Drugs, Herbals and Nutraceuticals: New Reports to Keep Your Practice Current

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Safety Concerns of Herbal Remedies

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It is estimated that the U.S. population spends between $4 billion and $5 billion annually on herbal medicines. (1,2) Between 1990 and 1997, the use of herbal remedies in the U. S. population increased from 2.5% in 1990 to 12.1% in 1997. (1) In 1998, it was estimated that 15 million adults concurrently take herbal remedies and vitamins along with prescription medications. (1) In addition, patients undergoing medical surgery appeared to use herbal medications more frequently than the general population. (3) In view of the fact that herbal remedy use seems to be escalating, it is important that the dental professional be aware of safety concerns about these products.

Regulatory Background

The Food and Drug Administration considers herbals as dietary supplements and allows herbal products to be marketed without proof of efficacy or safety. The DSHEA (Dietary Supplement and Health Education Act) of 1994 assigned responsibility for ensuring safety and efficacy of herbal products to the manufacturers. There is no requirement on the part of the manufacturer to submit documentation of product testing. In addition, DSHEA did not set standards for quality control and does not require any approval before supplements enter the market. Manufacturers can make statements and claims of nutritional support, particularly claims describing influence on body functions. Recently, a new ruling by the FDA allowed supplement manufacturers to make claims regarding serious health conditions without any pre-market review, but may not make claims to treat disease unless clinical evaluations proves otherwise. (4) In summary, manufacturers may now make claims that their product can be effective in treating or reducing a symptom or annoyance, but may not make claims of treating a specific disease without a pre-market FDA review.

There are no formal requirements from the FDA to the manufacturer to report adverse reactions caused by herbals. In the past however, reports from manufacturers and consumer groups have accounted for over 5000 suspicious herb-related adverse reactions to the World Health Organization before 1996, and over 2,500 adverse reactions to the FDA between 1993 and 1996, including 101 deaths. (1,4).

It is estimated that it would cost the manufacturer $350 million to confrm safety and efficacy of an herbal product. Since most herbal remedies are from plant sources and considered within the public domain, many of them cannot be patented and the manufacturer could not expect to recover the estimated $350 million cost of clinical testing. A recent trend is to isolate the active compounds from the plant to test for pharmacologic activity. (5) However, data from active

ingredients may not be representative of the herb itself since active ingredients are variably present in specific products. Presently therefore, consumers and health care professionals have little information to make decisions about safety, interactions or effectiveness.

Table 1 lists the popular herbal remedies along with their primary uses or actions. The remedies making up this list were takem from the Drug Topics Red Book and are considered the most popular according to consumer sales in pharmacies, chain store outlets and supermarkets. (6) Unless indicated as a topical effect, all remedies are used systemically. Topical agents such as aloe and arnica montana are used to treat wounds and contusions. Many of the agents on the list are used for their anti-inflammatory properties. Many agents are purported to support immune function, many are used to produce sedation and to reduce anxiety, some have anti-oxidant properties, and some are used as sources of plant estrogens proposed to be effective as hormone replacement therapy. Other herbs have antimicrobial properties, many are used to treat various cardiovascular problems, some are used for memory enhancement and to treat mental depression. Also, at least one herb, feverfew, is used to treat migraine headache. For the most part, none of the listed uses have been confirmed through controlled clinical trials. Some of the herbal remedies listed in Table 1 have been tested in placebo-controlled trials and shown beyond reasonable doubt to be effective in several conditions. These agents are listed in Table 2 along with references to the trials in which the data were gathered. The data on effectiveness of Ginkgo in treating dementia (vascular and Alzheimer's) came from nine randomized placebo-controlled trails using a total of 891 subjects. The overall results showed that Ginkgo effectively delayed the deterioration of cognitive functions in dementia patients (7). The studies on the effects of Ginkgo on intermittent claudication included 415 patients in eight trials. The overall result was that Ginkgo prolonged walking distance significantly more than placebo. (8) The effects of horse chestnut in treating venous insufficiency came from thirteen trials using 1083 patients. Horse chestnut showed a significant reduction of symptoms and signs of chronic venous insufficiency compared with placebo. (9) The effectiveness of kava for the treatment of anxiety was reviewed from seven studies using 377 patients. The results showed that kava reduced anxiety significantly more than placebo. (10) The effectiveness of St. John's Wort in treating mild-to-moderate mental depression was reviewed from 14 studies using a total of 1417 subjects. The data indicated St. John's Wort to be significantly more effective than placebo and equivalent to conventional antidepressants. (11)

Safety concerns of herbal remedies.

Table 3 lists the popular herbal remedies along with the main safety concerns. These safety concerns were compiled from literature reports and include adverse effects, and potential or suspected drug interactions. The safety concerns described in Table 3 are not identified in terms of either reported or theoretical effects, but represent statements taken from the referenced sources for each description. It is reasonable to assume that these effects could occur in patients taking the herbal remedies, particularly over long periods of time and with high doses. Reports are beginning to surface in the literature which document, in a more accountable way, adverse reactions caused by herbal remedies. Of the popular herbal remedies listed in Table 3, eight of these remedies were identified by Ang-Lee et al in a report in the Journal of the American Medical Association (12) of having the potential to cause adverse effects in patients undergoing medical surgery. These herbals included echinacea, ephedra, garlic, ginkgo, ginseng, kava-kava,

St. John's Wort, and valerian. The reader is referred to Wynn (4) for a discussion of the perioperative effects of these eight herbs.

The safety concerns about herbal remedies have come primarily from the medical community. However the same precautions may apply to the dental patient with a history of herbal use. In particular, precautions should apply in dental surgery for those herbs described in table 3 that affect blood clotting. In addition, some of the herbs above have the potential to interact with drugs that affect blood clotting such as aspirin and the nonsteroidal anti-inflammatory drugs.

As suggested previously by Wynn (4) and Karimi (13) the problem still remains in obtaining an accurate history of herbal use from the patient. The suggestion by Karimi (13) of including a supplement to the medical/drug history form asking the patient about the use of herbal remedies is a good one. Additional persistence however may be in order since one-half the patients who use alternative therapies fail to report this information on a form unless directly questioned. (14) Also patients may not feel comfortable in describing a history of herbal use in the belief that the use of herbal supplements is not related to medical or dental care. Many commercial herbal preparations are combination agents packaged under various brand names and the dental professional may not know the herbal ingredient when given a brand name by the patient. A start in the herbal history taking process may be to use table 3 as a reference guide and ask the patient to indicate which, if any, herbs listed in table 3 are being used. Once the herbs are identified, measures can then be taken to avoid herbal-drug interactions, and possibly to avoid other unwanted reactions in the patient.

Table 1. Popular Herbs and Primary Uses *

Aloe Topical healing agent for wounds

Arnica Montana Topical healing agent for contusions, bruises and sprains

Astragalus Improvement in immune function and disease resistance; enhances endurance and stamina

Bilberry Treat ophthalmologic disorders including macular degeneration

Black cohosh Treat vasomotor symptoms of menopause

Calendula Topical antibacterial, wound-healing agent

Cat's claw Antiinflammatory, antimicrobial

Cayenne Topical to treat inflammation and pain

Chamomile Mild sedative

Chasteberry Treat symptoms of menopause

CranberryTreat urinary tract infection

Devil's clawTreat inflammatory conditions

Dong quaiTreat symptoms of menopause, dysmenorrhea, premenstrual syndrome

EchinaceaImmune stimulant to treat colds and flu

Ephedra Bronchodilator in asthma, decongestant in allergies and colds, aid in weight loss

Evening primroseTreat symptoms of premenstrual syndrome and menopause

FenugreekRegulation of blood sugar

FeverfewPrevent migraine headache

GarlicLowering of blood cholesterol

GingerAntiemetic

Ginkgo bilobaTo increase peripheral blood flow in treatment of peripheral vascular insufficiency; memory enhancement; treat mild Alzheimer's disease

