Original Article

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Internal Medicine Section

Study of Adverse Effect Profile of Parenteral Zoledronic Acid in Female Patients with Osteoporosis

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ABSTRACT

Introduction: Osteoporosis is still a under recognized entity in the population. Osteoporosis-related fractures can be prevented if people at risk can be screened, diagnosed and treated early. Bisphosphonates remain the mainstay of osteoporosis treatment as they have multimodal action. Oral bisphosphonate therapy has, significant gastrointestinal side effects leading to noncompliance. Of late parenteral Zoledronic Acid is being used as once or twice yearly infusion for the treatment of osteoporosis.

Aim: Our article studies the side effect profile and tolerability of parenteral Zoledronic Acid, one of the most potent bisphosphonate used in clinical practice in patients with osteoporosis.

Materials and Methods: This study was done in KMC hospitals where 49 patients diagnosed with osteoporosis were included for the study. After obtaining a written informed consent each patient received one infusion of 5 mg Zoledronic Acid as per standard treatment protocol. Patient was monitored for clinical improvement and development of any adverse effects.

Conclusion: In our study all subjects reported significant pain relief after infusion of Zoledronic Acid. Zoledronic Acid had very few serious adverse effects that can be prevented through pre-infusion screening, maintaining good hydration and careful patient monitoring. In our population the patients only experienced mild symptoms of pyrexia, arthralgia myalgia and influenza like symptoms which resolved with symptomatic treatment.

Keywords: Bisphosphonates, Complications, Systemic bone disease

INTRODUCTION

Osteoporosis is a systemic bone disease characterized by low bone mass and micro architectural deterioration of bone tissue that progressively weakens bone density and alters the architecture within the bone. It is proven to be a major public health concern and is debilitating to the elderly population. Although the disease affects both sexes, it predominantly affects post-menopausal women with higher parity. If the disease is untreated it can lead to osteoporotic fractures in the hip or spine. Elderly people with these fractures require major surgeries and extensive physiotherapy to become ambulatory once again. Existing co-morbidities such as; hypertension, diabetes mellitus, obesity and hypothyroidism also complicate the treatment course due to the use of poly-pharmacy and their interactions.

Drugs approved for treatment of osteoporosis are bisphosphonates alendronate, residronate and zoledronic acid, the anti-resorptive drug denosumab, paratharmone analogue teriparatide, and strontium ranelate which is anti resorptive. Many studies have come which have proved the improvement in the bone mineral density and reduction of fractures after the use of these agents. It can reduce the quality of life and increase the morbidity and mortality among the vulnerable aging population [1-4].

Since the percentage of elderly population is rising, osteoporosis and its consequences emerge out as a significant economic burden to the society. Guidelines have been formulated for the prevention and treatment of this growing problem.

The complications, spinal compression fractures and hip fractures, are easier to prevent medically than treat surgically. Different treatment modalities have been used to try to effectively treat this disease: Vitamin D supplementation, alendronate, hormone replacement therapy, selective estrogen replacement therapy and calcitonin. However, these treatments have been inadequate because patients either forget their scheduled doses, or refuse to take their medication after symptoms have abated.

Bisphosphonates (BPs) have emerged as the first-line therapy for the prevention and treatment of osteoporosis and studies have shown that use of bisphosphonates reduce markers of bone turnover, significantly increase bone density, and decrease the risk of hip, vertebral, and other fractures. It has been used for the treatment of Paget's disease, bone metastased, hypercalcaemia secondary to tumours, and osteoporosis [5]. Zoledronic Acid used as a 5mg once yearly infusion has shown decrease bone turnover and increase bone mineral density over time and significantly reduce the risk of spinal and hip fractures over time in various studies. The HORIZON trial [6] has shown zoledronic acid to be efficacious in reducing vertebral, hip and other fractures.

AIM

Zoledronic Acid 5mg single infusion has been shown effective in decreasing bone turnover and increasing bone density for 12 months. It has been proven to have the highest affinity to bone surfaces, highest anti-resorptive activity, and maximum inhibition activity of farnesyl diphosphate synthesis. This drug has been proven to be efficacious with minimal adverse effects. The aim of this study is to analyze the adverse effect profile of zoledronic acid (i.e. frequency and type of adverse reaction, duration of reaction, management of the adverse reaction) in the South Indian Population.

