Lesson S47: Assessment of the Patient with a Drug Interaction

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Read this article, reflect on the information presented, then go online and complete the lesson post-test and course evaluation before the termination date below. (CME credit is not valid past this date.) You must achieve a score of 80% or better to earn CME credit.

TIME TO COMPLETE ACTIVITY: 2 hours
RELEASE DATE: March 1, 2016
TERMINATION DATE: February 28, 2017

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Professional Gaps

Most anesthesiologists rely on information provided by government agency oversight and clinical trials to evaluate the safety of pharmaceuticals. Pharmacogenomics has brought to light that patients absorb and metabolize drugs at different rates. Also, it is common for adults to consume over the counter herbal supplements which are unregulated and vary in composition. Anesthesiologists can be unaware of the many drug interactions that can occur with herbal supplements. A recent study identified the operating room as a location with excessive numbers of medication errors. It is important for anesthesiologists to understand the reasons for this finding and be knowledgeable of ways to reduce the risk of such errors.

Learning Objectives

At the completion of the activity, the reader will be able to:

1. List herbal compounds that may increase perioperative bleeding
2. Understand the significance of obtaining a complete history of herbs consumed
3. Appreciate the operating room (OR) as the “black hole” of medication errors
4. Tabulate means to decrease the incidence of medication errors
5. Recognize the most common causes of drug interactions
6. Be aware of the extent of the problem of medication errors in the United States
7. Differentiate between medication errors and drug interactions
8. Describe common reasons for medication errors in the OR
9. Incorporate methods to decrease medication errors into the “time out”
10. Present an anesthetic plan for a patient taking St Johns Wort
Case

An 85 year old woman fell and was found in her kitchen after being unable to summon help for almost 24 hours. X ray showed an intertrochanteric fracture. She was a widow and lived alone. Her daughter said she had been depressed recently and not sleeping well and her physician had prescribed her sertraline and zolpidem. She also gave a history of hypertension, managed with hydrochlorothiazide and nicardipine and hypothyroidism for which she took levothyroxine. The patient acknowledged taking all of her medications that morning. Although the daughter thought that her mother also took over the counter herbs, mainly on the advice of her friends, she did not know which ones. The patient was also unsure about her supplements but said that they were all good and came from a store that only sold natural products. She was scheduled for emergent pinning of her hip. The anesthetic management consisted of sevoflurane, midazolam, fentanyl and vecuronium all in moderate to low doses. Intraoperatively her pulse rate remained low, between 50-60 bpm. Her temperature stayed around 39 degrees C despite attempts at cooling. Muscle relaxation was reversed and she was transferred to the post anesthetic care unit. Forty-five minutes later, the nurse on the Post Anesthetic Care Unit (PACU) called the anesthesiologist to say that the patient was still not responsive.

Introduction

A recent study showed that an error and/or adverse drug event occurred with 1 of every 20 perioperative medications with 79% of these errors being classified as preventable.\(^1\) Medication errors in the operating room (OR) have been shown to be unacceptably high. More than one third of all medication errors led to an adverse drug event. It is estimated that 2 - 4% of all deaths in the United States are due to medical errors; and, when all steps in the medication process are considered (i.e. procuring the drug, prescribing it, dispensing it, administering it, and monitoring its impact) at least 1 medication error occurs per hospital patient per day.\(^2\) Adverse drug events occur in 3 - 6% of all hospital stays and 40% are preventable. Drug errors in anesthesia alone are estimated at 1:150 anesthetics and represent a major cause of medical malpractice claims.\(^3\) An added concern is that many patients often do not tell their physicians about their over-the-counter supplements, including herbal preparations, that have the potential to interact with anesthetic agents.

Medication Errors Incidence

Medications errors are defined as preventable events that may cause or lead to an inappropriate medication use or patient harm, according to the National Coordinating Council for Medication Errors Reporting and Prevention. They are identified as the single most preventable error in medicine today and the 4\(^{th}\) most common reported sentinel event. The operating room (OR) has been labeled the “black hole of medication safety” because of the high risk nature of the drugs and the frequency of drug use - amounting to 10,000 doses/year/doctor. Errors in the OR account for > 80% of error reports and are 5 times greater in frequency when compared to the rest of the hospital. Approximately 60% are due to incorrect ampoule usage or labeling.

