Need for Pharmaco-vigilance of Herbal Drugs: Safety and Quality Issues

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Abstract

yurveda, the knowledge of life, immortalized in the form of elegant Sanskrit verses in the *Samhitas* describes diagnosis and therapy of disease as well as ways to maintain positive health (Dahanukar and Thatte, 1983). Although the technical term "Pharmacovigilance" does not feature in ayurvedic texts, the spirit of pharmacovigilance is vibrant and is emphasized repeatedly in all major texts. The major goals of pharmacovigilance, namely to improve patient care and safety in relation to drug use, and thus promote rational drug use are recurrent themes of ayurvedic pharmacology (*Dravyaguna vigyan*) and therapeutics (*chikitsa*). The success of pharmacovigilance system is in the ability to prevent further adverse reaction successfully by understanding and using the information collected. The pharmaceutical and biotech industry is revolutionizing in a manner where innovation and pharmacovigilance are not polarized. The business models are maturing to the next level of niche busters and towards a coexistence of novel and the age old blockbuster strategies. Pharmacovigilance forms the backbone of the product life cycle due to a demand created by the need for new drugs and their regulation. Events such as thalidomide tragedy highlight the extreme importance of effective drug monitoring system for all medicines.

Keywords: Pharmacovigilance, Herbal drugs, Quality control.

Introduction

Pharmacovigilance is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines. Generally speaking, pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biologicals, herbalism and traditional medicines with a view to:

1. Identifying new information about hazards associated with medicines.

2. Preventing harm to the patients.

The traditional preparations comprise medicinal plants, minerals, organic matter, etc. Herbal drugs constitute only those traditional medicines which primarily use medicinal plant preparations for therapy. The earliest recorded evidence of their use in Indian, Chinese, Egyptian, Greek, Roman and Syrian

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texts dates back to about 5000 years. The classical Indian texts include *Rigveda, Atherveda, Charak Samhita* and *Sushruta Samhita*. The herbal medicines and traditional medicaments have been derived from rich traditions of ancient civilizations and scientific heritage (Dahanukar and Thatte, 1996).

The safety of herbal medicines has become a major concern to both national health authorities and the general public. The use of herbs in Traditional medicines continues to expand rapidly across the world. Many people now take herbal medicines or herbal products for their health care in different national health-care settings. There is a myth that herbal medicines do not have adverse effects and hence consumed by patients on their own. However, this is not true and herbal products are also likely to have adverse effects if taken without proper guidance. Mass media reports of adverse events tend to be sensational and give a negative impression regarding the use of Herbal medicines in general rather than identifying the causes of these events, which may relate to a variety of issues (Mann and Andrews, 2007).

It is high time we practice pharmacovigilance for herbal products as well. We need to look at the herbal drug regulations of India in comparison with those of highly regulated markets of EU which have been looking upon herbal products as a 'medicine'. It appears that the Indian regulations on herbal medicines are lagging behind the times and this article aims to serve as a reminder of this fact.

Challenges in Monitoring the Safety of Herbal Medicines

The WHO has taken the lead in tackling the need for drug safety monitoring since 1970 (resolution WHA23.13 on international monitoring of adverse reactions to drugs). The WHO International Drug Monitoring Program, together with the WHO Collaborating Centre in Sweden, the Uppsala Monitoring Centre (UMC), has instituted a coherent program of action for pharmacovigilance, which includes the establishment of a program for exchange of safety information, maintenance of the global WHO database of adverse drug reaction (ADR) reports (hereafter referred to as the global WHO database), and the provision of numerous guidelines on monitoring drug safety. It also seeks to bridge the gap between the industry and the regulatory authorities. As an immediate response to the need for pharmacovigilance for herbal medicines, the WHO has increased its efforts to promote their safety monitoring within the context of the WHO International Drug Monitoring Program (Anonymous, 2000; Edwards and Biriell, 1994).

Many herbs have shown positive results in-vitro, animal model or small-scale clinical tests, while studies on some herbal treatments have found negative

results. The partial list of herbs and herbal treatments with known or suspected adverse effects, either alone or in interaction with other herbs or drugs. They are as listed below (Table-1).

