HERBAL THERAPEUTICS

(1) AN INTRODUCTION TO HERBAL MEDICINAL PRODUCTS

By Jo Barnes, PhD, MRPharmS

The first in a series focusing on European herbal products, this article considers general issues including regulation and quality.

The Royal Pharmaceutical Society’s Code of Ethics states that pharmacists have a professional responsibility “not to recommend any (herbal) remedy where they have any reason to doubt its safety or quality”. Added to this is the question of efficacy. However, currently, many of us have to face the common problem that many herbal products are supplied with little information.

DEFINITION AND DESCRIPTION

Often called herbal medicines, herbal remedies or herbal products and also known as phytomedicines and phytotherapeutic agents, herbal medicinal products (HMPs) have been defined as “any medicinal product, containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.” Simply, this means that HMPs contain only herbs as active ingredients. Herbal medicines are complex mixtures which usually comprise at least 50 or so chemical constituents, although most contain many more. For the majority of these mixtures, the active constituents are, at present, unknown.

One of the basic tenets of herbal medicine is that interactions between different constituents occur, enhancing activity or reducing the likelihood of adverse effects. Such interactions may be additive, or truly synergistic in that compounds interact to produce an effect greater than the sum of the individual contribution of each. Although difficult to establish, true synergy between herbal constituents has been documented experimentally. However, if additive or synergistic interactions can occur, then it cannot be ruled out that negative interactions between herbal constituents may also occur.

In the United Kingdom, HMPs are generally considered by patients, the public, the media and many other groups to be “complementary” or “alternative” medicines. However, there is a view that HMPs with documented pharmacological activity and clinical efficacy lie alongside conventional medicines and some, such as semen preparations, are conventional medicines.

USE OF HERBAL MEDICINES

Most herbal medicines are purchased over the counter (OTC) for general well-being and for the prevention and treatment of common ailments. A survey involving 5,010 adults in England (response rate 59 per cent) carried out in 1998 found that almost 20 per cent had purchased OTC HMPs and 1 per cent had consulted a herbalist in the previous year. Use of OTC HMPs by patients and the public is not limited to symptoms or conditions suitable for OTC treatment, or where there is supporting evidence. Individuals with serious chronic illnesses, including cancer, HIV/AIDS, multiple sclerosis, asthma and so on, use HMPs. In some cases, this may be as well as, or instead of, prescription medicines and this may have implications for pharmaceutical care. HMPs are also used by the elderly and pregnant or breast-feeding women, and are administered by parents to children.

Individuals’ reasons for using HMPs include concern about the adverse effects of conventional drugs, and the perception that HMPs are “safe”. Related issues include non-professional sources of information and advice on HMPs, disclosure of use to health care professionals, and whether compliance with herbal medicines regimens is better than with conventional drug regimens.

REGULATION

Herbal products which are classed as “medicinal products” are available on the UK market as either licensed products or as herbal remedies exempt from licensing (referred to as “section 12”) and are subject to the provisions of the Medicines Act 1968. “Section 12” products are those compounded and supplied by herbalists on their own recommendation, those consisting solely of dried, crushed or comminuted (fragmented) plants (ie, they must not contain any non-herbal active ingredients) sold under their botanical name and with no written recommendations for use, and those made by the holder of a specials manufacturing licence. This category was ini-
Initially intended to allow herbalists to prepare remedies for their patients. However, manufacturers can legally sell products under this exemption. Furthermore, at present, there is no statutory regulation of herbalists in the UK, although this is under review.

In addition, there is a second group of unlicensed herbal products. These are those not classed as medicinal products (so the Medicines Act does not apply) and as long as no medical claims are made, they are sold as food supplements regulated by food legislation. In the UK, the Medicines Control Agency (MCA) has the statutory power to decide whether a specific product satisfies the definition of a “medicinal product”. In several cases, the same herb is available under all three categories.