GinsengSupport immune function; enhance physical and mental performance

Golden sealTreatment of gastritis; used in inflammation of mucosal membranes

Gotu KolaTopical aid in wound healing; promotes healing of tissues

Grapefruit seedAntifungal, antibacterial agent

Grape seedPotent anti-oxidant, treatment of allergies and asthma

Green tea Antioxidant used to reduce serum cholesterol levels; anti-carcinogenic activity

HawthornCardiotonic in treatment of mild heart failure, angina and peripheral vascular disorders

Horse chestnutTopical agent to treat varicose veins

HuperzineA Treatment of senile dementia and Alzheimer's disease

Kava kavaTo treat anxiety and induce sedation

Milk thistleAntioxidant, specifically for liver diseases

Red yeast riceUsed to reduce serum cholesterol levels

Saw palmettoTo improve symptoms of benign prostatic hyperplasia

Soy isoflavonesUsed to treat menopausal symptoms and to prevent bone loss

St. John's Wort Use to treat mild to moderate depression; topical agent to treat bruises and sprains

TurmericAnti-oxidant, anti-inflammatory

ValerianUsed as a sedative or hypnotic

YohimbeUsed in male erectile dysfunction

* Statements of primary use in the table were edited from the individual monographs published in the following sources:

Natural Therapeutics Pocket Guide 2000-2001 by LaValle JB, Krinsky DL, Hawkins EB, Pelton R, Willis NA. Published by Lexi-Comp, Inc. Hudson, Ohio, 2000.

The PDR for Herbal Medicines, first edition, published by Medical Economics, Inc Montvale NJ, 1998.

Table 2. Herbal remedies which have been shown in controlled clinical trials to be effective

Remedy	Indication	Trial results	Study reference
Ginkgo	Dementia	Ginkgo delays deterioration of cognitive functions	
Ginkgo	Intermittent claudication	Prolonged walking distance greater than placebo	
Horse chestnut	Chronic venous insufficiency (CVI)	Sig reduction of symptoms and signs of CVI	
Kava	Anxiety	Anxiety reduction greater than placebo	
St. John's Wort	Mild-to-moderate depression	Greater efficacy than placebo in mood elevation	

Table 3. Popular Herbs and safety concerns

Herb	Main safety concerns and potential/suspected drug interactions.
Aloe	None reported with topical use
Arnica Montana	None reported with topical use
Astragalus	May limit effects of immune suppressants (15)
Bilberry	May inhibit platelet aggregation; reports of unanticipated bleeding; may interact with NSAIDs and aspirin to cause bleeding; (16)
Black cohosh	May alter estrogen hormonal therapy (17)
Calendula	None reported
Cat's claw	May inhibit platelet activating factor; may interact with NSAIDs and aspirin to cause bleeding; (18)
Cayenne	May increase catecholamine secereton to blunt effects of antihypertensives. (19)
Chamomile	Additive sedation with CNS depressants (benzodiazepines; Anxiolytics) (20)
Chasteberry	May alter estrogen hormonal therapy. (21)
Cranberry	None reported
Devil's claw	May prolong bleeding; may interact with NSAIDs and aspirin to cause bleeding; (22)
Dong quai	May prolong bleeding; may alter estrogen hormonal therapy; sensitivity to sunlight; may blunt effects of antihypertensives; may interact with NSAIDs and aspirin to cause bleeding; (23)
Echinacea	May alter response to immunosuppressive therapy (12)
Ephedra	Elevates blood pressure; use vasoconstrictor with caution (24)
Evening primrose	May inhibit platelet aggregation; may interact with NSAIDs and aspirin to cause bleeding; (25)
Fenugreek	May alter insulin or oral antidiabetic drug dosings in diabetics (26)
Feverfew	May prolong bleeding; may interact with NSAIDs and aspirin to cause bleeding; (27)

Garlic	Irreversible platelet aggregation inhibitor; may prolong bleeding; may interact with NSAIDs and aspirin to cause bleeding; (28 –31)
Ginger	May inhibit platelet activating factor; may interact with NSAIDs and aspirin to cause bleeding; (32,33)
Ginkgo biloba	May inhibit platelet activating factor; may interact with NSAIDs and aspirin to cause bleeding; (34,35)
Ginseng	May prolong bleeding; may interact with NSAIDs and aspirin to cause bleeding; (36 – 39)
Golden seal	None reported
Gotu Kola	May cause contact dermatitis (40)
Grapefruit seed	None reported
Grape seed	May prolong bleeding; may interact with NSAIDs and aspirin to cause bleeding; (41,42)
Green tea	May prolong bleeding at high doses (43-45)
Hawthorn	None reported
Horse chestnut	May inhibit platelet aggregation; may interact with NSAIDs and aspirin to cause bleeding; (46)
Huperzine A	None reported
Kava kava	Coma has occurred with alprazolam; may potentiate alcohol and CNS depressants (47-49)
Milk thistle	None reported
Red yeast rice	Use with caution in individuals on anticoagulant medications; (50)
Saw palmetto	None reported
Soy isoflavones	None reported
St. John's Wort	Appears to elevate liver enzymes to rapidly metabolize many drugs rendering them less effective (51-54)
Turmeric	May prolong bleeding; may interact with NSAIDs and aspirin to cause bleeding; (55)
Valerian	May potentiate CNS depressants (56)
Yohimbe	May cause anxiety, insomnia, hypertension, tachycardia (57)

Herbal Remedies: Concerns from the Medical Community

Richard L. Wynn, Ph.D

A report from the medical literature in 1998 indicated that 15 million adults concurrently take herbal remedies and vitamins along with prescription medications (1). In addition, Eisenberg et al (2) reported that patients undergoing surgery appeared to use herbal medications more frequently than the general population. Also, Tsen et al (3) reported that 22% of patients who presented for preoperative evaluation were taking herbal medications. This followed a report by Kaye et al (4) who noted that 32% of patients in an ambulatory setting admitted to using herbal medications. The report by Kaye et al (4) also revealed that 70% of herbal users did not disclose their use to the health care provider. In view of the high number of medical patients taking herbal remedies coupled with the non-reporting of their use, the medical community has expressed concern that widespread herbal use in a medical surgical population could result in adverse effects during medical care, including unwanted herbal-drug interactions. (3,5,6)

This type of herbal information has not been forthcoming in the dental literature. Several isolated reports have expressed some concern by dental professionals for the potential for herbal remedy-induced adverse effects in the dental setting. Cohan and Jacobsen (7) described 20 of the most frequently used herbs and discussed precautions and potential herb-drug interactions. Karimi (8) discussed the potential impact of herbal remedies on dental patient management with the suggestion that the health history form include questions on the use of herbal supplements. Biron (9,10) has published some information to the dental hygiene community about considerations on the use of herbal remedies by dental patients. In an attempt to uncover other dental reports, this author searched the MEDLINE data base for articles published between January 1966 to the present, using the search terms *herbal medicine, dentistry.* Except four the four cited above, no other reports were found relative to herbal remedy medical use and dental patient care.

In view of the dearth of reports in the dental literature on herbal remedies, this present article describes recent published concerns by the medical community on some herbal remedies that could affect patient care. Ideally this information will translate to the dental practitioner as a knowledge base to be used for safe dental patient care.

Eight commonly used herbal remedies were identified by Ang-Lee et al (11) of having the potential to cause adverse effects in patients undergoing medical surgery. These herbals included echinacea, ephedra, garlic, ginkgo, ginseng, kava-kava, St. John's Wort, and valerian. The process of identification of these agents was according to surveys in the literature, 1999 sales data, and searches in textbooks and medical journals. (11) The following are descriptions of the effects, medical concerns and patient management for each of these herbal remedies.

