Short review

Safety profile of herbal drugs: urgent need for monitoring

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Background: In developing countries, herbal medicines are the natural answer to many ailments and are often locally available in affordable cost. Hence, their use remains popular and widespread in many countries. Due to the varying topography and climatic conditions, a variety of herbs and medicinal plants are found in Nepal.

The public generally considers natural products as safe. Also, the manufacture, sale, distribution and use of these medicines are not monitored by the regulatory authorities. Doctors also don't routinely take drug history regarding use of herbal drugs.

Several commonly used herbal drugs like gingko biloba, garlic, ginseng, peppermint oil, senna, primrose oil, isapghol, ephedra are reported to cause significant adverse drug reactions which can cause mild gastrointestinal upset to life threatening bleeding disorders.

The safety concern regarding allopathic drugs is strengthening and the awareness regarding this issue is increasing rapidly. However, monitoring the safety of herbal drugs is still problematic due to various reasons. Some of reasons are lack of accurate information regarding their safety profile, lack of information on the exact constituents of the conventional herbal formulations, adulteration in the drug formulations, poor manufacturing standards etc.

Conclusion: Team efforts involving doctors, pharmacists, pharmacologists, pharmacovigilance center personnel and drug regulatory authorities will be beneficial in implementing appropriate steps towards safe use of herbal drugs. The participation of patients and the manufacturers is also vital.

Worldwide, many initiatives have been taken in the recent past towards herbal drug safety. In Nepal the concept of drug safety issues is still in the infancy stage and the national drug controlling authority has taken the initial steps in monitoring the safe use of allopathic drugs. The need for an herbal drug safety monitoring system is very essential for a country like Nepal.

Key words: Herbal drug, safety profile, monitoring.

Introduction

The use of medicinal plants is accepted as the most common form of traditional medicine. Among the entire flora, it is estimated that 35 000 to 70 000 species have been used for medicinal purposes. Some 5000 of these have been researched. In developing countries, herbal medicines continue to play an important role in primary health care, especially where coverage of modern health services is limited. Even in industrialized countries, herbal medicines are increasingly popular. [1]Herbal medicines are the natural answer to many ailments and are often locally available. For this reason, their use remains widespread and they are popular in many countries. [2]

Public generally considers natural products such as 'health foods' and herbal remedies to be safe and beneficial. Consequently, these substances are largely unregulated contributing to the misconception that they are innocuous: patients don't feel the need to tell their physicians that they are using them, and physicians don't routinely ask patients if they are taking them. Yet these products have a

potential to alter the action of modern drugs, sometimes with adverse clinical effects.[3]

Many people believe that these products are natural and therefore free from side effects, but this is not necessarily the case. Various adverse reactions can occur.[4] A recent publication has suggested that adverse drug reactions to herbal remedies are even more under-reported than those to conventional over-the- counter (OTC) medicines.[5]

Due to the varying topography and climatic zones ranging from the plains of the 'terai' to the alpine grasslands, a variety of herbs and medicinal plants are found in Nepal that play an important role in self-medication.[6] A study from Western Nepal identified that self-medication was practiced by 39 families of the 112 surveyed in the study. Traditional home remedies accounted for 18.9 % of the drugs used for self-medication. The common sources of drugs used were the medical store and herbs and roots from the surrounding forests and also obtained from the courtyards of the houses.[7]

It is very much possible that many patients in Nepal would be taking herbal drugs. Many would be taking them concurrently with allopathic medicines. In this article, we attempt to provide an overview of the safety profile of herbal medicines and discuss the importance of monitoring the adverse drug reactions (ADRs) due to these drugs.

How safe are herbal drugs? Unlike synthetic pharmacologic agents, herbs are considered dietary supplements in the United States and are therefore not subject to careful review before marketing.[8] Because they are not classified as drugs, no proof of quality, efficacy, or safety is required from the manufacturers.[9] There are no regulations governing which herbs can be marketed for various conditions and their optimal recommended dosages. Dietary supplements are not permitted to be marketed for the treatment of health conditions, although they are used that way, and there is in fact evidence for such use. Guidelines concerning correct identification of the herb, labeling of active ingredients, and establishment of purity are nonexistent. Lack of quality control too often leads to misidentification and contamination with toxic ingredients including pesticides, chemicals, heavy metals, and hidden drugs with their resultant ill effects. Too often, these agents are surreptitiously included in herbal preparations. [10]

Toxicity profile of some commonly used herbal drugs: [11-14] Some of the commonly used herbal drugs that are known to cause side effects are mentioned below.

