

Challenges in pharmacovigilance of herbal medicines



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Outline

Background

- Why is there a need to monitor the safety of herbal medicines?

Challenges in pharmacovigilance of herbal medicines

- Characteristics of herbal medicines
- Utilisation of herbal medicines and related issues
- Regulatory framework for herbal medicines
- Methods for pharmacovigilance of herbal medicines

Future



Barnes J. Pharmacovigilance of herbal medicines. A UK perspective. *Drug Safety* 2003;26(12):829-851.

What are herbal medicines?

Medicines Act 1968

Herbal remedy is "a medicinal product consisting of a substance produced by subjecting a plant or plants to drying, crushing or any other process, or of a mixture whose sole ingredients are two or more substances so produced, or of a mixture whose sole ingredients are one or more substances so produced and water or some other inert substances"

New EU directive 2004/24/EC on Traditional Herbal Medicinal Products

Defines herbal substances, herbal preparations, herbal medicinal products

WHO definitions

Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products. In some countries, herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (e.g. animal and mineral materials)

ESCOP (European Scientific Co-operative on Phytotherapy; www.escop.com)

Herbal medicines "are medicinal products containing as active ingredients only plants, parts of plants or plant materials, or combinations thereof, whether in the crude or processed state".

- Includes plant juices, gums, essential oils and other directly derived crude plant products
- Does not include chemically defined isolated constituents
- Herbal should not be used as a general term for complementary/alternative medicines

Large numbers of individuals are using herbal medicines

Cross-sectional representative survey of random sample of adults in England (n = 5010) in 1998; response rate = 60%

Therapy	Use in previous year (95% CI)	Ever used (95% CI)
Acupuncture	1.6%	7.0%
Chiropractic	3.6%	10.3%
Homoeopathy	1.2%	5.7%
Herbalism	0.9% (0.6 – 1.3)	4.4% (3.6 – 5.1)
Hypnotherapy	0.7%	3.1%
Osteopathy	4.3%	13.0%
Reflexology	2.4%	5.4%
Aromatherapy	3.5%	8.2%
OTC homoeopathy	8.6%	14.6%
OTC herbal	19.8% (18.3 – 21.3)	31.4% (29.6 – 33.2)
Any of above	28.3%	46.6%
Other practitioner	1.6%	1.5%

Thomas KJ et al. Use and expenditure on complementary medicine in England: a population-based survey. *Comp Ther Med* 2001;9(1):2-11

The use of herbal medicines is increasing (USA)

	1990 (n = 1539)	1997 (n = 2055)	
Use of alternative medicine in past 12 months	33.8%	42.1%	P ≤ 0.001
Unsupervised use of herbal medicine in past 12 months	2.5%	12.1%	P ≤ 0.001

Eisenberg D et al. Unconventional medicine in the United States. Prevalence, costs and patterns of use. *New Eng J Med* 1993;328:246-252

Eisenberg D et al. Trends in alternative medicine use in the United States, 1990-1997. Results of a follow-up national survey. *JAMA* 1998;280(18):1569-75

The use of herbal medicines is increasing (Australia)

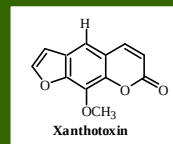
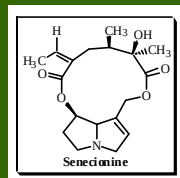
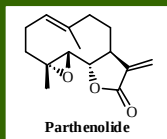
- Representative population cross-sectional surveys (by home interview) of persons > 14 years in South Australia (n = 3004, 3027 for 1993 & 2000)

Use of	1993	2000	P
Any non-Rx alternative medicines	48.5%	52.1%	<0.01
'herbal medicines'	9.9%	13.4%	<0.01
evening primrose oil	7.8%	8.0%	0.77
'ginseng'	3.0%	5.0%	<0.01
Chinese medicines	1.8%	3.2%	<0.01

