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Oriental Herbs –Western Drugs
Recognition and Prevention of Adverse Interactions

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Introduction

Today an increasing number of patients in Ireland are being treated simultaneously with both Western and Oriental medicine. It is not uncommon for patients to seek herbal treatment while taking a number of prescription drugs.[1] Safety is therefore an important issue as herbalists, doctors, pharmacists, and patients are concerned about possible negative interactions when simultaneously taking herbs and prescription drugs. Complicating things are estimates suggesting that 50-70% of patients fail to report herbal medicine use to medical doctors and many patients fail to report prescription drug use to herbal practitioners.[2] The Irish Pharmaceutical Union recently launched a campaign to encourage people to use medicines correctly and stated that one of the common errors made by patients was the mixing of drugs with herbal or other products without first checking potential adverse interactions.[3] Regrettably, at present, there is very little information published on herb-drug interactions. However, with a general understanding of pharmacology, one can anticipate potential interactions and thus take precautions to avoid adverse reactions.[4]

A potential interaction refers to the possibility that one substance may alter the clinical effectiveness of another substance when two or more substances are given at the same time. The net result may be an increase or a decrease in effect of one or both substances. As with modern drugs, herbal medicines interact with drugs in two general ways: pharmacokinetically and pharmacodynamically.

Pharmacokinetic Interactions

Pharmacokinetic interactions result in alterations of the herb-drug:

1. Absorption,
2. Distribution,
3. Metabolism
4. Elimination.

These interactions affect herb-drug action by quantitative alterations, either increasing or decreasing the amount of herb or drug available to have a therapeutic action on the body.

1. Absorption

The majority of all absorption occurs in the intestines, where herbs or drugs must pass through the intestinal wall to enter the blood. Several mechanisms may interfere with this process.

The absorption of herbs may be adversely affected when the herbs are given together with some drugs, due to binding in the gastrointestinal tract. Drugs such as Antepsin (sucralfate), Questran (cholestyramine) and Colestid (colestipol) may bind to certain herbs, forming an insoluble complex, and decrease absorption of both substances because the size of the insoluble complex is too large to pass through the intestinal wall. Gan Cao (Glycyrrhizae Uralensis radix/licorice root) for example, may reduce the absorption of oral tetracyclines.

Antacids such as Tagamet (cimetidine), Pepcid (famotidine), Axid (nizatidine), Zantac (ranitidine) and Losec (omeprazole) may neutralize, decrease or inhibit the secretion of the stomach acid. With the subsequent decrease of stomach acid, herbs may not be broken down properly, leading to poor absorption in the intestines. To minimize the risk of interaction, it is best if the drugs and the herbs are taken separately by two to three hours.

Finally, drugs that affect the gastrointestinal motility may affect the absorption of herbs. For example, Maxolon (metoclopramide) increases gastrointestinal motility and possibly decrease absorption of herbs as they stay in the intestines for a shorter period of time. Conversely, drugs such as Serenace (haloperidol) decrease gastrointestinal motility and may increase absorption of herbs. Therefore, it may be necessary to make an appropriate adjustment in the dosage of herbs if the patient is taking the above medication.

2. Distribution

After absorption, herbs or drugs need to be carried and released to different parts of the body in order to exert their therapeutic action.

At the present time, most drugs and herbs do not appear to have any clinically significant interactions affecting distribution and can be safely taken together. Interactions between herbs and drugs are more likely to occur during the distribution phase if the drug has a narrow range of safety index and are highly protein-bound. For example, warfarin is an anticoagulant medication, which is very highly bound to protein and has a very narrow range of safety index. Warfarin interacts with various drugs, vitamins, herbs and foods.

Some known examples that interact with Warfarin include aspirin, ibuprofen, vitamin E, fish oil (omega-3 fatty acids) some types of tea (e.g. chamomile) and green leaf vegetables. These items interact with Warfarin by enhancing its effectiveness and thus leading to prolonged bleeding, or by decreasing its effectiveness and thus increasing the risk of vascular thrombosis.

