Journal of Cranio-Maxillo-Facial Surgery 41 (2013) 558–563

Contents lists available at SciVerse ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

The observational study of delayed wound healing after tooth extraction in patients receiving oral bisphosphonate therapy

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ARTICLE INFO

Article history:
Paper received 4 March 2012
Accepted 16 November 2012

Keywords:
Bisphosphonate
Bisphosphonate related osteonecrosis of jaw
Oral bisphosphonate
Tooth extraction

ABSTRACT

Introduction: In this study, we investigated whether such a discontinuation of oral bisphosphonate (BP) for 3 months might influence the incidence of BP-related osteonecrosis of the jaw (BRONJ) and wound healing after tooth extraction in patients receiving oral BP therapy.
Material and methods: There were a total of 434 teeth in 201 patients (18 males and 183 females). The patients were divided into two groups depending on whether or not they underwent a 3-month discontinuation of BP therapy (BP− and BP+) before tooth extraction. In this observational study investigated delayed wound healing after tooth extraction in patients receiving oral BP therapy.
Results: In all cases of the BP− group, there were no BRONJ although there was delayed wound healing in two cases. However, in one case of the BP+ group, oral BP was continued because it was deemed high risk to discontinue treatment by the patient's physician. In this case, an intraoral fistula was still present with bone exposure at 120 weeks after extraction (BRONJ stage 1).
Conclusion: This study supports the idea of a drug holiday and encourages further clinical research on this topic of tooth extraction in patients receiving oral BP therapy.

1. Introduction

Oral bisphosphonate (BP) has been used to treat osteoporosis and osteopenia (Glover et al., 1994; Kanis et al., 1995; Rogers et al., 1997; Jantunen, 2002). Osteoporosis affects more than 10 million Japanese patients (Yoneda et al., 2010). Osteoporosis can arise in the context of other diseases, such as inflammatory bowel disease or primary biliary cirrhosis, as a result of medications, most commonly steroids, or as a consequence of postmenopausal aging (Haderslev et al., 2000; Bone et al., 2004). Marx et al first reported BP-related osteonecrosis of the jaw (BRONJ), implying that the destruction of the vascular complexity of the jaws mediated by the use of BP is responsible for necrosis and secondary infection of the bone matrix (Kobayashi et al., 2010). BRONJ adversely affects the quality of life, producing significant morbidity in affected patients (AAOMS, 2007; Ruggiero et al., 2009; Yoneda et al., 2010). The exact etiopathology of BRONJ has not been investigated in detail. However, several studies found that this condition affects different tissue and cell types. BP inhibits osteogenic cells, osteoclasts and human fibroblasts (Lam et al., 2007; Açil et al., 2011). Furthermore, BP restricts vasculogenesis and angiogenesis via the inhibition of the cell function of endothelial progenitor cells and mature endothelial cells (Ziebart et al., 2011). BP reduces the viability of oral keratinocytes, which corresponds to impaired mucosal wound healing (Landesberg et al., 2008). In addition, a reduction in the extracellular matrix protein production has been described (Simon et al., 2010). A recent cohort study reported the prevalence of BRONJ in patients with oral BP is 0.1% (Lo et al., 2010). The incidence

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http://dx.doi.org/10.1016/j.jcms.2012.11.023

of BRONJ is increased to 0.09–0.34% after tooth extraction (Mavrokokki et al., 2007). Otto et al reported that 7.8% of all patients with BRONJ were associated with oral BP therapy due to osteoporosis and the majority of affected individuals did not have any risk factors for BRONJ (Otto et al., 2011). To date, many investigators have reported methods for managing BRONJ (Rogers et al., 1997; Migliorati, 2003; Wang et al., 2003; Lenz et al., 2005; Magopoulos et al., 2007; Mavrokokki et al., 2007; Abu-Id et al., 2008; Carlson and Basile, 2009; Mücke et al., 2009; Ripamonti et al., 2009; Ruggiero et al., 2009; Stanton and Balasanian, 2009; Van den Wyngaert et al., 2009; Voss et al., 2012). Current therapeutic strategies only aim to control the symptoms of BRONJ, while radical removal of necrotic bone is limited to severe cases (Van den Wyngaert et al., 2007; Voss et al., 2012). There is an expert recommendation that osteotomy should only be carried out in stage three as classified by the American Association of Oral and Maxillofacial Surgeons (AAOMS, 2007). On the other hand, there are only a limited number of prospective studies available concerning the surgical treatment of BRONJ (Montebugnoli et al., 2007; Vescovi et al., 2007; Wutzl et al., 2008). Stockmann et al performed osteotomy of the affected jawbone region and primary wound closure to all patients of BRONJ and reported the success rate of the surviving patients to be 89% after 1 year (Stockmann et al., 2010). However, in Japan, the true incidence of BRONJ has been unclear, and appropriate approaches for prevention and treatment have not been established to date. Recently, there was a standard position paper reported by Japanese Societies that stated that a 3-month discontinuation of oral BP before dental treatment was recommended (Yoneda et al., 2010). Another report suggested that a longer discontinuation period of BP is associated with a reduction in the incidence of BRONJ (Marx et al., 2007). However, the optimal duration of discontinuation before dental treatment is controversial (Lenz et al., 2005; Magopoulos et al., 2007; AAOMS, 2007; Marx et al., 2007; Mavrokokki et al., 2007; Khan et al., 2008; Carlson and Basile, 2009; Ripamonti et al., 2009; Ruggiero et al., 2009; Stanton and Balasanian, 2009; Yoneda et al., 2010). In addition, no reports have evaluated the duration of discontinuation and the incidence of BRONJ in patients receiving oral BP therapy.

