

PERSPECTIVES

Jaw Bone Necrosis and Bisphosphonates: Microanatomical Questions

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Abstract

Reports of an association between bisphosphonate administration and osteonecrosis of the jaw (ONJ) recently appeared from several centers worldwide. In particular, it was noted that the most powerful bisphosphonate on the market, zoledronic acid, was implicated. This drug was recommended for — and successful in — the treatment of hypercalcemia of malignancy and generally for the alleviation of the symptoms of tumors metastasizing to bone. The dominant association of ONJ with zoledronic acid reflects the potency of this drug in the alleviation of problems caused by bone metastases, particularly multiple myeloma, in patients with long lasting, poor dental maintenance. The older, partially edentulous human mandible may contain sizeable tracts of dead bone and its bone tissue is also more highly mineralized than in other bones, but this does not seem to be a problem. Bisphosphonates cause excess bone mineralization and may perhaps interfere with capillary blood vessel maintenance — this would be critical at the junction of cortical bone with the mucoperiosteum. Osteocytic death results in excess mineralization. We need to know whether zoledronic acid or other bisphosphonates damage osteoblasts and osteocytes. *BoneKEy-Osteovision*. 2006 September;3(9):19-23.

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Bisphosphonate-induced osteonecrosis of the jaw (ONJ) has emerged as one of the more pressing problems facing clinicians and researchers in the bone and cancer fields. Besides bisphosphonates (1-6), there are in fact other causes of, and associations with, ONJ, which, even in the absence of radiation therapy, was well known before bisphosphonates (7-10). However, it is the recently-discovered link between therapy with intravenous zoledronic acid or pamidronate and ONJ that catapulted discussion of the disease to the forefront. Concerns continue to mount in the minds of both medical practitioners and patients.

An alarming sign has been the arousal of the sharks of the American legal trade, who see prospects for increasing their fortunes at the expense of the pharmaceutical industry and, potentially, of any medical practitioner who prescribed any of the bisphosphonates

for any reason whatsoever — including, for example, alendronate for osteoporosis: countless millions of prescriptions. This raises the specter of a huge increase in medical malpractice insurance, to be paid for by whom? Thus, irrespective of the biology of the situation, the bisphosphonate-ONJ association is concerning for any medical practitioner.

Why the jaws? Why any preference for the mandible? Why not all bones? The jaws bear teeth and the mandible has *denser* cortical bone, by any definition, than most bone in the body. Teeth are the only mammalian connective tissue structures (other than antlers in deer) that penetrate an epithelium. The oral epithelium is wet and colonized by myriads of microbes, not all of them beneficial. This microbial flora supports the development of 'dental' diseases that eventually invade bone. Occlusal and buccal

pit and fissure and interproximal carious lesions start in enamel, progress into dentine and then pulp, causing infection and inflammation of the pulp, termed pulpitis. Inflammation requires *lebensraum*, literally "living space", for its swelling component, which does not exist within a tooth. Therefore, if untreated, progression to the apical periodontal region is inevitable: this is an initiating event in a sequence that frequently leads to death in wild mammals. Advance outside the tooth domain is within bone soft tissue space, and is therefore considered a type of osteomyelitis.

Drugs that influence coronal caries include fluoride (13), which dramatically reduces enamel crystal solubility and delays onset. The microbiology and progress of dentine caries differ dramatically from that in enamel, and is apparently less influenced by fluoride. Caries may start at the base of occlusal and buccal pits and fissures where there is little or no enamel covering over dentine. The fluoridation of water supplies and toothpaste may have caused an epidemic of retarded caries, leading to more difficult diagnoses and delayed inception of meaningful treatment.

Gingival, cervical or cemental caries is that which develops at the neck of the tooth where enamel ceases. It may progress through any cementum and again involves invasion and destruction of dentine, leading to pulpitis. It is increasingly common in the aging population.

