Oral and Intravenous Bisphosphonate–Induced Osteonecrosis of the Jaws

History, Etiology, Prevention, and Treatment

Second Edition

Robert E. Marx, DDS

Professor of Surgery and Chief
Division of Oral and Maxillofacial Surgery
Miller School of Medicine
University of Miami
Miami, Florida

Quintessence Publishing Co, Inc

Chicago, Berlin, Tokyo, London, Paris, Milan, Barcelona, Istanbul,
São Paulo, New Delhi, Moscow, Prague, and Warsaw

Table of Contents

Dedication

I dedicate this book to my father and mother, Nicholas A. Marx, Sr and Eva M. Marx. Immigrants from World War I–torn Europe, they carved out a living and fostered a set of values in their family through the turmoil of the Great Depression, World War II, the Korean War, and the Vietnam War. On behalf of my brothers, Nicholas A. Marx, Jr and Carl M. Marx, I wish to express our profound gratitude for their hard work and uncounted sacrifices, allowing us to live the Great American Dream.

Preface to the Second Edition

It is my hope that the reader does not bypass the preface to the first edition of this book but reads it along with this preface.

Since the first edition, much knowledge has been gained and the battle lines have been drawn. That is, the Novartis drugs Zometa (zoledronate), 4 mg intravenously once monthly to treat cancer metastasis to bone or hypercalcemia of malignancy, and Reclast, 5 mg intravenously once yearly to treat osteoporosis, are the most toxic intravenous preparations that produce the majority of cases of intravenous bisphosphonate–induced osteonecrosis of the jaws (BIONJ). The Merck drug Fosamax (alendronate), 70 mg orally once weekly, is the most toxic oral preparation and produces the vast majority of oral BIONJ and has now been noted to also cause spontaneous femur fractures—the very entity it is designed to prevent—with long-term use. Zoledronate's enhanced toxicity is due to its greater potency and its intravenous route, whereas alendronate's enhanced toxicity is due to dose. That is, alendronate marketed as Fosamax is twice the dose (70 mg/week) compared to its competitors risedronate (Actonel, 35 mg/week) and ibandronate (Boniva, 150 mg/month, which amounts to 35 mg/week).

The battle lines are therefore drawn between those companies (and their paid consultants) and independent investigators and patients now pressing legal actions against those companies. The sad fact is that both Novartis and Merck continue to claim that their drugs do not cause BIONJ. This is curious when one considers that at the time of this book's printing, there have already been over 1,100 peer-reviewed publications with over 4,500 authors providing evidence supporting causation and none with evidence refuting it. Even the ICD-9 diagnostic codebook published by the American Medical Association has given this disease a specific code for the jaws: 733.45 is "drug-induced" osteonecrosis of the jaws. In addition, every specialty of dentistry and four or more societies of medicine have published position papers on the subject of bisphosphonates and jaw osteonecrosis; all of this for a condition that these drug companies claim does not even exist. The companies' major defense is that no randomized prospective trials have proved causation. This is also curious because the original Novartis studies and Merck studies were such randomized trials and their paid researcher never examined the mouth or explored their study patients' jaw complaints. It has since come to light that many patients actually developed BIONJ during the studies and even more patients developed BIONJ later. Currently, institutional research review boards reject randomized bisphosphonate studies with controls due to the safety risks of unnecessarily exposing patients to toxic drugs.

This sadness deepens when we realize the enormous financial support that these companies provide to many societies, journals, and individual physicians and dentists in return for denying an obvious causation and trivializing the impact of BIONJ. As a glaring example, the published bisphosphonate position paper by the American Society of Bone and Mineral Research identified that 19 of its 24 "experts" were paid consultants of these drug companies, including its committee chairman. In addition, another member, an oral and maxillofacial surgeon, was actually a paid consultant but did not disclose it.

Moreover, the editor of the *Journal of Oral and Maxillofacial Surgery* was a paid consultant and member of the American Association of Oral and Maxillofacial Surgeons Task Force on bisphosphonates during this time.

The importance of this book to the reader is that BIONJ is a very real disease that cannot be overlooked or dismissed due to drug-company denials or the podium testimonials of their paid consultants. The patients you and I see have real bone toxicity and exposed bone, often have pain, often have swelling, and often have secondary infections and/or fistulas, sinus exposures, and drainage. These patients, like all of our patients, come to us for an unbiased evaluation and our best efforts to prevent and treat this disease. If we believe these drug companies and their paid consultants, then 1,100 articles, 4,500 authors, and a mountain of evidence are wrong and every one of us who has treated these patients has been remiss.

