Editorial

Lessons from Contaminated Heparin

Most researchers and academics in drug safety focus their work on the toxicity and side-effect profiles of pharmacologically active agents. As a professional group, we have become experts at screening drug candidates for potential to cause harm to biological systems or potential to interact adversely with other therapeutic agents. We are vigilant in documenting adverse events through all phases of clinical trials and post-marketing. We constantly refine our screening techniques, making use of the latest available technologies. Consequently, in many fields of medicine the newer drugs have significantly more benign adverse-effect profiles than their predecessors. The public expects safer drugs and new research is delivering them.

Nevertheless, maintaining drug safety continues to be a difficult challenge. Discussions about drug safety with our colleagues in the regulatory authorities suggest that most of their time is spent not dealing with issues of drug toxicity but is instead spent dealing with issues of negligence and error. These are issues that we, as researchers and clinicians, rarely consider.

From reports to US health authorities in January 2008, one of the most serious recent challenges for drug safety was recognised when some patients undergoing dialysis were found to have acute hypersensitivity reactions, subsequently associated with the contamination of heparin-containing products with oversulfated chondroitin sulphate (OSCS), an impurity that is structurally similar to heparin [1]. Clusters of patients had been having such reactions from November 2007. The symptoms included, lowered blood pressure, facial swelling, tachycardia, urticaria and nausea. By April 2008, 81 deaths associated with contaminated heparin had been reported. Adverse effects of OSCS-contaminated heparin have been demonstrated in rodent and swine models, confirming a reduction in diastolic pressure with administration and that the effect is dependant both on dose and route of administration [2]. Contaminated heparin products have been found in Australia, Canada, China, Denmark, France, Germany, Italy, Japan, The Netherlands, New Zealand and the United States.

The source of the contamination was traced to a manufacturing facility in Changzhou, China, which was inspected by investigators from the US Food and Drug Administration in February 2008. Many inadequacies were reported with the facility itself, as well with suppliers of crude materials to the facility [3]. It is still unclear whether the contamination was accidental or due to replacing the correct raw materials with a cheaper substitute.

The impact of the contaminated heparin problem continued throughout 2008. As late as May, new recall notices were being issued for products, including heparin-coated thoracic drainage catheters and some devices used in cardiac surgery.

The example of heparin contamination highlights numerous problems for drug safety. The increasingly global nature of the pharmaceutical industry means that errors can be on a larger scale, more difficult to regulate and harder to track to their source. Industry purchases from networks of manufacturers, each of which has a further network of corporations and suppliers. Each supplier and manufacturer has to comply with its own local laws and regulations as well those of the country where its products are used. Then there are language and cultural differences to overcome. This can be a difficult challenge, even for people with the best of intentions. Industries do not exist for altruistic reasons of helping the sick. They are there to make a profit and that brings strong pressures to minimise costs. However, most pharmaceutical companies recognise that it is in their own best interests to comply with safety standards. If they breach standards, not only do they risk expensive legal process but they also lose credibility, which means that they lose business. The manufacturers of contaminated heparin clearly breached regulations.

While traditional toxicology and safety monitoring will continue to be core research activities for those interested in drug safety, we should always be prepared to look beyond our traditional horizons. A potential for error and negligence exists which can compromise drug safety throughout the manufacturing, distribution and storage process. Increasing globalisation has heightened the challenge of providing safe drugs. Let us hope that contaminated heparin is no more than a consequence of a world adjusting to new trading relationships and not a sign of things to come.

REFERENCES

[1] Kishimoto TK, Viswanathan K, Ganguly T, *et al*. Contaminated heparin associated with adverse clinical events and activation of the contact system. N Engl J Med 2008; 358**:** 2457-67.
[2] Kakkar AK, Bonnefoi M. Contaminated heparin. N Engl J Med 2008; 359: 1292-3.
[3] Friedman RL. Warning letter from the Centre for Drug Evaluation and Research (http://www.fda.gov/cder/warn/2008/320-08-01.pdf). Food Drug Admin 2008 [Accessed 25.10.08].

Seetal Dodd
(*Co-Editor-in-Chief*)
Department of Clinical and Biomedical Sciences
University of Melbourne
Melbourne
Australia
E-mail: SEETALD@BarwonHealth.org.au

Frank M.C. Besag
(*Co-Editor-in-Chief*)
Specialist Medical Department
Twinwoods Health Resource Centre
Milton Road
Bedfordshire, MK41 6AT
UK
E-mail: Frank.Besag@blpt.nhs.uk