Echinacea

The Tsen report indicated that among the herbal users presenting for pre-operative work-up, 33% were taking echinacea. (3) Echinacea, or purple cone flower, is a member of the daisy family and is native to the great plains states of the US. For Echinacea purpurea, the active ingredients are found in the whole plant; for Echinacea angustofolia, the active ingredients are found primarily in the root. Echinacea has

been used for the prevention and treatment of the common cold and flu. Specifically it has been used in the treatment of viral, bacterial and fungal infections of the upper respiratory tract. (11) Immunostimulatory effects of echinacea have been shown in various preclinical studies, (12-14) and it is thought to be an immunostimulant in humans when used for short periods of time. (11,13). Long term use of more than 8 weeks however may be associated with immunosuppression (15). Thus there could be a potential for increased risk of certain postsurgical complications such as poor wound healing and opportunistic infections. Concerns have also been expressed about the potential for echinacea to cause hepatotoxicity (11, 16) although actual documented cases are lacking. Ang-Lee et al. (11) have therefore suggested that patients should discontinue taking echinacea as far in advance as possible of medical surgery, particularly when compromises in hepatic function are anticipated. They did not differentiate between long term users and short term users for this recommendation.

Ginkgo biloba

The Tsen report indicated that among the herbal users presenting for pre-operative work-up, 18% were taking ginkgo biloba. (3) Ginkgo biloba comes from the leaf of the ginkgo (Maidenhair) tree It has been used for the treatment of peripheral vascular disease, cerebral vascular diseases, mild dementia, Alzheimer's disease, intermittent claudication, macular degeneration, memory enhancement, tinnitus, vertigo and erectile dysfunction. The primary activity of ginkgo is probably derived from flavoglycosides and terpenoids within the leaf extract. Ginkgo is an inhibitor of platelet activating factor, (17,18) an effect which raises concern for the perioperative period since platelet function may be altered. Four cases of spontaneous intracranial bleeding, (19-22) one case of spontaneous hyphema (23) and one case of postoperative bleeding following laparoscopic cholecystectomy (24) have been reported in association with ginkgo use. Based on the risk of bleeding in the surgical population, Ang-Lee et al. have recommended that medical patients should discontinue taking Ginkgo biloba at least 36 hours prior to surgery.(11) This time frame is based on the elimination half-lives of the terpenoid active ingredients after oral administration of Ginkgo.(25)

St. John's Wort

The Tsen report indicated that among the herbal users presenting for pre-operative work-up, 15% were taking St. John's Wort. (3). St. John's Wort comes from the flowering buds of the plant *Hypercium perforatum*. It has been used for the treatment of mild to moderate depression, melancholia, and anxiety. It has also been used topically for minor wounds, infections, bruises, muscle soreness and sprains (26). The primary activity of St. John's Wort is believed to be derived from the compounds known as hypericin and hyperforin (27). Although St. John's Wort is popular amongst consumers for the treatment of mild forms of depression, a recent report from a multicenter clinical trial concluded that St. John's Wort was ineffective in treating major depression. (28) St. John's Wort can cause drowsiness and photosensitivity. However the major concern with this herb is its effect on hepatic drug metabolizing enzymes. A report in the journal Lancet suggests that St. John's Wort can elevate levels of the drug metabolizing hepatic cytochrome P-450 system (29). Since this is the system which causes the breakdown of many drugs to inactive products, any elevation of this system will result in further breakdown and reduced effectiveness of other drugs. The report showed an interaction between St. John's Wort and the HIV-1 protease inhibitor Indinavir, where the blood level of the Indinavir was significantly reduced. Another article (30) reported acute rejection episodes in two heart transplant patients who had taken St. John's Wort for depression. Each patient recovered after the herb was discontinued. The effect was attributed to the P-450 induction activity of the herb. As a result of these two reports, the FDA has issued a public health advisory regarding this issue (31).

Drugs commonly used in the perioperative period in medical patients and metabolized by the P-450 system could be influenced by St. John's Wort to result in reductions of their effects. These include midazolam (Versed), diazepam (Valium), and triazolam (Halcion) (11). These drugs are also used in dentistry as pre-operative sedatives. Other drugs which have had reduction in actions in patients taking St. John's Wort were warfarin (Coumadin) (32) and digoxin (33). Ang-Lee et al. have suggested that the effectiveness of nonsteroidal anti-inflammatory drugs could be reduced by St. John's Wort (11). Based on the potential for St. John's Wort to diminish the actions of other drugs, Ang-Lee et al. have recommended that patients should discontinue taking St. John's Wort for at least 5 days prior to surgery. (11) This time frame was based in the elimination half-lives of hypericin and hyperforin (34,35).

Garlic

The Tsen report indicated that among the herbal users presenting for pre-operative work-up, 15% were taking Garlic (3) Garlic comes from the bulb of the plant *Allium sativum*. Common synonyms include "Comphor of the Poor', "Nectar of the Gods", and "Stinking Rose". It has been used for the treatment of hypertension and used as an antimicrobial. (36) It has been reported to lower serum lipid and cholesterol levels, (37) it may lower blood glucose, and it may decrease the incidence of thrombosis. (36) The effects of garlic are attributed to three active ingredients known as alliin, allicin and aljoen. The chief concern about garlic is its ability to inhibit platelet aggregation. (38) The ingredient aljoen irreversibly inhibits platelet aggregation and potentiates the effects of other platelet inhibitors such as prostacyclin, dipyrimadole and indomethacin, a nonsteroidal anti-inflammatory agent. (39,40) Recently, a report was published on the ability of allicin and thiosulfinate compounds in garlic to inhibit human platelet aggregation. (41) The report concluded that these compounds were more potent platelet inhibitors than aspirin at nearly equivalent concentrations. (41).

The medical concerns about garlic are its potential to irreversibly inhibit platelet aggregation. Therefore it is recommended that patients discontinue the use of garlic at least 7 days prior to surgery, particularly if other platelet inhibitors are given, or postoperative bleeding is anticipated. (11).

Ginseng

The Tsen report indicated that among the herbal users presenting for pre-operative work-up, 15% were taking Ginseng (3) Ginseng comes from the root of many different species of plants with the major three being Asian (Oriental) ginseng (*Panax schinseng*), American ginseng (*Panax quinquefolius*) and Siberian ginseng (*eleutherococcus senticosus*). Other species include Korean ginseng and Tienchi ginseng, which is grown in the northeastern regions of China. Ginseng has been used to enhance physical and mental performance, to protect the body against stress, to boost immune function and to restore homeostasis. Ginseng is often referred to as an adaptogen in its actions to protect against stress and restore homeostasis. (42) The effects of ginseng are attributed to the active ingredients known as ginsenosides, which include over 20 saponin triterpenes similar in structure to steroid hormones. (42) These ginsenosides are believed to act via hormone receptors in the hypothalamus, pituitary glands and other tissues. (43)

The medical concern about ginseng is its ability to inhibit blood clotting. Ginsenosides in laboratory rats prolong activated partial thromboplastin and coagulation time of thrombin. (44) Ginsenosides have been shown to inhibit platelet aggregation in vitro. (45,46) One report has shown that a constituent of ginseng known as panaxynol irreversibly inhibited platelet activity in humans.(47) Panaxynol was concluded to be the most potent antiplatelet agent in ginseng and its mechanism of platelet inhibition was chiefly due to the inhibition of thromboxane formation. (47) In platelet aggregation assays with human platelet rich plasma, Korean ginseng inhibited thrombin and collagen-induced platelet aggregation.(48) In

coagulation assays, Korean ginseng significantly prolonged activated partial prothrombin time and prothrombin time compared to control data. (48) Ang-Lee et al suggest that platelet inhibition caused by ginsenosides may be irreversible (11). The concerns about the effects of ginseng on blood clotting have resulted in the recommendation that patients should discontinue ginseng use at least 7 days prior to surgery. (11)

Kava kava

The Tsen report indicated that among the herbal users presenting for pre-operative work-up, 4% were taking Kava kava. (3) Kava kava comes from the dried root of the pepper plant *Piper methysticum*, native to the South Pacific. Kava kava is used as an anxiolytic and sleep aid. (49) It is claimed that kava kava induces relaxation without impairment of memory or motor function. (49,50) Kava kava was shown in studies with mice to have antinociceptive actions which were not antagonized by the opiate reversal agent naloxone. (51) The pharmacologic effects of kava kava are attributed to active ingredients known as kavalactones. (52) The kavalactones appear to induce anticonvulsant, analgesic and anxiolytic effects. (53) Kavalactones increase barbiturate sleep times in laboratory animals. (54). Kavalactones probably act through potentiation of the gamma aminobutyric (GABA) transmitter system to induce inhibitory effects in the CNS. (52) In addition, kavalactones weakly antagonize sodium and calcium neuronal channels within the CNS and stimulate potassium outward currents in neurons (53). These effects are similar to the actions of the antiepileptics carbamazepine, valproate and lamotrigine. (53). The kava whole root extract appears to exhibit greater activity than any single isolated kavalactone. (52)

The medical concern about kava kava is its potential to enhance the sedative effects of agents used within the regimen of balance general anesthesia . Therefore it would seem prudent to recommend discontinuance of kava kava prior to anesthesia. Peak plasma levels of the kavalactones occur 1.8 hours after an oral dose and the elimination half-life is 9 hours. (55) On the basis of these pharmacokinetics, Ang-Lee et al (11) have recommended discontinuance of kava kava for at least 24 hours prior to surgery.