The goal of this second edition is to update the reader on the newest data and best current recommendations to prevent and treat this disease. This edition includes a new, more accurate, and more simplified staging system as well as more information on the utility and shortcomings of the serum CTX test for oral bisphosphonate cases and therefore how to use it to the clinician's best advantage.

Some new management principles and surgical techniques are discussed in the text as well as in the sample cases. In addition, new data on osteopenia and osteoporosis allows the reader to better correlate prevention and treatment strategies with the treating physician. Finally, the new osteoporosis treatment of Reclast (zoledronate 5 mg IV once yearly) is reviewed and cases of BIONJ already caused by this drug presented.

It is this author's hope that this book allows all of those clinicians who actually see patients who take these drugs to better understand the problem and hopefully prevent at least a few patients from developing BIONJ, and if not, to treat them to the best outcome possible.

Preface to the First Edition

Discovery of a New Disease

"If you think you've discovered a new disease, you probably haven't reviewed the literature thoroughly enough." *–Anonymous*

The Three Stages of a Scientific Theory

Stage I: It is scoffed at and met with disbelief.
Stage 2: It is accepted as true but insignificant and trivial.
Stage 3: It is thought to be correct and even revolutionary. In fact, those who criticized it most now claim that they invented it and are the experts. *–Anonymous*

It is almost uncanny how the saga of bisphosphonate-induced osteonecrosis of the jaws demonstrates the wisdom of these two anonymous quotations. When patients first began to present in our office with exposed bone that was not associated with radiation therapy and we determined that the only common denominator was intravenous bisphosphonate therapy, I thought we had discovered a new disease, or at the very least a new complication of drug toxicity. However, as you will learn in chapter 1, I was wrong. In fact, it is the same disease as the notorious "phossy jaw" found in phosphate miners and match factory workers in the late nineteenth and early twentieth centuries, as described by numerous authors of the period.

When I issued a medical alert that described modern-day intravenous bisphosphonate–induced exposed bone that failed to heal and even worsened with surgical debridements, the reality of the condition was almost universally denied and the report widely disbelieved. I recall physicians and researchers from Novartis Pharmaceuticals attributing the exposure of bone to the patients' chemotherapy and use of dexamethasone, as well as peer reviewers for the *New England Journal of Medicine* asserting that it was "impossible" and "not a real entity" when they rejected my submission. Soon after, however, my colleague Dr Salvatore Ruggiero published a report of cases that he had seen, and this was followed by a flood of smaller case series and reports from around the world, all of which culminated in a critical mass of cases of bisphosphonate-induced osteonecrosis of the jaws so large that it could no longer be denied.

Stage 2 of this process was entered with reluctant acceptance by some and retorts of insignificance by others. "Letters to the Editor" began to appear, variously calling for "perspective," attributing the problem to "overreaction," and denying the existence of a cause-and-effect relationship. These were followed by an explosion of further studies reporting hard data. Our study appeared in the November 2005 issue of the *Journal of Oral and Maxillofacial Surgery*, and it was quickly followed by four separate studies in the December 2005 issue of the *Journal of the American Dental Association*. In the first 2 months of 2006, more than 200 additional reports were published in journals representing various specialties of medicine and dentistry from all corners of the globe. The significance of the disease became obvious even to the most ardent nonbeliever.

Stage 3 is now in full blossom. At this time nearly all associations of dental specialists, many medical specialist organizations, and some medical drug companies have issued official position papers from their so-called expert panels. These include the American Association of Oral and Maxillofacial Surgeons, the American Dental Association, the American Academy of Oral Medicine, the American Academy of Periodontology, the American Association of Oral and Maxillofacial Pathology, the American Society of Bone and Mineral Research, the Mayo Clinic, and Novartis Pharmaceuticals. Some, frankly, have been hastily compiled to show an interest and a public concern and hence have very little data or substance.

The purpose of this overview is not to take cheap shots at well-meaning specialty organizations presumably seeking to unravel this mystery, nor to engage in self-deprecation or self-aggrandizement. It is, instead, to make the point that there are no real "experts," including this author. Experts in oral and maxillofacial surgery, medical oncology, periodontology, bone science, pharmacology, and endocrinology, among others, each formed their own special panels to address the problem, but the inescapable truth is that none of these individuals were experts in bisphosphonate-induced osteonecrosis of the jaws. The modern form of this disease is simply too new for any group to have controlled research data or long-term experience.

