

Pharmacovigilance of Herbal Medicines

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Abstract: *Pharmacovigilance is essential for developing reliable information on the safety of herbal medicines as used in Europe and the US. The existing systems were developed for synthetic medicines and require some modification to address the specific differences of medicinal herbs. Traditional medicine from many different cultures is used in Europe and the US which adds to the complexities and difficulties of even basic questions such as herb naming systems and chemical variability. Allied to this also is the perception that a 'natural' or herbal product must be safe simply because it is not synthetic which means that the safety element of monitoring for such medicines can be overlooked because of the tag associated with such products. Cooperation between orthodox physicians and traditional practitioners is needed to bring together the full case details. Independent scientific assistance on toxicological investigation, Botanical verification can be invaluable for full evaluation of any case report. Systematic pharmacovigilance is essential to build up reliable information on the safety of herbal medicines for the development of appropriate guidelines for safe effective use.*

Keywords: Pharmacovigilance; herbal medicines; improved traditional medicine; regulation; research.

I. INTRODUCTION

Pharmacovigilance is defined as 'the study of the safety of marketed drugs under the practical conditions of clinical usage in large communities' (Mann and Andrews, 2002). The objective is to extend safety monitoring and detect drug adverse events that have previously been unrecognised despite evaluation in clinical trials. Although these methods were developed for monitoring pharmaceutical medicines they are also used for additional evaluation of the safety of other medicinal products including herbals, blood products, vaccines and even medical devices. As the use of herbal medicines has increased, so too have the reports of suspected toxicity and adverse events. Such unwanted reactions can be due to (i) side effects (usually detectable by pharmacodynamics and often predictable); (ii) reactions occurring as a result of overdose, overduration, tolerance, dependence-addiction (detectable either by pharmacodynamics or pharmacovigilance), (iii) hypersensitivity, allergic and idiosyncratic reactions (detectable by pharmacovigilance), (iv) mid-term and long-term toxic effects including liver, renal, cardiac and neuro-toxicity also genotoxicity and teratogenicity (detectable by in vitro and in vivo toxicological studies or by pharmacovigilance). As many herbal products on the market have not been thoroughly tested for their pharmacology and toxicology, pharmacovigilance has paramount importance in detecting unwanted reactions. In addition there is an ongoing problem with unexpected toxicity of herbal products due to quality issues, including use of poor quality herbal material, incorrect or misidentified herbs, incorrect processing methods, supply of adulterated or contaminated Herbs or products (Shaw, 2010a).

