

Problems in the pharmacovigilance of herbal medicines in the UK highlighted

Pharmacovigilance and regulation for herbal medicines is just as important as that for orthodox medicines, yet it appears not to be taken as seriously in some quarters. An international meeting was convened in London recently to try to remedy that. **Steven Kayne** reports

In his introduction to the opening session Sir Alasdair Breckenridge, chairman of the Medicines and Healthcare products Regulatory Agency (MHRA), said there were problems in the regulation of herbal medicines in the UK. These included:

- Lack of knowledge about the products being used
- Limited use of yellow card adverse drug reporting scheme — this may represent under-reporting rather than an indicating an absence of adverse reactions
- Variable manufacturing standards (particularly of unlicensed products) due to lack of knowledge, error or deliberate intent
- Ambiguity over nomenclature due to incomplete description of source materials or errors in translation from other languages
- Drug interactions with herbal medicines.

Sir Alasdair said that the MHRA is taking a prominent role in negotiations on the European herbal directive and the creation of Expert Working Groups in specific areas. The new UK Herbal Medicines Advisory Committee and extension of the yellow ADR reporting scheme to patients were important developments in maintaining safety.

Managing ADR risk

Philip Routledge, professor of clinical pharmacology, Wales College of Medicine Cardiff, and chairman of the Herbal Medicines Advisory Committee, deplored the lack of emphasis on pharmacovigilance in professional undergraduate and postgraduate courses. It is a vital responsibility for all involved in prescribing both orthodox and herbal medicines, he said. He emphasised that his comments included pharmacists and nurses whose newly acquired prescribing rights give ADR reporting a wider access. It is important that patients and consumers are prompted during a consultation to reveal if they are using herbal medicines because they are often reluctant to volunteer the informa-



Philip Routledge: pharmacovigilance is a vital responsibility

tion. Pharmacists could also intervene during purchases of herbal over-the-counter products and offer advice when appropriate.

Professor Routledge then considered strategies associated with managing the potential risk of using herbal medicines. He identified four actions:

- **Identification of risk** Professor Routledge told the audience that delayed-action human failures committed long before an emergency state may be a cause of a problem. He cited the *Titanic* as an example of actions having been taken that collectively resulted in the liner's loss.
- **Assessing the risk** Assessing the risk in terms of the chance of loss or injury is important. In any situation there are successive layers of defences, barriers and safeguards in place to repel hazards. But there are also, inevitably, deficiencies or holes in each of these and when circumstances conspire to cause the holes to become bigger and all aligned — as in a block of Swiss cheese — harm can result. The likelihood of this happening is a measure of the risk.
- **Monitoring the risk** Monitoring is not simple observation, said Professor Routledge, but should involve the active collection of data by judicious questioning

of patients and consumers. It is especially useful to know about a suspected side effect that is not mentioned in the patient information leaflet that comes with a medicine or a suspected side effect that has caused problems severe enough to interfere with everyday activities.

- **Managing the risk** If high potential uncertainty surrounding risk estimate or consequences (or risks or hazards currently unknown) more limiting action may need to be taken, reflecting the well established “precautionary principle”, he said.

Communicating effectively is a vital part of risk management. In particular the public should be accepted and involved as a partner, Professor Routledge concluded.

Bruce Hugman, consultant to the World Health Organization Drug Monitoring Centre at Uppsala, Sweden, suggested that communication involved addressing the mindset of both patients and professionals to dispel beliefs that are inconsistent with herbal medication. The former may think herbals are natural and therefore safe; the latter may consider their knowledge of herbals is sufficient or that the use of herbal medicines is inconsistent with modern health care. The messages should be clear, concise and accurate and be delivered by professional associations, health authorities and academic institutions.

The topic of risk was also covered by pharmacist and pharmacologist Peter De Smet, senior researcher at the Scientific Institute Dutch Pharmacists in The Hague, The Netherlands. Dr Smet identified a number of potential “risk modifiers” relating to the product (eg, quality), the patient (eg, health status, level of consumption) and the prescriber (eg, inappropriate preparation and

Welcome by Society's Vice-President

Welcoming delegates to the meeting, Gerald Alexander, Vice-President of the Royal Pharmaceutical Society of Great Britain, said that community pharmacists had an important role in informing patients on safety issues. The profession in Britain had been granted reporter status for adverse drug reactions some years ago and took its responsibility seriously. Colleagues should report suspected problems with herbal medicines as well as orthodox medicines.

Details

The Royal Pharmaceutical Society hosted this international conference entitled **Pharmacovigilance of herbal medicines — current state and future directions** at the Royal College of Obstetrics and Gynaecology London from 26 to 28 April. The conference, believed to be the first dedicated to the topic, attracted over 120 delegates from 30 countries.

prescribing of herbs), and suggested that these are important parameters in pharmacovigilance. Their presence or absence should therefore be systematically evaluated and reported in herbal pharmacovigilance. Epidemiological evaluations require adequate documentation of herbal medicines in health care records, he said.