Consequently, this text humbly presents only the truth *as it is known today*: The relevant history, the mechanism of action, the intended benefits of bisphosphonates, a clinical and cause-related correlation to osteopetrosis, the problems and prevention/treatment guidelines related to intravenous bisphosphonates, the problems and prevention/treatment guidelines related to oral bisphosphonates, and finally, samples of real cases that add realism to this complex disease are organized sequentially in chapters 1 to 7. The purpose of the book is to educate my colleagues in the dental profession, and perhaps some in the medical profession as well, based on our current knowledge and understanding. Furthermore, it is my hope that the prevention guidelines in chapters 5 and 6, combined with the clinical scenarios and case samples presented in chapter 7, lead to more than lip service in support of the noble concept of "preventive medicine" and that the treatment guidelines relieve the pain and suffering of as many individuals as possible.

6 Risks, Prevention, and Management of Oral Bisphosphonate–Induced Osteonecrosis

Oral bisphosphonates are cleared by the US Food and Drug Administration (FDA) only for the treatment of osteoporosis. Yet, they are often prescribed "off label" for osteopenia as well. Therefore, the number of individuals—mostly women—taking oral bisphosphonates is higher than the number of individuals who have actually been diagnosed with osteoporosis; this number is estimated at 14 million in the United States alone.

The three oral bisphosphonates used to treat osteoporosis on the US market today are alendronate, which is marketed under the name Fosamax by Merck and now also available in generic form; risedronate, marketed under the name Actonel by Procter and Gamble; and ibandronate, marketed as Boniva by Roche. To date, alendronate (mostly as Fosamax) has caused 96% of the cases of bisphosphonate-induced osteoneocrosis known to this author, primarily because of dosing. Fosamax is prescribed at 70 mg/week compared to Actonel at 35 mg/week and Boniva at 150 mg/month, which equates to 35 mg/week. That is, Fosamax is prescribed at twice the dose of these other two equally potent, equally absorbed drugs with the same 11-year half-life in bone. To comprehend the effect of this dose doubling, consider the consequences that would result if a patient on digitalis doubled his or her dose or if the drug aspirin or Tylenol were to have a half-life of 11 years. The digitalis patient would suffer a cardiac arrest, the aspirin patient would bleed to death, and the Tylenol patient would suffer from liver failure.

Etidronate (Didronel, Procter and Gamble) and tiludronate (Skelid, Sanofi Aventis) are generally prescribed exclusively for the treatment of Paget disease of bone, and no cases of osteonecrosis of the jaws induced by these drugs are known to the author. In 2007, an intravenous bisphosphonate, zoledronate 5 mg intravenously once every year (Reclast), was FDA-cleared for the treatment of osteoporosis.[1] As described in chapter 5, intravenous bisphosphonates have produced bisphosphonate-induced osteonecrosis of the jaws (BIONJ) in patients who have received as little as two doses. Reclast is too new to the marketplace to gauge the risk after the third dose because most patients have only received one or two doses at the time of this writing. The author is familiar with four cases already caused by Reclast, and more are anticipated as patients receive repetitive doses (Fig 6-1). In addition, many patients for whom Reclast is now prescribed have been taking an oral bisphosphonate and therefore accumulated bisphosphonates in their alveolar bone,

Table 2-2 Primary indications and dosage information for all currently available bisphosphonates

Bisphosphonate (proprietary name, manufacturer)	Primary indication	Contains nitrogen	Dose	Route	Relative potency
Etidronate (Didronel, Procter and Gamble)	Paget disease	No	300–750 mg daily for 6 months	Oral	1
Tiludronate (Skelid, Sanofi-aventis)	Paget disease	No	400 mg daily for 3 months	Oral	50
Alendronate (Fosamax, Merck)	Osteoporosis	Yes	10 mg/day; 70 mg/week	Oral	1,000
Risedronate (Actonel, Procter and Gamble)	Osteoporosis	Yes	5 mg/day; 35 mg/week	Oral	1,000
Ibandronate (Boniva, Roche)	Osteoporosis	Yes	2.5 mg/day; 150 mg/month	Oral	1,000
Pamidronate (Aredia, Novartis)	Bone metastases	Yes	90 mg/3 weeks	Intravenous	1,000–5,000
Zoledronate (Zometa, Novartis)	Bone metastases	Yes	4 mg/3 weeks	Intravenous	10,000+
Zoledronate (Reclast, Novartis)	Osteoporosis	Yes	5 mg/year	Intravenous	10,000+

