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Principles of pharmacovigilance

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Abstract

After a short historical survey of adverse drug reactions, this paper summarises the current organisation of pharmacovigilance in Europe, with its principles of reporting, assessing, understanding and preventing the adverse effects of medications. Issues related to contrast media are included to exemplify the principles. Respective responsibilities of the various stakeholders are described: the European Agency, EEC member states, manufacturers and, last but not least, health professionals.

The paper then focuses more specifically on spontaneous reporting, with the limits and biases that result from inevitable under-reporting. In the event of a new disease likely to be ascribed to a drug or a class of drugs, a conceptual framework for investigation is proposed, articulated on the criteria of:

- credibility
- causation
- re-assessment of benefit:risk ratio
- course of action.

In spite of its awkward methodological limitations, the author concludes that the principle of spontaneous reporting may be appropriate for investigating a new pathological entity such as nephrogenic systemic fibrosis (NSF).

A brief historical survey

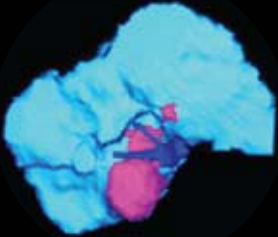
Physicians and, perhaps more particularly, governments have long been more concerned with the safety of drugs than with their efficacy. Hippocrates' principle of 'first not to harm' is widely remembered and it would be easy to find in the historical textbooks on pharmacy a number of regulatory measures taken even in ancient times in the hope of protecting people against iatrogenic hazards due to chemicals. Indeed, whatever doubts that could reasonably hang over the genuine benefits of medicines in antiquity, their toxic nature was clear for many: in ancient Greek, the word *pharmakon* referred not only to medicines and drugs but also to poisons.

Over and above the intrinsic toxicity of substances given to patients, the risks inherent in their preparation have received attention. To some extent, it has been easier for governments to attend to the quality of medicines (and to take appropriate regulations about their manufacture, conservation and supply) than to investigate directly the safety of their (supposedly) 'active' principles.


In fact, the story that initiated the modern organisation of drug monitoring occurred precisely at the encounter between a drug that was genuinely active – a sheer 'miracle' at the time – and a pitiful mistake in the manufacturing process. After German researchers discovered the antibacterial properties of the dye Prontosil in 1932 and, soon afterwards their French colleagues identified sulphanilamide as the active portion of the product, a new era began in the treatment of infectious diseases. At the end of 1937, a US company financed a massive advertising campaign to launch the 'Elixir of Sulfanilamide' – whose main defect was its formulation in a solvent containing 72% diethylene glycol.¹ The death toll was over 100 and many of the victims were children.

This health disaster led to important changes in the US law and, as early as 1938, the Federal Food, Drug and Cosmetic Act was passed. This required a certain amount of toxicological testing for drugs. According to the same law, the Food and Drug Administration (created in 1927 under the initial name of Food, Drug, and Insecticide Administration and shortened to FDA 3 years later) was given the power of seizing or withdrawing from the market products that proved to be toxic. However, it was not until 1962 before the FDA also insisted that drugs should be effective *before* their introduction to the market.

Among other safety incidents that impacted significantly on the organisation of pharmacovigilance, the most important are probably the thalidomide disaster (1959–61)^{2,3} and the practolol story (1974–76).^{4,5} The former is too well known to require thorough repetition but it may be useful to



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recall that, besides the brutal recognition of a fact to which little attention had been paid until then – namely that chemicals might have a toxic potential in the development of the human foetus – in the UK it also resulted in the passing of the Medicines Act (1968). This embraced all aspects of the control of medicines regarding safety, quality and efficacy. Directive 65/65/CE – the first European Directive on pharmaceutical products – was also a reaction to this incident.

