Jaw uptake of technetium-99 methylene diphosphonate in patients on biphosphonates: A word of caution

Abstract

Nitrogen-containing biphosphonates are a group of medications that are increasingly used in the management of Paget's disease, fibrous dysplasia, osteoporosis, multiple myeloma and metastatic prostate or breast cancer bone disease. On 2004 it was established that nitrogen-containing biphosphonates may induce jaw osteonecrosis and since then, a substantial number of publications has supported this finding. Jaw osteonecrosis may be asymptomatic, lasting for about a year or symptomatic, accompanied with mild or severe pain. Jaw osteonecrosis usually results in patients with poor dental hygiene, or subjected to invasive dental procedures. Its incidence increases with the length of nitrogen-containing biphosphonates treatment and appears to be higher for the Zometa™ users. It is important to early recognize this entity, since early intervention can make a significant difference to the outcome of this debilitating side effect. *We here report* three patients who had a positive technetium-99m methylene diphosphonate (^{99m}Tc-MDP) bone scan. One of these patients also had osteomyelitis and was treated aggressively. The other two were treated in a more conservative manner. Detailed dental examination supported the scintigraphic findings. Biopsy was performed only in one patient and also offered specimens for antibiotic cultures. *In discussion*, jaw biopsy is a debatable procedure in the setting of jaw osteonecrosis and many consider that it should be avoided in most cases, except if it is necessary to establish the diagnosis and suggest antibiotic treatment by obtaining samples for bacterial cultures. Although axial tomography and magnetic resonance imaging are useful in defining the extent of the disease, 3-phase ^{99m}Tc-MDP bone scan is the most sensitive imaging modality pinpointing the disease at its early stages. *In conclusion*, a 3-phase ^{99m}Tc-MDP scan with anterior and lateral views of the skull is indicated in all symptomatic or asymptomatic patients, with a history of long-term nitrogen-containing biphosphonate treatment, since this may lead to an early detection of the disease.

Hell J Nucl Med 2007 10 (3): 177-180 • *Abstracted online: 19 November 2007*

Antonios Zanglis, Dimitrios Andreopoulos, Marina Dima, Georgios Baltas, Nikolaos Baziotis

"Saint Savas" Oncology Hospital, Nuclear Medicine Department, Athens, Greece, PC 11 522

⁂

Keywords: ^{99m}Tc-MDP – Bone scan – Biphosphonates – Jaw osteonecrosis

Correspondence address:

Dr Antonios Zanglis,
Saint Savas Oncology Hospital,
Nuclear Medicine Department,
171 Alexandras Ave.,
PC 115 22 Athens, Greece
Tel.: +30 210 640-9376
E-mail: azanglis@yahoo.gr

Received:
6 June 2007
Accepted revised:
14 November 2007

Introduction

Patients with a history of malignancy are periodically tested with technetium–99m methylene diphosphonate (^{99m}Tc-MDP) bone scans for the early detection of metastases. Since the jaw region is an unlikely site for metastatic bone lesions, any increased activity of the tracer is usually considered as a benign "dental disease". The various causes of ^{99m}Tc-MDP uptake in the jaw have been reviewed elsewhere [1-3]. Common causes of focal ^{99m}Tc-MDP uptake in the jaw are related to prior surgical manipulations in the region (tooth extraction, root canal surgery), fracture and malignancy. Less common causes, like ossifying fibroma, odontoma, residual osteitis, osteomyelitis, enchondroma, osteoma (Gardner's syndrome), actinomycosis and lymphoma should also be included in the differential diagnosis [1-3].