Unfortunately, due to a lack of research, it is very difficult to predict whether an individual herb will interact with warfarin. Chan et al (1995) claims that Dan Shen (radix Salviae Miltiorrhizae) potentiates warfarin by increasing its plasma concentration and prothrombin time, however, Yu et al (1997) reported a case of increased coagulation caused by the interaction of Dan Shen with warfarin. Lo (1995) reported that the administration of warfarin and Dan Shen lowered the prothrombin time (increased coagulation) as compared with warfarin only. Backon (1986) reported interactions between warfarin and Sheng Jiang (Ginger), as ginger is an inhibitor of thromboxane snynthetase. Miller (1998) has reported that spontaneous bilateral subural haematomas have occurred with the combined use of warfarin and Ginkgo Biloba. These haematomas have been attributed to ginkgolide B, a potent inhibitor of platelet activating factor. Chung et al (1987) advises that it would be prudent therefore to avoid prolonged use of ginkgo together with aspirin, warfarin, heparin and non-steroidal anti-inflammatory drugs. Lee (1999) suggested, on the basis on one case history, that Dang Gui (Angelica sinensis) may increase prothrombin time and international normalized rates (INR). A number of reports claimed a decrease in INRs when Ginseng and Warfarin were used together.

Close observation of the patient's condition is the best precautionary measure. If the patient shows abnormal signs of increased bruising, petechia, purpura and bleeding then the dosage of herbs may need to be adjusted or withdrawn altogether and the patient's medical doctor should be advised immediately.

3. Metabolism

Most herbs and drugs are metabolised by the liver to inactive derivatives. The rate at which the liver metabolises these herbs and drugs determines the length of time these herbs or drugs stay active in the body. If the liver were induced to speed up its metabolism, herbs and drugs would be inactivated at a faster pace and the overall effectiveness of ingested substances would be lower. On the other hand, if the liver were induced to slow down its metabolism, herbs and drugs would be inactivated at a slower pace and the overall effectiveness of the substances would be higher.

In general, drugs that induce liver metabolism do not exert an immediate effect. The rate of liver metabolism changes slowly over several weeks. Therefore, the effect of increased liver metabolism is not seen until weeks after the initiation of drug therapy. For example, Epanutin (phenytoin) and Tegretol (carbamazepine) increase the rate of liver metabolism. Therefore, the herbs may be inactivated more rapidly and their overall effectiveness may be lower. Under such circumstances, the patient may need a higher dose of herbs to achieve the desired effectiveness.

On the other hand, drugs that inhibit liver metabolism have an immediate onset of action. The rate of liver metabolism may be greatly impaired within a few days. Therefore, the herbs may be inactivated more slowly and the overall effectiveness may be prolonged. In this case, one may need to lower the dosage of herbs to avoid unwanted adverse reactions. Examples of drugs that slow down liver metabolism include Tagamet (cimetidine), erythromycin and the antifungals Diflucan (fluconazole), Sporonox (itraconazole) and Nizoral (ketoconazole). Smith (1998) points out that the bioflavonoid quercitin present in many plants for example, Yu Xing (herba cum radice Houttunya cordatae) and Bai Gao (semen ginkgo bilobae) could interact with haloperidol, clozapine, olanzapine, tricyclic antidepressants to reduce metabolism of the liver enzyme 1A2 of the cytochrome P450 liver enzyme system.

4. Elimination

In addition to the liver, the kidney is also responsible for eliminating herbs and drugs from the body. If the kidney(s) were damaged, then the rate of elimination by the kidneys would be slowed down leading to an accumulation of herbs and drugs in the body. Important examples of drugs that damage the kidneys include Abelcet, Amphocil, Ambisome (amphotericin B), Methotrexate, Nebcin (tobramycin), and Gentimicin. As a safety precaution, it may be necessary to lower the dose of herbs to avoid unnecessary and unwanted adverse reactions

The pharmacokinetic interactions listed in this section include both theoretical and actual interactions. Though such interactions are possible, the extent and severity of each interaction will vary depending on the specific circumstances, such as dosage, sensitivity, body weight and metabolic rate.