In contrast with the above-mentioned 'Elixir of Sulfanilamide' story, which really concerned a 'miracle' drug, the thalidomide tragedy strikes us by its horrific contrast between the fairly trivial expected benefit (relief of nausea/vomiting in early pregnancy) and the atrocity of its safety consequences (phocomelia – i.e. defect of long bones in the limbs – in babies exposed *in utero*). This introduces us to the pivotal issue of the benefit:risk ratio.

The story of practolol is less well known as the drug, a recent chemical entity from ICI, was not then registered in a number of countries outside the UK. Essentially, this beta-blocker induced an 'oculo-muco-cutaneous syndrome' under the form of a fibrous transformation of mucosal tissues, resulting in particular in corneal perforations with subsequent blindness and, even worse, in potentially fatal plastic peritonitis. Yet the significant feature of this situation for the history of drug monitoring was that practolol – the first cardioselective beta-blocker – was developed and advertised as a marked improvement in drug safety, ironically exemplifying that drug monitoring is, *par excellence*, the field of *unexpected* events.

Together, these introductory stories summarise a large part of the historical developments in drug monitoring. For example, the need for a strong guarantee in the process of manufacturing is unfortunately not an archaic concern in a time where counterfeiting in medicines has become a major commercial and regulatory issue. Likewise, the question of a disproportionate benefit:risk ratio for

a new chemical entity regularly fuels controversies in modern pharmacy.^{6,7} Again, the recent Vioxx story illustrates that the risk of hidden toxicity is still present for any drug first promoted as an advance in patient safety.⁸

The last prototype example in the history of drug safety is probably that of benoxaprofen,⁹⁻¹² a new anti-inflammatory drug whose sales exploded as soon as it was introduced on the market, in the early 1980s. Within a few months, dozens of patients died of liver failure as a result of insufficient warning about a marked reduction in hepatic clearance of the product in the elderly. Although the cause of this 'unexpected' toxicity was perfectly known and, most probably, was quite easy to manage with appropriate recommendations for prescribing, the manufacturer chose a blunt withdrawal of the drug. This example highlights the possible threat hanging over every potential blockbuster as a consequence of a *scale change in exposure*: a toxicity unnoticed (if not undetectable) in the small populations exposed to a new chemical entity during its development may quickly become a major health problem if its promotion is too successful.

Responsibilities of the various stakeholders in pharmacovigilance

Although one may wonder whether the distinction has any relevance, modern regulations and procedures have consistently distinguished between the assessment of drug safety before the marketing authorisation and the post-marketing monitoring of drugs. The latter is usually referred to as 'pharmacovigilance' (a Greek-rooted neologism of dubious value – it means exactly the same as the term 'drug monitoring').

The respective responsibilities of the various stakeholders in pharmacovigilance have been defined by a number of texts, in particular Regulation (EC) No 726/2004 and Directive 2001/83/EC as amended by Directive 2004/27/EC.

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In order to ensure the adoption of appropriate regulatory decisions regarding medicinal products within the European Community, the member states must take all appropriate measures to encourage health professionals to report suspected adverse reactions to the competent authorities. They operate a pharmacovigilance system to collect and assess information likely to impact the benefit:risk ratio of drugs, such as adverse reactions, misuse or abuse. In collaboration with member states and the European Commission, the central agency (EMA) runs a data-processing network to facilitate the exchange of information and to allow all competent authorities to share the information at the same time.

The marketing authorisation holder has the duty of continuously ensuring post-marketing surveillance of its products and must have an appropriately qualified person at his disposal. The holder must record, report and keep a database of all suspected adverse reactions brought to his attention either directly (by the reporting of a health professional) or indirectly (e.g. by the medical literature). The basis for reporting may be:

- *Expedited* (i.e. within 15 days from receipt) for those reactions likely to be most significant (by and large, those which are serious or unexpected)
- Or *periodic*, in the form of a Periodic Safety Update Report (PSUR), 6-monthly for the first 2 years after authorisation and then yearly until the quinquennial renewal of the marketing authorisation. These PSURs must include appropriate information on the exposure, in particular the volume of sales of the medicinal product concerned.