The fundamental biologic action of all bisphosphonates is to inhibit bone resorption and hence bone turnover and renewal, which of course reduces serum calcium levels as well. The reason for this antiosteoclastic or antiresorption effect is the inhibition and/or irreversible cell death of the osteoclast. Upon intravenous administration of Aredia or Zometa, or upon oral administration of one of the oral bisphosphonates, the bisphosphonate is readily bound to the mineral crystals on every bone surface. Repeated doses of the bisphosphonate accumulate in the bone matrix (Fig 2-3). During normal bone remodeling, osteoclasts resorb the bone and ingest the bisphosphonate, which functions as an analogue of the isoprenoid diphosphate lipids. These isoprenoid diphosphate lipids are essential for farnesylation and geranylgeranylation of guanosine triphosphate (GTPase) enzymes, which prevent osteoclast apoptosis (cell death).[8] This biosynthetic pathway is also known as the *mevalonate branch pathway*. Microscopically, the osteoclast is observed to lose its normal ruffled border at the Howship lacuna resorption site, retract from the bone surface, and die (Fig 2-4). Without bone resorption and the concomitant release of bone-induction proteins such as bone morphogenetic protein (BMP) and insulin-like growth factors 1 and 2 (ILG_1 and ILG_2), old bone is not removed and new osteoid is not formed. The old bone thus survives far beyond its programmed lifespan. Because the osteocyte is not an immortal cell, it eventually dies, leaving dead bone behind. The function of

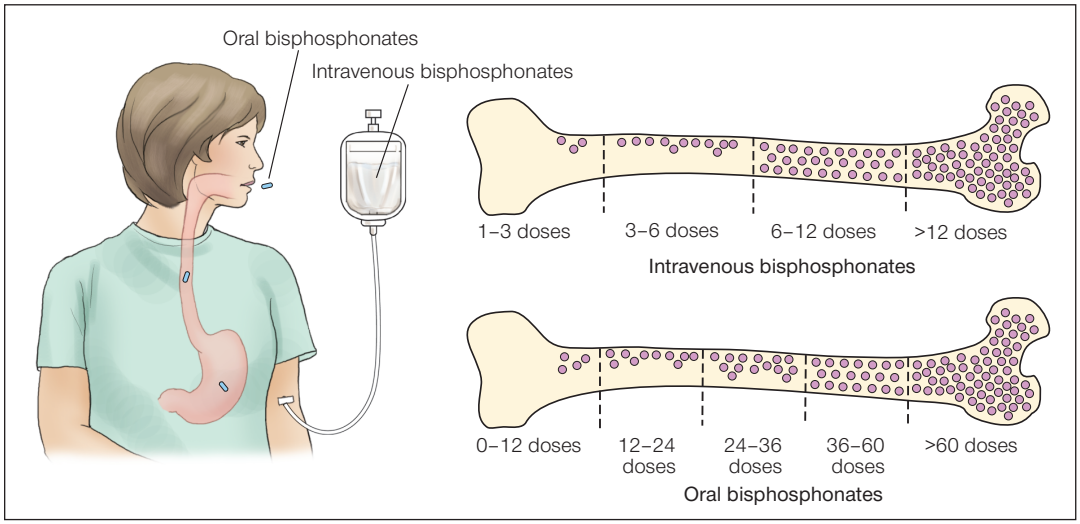


Fig 2-3 Repeated doses of both intravenous bisphosphonates and oral nitrogen-containing bisphosphonates accumulate in bone. However, the former accumulate toxic amounts much faster than the latter.

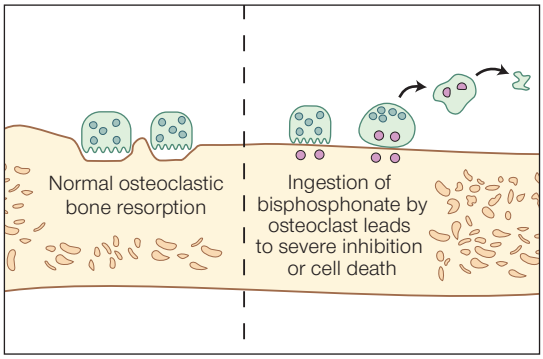


Fig 2-4a Osteoclasts that resorb bone containing a bisphosphonate ingest the bisphosphonate, which causes cell death (apoptosis).