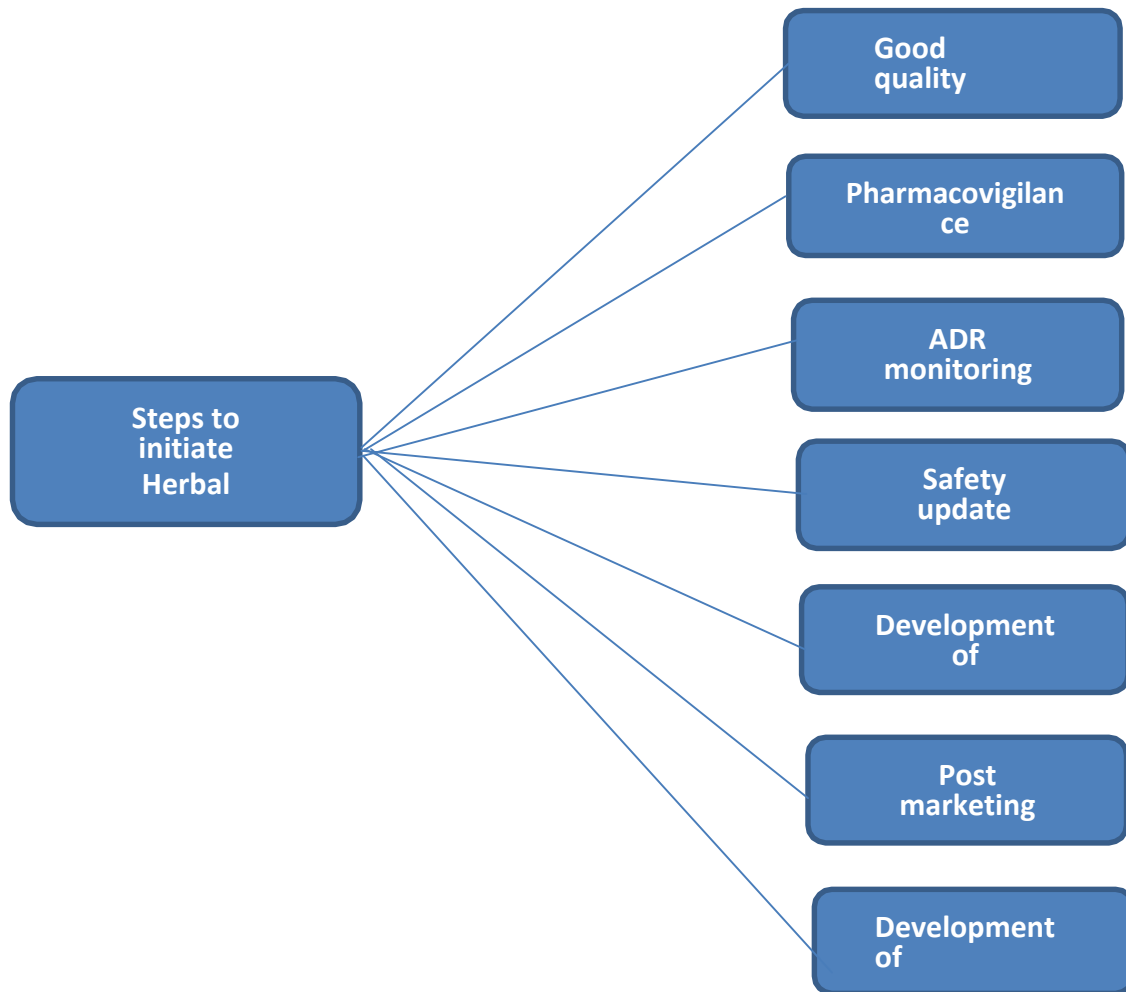
These quality issues can be addressed to some degree by improved regulation requiring GMP Standards for manufacturing. However medicinal herbs/products come from many countries with differing manufacturing standards and enforcement of regulations so poor quality products are likely to remain a problem. The safety of herbal medicines has become an issue for the regulatory authorities, as serious effects have been reported, including hepatotoxicity, renal failure and allergic reactions (Perharic et al., 1995; Nortier and Vanherweghem, 2007). The World Health Organisation, recognising the growing importance of the use of herbal medicines worldwide developed guidelines for the monitoring of herbal safety within the existing pharmacovigilance framework (WHO, 2004).

II. PHARMACOVIGILANCE AND THE WHO INTERNATIONAL DRUG MONITORING PROGRAMME

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of the adverse effects of drugs or any other possible drug-related problems.

Recently, its concerns have been widened to include the following: herbals traditional and complementary medicines

blood products biological medical devices and vaccines



III. QUALITY RELATED SAFETY ISSUE-EVIDENCE

Need of pharmacovigilance for herbal medicinal products

WHO defines traditional medicine as including diverse health practices, approaches, knowledge and beliefs incorporating plant, animal, and/or mineralbased medicines, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness. The inclusion of herbal medicines in pharmacovigilance systems is becoming increasingly important given the growing use of herbal products and herbal medicines globally. As an immediate response to the need for pharmacovigilance for herbal medicines, WHO has increased its efforts to promote herbal safety monitoring within the context of the WHO International Drug

Monitoring Programme. WHO survey showed that around 90 countries, less than half of WHO's Member States, currently regulate herbal medicines, and an even smaller proportion has systems in place for the regulation/qualification of providers of herbal medicines.

