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Herbal Medications: Implications for the Operating Room

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Abstract

US households have an increasing number of people using herbal medications as common self treatments. According to Hodges & Kam (2002), 32-37% of Americans have used herbal medications in the last year. Schmidt (2004) states that 1 in 3 Americans consume herbal products each year. Between 1990 and 1997, the use of herbal medicines increased 380% (Ernst, 2004). The interactions between herbal medications and anesthetic drugs become more important and meaningful due to the wide spread use. There are currently 15 million adults in the United States at risk for a potential adverse interaction with a prescription medication and an herbal medication, with 3 million of them being over the age of 65 (O'Malley, Trimble, & Browning, 2004). Herbal products, which are classified as dietary supplements, are marketed and sold in the United States and are not required to have Food and Drug Administration (FDA) approval or regulation. It is not uncommon for herbs obtained outside North America and Europe to be contaminated or adulterated, some with conventional drugs (Forrelli, 2003).

The purpose of the study was to examine the background, manufacturing, contents of herbal medications, information on the side effects, recommendations for discontinuing use before surgery, and recommendations for advancement with herbal medications. With the information gathered, a pocket size reference card (see appendix) was assembled for quick reference by medical personnel, which will include the herbal medication, what it is used for, side effects, and interactions with prescription drugs. The specific herbal medications reviewed were chamomile, echinacea, ephedra, garlic, ginger,

ginkgo, ginseng, kava, St John's wort, and valerian. The study concluded with recommendations for nursing research, practice, education, and health policy.

Herbal Medications: Implications for the Operating Room

Herbal medications have been used for medicinal purposes since ancient times and are becoming increasingly popular. United States (US) households have an increasing number of people using herbal meds as common self treatments. According to Hodges & Kam (2002), 32-37% of Americans have used herbal medications in the last year. One in three Americans consume herbal products each year (Schmidt, 2004). Between 1990 and 1997 that the use of herbal medicines increased 380% (Ernst, 2004).

People believe of herbal medications to be safe and natural, unlikely to cause harm, and have few side effects. Most patients believe that the use of herbal medication is more effective for health promotion (82%) than for treating serious illness (10%) (Lee et al., 2006). Due to the increased use of herbal medications, there is the potential for increased risk for encountering side effects for the patients taking these medications when undergoing surgery.

Purpose

The purpose of the study was to examine the background, manufacturing, contents of herbal medications, side effects, (such as alterations in laboratory values), and herb-drug interactions, specifically related to anesthesia. There is a relative lack of evidence based research in the field of herb-drug interactions. With the information gathered, a pocket size reference care was created, for quick reference by medical personnel, which included the herbal medication, what it is used for, side effects, and interactions with prescription drugs. See the appendix for the informational card.

Significance

The significance of the study was that a large part of the population (up to 32-37%) takes herbal medications with the thought that they are safe and natural without any side effects. The interactions between herbal medications and anesthetic drugs become more important and meaningful due to the wide spread use. Schmidt (2004) noted out that over 60 million Americans used herbal medications in 2000. There are currently 15 million adults in the US at risk for a potential adverse interaction with a prescription medication and an herbal medication, with 3 million of them being over the age of 65 (O'Malley et al., 2004). Of the more than 60 million Americans using alternative therapies, which include herbal medications, 18.4% are also taking prescription medication at the same time, leading to a high risk of herb-drug interaction (Forrelli, 2003).

Research Questions

The following research questions guided this project:

1. What are the manufacturing guidelines?
2. What are the contents of herbal medications?
3. Do the contents vary?
4. What do people use specific herbal medications for?
5. What are the side effects of specific herbal medications?
6. What herb-drug interactions are involved with herbal medications?
7. What are the recommendations for use or discontinuation before surgery?

Definitions

Adaptation- is described as a process by which a system seeks to restore or maintain homeostasis (Hansen, 1998).

Absorption- Absorption is the movement of drug from its site of administration to the systemic circulation (Katzung, 2004).

Conventional medicine- is medicine as practiced by holders of M.D. (medical doctor) or D.O. (doctor of osteopathy) degrees and by their allied health professionals, such as physical therapists, psychologists, and registered nurses. Other terms for conventional medicine include allopathy; Western, mainstream, orthodox, and regular medicine; and biomedicine ("National Center for Complimentary and Alternative Medicine [NCCAM]," 2007).

Distribution- the reversible movement of drug from the systemic circulation, the blood, to the tissues (Katzung, 2004).

Elimination- of the drug involves removal from the body via renal, biliary, or pulmonary processes with the kidneys function as the major organ for excretion (Katzung, 2004).

Herbal medications- a plant-derived product used for medicinal and health purposes (Hodges & Kam, 2002). - seed producing annuals, biennials, or perennials that do not develop woody tissue, die at the end of the growing season , and have medicinal ,savory, or aromatic qualities (O'Malley et al., 2004).

Homeostasis- is referred to as a state of internal balance or organization of function (Hansen, 1998).

Metabolism- the chemical conversion of a drug to inactive or active compounds that are more polar and water soluble, promoting excretion (Katzung, 2004).

Pharmacodynamics- are the actions of the drug on the body (Katzung, 2004).

Pharmacokinetics- are the actions of the body on the drug (Katzung, 2004).

Theoretical Framework

The theoretical framework used for this project is one of physiological origin. Hansen (1998) described adaptation and homeostasis which represent a balanced of forces within the body. Homeostasis is referred to as a state of internal balance or organization of function. Adaptation is described as a process by which a system seeks to restore or maintain homeostasis. Adaptation may be physiologic, psychological, or behavioral, through this framework physiological is emphasized and detailed.