Licensing

Linda Anderson, a principal assessor at the MHRA, explained that the vast majority of products consisting of herbal active ingredients are exempt from licensing in the UK under Section 12 of the Medicines Act 1968. She explained that the MHRA had no knowledge of the exempt products, their ingredients or their site of manufacture. However, by 2011, most manufactured herbal medicines will have to be registered as traditional medicines or have marketing authorisations.

Dr Anderson said herbal practitioners are not currently required to meet specific standards of training, competence, practice or conduct. An individual, regardless of his or her level of training, can set up a practice, see patients, prescribe and dispense potent herbs. Approximately 300 herbalists are currently registered with voluntary regulatory bodies. But statutory regulation of herbal practitioners is in the pipeline, she said, and will provide enhanced public safety.

Reporting ADRs

June Raine, of the MHRA, told delegates that it was 10 years since the UK yellow card scheme had been widened to encourage reporting of suspected adverse drug reactions in association with herbal medicines, including unlicensed products. Patients are now able to report suspected ADRs direct. Over 2,000 reports had been received in the first six months and it was clear that patient reports were a source of important safety signals.

Dr Raine outlined the new European regulatory framework and its implications for safety and pharmacovigilance of herbal medicines. She said that it contained important new legal provisions to strengthen pharmacovigilance and improve the provision of information to patients in order to provide for high standards of public health protection.

Ralph Edwards, director of the WHO Drug Monitoring Centre at Uppsala, Sweden, reported that the total number of reports in the WHO ADR database had exceeded 3.6 million. Of those, 41,439 had listed a herbal drug as suspected, interacting or concomitant. In 17,112 of these reports, the herbal drug was listed as a suspected or interacting drug. The US was the top reporting country, followed by France and Germany. The UK was fourth with 1,456 reports. The most frequently reported herbs were *Nicotiana tabacum* (1,426), *Ginkgo biloba* (595) and *Hypericum perforatum* (493) and the

most frequent ADRs were pruritus, urticaria and skin rash. There are, he said, three key questions to be answered in designing a robust reporting system:

- Who should report?
- What should be reported?
- How should it be reported?

Professor Edwards concluded that:

- We need to know much more about the safety of herbal and traditional medicines
- We need to educate reporters to get and give maximal, accurate information on what is taken
- Herbal medicines are often complexes of ingredients, and are used for multiple indications
- We need data mining or other sophisticated analysis, as well as experts, to attribute causation accurately

Quality issues

The quality problems associated with herbal manufacturing were discussed by Arnold Vlietinck, of the faculty of pharmaceutical sciences, University of Antwerp, Belgium, who explained that the nature of the herb and the manufacturing procedures both affect the quality of a final product. Herbals are used in the food and cosmetic industries as well as in medicines and the approach to stan-

Advertisement

dards applied in each sector differ widely. In the EU there are clear quality and safety requirements governing the registration of herbal medicinal products as well as guidelines for the collection and storage of source material, he said.

Sven Ascher, of Phytol GmbH, Germany, discussed the presence of mycotoxins in herbal medicinal drugs in his presentation. He explained that mycotoxins are contaminants in a wide variety of natural products. The UN Food and Agriculture Organisation (FAO) estimates contamination of 25 per cent of the world production of foodstuffs and 20 per cent of the EU cereal harvest. There are three main species involved: *Aspergillus* (aflatoxins B₁, B₂, G₁, G₂ and ochratoxin A), *Penicillium* (ochratoxin A and patulin) and *Fusarium* (fumonisins, zearalenon and trichothecenes). Relatively few data were available on herbs that are susceptible to contamination and screening is necessary to identify those herbs that may be involved, he explained. For example, aflatoxins have been detected in many samples of senna fruit, nuxvomica seed, figs, nutmeg, ginger root, cayenne pepper and agnus castus fruit.

Monique Simmonds, of the Royal Botanic Gardens, Kew, described quality assurance procedures for Chinese medicinal products. She said that the Chinese Pharmacopoeia (2005 English edition) is a reference point for identity and quality standards for Chinese herbs. However, species coverage is incomplete and there is mention of standards that are either difficult to locate or are unavailable in the West. Many tests specified do not differentiate substitutes, closely related species, or common adulterants (possibly toxic), she said. There are also differences between cultivated and wild specimens. There is also a significant problem with Chinese over-the-counter medicines. She told dele-

gates that her colleague had travelled extensively in China collecting reference samples and viewing methods of preparing herbs to facilitate accurate identification.