MacLennan A et al. Prevalence and cost of alternative medicine in Australia. *Lancet* 1996;347:569-573
 MacLennan A et al. The escalating cost and prevalence of alternative medicine. *Prev Med* 2002;35:166-73

Herbal medicines can cause adverse effects

- Inherently toxic constituents e.g. unsaturated pyrrolizidine alkaloids
- Adverse effects related to active constituents/desired pharmacological activities
- Interactions with other medicines: conventional, herbal, complementary medicines
- Effects in specific patient groups
- In recent years, several high-profile herbal safety concerns



Herbal medicines are chemically rich complex mixtures



Aspirin tablets

- Contain:
- Aspirin
 - (Inert excipients)



Tablets containing extract of St John's wort herb

- Contain:
- Hyperforin, adhyperforin, hypericin, pseudohypericin, isohypericin, protohypericin, protopseudohypericin, kaempferol, quercetin, luteolin, hyperoside, isoquercitrin, quercitrin, rutin, biapigenin, amentoflavone, catechins, tannins, other phenols etc etc
 - (Inert excipients)

Herbal medicines have a variable composition

- Numerous different chemical constituents: hundreds!
- Specific constituents often unknown; constituents responsible for effects often unknown
- Constituents differ with plant part (e.g. root, leaves)
- Other factors affect the profile of constituents in herbal material
 - environmental factors, e.g. climate, growing conditions, time of harvest
 - post-harvesting factors, e.g. storage conditions, processing, type of extract etc
 - standardisation for certain constituents is possible
 - few products standardised to known active constituent(s)
 - batch-to-batch and manufacturer-to-manufacturer variation occur
 - differ with plant part (e.g. root, leaves)
- Other quality problems
 - intentional/accidental botanical substitution: wrong/different species
 - Intentional/accidental adulteration: e.g. prescription medicines – corticosteroids etc

Herbal products containing the same herbal ingredient(s) but made by different manufacturers are not identical

- Profile of constituents in different manufacturers' products varies
- Analytical study of 8 St John's wort products
 - hyperforin content: 0.01% to 1.89%; at least 1% required for clinical efficacy
 - hypericins content: 0.03% to 0.29%; 57 to 130% of amount stated on label

De Los Reyes G, Koda RT. *Ann J Health-Syst Pharm* 2002;59:545-7
- Several other studies with other herbal products. See www.consumerlab.com
- Differences in bioavailability of standardised ginkgo products.

Kressmann S et al. Pharmaceutical quality of different Ginkgo biloba brands. *J Pharm Pharmacol* 2002;54:661-669

Kressmann S et al. Influence of pharmaceutical quality on the bioavailability of active components from Ginkgo biloba preparations. *J Pharm Pharmacol* 2002;54:1507-1514
- Evidence for safety (and efficacy) is product- or extract-specific



Utilisation of herbal medicines and related issues

- Used by a wide range of individuals
 - Maintenance of general health and well-being; enhancement; 'lifestyle' reasons
 - Prevention and treatment of minor ailments
 - Serious chronic disease
 - Special patient groups, e.g. children, elderly, those with reduced hepatic/renal function etc
- Perception that natural = safe
- Confusion over types of preparations, e.g. herbal/homoeopathic
- Lack of disclosure of use to healthcare professionals
- Healthcare professionals do not routinely ask patients about herbal and complementary medicine use; rarely record information on herbal use on patient records

Prevalence of concurrent use of herbal and conventional medicines

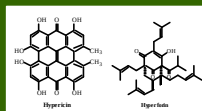
	1990 (n = 1539)	1997 (n = 2055)	
Unsupervised use of herbal medicine in past 12 months	2.5%	12.1%	P ≤ 0.001
Regular Rx med users (44%) concurrently using herbal and/or high-dose vitamin		18.4%	
Disclosure to physician	39.8%	38.5%	

Eisenberg D *et al.* Trends in alternative medicine use in the United States, 1990-1997. Results of a follow-up national survey. *JAMA* 1998;280(18):1569-75

Use of	1993	2000	P
Any non-Rx alternative medicine	48.5%	52.1%	<0.01
Disclosure to GP (users of alternative medicines)		45.0%	
Use with Rx medicines to treat the same condition		30.4%	

MacLennan A *et al.* The escalating cost and prevalence of alternative medicine. *Prev Med* 2002;35:166-73

Drug-herb interactions occur, e.g. St John's wort (*Hypericum perforatum* L.)