WHO Guidelines on safety monitoring of herbal medicines in pharmacovigilance systems Safety of herbal medicine is an important public health issue. The guidelines stresses upon: 1 The importance of process for monitoring the safety of herbal medicine within the pharmacovigilance system 1 Standard definitions of terms related to pharmacovigilance and safety monitoring of herbal medicine 1 Challenges in monitoring the safety of herbal medicine 1 Need for good communication for ensuring successful safety monitoring These guidelines aim to propose to member states a framework for facilitating the regulation of herbal medicines/ products used in traditional medicine. The issues covered

are following:

- ! Classification of herbal medicines!
- Minimum requirements for assessment of safety of herbal medicinal
- Minimum requirements for assessment of the efficacy of herbal medicinal
- Quality assurance of herbal medicinal products!
- Pharmacovigilance of herbal medicinal products!
- Control of advertisements of herbal medicinal products
- Safety issues related to herbal medicinal products

The uses of traditional and complimentary medicines are increasing rapidly in developed countries. Policy makers, health professionals and general public all over the world are wrestling with question about the safety, quality, availability, preservation, standardization and further development of this health care system. Despite of the immense potential of traditional therapies, many of them are untested and uses not properly mentioned in the labels as a result of this knowledge about their potential side effect are limited. The substitution of toxic Aristolochia species in traditional Chinese medicines has resulted in a case of serious renal toxicity and renal cancer in Europe, China and America.⁷ There are some diverse issues related to safety of traditional herbal medicines compelling to development of efficient pharmacovigilance system. Quality related safety issues: A particular plant Genus has several species that are used medicinally, and also different parts of a particular plant has difference in phytochemical constituents. Quality control of ethnic traditional medicines is different and gives rise to public health concern because majority of herbal products are unregulated. The problems include:

- ! Deliberate or accidental inclusion of prohibited or restricted ingredients!
- ! Demand outstripping supply of good quality ingredient!
- ! Substitution of ingredients
- ! Adulteration with heavy metals/ toxic elements and/or synthetic drugs
- ! Contamination with toxic substances!
- ! Difference between labeled and actual content!
- ! Lack of standardized manufacturing practice!
- ! Lack of authentication and reproducibility of herbal ingredients!
- ! Lack of information about safe use!

The specific aims of Pharmacovigilance are to:

- Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions
- improve public health and safety in relation to the use of medicines
- contribute to the assessment of benefit, harm, Effectiveness, and risk of medicines, encouraging their safe, rational, and more effective (including cost- effective) use
- promote understanding, education, and clinical training in pharmacovigilance and its effective communication to the public.

The WHO international drug monitoring program

- Under the WHO International Drug Monitoring Program, national pharmacovigilance centers designated by the competent health authorities are responsible for the collection, processing, and evaluation of case reports of suspected adverse reactions supplied by health care professionals (mainly spontaneous reporting by physicians of reactions associated with the use of prescribed medicines). The Program is described in two publications: Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance center, chapters 7 and 8; and The importance of pharmacovigilance: safety monitoring of medicinal products, especially chapters 3 and 4.
- The Program currently comprises a network of more than 70 national pharmacovigilance centers that operate independently, but whose functions are coordinated and facilitated by the WHO and the UMC. The UMC manages the global WHO database to which all case reports received by the national pharmacovigilance centers are sent. The UMC uses the global WHO database to identify/detect signals of new adverse reactions from the cumulative data and to communicate risk assessments back to the national pharmacovigilance centers and to others concerned with drug safety.