Potentially hazardous plants (eg, Digitalis and Claviceps purpurea) are controlled as prescription-only medicines and certain others are subject to dose (but not duration of treatment) and route of administration restrictions, or are pharmacy medicines.4

Evidence of the quality, efficacy and safety of an unlicensed herbal medicine will not have been assessed by the MCA. Also, many licensed HMPs (those that initially held a product licence of right under s25 of the Medicines Act 1968) have not necessarily undergone stringent testing because when product licences of right were reviewed, manufacturers of HMPs intended for use in minor self-limiting conditions were permitted to rely on bibliographical evidence to support efficacy and safety, rather than being required to carry out new controlled clinical trials.3

“Ethnic” medicines available in the UK include traditional Chinese medicines (TCM) and Ayurvedic medicines and these are subject to the same legislation as European herbal medicines. In the UK, there are further restrictions on certain toxic herbal ingredients found in products not licensed for human use (eg, Aristolochia species), and on other herbal ingredients that may be confused with (and therefore substituted for) them.1 Some manufactured (“patent”) TCM products contain conventional drugs as listed ingredients, some of which (eg, glibenclamide) are POMs. Non-herbal active ingredients of any type cannot legally be included in an unlicensed herbal remedy, and the inclusion of POMs represents an additional infringement of UK medicines legislation. For ethnic medicines that contain certain animal parts, restrictions under the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) also apply.4

The current system of licensing for HMPs does not give consumers adequate protection against poor quality and unsafe products, nor does it require manufacturers to provide appropriate information to consumers. Therefore a new European Union (EU) directive on traditional HMPs has been proposed and this aims to establish a new, simplified system of licensing for herbal medicines by 2005.1 New measures must be put in place to ensure that herbal medicines, manufacturers will be required to provide bibliographical data on safety, evidence that the herb has been used traditionally in the EU for at least 30 years (this can take 15 years’ non-EU use into account), and to manufacture products according to principles of good manufacturing practice (GMP). In essence, the new system will provide a guarantee of product quality and safety in normal use and thus the necessary reassurance for pharmacists that they are acting in accordance with the Code of Ethics with regard to provision of herbal medicines.

**Quality**

Manufacturers of licensed HMPs are required to satisfy the MCA that their products are made to GMP standards. However, while some established manufacturers of unlicensed HMPs also manufacture their products according to the principles of GMP, others do not and there is no guarantee that such products are of suitable pharmaceutical quality. It may be difficult for pharmacists to distinguish between unlicensed HMPs that are manufactured appropriately and those that are not. As a general guide, information likely to appear on packs of better-quality unlicensed HMPs (in addition to obvious indicators, such as batch number, expiry date and manufacturer’s details) includes:

1. Scientific botanical name (Latin binomial) of plant species
2. Plant part(s) used
3. Type of extract and equivalent quantity of raw material
4. Standardised constituent(s) and concentration(s)

It is common sense that cheap herbal products are unlikely to have been made to GMP standards. Crude herbal material is particularly prone to several specific quality hazards so it is important to ensure that marketed herbal products are of suitable quality. Pharmacists are advised to question the manufacturer if they are in any doubt about the pharmaceutical quality of a particular HMP.

**Contamination**

The quality of raw plant materials can be influenced by human error or unscrupulous operators. Accidental botanical substitution (misidentification of plant species) or even deliberate substitution can occur. For example, in the 1990s, reports of renal failure and renal cancer emerged from Belgium and Australia following the use of slimming products contaminated with Aristolochia species. This was due to the substitution of non-toxic herbs, including Stephania tetrandra and Clematis armandi, with Aristolochia species. Accidental or intentional contamination of herbal material with conventional drugs (eg, corticosteroids) or poisonous substances (eg, heavy metals, pesticide residues) and micro-organisms can also occur.

**Variable composition**

Being natural products, herbs do not have a consistent, standardised composition — the difference in vintages of wines has been used as an analogy.5 Different parts of the plant (eg, roots, leaves, bark) possess a different profile of constituents, and the content and concentration of constituents can be influenced by several factors including climate, growing conditions, time of harvesting, storage conditions (eg, light, temperature and humidity) and processing (eg, extraction and drying).

The variability in the content and concentrations of constituents, together with the range of extraction techniques and processing steps used by different manufacturers, results in marked variability in content and quality of commercially available HMPs. Both batch-to-batch and manufacturer-to-manufacturer variations in preparations of the same herb are inevitable.6 Important differences in the pharmaceutical quality (eg, content of active constituents and dissolution rates) of different brands of St John’s wort (Hypericum perforatum) and ginkgo (Ginkgo biloba) available on the United States market have been reported.6,7

**Standardisation**

Several manufacturers now produce standardised herbal extracts to attain better batch-to-batch consistency and therefore to achieve more consistent pharmaceutical quality.6 Such extracts are processed to contain a specific quantity of the active constituent(s) and, in some cases, unwanted or toxic constituents are removed. For example, standardised extracts of Ginkgo biloba leaf contain 22 to 27 per cent ginkgo flavonoid glycosides, 5 to 7 per cent terpene lactones, and less than five parts per million of ginkgolic acids, which are allergic. Standardisation is an important step where the active constituents are known.

