Clinically Important Drug-Herb Interactions

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Scope of the lecture

Herbal medicines are widely used throughout the world and most people consider them safe. As a result patients do not disclose such information to their clinicians. However, several commonly used herbal medicines have clinically significant pharmacokinetic or pharmacodynamic interactions with drugs causing either treatment failure or drug toxicity. Grapefruit juice increases bioavailability of many drugs most noticeably calcium channel blockers due to inhibition of intestinal CYP3A4 and P-glycoprotein. St. John's wort, a popular herbal antidepressant reduces blood level of over 40 drugs due to induction of cytochrome P-450 drug metabolizing enzymes or P-glycoprotein, causing treatment failure. St. John's wort also interacts with various SSRIs, SNRI and other antidepressant causing serotonin syndrome, a potential medical emergency. Clinically significant drug-herb interactions have been reported with other commonly used herbs such as ginkgo biloba, garlic, ginger, feverfew, and echinacea valerian and milk thistle. However, therapeutic drug monitoring can identify some clinically important drug-herb interactions. Many published reports clearly indicate great danger of using herbal medicines in organ transplant recipients, patients taking warfarin and patients with HIV being treated with HAART due to significant drug-herb interactions.

Learning Objectives

After attending this session audience will learn:

1. Common herbal products that cause clinically significant drug-herb interactions.
2. Class of drugs commonly encountered in drug-herb interactions.
3. How therapeutic drug monitoring can be utilized to identify certain drug herb interactions.

Extended Abstract

Introduction

According to WHO, approximately 80% world population relies on herbal medicines. In addition, many patients take herbal medicines concurrently with conventional drugs.
In U.S, the concurrent use of herbals and conventional drugs occurs in 20-30% patients.
60-85% Native Africans use herbals in combination with other drugs.
In Taiwan, 94% patients and in Korea 83% patients simultaneously use prescribed drugs and herbal supplements. Therefore, clinically significant drug herb-interactions are often encountered in outpatient clinical or emergency room depending on severity of such interactions. Drinking grapefruit juice in the morning with breakfast is popular but unfortunately many people also take their medications in the morning. Grapefruit juice increases toxicity of many drugs.

Most drug-herb interactions are pharmacokinetic in nature where the herbal supplement affects the metabolism of drugs. For example, St. John's wort increases hepatic metabolism of many drugs resulting in sub-therapeutic drug level. Drug-herb interaction may be also pharmacodynamic in nature where one herbal product may stimulate pharmacological response of a drug. Fortunately, only a fraction of over the counter medications and prescription medications account for most of the interactions with herbal supplements. Sood et al surveyed 1818 patients and identified 107 drug-herb interactions that had clinical significance. The five most common herbal supplements (St. John's wort, ginkgo, garlic, valerian and kava) accounted for 68% of such interactions and four different classes of prescription drugs (antidepressants, antidiabetic, sedatives and anticoagulation medications) accounted for 94% of all clinically significant interactions (2). Therapeutic drug monitoring is useful in identifying certain clinically significant drug-herb interactions because a patient may not disclose the use of herbal supplement to the physician. Shi and Klotz commented that drug-herb interaction certainly increases the risk of therapy with drugs with narrow therapeutic range such as warfarin, cyclosporine and digoxin (3). Fortunately, therapy with warfarin is monitored routinely using INR (international normalization ratio) while digoxin and cyclosporine are subjected to routine therapeutic drug monitoring.

Clinically Significant Grapefruit Juice-Drug Interactions

Furanocoumarins present in grapefruit juice inhibits intestinal CYP3A4 enzyme but not liver CYP3A4 enzyme. Therefore, bioavailability of certain drugs is increased if taken after drinking grapefruit juice. Components of grapefruit juice also inhibit P-glycoprotein, organic anion-transporting peptides and sulfotransferase. Effects of drinking grapefruit juice may last up to 12 h (4, 5). Although grapefruit juice extracts are sometimes used in herbal preparation, it is not an herbal medicine. Therefore, detail discussion on this topic is beyond the scope of this presentation. Nevertheless, clinically significant grapefruit-drug interactions are summarized in Table 1.