1. Gingko biloba: It can cause spontaneous bleeding. There have been several published incidents of bleeding problems associated with ginkgolide B, a platelet-activating factor inhibitor that is a component of ginkgo biloba.
2. Garlic: Garlic can lower cholesterol level. It can cause increased INR with warfarin, increased post-operative bleeding, hypoglycemia and increased bleeding with Aspirin, subdural haematoma.
3. Ginseng: It increases the body's resistance to stress and builds up general vitality. It can cause hypertension and mastalgia. Reports have linked ginseng to potential medication interactions with warfarin, alprazolam, donezepil and trazodone and digoxin. Ginseng should be avoided in patients who are on MAO inhibitors, Nifedipine and in cancer therapy.
4. Peppermint oil: Products containing this ingredient have been associated with bronchospasm, anaphylactoid reaction and duodenal ulcer perforation.
5. Senna extract: It has cathartic properties and is used for constipation. It can cause grand mal seizures, circulatory failure, hypertension and anaphylactic reaction. Regular use should be avoided if the patient is taking either thiazide diuretics or corticosteroids to prevent electrolyte imbalance.
6. Primrose oil: It has been used for various skin ailments as well as for pre-menstrual syndrome. It can cause undiagnosed temporal lobe epilepsy, especially in schizophrenic patients and those on drug therapy for epilepsy.
7. Isapghol: It is stated to possess demulcent and laxative properties. It can cause bronchospasm, asthma and intestinal obstruction. If swallowed dried, ispagula may cause oesophageal obstruction.
8. Ephedra: Adverse reactions reported range from high blood pressure, irregular heartbeat, nerve damage, injury, tremor, headache, seizures, heart attack, stroke, and death.
9. Liquorice: Used as an expectorant and carminative in food. Regular high doses should be avoided in conjunction with steroids including oral corticosteroids.

Problems in monitoring herbal drug toxicity: [13-18] Although, the safety profile of the herbal medicines is understood to an extent, it becomes very difficult to monitor their effects. The major problems in herbal drug safety monitoring are mentioned below.

1. Lack of accurate information regarding the safety profile: Evidence regarding the nature and incidence of

adverse effects caused by herbal medicines is woefully incomplete. Although there are number of herbal drugs available in the market, there is hardly any source of drug information sources unlike the allopathic ones.

2. Lack of information on exact constituents: Many times, the exact constituents of the herbal drug formulations are not known. The composition of the formulations may even change according to the raw materials. For example, the factors like the geographical location, climate, soil, season, storing, methods of extraction etc.

3. Combined use of allopathic and herbal medicines may cause ADRs: Many patients often take both the alternative as well as allopathic medicines for early symptomatic relief and better cure. There are reports of toxicity caused due to the drug interaction between the herbal medicine and the allopathic medicine. In the WHO database there are 30,912 reports involving drugs containing at least one herbal ingredient. In 11,561 cases the drug is reported as suspected or interacting. Of these 11,561 cases 252 are reported as interacting. Even though the number appears smaller, increasingly more reports are received by WHO ADR monitoring centre underlining the seriousness of the issue.[14]

4. Adulteration in the complementary drug formulations: . Many times, some of the complementary drug formulations are adulterated with corticosteroids for better symptom relief. This may predispose the patients to develop ADRs. Some herbs require specialist treatment after collection. For example high quality of Asian Ginseng comes from the plants of certain varieties that are at least 7 years old, and which have been fermented and dried before processing. This makes them very expensive and liable to adulteration, the most common adulterant being liquorice which has shown adverse reactions

5. Improper manufacturing: Unlike conventional drugs, herbal products are not regulated for purity and potency. Thus, some of the adverse effects reported for herbal products could be caused by impurities (e.g., allergens, pollen and spores) or batch-to-batch variability during the manufacturing process.

6. Lack of regulatory rules: The lack of proper regulation and licensing has complicated the situation and thereby making it difficult to ensure the quality of the herbal products. In many countries, herbal medicines are not regulated and not marketed as medicines but marketed as dietary supplements. British and US pharmacopoeia committees are trying to improve standards for these products. One issue in monitoring the standards is which chemical constituent should be monitored as the active constituents are not conclusively determined for many of these products.

7. Improper drug history: Many times, the users of herbal medicines often do not inform their doctor, and conventional healthcare professionals some times lack sufficient knowledge of herbal medicines to advice their patients responsibly.

Ensuring herbal drug safety- a multidisciplinary approach: [8,15,16]

Like any other system of medicines, in order to ensure safety of herbal drugs a team approach is essential. Some of the responsibilities of the key people involved in ensuring drug safety are mentioned below.

