thalidomide tragedy of the 1960s led directly to the initial development of the systems we have in place today, although it is only since the early 1990s that the term pharmacovigilance has become widely accepted.

Pharmacovigilance is defined by the World Health Organization as 'The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.' There are other definitions but this very broad one seems to be the most appropriate because there is a clear implication that the process is one of risk management. This is a concept that is

applicable to many aspects of modern life but, surprisingly, its explicit use in relation to pharmaceuticals is a fairly recent development.

Thalidomide is not merely of historical interest, as in recent years it has made a comeback on to the market in some countries but with very narrow indications and extensive safeguards. The reasons for this exemplify the point about risk management, as the risk of fetal malformation can be successfully managed by avoidance of the drug during pregnancy. It also demonstrates another concept that is central to the practice of pharmacovigilance – the balance of benefit and risk. Thalidomide has benefits in some diseases that are otherwise difficult to treat (e.g. refractory multiple myeloma) and these appear to outweigh the risk of fetal malformation if there is an effective pregnancy prevention scheme in place. A further point that thalidomide illustrates well – and which is relevant to many other drug safety issues – is that not everyone is at the same risk of a particular adverse effect. In this case, a substantial part of the population (including men and also women who are not of childbearing capacity) are not at risk of phocomelia.

Main Lessons Learned from Thalidomide

The thalidomide tragedy taught us many lessons:

- The need for adequate testing of medicines prior to marketing.
- The need for government regulation of medicines.
- The need for reporting systems to *identify* the adverse effects of medicines.
- The potential safety implications of unproven marketing claims.
- Most medicines cross the placenta and this results in fetal exposure.
- Avoidance of unnecessary use of medicines in pregnancy.
- That some risks can be successfully minimised.

The ramifications of the thalidomide tragedy were manyfold, but the key lesson for the development of pharmacovigilance was that active systems for detecting hazards are needed. Within a few years this had been taken forward with the introduction of voluntary (or 'spontaneous') schemes for reporting of suspected adverse drug reactions (ADRs). These have stood the test of time as an alerting mechanism or early warning system, and are covered in more detail in Chapter 3.

Scope and Purposes of Pharmacovigilance

In the past, the process of pharmacovigilance has often been considered to start when a drug is first authorised for use in ordinary practice. Nowadays, it is more commonly considered to include all safety-related activity beyond the point at which humans are first exposed to a new medicinal product.

The ultimate purpose of pharmacovigilance is to minimise, in practice, the potential for harm that is associated with all active medicines. Although data about all types of ADRs are collected, a key focus is on identifying and preventing those that are defined to be *serious*. This is generally defined as an ADR that meets at least one of the following criteria:

- Fatal
- Life-threatening
- Causes or prolongs hospitalisation
- Results in long-term disability
- All congenital anomalies.

The definition of serious also allows the application of medical judgement, such that a reaction can be considered serious even if there is not clear evidence that one of the above criteria is met. Non-serious reactions are important to individual patients and health professionals involved in their treatment, but they can usually be managed clinically and impact less on the balance of benefit and risk for individual products and on public health in general.

Thus, pharmacovigilance can be seen as a public health function in which reductions in the occurrence of serious harms are achievable through measures that promote the safest possible use of medicinal products and/or provide specific safeguards against known hazards. Pregnancy prevention in users of thalidomide is an example of such a safeguard; monitoring white blood cell counts to detect agranulocytosis (absent white blood cells) in users of the antipsychotic drug clozapine is another (see Chapter 7).

In order to minimise harms, there is first a need to identify and assess the impact of unexpected potential hazards. For most medicines, serious ADRs are rare, otherwise their detection would result in the drug not reaching (or being withdrawn from) the market. For products that do reach the market, serious hazards are seldom identified during pre-marketing clinical trials because sample sizes are

invariably too small to detect them. In addition, the prevailing conditions of clinical trials – selected patients, short durations of treatment, close monitoring and specialist supervision – usually mean that the frequency of ADRs will be underestimated relative to what will really occur in ordinary practice.