Anesthesia has been described as the “ODAM” profession in that anesthesiologists Order, Dispense, Administer, and Monitor drugs, all while multitasking in a complex work environment with little or no oversight or secondary verification.\(^4\) Perioperative syringe swap, ampoule changes, wrong drugs, inappropriate doses, connection of intravenous lines to epidural and other catheters, diversion of drugs
by health care workers, and failure to realize drug interactions have all been cited as errors that can cause serious harm.\(^5\) Communication errors can also occur especially when a pharmaceutical company changes strengths or ampoule size or color and that information is not relayed to the anesthetic team. It is not uncommon for an anesthesiologist to find that a drug has been replaced in the drawer. Many drugs have names that sound alike and may be misunderstood by a circulating nurse when a request is made to acquire the medication. Although bar code medicine administration was implemented in 1995 with all bar codes required to be added by the manufacturer in 2006, the system has not as yet found its way into the OR, despite being standard hospital practice. Bar coding, emphasizes the 5 “rights” of patients: correct patient, correct medicine, dose, time and route.

Other causes of drug errors are related to infection and contamination. To prevent the risk of spreading hepatitis, skin bacteria and other infections, single dose ampoules are required for use in the OR. Multiple doses should only be drawn up in pharmacy areas under sterile conditions. Syringes are single-use devices. Once the plunger of a syringe has been completely depressed in order to expel the syringe contents (i.e., intravenous medication), the internal barrel of the syringe is considered contaminated and must be discarded in an appropriate fashion. A syringe must only be used once to draw up medication, and must never be used again even to draw up the same medication from the same vial for the same patient. An intravenous fluid bag that has been spiked should be used within one hour and the old practice of preparing multiple infusions at the beginning of the day for a case list should be abandoned. Failures to adhere to these requirements, overseen by the Joint Commission, are very common causes or sepsis, especially in dental and pain clinics.

**Decreasing Errors**

Table 1 shows several strategies that have been implemented by departments of anesthesia to prevent look alike/sound alike errors.

<table>
<thead>
<tr>
<th>Table 1. Strategies to prevent errors caused by look alike / sound alike drugs.</th>
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</thead>
<tbody>
<tr>
<td>• Do not use abbreviations of drug names</td>
</tr>
<tr>
<td>• Separate drugs and prepared IV solutions is storage bins and automated dispensing machines</td>
</tr>
<tr>
<td>• Add generic and brand names to unit-dose packaging</td>
</tr>
<tr>
<td>• Use bolded lettering to emphasize the spelling of drugs in storage areas, including machines</td>
</tr>
<tr>
<td>• Add prompts for nurses to clarify indication for use when removing drugs from automated machines</td>
</tr>
<tr>
<td>• Include dosing limits for drugs with similar indications</td>
</tr>
<tr>
<td>• Add alerts to drugs with look alike/sound alike names (eg; hydroxyzine, hydralazine; tramadol, toradol; metformin, metronidazol)</td>
</tr>
<tr>
<td>• Remove drugs with potentially difficult names if possible</td>
</tr>
<tr>
<td>• Attempt to develop novel delivery systems for drugs with similar names</td>
</tr>
<tr>
<td>• Ensure that the anesthetic care provider and any one securing drugs on their behalf repeat the request both initially and at the time of delivery</td>
</tr>
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</table>
The National Health Service of the United Kingdom addressed the issue of medical errors by formulating recommendations to reduce errors in anesthesia, not all of which may be easily incorporated but should at least be considered. (See Table 2)

<table>
<thead>
<tr>
<th>Table 2. National Health Service Recommendations to Reduce Drug errors in Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Make all anesthetic care workers and technicians aware of problems with medical errors and adverse drug events</td>
</tr>
<tr>
<td>• Enforce checking procedures such as “time out”</td>
</tr>
<tr>
<td>• Lighting should always be adequate</td>
</tr>
<tr>
<td>• Drug storage areas should be consistent as to placement</td>
</tr>
<tr>
<td>• Ampoules should be read and reread prior to being drawn up</td>
</tr>
<tr>
<td>• Whenever possible, an administrator should prepare drugs</td>
</tr>
<tr>
<td>• All syringes should be labeled with content, dosage, time of drugs</td>
</tr>
<tr>
<td>• The International Color Coded Syringe System should be used</td>
</tr>
<tr>
<td>• Syringes should be pre-filled for emergency use</td>
</tr>
<tr>
<td>• Pharmacists should visit the ORs frequently to become familiar with the areas</td>
</tr>
<tr>
<td>• Anesthetic care teams must be alerted to any changes made by drug companies or vendor change made by the hospital administration</td>
</tr>
</tbody>
</table>