Table 1: List of herbs with known adverse effects

Name of Drug	Scientific name	Adverse effects	Reference
Aconite	*Aconitum* spp.	Heart palpitations and arrhythmias, hypotension, nausea, vomiting, abdominal pain, respiratory system paralysis	(Craft, 2004)
Aloe vera juice	*Aloe vera*	Potentially carcinogenic, with others can potentiate cardiac glycosides and antiarrhythmic agents. Cause allergic and toxic contact eczema in rare cases.	(Craft, 2004)
Anthroid laxatives	-	Abdominal pain, diarrhea, potentially carcinogenic, with others can potentiate cardiac glycosides and antiarrhythmic agents	(Aronson, 2009)
Areca nut	*Areca catechu*	Deterioration of psychosis in patients with preexisting psychiatric disorders; known carcinogen contributing to cancer of the mouth, pharynx, esophagus and stomach when chewed.	(Craft, 2004)
Aristolochic acid	*Aristolochia serpentaria*	Kidney toxicity associated with kidney failure; associated with development of cancer, particularly of the urinary tract, known carcinogen	(Aronson, 2009)
Atractylate	*Atractylis gummifera*	Liver damage, nausea, vomiting, epigastric and abdominal pain, diarrhea, anxiety, headache and convulsions, often followed by coma	(Aronson, 2009)
Bitter orange	-	Fainting, arrhythmia, heart attack, stroke, death	(Aronson, 2009)
Broom	*Genista tinctoria*	Uterotonic properties, nausea vomiting, and diarrhea, contraindicated for pregnancy and breast feeding.	(Aronson, 2009)
Buckthorn bark and berry	*Rhamnus frangula*	Vomiting and cramp-like prolonged use leads to the loss of electrolytes, especially potassium ions, which can result in hyperaldosteronism, inhibit intestinal motility and, in rare cases, cause cardiac arrhythmia, nephropathy, muscle weakness, edema, muscle weakness and accelerated bone degeneration.	(Craft, 2004)

Name of Drug	Scientific name	Adverse effects	Reference
Cascara Sagrada bark	*Rhamnus purshiana*	Abdominal pain, diarrhea, potentially carcinogenic.	(Craft, 2004)
Coltsfoot	*Tussilago farfara*	Liver damage, cancer	(Heather, 2004)
Comfrey		Hepatotoxicity Liver damage, cancer.	(Craft, 2004)
Country mallow	*Sida cordifolia*	Heart attack, heart arrhythmia, stroke, death	(Craft, 2004)
European Mistletoe	*Viscum album*	Toxic to cardio and central nervous systems, gastrointestinal bleeding	(Craft, 2004)
Ephedra	*Ephedra sinica*	Agitation and palpitations, hypertension, irregular heart rate, insomnia, nervousness, tremors and seizures, paranoid psychoses, heart attacks, strokes, and death", kidney stones	(Craft, 2004)
Flavonoids (contained in many medicinal plants)	-	Vomiting, diarrhea, headache, loss of appetite, gynecomastia; signs of overdose range from mild cardiac arrhythmias to life-threatening ventricular tachycardia, atrial tachycardia with AV block, stupor, confusion, hallucinations, impaired vision, depression, and/or psychoses.	(Craft, 2004)
Maidenhair tree	*Ginkgo biloba*	Mild gastrointestinal complaints, headaches, and allergic reactions are very rare side effects.	(Craft, 2004) (Heather, 2004)
American Ginseng	*Panax quinquefolius*	Insomnia, hypertension, and edema have been reported as symptoms of overdose.	(Craft, 2004) (Heather, 2004)
Hawthorn	*Crataegus monogyna*	Potentiates digitalis activity, increases coronary dilation	(Craft, 2004)
Horse chestnut	*Aesculus hippocastanum*	Allergic reaction, inflammation of the mucous membranes in the gastrointestinal tract can occur as a rare side effect after internal use.	(Craft, 2004)
Kava	*Piper methysticum*	Potentates CNS sedatives, sedation, oral and lingual dyskinesia, torticollis, oculogyric crisis.	(Craft, 2004)
Khat	*Catha edulis*	Chronic liver dysfunction	(Craft, 2004)

Name of Drug	Scientific name	Adverse effects	Reference
Liquorice root	*Glycyrrhiza glabra*	Hypokalemia, hypertension, arrhythmias, edema	(Heather, 2004)
Lobelia	*Lobelia inflata*	Toxicity, rapid heartbeat, hypotension, coma, death	(Craft, 2004)
Milk thistle	*Silybum marianum*	Dyspeptic complaints, liver and gallbladder complaints.	(Craft, 2004)
Pennyroyal	*Mentha pulegium*	Liver damage	
Pyrrolizidine alkaloids		Hepatotoxic and carcinogenic effects, liver damage	(Craft, 2004)
Reserpine	*Rauvolfia serpentina*	Sedation, inability to complete tasks, mental depression, nasal congestion, increased gastric secretion and mild diarrhea	(Craft, 2004)
Safrole	*Sassafras albidum*	Liver damage	(Craft, 2004)
Senna	*Senna alexandrina (Cassia senna)*	Abdominal pain, diarrhea, potentially carcinogenic, with others can potentiate cardiac glycosides and antiarrhythmic agents, liver damage	(Craft, 2004)
Valerian	*Valeriana officinalis*	Drowsiness, GI upset, headache, palpitations, insomnia, over-sedation, overstimulation	(Craft, 2004)
Yohimbe	*Corynanthe yohimbe*	Rapid heart rate, hypertension, hypotension, heart problems, death, congestion of gentiles,nausea	(Craft, 2004)