Valerian

Valerian comes from the root of the plant Valeriana officinalis. Valerian is used as a sedative and hypnotic (56) and has been used as a treatment for insomnia (57). It has also been used to treat restless motor syndrome and muscle spasms (58). The sedative actions of valerian are probably mediated through modulation of GABA neurotransmission and receptor function. (59,60) The pharmacologic effects of valerian are attributed to the active ingredients valepotriates and valeric acid. (61)

The medical concern about valerian is similar to kava kava in that it has the potential to enhance the sedative effects of agents used within the regimen of balance general anesthesia . Therefore it would seem prudent to recommend discontinuance of valerian prior to anesthesia. Ang-Lee et al (11) have suggested that some patients could be dependent on valerian and caution should be taken in the abrupt discontinuation in these patients because of the risk of inducing benzodiazepine-like withdrawal symptoms.

Ephedra

Ephedra is known as Ma-Huang and consists of the dried, young branches of the plants *Ephedra sinica, Ephedra shennungia* or other ephedra species. *Ephedra sinica* grows mainly in Mongolia and the bordering area of China. Historically ephedra has been used as a bronchodilator and for the treatment of other respiratory tract conditions such as bronchitis and bronchspasms.(62) In modern society, it is used as an appetite suppressant to promote weight loss and as a central nervous system stimulant and as a decongestant in the treatment of allergies, sinusitis and hayfever. (63) Ephedra is a collective term for a

number of specific ephedrine-type alkaloids found in Ma-Huang. These alkaloids include ephedrine, pseudoephedrine, norephedrine, methylephedrine and norpsuedoephedrine. The potency of standardization of ephedra is usually attributed to the ephedrine content. (64)

Ephedrine is both an alpha and beta adrenergic agonist. It enhances the release of norepinephrine from sympathetic neurons. Ephedrine stimulates heart rate and cardiac output and has a tendency to increase arteriolar peripheral resistance leading to increases in blood pressure. Activation of the beta-adrenergic receptors in the lungs promotes bronchodilation. Ephedrine is a potent CNS stimulant, but less so than amphetamine (65). After oral administration, the effects of ephedrine may last for several hours. Ephedrine has a half-life of 3 to 6 hours and is excreted in the urine as the unchanged compound. (65) According to Ang-Lee et al. (11) and the Food and Drug Administration (66) the sympathomimetic effects of ephedrine have been associated with more than 1,070 reported adverse events including fatal cardiac episodes and central nervous system complications.

The medical concern about patients taking ephedra and undergoing anesthesia and surgery is that ephedrine may cause intraoperative ventricular arrhythmias with anesthetics such as halothane. (67) Ephedrine may also affect cardiovascular function by causing hypersensitivity myocarditis. (68) Long term use may result in tachyphylaxis from depletion of endogenous catecholamine stores which may contribute to perioperative hemodynamic instability (11). Concomitant use of ephedra and monoamine oxidase inhibitors can result in life-threatening hyperpyrexia, hypertension and coma. (11) Based on the reported cardiac risks of ephedra including myocardial infarction, stroke, and cardiovascular collapse from catecholamine depletion, Ang-Lee et al, have recommended that patients discontinue this herb for at least 24 hours prior to surgery. (11)

Comment

How do these medical concerns described above translate to the dental setting? Certainly the same precautions would apply to those dental situations in which preoperative sedation and general anesthesia are used. Also, similar precautions would apply in dental surgery for those herbs described above that affect blood clotting. In addition, some of the herbs above have the potential to interact with drugs that affect blood clotting such as aspirin and the nonsteroidal anti-inflammatory drugs.

The problem remains in obtaining an accurate history of herbal use from the patient. The suggestion by Karimi (8) of including a supplement to the medical/drug history form asking the patient about the use of herbal remedies is a good one. Additional persistence however may be in order since one-half the patients who use alternative therapies fail to report this information on a form unless directly questioned. (69) Also patients may not feel comfortable in describing a history of herbal use in the belief that the use of herbal supplements is not related to medical or dental care. Many commercial herbal preparations are combination agents packaged under various brand names and the dental professional may not know the herbal ingredient when given a brand name by the patient. A start in the herbal history taking process may be to simply include the list of the eight herbs in this present report and ask the patient to indicate which, if any, are being used. Additional herbal names could be added to the check off list as information evolves.

Once the herbs are identified, a number of resources, in addition to this present report, are available to check for effects of the herb on dental treatment and the potential for herbal-drug interactions. The following are some suggested printed sources and WEB sites.

Bisphosphonates, Hypercalcemia of Malignancy and Osteonecrosis of the Jaw.

R.L.Wynn

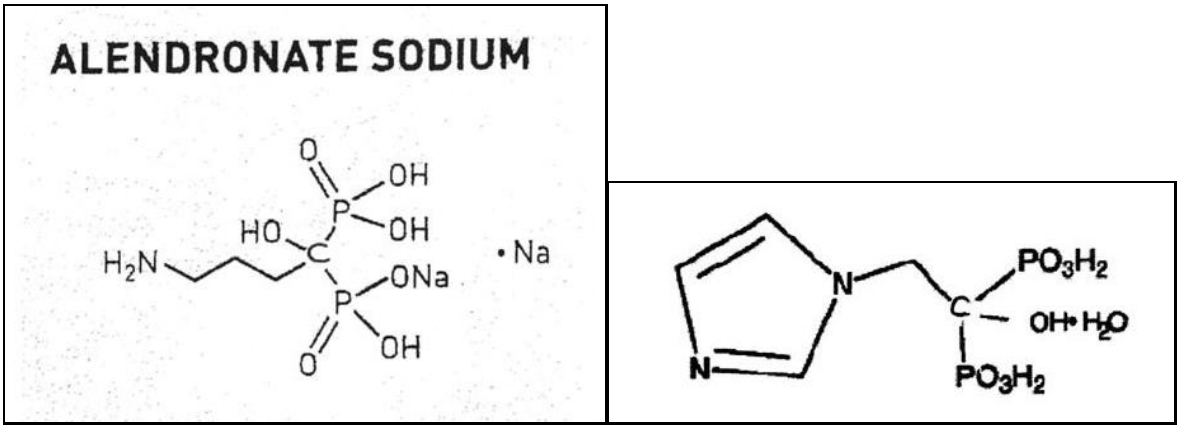
What are the Bisphosphonates?

According to a report in Chemical and Engineering News, (2) a group of chemicals called pyrophosphates were identified by Herbert Fleisch at the University of Berne, Switzerland in the 1960's as substances that were present in blood and urine that prevented the formation of calcium phosphate crystals. (2) He suggested that pyrophosphates were an important regulator of bone mineralization and demineralization and that they could be used to prevent abnormal calcification and excessive bone destruction. (3) Because pyrophosphates were rapidly broken down enzymatically in the body, the bisphosphonate analogs were developed which were not broken down as easily. (2,3) The oxygen within the P-O-P pyrophosphate structure was replaced with a carbon to produce the metabolically stable P-C-P structure, the core unit of the bisphosphonate drug molecule. The first publications on the actions of bisphosphonates to block calcification and bone destruction occurred in 1969 by Fleisch and co-workers (3,4).