Nomenclature

Mohammed Farah, of the WHO International Drug Monitoring Centre, Uppsala, Sweden, said that it is often unclear which species of plant and part of plant are implicated in an ADR report because of a multiplicity of synonyms and common names and translation errors in the case of Chinese and Ayurvedic herbs. Dr Farah favoured the Anatomical, Therapeutic and Chemical (ATC) classification advocated by De Smet. This gave an exact description of all the necessary information. By way of illustrating the possible diversity, he noted that *Aesculus hippocastanum* had five active ingredients in the plant, 12 in the seed, nine in the flower and 12 in the bark. Products should be accurately labelled so that the exact source could be identified. The ATC system does have some deficiencies when applied to products with widely differing therapeutic uses and for combination products. The absence of an authoritative reference source detailing the exact nomenclature that may be used to describe herbal source material has caused severe difficulties in collating data on toxicity. This has led to the publishing of 'Accepted scientific names of therapeutic plants and their synonyms' — a collaboration between the WHO International Drug Monitoring Centre, Kew Gardens and Uppsala University.

The theme of nomenclature was also taken up by Bob Allkin, information scientist at the Royal Botanic Gardens, Kew. He said that there are many more botanical names than there are species of plant. Existing plants are given new or incomplete names in different parts of the world, and misspelt and mis-

applied names are replicated in the literature. Inaccurate nomenclature compromises the applicability safety data in managing risk. The International Plant Name Index (at www.ipni.org) could be of assistance in obtaining information. It is hoped that international co-operation will result in a total comprehensive reference source in the future, said Mr Allkin.

Interactions

Zhou Shufeng, assistant professor in the department of pharmacy at the National University of Singapore, discussed herb-drug interactions. He said that there are 11,145 species of herbal plants worldwide and 534 species of plants are used in traditional Chinese medicine. Around 30 per cent of Caucasians and 80 per cent of Chinese people use herbs. In many cases they are combined with prescribed drugs, either intentionally or unintentionally. Herb-drug interactions are difficult to characterise, resolve and predict, he said. The situation is made worse because 70 per cent of users do not reveal that they are using herbs to their doctors or pharmacists in Western countries. Dr Shufeng gave examples of interactions between a number of Chinese herbs and orthodox drugs (eg, danggui and danshen both interact with warfarin). Western herbal medicines include St John's wort (interacts with anticoagulants, opiates, oral contraceptives), garlic (interacts with warfarin and chlorpropamide), ginkgo (interacts with trazodone, warfarin and digoxin) and ginseng (interacts with alcohol).

It is important that labeling of herbal medicines specifies the dose and route of administration and gives details of the manufacturer. A statement such as "It is not advisable to take this preparation with..." would also help minimise herb-drug interactions, Dr Shufeng concluded.

Views and problems reported by practitioners

A number of practitioners of the various types of herbal medicines outlined the problems they had been experiencing.

Alex Dodoo, of the National Centre for Pharmacovigilance at the University of Ghana Medical School in Accra, reported many difficulties in collecting information on potential adverse drug reactions resulting from herbal medicines in his country. There, medicines are inadequately labelled and many practitioners are poorly trained. In a survey of 12 healers, 90 per cent of the respondents had safety concerns about allopathic medicines and 75 per cent said herbal medicines had no side effects.

Ally Broughton, of the National Institute of Medical Herbalists, reported that a modified yellow card scheme had been implemented by the NIMH in 1994 as part of a formal pharmacovigilance reporting system for herbal medicines prescribed by herbal practitioners. A total of 42 yellow card reports

have been submitted since the initiation of the scheme, he said.

Judith Harris, senior lecturer in complementary medicine at Thames Valley University, described ARIA, the Adverse Events in Aromatherapy Reporting System. She explained that 74 members of the International Federation of Professional Aromatherapists (IFPA) volunteered to monitor their practice for nine months. During this time they recorded the number of treatments delivered and filled in an ARIA form for any skin reactions that either they or their clients observed. A total of 4,229 treatments were reported, with one minor skin reaction filed. The system is being rolled out to all members of IFPA, she said.

Tony Booker, president of the Register of Chinese Herbal Medicine, outlined a yellow card scheme operated by his colleagues. The RCHM was set up in 1987 to regulate the practice of Chinese herbal medicine in the

UK. It now has over 500 qualified members. To date only 3 per cent of practitioners have completed a card, he said, adding that the monitoring of liver enzymes could provide a method of identifying adverse reactions.

Joanne Barnes, formerly of the University of London School of Pharmacy and currently associate professor in herbal medicine at the school of pharmacy, University of Auckland, New Zealand, presented a paper investigating the use of herbal medicines by consumers and the reporting of ADRs. She said that large numbers of medicines are purchased by consumers from a variety of outlets and are usually chosen on the basis of non-professional advice. Dr Barnes identified a possible user bias against reporting herbal ADRs. However, she had previously shown that 90 (11 per cent) of the pharmacists in a sample had provided 107 reports of suspected ADRs associated with herbal and Chinese medicines within the 12 months preceding the study.