In this study, we investigated whether or not they underwent a 3-month discontinuation of BP therapy, the various factors related to the incidence of BRONJ, and the wound healing after tooth extraction in patients receiving oral BP therapy.

2. Material and methods

There were a total of 434 teeth in 201 patients included in this observational study (comprising 18 males and 183 females). Surgical removals of teeth were performed by dentists in the Department of Oral and Maxillofacial Surgery, Kakogawa East City Hospital, Kakogawa, the Department of Oral and Maxillofacial Surgery, and the Department of Regenerative Oral Surgery, Nagasaki University Graduate School of Biomedical Sciences, the Department of Oral and Maxillofacial Surgery, Shakaihoken Kobe Central Hospital, Kobe, the Department of Oral and Maxillofacial Surgery, Shinsuma Hospital, Kobe and the Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine. The Institutional Review Board of the Hospitals approved this study. Before surgery, each patient provided full informed consent about BRONJ and other risks.

The definition of BRONJ was described according to the American Association of Oral and Maxillofacial Surgeons position paper (AAOMS, 2007; Ruggiero et al., 2009). BRONJ can be diagnosed by the following three characteristics: 1. Current or previous treatment with a BP. 2. Exposed bone in the maxillofacial region that has persisted for more than 8 weeks. 3. No history of radiation therapy to the jaws.

All of the patients were investigated with regard to demographics, medical background, type and duration of oral BP use, whether or not they underwent a discontinuation of oral BP before tooth extraction, the duration of such discontinuation, additional surgical procedures such as incision, bone removal, root amputation and suturing, whether antibiotics were administered before extraction, the condition of the bone around the root of the tooth, and the duration of follow-up and primary wound healing with no evident sign of infection. All patients and the surgical removal of teeth were divided into two groups depending on whether they underwent a 3-month discontinuation of BP therapy (BP− and BP+ group) before tooth extraction (Table 1). In BP− group, it was possible to discontinue oral BP for a 3-month period before tooth extraction. In BP+ group, it was impossible. The patients had a mean age of 71.5 ± 9.6 years (range: 35–94 years). Of the 201 patients, 139 were taking BP because of a diagnosis of primary osteoporosis and 62 patients were taking BP because of secondary osteoporosis due to steroid use, autoimmune disease, diabetes mellitus (DM) or collagen disease. The common histories of disease were hypertension (53 patients) and rheumatism (27 patients). There were 20 patients with cancer, 20 patients with DM and 3 patients with dialyzes as systemic risk factors for BRONJ. However, none of the patients with cancer had received intervenous BP. There were 15 patients receiving immunosuppressive agents and 55

Table 1
The characteristics and demographics of the patients receiving oral BP

Factor (overlapping distribution)	BP− group ($n = 101$)	BP+ group ($n = 111$)
Age and gender ($n = 212$)		
Age	Average, 71.8; range 39–94	Average, 71.1; range 35–89
Gender		
Male	7 (6.9)	12 (10.9)
Female	94 (93.1)	99 (89.1)
Bisphosphonate ($n = 212$)		
Alendronate	55 (54.5)	68 (61.3)
Risedronate	43 (42.6)	34 (30.6)
Alendronate/risedronate	2 (2.0)	5 (4.5)
Minodronate	0 (0)	1 (0.9)
Unknown	1 (1.0)	3 (2.7)
The duration of oral BP administration		
Duration	Average, 23.6 months; range 1–180	Average, 32.6 months; range 1–120
More than 3 years[a]	21 (20.8)	33 (29.7)
Less than 3 years	61 (60.4)	57 (51.4)
Unknown	19 (18.8)	21 (18.9)
The histories of disease ($n = 212$) (overlapping distribution)		
Osteoporosis	72 (71.3)	76 (68.5)
Hypertension	24 (23.8)	32 (28.8)
Rheumatism	7 (6.9)	21 (18.9)
Diabetes mellitus[a]	7 (6.9)	16 (14.4)
Cancer[a]	12 (11.9)	8 (7.2)
Angina pectoris	7 (6.9)	5 (4.5)
Cerebral infarction	6 (5.9)	5 (4.5)
Myocardial infarction	2 (2.0)	2 (1.8)
Renal insufficiency including dialysis[a]	1 (1.0)	2 (1.8)
Other	35 (34.7)	48 (43.2)
Drug-induced risk factor (overlapping distribution)		
Steroid therapy[a]	20 (19.8)	39 (35.1)
Anticancer therapy[a]	12 (11.9)	8 (7.2)
Immunosuppressive therapy[a]	5 (5.0)	11 (9.9)

BP− group: it was possible to discontinue oral BP for a 3-month period before tooth extraction.
BP+ group: it was impossible to discontinue oral BP.
[a] Risk factors of BRONJ.