During pre-marketing clinical development and research on new medicines, the aims of pharmacovigilance are rather different from the broad public health functions described here. In volunteer studies and clinical trials, there is a need to protect individuals exposed to experimental products (from which they may derive no benefit) from potential harm. There is also a need to gather information on risks (including the frequencies at which they happen) in order to make a provisional assessment of safety and to plan for post-marketing safety development (see Risk Management Planning in Chapter 5).

Development of Pharmacovigilance

We next consider some of the most important examples of drug safety issues and discuss how they have affected the development of pharmacovigilance practice from the 1960s to the present day.

Practolol

In the early 1970s another drug safety disaster occurred; this was the oculo-mucocutaneous syndrome, a multi-system disorder, caused by practolol (Eraldin), a cardioselective beta-blocker used to treat angina and hypertension. As in the case of thalidomide, several thousand individuals were permanently damaged before the association was recognised. The fundamental problem in this instance was a failure of timely identification, as despite having an early warning system in place, the system was dependent on doctors suspecting an association between drug and disease. Probably because of the unusual nature of the syndrome – dry eyes, skin rash and bowel obstruction – and a long latency period (averaging almost 2 years in respect of the onset of the most serious bowel manifestations), relevant cases were not reported until the association was identified in the medical literature. Around 3000 cases were then retrospectively reported to the UK Yellow Card spontaneous ADR reporting scheme (see Chapter 3),

an example of the potential effect of publicity on ADR reporting. Interestingly, subsequent attempts to develop an animal model of practolol toxicity failed, indicating that the problem could not have been predicted from pre-clinical studies.

Main Lessons Learned from Practolol

- Some adverse effects are not predictable from pre-clinical studies.
- Spontaneous reporting schemes are not always effective at identifying new ADRs.
- Health professionals may not be able to identify long latency effects and clinical manifestations not known to be related to other drugs as ADRs.
- Additional, proactive and more systematic methods of studying post-marketing safety are needed.

The overriding message from practolol was that spontaneous ADR reporting alone is insufficient as a means of studying post-marketing safety. Thus, in the late 1970s various schemes designed to closely monitor the introduction of new drugs were suggested, but few implemented. The basic idea was that initial users of new drugs would be identified through prescriptions and monitored systematically rather than waiting for someone to recognise a possible adverse effect. The concept did come to fruition in New Zealand and in England in the late 1970s with the development of nationwide prescription-event monitoring (PEM) programmes (see Chapter 3).

Benoxaprofen

The first drug studied by PEM in England was benoxaprofen (Opren), a non-steroidal anti-inflammatory drug (NSAID) which frequently produced photosensitivity reactions (i.e. rashes in light-exposed areas). A published case series from Northern Ireland of five deaths related to hepatic and renal failure led to withdrawal of the drug in 1982, although the PEM study did not reveal any indication of these effects. Many of the patients who experienced serious ADRs with benoxaprofen were elderly; this was a result of reduced excretion of the drug as a consequence of renal impairment. Even though it is well-recognised that many patients who use NSAIDs are elderly (e.g. for arthritis or chronic pain), benoxaprofen had not been adequately studied in this population prior to marketing. A reduction in the dosage recommendations for the elderly was implemented briefly, but benoxaprofen was withdrawn soon afterwards.

Because the usage of benoxaprofen took off rapidly after launch and an important adverse effect – photosensitivity reactions – was common, a large number of spontaneous reports were received in a short period of time, swamping the primitive computer systems then used and pointing to the need for purpose-designed databases. The issue also illustrated the need for patients to be properly informed about possible ADRs and how to minimise the risk – in this case by avoiding exposure to the sun. It was therefore influential in moving towards the introduction of patient information leaflets, which became compulsory in the European Union (EU) during the 1990s.