Mechanisms to maintain homeostasis may be compensatory mechanisms, homeostatic mechanisms, control systems, or regulatory systems (Hansen, 1998). Feedback loops serve as adaptive mechanisms that work in either a negative or positive direction. The majority of adaptive responses are negative feedback loops. Negative feedback loops act to restore homeostasis by inducing changes in the opposite direction of a force perturbing the system. Positive feedback loops are usually maladaptive. In positive feedback loops, the response to a disruptive force is in the same direction as the force, increasing to disruption of the system.

Physiologic adaptive responses act to restore system homeostasis that has been disrupted by any event including environmental or behavioral changes, stress, or disease. The adaptive responses are regulated a three physiologic levels: the nervous system, which mediates rapid but short-acting responses; the endocrine system, which is a slower response with longer-lasting effects; and by local, tissue specific mechanisms mediated by cytokines and other secreted mediators or by intracellular proteins influencing genetic processes (Hansen, 1998).

Adaptation mechanisms are essential to human function, and the responses may not fully restore homeostasis until the disrupting force is removed. Adaptation mechanisms do consume energy, and are not all equal in restoration (Hansen, 1998). Adaptation processes are also limited by age of the person. Very young persons present immature systems where adaptation can be limited due to immaturity. The adaptation of the elderly is limited by normal tissue changes with aging. Homeostatic end points vary among individuals and are often adjusted based on age, sex, height, or weight.

When taking medication whether it is prescription or herbal, the goal is to achieve a desired benefit with minimal side effects. Pharmacokinetics are the actions of the body on the drug (Katzung, 2004). Pharmacokinetics deals with to processes of absorption, distribution, and elimination and how they effect how rapidly and for how long the drug will appear at the target organ (Katzung, 2004). Pharmacodynamics are the actions of the drug on the body and the relationship between drug concentration at the site of action and the physiologic response (Katzung, 2004).

When ingesting a drug, the amount of drug that remains unchanged and reaches systemic circulation is called bioavailability (Katzung, 2004). The rate of absorption influences the bioavailability. Absorption is the movement of drug from its site of administration to the systemic circulation (Katzung, 2004). When a drug is administered orally the drug may be incompletely absorbed. This incomplete absorption may be due to multiple factors including being too hydrophilic, too lipophilic, or due to reverse transporter in which a pump actively pumps the drug out of the gut wall (Katzung, 2004). The rate of absorption is influenced by the site of administration, drug formulation, first-pass effect and patient factors (Katzung, 2004).

The distribution of a drug is the reversible movement of drug from the systemic circulation, the blood, to the tissues (Katzung, 2004). Distribution occurs first to the well perfused organs such as the heart, liver, kidney, and brain, then to other tissues such as muscle, viscera, skin, and fat at a slower rate (Katzung, 2004). The blood-brain barrier restricts all drugs from crossing into the central nervous system. Distribution is influenced by the volume of distribution, protein binding, and drug reservoirs (Katzung, 2004).

Metabolism is the chemical conversion of a drug to inactive or active compounds that are more polar and water soluble, promoting excretion (Katzung, 2004). The liver is the main organ of metabolization of drugs (Katzung, 2004). Other organs that play a role are the gastrointestinal tract, the lungs, the skin, and the kidneys (Katzung, 2004). Exogenous substances including drugs undergo hepatic biotransformation that results in the end products are generally inactivated or more water-soluble substances that can be excreted in bile or urine (Morgan, Mikhail, & Murray, 2002).

Hepatic biotransformation has two types of reactions. Phase I reactions modify reactive chemical groups through mixed function oxidase of the cytochrome P-450 enzyme systems, resulting in oxidation, reduction, deamination, sulfoxidation, dealkylation, or methylation (Morgan et al., 2002). Barbiturates and benzodiazepines are inactivated by phase I reactions (Morgan et al., 2002). Phase II reactions, which may or may not follow a phase I reaction, involve conjugation of a substance with glucuronide, sulfate, taurine, or glycine, which leads to the conjugated compound ready to be eliminated through urine or bile (Morgan et al., 2002).

Some enzyme systems like the cytochrome P-450 can be induced by drugs like ethanol, barbiturates, ketamine, and possibly benzodiazepines (Morgan et al., 2002). This means that they increase the production of the enzymes that metabolize those drugs. That can result in a lower circulating level and increased tolerance to the drugs' effects (Morgan et al., 2002). More often the cytochrome P-450 enzyme induction promotes tolerance to other drugs that are metabolized by the same enzymes, or cross-tolerance (Morgan et al., 2002). The opposite is also true in that some agents such as cimetidine and chloramphenicol can prolong the effects of drugs by inhibiting the cytochrome P-450 enzymes (Morgan et al., 2002).

Elimination of the drug involves removal from the body via renal, biliary, or pulmonary processes with the kidneys function as the major organ for excretion (Katzung, 2004). Other routes of elimination are: sweat, saliva, tears, breast milk, hair, and skin, but are usually not clinically significant (Katzung, 2004).

Limitations

The limitations of this research project are as follows:

- There is a limitation to the number of research articles collected and analyzed. A search was done on OVID data base using the key words: herbal medications and herbal medications plus anesthesia. The search was also limited to the years 2000 and newer. From the articles gathered, additional articles were obtained from the references lists.
- The research projected was limited on specific herbal medications covered, limiting to the most popular according to the research conducted.

- There are limited clinical trials on herbal medications, which limit the number of actual studies to be compared.
- This project was limited to review of other studies. No research was actually conducted.
- There is limited research in pediatric and obstetrics, and was therefore not covered in this research article.