Clinically Significant Drug Interactions with St. John's wort

Majority of drug-herb interactions reported in the literature involve St. John's wort, wort, an herbal antidepressant which is sold in the United States as an alcoholic or dried extract of hypericum, a perennial aromatic shrub with bright yellow flowers that bloom from June to September. The flowers are believed to be most abundant and brightest around June 24th, the day traditionally believed to be the birthday of St. John the Baptist and hence the name St. John's wort. Therefore, in this presentation, major emphasis is placed on drug interactions involving St. John's wort.

Hypericin, hyperforin and quercetin are major constituents in St. John's wort that mediate reduction of intestinal absorption as well as bioavailability of many drugs by induction of intestinal P-glycoprotein drug efflux pump (MDR1: multidrug resistant 1 expression), and induction of activities of both intestinal and liver cytochrome P-450 mixed function oxidase (CYP) enzymes responsible for metabolism of many drugs. Hyperforin appears to play major role in activating pregnane X receptor leading to the transcriptional activation of genes that regulate activities of CYP3A4 and other cytochrome subtype enzymes responsible for drug metabolism. Therefore, St. John's wort preparations with low hyperforin (<1%) content may not cause any clinically significant interaction with any drugs (6). In general it is considered that St. John's wort induces CYP3A4, CYP2E1 and CYP2C19 with no effect on CYP1A2, CYP2D6 and

CYP2C9. However, St. John's wort also induces clearance of drugs that are not metabolized via liver enzymes, for example digoxin, and fexofenadine which are well known P-glycoprotein substrates (7). Although most drug-herb interactions involving St. John's wort are pharmacokinetic in nature, pharmacodynamic interactions of certain antidepressants with St. John's wort have also been reported.

Most important pharmacokinetic drug interactions with St. John's wort involve immunosuppressants, warfarin and antiretrovirals because treatment failure may have serious consequences to these patients. Transplant recipient taking cyclosporine or tacrolimus may face acute organ rejection due to self-medication with St. John's wort because St. John's wort induces metabolism of both drugs thus reducing whole blood concentrations of these drugs by more than 50%. Ernst commented that St. John's wort can endanger the success of organ transplantation due its interaction with cyclosporine leading to several cases of organ rejection (8).

Warfarin therapy should be carefully controlled by measuring the clotting capacity of blood (using International Normalization Ratio; INR). A patient attending a Coumadin clinic must avoid St. John's wort because of potential failure of warfarin therapy due to increased clearance of warfarin. Jiang et al studied interaction of warfarin and St. John's wort using 12 healthy subjects and concluded that St. John's wort significantly induces clearance of both S and R-warfarin which in turn resulted in a significant reduction in pharmacological effect of racemic warfarin (9).

Patients suffering from AIDS and receiving HAART Therapy (highly active antiretroviral therapy) must not take St. John's wort or other herbal supplements due to possibility of treatment failure from drug-herb interactions. Clinically significant interactions of antiretroviral agents with St. John's wort have been documented. Therefore patients with AIDS taking amprenavir, atazanavir, zidovudine, efavirenz, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, and saquinavir must avoid concomitant use of St. John's wort (10). St. John's wort was shown to reduce the area under the curve of the HIV-1 protease inhibitor indinavir by a mean of 57% (11).

Reduced concentration of nevirapine due to administration of St. John's wort has also been also been reported (12).

Interaction between St. John's Wort and digoxin is of clinical significance. Johne et al reported that 10 days usage of St. John's wort resulted in a 33% decrease of peak and 26% decrease in trough serum digoxin concentrations. The mean peak digoxin concentration was 1.9 ng/ml in the placebo group and 1.4 ng/ml the group taking St. John's wort (13). Clearance of imatinib mesylate, an anticancer drug is also increased due to administration of St. John's Wort resulting in reduced clinical efficacy of the drug (14). St. John's wort also showed significant interaction with another anticancer drug irinotecan. (15). Many benzodiazepines are metabolized by CYP3A4 and as expected St. John's wort reduces plasma concentrations of alprazolam, midazolam and quazepam. St. John's wort also reduces plasma concentration of antiepileptic drug mephenytoin. Theophylline is metabolized by CYP1A2, CYP2E1, and CYP3A4. Reduced plasma concentration of theophylline due to intake of St. John's wort has also been reported (16).

