



BRIEF REPORT

Effect of pamidronate infusion time on renal function in patients with multiple myeloma[☆]

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KEYWORDS

Pamidronate;
Zoledronate;
Biphosphonates;
Renal failure;
Multiple myeloma

Abstract

Introduction: Administration of biphosphonates in patients with renal failure requires a dosage adjustment.

Objectives: Analyse renal function evolution in multiple myeloma patients after reducing infusion time for 90 mg pamidronate by 2 h.

Methods: In 2007, a retrospective study was carried out on all patients who presented multiple myeloma and bone metastasis treated with pamidronate administered every 4 h. Following a review of the literature, a protocol for administering pamidronate every 2 h was created in partnership with Haematology, and a specific dose reduction framework was established for patients with baseline renal failure. Additionally, a prospective follow-up study of those patients' renal function was completed to analyse its evolution after the change in infusion time.

Results: A total of six patients received 90 mg pamidronate every 4 h. 33.32% of the patients (2/6) presented baseline renal insufficiency, and therefore needed to have the pamidronate dose adjusted according to the new protocol. Subsequently, all of them received the treatment every 2 h, and one patient (16.6%) experienced altered renal function after two treatment cycles.

Discussion: Reducing administration time for pamidronate from four to 2 h did not lead to significant variations in patients' renal function. This therapeutic practice can improve patients' quality of life by shortening their hospital stay without aggravating their renal function.

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PALABRAS CLAVE

Pamidronato;
Zoledronato;
Bifosfonatos;
Insuficiencia renal;
Meloma múltiple

Influencia del tiempo de perfusión de pamidronato en la función renal de pacientes con mieloma múltiple

Resumen

Introducción: La administración de bifosfonatos requiere un ajuste de dosis en pacientes con insuficiencia renal.

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Objetivos: Analizar la evolución de la función renal tras reducir 2 h el tiempo de infusión de pamidronato en pacientes con mieloma múltiple.

Métodos: Estudio descriptivo retrospectivo de los pacientes que presentaban mieloma múltiple y metástasis óseas tratados con pamidronato administrado en 4 h. Se elaboró un protocolo conjunto con Hematología para administrar pamidronato en 2 h, realizándose un seguimiento prospectivo de la función renal de dichos pacientes.

Resultados: Un total de 6 pacientes recibieron pamidronato en 4 h. Posteriormente, todos recibieron la administración en 2 h, y uno de ellos (16,6%) evidenció alteración de la función renal.

Discusión: La reducción en el tiempo de administración de pamidronato no mostró variaciones significativas en la función renal de los pacientes. Esta práctica terapéutica podría mejorar la calidad de vida de los pacientes, al disminuir el tiempo de estancia hospitalaria, sin empeorar su función renal.

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Introduction

Biphosphonates are the standard treatment for the prevention of skeleton-related events (SRE)^{1,2} in patients with breast cancer or multiple myeloma with bone metastasis, a complication which nearly half of these patients develop.^{3,4} Numerous studies demonstrate the effectiveness of both pamidronate (90 mg) and zoledronate (4 mg) in SRE prevention.⁵⁻⁷ Both drugs are similarly effective, but the zoledronate's advantage over pamidronate with regard to administration time (15 minutes vs two to four hours) has been reduced by the appearance of a safety warning so severe as to indicate that patients receiving zoledronate instead of pamidronate have 9.5 times more risk of developing mandibular osteonecrosis.^{8,9}

However, in addition, the biphosphonates may produce adverse effects in the kidneys. If the drugs are administered intravenously, these effects are related to the dose administered and the perfusion time, and become more pronounced as perfusion speed increases, which makes monitoring these patients' renal function necessary.^{7,9}

However, there is some debate about its infusion time, since according to its technical leaflet,¹⁰ a dose of 90 mg should be administered over two hours for patients with breast cancer, while administering 90 mg over four hours is recommended for patients with MM. However, some of the studies on which its approval for indication in MM⁷ was based, and the last update issued by the American Society of Clinical Oncology (ASCO),¹¹ recommended administering it over two hours in MM patients.

Our objective is therefore to evaluate renal toxicity in MM patients treated with pamidronate in an intravenous perfusion administered over four and two hours.

Method

Using the intranet to obtain patients' laboratory tests before they were treated with pamidronate, we performed a descriptive retrospective analysis of renal toxicity in patients with MM treated with pamidronate infused over four hours to see whether receiving the drug over four hours modified their renal function. Following a bibliography review on

pamidronate's method of administration and renal toxicity, we met with the Haematology Department to draw up a protocol so that both services would agree to use pamidronate to prevent SRE in MM patients, and to infuse it over two hours instead of the four hours employed previously.

From that moment, we carried out a prospective follow-up study of renal function for all patients prior to each treatment cycle (two-hour infusion).

With regard to adjusting the dose in the case of RF, there are no specific guidelines for reducing pamidronate dose according to kidney function. However, the ASCO proposes decreasing the standard 90 mg dose in the case of pre-existing RF in the same way as the zoledronate dose is decreased according to its technical leaflet, without specifying exact numbers. Therefore, based on the ASCO's proposal, we have determined the following dose initiation protocol (Table 1). This was also applied to patients who were already being treated with pamidronate over four hours, according to their two-hour clearance prior to administering the dose. As stated above, nephrotoxicity seems to be related to infusion time.