Biphosphonates are powerful osteoclast inhibitors, with anti-tumor and anti-angiogenic properties and whose half-life in the human body, once incorporated into bone tissue, is in the range of years. Their use has been associated with hallucinations [4], uveitis [5, 6], iritis [7, 8], scleritis [9], hearing loss [10], skin rash [11], ulcerative esophagitis [12] and lymphopenia [13] and recently, cases of jaw osteonecrosis, as a result of biphosphonate use, appeared in the literature as well [14-32]. Nitrogen-containing biphosphonates in tablet form, commonly used in treating osteoporosis in post-menopausal women and Paget's disease, include Fosamax™ (Alendronate: 4-amino-1-hydroxybutylidene-1, 1-bisphosphonic acid monosodium trihydrate) and Actonel™ (Risedronate: 1-hydroxy-2-(3-pyridinyl)ethylidene 1,1-bisphosphonic acid monosodium hemi-pentahydrate). Nitrogen-containing biphosphonates for intravenous use, including Aredia™ (Pamidronate: (3-amino-1-hydroxypropylidene) 1, 1-bisphosphonic acid disodium salt pentahydrate) and Zometa™ (Zolendronic acid: 1-hydroxy-2-(1^{H}-imidazol-1-yl) ethylidene-1, 1-bisphosphonic acid monohydrate), significantly reduce skeletal-related events

in patients with multiple myeloma and other cancers (i.e. breast, prostate) [20, 22, 29, 32]. Long-term biphosphonate use can result in suppression of bone turnover and compromise the healing of even usual microinjuries within the bone, that occur as a result of daily stresses [18]. Although computerized tomography (CT) and magnetic resonance imaging (MRI) are useful in defining the features and extent of the osteolytic lesions, ^{99m}Tc-MDP 3-phase bone scan has been found as the most sensitive imaging method in detection of jaw osteonecrosis at an early stage and the authors of a recent article propose its employment as a screening test to detect subclinical cases in patients on long-term biphosphonate use [33]. Biopsies are recommended only if metastatic disease is suspected and any additional dental trauma should be avoided, as it may further precipitate and delay wound healing in this relatively avascular tissue. However, whenever biopsies are performed, tissue microbial cultures should always be obtained [34]. The true incidence of jaw osteonecrosis is hard to determine and most likely it represents an under-recognized entity, closely related with the length of the exposure to the biphosphonate use and the type of the received bisphosphonate. In multiple myeloma patients, receiving intravenous zolendronic acid (Zometa™) for 36 months, up to 15% of them developed jaw osteonecrosis, but this complication appeared in only 4% of the patients receiving pamidronate (Aredia™) for the same period of time [19, 20, 34]. It has been recently suggested that sequential imaging with technetium-99m 3-methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI) and fluoro-18 fluorodeoxy-glucose (^{18}F-FDG) can help differentiate between jaw osteonecrosis and malignancy, avoiding biopsy, which is an invasive procedure and can complicate things for the patient [35], as previously explained. Cost and non-availability of the positron emission tomography (PET) equipment in most nuclear medicine departments though, render this approach of highly questionable clinical value.

The objective of this communication is to sensitize the nuclear medicine physicians to this emerging epidemic [20] that accompanies the long-term nitrogen-containing biphosphonate administration and may either escape undetected, especially at the asymptomatic phase of the disease, or misinterpreted. Therefore, three typical cases will be presented, showing the potential of this simple, ubiquitous and simple procedure of ^{99m}Tc-MDP bone scan, in the diagnosis and management of these patients.