Communication is an important concern. During the time out or huddle at the beginning of a case, drugs such as antibiotics or anticoagulants should be discussed with the assurance that all members of the team are aware of the medications to be given, the dosage and times and any allergies that the patient may have expressed. It is also important to recognize that should an error occur, an incident report must be generated. Blame and guilt should not be assigned; rather the error should be recognized as a systems breakdown and a root cause analysis generated. Thus a mechanism can be put in place to prevent a similar error from occurring again.

**Pharmacogenomics**

Even if no obvious ME has occurred, adverse reactions may still occur. The majority of drug metabolism, especially with drugs used in anesthesia, is via the Cytochrome P (CYP) 450 system. The CYP family comprises 57 genes with 18 families and 44 subfamilies.\(^6\) The most common drug metabolizers are CYP2D6 (i.e., family 2 subfamily D and gene number 6) but patients may have numerous alterations in genomic makeup. To apply this concept to the efficacy of medication, one must know whether the patient is an ultrarapid metabolizer with increased metabolic activity; an extensive metabolizer which would be a normal rate; or a poor metabolizer with little or no metabolic activity.

Metabolism can inactivate a drug or activate a drug, as is the case with “prodrugs” such as codeine or tramadol which require metabolism to produce an active metabolite. Thus in order to accurately determine the effect of a drug on an individual, the entire genome must be sequenced.

There is considerable variation in individual response to antiplatelet and anticoagulant drugs.\(^6\)
Unexpected results become of special importance when herbal preparations are added as many of them impact the CYP system, both blocking and increasing the absorption and metabolism. This is especially true with cardiac medications. The future of pharmacogenetics promises the accurate prediction of drug effects to maximize efficacy, minimize toxicity and provide personalized care will be available.

**Herbal Supplements**

The word “herbal” was applied to books printed in Western Europe during the years 1470 - 1670 known as “herbalis liber.” These books contained the names and descriptions of plants and their properties. The book contained plant lore, the medicinal properties of herbs and many illustrations to help in identification. Historical accounts of herb usage were drawn from ancient scrolls, written manuscripts and incunabula (books printed before 1501) and included accounts from places such as China, India, Greece and Mesopotamia. Medicine men, apothecaries, physicians or shaman were those familiar with the toxic, hallucinatory, aromatic, culinary and healing powers of plants and herbs and were considered to be of high rank in society. Ancient herbs have been transformed into modern chemistry, toxicology and pharmacology. Old herbal remedies, homeopathy, aromatherapy and the use of many preparations of herb extracts remain a significant part of complementary medicine today.

Herbs are derived from flowers, shrubs, trees, algae, ferns, fungi, seaweeds and grasses. They are used not only to treat diseases but also to improve the quality of life. All parts of plants are used. Some are most potent fresh, and other can be dried or preserved in alcohol (tinctures), steeped as teas (infusions), simmered (decotions), extracted by vinegar (acetacts), syrups, vegetable glycerin or honey. Freeze dried herbal powders are made into tablets, capsules, pastes or concentrates (4-6 times regular strength). Herbs may also be given as suppositories, creams, liniments, oils (aromatherapy) or baths. Difference in potency comes from species differences among the roots, plants or fruits, growing conditions and the methods used to extract active ingredients.

