

The Interrelationship between Periodontitis and Systemic Diseases

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Cardiovascular diseases such as atherosclerosis and myocardial infarction occur as a result of a complex set of genetic and environmental factors. Analysis of all the common risk factors for stroke and heart attack, including age, smoking, high levels of serum lipids, diabetes and socioeconomic status can only account for one-half to two-thirds of the variation in the incidence of cardiovascular disease.

Numerous studies show that oral infection, especially periodontitis, may affect the course and pathogenesis of a number of systemic diseases, such as cardiovascular disease, bacterial pneumonia, diabetes mellitus and low birth weight. Evidence in support of an association between periodontal and cardiac conditions has been demonstrated and several theories have been proposed to explain the link.

In the early 20th century, Sir William Osler fully appreciated what was killing his patients with endocarditis. The theory of focal infection was firmly believed in and promulgated during that period. A focal infection is a localized infection that can disseminate microorganisms or toxic products to contiguous or distant tissues. The teeth and jaws, tonsils, sinuses, fingers

and toes, bronchi and the gastrointestinal tract were the obvious sources blamed for such diseases as arthritis, nephritis and endocarditis. As a result of this theory, many physicians of the era often recommended preventive full mouth extractions whenever a 'focal infection' became suspected. These ideas were anecdotal and in time the theory fell on the wayside because these drastic treatments never quite reversed the course of the disease. Furthermore, many patients with the same diseases had no evident focus of infection and foci of infection are as common in apparently healthy persons as those with disease. With the recent progress in classification and identification of oral microorganisms and the realization that certain microorganisms are normally found only in the oral cavity this idea of bacterial

dissemination via the blood stream through discontinuities of the oral tissues, has resurged.

The teeth are the only non-shedding surfaces in the body and bacterial levels can reach more than 10^{11} microorganisms per mg of dental plaque. Periodontal diseases are bacterial infections that destroy the attachment fibers and supporting bone (periodontium) that hold teeth. The consequence of such events can be measured as the 'gums' separate from the teeth, forming pockets. These are shallow at first but can eventually deepen, at a variable rate, depending on bacterial and host factors that set the stage. Increasing pocket depths are a sign of the disease progressing as more periodontal tissues

TREATING YOUR POST-MENOPAUSAL OSTEOPOROSIS

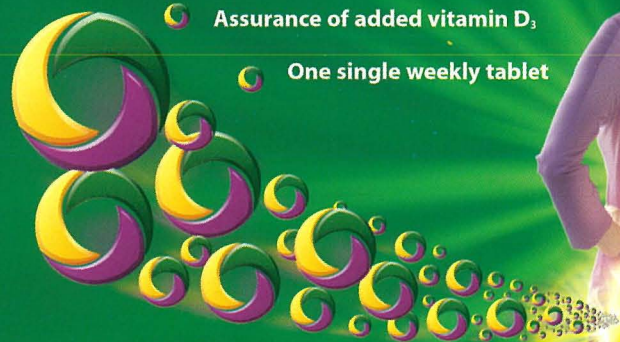
FOSAVANCE™ Tablets
 (alendronate sodium/colecalciferol)

are a logical progression

● Reduces the risk of hip and vertebral fractures¹

● Assurance of added vitamin D₃

● One single weekly tablet



T O O T H

Periodontal and Cardiovascular Disease

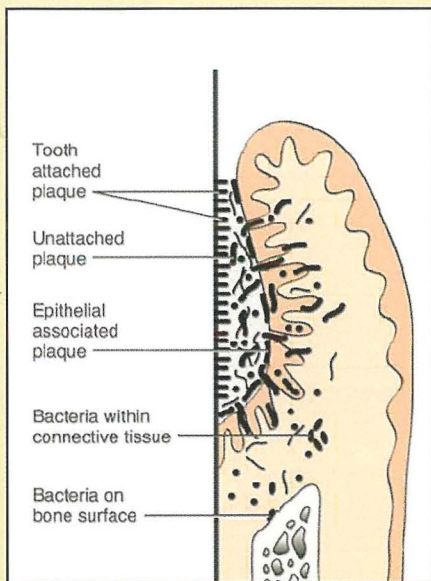


Figure 1: Plaque-bacteria associated with the crown / root surface and periodontal tissues

which approximately 500 species have been encountered. These infections are predominantly anaerobic, with gram-negative rods being the most common isolates. Their endless presence burden and challenge the host continuously. In the depths of periodontal pockets, the anatomic closeness of these microfloras and the bloodstream facilitates bacteremia and systemic spread of bacterial products, components and immunocomplexes.