Cases description

The patient of *case-1* was a fifty-four years old female, with a history of right kidney removal twenty-five years ago, due to a coral stone. Five years ago, she developed ovarian cancer and was subjected to surgery for removal of the ovaries and hysterectomy. She had also developed serious osteoporosis accompanied by hypercalcemia (10.9 mg/dL) and she was placed on Zometa™ *per os* for three years, until she developed persistent pain in the right mandible with a non-healing ulceration, following a tooth extraction. Dental examination revealed the typical findings suggestive of jaw osteonecrosis, such as the non-healing extraction socket, presence of exposed bone, gingival swelling and purulent discharge. Zometa™ was discontinued and a conservative approach to her jaw problem was chosen, based on chlorhexidine rinses and antibiotics administration. Two years later she was hospitalized for ovarian cancer metastatic disease and she was referred to our department for a bone scan with ^{99m}Tc-MDP. The patient in case-1 was a symptomatic patient with an established jaw osteonecrosis, as previous history, clinical examination and treatment records revealed. Based on the literature recommendations [33], a 3-phase bone scan was performed, with jaw as the area of interest and the results are shown in Figure 1. The blood pool image revealed an area of ^{99m}Tc-MDP extravasation in the right mandible and in the area shown by the arrow (Fig. 1, upper tier). The delayed images showed a photopenic area (Fig.1, lower tier-center), adjacent to a region of increased osteoblastic activity (Fig. 1, lower tier-left). These findings were consistent with jaw osteonecrosis (photopenic area), with an adjacent region in the right mandible suggestive of an active inflammation. The scintigraphic findings were verified on biopsy and part of the bone was found infiltrated by bacteria and inflammatory cells (osteomyelitis). The patient was placed on a regimen of antibiotics, after curettage and debridement of the necrotic tissues. However, the patient continued to experience significant pain, while mastication became impossible from the affected side.

Case-2 was a seventy-seven year old male with metastatic prostate cancer. He was started on Zometa™ (intravenous monthly injections), until 5 teeth from the mandible literally fell-off 3 months after the onset of therapy, while the patient experienced no symptoms (pain) on mastication. The biphosphonate administration was discontinued and the patient was

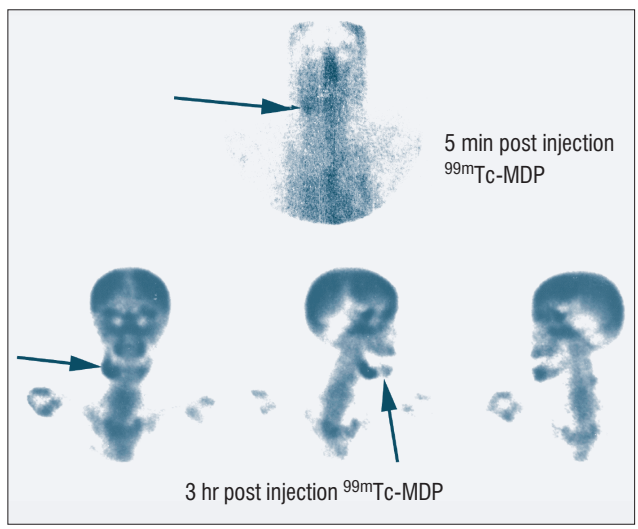

Figure 1. Three-phase ^{99m}Tc-MDP scan of case-1 patient with a known jaw osteonecrosis. The blood-pool image (upper tier) shows the area of the extravasation of the administered radiopharmaceutical, a finding suggestive of osteomyelitis. The delayed images indicate the presence of a photopenic area (arrow, lower tier-center) adjacent to the area with increased osteoblastic activity in the right mandible (arrow, lower tier-left).

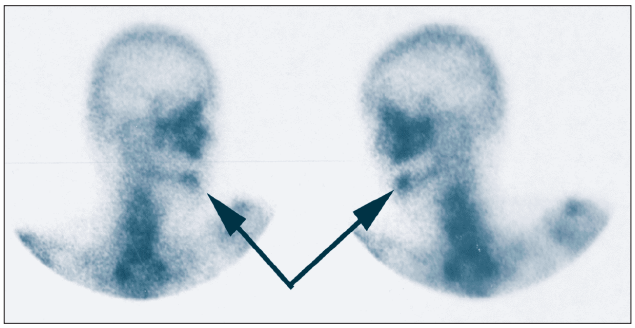

Figure 2. Technetium-99m-MDP scan of the asymptomatic patient of case-2, with a history of metastatic prostate cancer, who received only a short course of Zometa™. The arrows indicate the regions of increased osteoblastic activity in the mandible.