MATERIALS AND METHODS

This prospective observational study was conducted in Kasturba Medical College Teaching Hospitals from February 2014 to June 2015. Forty nine female patients with symptomatic osteoporosis were included in the study. Male patients, patients with renal failure, patients with severe cardiac or pulmonary dysfunction, cirrhosis of liver and patients who did not give informed consent were excluded from the study. No controls were included in the study. Written informed consent was obtained from all the subjects. Patients were characterized based upon their age, sex, registered pain

scale (analogue scale) and indication for infusion. A comprehensive medical physical examination was always undertaken prior focusing on; creatinine levels, electrocardiogram, vitamin D levels, haemoglobin and renal function tests. A pre-infusion lumbar-sacral spinal x-ray, anterior and lateral views, was also taken for future comparison during follow-up examinations. The patients were hospitalized for a minimum of one day if their symptoms abated before 24 hours or asked to remain in the hospital until their post infusion symptoms were relieved. The dose of zoledronic acid was 5mg in 100ml of normal saline over a period ranging from 45 minutes to 1 hour. Adequate fluid hydration was maintained. The patients were carefully monitored for the commonly listed adverse effects: myalgia, arthralgia, influenza-like symptoms, atrial fibrillation, stroke, rising creatinine, or jaw necrosis.

RESULTS

Forty nine patients were included in the study with proven osteoporosis. Youngest patient in our study was 51-year-old while oldest was 88-year-old. Majority of our patients were in 61-70 years group [Table/Fig-1].

Co-morbidities in the study group included diabetes (40%), hypertension (40%), dyslipidaemia (52%) and ischemic heart disease (6%).

Seventy seven percent of patients experienced infusion related symptoms, pyrexia and myalgia being the commonest, influenza like symptoms i.e. fever, myalgia, arthralgia and headache were seen only in six patients [Table/Fig-2]. Fever lasted for at longest 48 hours after which the same dissipated on its own [Table/Fig-3]. The patients that experienced symptoms longer, although medically fit, were on multiple medications concurrently.

The blood pressure remained stable during the infusion and during the hospital stay. There was no significant effect on glycaemic control of the subjects.

DISCUSSION

All the patients received intravenous zoledronic acid infusion 100 ml over 45 minutes to 1 hour. They also received adequate hydration before and after the infusion. Patients were observed for clinical improvement and appearance of any adverse effects.

It is clear that mild symptoms of pyrexia, myalgia, arthralgia and influenza- like syndrome were the most common adverse effects observed in our sample size. Serious side effects such as atrial fibrillation, sudden cardiac arrest and stroke were not recorded

Age group	Number	Percentage
51-60 y	4	8.2%
61-70y	27	55.1%
71-80y	16	32.6%
>80y	2	4.1%

[Table/Fig-1]: Patient Characteristics

Symptom	Number of Patients	Percentage
Pyrexia	38	77.5%
Myalgia	32	65.3%
Headache	18	36.7%
Influenza-like Symptoms (Fever, Arthralgia, Myalgia, Headache)	06	12.2%
Arthralgia	06	12.2%
Renal toxicity	0	0%
Osteonecrosis of jaw	0	0%
Atrial fibrillation	0	0%
Atypical femoral fractures	0	0%

[Table/Fig-2]: Frequency of adverse effects

Duration of Symptoms (Fever, Arthralgia, Myalgia, Headache)	Number of Patients
< 24hours	12
2 Days	22
3 Days	6

[Table/Fig-3]: Duration of adverse effects.

at all, even with existing co-morbidities such as diabetes mellitus, hypertension, or chronic obstructive pulmonary disease. This may be due to the exclusion of patients that were deemed medically unfit for infusion. Any renal complications, acute renal failure or interstitial nephritis were not seen in our cohort as these have been associated with an infusion period of less than 15 minutes.

Febrile reaction: Parenteral zoledronic acid is most commonly associated with adverse effects of fever, myalgia, fatigue and influenza-like symptoms [7]. In our study these symptoms were seen in 78% of the patients. The symptoms started within 16 hours of the infusion and relieved completely within three days of drug infusion. This acute-phase reaction is believed to be mediated by the release of inflammatory cytokines like tumour necrosis factor alpha and interleukin 6 [8]. Paracetamol 500mg given three to four times daily for two days following zoledronic acid abated these symptoms in our study. Same strategy was tried in other studies also [9].