Pharmacokinetic

- Emergence of evidence that SIW induces CYP3A4, CYP1A2, CYP2C9 and affects P-glycoprotein
- Leads to loss of, or reduction in, therapeutic effect of certain drugs
- Warfarin, cyclosporin, digoxin, theophylline, HIV protease inhibitors, anticonvulsants, oral contraceptives
- Many other drugs are metabolised by these CYP enzymes
- New reports: irinotecan

Pharmacodynamic

- risk of increased serotonergic effects in patients taking selective serotonin reuptake inhibitors (SSRIs) and triptans
- SIW no longer thought to have MAOI activity. Avoidance of tyramine-containing foodstuffs and medicines containing sympathomimetics not considered necessary

Summarised in: Barnes J, Anderson LA, Phillipson JD. St John's wort (*Hypericum perforatum* L.): a review of its chemistry, pharmacology and clinical properties. *J Pharm Pharmacol* 2001;53:583-600

Regulatory framework: herbal medicines (UK)

- About 600 licensed herbal medicines in the UK (small proportion of products on market)
- Were permitted to use bibliographic evidence to support efficacy and safety rather than conduct tests and trials
- Holders of MAs for licensed herbal medicines are required to comply with regulatory provisions on pharmacovigilance
- Most products currently on UK market are sold as unlicensed products; many manufacturers ignore conditions for this (e.g. use brand names)
- Currently, these manufacturers are not required to inform competent authority before placing a product on the market nor to comply with regulatory provisions on pharmacovigilance
- Limited range of regulatory actions available in response to safety concerns with unlicensed herbal medicines; some require voluntary co-operation of manufacturers
- Practitioners of herbal medicine are at present not regulated in the UK

For many herbal medicines, there is a lack of reliable information on aspects relevant to safety

Lack of information on:

- active constituent(s), metabolites
- pharmacokinetics
- pharmacology
- toxicology
- adverse effects, frequencies; effects of long-term use
- drug-herb and herb-herb interactions; interactions with food, alcohol
- use in special patient groups (elderly, children, gender effects, different genetic profile, those with renal/hepatic disease etc)
- contraindications, warnings; use in pregnancy and lactation

Difficult to assess potential benefits and potential risks

Difficult to compare risk-benefit profile of HMs with that of conventional drugs

Some herbal medicines may have more favourable safety profile than conventional drugs, but risk-benefit comparisons should be made for each case

Herbal medicines are widely available

Available from:

- Doctor's prescription??
- Pharmacies
- Health-food stores
- Supermarkets
- Via Internet
- Medical herbalists
- Herbal shops eg TCM outlets
- Other complementary/alternative medicine practitioners
- Etc

Many sources do not involve interaction with a qualified health care professional
→ Inappropriate or unsafe use?

Poor pharmaceutical quality of herbal medicinal products obtained from some of these sources

CSM/MHRA 'yellow card' for suspected ADR reporting

(Committee on Safety of Medicines/Medicines and Healthcare products Regulatory Agency)



- established in 1964; always applied to licensed medicines, including licensed HMPs
- October 1996: extended to unlicensed herbal remedies for recognised reporters
- Recognised reporters are: doctors, dentists, coroners, hospital (since 1997) and community pharmacists (since 1999), nurses, midwives, health visitors (since 2002)
- Community pharmacists specifically encouraged to report for herbal medicines
- Pilot of patient reporting via NHS Direct (2002)
- Proposal for a direct patient suspected ADR reporting system