Figure 1 shows the structure of alendronate (Fosamax), the first bisphosphonate drug developed by Merck and approved by the FDA in 1996 for the treatment of osteoporosis. (2) The figure shows the P-C-P unit and the two (bis) phosphonate (- PO_3H_2) groups. Figure 2 shows the structure of zoledronic acid (Zometa). This agent differs from alendronate in the presence of the 5-membered imidazole ring (a heteroaromatic moiety) which replaces the amino (H_2N-) group. Note the presence of the P-C-P group in zoledronic acid.

Figure 1

Figure 2



Other bisphosphonates currently approved as drugs by the FDA include etidronate (Didronel), ibandronate (Boniva), pamidronate (Aredia), risedronate (Actonel) and tiludronate (Skelid). These have structures similar to either alendronate or zoledronic acid. The most potent bisphosphonates are those containing a heteroaromatic group, with zoledronic acid being the most potent of the class. (5) It is important to note that the bisphosphonates are not the same chemically as phosphorous, although they contain the phosphorous (P) atom within the contextual arrangement of the phosphonate group.

Uses of the Bisphosphonates

Bisphosphonates are indicated for either the treatment and prevention of osteoporosis (i.e. alendronate) or for the treatment of hypercalcemia of malignancy and bone metastases of solid tumors (i.e. zoledronic acid). They are effective in osteoporosis because of their ability to induce osteoclasts to self-destruct. (6)

One review of osteoporosis describes it, in part, as a result of the enhanced ability of osteoclasts to carve out bone cavities or resorption pits causing an excess loss of calcium, along with the failure of the osteoblasts to build new bone. (6) The destruction of osteoclastic activity by the bisphosphonates results in a decreased rate of bone resorption and an indirect increase in bone mineral density. (6)

The actions of the drugs in the treatment of hypercalcemia of malignancy is much more complex. According to a recent review by Dr. A.F. Stewart published in the New England Journal of Medicine, (7) there are at least two major types of hypercalcemia associated with cancer. One is known as humoral hypercalemia of malignancy (HHM) which is caused by the systemic secretion by the malignant tumor of a protein known as parathyroid hormone related protein or PTHrP. (7) This protein causes increased bone resorption and enhances the renal retention of calcium. (8) Essentially any tumor may cause this syndrome and those that commonly cause it are squamous cell cancer of head and neck, esophagus, cervix or lung, renal cancer, ovarian cancer, endometrial cancer, certain lymphomas and breast cancer. (8) Bone metastases are minimal or absent in HHM. The other type of hypercalcemia associated with cancer is known as local osteolytic hypercalcemia. (7) In this condition, bone metastases are common and extensive and the hypercalcemia results from the marked increase in osteoclastic bone resorption in areas around the malignant cells within the bone marrow space. Typical cancers associated with metastases into bone resulting in local osteolytic hypercalcemia are breast cancer, multiple myeloma and lymphoma. (7,8)

Regardless of the cause, hypercalcemia of malignancy is associated with a very poor prognosis producing symptoms of dehydration, confusion, renal dysfunction eventually leading to coma and renal failure. (7) Hypercalcemia is reported to occur in 20 to 30 percent of patients with cancer at some time during the course of their disease and its detection signifies a dismal prognosis with approximately 50 percent of such patients dying within 30 days. (9)

Use of the intravenous bisphosphonates in hypercalcemia of malignancy

The intravenous bisphosphonates pamidronate and zoledronic acid are effective in hypercalcemia of malignancy because they block osteoclastic bone resorption (7). They are considered the first line drugs used to treat this condition. (7) The oral bisphosphonates such as alendronate (Fosamax) and risedronate (Actonel) are not useful in the treatment of hypercalcemia of malignancy because they are very poorly absorbed from the gastrointestinal tract and lack the potency of the intravenous agents.

Intravenous bisphosphonate therapy is usually initiated as soon as hypercalcemia of malignancy is observed . These drugs are so effective that serum calcium levels usually begin to fall within 12 hours after therapy with the lowest point in serum calcium occurring within 4 to 7 days after dosing. Approximately 60 – 90% of patients will result in a return to normal serum calcium levels within 4 to 7 days after dosing with the response lasting from one to three weeks. (7) A typical intravenous dose of zoledronic acid is 4 mg over a 15 min period. Intravenous pamidronate is 60-90 mg over a 2 hour period. Response after a single dose with either agent will last from 1 to 3 weeks. (10,11) Zoledronic acid seems to have a slightly better efficacy than pamidronate in that there is a slightly greater mean reduction in serum calcium levels. (7) Pamidronate is less expensive and zoledronic acid has a much shorter time of administration of dose. Oftentimes in cases of malignancies, bisphosphonates are used in conjunction with hydration with intravenous saline, and diuresis with furosemide after rehydration is achieved.

Intravenous bisphosphonates are most often used in the treatment of breast cancer metastatic to bone in order to prevent skeletal complications, (12) to prevent skeletal complications in advanced prostate cancer,(13,14) and to provide an antitumor effect in the treatment of multiple myeloma. (15,16)

How do the bisphosphonates block osteoclastic bone resorption?

Currently it is thought that the cellular mechanism of the bisphosphonates involves inhibition of an enzyme which regulates signaling proteins within the osteoclast. This enzyme, known as farnesyl diphosphate synthase, is a key player in maintaining signaling protein function to allow for osteoclastic bone resorptive activity. Its inhibition by the bisphosphonates results in the suppression of osteoclastic bone resorption and suppression of calcium release from bone. (17,18)

In addition to its inhibitory effect on osteoclastic activity, zoledronic acid may exert its effect in multiple myeloma by interfering with bone marrow activities. Muiltiple myeloma plasma cells locate in bone marrow by binding to stromal cells and to molecules in the extracellular matrix. Activation of signaling pathways within the stromal cells promotes myeloma cell proliferation and survival. Bisphosphonates inhibit the survival of stromal cells and suppress the contact between multiple myeloma plasma cells and stromal cells. (19)

In vitro studies have demonstrated the antitumor potential of zoledronic acid on myeloma cell lines. (20) Zoledronic acid interfered with myeloma bone marrow stromal cells by reducing proliferation, increasing apoptosis and modifying the pattern of expression of adhesion molecules. (21)

Percent incidence injcancer patients

Two recent reports in the medical literature have attempted to assess the percent of cancer patients developing ONJ after bisphosphonate treatment. Maerevoet et al (40) reported that among 194 patients treated with zoledronic acid every 3 to 4 weeks, 9 developed ONJ. Before receiving zoledronic acid, six had received pamidronate 90 mg every 3 to 4 weeks. The median duration of treatment with pamidronate was 39 months and for zoledronic acid 18 months. The incidence of ONJ in these patients was calculated to be 4.6%. Durie et al (41) described the results of a survey by the International Myeloma Foundation in 2004 to assess the risk factors of ONJ. Out of 1203 respondents, 904 had myeloma and 299 breast cancer. Of the myeloma patients, 62 developed ONJ and 54 had suspicious findings. Of the breast cancer patients, 13 had ONJ and 23 had suspicious findings. The total number of cases of either ONJ or suspicious findings was 152. ONJ developed in 10% of 211 patients receiving zoledronic acid compared to 4% of 413 receving pamidronate. The mean time to onset of ONJ among patients taking zoledronic acid was 18 months; the mean time to onset after pamidronate was 6 years.

July 2007 E-news letter

Lexi-Comp E-newsletter September 25, 2008

R.L.Wynn

Prevalence rate of necrotic jaw bone in patients taking Fosamax-type drugs continues to be low. Plus, more on dental implant success in Fosamax patients.