Main Lessons Learned from Benoxaprofen

- Uncertainty about cause and effect from individual case reports – further impetus to the need for formal post-marketing studies in patient cohorts of sufficient size.
- The need to study a drug in populations most likely to use it (e.g. the elderly).
- The need for purpose-designed computer systems to handle ADR reports more promptly and effectively.
- The concept of intensive surveillance of new drugs, later achieved in the UK by the introduction of the Black Triangle scheme (see Glossary).
- The need for patients to be informed about possible ADRs.

Benoxaprofen was just the first of a series of NSAIDs withdrawn for various safety reasons in the 1980s. During this decade, pharmaceutical companies started to conduct their own post-marketing surveillance studies and UK guidelines related to their conduct were drawn up in 1987. However, initially, the value of such studies turned out to be limited because they usually lacked comparator groups and often failed to meet the planned sample size. The UK guidelines were revised in 1993 with the aim of improving the quality of studies. The principles of the revised Safety Assessment of Marketed Medicines (SAMM) guidelines also became a blueprint for the first EU level guidance on the topic.

Development of Pharmacoepidemiology

Epidemiology is the study of the distribution and determinants of health and disease in populations. During the mid-1980s, the term pharmacoepidemiology was first used to mean the scientific discipline

of the study of drug use and safety at a population level. The discipline developed strongly during the 1990s with the increasing use of computerised databases containing records of prescriptions and clinical outcomes for rapid and efficient study of potential safety hazards. In some instances, prescription records are held in a separate database to clinical events, and linkage between the two databases needs to be achieved (through common identifiers in the two sets of data) in order to study adverse events at an individual patient level.

Towards the end of the 1980s, pharmacovigilance and pharmacoepidemiology started to investigate the problem of dependence on benzodiazepines – so-called minor tranquillisers such as chlordiazepoxide (Librium) and diazepam (Valium) which had been introduced in the 1960s. Advice was issued to limit the dosage and duration of such treatments and this issue brought into focus the problems faced in dealing with the misuse and abuse of prescription drugs. This is another example of a situation where spontaneous ADR reporting failed to highlight an important concern, the issue eventually coming into focus as a result of pressure from advocates for groups of affected patients.

As well as the problem of delayed identification of real hazards, pharmacovigilance has suffered from the reverse, the apparent identification of hazards that turn out not to be real. To some extent this is inherent in a system that relies much on clinical suspicions – sometimes these will be wrong. The consequences are that sometimes a drug is unnecessarily withdrawn, or people become too scared to use it. For example, Debendox (or Bendectin), a combination product containing the antihistamine doxylamine, was widely used for the treatment of nausea and vomiting in pregnancy in the 1970s. It was withdrawn in the early 1980s on the basis of concerns that it might cause fetal malformations, a concerted campaign against the drug and impending litigation. At the time, the evidence of a hazard was very weak, but it was not possible to exclude a significant risk to the fetus. Subsequently, many studies of this potential association were performed and, collectively, they provided no evidence of an increased risk of fetal malformations. This example illustrates the intrinsic difficulty of disproving the existence of a hazard once concern has been raised.

A more recent, very high profile example illustrating the same point was the suggestion made in late 1990s that the combined measles, mumps and rubella (MMR) vaccine might be a cause of autism in children.

Despite there being little evidence for this suggestion, it was impossible to completely disprove and hard to convince worried parents. Some years later the paper that provoked this concern was discredited and retracted but in the meantime vaccine campaigns were damaged and a significant number of cases of measles occurred in the UK for the first time in many years.