Assumptions

The following assumptions are made for this research project:

- All of the information found in journal articles is correct.
- The herbal medications are taken for therapeutic reasons.
- Everyone reacts in a similar manner to the herbal medications.
- The studies done comparing the same herbal medications studied the same active ingredient.
- The doses of herbal medications used in the research were therapeutic doses.

Literature Review

Pharmaceutical agents are often seen as expensive, costly, high risk, and for the treatment of illness or disease, whereas herbal medications are seen as natural, safe, and for promoting health (O'Malley et al., 2004). There are programs that exist that promote the use of natural herbs to boost immunity and promote better health (Schmidt, 2004). In analyzing money spent, in 1997, the total out of pocket expenditure for herbal medicines was $5.1 billion (Ernst, 2004; O'Malley et al., 2004). Ansani, Ciliberto, & Freedy (2003) estimate that sales are growing by approximately 59% each year.

More than 1,500 herbal remedies are sold in the United States (Schmidt, 2004). However, despite the popularity, little is actually know about the medicinal properties of these products (Schmidt, 2004). Patients taking herbal medications may not even know the type of ingredients in the medications. Lee et al. (2006) conducted a study comparing the use of no herbal medication, self prescribed or over the counter herbal medication and herbal medications prescribed by a traditional Chinese medicine practitioner. Of the 47 people who took these medications prescribed by a traditional Chinese medicine practitioner, only 27 knew all or some of the herbal ingredients used in the prescription.

Because herbal medications are over the counter, many times there is not documentation of their usage, and physicians and operating room personnel may not know patients are taking them, which could lead to complications when undergoing surgery. Herbal medications are not always safe or without side effects, which could lead to serious potential problems. Ang-Lee, Moss, & Yuan (2001) also noted that those patients using herbal medications are less likely to seek conventional diagnosis and therapy.

Background

Herbal medications have been used for medicinal purposes since ancient times. Herbs have been used as natural alternatives to medical treatment. In the early 1900's, herbs were a mainstay of pharmacopeia in the United States. Approximately one-quarter of current pharmaceutical agents originated in whole or in part from naturally occurring chemicals in plants (O'Malley et al., 2004). There are medications in use today that were discovered in herbal form. Examples include digitalis, reserpine, and aspirin, which are part of standard medical therapy for cardiovascular disease (O'Malley et al., 2004).

Currently, 122 distinct chemical substances derived from plants are important pharmaceutical agents (Hodges & Kam, 2002).

Patients take herbal medications for many different reasons. A survey was conducted in 2002, by the National Center for Complimentary and Alternative Medicine, which reported the reasons people took supplements. The reasons people took herbal products or natural supplements were: Health/good for you (16%), arthritis (7%), memory improvement (6%), energy (5%), immune booster (5%), joint pain (4%), supplement diet (4%), sleep aid (3%), prostate (3%), don't know / no reason specified (2%), all others (45%) (NCCAM," 2007).

Herbal medications may affect patients by many different mechanisms including: direct intrinsic pharmacological effects; pharmacodynamic interactions including alteration of the action of conventional drugs at effector sites; and pharmacokinetic interactions such as alteration of the absorption, distribution, metabolism, and elimination of conventional drugs (Ang-Lee et al., 2001).

Lack of information—patient/doctor communication

Statistics show that more than 60% and up to 70 % of patients fail to disclose to their physicians the use of herbal medications (Forrelli, 2003; Ang-Lee et al., 2001). This leads to potential miscommunication about adverse effects, and also hinders the gathering of information on herb-drug interactions. The reasons for the non-disclosure include patients' belief that physicians are not knowledgeable about herbal medications, that physicians are prejudiced against the use of herbal medications, fear of admitting unconventional therapies, perception that the use of herbal medications is unrelated to medical care, and failure to consider herbal medications as medications. In order to get

patients to reveal there herbal medication use, physicians must specifically elicit questions geared toward alternative therapies. When herbal medication usage is identified, one in five patients is unable to identify the preparation they are taking (Ang-Lee et al., 2001).

Manufacturing and safety

Herbal products, which are classified as dietary supplements, are marketed and sold in the United States and are not required to have Food and Drug Administration (FDA) approval or regulation. Herbs were classified as dietary supplements in the Dietary Supplement Health and Education Act of 1994 (Ang-Lee et al., 2001). Also, many of these herbs do not qualify for United States Pharmacopeia (USP) designation for meeting standards of strength, quality, purity, and labeling. If the herb does not have or carry FDA approval or meet USP guidelines, it may have a National Formulary (NF) symbol, which indicates the product has been used extensively without documented adverse effects (O'Malley et al., 2004). That also means that these products are able to bypass animal studies, pre-marketing controlled clinical trials, and post-marketing surveillance. Many times herbal medications bypass any federal regulations. The 1994 Dietary Supplement Health and Educational Act (DSHEA) required manufacturers to ensure that products placed on the market are safe (O'Malley et al., 2004), Therapeutic claims can be promoted as long as the information is not misleading or product specific (O'Malley et al., 2004). Claims of efficacy are usually based on anecdotal clinical experiences (Schmidt, 2004). Manufacturers do not have to submit data to the FDA if product ingredients were marketed before 1994. Today, the FDA requires the list of new food ingredients for review 75 days prior to the product going to market.