Periodontal disease results from bacterial (product) invasion of the epithelial attachment at the gingival crevice. Its progression depends largely upon the host response as well as the nature of the causative microbes. The destruction of the periodontal ligament and associated bone is another class of soft tissue infection within bone — osteomyelitis.

All these *dental* diseases are to a large extent avertable through patient and dentist education, but they are not prevented and are widespread, leading to loss of teeth and/or the retention of abnormal and

potentially infected tissue within the jaw bone.

Why any association with bisphosphonates and why zoledronic acid in particular? All the bisphosphonates studied to date lead to an increase in bone density at the microscopic fabric scale (11), irrespective of any clinically detectable increase in radiographic bone mineral mass (12). This can be explained at least partially by a reduction in bone replacement, leading to more older, and thus inherently better, mineralized bone (14). But is this all? The most important function of osteocytes is the down-regulation of bone mineralization (15). Kill osteocytes and bone hypermineralizes. Dead bone is less attractive to osteoclasts, though it will be resorbed — and this may be support for the widespread, but largely unfounded, hypothesis that osteocytes in some way regulate bone turnover.

But suppose that bisphosphonates kill or maim osteoblasts and osteocytes. Then the ingress of extra mineral is easily explained. Little research has been directed at this possibility, though the reverse, some stimulation of osteoblast-like cell lines, has been noted *in vitro* (16;17). However, deleterious effects of bisphosphonates on capillary blood vessel survival and proliferation have been reported (18;19) and pericytes are major contenders for recruitment as new bone-forming cells. Albeit that osteocytes survive at distances of up to 150 microns from the nearest capillary, any effect of bisphosphonates on capillary survival would cause osteocytic death and excess bone mineralization.

Not all bone is the same. The fabric density of aged human mandibular bone is higher than any other in man (21), except that in the auditory ossicles. This high level of mineralization is — as in the auditory ossicles — associated with and partly explained by the existence of widespread tracts of evidently dead bone in which osteocytic lacunae and their canaliculi are mineralized (20). Erstwhile Haversian canal contents are mineralized. Aged trabeculae, originally medullary in position, are exteriorized through inwards drift of the

alveolar (would-be tooth-supporting bone) cortex following tooth loss. This bone is dead.

Does this matter? No. It is normal and asymptomatic. Furthermore, dental surgery today frequently involves the placement of dead structures, ranging from dead allograft and xenograft bone, through hydroxyapatite ceramic and metal implants, as well as the causation of extensive bone death during surgery — all with no reported clinical problems. So bone tissue necrosis cannot be the problem. (By whatever means osteocytes die, by necrosis or apoptosis, the remaining cell debris cannot be macrophaged; it is rendered harmless by mineralization. Whole cells may be preserved in this way and 'liberated' by the demineralization that precedes classical decalcified section histology (22). Apoptotic osteocyte debris calcifies as mini-pearls within lacunae. Cell autolysis may leave no recognizable structure, but the lacunar contents still mineralize). It must be the death of the bone marrow — myelonecrosis — that matters. But why should this be important? Avascular necrosis of the head of the femur is common enough, but not life-threatening.

The mandible has at its oral surface, and many other sites, a thin mucoperiosteum. The presentation of many or most of the bisphosphonate-associated ONJ cases is of dead oral mucosa overlying the dead bone. Which came first? Interruption of the blood vessel supply with ensuing death to the mucous membrane or to the bone? Are these blood supplies interlinked? What are the variations in the blood vessel arrangement at this critical juncture? The classical view would be a longitudinal Haversian canal arrangement in the cortex with some net venous outflow from bone to periosteum. However, our own unpublished studies show that this is not so simple, and that the small blood vessels in the juxta-oral mandibular cortex may run perpendicular to its surface, in a transverse direction. Microanatomy does not show which way the blood flows, of course, but if the supply of oral mucous membrane and superficial

cortex is interlinked, then the problem could start in either tissue.

Conflict of Interest: The author reports that no conflict of interest exists.

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