

Introduction

Dr R G Hughes - Consultant in Pharmaceutical Development

Although the cardiotoxicity of drugs (either for cardiac or non-cardiac disease) has long been recognised as a potential problem in drug development, it has only relatively recently come to the fore as a major commercial problem for the drug industry. It is thus extremely timely that my collaborators have put together a detailed report on the problem/ phenomenon from a variety of perspectives.

To set the scene on this topic and to provide a commercial background, we have a chapter (written by Jo Pisani and Yann Bonduelle of PwC) on the commercial implications of cardiac toxicity. This chapter examines the size and nature of the challenge posed by cardiotoxicity to the pharmaceutical industry in recent years, the potential future challenge and how companies can manage the risks. Although there is a regrettably increasing list of drugs that have been withdrawn for reasons of cardiotoxicity, in many cases it has proved difficult to identify the exact agent responsible for a cardiotoxic event, and there is only a limited number of good commercial case studies available from which to draw conclusions.

In the last thirty years as many as twenty major drugs (i.e. actual or potential class leaders) have been associated with cardiotoxicity. These drugs have spanned more than twelve drug classes in as many disease areas. To date it appears that the four classes most associated with cardiotoxicity are the COX-2 inhibitors, anthracyclines, fluoroquinolone antibiotics and, more recently, some targeted cancer therapies. In the last thirty years, cardiotoxicity has been the reason for 28 per cent of all drugs withdrawn in the US. A safety signal may only appear after several tens of thousands, or even millions, of patients have been treated, and for this reason it is almost impossible to detect rarer or less severe cardiotoxic adverse events until the drug is on the market and widely prescribed.

The majority of products withdrawn owing to cardiotoxicity have been at a fairly advanced stage in their lifecycles, at an average of seven years from launch. Consequently, the average annual sales of these products have represented a significant proportion of total company sales and value. Once a potential cardiotoxicity signal has been detected, regulators and companies are quick to act, resulting in one of three outcomes: termination of the drug during development; restriction of product use following detection of cardiotoxicity during large-scale use of the product, resulting in labelling changes; or a 'black-box' warning, or voluntary or requested withdrawal of the product from the market following detection of CT during large scale use of product. Each of these actions has consequences for the company, shareholders, patients and physicians and these are discussed in some detail in this chapter.

It is easy to think of the heart as merely a pump for circulating blood around the body, however it is in reality a very complex system whose details are as yet not fully understood although great strides have been made in recent years in achieving the level of understanding that we have today. The heart is both a mechanical and electrical device. Its workings can be recorded by a variety of techniques from ultrasound to electrocardiology and these techniques are used to evaluate the toxicity of drugs in preclinical development (*in vitro and in vivo*) and in early stage clinical development.

Turning to the more technical and medical aspects of the problem of cardiac toxicity of drugs, the next four chapters, written by Professor Derek Terrar - Professor of Cardiac Electrophysiology, University of Oxford discuss successively:

- The pharmacology of the heart
 - what the key pharmacologic processes are including drug action and the heart
 - Ion channels and what they are and do
 - Which enzymes and other proteins are important?
 - Which proteins are involved in the contractile process
- The electrical activity in the heart
 - Description of the important electrical processes
 - Electrogenic transporters and their influence on membrane potential.
 - Detailed models of electrical activity in ventricular myocytes
 - Genes associated with ion channels
 - Description of an electrocardiogram
- Mechanisms of Cardiac Toxicity
 - QT interval prolongation
 - QT interval shortening
 - Torsade des Pointes
 - Short and long term functional changes
 - Gene related adverse events
- Preclinical determination of Cardiac Toxicity
 - *In Vitro*
 - hERG testing
 - Purkinje Fibres
 - Myocytes (action potentials and currents)
 - Papillary muscles

- Langendorf Hearts
 - Cardiac Wedge
- In each case discussing the advantages and disadvantages of each technique

- *In vivo* telemetry

These four chapters give the reader a thorough understanding of what is going on in the normal heart and the preclinical techniques by which drug induced abnormalities can be detected at an early stage.

If drugs are essentially “clean” at the preclinical stage or the potential risk to patients can be assessed to be outweighed by the potential benefit (e.g. with drugs for life threatening diseases such as cancer) then they can be tested in healthy volunteers. Increasingly cardiac side effects are being assessed in first administration to man studies and these may indicate that a thorough study of their effects on the heart is necessary. The clinical trial design (both early and later phase) with their techniques and procedures are discussed in detail in Chapter 6 by Daniel Goodman (Entelligent Solutions, Inc) and Eileen Daniel (Reliance Clinical Research Services). The methods of data collection are discussed as are their interpretation.

All the activities in the preclinical and clinical phases are of course subject to eventual regulatory review. Regulation has become considerably stricter of late as discussed in Chapter 7 by Dr Tom Donnelly of Reliance. He notes that, thankfully, the regulatory requirements have become harmonised to a considerable degree and that the ICH recommendations and guidelines have been adopted into the regulations of most major jurisdictions.

But the story of cardiac toxicity is not over yet! We expect novel techniques and further challenges that are discussed in Chapter 8. Finally we hope that the reading list and references, the glossary and list of web sites will be useful to the reader.

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