Microorganisms may gain entrance to the blood and circulate throughout the body but are usually eliminated by the reticuloendothelial system within minutes (transient bacteremia) and as a rule lead to no other clinical symptoms. However, if the disseminated microorganisms find favorable conditions, they may settle at a given site and, after a certain time lag, start to multiply (infective endocarditis, brain abscess, cavernous sinus thrombosis, sinusitis, lung abscess/infection, prosthetic joint infection).

Some gram-positive and gram-negative plaque bacteria have the ability to produce diffusible proteins, or exotoxins which are lethal poisons which cause local injury. Conversely, endotoxins are part

of the outer bacterial membranes released after cell death. When introduced into the host, these lipopolysaccharides give rise to a large number of pathological manifestations not just locally but even at a distance from the site (cerebral infarction, acute myocardial infarction, abnormal pregnancy outcome, persistent pyrexia, idiopathic trigeminal neuralgia, toxic shock syndrome, systemic granulocytic cell defects, chronic meningitis).

Inflammation in tissues distant from the infection may also develop through the effects of soluble antigen entering the bloodstream and reacting with circulating specific antibody. These immunocomplexes may give rise to a variety of acute and chronic inflammatory reactions at the sites of deposition (Behçet's syndrome, chronic urticaria, uveitis, inflammatory bowel disease, Crohn's disease).

Most researchers believe that the increased risk to the progression of coronary heart disease is caused by an exaggerated inflammatory response to periodontal pathogens such as *Porphyromonas gingivalis* in a susceptible host.

are destroyed and the teeth eventually become loose.

Human periodontal infections are associated with complex microfloras in

FOSAVANCE™ Tablets (70 mg Alendronate Acid as Alendronate Sodium Trihydrate and 70 micrograms [2,800 IU] Calcitriol (vitamin D₃))

ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics before prescribing.

PRESENTATION

Capulet-shaped, white to off-white tablets marked with an outline of a bone image on one side, and "110" on the other, containing 70 mg alendronate acid as alendronate sodium trihydrate and 70 micrograms (2,800 IU) calcitriol (vitamin D₃).

USES

Treatment of post-menopausal osteoporosis in patients at risk of vitamin D insufficiency. Fosavance™ reduces the risk of vertebral and hip fractures.

DOSEAGE AND ADMINISTRATION

The recommended dosage is one (70 mg/70 microgram) tablet **once weekly**.

Patients must be advised to follow the instructions below.

For optimum absorption of alendronate: Take at least 30 minutes before the first food, beverage, or medicinal product (including antacids, calcium supplements, and vitamins) of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate. The following instructions should be followed **exactly** in order to minimise the risk of oesophageal irritation and related reactions:

- Swallow Fosavance™ only upon arising for the day with a full glass of water (not less than 200 ml or 7 fl. oz).
- Do not chew the tablet or allow the tablet to dissolve in the mouth because of a potential for oesophageal irritation.
- Do not lie down until after the first food of the day which should be at least 30 minutes after taking the tablet.
- Do not lie down for at least 30 minutes after taking Fosavance™.
- Do not take at bedtime or before rising for the day.

Patients should receive supplemental calcium if intake is inadequate. Additional supplementation with vitamin D should be considered on an individual basis taking into account vitamin D intake from vitamins and dietary supplements. Equivalence of 2,800 IU of vitamin D weekly in Fosavance™ to daily dosing of vitamin D-400 IU has not been studied. Use in the elderly: No dosage adjustment is necessary. Use in renal impairment: No dosage adjustment is necessary for patients where GFR is greater than 35 ml/min. Alendronate is not recommended for patients with renal impairment where GFR is <35 ml/min. Use in children: Not recommended.

CONTRA-INDICATIONS

Oesophageal abnormalities and other factors which delay oesophageal emptying, such as stricture or achalasia, inability to stand or sit upright for at least 30 minutes. Hypersensitivity to alendronate or to any of the excipients. Hypocalcaemia.