For patients who developed RF during the treatment without any other apparent cause, the ASCO recommended radical suppression of pamidronate. Pamidronate could then be started once again at the same initial dose (depending on baseline creatinine clearance) once creatinine levels had been re-established within a range of +10% of the baseline levels. RF was defined as a 0.5 mg/dl increase in serum creatinine in patients with a baseline serum creatinine below 1.4 mg/dl and increases of more than 1 mg/dl in patients

Table 1 Protocol for decreasing dosage and infusion time according to baseline creatinine clearance

Initial creatinine clearance (ml/h)	Recommended pamidronate dose (mg)
>60	90 in 2 h
50-60	80 in 2 h
40-50	70 in 2 h
30-39	60 in 2 h
<30	60 in 4 h

with a baseline serum creatinine above 1.4 mg/dl. This definition is used in most clinical trials, and was adopted by ASCO itself.

Given that our new administration time does not equal that stated on the technical leaflet, we drew up an informed consent form which the patient had to fill out before beginning treatment with a shorter administration time.

Measuring toxicity

In this study, we use the latest version of the common toxicity criteria issued by the WHO CTCAE version 3.0 (Common Terminology Criteria for Adverse Events)¹² (Table 2).

Results

The study was performed in a four level local hospital and included six patients (three men and three women) diagnosed with MM, with a mean age of 75 years (range: 69-82) and a mean number of 11 cycles (range: 4-16).

The data on kidney function before and after pamidronate administration, the dose received and the number of cycles of each are shown in Table 3.

Baseline renal failure was present in 33.3% of the patients (2/6), who therefore needed to have the pamidronate dose adjusted to 80 mg according to the new protocol.

Of the six patients, five presented a well-preserved kidney function throughout the entire study period, whether with the drug infused over four or two hours, and did not reach a 10% difference with respect to initial creatinine level at any time. However, in one patient the disease progressed and was the cause of death.

In the only patient who suffered a decrease in kidney function (patient 6), a decrease believed by the doctor to be caused by disease progression, clearance decreased from 57 to 31 ml/h. If we examine serum creatinine, it went from 1.41 to 2.23 (+0.82 mg/dl), and did not increase more than 1 mg/dl. Therefore, stopping treatment was theoretically not indicated. As a result, if we apply the WHO toxicity scale, only one patient experienced grade 2 toxicity, and the doctor did not consider it to be caused by the pamidronate; even so, due to the patient's general decline, it was decided to discontinue the treatment.

Discussion

Our study reveals how a close relationship between the Pharmacy and Haematology Departments allowed us to improve user satisfaction by decreasing their hospital stays without significantly affecting their kidney function. Despite there being one case of grade 2 toxicity, the doctor feels that this was not related to the treatment, and the rate is similar to data from medical literature, which estimate it at 12%¹⁴. At the same time, patients' safety increases with the prospective

Table 2 Common toxicity criteria from the World Health Organization

Adverse event	Degree of toxicity				
	1	2	3	4	5
Creatinine	<UNL-1.5 x	UNL<1.5-3.0	UNL<3.0-6.0	<UNLxULN	Death
UNL indicates upper normal limit.					

Table 3 Characteristics of included patients

Patient and no. total cycles (2 and 4 h)	Initial creatinine clearance (ml/h)				
	Baseline (before first P dose over 4 h)	Before first P dose over 2 h)	2 h infusions		
			Cycle 1	Cycle 2	Cycle 6
Patient 1: 16 cycles	60	62 (cycle 15)	64	Death	–
Patient 2: 13 cycles	97	95 (cycle 7)	97	95	97
Patient 3: 11 cycles	62	62 (cycle 5)	57	55	52
Patient 4: 11 cycles	55	55 (cycle 5)	54	54	55
Patient 5: 11 cycles	86	87 (cycle 5)	89	89	86
Patient 6: 4 cycles	53	57 (cycle 2)	36	31	–

The MDRD-4 formula¹³ was used to calculate creatinine clearance.

Patients 4 and 6 received 80 mg instead of 90 mg beginning with cycle 1 (first two-hour infusion cycle) according to the protocol shown in Table 1.

P indicates pamidronate.

follow-up of their kidney function which enables us to decrease the drug toxicity. We believe that this study serves as a starting point for potential future investigations, most of all because it establishes a specific dose reduction schedule for pamidronate in patients with pre-existing RF, and because it questions some of the current guidelines that do not seem to be based on the best available evidence. Therefore, although we use ASCO's criteria to define RF and interrupt treatment, we think that this "all or nothing" rule harbours significant limitations. The first limitation is categorically suspending a drug if it exceeds a cut-off point ($+0.5$ or $+1$ mg/dl with respect to baseline) without recommending lower doses. For our patient, who presented decreased kidney function, the recommendations indicated maintaining the dose since the definition of RF had not yet been met; it would perhaps have been more appropriate to decrease the dose to 60 mg, as shown in our initial pamidronate dosage table, instead of waiting until creatinine levels either stabilised to continue with the full dose, or rose higher at which point treatment would be stopped.

Secondly, and more interestingly, this cut-off point is based on a serum creatinine measurement and not creatinine clearance, although numerous studies^{15,16} show that there is a better correlation between creatinine clearance (calculated using any existing method) and decrease in kidney function than between serum creatinine and decreased kidney function. This is particularly true in elderly patients, and those with MM are generally elderly. One example is the study carried out in Canada with 2,781 patients, in which half of the patients presented normal serum creatinine values and decreased glomerular filtration.¹⁷

This study presents many limitations, such as the low number of patients due to the type of hospital and the prevalence, which prevents us from completing a statistical analysis. Furthermore, we cannot submit a validated quality of life questionnaire that could confirm the conclusion that patient satisfaction increases when a four-hour drug infusion is replaced with a two-hour infusion. It was not possible to be measured, which, in addition to the low number of cases at our disposal lead us not to consider it. Even so, we believe that interaction with haematology departments in particular and all other services in general is fundamental for pharmacy development and enables rational, safe medication use.

Conflict of interest

The authors affirm that they have no conflicts of interest.

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