Oral Contraceptives and 'Pill Scares'

This major pharmacovigilance story began in the late 1960s when it was discovered through spontaneous ADR reporting – and later confirmed in formal studies – that combined oral contraceptives (OCs) (containing an estrogen and a progestogen) increased the risk of venous thromboembolism (VTE). This led to a reduction in the dose of estrogen to 20–30 μg ethinylestradiol, which lessened (but did not abolish) the risk without compromising efficacy. Nevertheless, when the risk of thrombosis became public knowledge (highlighted by media 'pill scare' stories in some countries), many women became very worried and stopped taking OCs. When OCs are stopped abruptly by sexually active women, without immediate use of an effective alternative, unintended pregnancies occur and rates of induced abortion increase.

There have been several 'pill scares' over the years related to VTE and also to other safety issues such as a possible association with myocardial infarction and a small increase in the risk of breast cancer. In each of these scares, many women stopped using OCs and the public health impact, in terms of unintended pregnancies, was considerable. This has been particularly unfortunate because pregnancy itself is riskier (with higher rates of VTE for example) than using any OC.

In 1995, a World Health Organization (WHO) study of OCs found a twofold increase in the risk of VTE when use of third-generation (3G) OCs was compared with second-generation (2G) OCs. The difference between these pills was the progestagen component; desogestrel or gestodene for 3G OCs and levonorgestrel for 2G OCs. This was surprising, as it had always been considered that VTE risk was simply related to the dose of estrogen in the pill. Within about 3 months of the WHO study, the results of two other studies reached similar conclusions. Arguments were put forward that the associations seen in these studies were not necessarily causal and that 3G

OCs might have benefits that would compensate for the increase in VTE risk. However, there was general agreement that although the *relative* risk of VTE was doubled with 3G pills, the *absolute* level of risk (see Chapter 2) was very low, as VTE is rare in healthy young women, even if they take the pill. Thus, there was general agreement that 3G OCs should not be withdrawn from the market.

The UK's Committee on Safety of Medicines (CSM) decided that the emerging information on VTE risk should be shared with doctors and patients, but faced several challenges around communicating the risks of the OC pill. Scare stories had already been published in the British press and despite CSM messages that no one should stop taking OCs, many women did, and hundreds of unintended pregnancies subsequently occurred. It seemed that women had acted on information provided by the mainstream media, rather than on advice provided by a national medicines advisory committee. Interestingly, the pill scare that occurred in the UK in 1995 was not seen in other countries, even those where use of OCs is high. There could be many reasons for this, including the role of the British press in risk communication.

Following the 1995 pill scare, more studies were carried out and the effects of the various progestagens on blood clotting investigated. Ultimately, it was shown that there were plausible differential effects of these agents on clotting and further pharmacoepidemiological studies have now convinced most scientists that the observed association was causal and that 2G pills have the lowest risk of VTE. It has also been acknowledged that the risk communication tools used in 1995 were inadequate and, in many respects, pharmacovigilance risk communication at that time failed to prevent serious public health outcomes. In 1997, the WHO convened a meeting of experts to consider how communication in pharmacovigilance could be improved (see Chapter 4). Since then, there have been other significant developments in risk communication for all medicinal products and many of these have been informed by lessons learned from OC pill scares.

Main Lessons Learned from the OC Safety Issues

- Drugs are sometimes marketed at a higher dose than is required for efficacy.
- There may be differences in safety between drugs of the same class.
- Harm can result from poor communication of safety warnings.

- When communicating risks of medicines, it is important to distinguish between relative and absolute risks (see Chapter 2) and to explain the difference in plain language.
- Uncertainty and debate about risks can fuel public concern.
- The power of the media to influence users may be greater than the authorities.
- The need for greater international cooperation in pharmacovigilance.
- The need to develop more effective communication tools.
- Risk communication is a specific skill in pharmacovigilance.

An important point about the OC issues discussed is that the data on which they were based did not, after the initial signal in the 1960s, come from spontaneous ADR reporting. Despite that, causation was debatable because the studies were not randomised trials but observational pharmacoepidemiology studies. VTE is a sufficiently rare outcome in young women that it would be extremely difficult to conduct a large enough randomized clinical trial to detect a doubling of risk.