PRECAUTIONS

Alendronate can cause local irritation of the upper gastro-intestinal mucosa and potentially worsen any underlying disease. Use with caution in patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, or ulcers, or with a recent history (within the previous year) of gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty. Oesophageal reactions (sometimes severe and requiring hospitalisation, such as oesophagitis, oesophageal ulcers and oesophageal strictures, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate. Physicians should be alert to any signs or symptoms of a possible oesophageal reaction, and patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on or following retrosternal pain, or new or worsening heartburn. The risk of severe oesophageal adverse reactions appear to be greater in patients who fail to take alendronate properly and/or continue to take alendronate after developing symptoms suggestive of oesophageal irritation. It is very important that the full dosing instructions are provided to, and understood by the patient. Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems. While no increased risk was observed in extensive clinical trials with alendronate, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe with complications. A causal relationship cannot be ruled out. Bone or joint muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating. From start of treatment, onset of symptoms varied from one day to several months. A subset had recurrence of symptoms when re-challenged. Patients should be instructed that if they miss a dose of Fosavance™, they should take one tablet on the morning after they remember. They should not take two tablets on the same day, but should return to taking one tablet once a week, at originally scheduled

on their chosen day. Cause of osteoporosis other than oestrogen deficiency and ageing should be considered. Correct hypocalcaemia before initiating therapy. Other disturbances of mineral metabolism should also be effectively treated. The content of vitamin D in Fosavance™ is not suitable for correction of vitamin D deficiency. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with Fosavance™. Calcitriol (vitamin D₃) Monitor urine and serum calcium in patients with disease associated with unregulated over-production of calcitriol (e.g. leukaemia, lymphoma, sarcoidosis) as vitamin D may increase the magnitude of hypercalcaemia and/or hypocalcaemia. Patients with malabsorption may not adequately absorb vitamin D. Excipients: Patients with rare hereditary problems of fructose intolerance, galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrose isomaltase insufficiency should not take Fosavance™ because it contains lactose and sucrose. Drug interactions: Food, beverages (including mineral water, calcium supplements, antacids, and some oral medicinal products) may interfere with absorption of alendronate. Therefore, patients must wait at least 30 minutes after taking Fosavance™ before taking any other medicinal product. Use in pregnant and lactating: alendronate has not been studied in pregnant or breastfeeding women and should not be given to them.

SIDE EFFECTS

The following adverse experiences have been reported during clinical studies and/or post-marketing use of alendronate. No new adverse reactions have been identified for Fosavance™. Common (>2.0% and <10%) Gastro-intestinal: abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer, dysphagia, abdominal distention, acid regurgitation. Musculoskeletal (bone, muscle or joint) pain: Myalgia/aches. Uncommon (>0.1% and <1%) Gastro-intestinal: nausea, indigestion, vomiting, gastritis, oesophageal, oesophageal erosions. Skin rash, pruritus, erythema. Rare (<0.01% and <0.01%) Back as a whole: hypersensitivity reactions including urticaria and angioedema. Transient symptoms as in an acute-phase response: Symptomatic hypocalcaemia, often in association with predisposing conditions (see Precautions). Gastro-intestinal: oesophageal stricture, oesophageal ulceration, upper gastro-intestinal (UGI) perforation, ulcers, bleeding (see Precautions). Localised osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing. Skin rash with photosensitivity. Special senses: uvulitis, scleritis, episcleritis. Isolated cases of severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Laboratory test findings: In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively of patients taking alendronate 10 mg/day versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dl (2.0 mmol/l) and serum phosphate to <2.0 mg/dl (0.65 mmol/l) were similar in both treatment groups.

PACKAGE QUANTITIES AND BASIC UNIT COST

Fosavance™ Tablets £22.80 for 4 tablets.

UNN Date of review: September 2005

Marketing Authorisation Numbers: Fosavance™ Tablets EU 1.0531.0102

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REFERENCES: 1 Black DM, Thompson DL, Bauer DC et al. Fracture risk reduction with alendronate in women with osteoporosis – the Fracture Intervention Trial. *J Clin Endocrinol Metab* 2000;85(11):4118-4124.



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S PATIENTS



alendronate sodium/calcitriol

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