Pharmacodynamic Interactions

Pharmacodynamic interactions cause alterations in the way the herb or drug affects a tissue or organ system either through synergistic or antagonizing effects. These interactions are generally more difficult to predict and prevent than pharmacokinetic interactions. Most of the pharmacodynamic interactions known now are documented through actual case histories as opposed to laboratory experiments. The best way to prevent this type of interaction is to follow the patient closely and monitor all clinical responses including signs, symptoms and any abnormal reactions

Analysing the therapeutic effect of the herbs and drugs best identifies pharmacodynamic types of herb to drug interactions. Simultaneous use of herbs and drugs with similar therapeutic actions will undoubtedly pose potential risk of interactions. For example, Suan Za Ren (Semen Ziziphi spinosae/sour jujube seed) has a synergistic effect with many other sedatives and hypnotic agents. Dang Gui (Radix Angelicae sinensis) may potentiate the effect of benzodiazepines. Giovanni (2000) states that Gan Cao (Glycyrrhizae / licorice root) used as a single herb and only at very high doses may potentiate the effects of hydrocortisone due to inhibition of the catalytic enzyme 11B-hydroxysteriod dehydrogenase.

Chen (1999) points out that the highest risk of clinically significant interactions occurs between herbs and drugs that have sympathomimic effects, cardiovascular effects, diuretic effects, anticoagulant effects and anti-diabetic effects.

Herbs with sympathomimic effects may interfere with anti-hypertensive and antiseizure drugs. The classic example of an herb with sympathomimic effects is Ma Huang (Ephedrae sinica), which contains ephedrine, pseudoephedrine, norephedrine and other ephedrine alkaloids. Ma Huang may interact with many other drugs and disease conditions and should always be used with caution in patients who have hypertension, epilepsy, diabetes, and thyroid conditions. Ma Huang may potentate the effects of MAOI Antidepressants, phenothiazines, theophylline and Xanthine derivatives.

The use of herbs with a diuretic action and diuretic drugs may have synergistic effects, making hypertension more difficult to control or hypotensive episodes more likely. The dosage of herbs and/or drugs must be adjusted to achieve optimal treatment outcome. Commonly used diuretic herbs include Fu Ling (Poria Cocos/China root), Zhu Ling (Sclerotium Polypori Umbellati), Che Qian Zi (Semen Plantaginis/plantago seeds), and Ze Xie (Rhizoma Alismatis Plantago-acuaticae). In addition Gan Cao (Glycyrrhizae / licorice root) may cause sodium retention and excessive potassium depletion but this only occurs in very high doses over a prolonged period of time.

Herbs with anticoagulant effects include herbs that have blood-activating and blood-stasis-removing functions. Such herbs may interfere with anticoagulant drugs, such as warfarin, to prolong the bleeding time. Herbs that interfere with warfarin include Dan Shen (Salviae Miltiorrhizae), Dang Gui (Angelica Sinensis), Chuan Xiong (Radix Ligustici Wallichii /Szechuan lovage root), Tao Ren (Semen Persicae/peach kernel), Hong Hua (Flos Carthami Tinctorii/Safflower Flower) and Shui Zhi (Hirudo seu Whitmania). The synergistic interaction between herbs and warfarin may be advantageous for the patient as the dosage of both the herbs and the drugs can be reduced without compromising clinical effectiveness. The reduction in dosage will also decrease the frequency and severity of side effects of the drugs. Optimal treatment, however, is directly dependent on careful titration of the herb and drug, cooperation from the patient, and good communication between the doctor and herbalist.