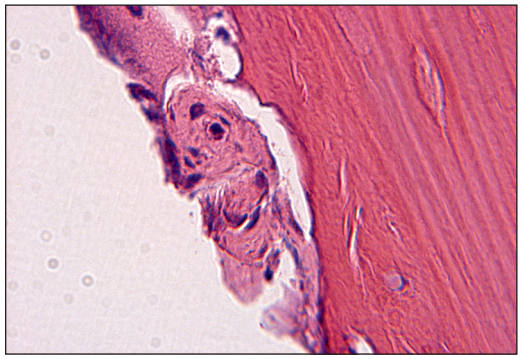


Fig 2-4b Photomicrograph of an osteoclast with loss of its ruffled luster, vacuolated cytoplasm, and early nuclear disruptum after bisphosphonate ingestion (original magnification ×40; hematoxylin-eosin stain).

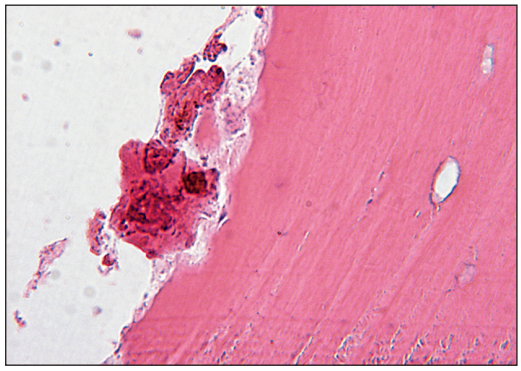


Fig 2-4c Photomicrograph of a retracted, dying osteoclast with complete description of nuclei from a patient with bisphosphonate-induced osteonecrosis (original magnification ×40; hematoxylin-eosin stain).

Case 5 *(cont)*

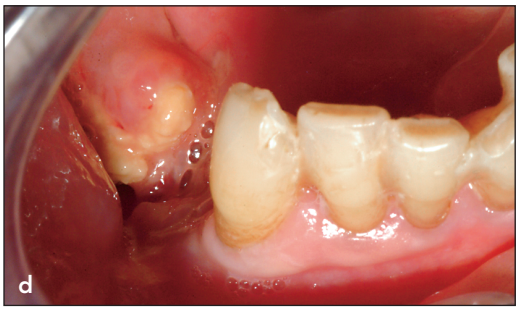
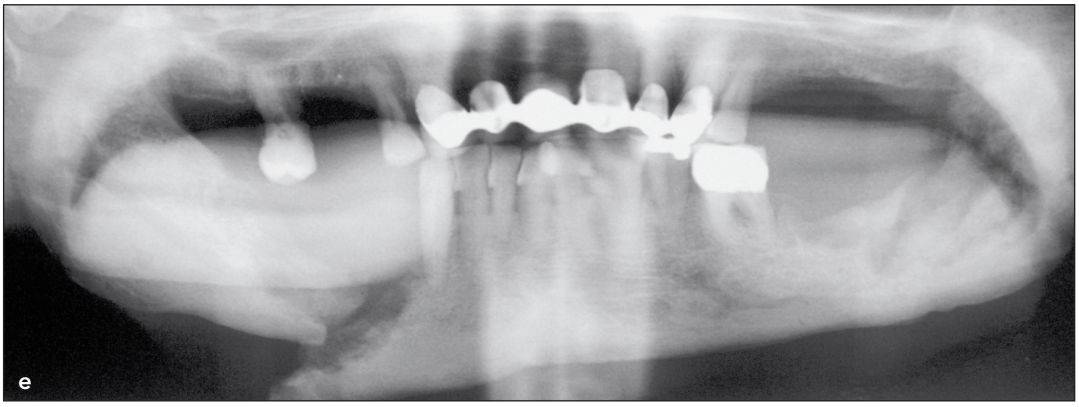


Fig 7-5d Clinically evident exposed bone resulting from a displaced proximal fracture segment.

Fig 7-5e Pathologic fracture on the right side and extensive osteolysis in the left third molar/ramus area.



Outcome

This man had an excellent response to his chemotherapy: He continued Zometa therapy and experienced a gradual reduction of skeletal pain, union of his fractures, and control of his myeloma proteins. His mandible also responded well to the initial double antibiotic therapy followed by the ongoing penicillin VK and 0.12% chlorhexidine therapy. By April 2006, he was able to walk with the assistance of a walker and able to maintain a normal diet. Although the bone in his mandible remained exposed and the orocutaneous fistula persisted, they were no longer causing him pain and there was no drainage. However, in June 2006, he returned with severe pain and deviation of his mandible to the right with a recurrence of infection and drainage.