For herbs where the active constituents are not known, products may be standardised on their content of certain marker compounds (eg, chemicals characteristic of the herb or chemicals present in large quantities).3 However, this approach makes assumptions about the relationship between the quantity of marker compounds and that of the unknown active constituents. The quality of HMPs (ie, the profile of constituents in the final product and the presence or absence of contaminants) has implications for efficacy and safety. Because the composition of products varies between manufacturers, evidence of efficacy and safety should be considered to be extract- or product-specific. Evidence should be extended only to those products that are essentially similar, ie, pharmacologically equivalent and bioequivalent. For example, most clinical trials of ginkgo have tested the standardised Ginkgo biloba leaf extracts EGb-761 and LI-1370, but it should not be assumed that the results of these studies apply to other ginkgo leaf extracts (which may have a different profile of constituents) or to other preparations of ginkgo leaf, such as tinctures and teas. Beware that many systematic reviews and meta-analyses of clinical trials of herbal medicines ignore important details of the products tested, such as the type of extract and the formulation.

In the UK, the quality and safety standards of herbal medicines are a particular concern. In 2000, the MCA set up an Ethnic Medicines Forum which aims to help and encourage the ethnic medicines sector to achieve improvements in safety and quality standards in relation to unlicensed ethnic medicines, and to raise awareness of medicines legislation among operators within the sector.3,4
CONTINUING PROFESSIONAL DEVELOPMENT

SUMMARY

In 2000, there was almost £65m in sales of licensed and unlicensed herbal products, an increase of 50 per cent over the previous five years. At present, around 50 per cent of these sales are made in pharmacies, although this proportion has decreased slightly since 1998 in favour of health-food stores and supermarkets. Whether you choose to sell herbal products or not, with their increasing use, it is highly likely that you will be asked for advice. You will also have to consider other implications of use of herbal products such as interactions with conventional drugs.

The use of HMPs in a science- or evidence-based manner is known as (rational) phytotherapy. Later articles will focus on the therapeutic use of HMPs in various conditions, and will discuss evidence to support their efficacy and safety. The final article in this series will cover interactions between HMPs and conventional drugs.

SAFETY ASPECTS

Generally, information on herbal medicines is lacking in several areas, including active constituents, metabolites, pharmacokinetics, pharmacology, toxicology, adverse effects and their frequencies, effects of long-term use, drug-herb interactions, interactions with food and alcohol, use by specific patient groups (eg, children, elderly, individuals with renal or hepatic disease, individuals with a particular genetic profile) and contraindications and warnings (eg, use in pregnancy and lactation).

Adverse effects associated with certain HMPs can be classed into several types, including: type A (common, usually dose-related), type B (uncommon, unpredictable, unrelated to dose, usually serious), type C (those occurring with chronic use), type D (delayed effects occurring remote from use eg, carcinogenic reactions with Aristolochia species) and type E (end of treatment effects).

At present, the main method of generating signals of potential safety concerns associated with HMPs is spontaneous reporting. In the UK, the Committee on Safety of Medicines’ (CSM) yellow card scheme for adverse drug reaction (ADR) reporting has always applied to licensed HMPs, and was extended to include unlicensed herbal products in 1996. Community pharmacists, formally included in the scheme since November 1999, are asked by the CSM to report for conventional OTC medicines and HMPs in particular. There is no mandatory manufacturer reporting of suspected ADRs associated with HMPs, except for licensed products.

The yellow card scheme has recognised limitations, including under-reporting, which is likely to be greater for HMPs than for conventional drugs. Because of the belief that HMPs are “safe”, consumers may not associate ADRs with their use of such products, and also may be reluctant to report ADRs associated with these products to their doctor or pharmacist. Pharmacists are encouraged to ask patients about their use of herbal products and to be vigilant to the possibility of herbal ADRs. If a serious ADR is suspected, the CSM recommends that a sample of the product is retained.

REFERENCES