A dietary supplement must meet all of the following conditions according to the National Center for Complimentary and Alternative Medicine:

> 1) It is a product (other than tobacco) intended to supplement the diet, which contains one or more of the following: vitamins; minerals; herbs or other botanicals; amino acids; or any combination of the above ingredients. 2) It is intended to be taken in tablet, capsule, powder, softgel, gelcap, or liquid form. 3) It is not represented for use as a conventional food or as a sole item of a meal or the diet. 4) It is labeled as being a dietary supplement (NCCAM, 2007, p. http://nccam.nih.gov/health/bottle)

The FDA can remove a product from market if it suspects a herbal agent is unsafe. However, it must be shown to be unsafe before it will be removed. Hodges & Kam (2002) noted that there were at least 43 cases of serious adverse reactions related to the use of ephedra, including hypertension, palpitations, tachycardia, cerebrovascular accidents, seizures, reposts of myocardial infarction, myocarditis, fatal cardiac arrhythmias, acute hepatitis, mania, psychosis, nephrolithiasis, anxiety, tremors, and insomnia. Haller & Benowitz (2000) further stated that 140 reposts of adverse events related to the use of ephedra submitted to the FDA between June 1, 1997-March 31, 1999, were reviewed. While the published article appeared in December 2000, the FDA did not prohibit the sale of ephedra until 2004 (NCCAM, 2007).

Evidence for efficacy in clinical trials before marketing and evidence for interactions are very limited since herbal products are not required to be tested (O'Malley et al., 2004). When there has been some testing on herbs, the trials are often small in sample size, have short study timelines, and the variable outcomes have failed to demonstrate

efficacy of the agent (O'Malley et al., 2004). Herbs cannot be patented, therefore, the incentive for manufacturers to pursue clinical trials is low. Additionally average estimated cost to bring a new prescription medication to market is $350 million, for research and regulatory requirements (O'Malley et al., 2004).

Assuring quality is difficult because there are many factors that influence the herbal plant and associated benefits. These include the age of the plant, temperature, daylight length, atmosphere, sampling, toxic residues, manufacturing and preparation, environmental conditions, rainfall, altitude, soil, microbial contamination, deterioration, heavy metal contamination (O'Malley et al., 2004).

Herbal products are not regulated for purity or potency in the US, which provides little assurance that the herb will have its predicted pharmacological effect. Ang-Lee et al. (2001) pointed out that due to lack of consistent potency, products can vary from manufacturer to manufacturer and from lot to lot within a manufacturer. Consumers have no way to verify that a products is what is says it is or that is contains what is should. Commercial St. John's wort preparations have been shown to vary by 47% to as much as 165% of their labeled hypericin concentrations, and only 25% of commercially available ginseng products are authentic (Forrelli, 2003).

It is not uncommon for herbs obtained outside North America and Europe to be contaminated or adulterated, some with conventional drugs (Forrelli, 2003). Published analyses of herbal supplements have found differences between what was listed on the label and what was actually in the bottle (NCCAM, 2007). This means that you may be taking less--or more--of the supplement than what the label indicates. Herbal medications from Eastern origin may be contaminated with heavy metals, pesticides, and

even conventional drugs (Ang-Lee et al., 2001; Ernst, 2004). The herbal medication PC-SPES, which is an herbal medication used to treat prostate cancer by both alternative and conventional practitioners, was allegedly contaminated with warfarin, diethylstilbestrol, and indomethacin and therefore removed from the market (Forrelli, 2003). Saper et al. (2004) conducted a study and concluded that 20% of herbal medications contained heavy metals which included lead, mercury, and/or arsenic. Postmarketing surveillance is not a requirement for herbal medications. Because the contents for the herbal medications or the contaminants are not known, this can lead to lack of knowledge of actual side effects of the herbs and misinterpretation of what is causing the side effects.

Pharmaceutical drugs must undergo testing in which a certain chemical is isolated and concentrated, however herbal medications are not held to the same standards. It is difficult to identify the active ingredient, the proper dose to achieve an effect, and metabolism and disposition (Moss & Yuan, 2006). Herbs in their growing state contain low concentrations of their active parts, and high concentrations of their buffering agents. Standardization of the amount is a way to provide consistency. It may also be a way to guarantee the safety and effectiveness of herbs in the use of clinical trials (Forrelli, 2003). Forrelli (2003) stated that many products have standardization and contain a certain amount of what is believed to be the active chemical. The active ingredient(s) in many herbs and herbal supplements are not known. There may be dozens, even hundreds, of such compounds in an herbal supplement (NCCAM, 2007). Due to lack of clinical trials, there may be confusion about the active chemical of the herb. St. John's wort is an example. It was thought that the key chemical affecting mood disturbance was hypericin, but researchers later found that hypaphorine is actually the active ingredient (Forrelli,

2003). The next problem is that some of the products are being standardized to contain hypericin, while others contain hypaphorine (Forrelli, 2003).

The patient's belief that herbal medications are safe and will not cause harm is a misconstrued belief because some of the herbal medications have been shown to cause serious harm. More than 5000 suspected adverse reactions to herbal medications were reported the World Health Organization before 1996. Since 1993, the FDA has received approximately 7,000 reports of adverse reactions of using dietary supplements (Schmidt, 2004). That includes 101 deaths associated with herbal medication. Adverse effects of herbal medications are most likely underreported due to lack by physician's ability to identify the herbal medication that causes the adverse effect, and that patients are unlikely to report to their physician the adverse effects. That means that the herbal medication safety profiles are limited.

Specific herbal medications

Ang-Lee et al. (2001) stated that the eight most common herbal medications that clinicians are likely to encounter are: echinacea, ephedra, garlic, ginkgo, ginseng, kava, St John's wort, and valerian. Ernst (2004) noted that the top 10 herbal medications used are, in order of most usage, Ginkgo, echinacea, garlic, ginseng, soy, saw palmetto, St John's wort, valerian, cranberry, and black cohosh.