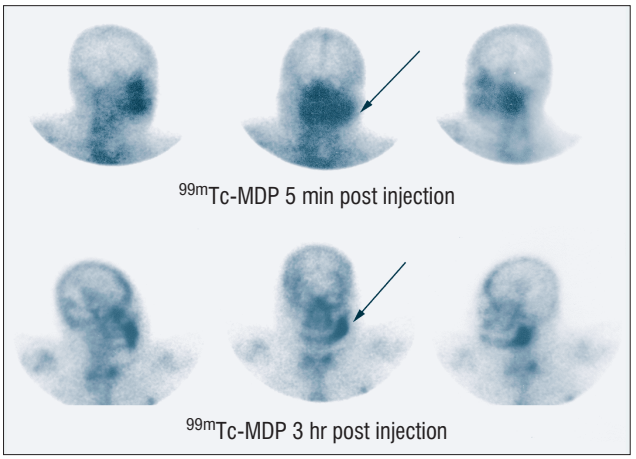

Figure 3. Technetium-99m-MDP scan of the symptomatic patient of case-3 with a history of breast cancer and under long-term Zometa™ treatment. The arrows indicate the regions of increased ^{99m}Tc-MDP extravasation (5 min post-injection) and of the increased osteoblastic activity in the mandible (3 hr post-injection image).

seen in our department for a routine bone scan with ^{99m}Tc-MDP, prior to rhenium-188 1, 1-hydroxyethylidene diphosphonate (^{186}Re-HEDP) administration. An increased uptake of ^{99m}Tc-MDP in the anterior mandible was noticed, suggesting that a reparative process was taking place, following the apparent osteonecrotic process, which caused the painless teeth loss (Fig. 2). On dental examination, bone exposure was observed, without any evidence of active infection, a finding consistent with the presumed diagnosis of jaw osteonecrosis. For this patient, based on history and dental examination findings, it was not considered necessary to perform a 3-phase ^{99m}Tc-MDP bone scan. The patient was managed for his dental problem conservatively (mouth rinses with chlorhexidine).

Case-3 was a fifty-five year old female with a history of breast cancer, placed on Zometa™ (intravenous monthly injections) for the last 3 years. She was referred to our department for a routine follow-up ^{99m}Tc-MDP bone scan. She mentioned jaw pain during mastication, with moderate swelling on inspection and her Ca-15-3 and tissue polypeptide antigen (TPA) tumor markers were within normal levels for the last 3 years. The patient in case 3 was a symptomatic (jaw pain) female with a history of breast cancer and the findings of a routine ^{99m}Tc-MDP scan in another nuclear medicine laboratory were unremarkable, except for an are of increased osteoblastic activity in the mandible, presumably due to metastatic disease from breast cancer. Since this was an unlikely area of metastatic breast cancer spread, the suspicion for the presence of an evolving jaw osteonecrosis, secondary to the long term of Zometa™ use, was raised. Therefore, a 3-phase ^{99m}Tc-MDP scan was performed in our department, which revealed the inflammatory component of an ongoing jaw osteonecrotic process (Fig. 3). Careful review of her previous dental history revealed that the patient had a tooth extraction 3 years ago and 3 months after the onset of Zometa™ use. The patient was subjected to a careful dental examination, which revealed the typical findings of jaw osteonecrosis, such as the non-healing extraction socket, presence of exposed bone, gingival swelling and purulent discharge. The patient was managed for her jaw problem conservatively (mouth rinses with chlorhexidine and antibiotics). This case shows that a region of increased osteoblastic activity in the jaw can be easily confused with metastatic disease and a 3-phase ^{99m}Tc-MDP scan helps the differential diagnosis, along with a careful history and dental examination.

