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CLINICAL SAFETY OF ZOLINDRONIC ACID IN OSTEOPOROSIS: A DESCRIPTIVE CROSS SECTIONAL STUDY

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ABSTRACT All bisphosphonates incuding zolindronic acid improve BMD in ostreoporosis and decrease risk of spine, hip and other non vertebral fractures significantly. The purpose of this study was to assess safety of zolindronic acid in osteoporosis in kashmiri population. This was a descriptive cross sectional study conducted in teritiary care hospital of kashmir valley. 77 patients were enrolled in the study with documented osteoporosis who received 5 mg zolindronic acid infusion with adequate prior hydration. All pts were followed for immediate adverse effects following infusion. Mild symptoms did occur in the form of fever, arthralgias, myalgias, muscle cramps and nausea. Majority of the symptoms subsided within two to three days of infusion. Our observations conclude that zolindronic acid is very much safe and fairly tolerated drug in osteoporosis.

KEYWORDS : Zolindronic acid, Osteoporosis, Bisphosphonates.

INTRODUCTION

Bisphosphonates define a class of drugs widely indicated since 1990s to treat osteoporosis in men and women. Their effectiveness in treating osteoporosis and other conditions is related to their ability to inhibit bone resorption [1,2,3].

FDA approved indications of bisphosphonates are:

- Post menopausal osteoporosis
- Osteoporosis in men
- Glucocorticoid induced osteoporosis
- Hypercalcemia of malignancy
- Paget disease of bone
- Malignancies with metastasis to bone
- Non fda approved indications are
- Osteogenesis imperfecta in children and adults
- Prevention of glucocorticoid induced osteoporosis

Bisphosphonates are structurally similar to native pyropho sphates and are divided inti 2 groups Nitrogen containing and Non nitrogen containing bisphosphonates:

Nitrogen containing are Zolindronic acid, alendronate, risedronate, ibandronateand pamidronate. Non nitrogen conyaining are etidronayte, clodronate and toludronate. All bisphosphonates inhibit bone resorption by attaching to hydroxypatite binding sites on the bone particularly in area of active resorption. As osteoclasts resorp bone the bisphosphonate embedded in the bone is released and impairs the osteoclasts ability to continue bone resorption [2,4,5]. Nitrogen containing bisphosphonates are much more potent antiresorptive than Non nitrogen containing bisphosphonates. Also Non nitrogen containing bisphosphonates are found to have high potential to inhibit bone mineralization and can cause osteomalacia.For this reason they are no longer in broad based use. Alendronate reduces vertebral fracture risk by about 50%, hip fractures, and other nonvertebral fractures by about 30% [6,7]. Risedronate reduces vertebral and nonvertebral fractures by about 40% [8]. Zolindronic acid reduces vertebral fracture risk by 70% and other non vertebral risk by 35% [9,10]. It is administered as 4 mg/5mg IV infusion over 15 to 30 minutes yearly. Bisphosphonates are usually well tolerated. Common adverse effects include GI intolerance and acute phase reactions. Acute phase reaction generally described as fever, myalgias, fatigue chills and arthalgias. Symptoms are typically transitory resolving within 3 to 7 days of infusion and can be reduced by common antipyretics and antihistaminics.

MATERIALS AND METHODS

This was a cross sectional study conducted in our tertiary care hospital. 77 patients were included in the study who had documented Osteoporosis on dual energy X-ray absorptiometry. The patients were given intravenous infusion of 5mg Zolindronic acid.

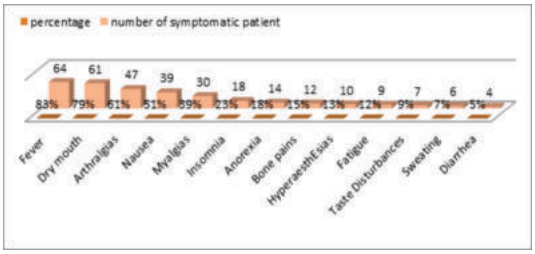
RESULTS

A total of 77 patients were included in our study. 73 females and 4 males. Predominant age group was between 51-60 years (n=34) followed by 61-70 years (n=22), 41-50 (n=17), 71-80 (n=2) and >80 years (n=2).

The co morbidities in our patients were in order as postmenopausal (n=58), hypertension (n=41), Hypothyroidism (n=24), Diabetes mellitus 15 (n=15), corticosteroid intake (n=5), COPD (n=4), smokers (n=4), hyperparathyroidism (n=4), Rheumatoid arthritis (n=1).