Chamomile

Chamomile is primarily taken as a beverage in the form of tea. Chamomile has been used to calm nerves and decrease anxiety. It can also be used to help with a common cold, diarrhea, and mouth ulcers, and irritation causes by cancer treatments (Schmidt, 2004). Due to the sedative effects chamomile may exacerbate drowsiness caused by

benzodiazepines, such as lorazepam, barbiturates, such phenobarbital, and narcotics (Schmidt, 2004). Chamomile may also play a role in increasing the risk of bleeding when taken in combination with anticoagulant drugs or over the counter pain relievers such as aspirin, ibuprofen, and naproxen (Schmidt, 2004).

Echinacea

Echinacea is used primarily for preventing and treating the common cold, and viral, bacterial, and fungal infections of the upper respiratory tract (Ang-Lee et al., 2001; Hodges & Kam, 2002). Many people believe that echinacea will shorten the duration of a cold, although research has not established this (Schmidt, 2004). Echinacea may be useful in decreasing the severity and duration of upper respiratory tract infections, but is not useful as a prophylaxis, this was established by analysis of clinical trials (Hodges & Kam, 2002).

Echinacea may also be used topically for the treatment of wounds and burns (Schmidt, 2004). Studies have shown that echinacea may alter the actions a variety of prescription drugs including immunosuppressants, drugs for rheumatic diseases, drugs for dysrhythmias, antifungal drugs, or drugs to prevent rejection of transplant organs (Schmidt, 2004). Echinacea can be toxic to the liver, should not be taken more than eight weeks, and should not be taken with other medications that can cause liver damage (Schmidt, 2004). Taking echinacea longer than eight weeks is associated with immunosuppression and increased risk of postoperative complication including impaired wound healing and opportunistic infections (Ang-Lee et al., 2001). Taking echinacea in excess may lead to the over stimulation and then suppression of one's immune system,

particularly T cells (Schmidt, 2004). Echinacea should not be taken by individuals waiting a transplant (Ang-Lee et al., 2001).

Echinacea has been associated with allergic reactions, therefore should be used in caution with patients with asthma, atopy, or allergic rhinitis (Ang-Lee et al., 2001). Echinacea has not been shown to interact with traditional drugs, although should not be taken with hepatotoxic drugs (Hodges & Kam, 2002).

Ephedra

Ephedra is used to promote weight loss, increase energy stores, and treat asthma and bronchitis (Ang-Lee et al., 2001). It has been used for more than 5,000 years in China and India to treat conditions such as colds, fever, flu, headaches, asthma, wheezing, and nasal congestion (NCCAM, 2007). The active ingredient in ephedra is ephedrine, which is a non-catecholamine sympathomimetic agent that exhibits alpha 1, beta 1 and beta 2 activity by acting directly at the adrenergic receptors and by indirectly releasing endogenous norepinephrine (Ang-Lee et al., 2001). The potential side effects of ephedra are cardiovascular hazards including myocardial infarction, stroke, and hemodynamic collapse from catecholamine depletion (Ang-Lee et al., 2001). The sympathomimetic effects have been linked with more than 1070 reported adverse events, including fatal cardiac and central nervous system complications (Ang-Lee et al., 2001). Serious adverse events such as stroke, heart attack, and sudden death were reported in 37 cases (NCCAM, 2007). Ephedra causes dose dependent increases in blood pressure and heart rate (Ang-Lee et al., 2001).

In 2004, the FDA banned the U.S. sale of dietary supplements containing ephedra (NCCAM, 2007). The FDA found that these supplements had an unreasonable risk of

injury or illness--particularly cardiovascular complications--and a risk of death. The ban does not apply to traditional Chinese herbal remedies or to products like herbal teas regulated as conventional foods (NCCAM, 2007).

Garlic

Garlic is one of the most studied medicinal plants. Garlic is best know to have positive effects on the cardiovascular system, modifying the risk of developing atherosclerosis by lowering blood pressure, to help lower cholesterol, and also decrease blood clot formation or thrombis formation in narrowed arteries (Schmidt, 2004 & Ang-Lee et al., 2001). Garlic may also be taken to help relieve symptoms of an upper respiratory tract infection due to the antibiotic effects it has (Schmidt, 2004). Other effects of garlic can include altering blood sugar levels and lowering blood pressures (Schmidt, 2004). Hodges & Kam (2002) & Miller (1998) state that the effects of garlic on hypertension is very short, lasting less then 2 hours. Randomized trials of garlic's effectiveness on lowering cholesterol have been shown to be effective if reducing total cholesterol levels (Hodges & Kam, 2002).

The active ingredients in garlic are allicin and allicin. Allicin has been shown to decrease systemic and pulmonary vascular resistance in laboratory animals, but has failed to show effectiveness in humans (Ang-Lee et al., 2001).

Garlic inhibits platelet aggregation in a dose-dependent fashion, and may potentate other platelet inhibitors. Garlic has been shown to increase INR when taken with warfarin, and should therefore be avoided in combination (Hodges & Kam, 2002). Garlic should also be avoided in persons taking aspirin and other non-steroidal anti-inflammatory drugs due to the enhanced antiplatelet activity (Hodges & Kam, 2002).