Hormone Replacement Therapy (Menopausal Hormone Therapy)

Later in life, women have also been prescribed sex hormones as replacement therapy (HRT, now renamed menopausal hormone therapy; MHT). In this age group, the baseline risks of VTE, arterial cardiovascular disease and various cancers are much greater and therefore it has been more feasible to study them in clinical trials, although studies have needed to be large and long-term. Therefore, observational studies of these outcomes were performed first and, in general, they appeared to show that HRT *reduced* the risk of arterial disease outcomes such as myocardial infarction and stroke. HRT was never authorised for the purpose of reducing cardiovascular risk, but in the 1980s and 1990s, on the basis of results from observational studies and much pharmaceutical company promotion, it was widely used for this purpose. The fundamental problem in performing such studies is that women using HRT may be healthier to start with and it is difficult to address all possible *confounding* factors (see Glossary) in the design and analysis of observational studies. Another important point is that the outcome in question is a *benefit* (i.e. a reduction in risk) and, because of such *biases* (see Glossary), observational studies

rarely provide convincing evidence of benefit. It is generally accepted that randomised trials are needed to establish efficacy and benefit.

Eventually, large randomised trials of HRT were set up (e.g. the Million Women Study), but some studies had to be stopped early because they showed the opposite of what was expected – an *increase* in cardiovascular risk. Warnings were then issued by regulatory authorities and, because there is no major downside to suddenly stopping HRT, communication was intrinsically easier than with OCs. Indeed, the intended effect of the warnings was that women who were inappropriately using long-term HRT should stop taking it. However, conveying the right messages was not straightforward because there were multiple risks involved, and they are time-dependent and cannot simply be expressed as a proportion (e.g. 1 in 100). In 2007, the UK authorities published a report on HRT which included estimates of risk for several adverse outcomes, expressed in clear language. Since then, further studies of HRT have been published and discussion of the risks and benefits of these products continues, and is likely to for some time to come.

Selective Serotonin Re-uptake Inhibitors

Selective serotonin re-uptake inhibitors (SSRIs) are antidepressants which were brought to the market in the late 1980s and have since largely replaced older, tricyclic antidepressants such as amitriptyline. The main reason why they have done so – apart from effective marketing – is that they are less toxic to the heart in overdose (i.e. there is a greater margin of safety in relation to dose). Depressed patients are at risk of taking an overdose and therefore this is potentially an important advantage.

There have been two controversial issues with SSRIs: withdrawal reactions and a possible increase in the risk of suicide. Problems experienced by patients when they stop treatments are often quite difficult to assess because they could possibly be related to recurrence of the disease. Nevertheless, the potential for SSRIs to produce withdrawal reactions was identified during their development, and when spontaneous reports were received post-marketing it was hardly a new *signal* (see Glossary). There were very large numbers of such reports received, but few were serious and the level of usage of the drugs was high. Over a period of years it became clear that the problem was

occurring much more commonly than initially thought, particularly in users of paroxetine (Seroxat), a fairly short-acting drug. Ultimately, greater care was needed in withdrawing patients more gradually from these drugs. Suggestions have been made that SSRIs are drugs of dependence but most scientists do not accept this because features such as craving and dose-escalation are generally absent. Importantly, it emerged that the nature of some of the more unpleasant symptoms patients experienced – such as 'electric shock' sensations in the head – was being lost in the data processing systems. This was often a result of inadequate coding. Such cases often became 'paraesthesia' (a tingling or prickling sensation), something that hardly conveys how unpleasant such sensations can be. Thus, it was recognised that we needed better ways to capture unusual patient experiences and this gave considerable impetus to allowing patients to report their adverse reactions to the authorities. That approach had been used in the USA and some other countries for many years, but hardly at all in Europe until the early years of the twenty-first century.

