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Poisons Centres and the Reporting of Adverse Drug Events

The Case for Further Development

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Last year, we celebrated the 20th anniversary of *Drug Safety* and recognised its importance as the official journal of the International Society of Pharmacovigilance (ISoP).[1] As the journal starts its 21st year of publication, it is timely to comment on the journal's links with medical toxicology, which was, after all, its original title.

In 1986, we shared Ralph Edwards' enthusiasm for the original remit to cover chemical and drug poisoning, as well as adverse drug reactions (ADRs).[1] However, within 4 years, it was apparent that manuscripts on ADRs were being submitted in far greater numbers than those on toxicology. It was recognised, nevertheless, that the journal was performing an important function in encouraging high-quality reviews of medical/clinical toxicology. Therefore, over the years, *Drug Safety* has published many important toxicology reviews, discussion papers and original research papers covering not only drug toxicity but also toxicity caused by chemicals and natural toxins.

However, in practice, the work on what are now referred to more correctly as adverse drug events (ADEs) has had a much greater impact than clinical toxicology on both patients and clinicians, with the result that pharmacovigilance has developed more quickly. Furthermore, many commentators, including Buckley and Smith in 1996,[2] have been forced to conclude that the evidence-base for clinical toxicology is weak. A recent systematic review by the Medical and Surgical Subgroup of the NICE (National Institute for Health and Clinical Excellence) Clinical Guideline Development Group on the management of self-harm,[3] of which Glyn Volans was chairman, also found little evidence other than expert opinion or clinical experience to support a number of the strategies for management of poisoning both outside hospital and in the emergency department. However, we are aware that this situation is currently being addressed, and that evidence-based reviews are now being undertaken across the breadth of medical toxicology.

When *Drug Safety* became the official journal of ISoP in December 2005, it might have been thought that its remit would no longer involve poisons centres and clinical toxicologists. However, they continue to make relevant a contribution to the journal.

Poisons centres have had a significant impact on drug safety. For example, evidence accumulated by poisons centre surveillance of the severe effects of dextropropoxyphene/paracetamol (acetaminophen) [coproxamol] overdose was a key influence on the decision to restrict its use, whereas evidence submitted to regulatory authorities that severe effects had not been reported following overdose of ibuprofen was an important consideration in the decision to make this drug more widely available.

Nevertheless, the benefits of interaction between pharmacovigilance and clinical toxicology have yet to be fully realised. We would therefore like to offer our thoughts on the potential to develop ADE reporting by poisons centres.

1. Background

Throughout a history spanning >50 years, poisons centres have found that a small but important part of their work has been concerned with ADRs/ADEs. Health professionals (and the public in those countries where poisons centres are advertised to the public), have a high awareness that poisons centres offer 24-hour access to specialists with expertise in recognition and treatment of ADEs, information resources and to clinical and laboratory facilities. Both patients[4] and physicians[5] recognise the value of being able to obtain information by telephone about adverse reactions resulting from medication use.

For pharmacovigilance, the value of poisons centres lies in their potential as a source of new information. The patterns of ADE reporting to poisons centres have been found to differ from reporting to pharmacovigilance centres and to detect problems that would not otherwise be reported.[6] Also, because poisons centres are usually contacted by health professionals soon after the event, they have opportunities to request complete case histories and key information that may be lacking from spontaneous case reports. For example, from data on the circumstances of events, they may be able to identify and draw attention to causes of medication error or unintentional poisoning, and recommend changes to medications, their packaging or the accompanying prescribing information in order to improve drug safety.

Poisons centres have always recognised the importance of generating evidence to influence both the management of acute poisoning and the implementation of measures to prevent or minimise ill-health due to chemicals, including drugs.

Toxicovigilance and pharmacovigilance have similar objectives and scope (table I). In practice, toxicovigilance is achieved through a range of activities, undertaken mainly, although not exclusively, by poisons centres. Clinical adverse events and hazards can be identified by retrospective analysis of, detailed case reports or poisons centre databases to identify new patterns in cases of poisoning,[7] or by prospective observational studies designed to answer specific questions, for example, to identify hazards associated with products and their use that can result in recommendations to improve drug safety.[8,9]

Table I. Scope of toxicovigilance and pharmacovigilance

Toxicovigilance
WHO definition: the active process of identifying and evaluating toxic risks in a community in order to reduce or remove them[10]
Several authors have expanded this definition to clarify that it encompasses exposures to the range of household, occupational or environmental chemicals and products, and to show its relationship to pharmacovigilance[11]
Pharmacovigilance
WHO definition: The science and activities related to the detection, assessment, understanding and prevention of adverse reactions or any other drug-related problems[12]