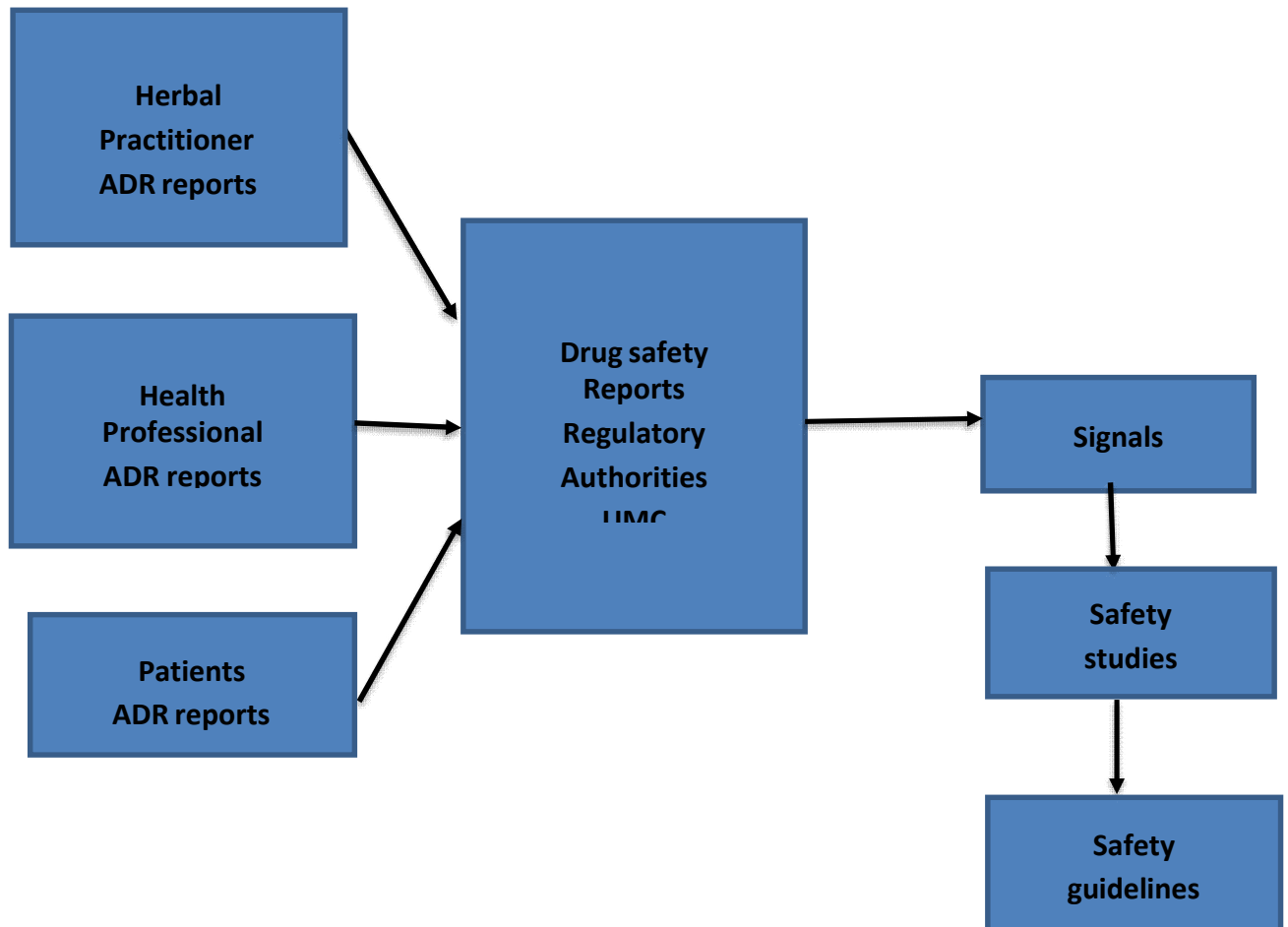
IV. CHALLENGES OF HERBAL PHARMACOVIGILANCE

Specific challenges

Unlike synthetic medicines, herbal medicines are typically Chemically rich and complex products and not isolated single compounds. A number of factors can influence the qualitative and quantitative chemical profile including:

- Geographical origin – climate, soil, photoperiod.
- Genotype.
- Parts of the plant – leaves, stems, root, root bark, etc.
- Harvesting time (year, season, time of day) and conditions.