Discussion

Osteonecrosis of the jaw has been reported in cancer patients receiving pamidronate or zolendronic acid and in osteoporotic patients receiving alendronate [14-19]. Jaw osteonecrosis presents as an exposure of the mandible or maxilla and it can be either painful or painless. Unlike osteoradionecrosis, jaw osteonecrosis involves the maxilla fairly frequently (1 out of 3 patients), although the mandible is the most likely site of involvement (2 out of 3 patients) and about one fifth of the cases develop spontaneously, in patients who did not have any dental procedures performed. It is believed that jaw osteonecrosis results from the inability of the hypodynamic and hypovascular bone to meet the demands of repair and remodeling, as a result of the normal stress of mastication, or following a tooth extraction and/or tooth infection. The estimated incidence of jaw osteonecrosis, associated with long-term use of biphosphonates, can reach up to 15% (for 3-years use) and it seems that zolendronate, alone or in combination with pamidronate, carries the highest risk [20]. Additional risk factors are dental procedures, poor dental hygiene, corticosteroid therapy and local radiotherapy. Careful history taking with physical examination can help us manage the patient in most cases. Biopsy should be reserved for highly suspicious cases for the presence of metastatic disease. The nuclear medicine physician can be even more helpful, by suggesting a ^{99m}Tc-MIBI bone scan, which shows no jaw uptake in inflammatory or other benign conditions [35]. *In conclusion*, our findings suggest that in patients who complain even for mild jaw pain, a 3-phase ^{99m}Tc-MDP scan is indicated, along with a careful review of the dental history of the patient, since it

may reveal changes compatible with either the reparative phase of an osteonecrotic process, or bone infection (osteomyelitis). Any increased uptake of ^{99m}Tc-MDP in the jaw region in this category of patients should urge for a careful dental examination and the finding should be communicated to the physicians in charge. Even a routine follow-up ^{99m}Tc-MDP bone scan is a sensitive test for detecting jaw osteonecrosis in patients with osteoporosis, bone metastatic cancer, Paget's disease or fibrous dysplasia and receiving biphosphonates, usually for a long period. It should be kept in mind that this debilitating side effect can develop even after a short course of this medication, without any predisposing risk factor and can be totally asymptomatic. Therefore, it is imperative to include anterior and lateral views of the skull in these patients. Early detection can help managing this intractable side effect with conservative measures.