The possibility that any drug might increase the risk of an outcome associated with the disease it is being used to treat is invariably difficult to evaluate. Suicidal feelings and actions are relatively common in depressed patients and it is not surprising when they occur in a patient who has recently started treatment. Nevertheless, around 1990, a clinician in the USA saw several patients treated with fluoxetine (Prozac) who had suicidal thoughts and he published a case series suggesting that the drug might be responsible. This prompted a review of all the clinical trial data for the drug which did not support the proposition, but it was never completely refuted.

Over the years more clinical trial data accumulated for various drugs in the class and studies were conducted in children and adolescents, the latter being a high-risk group for suicide. Even in severely depressed patients, completed suicides are rare in clinical trials and therefore the evidence available relates mostly to attempted suicide (also uncommon in trials) and thoughts of suicide measured on various scales. Trials of paroxetine in children produced adverse findings – an increased risk of suicidal behaviour and hostility – which for some time were known only to the manufacturer. When the regulatory authorities eventually received the data, they issued warnings against the use of this drug in children. The company was investigated and prosecution considered, but the law was found to be insufficiently clear that the company was obliged to submit concerning clinical trial

data immediately to the authorities when a trial was being conducted outside the authorised indication. Again, this issue pointed to the potential importance of clinical trials in the assessment of safety and raised concern about a lack of transparency with clinical trial data. Considerable steps have since been taken towards making clinical trial data publicly available through mechanisms other than publication in the literature which is slow and selective. There is still some uncertainty as to whether SSRIs directly increase the risk of suicide in adults, but there is general agreement that the early phase of treatment is a high-risk period and that careful monitoring of patients is required.

COX-2 Inhibitors

What have been the most prominent drug safety issues of the twenty-first century? One of the most important has been the increased risk of cardiovascular outcomes associated with selective COX-2 inhibitors (coxibs). This possibility was first uncovered in basic research but not followed through. The first clinical indication of a problem came from the VIGOR trial which was published in 2000. At the time, two drugs in the class – rofecoxib and celecoxib – had just been authorised. The VIGOR study was a randomised comparison of rofecoxib with naproxen (a standard NSAID), designed to establish whether there was a difference in the rates of serious gastrointestinal adverse effects (e.g. bleeding) of these two drugs. In that respect, rofecoxib was clearly preferable and the trial results led to rapid uptake of coxibs, on the basis that they were supposedly safer. However, the VIGOR study also found an important difference in the rate of cardiovascular events such as myocardial infarction which were five-fold more common in patients taking rofecoxib than with naproxen. This information was included in the original publication but lacked prominence and was presented as a fivefold reduction with naproxen rather than an increase with rofecoxib. The paper was subsequently the subject of extensive criticism.

Over the years there have been suggestions that standard NSAIDs reduce the risk of cardiovascular outcomes (as aspirin does) and a potential explanation for the finding in the VIGOR study put forward was that naproxen is cardioprotective whereas rofecoxib is not.

Ultimately, it took a large clinical trial comparing rofecoxib with placebo to establish beyond any doubt that this was an adverse effect of rofecoxib (rather than a lack of benefit) and the findings of that study led to the drug being withdrawn from the market in late 2004. This event sent shockwaves around the world leading people to question why such a trial had not been carried out much earlier, before millions of people had used the drug. It also left a big cloud hanging over the remaining drugs in the class; some were later withdrawn but some remain on the market. At one stage, the proposition that coxibs might be given to people at high risk of gastrointestinal bleeding and low risk of cardiovascular disease seemed reasonable, but it has since been discovered that, to a considerable extent, risk factors for these problems overlap in individual patients. To make matters even more complicated, it appears that some standard NSAIDs also increase the risk of cardiovascular events and the ability to assess the relative safety of drugs in the same class remains rather limited. This issue was a major driver of the considerable increase in post-marketing regulation, and focus on post-authorisation safety studies, which came to fruition in Europe in 2012 and is discussed in Chapter 5.

Two other notable drug safety issues of recent years are also important: the differing hazards associated with three glitazone drugs used to treat type 2 diabetes, and the association of pandemic flu vaccine with narcolepsy.