St. John's wort has significant interaction with oral contraceptives leading to contraception failure (17). St. John's wort also induces both CYP3A4 catalyzed sulfoxidation and 2C19 dependent hydroxylation of omeprazole (18). Tannergren et al reported that repeated administration of St. John's wort significantly decreases bioavailability of R and S-verapamil. This effect is caused by induction of first pass metabolism by CYP3A4 most likely in the gut (19). Xu et al reported that treatment with St. John's wort significantly increases the apparent clearance of gliclazide, a drug which is used in treating patients with Type II diabetes mellitus (20). Sugimoto et al reported interactions of St. John's wort with cholesterol lowering drugs simvastatin and pravastatin. (21). Although St. John's wort does not induce N-acetyl transferase, the enzyme responsible for metabolism of procainamide, St. John's wort increased bioavailability of procainamide in mice if administered one hour before feeding them with procainamide. This is a grapefruit juice like interaction (22). Several reviews dealing with drug-herb interactions also discussed St. John's wort-drug interactions in detail (23, 24).

Although pharmacokinetic interactions of drugs with St. John's wort are more common, there are also clinically significant pharmacodynamic interactions of certain antidepressants with St. John's. St. Hyperforin, an active component of St. John's wort is responsible for its effect. Many antidepressant drugs also exert their pharmacological effects by similar mechanism. Therefore if a patient takes antidepressant medication such as fluoxetine, sertraline, paroxetine and venlafaxine along with St. John's wort, serotonin syndrome may occur (25). Taking St. John's wort along with buspirone may also cause serotonin syndrome (26). Important pharmacokinetic drug interactions involving St. John's wort are summarized in Table 2. Important pharmacodynamic drug interactions are listed in Table 3.

Interactions of Warfarin with Herbal supplements

Warfarin therapy must be critically monitored by measuring INR because warfarin is known to interact with many drugs and herbal supplements. Warfarin acts by antagonizing the cofactor function of vitamin K. Although clinical efficacy of warfarin varies with intake of vitamin K and genetic polymorphisms that modulate expression of CYP2C9, the isoform responsible for clearance of S-warfarin, several herbal supplements also have significant effects on metabolism of warfarin. Herbal supplements that may potentiate the effect of warfarin thus increase the risk of bleeding include angelica root, arnica flower, anise, borage seed oil, bromelain, chamomile, fenugreek, feverfew, garlic, ginger, horse chestnut, licorice root, lovage root, meadowsweet, passionflower herb, poplar and willow bark. Anticoagulant effect of warfarin also increases if combined with antiplatelet herbs such as danshen, and ginkgo biloba. Conversely, vitamin K containing supplement such as green tea extract may antagonize the anticoagulant effect of warfarin (27, 28). Important warfarin-herb interactions are summarized in Table 4.

Dangerous Drug Interactions with Kava

Kava, an herbal sedative with antidepressant properties, is the most commonly cited herb related to liver toxicity due to the presence of kavalactones in the alcoholic extract of kava. In January

2003, kava was banned in the European Union and Canada; and the FDA issued another warning. By 2009, more than 100 cases of hepatotoxicity have been linked to kava exposure. Many have followed co-ingestion with alcohol which appears to potentiate the hepatoxicity (29). Although liver damage is the most widely documented toxicity of kava, several cases involving severe CNS depression have been reported when the herbal is combined with other sedatives and hypnotics. One such case report described a 54 year old male who became comatose after three days of kava ingestion while taking alprazolam, cimetidine and terazosin. It was thought that the adverse reaction was related to pharmacodynamic interaction between kava and alprazolam (30). Kava lactones also inhibit CYP1A2, (56%), CYP2C9 (92%), CYP2D6 (73%) and CYP3A4 (78%) but has no effect on CYP2A6, and CYP2E1. Because of such inhibition, toxicities of drugs that are metabolized through these enzymes are increased if taken with kava (31). No one should take kava