Bibliography

1. D' Avignon MB, Baum S. Increased jaw radioactivity on bone imaging. *Semin Nucl Med* 1982; 12: 219.
2. Lyons KP, Jensen JL. Dental lesions causing abnormalities on skeletal scintigraphy. *Clin Nucl Med* 1972; 4: 509-512.
3. Eversole LR, Rovin S. Differential radiographic diagnosis of lesions of the jawbones. *Radiology* 1972; 105: 277-284.
4. Foley-Nolan D, Daly MJ, Williams D et al. Pamidronate associated hallucinations. *Ann Rheum Dis* 1992; 51: 927-928.
5. Ghose K, Waterworth R, Trolove P et al. Uveitis associated with pamidronate. *Aust N Z J Med* 1994; 24: 320.
6. De S, Meyer P, Crisp AJ. Pamidronate and uveitis. *Br J Rheumatol* 1995; 34: 479.
7. Stewart GO, Stuckey BG, Ward LC et al. Iritis following intravenous pamidronate. *Aust N Z J Med* 1996; 26: 414-415.
8. Siris ES. Bisphosphonates and iritis. *Lancet* 1993; 341: 436-437.
9. Leung S, Ashar BH, Miller RG. Bisphosphonate-associated scleritis: a case report and review. *South Med J* 2005; 98: 733-735.
10. Murdin L, Yeoh LH. Hearing loss treated with pamidronate. *J R Soc Med* 2005; 98: 272-274.
11. Phillips E, Knowles S, Weber E, Shear NH. Skin reactions associated with bisphosphonates: a report of 3 cases and an approach to management. *J Allergy Clin Immunol* 1998; 102: 697-698.
12. Maconi G, Bianchi Porro G. Multiple ulcerative esophagitis caused by alendronate. *Am J Gastroenterol* 1995; 90: 1889-1890.
13. Liote F, Boval-Boizard B, Fritz P et al. Lymphocyte subsets in pamidronate-induced lymphopenia. *Br J Rheumatol* 1995; 34: 993-995.
14. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003; 61: 1115-1117.
15. Migliorati CA. Bisphosphanates and oral cavity avascular bone necrosis: *J Clin Oncol* 2003; 21: 4253-4254.
16. Ruggiero SL, Mehrotra B, Rosenberg TJ et al. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004; 62: 527-534.
17. Maerevoet M, Martin C, Duck L. Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med* 2005 7; 353: 99-102.
18. Woo SB, Hande K, Richardson PG. Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med* 2005 7; 353: 99-102.
19. Durie BG, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med* 2005 7; 353: 99-102.
20. Dimopoulos MA, Kastritis E, Anagnostopoulos A et al. Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. *Haematologica* 2006; 91: 968-971.
21. Migliorati CA, Siegel MA, Elting LS. Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. *Lancet Oncol* 2006; 7: 508-14. Erratum in: *Lancet Oncol* 2006; 7: 533.
22. Sanna G, Preda L, Bruschini R et al. Bisphosphonates and jaw osteonecrosis in patients with advanced breast cancer. *Ann Oncol* 2006; 17: 1512-1516.
23. Carneiro E, Vibhute P, Montazem A, Som PM. Bisphosphonate-associated mandibular osteonecrosis. *Am J Neuroradiol* 2006; 27: 1096-7.
24. Badros A, Weikel D, Salama A et al. Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. *J Clin Oncol* 2006; 24: 945-952.
25. Naveau A, Naveau B. Osteonecrosis of the jaw in patients taking bisphosphonates. *Joint Bone Spine* 2006; 73: 7-9.
26. Thakkar SG, Isada C, Smith J et al. Jaw complications associated with bisphosphonate use in patients with plasma cell dyscrasias. *Med Oncol* 2006; 23: 51-56.
27. Markiewicz MR, Margarone JE 3rd, Campbell JH et al. Bisphosphonate-associated osteonecrosis of the jaws: a review of current knowledge. *J Am Dent Assoc* 2005; 136: 1669-1674.
28. Merigo E, Manfredi M, Meleti M et al. Jaw bone necrosis without previous dental extractions associated with the use of bisphosphonates (pamidronate and zoledronate): a four-case report. *J Oral Pathol Med* 2005; 34: 613-617.
29. Olson KB, Hellie CM, Pienta KJ. Osteonecrosis of jaw in patient with hormone-refractory prostate cancer treated with zoledronic acid. *Urology* 2005; 66: 658.
30. Sanna G, Zampino MG, Pelosi G et al. Jaw avascular bone necrosis associated with long-term use of biphosphonates. *Ann Oncol* 2005; 16: 1207-1208.
31. Migliorati CA, Schubert MM, Peterson DE et al. Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy. *Cancer* 2005; 104: 83-93.
32. Vannucchi AM, Ficarra G, Antonioli E et al. Osteonecrosis of the jaw associated with zoledronate therapy in a patient with multiple myeloma. *Br J Haematol* 2005; 128: 738.
33. Chiandussi S, Biasotto M, Dore F et al. Clinical and diagnostic imaging of bisphosphonate-associated osteonecrosis of the jaws. *Dentomaxillofac Radiol* 2006; 35: 236-243.
34. Mehrotra B, Ruggiero S. Bisphosphonate complications including osteonecrosis of the jaw. *Hematology Am Soc Hematol Educ Program* 2006; 356-360.
35. Catalano L, Del Vecchio S, Petruzziello F et al. Sestamibi and FDG-PET scans to support diagnosis of jaw osteonecrosis. *Ann Hematol* 2007; 86: 415-423.