The marketing authorisation holder may also undertake post-authorisation studies, e.g. in order to assess more accurately the safety of its product in varied situations (such as specific sub-populations). Finally, the holder must ensure that any request from the regulatory authorities is answered fully and promptly. A number of guidelines are available for expedited reporting, PSURs and company-sponsored post-authorisation studies.

Due to their financial cost, their expected duration and their logistic burden, safety post-authorisation studies are more the exception than the rule. Therefore, it is clear that the main source of pharmacovigilance data remains spontaneous reporting. This gives a pivotal responsibility to health

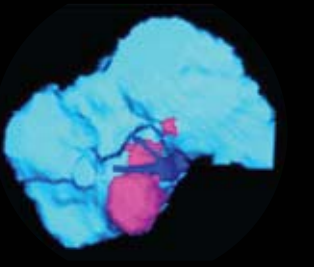
professionals and, more specifically, to physicians and nurses who are often in the best position to witness suspected drug reactions. In the imaging world, radiologists, cardiologists, nuclear medicine physicians and other health professionals using imaging agents have the professional duty of reporting significant reactions of which they may be aware, even if such reactions are already recognised as expected hazards. This is the main way to catch a potential alert signal.

In some countries (such as France), the law may even include a mandatory requirement for health professionals to report serious or unexpected reactions. However, this may be regarded as a provision of dubious relevance, as it is difficult to conceive any form of sanction in the case of non-reporting. The report should be made to the 'Centre Régional de Pharmacovigilance' in France and to similar official collecting bodies in other European countries. It is useful to inform the manufacturer at the same time.

Under-reporting

Under-reporting is the main limitation of pharmacovigilance based upon spontaneous reporting as illustrated by the following story: during the 1960s, it was estimated in the UK that nearly 3000 young asthmatics had died from excessive use of pressurised aerosols containing bronchodilating agents, whereas only six doctors in that country had reported a potential association between overuse of aerosols and sudden death.¹³ Even today it is estimated that, at best, the rate of reporting does not exceed one report out of 10 actual drug reactions and may be far below this figure (< 1/100) in a number of instances.

Reasons for under-reporting are many and include overwork, inadvertence or negligence, lack of recognition of the iatrogenic nature of a disease (particularly if there is a long time interval between drug intake and the reaction), reluctance to report suspicions without a definite proof of cause, and fear of litigation. Inasmuch as the absolute number of reports corresponds only to a small minority of the actual cases, the frequencies of adverse events calculated on the basis of spontaneous reporting are often open to massive biases: for example, an individual physician interested in (or obsessed by) a particular reaction can easily make a significant difference to the data generated. Possibly induced by vested interests or manipulated by pharmaceutical promotion, such biases may account for selective reporting of reactions related to one product even if



it corresponds to a class effect, thereby contributing to a distorted perception of a higher occurrence for a specific product in the class.

The causal assessment of a drug-related reaction relies, above all, on an *exclusion* diagnosis (the disease under consideration was not caused by a non-drug 'natural' aetiology such as an infection, a vascular or an auto-immune disease, etc.). It is of paramount importance to understand that the performance of spontaneous reporting in recognising actual iatrogenic complications decreases in proportion to the 'background noise' – that is, the frequency of similar clinical pictures *unrelated* to the drug under consideration. Markedly reduced as it is by under-reporting, the observed frequency of a drug-induced disease may be quite easily obscured in the expected frequency of the same disease when it is not caused by the medicinal product. This is generally the case with complications such as hepatitis, bleeding, stroke, phlebitis, renal failure and depression as their expected number independently of any drug exposure is already high, particularly in some subpopulations such as geriatric patients. As a typical example, autism, the reported hazard of MMR vaccines is not unusual in the general, non-vaccinated paediatric population.¹⁴

So, inasmuch as under-reporting generally conceals the actual fluctuations of frequency in an iatrogenic disease, the only situation where spontaneous reporting may quickly have a clear significance in terms of drug-induced causation is when the baseline incidence of the reported disease is extremely low. This was the case with the above-mentioned phocomelias after thalidomide or with vaginal adenocarcinomas in young females after diethylstilbestrol.