Regulation

National regulation and registration of herbal medicines vary from country to country. Where herbal medicines are regulated, they may be categorized as either prescription or non-prescription medicines. Herbal products may also be categorized other than as medicines. Moreover, the regulatory status of a particular herbal product may differ in different countries. The national regulatory framework usually also includes involved qualified providers and distributors of the respective substances. Regulatory status consequently determines the access to or distribution route of these products (Mann and Andrews, 2007).

Quality Assurance and Control

Quality assurance and control measures, such as national quality specification and standards for herbal materials, good manufacturing practices (GMP) for

herbal medicines, labeling, and licensing schemes for manufacturing, imports and marketing, should be in place in every country where herbal medicines are regulated. These measures are vital for ensuring the safety and efficacy of herbal medicines. Weak regulation and quality control may result in a high incidence of adverse reactions attributable to poor quality of herbal medicines, in particular, resulting from adulteration with undeclared potent substances and/or contamination with potentially hazardous substances and residues (Patel and Patel, 2011).

The requirements and methods for quality control of finished herbal products, particularly for mixture herbal products, are far more complex than for other pharmaceuticals. The quality of such products is influenced by the quality of the raw material used. Good agricultural and good collection practices for medicinal plants, including plant selection and cultivation, are therefore important measures.

Safety Monitoring of Herbal Medicines

The most common sources of information on adverse events and reactions to medicines are clinical trials and spontaneous reports (voluntary, unsolicited communications on marketed medicinal products). The latter ordinarily far exceed the former in numbers and type, especially serious reports, over the lifetime of a product. In some countries, adverse reaction reporting by physicians is mandatory; such reports are regarded as spontaneous (Anonymous, 2004.)

In many countries, providers of herbal medicines other than physicians, dentists, pharmacists, and nurses are excluded from reporting systems. If adequate coverage of herbal medicines is to be achieved, national reporting schemes should be developed to include all providers of herbal medicines (both prescribers and dispensers), and providers of traditional, complementary, and alternative medicine, according to national circumstances (Mann and Andrews, 2007).

Pharmacovigilance Software

PvNET is a comprehensive pharmacovigilance solution with adverse event reporting, adverse drug reactions (ADR) data management and regulatory reporting of ICSR (Individual Case Safety Report) that goes beyond mere compliance (Shetti *et al.,* 2011).PvNET is an across-the-board drug safety software successfully audited against GMP standards, 21 CFR compliance and ICH E2B.

Discussion and Conclusion

Although the National Pharmacovigilance program has encouraged reporting of all suspected drug-related adverse events including those caused by herbal/ traditional/alternative medicines, the number of reports related to ayurvedic / herbal drugs has been abysmally low.

Several challenges that preclude identification and reporting of adverse reaction to ayurvedic drugs can be identified related to detection, assessment and preventation of adverse reaction.

The path is full of obstacles, including method to study drug safety problem which have not evolved in Ayurveda. Although information related to medicines exists in the verses of ancient treatises of ayurveda, it is not easily accessible. Signal detection is difficult because there is an inherent belief about safety of ayurvedic medicines leading to lack of reporting and collection of reports relating to any formulation. Lack of quality assurance and quality control in manufacture of ayurvedic medicines, which act as a confounding factor in diagnosis the adverse reaction. The success of pharmacovigilance system is in the ability to prevent further adverse reaction successfully by understanding and using information collected with ayurvedic medicines, the challenges would be multiple levels. Communication between the practitioners and policy makers of orthodox Western medicines and traditional medicines is not adequate. The patients are not adequately aware that ayurvedic medicines can cause adverse reaction and can take medicines for years on and with no monitoring as they believe that these medicines can do no harm (Tnatte and Bhalerao, 2008).

In this review, based on observations there are several ways we can move forward in attempting to embrace pharmacovigilance system in ayurveda.

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