Table 1: depicts adverse effects reported in our patients in order of decreasing frequency.

Symptoms	Number of patients	Percentage
Fever	64	83
Dry mouth	61	79
Arthralgias	4	61
Nausea	9	51
Myalgias	30	39
nsomnia	18	23
Anorexia	14	18
Bone pains	12	15
Hyperaesthsias	10	13
Fatigue	9	12
Taste Disturbances	7	9
Sweating	6	7
Diarrhea	4	5



Graph 1: Showing number and percentage of adverse reactions respectively.

Table 2: Depicting average time of onset and duration of adverse reaction respectively.

Adverse drug reactions	Average time of onset (Hours)	Average duration (Days)
Fever	12	2 ±1
Dry mouth	8	3 ±1

Arthralgias	24	7 ±2
Nausea	6	3 ±1
Myalgias	24	6 ±2
Insomnia	12	3 ±1
Anorexia	8	5 ±2
Bone pains	24	5 ±2
Hyperaesthsias	24	2 ±1
Fatigue	12	6 ±2
Taste Disturbances	12	3 ±1
Sweating	12	2 ±1
Diarrhea	24	2 ±1

DISCUSSION

Seventy seven subjects were enrolled in our study with documented osteoporosis. Youngest patient in our study was 41 year old and oldest being 85 years of age. Most of our subjects were in 61-70 year age group (28%). Comorbities in our study patients included postmenopausal (75%), hypertension (53%), hypothyroidism (31%), diabetes mellitus (19%), corticosteroid intake (6%), COPD (5%), smokers (5%), hyperparathyroidism (5%) and rheumatoid arthritis (1.2%). All subjects in our study received zolindronic acid 5 mg intravenous infusion over 15 to 30 minutes with adequate prior hydration. All patients enrolled in the study were followed closely for appearance of adverse reactions to document safety of zolindronic acid.

The commonest adverse reaction observed was fever seen in 83% of the patients. Most of the patients became febrile within 12 hours of infusion and it subsided in 2 to 3 days with paracetamol. Fever has been reported in 21% of patients receiving zolindronic acid for metastatic prostatic cancer [12]. 55% females with breast cancer and bone metastasis who received zolindronic acid experienced fever compared to 33% in the placebo arm [13]. In a phase III study of patients with breast cancer or myeloma, the incidences of fever and myalgia from zoledronic acid were equivalent to those from pamidronate—over 30% of patients [14,15].Typically occuring within 48 h of infusion, fever is usually low-grade, though occasionally associated with rigors [16–19]. Accompanying bone pain has also been reported in over half of the patients [14, 15]. In our reference study 15% of patients experienced bone pains 12 to 24 hours after infusion. The pain, however, may occur without fever and usually starts about 12 h after infusion, commonly felt in spines, ribs, and lower limbs, not necessarily near the site of metastases. Severe pain limiting daily activity and lasting several days has been described uniquely among patients with cystic fibrosis receiving pamidronate [20]. Arthralgias and myalgias wre reported in 61% and 39% respectively in our study. For the elderly, these musculoskeletal symptoms may cause an unsteady gait; therefore, fall precautions should be exercised [21]. Nausea and anorexia was observed 51% and 18% of our study patients respectively. Clinical trials on zolindronic acid suggest that almost 1 in 3 patients experience such adverse effects with the first infusion and incidence decreases significantly with subsequent infusions [22]. other less common events reported were insomnia 23%,hyperaesthesias 13%,fatigue 12%,taste disturbances 9% and diarrhea in 5% of the patients. These inflammatory reactions appear to be the result of an increase in cytokine release from macrophages and monocytes. The reactions typically are self-limited and resolve completely within 24 to 48 h. Supportive and symptomatic management with NSAIDs , acetaminophen and antihistaminics is sufficient. Dose reduction for the first treatment or a test dose does not appear to help reduce the incidence or severity of reactions during the treatment, but pre-medication with acetaminophen or ibuprofen may help [15].

CONCLUSION

Zolindronic acid and other bisphosphonates are of paradigm importance in the management of osteoporosis. Minor adverse reactions are expected with majority of formulations especially those with intravenous route of administration. These acute phase reactions are usually self limiting and fairly tolerated by the patients with some requiring antipyretics and antihistaminics for symptomatic relief.

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