Repeat Examination

The patient had developed an obvious fracture of the right midbody of the mandible (Figs 7-5d and 7-5e). His jaw was deviated to the right, as was his occlusion (Figs 7-5f and 7-5g), and the orocutaneous fistula was draining a significant amount of pus. Additionally, the left side of the mandible had developed a small bone exposure of 0.3 cm × 0.3 cm (Fig 7-5h), although it remained uninfected and pain-free, representing a Stage I intravenous bisphosphonate–induced osteonecrosis.

Repeat Assessment

1. Although this man's multiple myeloma was under control and he had remained asymptomatic related to his jaw osteonecrosis for more than 2 years, the ongoing Zometa therapy has caused additional necrotic bone to form and led to a pathologic fracture of the right midbody area of the mandible along with clinically exposed bone in the left angle/ramus area.
2. At this time, the right side represents a Stage III bisphosphonate-induced osteonecrosis with a pathologic fracture and the left side a Stage I bisphosphonate-induced osteonecrosis.
3. The presence of a fracture indicates the need for surgery and represents the only likely resolution of the pain and infection in this area. With a medical clearance from the patient's oncologist, a resection of the right hemimandible is appropriate.
4. Because the left side is asymptomatic and remains a Stage I, surgery is not required for that area and would only add to the complexity of the current treatment. If it were to progress to a pathologic fracture, and hence a Stage III osteonecrosis, it could also require a resection.
5. A right hemimandibulectomy surgery without immediate reconstruction is planned because of the presence of significant clinical infection. Although a bone graft was ruled out immediately, a titanium plate might be considered a reasonable option because most of the actual infected tissue is to be removed and the approach is routinely successful in cases of osteoradionecrosis. The decision to defer reconstruction with a titanium plate has been made not only because of the presence of overt infection but also because of the immune compro-

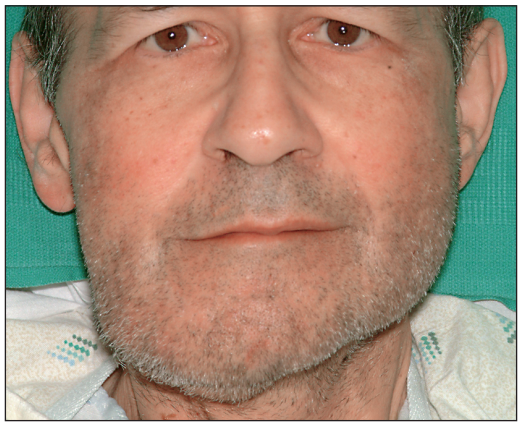


Fig 7-5f Jaw deviation to the right resulting from a pathologic fracture in the right midbody region.

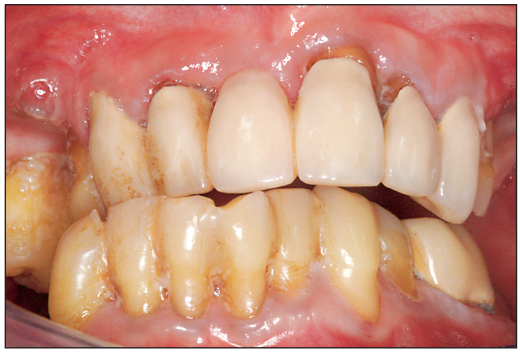


Fig 7-5g Malocclusion caused by the pathologic fracture.

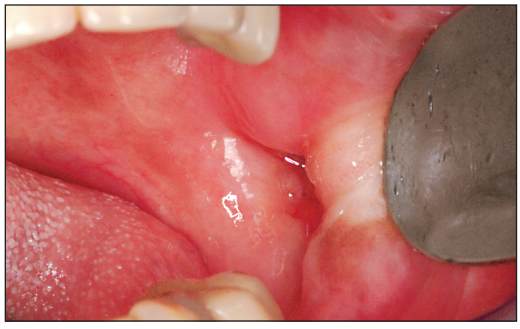


Fig 7-5h Development of a small mucosal opening over the damaged bone in the left posterior mandible, advancing the condition to a Stage I intravenous bisphosphonate–induced osteonecrosis in this area.