Two reports are described in this month's newsletter relative to users of oral bisphosphonates. First, a low prevalence of osteonecrosis of the jaw bone (ONJ) was reported in a published comprehensive literature review on the prevalence, risk factors and clinical manifestations of osteonecrosis of the jaw in patients receiving oral bisphosphonates for the treatment of osteoporosis. From a thorough search of the literature, the study authors identified only twenty-six cases of ONJ. The most commonly affected site was the mandible (16 patients), followed by the maxilla (6 patients). Among the 23 patients whose age was reported, 18 (78%) were $\geq$ 60 years. Among the 23 patients whose sex was reported, only 3 (13%) were men. Of 15 patients with a history of invasive dental treatment,12 (80%) had undergone dental surgery or experienced dental trauma at the site of ONJ. No clear relationship was observed between the duration of bisphosphonate therapy and the development of ONJ. Compared with the estimated millions of patients taking oral bisphosphonates, this study found the prevalence of ONJ to be very low. The second report is described at the end of this newsletter about the success of dental implants in bisphosphonate users. The

report showed that patients who take oral bisphosphonates are no more at risk of implant or bone graft failure than other patients.

The report on low prevalence rate of ONJ in Fosamax users

It has been very difficult to obtain and assess accurate numbers describing the rate of prevalence of ONJ in oral bisphosphonates users. This author's experience has heard a variety of anectdotal descriptions by dentists and hygienists of patients expressing/and or exhibiting jaw bone problems and taking bisphosphonates but none of these descriptions are usually published and have inconsistent interpretations as to any cause and effect. Thus until adequate observation studies are conducted and reported, the very best we can do is to accurately search the literature for reports on the presence of ON J in oral bisphosphonate users and make comparisons to the oral bisphosphonate general population in the hopes of assigning some acceptable quantitative measure to its incidence.

Thus, the study described in this month's newsletter is an important contribution to this process. The study authors were four physicians and one PhD who had associations with the University of Pennsylvania, University of Colorado Health Sciences Center, Roche Laboratories and Cerner Life Sciences in California. The lead study author was Michael Pazianas M.D. and the entire report was published in Clinical Therapeutics/Volume 29, Number 8, 2007 pp 1548 1558. It is entitled "A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates: prevalence, risk factors, and clinical characteristics."

Method

In the study, the MEDLINE database (United States) and the EMBASE database (Europe) were searched for medical literature articles reporting ONJ in oral bisphosphonates users. In addition, the Cochrane Database of Systematic reviews and the Cochrane Central Register of Controlled Trials were searched to capture all key reviews. Also, the Web sites of the American Society of Bone and Mineral Research, the National Osteoporosis Foundation International Symposium, and the International Osteoporosis Foundation World Congress were searched for conference published abstracts. The search strategy consisted of combining medical subject headings and/or text words including bisphosphonates, alendronate, risedronate, ibandronate, etidronate, clodronate, zoledronic acid, pamidronate and ONJ. The study used a variety of inclusion and exclusion critera for article acceptance for review. And for purposes of the review, a case of ONJ was defined as the presence of nonhealing exposed necrotic bone in the maxillofacial region in patients receiving bisphosphonates for treatment of osteoporosis.

From those articles accepted in the study, the following data were extracted: population characteristics (age, sex, comorbitities, concomitant medications, history of dental surgery or trauma, number of patients with ONJ), bisphosphonate treatment characteristics (specific bisphosphonate, dose, route of administration, treatment duration), clinical manifestations (site, signs, symptoms, time to onset of ONJ), and the treatment protocol to manage the ONJ. The study did not include the use of intravenous bisphosphonates in cancer patients.

The investigators identified 195 reports for full review. Of these, 11 met all the inclusion criteria, which consisted essentially of patients receiving bisphosphonates for the treatment of osteoporosis only; reported data included the baseline characteristics of the study population, the characteristics of bisphosphonates treatment, the clinical features of ONJ, the treatment protocol used to manage ONJ, or the prevalence of ONJ in patients with osteoporosis treated with bisphosphonates; and the publication involved a case report, case series, or observational study.

Results

Twenty-six cases of ONJ were reported in patients receiving bisphosphonates for the treatment of osteoporosis in the 11 reports. Seventeen cases were in the United States, 4 cases in Australia, 3 cases in Italy and 1 case in Singapore. The remaining case location was not specified. No studies ever specifically investigated the prevalence of ONJ in patients receiving bisphosphonates for treatment of osteoporosis.

Age/sex information

The mean age of patients with ONJ was 68 years (range 39-83 years). ONJ was more common in female than male (8:1 ratio).

Medical history

Two patients were taking corticosteroids. Fifteen patients had a history of dental surgery. ONJ developed in 11 patients after tooth extraction and in 1 patient after periodontal surgery.

Specific drug and dose involved

Twenty-three patients received alendronate (Fosamax); one patient each received risedronate (Actonel) or pamidronate (Aredia); one patient received a combination of alendronate (Fosamax) and zoledronic acid (Zometa). No cases of ONJ were reported in patients receiving ibandronate (Boniva) or etidronate (Didronel).

Ten cases on ONJ provided information on the drug doses. Alendronate (Fosamax) was orally administered at a daily dose of 10 mg in 4 patients, at a weekly dose of 40 mg in 3 patients and at a weekly dose of 70 mg in 3 patients. No cases on ONJ were observed in patients treated with a monthly bisphosphonates regimen.

Duration of drug use

Ten patients received alendronate (Fosamax) for a mean duration of 40 months (range 12-72 months). The break down of duration data was 12 months for 1 patient, 24 months for 1 patient, 28 months for 1 patient, 36 months for 3 patients, 43 months for 1 patient, 55 months for 1 patient, 60 months for 1 patient and 72 months for 1 patient. No clear duration and onset of effect could be assessed from the reports.

Clinical manifestations of ONJ

Ten reports described the site of ONJ in 22 patients receiving bisphosphonates for the treatment of osteoporosis. Sixteen cases described the mandible site, and 6 decribed the maxilla site. The most common presenting signs and symptoms of ONJ were pain,

(n=9), fistula/sinus (n=4), nonhealing open wound (n=4) , discharge (n=1) and bleeding (n=1).

Management

Treatment was reported in 10 publications for 23 patients. Most common treatment modality was sequestrectomy (n=10), antibiotics (n=9), surgical/local debridement (n=4), mouth rinses (n=6), periodontal flap surgery (n=6) and curettage (n=1).

Study interpretation

This present report continues the observation that age, dental extractions and use of corticosteroids are probable factors that increase the risk of developing ONJ in patients taking bisphosphonates for osteoporosis. These three factors have also been observed in other studies of ONJ. This current report noted that the majority of patients with ONJ were women over 60 years of age. Only 1 patient was less

than 40 years of age. Also, 12 of the 15 patients for whom a dental history was reported had undergone a dental extraction or dental surgery before development of ONJ. And finally, among the patients in this review who were taking concomitant medications, 20% were taking a corticosteroid when ONJ was observed.

This study was important in that it adds more information about the prevalence of ONJ occurring in patients taking the Fosamax-type drugs to treat osteoporosis. The authors state in their conclusion that "considering that millions of patients have been prescribed bisphosphonates for the treatment of osteoporosis, the relative prevalence of ONJ in these patients is low".

The report on the success of dental implants in bisphosphonate users.

The dental implant study, published in the Journal of Oral and Maxillofacial Surgery Vol 66: 1022-1024, 2008 (Bell BB, Bell RE Oral bisphosphonates and dental implants: a retrospective study) was an analysis to determine whether patients who took oral bisphosphonates were at a greater risk of implant and bone graft failure than other patients. The study showed that patients who take oral bisphosphonates are no more at risk of implant or bone graft failure than other patients.

The medical records for all patients who had been seen since 1990 were reviewed, and those patients who took Fosamax-type drugs prior to surgery were used for the study population. One hundred implants were placed in 42 patients. Thirty of those also received bone grafts totaling 68 grafts. Patients had been taking bisphosphonates from 6 months to 11 years prior to implant surgery. Thirty-four patients were taking alendronate (Fosamax) at the time of surgery, 6 were taking risedronate (Actonel) and 2 were taking ibandronate (Boniva). All 42 patients were called in for a follow-up appointment to examine their jaws. The average length of follow-up was 3 years and 1 month with a range of 4 months to 7 years and 5 months.