Schmidt (2004) states that studies have been completed that have shown garlic, when used in combination with other anticoagulants such as aspirin, warfarin, dipyridamole, and indomethacin, or with antiplatelet drugs such as clopidogrel, it can increase the risk of spontaneous and excessive bleeding. Ang-Lee et al. (2001) believe that it carries irreversible platelet inhibition, and should be discontinued at least seven days before surgery.

Ginger

Schmidt (2004) stated that studies have shown that ingestion of ginger for patients receiving chemotherapy can decrease the severity of nausea and length of time that patient feel nauseated. Ginger increases the stomach's acid level, and could therefore interfere with the effects of drugs that decrease stomach acid such as Pepcid or Nexium (Schmidt, 2004). Ginger has also been shown to lower blood sugar levels, and it may counteract the effects of certain drugs to treat high blood pressure or dysrhythmias (Schmidt, 2004). If taken with drugs such as warfarin, the herb may contribute to spontaneous or excessive bleeding, and can cause increased drowsiness if used with benzodiazepines, barbiturates, and narcotics (Schmidt, 2004). Few side effects are linked to ginger when it is taken in small doses, and the side effects most often reported are gas, bloating, heartburn, and nausea (NCCAM, 2007).

Gingko

Gingko is one of the world's oldest herbal remedies and is used as a natural blood thinner and antioxidant (Schmidt, 2004). Schmidt (2004) & Ang-Lee et al. (2001) stated that gingko has many uses including: acting on blood vessels to improve blood flow; decreasing the pain of peripheral vascular disease and claudication; improving short term

memory and concentration; and decreasing vertigo, headaches, and mood disturbances in persons with cerebral blood flow insufficiency. It is also useful for treatment of cognitive disorders, age-related macular degeneration, erectile dysfunction, and altitude sickness (Schmidt, 2004; Ang-Lee et al., 2001).

The active ingredient in gingko is thought to be effective due to terpenoids and flavonoids (Schmidt, 2004). Numerous studies of ginkgo have been done for a variety of conditions. Some promising results have been seen for Alzheimer's disease/dementia, intermittent claudication, and tinnitus among others, but larger, well-designed research studies are needed (NCCAM, 2007).

Because of gingko's blood thinning properties, it can react with anticoagulants leading to spontaneous and excessive bleeding, and it can interact with over the counter pain relievers such as ibuprofen, aspirin, and naproxen (Schmidt, 2004; Hodges & Kam, 2002). Ginkgo may alter platelet function by inhibition platelet-activating factor (Ang-Lee et al., 2001). Gingko can also be used as an antioxidant, or to modulate neurotransmitter receptor activity (Ang-Lee et al., 2001). Ginkgo has been shown to decrease the effectiveness of anticonvulsant therapy in patients taking carbamazepine or valproic acid (Schmidt, 2004). It is best if gingko is discontinued at least 36 hours prior to surgery (Ang-Lee et al., 2001).

Ginseng

Ginseng is probably the most expensive and popular herbal medications sold and taken (Hodges & Kam, 2002). Ginseng is taken primarily to reduce stress and the effects of aging. It is also known as "adaptogen" because it protects the body against stress and restores homeostasis (Ang-Lee et al., 2001).

Ginseng has been shown to increase the effects of bleeding when taken with warfarin, and when used with digoxin the herb may interfere with the pharmacologic action, and the ability to monitor digoxin activity (Schmidt, 2004). Patients on ginseng should not use morphine because it has been found to block palliative effects of the drug (Schmidt, 2004). It is also thought to lower postprandial blood glucose in people with type 2 diabetes mellitus and those without diabetes (Ang-Lee et al., 2001). Ginseng has an underlying mechanism that appears to be similar to that described for steroid hormones (Ang-Lee et al., 2001).

Lee et al. (2006) stated that because there is concern about taking ginseng and producing irreversible platelet inhibition, the recommendation is that it should be stopped 7 days prior to surgery. In the study Lee et al. found no association between ginseng and prolonged preoperative International Normalized Ratio (INR) or activated partial thromboplastin time (aPTT) or excessive bleeding in any cases, however the ginseng was not used in an isolated form. One must also watch for hypoglycemia, especially in those that have fasted before surgery (Ang-Lee et al., 2001). Ang-Lee et al. (2001) noted that ginseng is believed to cause irreversible platelet inhibition and is al recommended that patients discontinue it at least seven days prior to surgery.

Kava

Kava is used to treat anxiety and relieve insomnia and nervousness, and its active ingredients have been shown to be a sedative and muscle relaxant (Schmidt, 2004; Ang-Lee et al., 2001). Kava has gained popularity as an anxiolytic and sedative (Ang-Lee et al., 2001). The pharmacological activity of kava appears to be kavalactones (Ang-Lee et al., 2001).

Kava has dose dependent effects on the central nervous system, including antiepileptic, neuroprotective, and local anesthetic properties (Ang-Lee et al., 2001). Kava has been shown to have effects on the liver and the US FDA began an investigation into the safety after serious side effects in several people in Europe, and kava is no longer available in Europe (Schmidt, 2004). Kava is a depressant and should not be taken with alcohol, sleeping pills, or sedatives. Kava can increase drowsiness when combined with benzodiazepines, barbiturates, and narcotics (Schmidt, 2004).

Kava is one of the first herbs thought to interact with anesthesia due to its psychomotor effects (Ang-Lee et al., 2001). Kava may work by potentiating gamma-aminobutyric acid (GABA) inhibitory neurotransmission, and lead to sedative-hypnotic effects (Ang-Lee et al., 2001). The kavalactones increase barbiturate induced sleep time in laboratory animals (Ang-Lee et al., 2001). Overuse of kava can cause a skin condition called kava dermopathy, which is reversible scaly cutaneous eruptions (Ang-Lee et al., 2001).