**Trends in the Usage of Herbs**

Patients who also seek conventional health care commonly use herbs because they are readily available and potentially effective, and do not require visits to physicians or pharmacy co-pays. Tens of thousands of herbal products and preparations are available in the United States. Studies have shown that as many as 70% of patients do not reveal their use of these agents to their treating physicians because they view them as “natural supplements” rather than a form of medicine.\(^7\)

The recent resurgence in herb use in the United States may be occurring for several reasons. Patients may have experienced poor results or uncomfortable side effects with prescription pharmaceuticals; and patients sometimes seek alternatives to the high cost of pharmaceuticals. More people are exposed to cultures with strong ties to herbal medicine through travel or through immigration of these groups to the United States. Herbal supplements are readily available in many food stores and specialty stores and these natural products are widely advertised as “safe”. Some herbs actually do exert beneficial effects. Current trends in nutrition have moved toward eating less meat and promoting greater consumption of leafy vegetables and leafy herbs. The American Heart Association has recommended decreasing salt intake and herbal substitutes are used instead, such as basil, black pepper, garlic powder, mace, marjoram, onion powder, parsley, sage, savory, thyme, cayenne pepper. There are recommendations to increase fiber intake which is often extracted from herbs. Natural forms of antioxidant vitamins (such as A and C) are commonly supplied as herbal preparations.
More than 50% of the adult population seen at hospitals in the United States take herbal medicines, multivitamins, or both, along with prescription drugs.\textsuperscript{7-9} Annual expenditures on herbal therapies exceed $10 billion. This underscores the necessity for anesthesiologists to be aware of the pharmacodynamics and pharmacokinetics of these self-prescribed formulations, and be able to provide adjunctive therapy for treatment of unexpected drug-induced responses perioperatively. In line with herbal use, over 50% of adult Americans have used at least one alternative therapy in recent years. Relaxation techniques and herbs have been advocated to treat chronic medical conditions such as diabetes, cancer, arthritis or AIDS. It is not uncommon for insurance plans and managed care organizations to offer reimbursement for alternative treatments. Coverage of chiropractic treatment is mandated by law in several states. Insurance plans generally require physician referral for these services, highlighting the importance of physician awareness for less conventional therapies.

**Drugs Derived from Herbs**

Approximately 30% of all pharmaceuticals are derived from plants.\textsuperscript{8} Table 3 lists some drugs derived from plants that are commonly used in the perioperative period.

<table>
<thead>
<tr>
<th>Plant</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Atropa belladonna</em></td>
<td>Atropine</td>
</tr>
<tr>
<td><em>Digitalis purpura</em></td>
<td>Digitalis</td>
</tr>
<tr>
<td><em>Papaver somniferum</em></td>
<td>Codeine</td>
</tr>
<tr>
<td><em>Cephaelis ipecacuanha</em></td>
<td>Ipecac</td>
</tr>
<tr>
<td><em>Physostigma venenosum</em></td>
<td>Physostigmine</td>
</tr>
<tr>
<td><em>Ephedra sinica</em></td>
<td>Ephedrine</td>
</tr>
<tr>
<td><em>Erythroxylon coca</em></td>
<td>Cocaine</td>
</tr>
<tr>
<td><em>Datura fastuosa</em></td>
<td>Scopolamine</td>
</tr>
<tr>
<td>Willow</td>
<td>Aspirin</td>
</tr>
</tbody>
</table>

**Government Regulations Affecting Herbal Supplements**

Herbal remedies are not held to the same Food and Drug Administration (FDA) standards and regulations as the pharmaceutical industry. Phased trials are not required although some companies provide scientific data to consumers. In general, individual herbs are not patented but blends can be patented.

The Dietary Supplement Health and Education Act of 1994 places the burden of product safety on the manufacturer, but the FDA has the responsibility of proving that a product is unsafe and must be removed from the market. The FDA does not test all herbal preparations before they are available over the counter. In 1998, the FDA issued the “Regulations on Statements Made for Dietary Supplements Concerning the Effects of the Product on the Structure of Function of the Body.” These regulations state that “dietary supplements that expressly or implicitly claim to diagnose, treat, prevent or cure a disease” must be classified as drugs and, therefore, must meet the safety and effectiveness standards of the Food, Drug and Cosmetic Act. The definition of disease is “any deviation from, impairment of, or interruption of the normal structure of function of any part, organ or body system that is manifested by a characteristic set of one or more signs or symptoms.” This definition allows the claim “promotes vascular health” while disallowing the statement “decreases blood pressure.” In response to the regulations,
herb manufacturers typically market their product as “not intended to diagnose, treat, cure or prevent any disease” and thus bypassing any FDA drug regulations. In response to claims made for such effects as weight loss, the manufacturer must also add “this statement has not been evaluated by the Food and Drug Administration.”