Glitazones

Troglitazone was the first of the three glitazones to be marketed in the late 1990s. These drugs are oral hypoglycaemics which work by activating peroxisome proliferator-activated receptors (PPARs). Soon after marketing, a considerable number of case reports of severe hepatoxicity with associated liver failure were received and the drug was rapidly withdrawn in Europe. At the time, the next in class, rosiglitazone, was in the later stages of development and regulatory authorities therefore considered very carefully whether it might also be associated with a similar level of hepatotoxicity. They concluded (and were eventually proven right) that it was probably different in this regard. Rosiglitazone became a very widely used drug in the first few years of the twenty-first century and it was soon followed by

pioglitazone. Studies of cardiovascular risk were performed with these drugs in the expectation that an effective anti-diabetic drug would reduce the risk. However, when these studies were brought together in a meta-analysis (which combines the results of multiple studies; see Chapter 3) published in 2007, the opposite appeared to be the case for rosiglitazone. This concern was the subject of considerable debate and further study but, within a couple of years, it led to the demise of the drug. Much of that debate was about its relative cardiovascular safety compared with pioglitazone.

Given that the benefits of the two drugs appeared broadly equal, and that most of the available evidence suggested that pioglitazone was safer, it was allowed to remain on the market. Interestingly, pioglitazone also appears to be associated with its own particular important safety problem, bladder cancer. This was originally identified in animal studies and in the last few years has been confirmed in humans. However, the level of risk is quite low, and considered manageable and to be outweighed by the benefits of the drug in effectively treating type 2 diabetes. The safety issues experienced with glitazones are remarkable. Despite the apparent similarities of the drugs, they appear to be associated with different important adverse effects affecting different organs.

Pandemrix

In 2009, there was an influenza pandemic reflecting the global spread of a new strain of human flu H1N1 virus. In many countries, mass vaccinations were undertaken with Pandemrix. In Finland and Sweden, case reports of a vaccinated children and adolescents developing narcolepsy – a brain disorder causing episodes of sudden onset of sleep at inappropriate times – were soon received. Formal studies have since confirmed this as a rare risk but only in young people, and the mechanism for this effect remains unclear. The effect has therefore been recognised in the product information and it has been recommended that this vaccine should no longer be used in patients under 20 years unless no other suitable vaccine is available. This example illustrates the effectiveness of the intensive ADR monitoring systems which were put in place to cover mass vaccinations during a pandemic in picking up an unusual and important adverse reaction.

Main Lessons Learned from Recent Major Safety Issues

- The need for vigorous follow-up of safety signals with appropriate studies.
- That drugs within the same class can have markedly different risks and the need for studies that address this possibility.
- The difficulty of assessing outcomes that are related to the drug indication.
- The potential value of randomized controlled clinical trials in assessing safety and the importance of the choice of comparator drug(s).
- Important safety data can emerge from clinical trials performed for other purposes.
- The need for greater transparency and increased availability of clinical trial data.
- The potential importance to safety of off-label use (e.g. in children).
- There is a need to evaluate medicines adequately in children and adolescents.
- The need for greater patient involvement in drug safety.
- The complexity of evaluating and communicating multiple risks (and benefits).
- The need for regulatory authorities to have sufficient powers to ensure that companies have adequate pharmacovigilance systems and proactively investigate potential risks with marketed products.

Conclusions

The issues discussed are necessarily selective and our discussion of them is broad. The intention is primarily to illustrate that pharmacovigilance experienced many teething problems in its early years and that most of its developments have been in response to quite specific lessons learned from landmark safety issues. In this chapter, we have tried to illustrate what pharmacovigilance is and, by describing important examples, how it has progressed over a period of more than half a century. Despite that progress, no one should doubt that there is still a long way to go. The current limitations of the discipline and how we might eventually overcome them are considered in Chapter 9.