Investigation of an unexpected drug safety problem

In its principle of continuous surveillance over the whole life of a medicinal product, pharmacovigilance obviously extends beyond the scope of *unexpected* reactions. For example, there is probably much room for improvement in the assessment and practical management of well recognised drug hazards such as those related to iodinated contrast media. Although these adverse reactions are comprehensively discussed in pharmacological textbooks, reporting by practitioners (radiologists, in particular) is still topical and may contribute, for example, to a better recognition of potential risk factors or to optimisation of their medical management.

This notwithstanding, early recognition of as yet unrecognised drug reaction is obviously the major justification for continuous post-marketing surveillance.

Thus, when a new disease is reported as potentially ascribable to a drug or a class of drugs, what should be the intellectual framework to interpret any available data? Essentially, analysis of the reporting input will rest on the criteria of:

- credibility
- causation
- re-assessment of the benefit:risk ratio
- course of action.

Credibility

New as it seems, the new disease must be precisely characterised. It must also comply with a minimum of medical or pharmacological consistency: a cancer, for example, cannot occur within a few days after drug exposure. Further, the reporters (as well as any opinion leaders commenting on the situation) must also have at least a minimum of credibility and must not be suspected of vested interests in ascribing specific toxicities to the competing drugs of their sponsors.

Causality

Regarding causation, Hill's criteria¹⁵ are classical and may be found in any textbook of epidemiology. However, an important issue in pharmacovigilance is often that, although such criteria may not be fulfilled, clinical or regulatory decisions must be taken in practice without undue delay.

In pharmacy, an important issue is whether a new hazard is ascribable to a specific drug or to a pharmacological/therapeutic class. Likewise, when a new pathological entity is described, another question is that of the confounding factors: are there any changes in environment that could account for or contribute to this new disease? For example, one may wonder whether a condition such as nephrogenic systemic fibrosis (NSF) may be influenced by any kind of recent change in the exposure of dialysed patients. This condition, first diagnosed in 1997,¹⁶ occurs in patients with advanced renal disease, is mainly characterised by skin thickening (and far more rarely, may involve lungs, liver, heart or muscles) and may be associated with previous use of gadolinium-containing magnetic resonance imaging (MRI) contrast agents.¹⁷

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Likewise, the question of biological plausibility is a tricky one: the history of therapeutics is full of products which proved to be devoid of the benefits that *should have* existed on the basis of theoretical arguments of pharmacological plausibility, whereas other drugs were withdrawn from the market because of their indubitable but pharmacologically unexplained toxicity. To sum up, the message is quite clear: it is not *because* it appears biologically plausible that a drug hazard exists, and, conversely, it is not *because* it is unexplainable on a pathophysiological basis that it cannot exist.

Benefit:risk ratio

The re-assessment of the benefit:risk ratio of a drug includes an evaluation of the severity and the irreversibility/lethality of its hazards, as well as the definition of the populations at risk and of any therapeutic alternatives if they exist. Actually, a severe and unexpected toxicity may prove to be acceptable if there is no alternative in a serious indication.

Course of action

Finally, the thorough assessment of a new iatrogenic hazard presupposes that each of the concerned stakeholders complied with its duties. Namely, the health professional reported their suspicions, the manufacturer(s) transmitted without delay and with all due details the cases that were brought to their attention. Meanwhile the regulatory authorities took all appropriate measures and elaborated relevant recommendations to reinforce patient safety and ensure that the benefit:risk ratio remained medically and ethically acceptable.