Government studies have determined that there is little standardization in the amount of active ingredients in herbal products and there is no consistent growth stage for harvesting. In 2015, the New York Times reported that herbal compounds were often found to contain inert substances such as rice, whey, or peanuts and some were found to have drugs such as steroids and sildenafil. The report further went on to note that 79% of herbs tested with DNA coding did not have herbal ingredients. The FDA estimates that 70% of dietary companies do not follow basic quality control. Only 0.3% of supplements sold in the US have been tested and as many as 20% of cases of drug induced liver failure are related to herbal intake.

**Common Herbs and Interactions**

Many herbs may increase or decrease the activity of the CYP isozymes either by inducing the biosynthesis of an isozyme (i.e., enzyme induction) or by directly inhibiting the activity of the CYP (i.e., enzyme inhibition). Changes in CYP enzyme activity will further affect the metabolism and clearance of other drugs. A drug can accumulate to toxic levels if an herb inhibits the CYP-mediated metabolism of the drug. Such interactions are especially important to consider with drugs that have major side effects (opioids causing dependence) or drugs with small therapeutic windows.

Induction and inhibition of the CYP system is variable. When metabolic function is inhibited, drugs are not broken down and can accumulate. Induction causes drugs to be metabolized faster. Both effects require adjustment of drug dosages.

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Inhibition caused by:</th>
<th>Induction caused by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>Camomile, grapefruit, ginko, kava</td>
<td>Garlic, ginko, St Johns Wort</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>Camomile, ginko, grapefruit</td>
<td>St Johns Wort</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Feverfew, grapefruit, kava</td>
<td>Ginko, St Johns Wort</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Feverfew, ginko, grapefruit, kava</td>
<td>St Johns Wort</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Garlic, kava</td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Garlic, goldenseal, kava</td>
<td></td>
</tr>
</tbody>
</table>

Other herbs may have additional interactions with anesthetic agents. Table 5 lists some of the common herbal preparations that may interact with anesthetic agents.
Table 5. Herbal Medications and Anesthesia

| Echinacea offsets immunosuppression, inhibits HME* |
| Garlic augments heparin, NSAIDs |
| Ginger, Gingko, and Ginseng increase bleeding time |
| St John’s Wort reacts with MAO inhibitors, tetracycline |
| Kava-kava reacts with ethanol and creates excessive sedation |
| Feverfew inhibits platelet activity |
| Ephedra interacts with inhalation anesthetics causing dysrhythmias; also hypertension |
| Ginseng causes hypertension, hypoglycemia, reacts with MAO inhibitors |

*HME=hepatic microsomal enzymes

St Johns Wort is recognized as a drug in Europe. Its active ingredients, hypercin and flavinoids, inhibit monoamine oxidase (MAOI), GABA receptors and serotonin receptors (SSRIs). It can precipitate opioid withdrawal though an effect on the CYP3A4 system and is used for anxiety and depression. It decreases the effectiveness of cyclosporine and digoxin, while causing hypertension with Dexatrim® and Acutrim®. Combined with other SSRIs (fluoxetine), a serotonergic syndrome may develop with autonomic dysfunction, hyperthermia and death. Fatal results may also follow combination with MAO inhibitors such as phenelzine.

Grapefruit inhibits and induces the metabolism of many drugs through inhibition of CYP3A4 and other parts of the CYP system. The bioavailability of many drugs including benzodiazepines, sertraline, some statins, nicardipine, losartan, verapamil, levothyroxine, amiodorone, codeine, tramadol, zolpidem and oxycodone among others is increased.

Summary

Science has only scratched the surface of drug and herbal interactions. A complete history should be obtained preoperatively, including careful questioning about all over-the-counter preparations. Patients should be educated that herbs need to be discontinued prior to anesthesia and should be used with guidance from their physicians. A consideration in the PACU in the differential diagnosis of any abnormal finding should be drug interaction. Recommendations should be implemented to decrease medication errors and adverse drug events in the operating room.

