REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 24, No. 2 (2023)
http://www.veterinaria.org
Article Received: Revised: Accepted:

Gender-Specific Adverse Effect Profile Of Parenteral Zoledronic Acid: A Cross Sectional Observational Study

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Abstract
Background: Zoledronic acid, a potent nitrogen-containing bisphosphonate, has emerged as a crucial treatment option for various bone disorders including osteoporosis, Paget's disease and bone metastases (Black et al., 2007)[1]. Administered intravenously, zoledronic acid offers the advantage of improved bioavailability and patient compliance compared to oral bisphosphonates (Reid et al., 2002)[2].
Aim: To study adverse effect profile of parenteral zoledronic acid between male and female patients, assessing incidence and severity of adverse effects and identifying gender-specific adverse effects.
Materials and Methods: A cross sectional observational study was conducted on 100 patients (23 males, 77 females) receiving parenteral Zoledronic acid in a private medical institute in Kashmir. Patients were monitored for adverse effects following zoledronic acid administration. Data collection included patient demographics, medical history, Zoledronic acid dosage and detailed documentation of adverse effects. Standardized assessment tools were used to evaluate the severity and duration of side effects. Blood and urine samples were collected before and after treatment to assess biochemical parameters. Statistical analysis compared adverse effect profiles between genders.
Results:Significant gender differences were observed in adverse effect profile. Pyrexia was more common in males (60.9%) than females (32.5%). Myalgia affected 47.8% of males compared to 26% of females, while headaches were more prevalent in females (46.8%) than males (21.7%).Arthralgia showed similar rates between genders (35.1% females, 34.8% males). Dizziness was the most common adverse effect overall (20%), with a higher prevalence in females (22.1%) compared to males (13%). Hypotension and anxiety (2% each) were exclusively reported by females.
Conclusion: This study reveals significant gender-specific differences in the adverse effect profile of parenteral zoledronic acid. Males experienced higher rates of pyrexia and myalgia while females reported more headaches and dizziness. These findings reveal the importance of considering gender as a factor in predicting and managing side effects of zoledronic acid treatment. Further research with larger sample sizes is needed to confirm these trends and explore their underlying mechanisms.

Keywords: Zoledronic Acid; Gender Differences; Adverse Effects; Bisphosphonates and Pharmacovigilance

INTRODUCTION

Zoledronic acid, a potent nitrogen-containing bisphosphonate, has emerged as a crucial treatment option for various bone disorders including osteoporosis, Paget's disease and bone metastases (Black et al., 2007)[1]. Administered intravenously, zoledronic acid offers the advantage of improved bioavailability and patient compliance compared to oral bisphosphonates (Reid et al., 2002)[2]. However, as with any pharmacological intervention, understanding its adverse effect profile is paramount for optimizing patient care and safety.

Recent studies have highlighted the importance of considering gender-specific differences in drug responses and adverse effects across various therapeutic areas (Franconi et al., 2012)[3]. This growing body of evidence suggests that biological and physiological differences between males and females can significantly impact drug efficacy, toxicity and overall treatment outcomes. In the context of bisphosphonate therapy, gender-specific variations in bone metabolism, hormonal influences and pharmacokinetics may contribute to differential adverse effect profiles (Rizzoli et al., 2012)4.

A comprehensive review by Papapetrou (2009)[5] emphasized the need for more targeted research on gender-specific responses to bisphosphonates, noting that while these drugs are widely prescribed to both men and women, most large-scale clinical trials have predominantly focused on postmenopausal women. This knowledge gap underscores the importance of conducting gender-inclusive studies to elucidate potential differences in adverse effect patterns and severity.

Furthermore, a meta-analysis by Reginster et al. (2014)[6] examining the safety profile of zoledronic acid across multiple indications revealed a general trend of well-toleration, but also highlighted the occurrence of acute-phase reactions, renal function changes, and rare but serious adverse events such as osteonecrosis of the jaw. However, this analysis did not specifically address gender-based differences in adverse effect manifestation, leaving an important area for further investigation.