Hodges & Kam (2002) suggested that kava should not be taken in combination with benzodiazepines, barbiturates, and alcohol. Kava also interacts with levodopa to potentate Parkinson symptoms (Hodges & Kam, 2002). Kava should not be taken for a minimum of 24 hours before surgery (Ang-Lee et al., 2001).

St John's wort

St John's wort is taken to help relieve depression. Schmidt (2004) & Ang-Lee et al. (2001) stated that St John's wort has not been shown to be effective in clinical trials in major depression, however it has been shown to be as effective as certain prescription antidepressants for mild to moderate depression. They also stated that St John's wort has

fewer side effects then prescription antidepressants (Schmidt, 2004). The mechanism of action of St John's wort is that it inhibits serotonin, norepinephrine, and dopamine reuptake by neurons (Ang-Lee et al., 2001).

A side effect of St John's Wort is that it induces the cytochrome P450, which is used to break down approximately 50% of all drugs (Schmidt, 2004). That leads to potential risk for faster or unpredictable break down of other medications. Some common medications used in the perioperative period that involve the cytochrome P450 system are alfentanil, midazolam, lidocaine, calcium channel blockers, and serotonin receptor antagonists (Ang-Lee et al., 2001). Other side effects include increased sensitivity to sunlight, anxiety, dry mouth, dizziness, gastrointestinal symptoms, fatigue, headache, or sexual dysfunction (NCCAM, 2007). St John's wort can decrease chemotherapy blood levels by 49%, and can last for up to three weeks after discontinuation (Schmidt, 2004). It is recommended that it be discontinued five days prior to anesthesia (Ang-Lee et al., 2001).

Drug-herb interactions are important with St John's wort. St John's wort increases serotonin levels and a serotonin syndrome may occur when taken with other serotoninergic drugs such as serotoninergic reuptake inhibitors and tricyclic antidepressants (Hodges & Kam, 2002). St John's wort is a potent inducer of the hepatic cytochrome P450 system (Hodges & Kam, 2002). Due to this initiation St John's wort should be avoided in combination with digoxin, theophylline, cyclosporin, warfarin, anticonvulsant drugs and antiretroviral drugs (Hodges & Kam, 2002).

Valerian

Valerian is used as a sedative, especially in the treatment of insomnia and anxiety, and virtually all herbal sleep aids contain valerian (Ang-Lee et al., 2001 & NCCAM, 2007). Valerian produces dose-dependent sedation and hypnosis, and the effects appear to be mediated through modulation of GABA neurotransmission and receptor function (Ang-Lee et al. 2001; Hodges & Kam, 2002). In experimental animals, valerian increases barbiturate-induced sleep time, and withdrawal can mimic an acute benzodiazepine withdrawal syndrome with effects on the cardiac system and delirium (Ang-Lee et al., 2001). Hodges & Kam (2002) say that valerian should be avoided in combination with benzodiazepines, barbiturates and alcohol. It can be expected that valerian may potentate the sedative effects of anesthetics and adjuvants, such as midazolam that act at the GABA receptor (Ang-Lee et al., 2001 Caution should be taken with abrupt discontinuation due to the withdrawal syndrome, therefore should be tapered off slowly, over a few weeks, prior to surgery (Ang-Lee et al., 2001).

Side effects of herbal medications

The risk of using herbal medications includes use of the product, the interaction of the product with the patients' physiology, and the interaction of the herbal with prescription medications (O'Malley et al., 2004). Groups of people of particular concern with the use of herbal medications are those with chronic illness, impending surgery, those on prescription medication, the elderly, persons with existing renal and liver disease, and diabetics (O'Malley et al., 2004). Children and pregnant patients have not been studied extensively. Before taking herbal medications patients should be counseled to know the current pharmacokinetics of the herb they are taking or how the herb is absorbed,

distributed, possible side effects, and potential interactions. Education material presented to patients are to be at a fourth grade level, is it possible to education patients on all of the risks with limited levels of education? Side effects of herbal medications may be mistaken for an exacerbation of the current problem, poor treatment response, or the development of another medical problem.

Lee et al. (2006) and Schmidt (2004) stated the most common adverse effects of herbal medicine relevant to anesthesia providers include impaired coagulation, cardiovascular side effects, electrolyte disturbances, dysrhythmias, stroke, and prolongation of the effects of anesthetic agents.

One of the most important interactions is with the cytochrome P450 system. The cytochrome P450 is involved in the metabolism of multiple drugs. The CYP3A4, part of the cytochrome P450 system, is at least partially involved in the metabolism of 60% of drugs (Bailey & Dresser, 2004). The herbal medications alter the CYP3A4, which can make the drugs less active, more readily excreted, or both (Bailey & Dresser, 2004). A specific herbal medication, St John's wort, can increase the activity of CYP3A4, there by increasing the oxidation of drugs, and making less available (Bailey & Dresser, 2004).

Lee et al. (2006) did a study comparing the use of no herbal medication, self prescribed or over the counter herbal medications, and herbal medication prescribed by a traditional Chinese medicine practitioner. Their results include:

- In the study, they found that patients who took herbal medications by prescription were more likely to have a perioperative event than non users. Patients with any perioperative events stayed in the hospital substantially longer then patients without perioperative complications.