Study results

There were 5 implant failures out of 100 implants placed, giving a 95% success rate. The study authors commented that this rate was comparable to the success rate of 96.5% for 734 implants placed in patients not taking bisphosphonates by one of the authors in 2006. No patients showed signs of ONJ. This was a limited study that showed that in 42 patients, implant placement and oral bone grafting appeared to be safe and successful in patients taking bisphosphonates for osteoporosis.

This study adds to some previous reports of implant success in bisphosphonates patients. In a previous newsletter (see archive entitled Fosamax-type drugs do not cause osteonecrosis of the jaw in patients having dental implants) a report was described that showed that implant surgery on patients receiving Fosamax-type drugs did not result in bisphosphonate-associated osteonecrosis of the jaw (ONJ). That study, out of the Dentistry/Oral Surgery group at Montefiore Medical Center, Albert Einstein College of Medicine, reported that of 115 patients taking oral bisphosphonates none showed evidence or had symptoms of osteonecrosis after implant placement. This report had findings similar to a previous report by Dr. M Jeffcoat who showed success in implant placement and no signs of necrosis in patients taking oral bisphosphonates. The Jeffcoat report was published in 2006 in the International Journal of Oral and Maxillofacial Implants Vol 21: 349.

July 2007 E-news letter

R.L.Wynn

I'm 60 years old and taking Fosamax for osteoporosis. I'm concerned that dental treatment could cause jawbone problems. Are there other drugs I can take?

Of course your answer is "check with your doctor". Since this question is often asked by the dental patient, the following is the low-down of what is available in addition to Fosamax for patients to take for osteoporosis. These include other oral bisphosphonates within the Fosamax family, supplements containing calcium and vitamin D, estrogen hormonal therapy, and three other drugs known as raloxifene (Evista), calcitonin and teriparatide (Forteo). Except for the calcium and vitamin D supplements, each of the other alternatives present their own set of problems as described below.

Other oral bisphosphonates - risedronate (Actonel) and ibandronate (Boniva).

In addition to alendronate (Fosamax), cases of osteonecrosis of the jaw (ONJ), albeit rare, have been reported in patients taking either risedronate (Actonel) or ibandronate (Boniva). Among the class of oral bisphosphonates, more cases have been associated with Fosamax than with Actonel or Boniva. Also, there is no evidence to suggest that the risk of ONJ is less when taking monthly doses of Boniva. Zoledronic acid under the band name of Reclast has recently been approved as a once annual 15 minute intravenous infusion of a dose of 5 mg to prevent osteoporosis. This dosing was associated with a significant improvement in bone mineral density and bone metabolism markers. It is unknown whether this dosing schedule places the patient at risk for ONJ.; however, data do show a higher risk of serious atrial fibrillation in patients receiving ReClast compared to patients receiving placebo (Black DM, et al. NEJM 356:1809-1822)

Presently, the current estimates of the frequency of occurrence of ONJ in oral bisphosphonate users are the following. The American Dental Association has stated (and described in a previous newsletter) that the incidence is estimated to be 0.7 cases in 100,000 person years of exposure to oral bisphosphonates. The Medical Consultants of Consumer Reports On-Health Bulletin reported an incidence of 1 case for every 20,000 users of oral bisphosphonates. A recent report from Australia estimated that the frequency of ONJ in osteoporotic patients mainly on weekly oral alendronate (Fosamax) ranged from a minimum of 1 in 8,470 to a maximum of 1 in 2,260 (0.01% to 0.04%) patients. In all cases, the chances of acquiring ONJ increase with dental extractions, but not with dental cleanings or routine dental care.

Calcium and Vitamin D Supplements without bisphosphonates

Calcium, consumed in optimal amounts, will continue to build new bone tissues as you age, according to the National Institutes of Health (NIH). It has been advised to get a daily intake of 1,000 – 1,500 mgs of calcium from diet or supplements. Good dietary sources of calcium are low-fat diary products such as milk, yogurt and cheese, leafy green vegetables such as broccoli and spinach, sardines and salmon with bones, and other foods fortified with calcium. Vitamin D is necessary each day to allow for absorption of calcium from the diet. It is now suggested that 400-800 IUs of vitamin D daily seems to be an optimal dose for most people. Also include some physical activity several times a week. Weight-bearing exercises are suggested and include walking, jogging, stair climbing, weight training, tennis and dancing.

Estrogen hormonal therapy (Premarin or Prempro)

Estrogen replacement therapy with or without progestin has been the mainstay over the years for the prevention and treatment of postmenopausal osteoporosis. Estrogen replacement therapy is not associated with ONJ. However, because of risks for blood clots and cardiovascular disease, estrogen replacement therapy is no longer recommended as the first line drug for osteoporosis prevention.

Premarin (conjugated equine estrogen), has continued to decline is use ever since a recommendation by the Food and Drug Administration in 2003 to limit the use of estrogen and estrogen with progestin therapies for post menopausal women. Up to the early 90s, studies had suggested that long-term estrogen users had lower than average heart attack rates. The HERS study report in 1998 (Hulley S, et al JAMA 1998;280:605-13) showed that women who took estrogen for four years saw cholesterol levels go down

but they suffered increases in blood clots and no reduction of heart disease. A follow-up study (Grodstein F, et al Ann Intern Med 2000; 133:933-41) reported that estrogen at daily doses of 0.625 mg or greater and in combination with progestin may increase the risk for stroke. It was suggested that postmenopausal hormone replacement therapy may be beneficial for those who do not have coronary artery disease but not for those who already have it. In view of these reports, many physicians are endorsing estrogen as a short term remedy for hot flashes and other acute symptoms of menopause, but are questioning continued treatment for more than four or five years.

Estrogen therapy may increase the risk of dementia. Shumaker et al (JAMA 2004; 291:3005-7) evaluated the effects of estrogen on the incidence of mild cognitive impairment and probable dementia in older women. They showed that estrogen therapy resulted in an increased risk for dementia and mild cognitive impairment and concluded that the use of hormone therapy to prevent dementia or cognitive decline in women 65 years of age or older is not recommended. Espeland et al (JAMA 2004; 291:2959-68) showed that estrogen therapy had an adverse effect on cognition in women 65 years of age or older, which was greater among women with lower cognitive function at the initiation of treatment.

A sharp decrease in female breast cancer incidence rates from 2002 to 2003 was reported in women 50 tom 69 years old (Jemal A, et al Breast Cancer Res 2007; 9:R28). It was suggested that this decrease may reflect the early benefit of the reduced use of hormone replacement therapy.

Raloxifene (Evista), Calcitonin, Teriparatide (Forteo)

None of these drugs are associated with ONJ. Raloxifene (Evista) has been marketed for years as a first line drug for osteoporosis prevention and treatment. It is a selective estrogen receptor modulator or SERM which acts on estrogen recptors in bone but not in breast tissue. Theoretically, Evista prevents bone loss with no risk of causing breast cancer. However, many women cannot tolerate the side effects of hot flashes and night sweats, and there are reports of increased risk for blood clots.

Calcitonin is a peptide sequence similar to human calcitonin. This peptide directly inhibits osteoclastic bone resorption thus inhibiting the loss of calcium from bone. It is not as effective or potent as the bisphosphonates in the prevention of loss of calcium from bone. This agent cannot be taken orally but is administered either as injection (intramuscular or subcutaneous) or as a nasal spray. The FDA has indicated calcitonin to be used for the treatment of osteoporosis in women > 5 years postmenopause. Problems that have occurred with its use include a runny, irritated nose from the nasal spray, flushing in the face and hands after spray or injection, and hypertension, nausea and rash.

Teriparatide (Forteo) is approved for the treatment of osteoporosis in postmenopausal women at high risk of fracture and the treatment of primary or hypogonadal osteoporosis in men at high risk of fracture

Teriparatide (Forteo) is a recombinant formulation of endogenous parathyroid hormone (PTH), containing a 34-amino-acid sequence which is identical to the N-terminal portion of this hormone. The pharmacologic activity of teriparatide is similar to the physiologic activity of PTH, stimulating osteoblast function, increasing gastrointestinal calcium absorption, and increasing renal tubular reabsorption of calcium. Treatment with teriparatide increases bone mineral density, bone mass, and strength. In postmenopausal women, it has been shown to decrease osteoporosis-related fractures.