Drug Interactions with Ginkgo Biloba

Ginkgo biloba is a popular herbal supplement promoted for sharpening memory and improving circulation. Ginkgo biloba is an inhibitor of platelet activating factors thus making this supplement dangerous when taken with warfarin or other anticoagulant drugs. However, ginkgo biloba can also induce liver enzymes thus causing treatment failure with drugs that are metabolized by the cytochrome P-450 liver enzymes. A 55 year old man suffered a fatal seizure with no evidence of non-compliance (phenytoin and valproic acid) as evidenced by therapeutic range of both drugs for last one year. Autopsy report showed sub-therapeutic serum levels of phenytoin (2.5 μg/mL) and valproic acid (26 μg/mL). He self-medicated with ginkgo biloba. Ginkgo induces CYP2C9 and CYP2C19 activity that metabolizes phenytoin and valproic acid thus causing treatment failure (32). Ginkgo biloba also has other clinically significant interactions with other drugs (33). These interactions are listed in Table 5.

Other Important Drug-Herb Interactions

Ginger and garlic supplements are popular but both supplement increases bleeding risk in patients taking warfarin. Ginger increases antiplatelet activity of nifedipine, a calcium channel blocker. Feverfew reduces immunosuppression of cyclosporine and tacrolimus. Interestingly milk thistle which has protective effects on the liver and is often used in patients with liver disease or hepatitis C infection protects the liver from toxicity of acetaminophen, cisplatin and cyclosporine (23). Other important drug-herb interactions are summarized in Table 6.

Table 1. Clinically significant grapefruit juice-drug interactions

Drug class	Examples of drugs with increased bioavailability
Calcium channel blockers	Felodipine, Manidipine, Nicardipine, Nifedipine, Nimodipine, Nitrendipine, Pranidipine, Verapamil*
Benzodiazepines	Alprazolam*, Diazepam*, Midazolam, Triazolam*, Quazepam
Statins	Atorvastatin, Lovastatin, Pitavastatin, Simvastatin
Cardioactive	Amiodarone*
Immunosuppressant	Cyclosporine*, Tacrolimus*
Anticonvulsant	Carbamazepine*
Antibiotic	Erythromycin, Clarithromycin
Protease inhibitors	Amprenavir*, Saquinavir*
Proton pump inhibitors	Lansoprazole, Omeprazole
Narcotic analgesic	Methadone*, oxycodone*
Analgesic	Acetaminophen

*These drugs are routinely or less commonly subjected to therapeutic drug monitoring, which may identify such interactions.

Table 2. Clinically significant pharmacokinetic drug interactions with St. John's wort

Class of drug	Example	Clinical effect
Immunosuppressant	Cyclosporine*, Tacrolimus*	Possibility of organ rejection due to 30-50% reduction in trough due to CYP3A4 induction. No interaction with mycophenolic acid.
Protease Inhibitors	Atazanavir*, Lopinavir*, Indinavir*	Significantly reduced level, for example, AUC of indinavir reduced by 57% due to induction of CYP3A4
NNRTI	Nevirapine	Reduced level due to induction of CYP3A4.
Anticoagulant	Warfarin (INR monitoring)	Reduced level due to induction of CYP2C9
Cardioactive	Digoxin	Trough concentration reduced by 26% due to induction of P-glycoprotein
Antianginal	Ivabradine	Reduced level due to induction of CYP2C9
Anticonvulsants	Phenytoin*, Carbamazepine*, Phenobarbital*	Reduced efficacy due to induction of CYP3A4.
Anticonvulsant	Mephenytoin	Reduced efficacy due to induction of CY2C19.
Calcium Channel Blocker	Nifedipine, Verapamil*	Reduced level due to induction of CYP3A4.
Antihistamine	Fexofenadine	Decreased level due to induction of P-glycoprotein
Benzodiazepines	Alprazolam*, Midazolam, Quazepam*	Reduced blood level due to induction CYP3A4
Anticancer	Irinotecan, Imatinib	Reduced blood level due to induction CYP3A4
Tricyclic antidepressant	Amitriptyline*	Reduced blood level due to induction CYP3A4
Statins	Atorvastatin, Simvastatin	Reduced blood level due to induction CYP3A4
Oral Contraceptives	Norethindrone Ethinyl Estradiol	Reduced blood level due to induction CYP3A4 and CYP1A2
Antiasthmatic	Theophylline*	Reduced blood level due to induction of CYP1A2
Proton Pump Inhibitor	Omeprazole	Reduced level due to induction of CYP2C19
Hypoglycemic agent	Gliclazide	Reduced level due to CYP2C9 induction
Opioid	Methadone*	Trough concentration reduced by 47% due to induction of CYP3A4.
Opioid	Oxycodone*	AUC reduced by 50% and half-life shortened from 3.8 h to 3 h.