Anti-diabetic herbs may interfere with anti-diabetic drugs by the enhancing hypoglycaemic effects. The dosage of herbs and drugs must be balanced carefully to effectively control the blood glucose level without causing hyper- or hypoglycaemia. Herbs with definite hypoglycaemic effects include the following pairs of herbs: Zhi Mu (Radix Anemarrhena Asphodeloidis) and Shi Gao (Gypsum Fibrosum); Xuan Shen (Radix Scrophularia Ningpoensis) and Cang Zhu (Rhizoma Atractylodis); and Shan Yao (Radix Dioscorea Oppositae/Chinese yam root) and Huang Qi (Radix Astragali /milk-vetch root).

Discussion:

Drug to drug interactions are a much more common and serious problem than either herb-drug or herb-herb interactions. A research study to estimate the incidence of serious and fatal adverse drug reactions in hospitalised patients, for example, published in the Journal of the American Medical Association in 1998 states that properly researched, regulated, prescribed and properly used drugs are the fourth most common cause of death in the USA. This is over 100,000 deaths per year. The study also reported that over 2 million serious adverse drug reactions (defined as requiring hospitalisation or causing permanent disability) occur each year in the USA. A report by Professor Breckenridge of Liverpool University claims that up to 20,000 deaths a year in Britain may be linked to adverse drug reactions, that adverse drug reactions may be implicated in 5% of all hospital admissions and that they may occur in as many as one in five hospital in-patients. Among patients taking five or more drugs, there is a 50% chance of an adverse reaction. [14,15].

As Practitioners of Chinese Herbal Medicine use very complex herbal prescriptions tailored to the individual patient we would very seldom use the herbs discussed in this paper on their own. They are usually combined with other herbs in a formula in such a

way to modulate their potential side effects. Ephedrine, for example has pronounced sympathomimetic effects, but the source of it, the plant Ma Huang (Ephedrae sinica), has considerably less sympathomimetic effects when given as a whole because the balance of alkaloids contained in it, is such that through checks and balances it results in fewer, less severe side effects. Nevertheless, if Ephedrae sinica is used unwisely it may cause sympathomimetic effects in patients with prostatic enlargement to the extent that urination ceases or may precipitate a glaucoma attack or stroke in hypertensive patients. These effects were well known to Practitioners of Chinese Herbal Medicine so Ma Huang has always been combined with other herbs (e.g. Radix Paeoniae Lactiflorae - Bai Shao) in order to further minimize its side effects.

Many patients now self prescribe single herbs like Ginseng and studies has shown that the use of single herbs carriers a greater risk of interaction with drugs than personalized Chinese herbal formula. The potential for adverse interaction increases with the simultaneous use of a number of drugs and a number of single herbs. However, the situation is often more complex as it is not uncommon for one patient to seek care from several doctors for an ailment. As a result, a patient may be taking multiple drugs and herbs simultaneously. It is extremely very difficult to predict whether the combination of all these medications will lead to adverse interactions.

Conclusion

The probability that herbs are being combined with prescription drugs is quite high. Lambrecht et al (2003) conclude that herb-drug interactions remain relatively rare when considering the increasing number of people taking herbal products. The fact that only a small number of case reports have been reported is a sign that the majority of herbal medications are relatively safe. In advising patients regarding herb-drug adverse interactions it is a good rule of thumb is to advise them to:

1 Take as few drugs and single herbs as possible.
2 Take herbs and drugs at different times. As most drugs are taken with meals to reduce stomach irritation is it better to take herbs at least two hours before or after meals.
3 Avoid taking herbs that have known adverse interactions with drugs, for example, Dang Gui with Warfarin; Fuling with diuretics; or Ma Haung with antihypertensives.
4. Avoid herbs where there are symptoms of liver or renal failure

An open-minded approach, allowing enough time to obtain information from the patient on their use of drugs and herbs is essential. If the patient feels the medical or herbal practitioner is critical and judgemental, they are less likely to divulge their concurrent use of Western and Oriental Medicine.

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