- Storage, processing, extraction.
- Combinations of herbs and/or processing of the combined Herbs



V. PHARMACOVIGILANCE OF HERBAL MEDICINE

1. Herbal medicines and dietary supplements

The classification and regulation of herbal products may vary between different countries/jurisdictions. In the EU they are classified as herbal medicines (regulatory implications) with requirements for safety and quality standards. Some herbs maybe supplied as food supplements. In the US, herbal products are classified as dietary supplements or botanicals, not medicines. Quality will vary although GMP requirements were issued by the FDA in 2007. Pharmacovigilance reporting is not compulsory for manufacturers.

2. Nomenclature and what was used

Adverse reaction reports, whether submitted to regulatory authorities or published in the medical literature, are meaningless if the medicinal herb(s) or ingredients in a product cannot be identified. Names for medicinal herbs include the Latin scientific name, the common or vernacular name, the pharmaceutical name or pharmacopoeal name or the specific herbal drug names (as used in Traditional Chinese Medicine (TCM)). Herbal prescriptions, product packaging or labels may have one or more of these (occasionally No label) depending on source and regulatory status of the product. These have to be interpreted with care as even the scientific names may have synonyms.

3. Initiatives to address nomenclature and quality issues

There is currently no single reference list of medicinal plants which presents an authoritative view on their current scientific name and linking all synonyms of those plants that are found in the literature. The only names that are standardised are Latin scientific names (e.g. *Bupleurum chinense* DC.); their standardisation is achieved through the 'International Code of Nomenclature of algae, Fungi, and plants' (ICN formerly ICBN).

4. Source—users of herbal medicine

Surveys have shown that consumers tend to self-preserving herbal medicines without consulting a professional herbal practitioner or other health professional (Barnes et al., 1998; Ipsos Mori, 2008). Products can be bought over-the-counter from pharmacies, markets or the internet without any consultation with a health professional. Herbal medicines are prescribed by Orthodox medical professionals in few European countries (e.g. Germany). Consumers may not be aware that adverse effects of Herbal medicines can be reported to their general practitioner or know how to report to regulatory authorities. In addition, consumers may not associate the herbal product with the effect. A number of studies have shown that consumers are reluctant to admit to their physician that they have been using herbal medicines (Barnes, 2003).

5. Identifying adverse reactions

The classification of types of adverse reactions is well established in orthodox medicine and applies equally to herbal medicine. Adverse reactions are classified as (Edwards and Aronson, 2000):

- Type A (acute/augmented); dose related and explained by pharmacology of herbs.
- Type B (bizarre/idiosyncratic); not dose related or predictable by Pharmacology.
- Type C (chronic/cumulative): cumulative effect.
- Type D (delayed onset) carcinogenic, genotoxic.

6. Pharmacovigilance methods

A range of methods are used for post marketing monitoring of drug safety including spontaneous reporting and prescription event monitoring (DynPage UMC). These methods can be used for monitoring herbal safety but require modification to address specific challenges such as botanical nomenclature, quality, Adulteration, labelling issues, prescriber/reporter differences and Under-reporting.

7. Monitoring for herb–drug interactions

There is a perception that herbal medicines are safe, even if taken at the same time as prescription drugs (Delgoda et al., 2004). Herbs may be used to treat the primary condition or to reduce the side effects of their conventional treatment. Under-reporting of suspected interactions between herbs and drugs is of increasing concern and arises from the same reasons as under-reporting of herbal ADRs.

8. Herbal practitioners

Herbal practitioners are potentially a useful source of information on ADRs but with varying levels of professional regulation in Europe they are not necessarily recognised as ADR reporters. Some herbal practitioner organisations have established their own reporting schemes but these are not necessarily linked to official agencies. There are benefits to reporting by trained herbal practitioners.

9. Minimum requirements for ADRs

Various groups have produced guidelines for reporting adverse events and clinical trials (Gagnier et al., 2006; Kelly et al., 2007) including herbal products. The requirements for case reports include essential case details: patient demographics (age, gender) relevant medical history, symptoms, abnormal laboratory results, drug identification, reason for use, dose, time course (duration of use, onset of symptoms) and details of adverse event.

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