*These drugs are routinely or less commonly subjected to therapeutic drug monitoring, which may identify such interactions.

Table 3. Pharmacodynamic interaction with St. John's wort

Drug class	Examples	Interaction
SSRI (Selective serotonin reuptake inhibitor)	Fluoxetine, Sertraline Paroxetine	Possibility of serotonin syndrome
SNRI (Serotonin and norepinephrine reuptake inhibitor)	Venlafaxine	Possibility of serotonin syndrome
Other Antidepressant	Bupropion, Buspirone	Possibility of serotonin syndrome
Anti-migraine agent	Eletriptan	Possibility of serotonin syndrome

Table 4. Clinically Significant Warfarin-Herb Interactions

Herbs that Potentiates effect of warfarin	Herbs that reduces efficacy of warfarin
Angelica Root, Arnica Flower, Anise, Bogbean, Borage Seed Oil, Bromelain, Boldo, Borage, Chamomile, Coenzyme Q10, Danshen, Dong Quai, Devil's Claw, Fenugreek, Feverfew, Garlic, Ginger, Grape seed, Ginkgo biloba, Horse Chestnut, Licorice, Meadowsweet, Passionflower Herb, Fish oil supplements, Evening primrose oil, Horse chestnut, Royal jelly, Saw Palmetto, Willow Bark **Increased INR indicates potentially significant interaction and increased risk of bleeding.**	St. John's wort, Green tea extract, Milk Thistle, Goldenseal **Reduced INR is an early indication of treatment failure**

Table 5. Drug interactions with ginkgo biloba

Drug	Comments
Aspirin, Ibuprofen, Diclofenac	Ginkgo biloba is a potent inhibitor of platelet activating factors and may increase bleeding risk if taken with aspirin. A case report of a70 year old man who was taking aspirin (325 mg) developed hematoma one week after staring ginkgo biloba. He was advised to stop taking ginkgo.
Warfarin (INR)	Significantly increased risk of bleeding with concurrent use of ginkgo.
Trazodone	Trazodone is an SSRI which may cause coma if taken with ginkgo. This is possibly a pharmacodynamic interaction because gingko binds with benzodiazepine and GABA receptors.
Phenytoin*	Treatment failure due to reduced blood level as a result of induction of CYP2C9 by ginkgo
Valproic acid*	Treatment failure due to reduced blood level as a result of induction of CYP2 C19 by ginkgo
Omeprazole	Reduced plasma level
Ritonavir*	Reduced plasma level

Table 6. Other clinically important drug-herb interactions

Herbal Supplement	Interacting drug	Clinical effect
Garlic, Ginger	Warfarin	Potentiation of effect of warfarin (increased INR) with increased risk of bleeding.
Garlic	Saquinavir, Ritonavir	Reduced plasma level due to induction of CYP3A4.
Garlic	Chlorpropamide	Hypoglycemia because components of garlic have hypoglycemic properties.
Ginger	Nifedipine	Ginger increases antiplatelet activity of nifedipine, a calcium channel blocker.
Feverfew	Iron tablets	Reduced absorption
Feverfew	Cyclosporine, Tacrolimus	Reduced immunosuppression
Echinacea	Ketoconazole, Methotrexate	Increased liver toxicity
Echinacea	Simvastatin, Lansoprazole	Increased effect
Flaxseed oil, Saw Palmetto	Aspirin (325 mg)	Increased risk of bleeding
Bromelain	Naproxen	Increased risk of bleeding
Valerian	Alprazolam, Midazolam, Zolpidem, Zaleplon, Eszopiclone, Barbiturates, Alcohol	Increased sedation
Milk thistle	Acetaminophen, Cyclosporine, Cisplatin	Reduced liver toxicity associated with these drugs

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