From the 1980s onwards, the role of poisons centres in toxicovigilance has been supported by the International Programme on Chemical Safety (IPCS) particularly through the INTOX project. This international collaboration between poison centres has promoted international standardisation and harmonisation of human data on acute poisoning and developed tools for data collection and reporting (http://www.who.int/ipcs/poisons/intox/en/index.html), with the objective of facilitating multicentre studies across national boundaries. One such tool is the Poisoning Severity Score (PSS), a standardised severity grading of the clinical findings in cases of acute poisoning[13] developed by the INTOX project in collaboration with the European Association of Poisons Centers and Clinical Toxicologists (EAPCCT) and the European Union (EU), an effective joint venture which has ensured wide acceptance of this tool.

These achievements are important for poisons centre collaboration in pharmacovigilance as well as in toxicovigilance; however, despite significant published contribution to the body of evidence on drug safety, there is little evidence that poisons centres are reporting directly to national or international pharmacovigilance centres. In the US, a survey of poisons centres in 1999[14] found that although many centres had published reports of ADEs, there was a low rate of reporting to the US FDA Medwatch spontaneous surveillance programme. Reasons included having no regular routine procedure for reporting to Medwatch, lack of time and inability to determine causality.

The situation in Europe appears very similar. Although several poisons centre workers in Europe have drawn attention to the underutilisation of poisons centres as a source of ADE reports, staff working in pharmacovigilance in Member State regulatory authorities and in the European Medicines Agency reported that they seldom used, or considered using, poisons centres as data sources for signal detection or safety issue assessment in their country.[15]

The practical benefits for a pharmacovigilance centre of close collaboration with a poisons centre were described in the guidelines for pharmacovigilance centres published by the Uppsala Monitoring Centre. The links between pharmacovigilance and toxicovigilance were also discussed and promoted by the IPCS at the WHO Annual Meeting of National Centers participating in the WHO Program for International Drug Monitoring in October 2002,[16] but no progress has been reported to date. On reviewing abstracts from the North American Congress of Clinical Toxicology Annual Meetings in 2005[17] and 2006,[18] and the European Association of Poisons Centres and Clinical Toxicologists XXV International Congress in 2006,[19] we found reports of important ADEs but most gave no clear evidence of links to pharmacovigilance systems. Some of these are included in the list below.

2. Proposal

Our proposal is that pharmacovigilance centres and poisons centres should collaborate to design and promote mechanisms to facilitate and encourage poisons centres to contribute to pharmacovigilance by reporting ADEs to the relevant national centres.

To start the debate we offer the following classification of the cause of ADEs referred to poisons centres. An understanding of the reasons why people report ADEs to poisons centres could thus have implications for both service development and for surveillance as in the examples included.

3. Reasons for Referring Adverse Drug Events to Poisons Centres

1. Service related: enquirers recognise events to be ADEs rather than poisonings, but find poisons centres to be the best source of immediate information and advice. Information obtained as a result of such enquiries have enabled poisons centres to undertake reviews of celecoxib[20] and a new macrolide antibacterial, telithromycin.[21]

2. Diagnostic: clinical findings interpreted by enquirers as indications of overdose are, in fact, ADEs caused by drugs given in the correct dose by the correct route, e.g. dystonic reactions to metoclopramide.

3. ADEs have triggered suicidal behaviour in the form of a drug overdose.[22]

4. ADEs caused by drugs used as antidotes, e.g. acetylcysteine,[11] fomepizole.[12]

5. ADEs caused by drugs in development,[23] unlicensed drugs, e.g. herbal preparations or imported drugs[24] or drugs used off-license.[25] The latter category includes off-license use of medicine in children that is often unavoidable.[26]

6. Errors in prescribing or dispensing to neonates,[27] children[28-31] or adults.[10]

7. Drug abuse/misuse. An ever widening range of chemicals and licensed drugs are abused, with potential for serious interactions with drugs.[32]

4. Conclusions

Like all readers of *Drug Safety*, we have a commitment to the Erice Declaration of the critical role of communication in drug safety.[33] As one response to this, we offer the suggestion, based on the examples listed above, that poisons centres, if properly supported, could do much more to contribute high quality, standardised data to pharmacovigilance networks/systems. Beyond that, poisons centres could also contribute experience and expertise to the development of the WHO World Alliance for Patient Safety,[34] as there are many instances where poisons centres have looked beyond the toxicity of a product to investigate hazards and problems associated with its use and as a result have been able to make recommendations for improving patient safety. We hope, therefore, that this brief commentary will act as a stimulus to further debate and actions, perhaps led by ISoP.

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