Renal toxicity: Acute kidney injury has been reported with bisphosphonates. The mechanism proposed are pre-renal azotaemia, drug induced acute tubular necrosis [10]. The patients who are at high risk to develop renal toxicity include those with pre-existing kidney disease, elderly patients, patients with other co-morbidities and on other medications which are nephrotoxic especially diuretics. Also, hydration status of the patients during the infusion plays an important role [11]. In our study though we had most patients with diabetes and hypertension, no renal toxicity was observed upto one week after infusion of zoledronic acid. The renal toxicity begins shortly begins after the infusion. Studies have shown that the maximum rise of serum creatinine occurred at 9-11 days after infusion [12]. Our patients were monitored with renal function tests on day 2, day 7 and day 28. Renal failure secondary to tubular necrosis or prerenal cause has complete recovery. According to studies done by Berenson and Hirschberg kidney injury is more likely with rapid infusions (<15 min) [13].

Various studies depict the nephrotoxicity after infusion of zoledronic acid is low, ranging from 0–9%. However many large studies have shown no difference in nephrotoxicity between zoledronic acid versus placebo [14]. Pre-infusion evaluation of renal function (i.e. serum creatinine assessment) should be done for all patients. Zoledronic acid is contraindicated in patients with creatinine clearance (CrCl) <35 ml/min. In patients with chronic kidney disease oral Ibadronate is found safer.

Rarer Complications

Osteonecrosis of the jaw: Osteonecrosis of the jaw (ONJ) is though a rare but a devastating complication that follows infusion of bisphosphonates [15]. Pre-existing periodontal disease, alcohol and tobacco use, concomitant use of steroids are risk factors for the development of ONJ. Bisphosphonates decrease bone remodeling due to inhibition of osteoclast, hence making the bone acellular and avascular [16]. Good oral hygiene practices have to reinforced in patients

Atrial fibrillation: In the HORIZON-PFT trial the incidence of Atrial Fibrillation (AF) was 1.3% versus 0.5% in those receiving placebo [6]. However, studies later which looked at a correlation between zoledronate therapy and AF had conflicting results [17]. In our study we did not find any cardiac dysrhythmias upto 28 day follow-up.

Atypical femoral fractures: Atypical femoral fractures have distinctive features like location in the sub trochanteric region and

shaft of femur, transverse or short oblique orientation, no associated trauma, a medial spike when the fracture is complete, and absence of comminution [18]. Secondary analysis HORIZON-PFT showed a low rate of atypical femoral fractures (2.3 per 10,000 patient-years), [6]. In our study we did not find any such events. However, more prolonged monitoring needed to looks for the same.

Also, in our study there were no infusion site reactions like erythema, pruritis or pain, no symptoms or signs of symptomatic hypocalcaemia.

In our observational study, zoledronic acid is a drug with very few serious adverse effects that can be prevented through pre-infusion screening, and careful patient monitoring. In our population the patients only experienced mild symptoms of pyrexia, arthralgia and myalgia which completely resolved with symptomatic treatment. Also, head to head comparison of zolendronate with newer therapies like denosumab has not found any major adverse effects that could deter the use of zolendronate [19].

LIMITATION

The limitations of our study was that we had a small sample size, study was limited to females with osteoporosis only, it was a single center study, co-medication drug analysis and monitoring of biochemical markers of bone changes were not done. The effect on serum calcium has not been analysed in this study. However, in the study sample, zolendronic acid infusion was well tolerated.

CONCLUSION

Parenteral Zoledronic Acid is an upcoming treatment option for osteoporosis. Though this treatment has been well established, the routine usage of parenteral zoledronic acid has been limited because of the cost and fear of adverse drug reaction like nephrotoxicity and cardiotoxicity. According to our study the drug is well tolerated with common but minimal self-limiting adverse reactions. However, stringent pre-infusion screening of co-morbidities especially creatinine clearance has to be done. Also, zoledronic acid given as an infusion of 45-60 minutes has been found safe according to our study.

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