Management of the Case

The anesthesiologist responded promptly to the PACU. The patient remained responsive only to deep stimulation. Vital signs were stable as was oxygen saturation. The pupils responded quickly to light. Arterial blood gas analyses were also normal. The patient’s daughter was by her side and she offered that following the discussion with the anesthesiologist earlier she had gone to her mother’s home. There she found, along with the prescription medications, an almost empty bottle of St Johns Wort. She also offered that her mother had been concerned recently about weight gain and had restricted her diet, mainly to grapefruit. The anesthesiologist again reviewed the anesthetic record and considered that the slight temperature rise along with the bradycardia could be accounted for by interaction with St Johns Wort and sertraline. Inhibition of metabolism of her cardiac medications could cause bradycardia. The delayed return to consciousness was probably related to accumulation of midazolam and narcotics.
because of inhibition of the CYP3A4 system. He advised continued monitoring. After 3 hours, the patient awoke without further sequelae. She was advised to decrease her herbal consumption.

Dr. Elizabeth A.M. Frost, who is the editor of this continuing medical education series, is clinical professor of anesthesiology at The Mount Sinai School of Medicine in New York City. She is the author of Clinical Anesthesia in Neurosurgery (Butterworth-Heinemann, Boston) and numerous articles. Dr. Frost is past president of the Anesthesia History Association and former editor of the journal of the New York State Society of Anesthesiologists, Sphere. She is also editor of the book series based on this CME program, Preanesthetic Assessment, Volumes 1 through 3 (Birkhäuser, Boston) and 4 through 6 (McMahon Publishing, New York City).
REFERENCES


Further Reading

- [www.herbs.org](http://www.herbs.org) *Herb Research Foundation*
- PDR for Herbal Medicines.
- Lu WI, Lu DP Impact of Chinese herbal medicines on American Society and Health Care system. *Evid Based Comple Alternat Med* 2014; 2014; 251891
Visit [www.mssm.procampus.net](http://www.mssm.procampus.net) today for instant online processing of your CME post-test and evaluation form. There is a registration fee of $15 for this non–industry-supported activity. For assistance with technical problems, including questions about navigating the Web site, call toll-free customer service at (888) 345-6788 or send an e-mail to Customer.Support@ProCEO.com. For inquiries about course content only, send an e-mail to ram.roth@mssm.edu. Ram Roth, MD, is director of PreAnesthetic Assessment Online and assistant professor of anesthesiology at The Icahn School of Medicine at Mount Sinai, New York, NY.

Post-test

1. Regarding medication errors in the operating room
   a. Very few are preventable
   b. More than 30% lead to adverse drug events
   c. They are now prevented by coding systems
   d. They rarely result in adverse drug events

2. Adverse drug events in hospitals
   a. Occur in 3-6% of all hospital stays
   b. Have been deemed preventable in 40%
   c. Occur with an incidence of about 1 medical error/hospital patient/day
   d. All of the above

3. The definition of a medical error is
   a. A preventable error that may cause or lead to patient harm
   b. Variable depending on the location
   c. Constantly subject to change
   d. None of the above

4. Errors due to miscommunication are most likely to occur
   a. In the huddle
   b. During a time out
   c. When pharmaceuticals companies change strengths or ampoule size or color
   d. During the preanesthetic visit

5. Regarding infection prevention
   a. Multiple doses can be safely administered from a single dose ampoule in the OR.
   b. A practice of 1 needle and 1 syringe from a single vial is required for each patient.
   c. A syringe barrel can be re-used if the needle is changed.
   d. All of the above.
6. Medical errors may be decreased by
   a. Ensuring adequate lighting
   b. Maintaining consistent drug storage areas
   c. Avoidance of drug abbreviations
   d. All of the above

7. Herbs that can increase perioperative bleeding include
   a. Garlic and ephedra
   b. Ginseng and St Johns Wort
   c. Gingko and ginger
   d. Feverfew and Echinacea

8. Regarding St Johns Wort
   a. Digoxin should be given in decreased dosages
   b. It is both an MAO and SSR inhibitor
   c. Opioid withdrawal is prevented
   d. It has no effect on CYP isoenzymes

9. Grapefruit
   a. May either inhibit or induce CYP isoenzymes
   b. It allows accumulation of several cardiac drugs and pain medications
   c. The bioavailability of the benzodiazepines is increased
   d. All of the above

10. Regarding all herbal preparations
    a. Use in the US is on the decline
    b. The government maintains strict control
    c. They are not held to the same quality standards as pharmaceuticals
    d. The FDA allows the manufacturers to make medical claims of effectiveness