1. Doctors: The responsibility of tracking down ill effects of herbal therapy is in the hands of physicians and patients, as manufacturers are not required to report such adverse events to the drug regulatory authority even in countries like the United States of America where the use of drugs are monitored carefully. The doctors should be **a**ware of use or misuse of traditional medicine by patients and should be aware of traditional medicine information centers. They should also be keen in promptly reporting any suspected ADRs to the ADR reporting centers. The doctors should also have adequate knowledge of potential side effects of traditional medicines.

2. Pharmacists/Pharmacologist: Pharmacists and Pharmacologists should report any suspected ADRs related to the herbal medicines and should document it. They should also educate their colleagues and their students regarding the possibility of ADRs due to these agents.

3. Role of Pharmacovigilance Centers: The pharmacovigilance centers should record and monitor ADRs due to herbal medicines and they should also harmonize the use of certain accepted and important terms in traditional medicines. These centers should also strive to establish the causal relationship between the herbal drug and the ADRs and their predictability in the future.

4. Role of patients: Being the ultimate users, patient involvement is paramount in preventing, identifying and managing the ADRs due to herbal products. The patients should not take traditional medicines, if pregnant or attempting to become pregnant without consulting a qualified medical practitioner. They should also exercise caution if they are nursing mothers. Extra care should be taken while giving these medicines to children. The patient should prefer only those herbal medicines that clearly label all the ingredients mentioned in it. The patients before taking any OTC medications should keep in mind the possible interactions between the OTC medication and the herbal drug. Patients

should be careful while taking drugs from two different system of medicine (for example, allopathic and herbal medicines). This may predispose them towards ADRs.

5. Role of manufacturers: Herbal drug manufacturers should introduce package inserts with details of ingredients, indications, ADRs, precautions and contraindications regarding their herbal products. A review of published adverse drug reactions of herbal medicines has identified the main cause of such events to be contamination and adulteration. Hence the quality assurance is vital. [19]

6. Role of drug regulatory authority: The drug regulatory authority of any country has a vital role in prudent use of medicines. The drug regulatory authority should have stringent quality assurance regulation at the site of manufacturing and should propose laws to regulate herbal products. Random sampling of raw materials, in process materials and final products should be carried out. They should also insist on maintaining documentation of procedures and verification by the manufacturers, distributors and other concerned personnel. In many instances, the herbal medicines are promoted under dietary supplements. The regulatory authorities should clearly classify the dietary supplements from dietary supplements.

Current status of herbal drug safety issues worldwide: The use of herbal medicines poses sensitive challenges to drug regulatory authorities responsible for the safety, efficacy and quality of medicines both nationally and internationally. An informative presentation on these issues was made by the WHO Programme on Traditional Medicines at the Twenty-third Annual Meeting of National Centers participating in the WHO International Drug Monitoring Programme held in Tunisia in November 2000. [1]

The following recommendations were made by the working group regarding the monitoring of herbal drug safety.

1. A monitoring and surveillance system for herbal medicines should be developed in each country
2. Basic information should be made available to all countries, and access improved to international data bases
3. Pharmacovigilance activities should be strengthened between the WHO Programme on Traditional Medicines and the Uppsala Monitoring Centre
4. Adverse drug reaction reporting forms for herbal medicines should be in a similar format as those currently used for pharmaceuticals.
5. Education of health professionals on the rational use of herbal medicines should be carried out by qualified herbalists
6. Public information and educational tools for consumers should be developed.
7. Collaboration with poison control centers should be established
8. Health authorities should promote the development of pharmacognosy

Current status of herbal drug safety issues in Nepal: In countries like Nepal, where plenty of medicinal plants are available, the use of these drugs is a reality. However, the data regarding the monitoring of herbal drug safety are lacking in Nepal. Recently the Department of Drug Administration (DDA), Kathmandu, the National drug regulatory authority of Nepal has taken steps to establish an ADR monitoring program in Nepal. It has been given an associate member status by the Uppsala Monitoring Center, Sweden, the WHO collaborating Center for International Drug Monitoring. The ministry of Health and Population, Nepal has designated DDA as the national center for ADR monitoring. [20] However, as of now to the best of our knowledge, there is no mechanism available in the country to monitor herbal drug safety.

Conclusion

Although herbal drugs may be associated with considerable amount of side effects, the use of these drugs cannot be ignored. Moreover, they are available at low cost and are accessible even in remote locations. In many circumstances, these agents are available as house hold remedies. As the developing countries are moving towards the era of patenting of drug formulations, the use of our own indigenous drugs dear more attention. It is essential to ensure that the herbal products are prescribed after having correct drug information and a thorough drug history is taken before prescribing them. Even before administering an allopathic drug, a thorough drug history for herbal medicines should be taken.

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