- In the same study comparing INR and aPTT results in patients that had those lab tests ordered for the normal treatment or their surgery, there was no significant difference in the incidence of prolong INR or aPTT among 45 patients taking ginger with 278 who did not, and the same for 48 patients taking ginseng compared to 275 patients not taking ginseng.
- Herbal medications by prescription users were more than 2 times more likely to experience hypokalemia or impaired hemostasis then compared to nonusers.
- Despite the high prevalence of herbal medication use in this study, there was no clinically significant negative impact on intraoperative and postoperative care.

Lee et al. (2006) noted the second American Society of Regional Anesthesia Consensus Conference on Neuroaxial Anesthesia and Antithrombotic Therapy stated "Herbal drugs, by themselves, appear to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia." (p. 460)

Recommendations for stopping before surgery

Lee et al. (2006) recommended that all herbal medicines should be stopped two weeks prior to surgery. Specific lengths of time related to specific herbal medications are listed under the specific herbal medication. However, there is limited information on the epidemiology of herbal medications related to perioperative events in clinical practice. And there are no studies that have examined the clinical outcomes of surgical patients taking herbal medications within two weeks of surgery (Lee et al., 2006).

The American Society of Anesthesiologists has no official standards or guidelines on the preoperative use of herbal medications (Ang-Lee et al., 2001). Public and professional educational information released by the organization suggest that patients discontinue their herbal medication usage at least 2-3 weeks prior to surgery (Ang-Lee et al., 2001).

Recommendations

There are many areas in talking about herbal medications that could be expanded upon and investigated further. Recommendations in practice would include: medical personnel, whether physicians, physicians assistants, nurse practitioner, or CRNA's should be aware of the side effects of herbal medications. Care must be taken to interview each patient with regards to their specific use of herbal medications, and need to be asked specifically about their use. Medical personnel should also be aware of the recommended discontinue time prior to surgery to help eliminate unnecessary risk. Medical personnel should follow the institutions policy of herbal medications usage before surgery.

Recommendations for research are plentiful. Research and clinical trials showing the efficacy of a product would be the gold standard in establishing use for herbal medications. There are herbal medications out there that have shown promise for use instead of conventional medicine treatment. Identification of the active ingredients in herbal medications would also be beneficial in the efficacy of herbal medications. Identification would also allow consumers to be better informed when purchasing herbal medications on whether or not the product they are buying contains and active ingredient. Dosing also needs to be established for effective use. Research also needs to be

conducted on the side effects of herbal medications, and to be able to show a risk benefit analysis. There needs to be a national registration for side effects related to herbal medications so that physicians and consumers have some where to go and learn and report side effects. This could also lead to establishing more definitive side effect profiles.

Recommendations for education include: education to personnel directed involved in patient care that deal with the patient prior to surgical procedures. The general public must also be educated on herbal medications, regulations, contents, side effects, efficacy, and safety.

Health policy in this country should be looked at for safety reasons. Ephedra is a good example of this. It took the FDA years of adverse side effects reports to remove ephedra from the market. More strict guidelines in the market placement of herbal medications are needed. Faster investigations into reports of adverse and especially serious adverse side effects are needed.

Summary

The use of herbal medications is common and here to stay. If you ignore the use of herbal medications they will NOT go away. Therefore the general public as well as medical personnel need to be educated about herbal medications. There is important information in understanding the background and manufacturing of herbal medications. For herbal medications to become more useful and more accepted in conventional medicine the efficacy, active ingredients, dosing, and side effects need to be established.

People often associate herbal medications with natural and safe. Remember natural doesn't always equal safe as shown in the specific herbal medications like ephedra.

Herbs are drugs, and effect body systems similar to pharmacological drugs. Herbal medications do have side effects that can be harmful or even deadly. Due to the wide spread and sometimes secretive use, the implications for undergoing surgery remain an evolving challenge. It is important for healthcare personnel to understand the implications for use, side effects, and drug-herb interactions in working with patients that take herbal medications. There is a place for herbal medications in conventional medicine. History has shown that the use of herbal medications can lead to pharmacologic drug manufacturing. Currently, 122 distinct chemical substances derived from plants are important pharmaceutical agents (Hodges & Kam, 2002). That shows promise for investigation and understanding of herbal medications.

	USES	SIDE EFFECTS	DRUG INTERACTIONS	RECOMMENDED STOP TIME BEFORE SURGERY
Chamomile	calm nerves and decrease anxiety	can exacerbate drowsiness	increases drowsiness with benzodiazepines, such as lorazepam, barbiturates, such phenobarbital, and narcotics	no specific recommendation, general recommendation stop 2 weeks before surgery
Echinacea	preventing and treating the common cold, and viral, bacterial, and fungal infections of the upper respiratory tract	Echinacea can be toxic to the liver, should not be taken >8 weeks	should not be taken with other medications that can cause liver damage	no specific recommendation, general recommendation stop 2 weeks before surgery
Ephedra	promote weight loss, increase energy stores, and treat asthma and bronchitis	cardiovascular hazards including myocardial infarction, stroke, and hemodynamic collapse from catecholamine depletion	removed from market	removed from market
Garlic	positive effects on the cardiovascular system by modifying the risk of developing atherosclerosis by lowering blood pressure, cholesterol, and blood clot formation in narrowed arteries	inhibits platelet aggregation in a dose-dependent fashion	potentates other platelet inhibitors	discontinued at least 7 days before surgery
Ginger	decreases the severity and length of nausea	increases the stomach's acid level, and could therefore interfere with drugs that decrease stomach acid such as Pepcid or Nexium	If taken with drugs such as warfarin, may contribute to spontaneous or excessive bleeding, and increased drowsiness if used with benzodiazepines, barbiturates, and narcotics	no specific recommendation, general recommendation stop 2 weeks before surgery

Appendix

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