Other UK spontaneous reporting systems for herbal medicines

- Phytonet (<http://www.escop.com/phytonet.htm>) - dormant
 - set up by ESCOP (European Scientific Co-operative on Phytotherapy)
 - password-protected, Internet-based reporting system for conventional healthcare professionals, herbal practitioners and the public
 - feeds reports, where appropriate, into WHO UMC
- NIMH (National Institute of Medical Herbalists) scheme set up in January 1994
- RCHM (Register for Chinese Herbal Medicine) scheme
- Manufacturers: British Herbal Medicine Association voluntary code of practice
- Medical Toxicology Unit at Guy's and St. Thomas' Hospital Trust, London
- Important that reports are all fed into one system (ie CSM/MHRA ADROIT system) so that signals are not diluted

Advantages and limitations of spontaneous reporting schemes

Advantages

- monitor all medicines, including all herbal medicines, all the time for all patients
- early warnings of undocumented safety concerns, important as limited information on herbal safety
- relatively cheap, important as herbal industry may not have resources to conduct large PMS studies

Limitations

- under-reporting, likely to be greater for herbal medicines
- poor quality of data provided by reporter; yellow card does not cater well for herbals
- report does not necessarily imply a causal relationship
- cannot estimate frequency of an ADR or herbal interaction
- suspected ADRs identified outside the formal system, eg herbalists, health-food stores

Respondents' perceived action following serious adverse effect to herbal medicine and conventional OTC medicine (% of total; row totals = 100%)

Action	YcYh	NcNh	YcNh	NcYh
Continue taking	2.1	95.9	0.2	1.7
Stop immediately	63.5	21.0	3.5	12.0
Consult GP	30.3	42.9	26.0	0.8
Consult pharmacist	6.6	85.4	2.9	5.0
Consult other HCP	1.7	91.4	0	6.8

Barnes J, Mills S, Abbot NC, Willoughby M, Ernst E. Different standards for reporting ADRs to herbal remedies and conventional OTC medicines: face-to-face interviews with 515 users of herbal remedies. *Br J Clin Pharmacol* 1998;45:496-500

There are several difficulties in communicating information on herbal safety concerns

Dear Doctor/Pharmacist letters

- e.g. information on St John's wort drug interactions

Current Problems in Pharmacovigilance

But:

- many purchases from outlets with no HCP and without professional advice
- no statutory regulation of herbal practitioners – yet!
- how users (also other stakeholders) interpret and act on information on herbal safety concerns needs to be explored

Herbal Safety News on the MHRA website

(<http://www.mhra.gov.uk>) rapid communication of information, but passive



New regulatory framework for traditional HMPs

New EU directive for new system of licensing for traditional herbal medicinal products - "traditional use" directive

Directive 2004/24/EC on Traditional Herbal Medicinal Products – requires member states to implement into national legislation by end October 2005; 7-year transition period to end April 2011

Features:

- evidence of 30 years' traditional use; take account of 15 years' non-EU use
- labelling statement re evidence relies on traditional use
- no POMs: no products that "can be" authorised via conventional route
- **bibliographic data on safety with expert report (no new tests/trials)**
- **quality dossier required; requirement for manufacture to GMP principles**
- **compliance with pharmacovigilance requirements in 2001/83/EC**

Also:

Herbal Medicine Regulatory Working Group set up to develop proposals for statutory regulation of herbal medicine practitioners in the UK

Pharmacovigilance of herbal medicines: future

- Emergence of new safety concerns with continued widespread use
- ? Use of herbal medicines in preference to conventional medicines where equivalence and more favourable benefit-risk profile shown
- New EU THMPD places greater emphasis on demonstrating safety; basic improvements in pharmacovigilance
- ? Extension of yellow card scheme to patients and registered herbalists
- Development of pharmacovigilance tools applicable to herbal medicines (e.g modified prescription event monitoring)
- Pharmacogenetics and pharmacogenomics
optimising treatment, including reducing potential for ADRs, on the basis of a patient's genotype has barely been discussed in the context of herbal medicines.

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