Teriparatide (Forteo) is administered by subcutaneous injection into the thigh or abdominal wall. Initial administration usually occurs under circumstances in which the patient may sit or lie down, in the event of orthostasis. Suggested frequency of dosing is once daily. This drug is very expensive.

Fosamax and Osteonecrosis of the Jaw – Some New and Frequently Asked Questions

The alendronate (Fosamax) drugs, known as the oral bisphosphonates, continue to be the cornerstones of treatment for prevention of osteoporosis. Unfortunately they are associated with osteonecrosis of the jaw bone (ONJ) particularly if dental surgery is performed in long term Fosamax users. A number of frequently asked questions have arisen relative to the incidence, risk factors, the mechanism of ONJ, symptoms of ONJ, and whether discontinuation of the drugs prior to dental surgery reduces risks of ONJ. All these questions and more are answered below.

1. According to the experts, what is the incidence of osteonecrosis of the jaw in Fosamax users?

Presently, the current estimates of the frequency of occurrence of ONJ in oral bisphosphonate users are the following. The American Dental Association has stated (and described in a previous newsletter) that the incidence is estimated to be 0.7 cases in 100,000 person years of exposure to oral bisphosphonates. The Medical Consultants of Consumer Reports On-Health Bulletin reported an incidence of 1 case for every 20,000 users of oral bisphosphonates (0.005%). A recent report from Australia estimated that the frequency of ONJ in osteoporotic patients mainly on weekly oral alendronate (Fosamax) ranged from a minimum of 1 in 8,470 to a maximum of 1 in 2,260 (0.01% to 0.04%) patients. If extractions were performed, the frequency increased to 0.09% -0.34%.

2. What numbers can I use to tell the dental patient their risk of developing ONJ with Fosamax?

The ADA suggest that the patient be informed that there is a very low risk of developing ONJ. The true risk posed by oral bisphosphonates remains uncertain, but researchers agree that it appears to be very small. All the data seem to point to a risk of approximately 0.1% of total users and that the risk increases with dental extractions to approximately 0.5%. Also, be aware that the risks of developing ONJ can be minimized but never totally eliminated. Good oral hygiene along with regular dental care is the best way to lower the risk of developing ONJ.

3. Is the risk of acquiring osteonecrosis of the jaw bone diminished with the use of other oral bisphosphonates compared to Fosamax?

In addition to alendronate (Fosamax), cases of osteonecrosis of the jaw (ONJ), albeit rare, have been reported in patients taking either risedronate (Actonel) or ibandronate (Boniva). Among the class of oral bisphosphonates, more cases have been associated with Fosamax than with Actonel or Boniva. Also, there is no evidence to suggest that the risk of ONJ is less when taking monthly doses of Boniva. Zoledronic acid under the band name of Reclast has recently been approved as a once annual 15 minute intravenous infusion of a dose of 5 mg to prevent osteoporosis. This dosing was associated with a significant improvement in bone mineral density and bone metabolism markers. It is unknown whether this dosing schedule places the patient at risk for ONJ; however, data do show a higher risk of serious atrial fibrillation in patients receiving ReClast compared to patients receiving placebo (Black DM, et al. NEJM 356:1809-1822)

4. Will Fosamax or the other oral bisphosphonates continue to be the standard treatment for osteoporosis?

Yes. The oral bisphosphonates continue to be most effective class of drugs in reducing the risk of osteoporotic fractures and are the first line therapy in the treatment of osteoporosis. Fosamax has been shown to prevent bone loss at the spine and hip in postmenopausal women, and to reduce fractures by approximately 50%. Risedronate (Actonel) produced a 30% reduction in hip fractures. Fosamax continues to be in the top 50 of most widely prescribed drugs in this country. By 2006, over 190 million prescriptions were dispensed worldwide.

5. Do we know how the jaw bone becomes necrotic from Fosamax?

This question has not been answered and information is only speculative at this time. Osteoporosis can occur due to age related changes in the number of osteoclasts and bone resorption sites. This overwhelms the production of new bone by osteoblasts and a decrease in bone mass occurs. By inhibiting osteoclastic activity, the oral bisphosphonates seemingly arrest the osteoporotic syndrome. In the process however, the maxilla and mandible, upon continued exposure to the bisphosphonates, are unable to repair themselves from injury from mechanical forces or invasive surgery such as tooth extraction. This coupled with a reduction in bone blood supply by the bisphosphonates (antiangiogenic effect) leads to jaw bone necrosis.

6. What are the factors that increase the risk of jaw bone necrosis in Fosamax users?

Patients wih a history of periodontal disease and dental abcessess are at increased risk. Also, dento-alveolar trauma will increase the risk. The use of chronic steroids such as prednisone has been identified as a risk factor. Other factros are the duration of exposure and age, with longer treatment regimens and age over 65 years associated with a greater risk of developing the disease. Patients identified with jaw bone necrosis typically were exposed to oral bisphosphaonets for 3 years or longer.

7. What are the symptoms that a Fosamax patient would experience which could indicate necrotic jaw bone?

Tooth mobility, mucosal swelling, and/or ulceration. Clinical symptoms would include a non-healing extraction site, exposed bone surrounded by inflamed soft tissue, and purulent discharge at site of exposed bone. Exposed bone is usually more prevalent in areas such as tori and the mylohyoid ridge.

8. What kind of dental procedures can be performed in Fosmax users with no increase in risk for ONJ

According to American Dental Association , all routine procedures can be carried out. Routine dental treatment should not be modified on the basis of oral bisphosphonates on board the patient. However, presence of risk factors such as steroid use, over 65 years of age or prolonged exposure to the oral bisphosphonates may require consultation with an expert in metabolic bone disease prior to routine dental treatment.

9. Is dento-alveolar surgery contraindicated in Fosmax users?

No. According to Ruggiero and Drew (J Dental Research 2007; 86(11):1013) in asymptomatic patients receiving oral bisphosphonate therapy, dento-alveolar surgery is not contraindicated.

10. Is a so-called "drug holiday" an effective way to reduce the risks of ONJ in Fosmax users prior to dental-alveolar surgery?

A "drug holiday" is a discontinuance of bisphosphonate for a length of time thought to achieve a reduction of risk of ONJ. It is suggested that one consider interrupting bisphosphonate treatment for 3-4 weeks prior to surgery and re-starting after bone healing. Based on AAOMS guidelines (American Society of Oral and Maxillofacial Surgeons) patients who have taken an oral bisphosphonate for more than 3 years, discontinuation of the oral bisphosphonate for 3 months prior to oral surgery may reduce the risk. The bisphosphonate can be started once osseous healing has occurred.

For individuals who have taken a bisphosphonate for less than 3 years and have no other risk factors for ONJ, no alteration or delay in the planned surgery is necessary. (Ruggiero and Drew).

11. In patients about to begin oral bisphosphonate therapy, should the bisphosphonate be delayed until dental health is optimized?

No. It does not appear necessary for patients to initiate prophylactic dental treatment prior to initiating oral bisphosphonate therapy for osteoporosis. It would be prudent however to encourage these patients to maintain an optimal level of dental health .

12. Is diagnostic imaging useful in assessing those bisphosphonate individuals at risk for ONJ?

Imaging moldalities have proved helpful in determining the extent of existing necrotic process, but have not been able to demonstrate any efficacy in assessing patients at risk for ONJ. According to the experts, panoramic and periapical radiographs probably will not reveal significant changes in early stages of osteonecrosis and they are poor screening tools for prediction. Computerized tomography (CT) scan also has not proved helpful with early identification of osteonecrosis in asymptomatic patients

Anti-oxidant Outline

R.L.Wynn

Free Radicals

Vitamin C

Vitamin E

Beta-carotenes

Selenium

Four Habits

Coenzyme Q-10

Alpha-lipoic acid

Chocolate

Quercetins

Pomegranate

Yerba mate

Acai' berry

www.ars.usda.gov/nutrientdata/ORAC