Conclusion

The preceding conceptual framework is certainly appropriate to the assessment of a new entity such as the cases of nephrogenic systemic fibrosis (NSF) recently associated with gadolinium-based contrast agents for MRI.^{16,17} Of paramount relevance, in particular, is the need to characterise as precisely as possible the clinical, para-clinical and laboratory features related to this new entity, the potential risk factors (Renal failure? Other pathological co-factors? Medicinal treatments?), as well as the identification of products likely to be involved.

In spite of the complexity of the issue, it is important to emphasize that the rarity as well as the novelty of the disease fulfil the criteria that maximise the value of spontaneous reporting in pharmacovigilance, since the 'background noise' for such a clinical entity is near zero. This means that every spontaneous report, so long as it is precisely documented, is likely to represent a significant contribution to the investigation, the recognition and the practical management of this intriguing new disease.

Conflict of interest: Dr Girard works as an independent consultant for the pharmaceutical industry, including GE Healthcare.

Key Learning

- From its inception through to the present day, the history of therapeutics has been marked by *unexpected* reactions to medicines, some of them accounting for health disasters
- Regulatory authorities, manufacturers and health professionals are the main stakeholders in the organisation of post-marketing surveillance of drugs (pharmacovigilance)
- Although much pharmacovigilance relies on spontaneous reporting from health professionals, the system may be skewed by under-reporting
- When a new disease emerges as potentially ascribable to a drug or a class of drugs, its investigation should meet the criteria of credibility, causality, benefit:risk assessment, and course of action
- For hazards such as nephrogenic systemic fibrosis (NSF), whose spontaneous frequency is negligible, spontaneous reporting may be an efficient tool of investigation

References

1. Gelling E, Cannon P. Pathological effects of Elixir of Sulfanilamide (diethylene glycol) poisoning. *JAMA* 1938;**111**:919–96.
2. McBride W. Thalidomide and congenital abnormalities. *Lancet* 1961;iii:1358.
3. von Lenz W. Die Thalidomide embryopathy. *Dtsch Med Wochenschr* 1961;**86**:2555.
4. Girard M. Testing the methods of assessment for adverse drug reactions. *Adverse Drug React Acute Poisoning Rev* 1984;**4**:237–42.
5. Nicholls JT. Adverse effects of proctolol. *Ann Clin Res* 1976;**8**:229–31.
6. Moynihan R, Cassels A. *Selling sickness. How drug companies are turning us all into patients*. Crows Nest, Australia: Allen & Unwin, 2005.
7. Moynihan R, Smith R. Too much medicine? *BMJ* 2002;**324**:859–60.
8. Graham DJ. COX-2 inhibitors, other NSAIDs, and cardiovascular risk: the seduction of common sense. *JAMA* 2006;**296**:1653–6.
9. Lessons from the benoxaprofen affair. *Lancet* 1982;**2**:529–30.
10. Lessons from benoxaprofen. *Lancet* 1982;**2**:667.
11. Brooks PM, Birkett D. Release of new drugs. The lessons of benoxaprofen. *Med J Aust* 1983;**1**:251–2.
12. Naude SP, Anderson R. Benoxaprofen – could the side-effects have been prevented? *S Afr Med J* 1982;**62**:427.
13. Inman WHW. Detection and investigation of adverse drug reactions. In: Davies DM, ed. *Textbook of adverse drug reactions*, 3rd edition. Oxford, UK: Oxford University Press, 1989: pp. 49–62.
14. Taylor B. Vaccines and the changing epidemiology of autism. *Child Care Health Dev* 2006;**32**:511–9.
15. Hill AB. The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine* 1965;**58**:295–300.
16. Kuo PH, Kanal E, Abu-Alfa AK, et al. Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. *Radiology* 2007;**242**:647–9.
17. Grobner T, Prischl FC. Gadolinium and nephrogenic systemic fibrosis. *Kidney Int* 2007;**72**:260–4. Epub 2007 May 16.