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British Journal of Oral and Maxillofacial Surgery 53 (2015) 1007–1011

BRITISH Journal of Oral and Maxillofacial Surgery

www.bjoms.com

Role of intravenous dosage regimens of bisphosphonates in relation to other aetiological factors in the development of osteonecrosis of the jaws in patients with myeloma

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Accepted 6 October 2015
Available online 1 November 2015

Abstract

The aim of this case-control study was to identify possible explanatory risk factors for the development of bisphosphonate-related osteonecrosis of the jaws (BRONJ) by estimating the effects of intravenous dosage regimens of bisphosphonates, coexisting diseases, and other drugs on 201 patients with multiple myeloma, with or without BRONJ. We compared sex, treatment with bisphosphonates, incidence of diabetes, and the taking of drugs such as corticosteroids and chemotherapy in patients who had BRONJ (n = 44) and patients who did not (n = 157). Among the bisphosphonates given intravenously zoledronic acid showed a stronger correlation with BRONJ than pamidronic acid. The risk of developing BRONJ increased dramatically at cumulative intravenous doses of more than 78 mg of zoledronic acid or 600 mg of pamidronic acid, which corresponds to treatment for 18 months or longer. Diabetes mellitus correlated significantly with the development of BRONJ ($p = 0.01$) while there was no correlation with sex, simultaneous treatment with corticosteroids, or chemotherapy. In conclusion, treatment with zoledronic acid, high doses of pamidronic acid, and the coexistence of diabetes mellitus seem to be associated with the development of BRONJ.

Keywords: Bisphosphonates; Intravenous; Osteonecrosis of the jaw; Myeloma patients; Risk factors.

Introduction

The first modern report of bone necrosis of the jaws as a result of overexposure to phosphorus dates back to 1944 and was noted in workers in phosphorus-rich working environments.[1] The first report of bone necrosis of the jaw after treatment with bisphosphonates was to our knowledge published in 2003,[2] and this was followed by similar observations by others. Since then diagnostic criteria for bisphosphonate-related osteonecrosis of the jaw (BRONJ) have been established. These are: current or previous treatment with bisphosphonates, more than 8 weeks exposure of necrotic bone, and no history of radiation. [3] Other common clinical findings are

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http://dx.doi.org/10.1016/j.bjoms.2015.10.006

pain, swelling, paraesthesia of the inferior alveolar nerve, and secondary infections.

Bisphosphonates are mainly used in the treatment of osteoporosis and malignancies associated with hypercalcaemia and with bony involvement, such as multiple myeloma and skeletal metastases from solid tumours.[4–6] Their benefits include reduction of bony pain, fewer fractures, and improved quality of life.[7] Some antitumour activity has also been recorded, particularly in patients with multiple myeloma,[8] the probable cause of which is inhibition of angiogenesis by bisphosphonates. This effect on the blood supply could also be one of the mechanisms that contribute to bony necrosis of the jaw by causing detrimental ischaemia of the jaw.[9,10]

Bisphosphonates have a high affinity with calcium and are rapidly eliminated from plasma, but they bind to the hydroxyapatites in bone where they can remain for as long as 10 years.[11] The non-bound fractions are excreted through the kidneys. The bisphosphonate that is absorbed into the bone is eventually eliminated during resorption and remodelling.[8] The bioavailability after oral intake of bisphosphonates is poor compared with that after injection.[12] The main hypothesis about the emergence of BRONJ is thought to be drug-mediated inhibition of osteoclast function,[13,14] and its reported incidence in patients treated with parenteral bisphosphonates increases with the duration of treatment, reported ranges being from 0.8%-2.8%.[15–18] The second generation of bisphosphonates such as zoledronate and pamidronate contain nitrogen, which renders them more potent than the first generation.[8]

It has been suggested that the reason for the predisposition of BRONJ for the jaw is that the alveolar bone turnover is roughly 5-10 times higher than that in the long bones.[19] The mandible is affected twice as often as the maxilla, with regions of thin bone having the highest risk of developing osteonecrosis.[19] The dense quality of the mandibular bone, compared with that of the maxilla, is thought to be one reason for the higher incidence in the mandible.

Local risk factors for the development of BRONJ have been described as dental procedures, inflammatory conditions of the jaw, and poor oral hygiene.[20] Several systemic risk factors have also been suggested, including corticosteroids, obesity, smoking, alcohol misuse, and anticancer drugs.[21,22] Once BRONJ associated with intravenous bisphosphonates has developed, it is a chronic condition with a poor prognosis for cure or spontaneous recovery, which greatly detracts from the quality of life of these already sick patients. It is therefore important to identify the risk factors for its development and to implement the necessary preventive measures in those at risk.

The purpose of this explanatory case-control study was to identify possible risk factors for its development by estimating the combined effects of different intravenous dosage regimens with coexisting conditions and drugs in patients with myeloma.

Patients and methods

Subjects and study design

The study was designed as a retrospective case-control study. The cases were consecutive patients referred to three oral and maxillofacial surgery clinics in Stockholm, Sweden (Division of Oral and Maxillofacial Surgery, Department of Dental Medicine, Karolinska Institutet, Division of Oral and Maxillofacial Surgery, Karolinska University Hospital, Solna, and Stockholm South General Hospital) during the period 2002-09. Forty-five patients with multiple myeloma who had also been diagnosed with BRONJ were included. One patient was excluded because the records were incomplete, leaving 44 patients for analyses (the study group). We used the diagnostic criteria recommended by American Association of Oral and Maxillofacial Surgeons to diagnose BRONJ.[3] The control group consisted of 176 patients with multiple myeloma but without BRONJ who were identified through the Swedish Cancer Registry and were matched for type of myeloma and year of diagnosis in the Stockholm area (1987-2005). Nineteen controls had to be excluded because their medical records were incomplete so 157 were available for analyses. The study was approved by the regional ethics review board in Stockholm.

Data collection

Data on all patients were obtained from their medical records. Information was collected about age, sex, type of myeloma, type of chemotherapeutic agent, treatment with bisphosphonates, corticosteroids, or thalidomide, and concurrent diabetes (Tables 1 and 2). The type of bisphosphonate, dose, and duration of treatment were recorded, as were the treatment periods of corticosteroids and thalidomide (Table 2). We also wanted to collect data about body mass index, smoking, and alcohol use, but these data were not consistently noted in the patients' records, making this unhelpful.

Statistical analyses

The chi square test and Fisherś exact test, as appropriate, were used to investigate whether the distribution of the categorical variables differed significantly between the study and the control groups. The Wilcoxon Mann Whitney test was used for continuous variables. Unconditional logistic regression was used to estimate odds ratios (OR) and associated 95% CI. The base multivariate model included year of diagnosis, type of myeloma, age, and sex. The remaining factors such as various pharmacological treatments and diabetes were added to the model in a stepwise fashion. We used a likelihood ratio test to examine which of the factors significantly improved the model. All data analyses were processed in Stata ®/IC (version 10.0, StataCorp) software. Probabilities of less than 0.05 were accepted as significant.