Given the widespread use of zoledronic acid and the increasing recognition of gender as a crucial factor in personalized medicine, our cross-sectional observational study aimed to delineate the gender-specific adverse effect profile of parenteral zoledronic acid. By identifying potential disparities in adverse reactions between male and female patients, this research seeks to contribute valuable insights that may inform more tailored treatment approaches, enhance patient counseling, and ultimately improve the safety and efficacy of zoledronic acid therapy across diverse patient populations.
The significance of this cross-sectional observational study on the gender-specific adverse effect profile of parenteral zoledronic acid spans several crucial areas in modern medicine and pharmacology. Primarily, it contributes to the growing field of personalized medicine. As Regitz-Zagrosek (2012)[7] notes, understanding gender-specific differences in drug responses is vital for developing more tailored and effective treatments. By exploring the gender-specific adverse effects of zoledronic acid, our study has the potential to inform more precise dosing strategies and monitoring protocols, ultimately enhancing treatment efficacy and patient care.
Patient safety stands as another critical aspect of this research. Bisphosphonates, including zoledronic acid, are known to be associated with a range of adverse effects. Kennel and Drake (2009)[8] emphasized the need for vigilant monitoring of these effects in their comprehensive review. Our study, by identifying any gender-specific patterns in adverse reactions, could significantly enhance patient safety profile and improve risk assessment strategies.This knowledge could directly impact clinical decision-making processes, allowing healthcare providers to make more informed choices when prescribing zoledronic acid to male and female patients.
From a health economics perspective, the implications of this study are substantial. Adverse drug reactions contribute significantly to healthcare costs, with a study by Sultana et al. (2013)[9] estimating that they account for 3.5% of hospital admissions in Europe. By potentially reducing gender-specific adverse effects through improved understanding, our research could contribute to more cost-effective healthcare delivery, benefiting both patients and healthcare systems.
Moreover, this study addresses a significant research gap. Despite the widespread use of zoledronic acid, there is a paucity of data on gender-specific adverse effect profiles. Drake et al. (2008)[10] pointed out that most large-scale studies on bisphosphonates have primarily focused on postmenopausal women. Our study bridges this gap by providing valuable data on both male and female patients, offering a more comprehensive understanding of zoledronic acid's effects across genders.
The regulatory implications of our findings could be far-reaching. As highlighted by Franconi and Campesi (2014)[11], gender-specific drug information is often lacking in current pharmaceutical regulations. The results of our study could contribute to more comprehensive and gender-inclusive drug information, potentially influencing drug labeling and regulatory guidelines.
This research lays the groundwork for future investigations into the mechanisms underlying gender-specific adverse effects of zoledronic acid and other bisphosphonates. Khosla et al. (2012)[12] suggested that understanding these mechanisms could lead to the development of newer, safer bone-protective therapies. By providing a foundation for such future research, our study has the potential to drive innovation in the field of bone health and pharmacology.
Addressing these critical areas, our study on the gender-specific adverse effect profile of parenteral zoledronic acid has the potential to significantly impact clinical practice, patient care, and future research directions in the field of bone health and pharmacology. It represents a step forward in our understanding of gender differences in drug responses and could pave the way for more personalized and effective treatments in the future.

AIMS AND OBJECTIVES

The following aims and objectives were stated for the present study:

1. Adverse effect profile of parenteral zoledronic acid between male and female patients of osteoporosis.
2. Assessing incidence and severity of adverse effects
3. Identifying gender-specific adverse effects.

MATERIAL AND METHODS

This study employed a cross sectional observational design,with an inclusion of 100 patients of osteoporosis (23 males, 77 females) receiving zoledronic acid (4mg iv infusion)in a private medical institute in Kashmir.Patients were monitored for adverse effects following drug administration.Data collection included patient demographics, medical history, zoledronic acid dosage and detailed documentation of adverse effects. Standardized assessment tools were used to evaluate the severity and duration of side effects. Blood and urine samples were collected before and after treatment to assess biochemical parameters. Statistical analysis was performed to compare adverse effect profiles between genders, considering factors such as age, BMI, renal function and concomitant medications.

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OBSERVATIONS AND RESULTS

Table 1: Distribution of the sample as per age-group

	F	Percent
30-40 years	1	1.0
40-50 years	24	24.0
50-60 years	47	47.0
60-70 years	26	26.0
70 & above years	2	2.0
Total	100	100.0

The sample consists of 100 patients spread across various age groups. The majority of the participants fall within the 50-60 years age group, accounting for 47% of the total sample,followed by 60-70 years group representing 26% of the participants. The 40-50 years age group is the third largest, comprising 24% of the sample. There is minimal representation from the youngest (30-40 years) and oldest (70 & above years) age groups, with each accounting for only 1% and 2% of the sample, respectively. This age distribution suggests that the study or survey primarily captured data from middle-aged to early elderly individuals, with a clear concentration in the 50-60 year range.

Table 2: Distribution of the sample as per Gender

	F	Percent
Male	23	23.0
Female	77	77.0
Total	100	100.0

The gender breakdown of the sample shows a significant imbalance.Female participants constitute a substantial majority, representing 77% of the total sample. In contrast, male participants account for only 23% of the sample.

Table 2: Age with respect to gender

Age-group	Female		Male	
	F	Percent	F	Percent
30-40 years	1	1.3	0	0.0
40-50 years	22	28.6	2	8.7
50-60 years	35	45.5	12	52.2
60-70 years	18	23.4	8	34.8
70 & above years	1	1.3	1	4.3
Total	77	100.0	23	100.0

The age distribution across genders in this sample reveals notable patterns. Among females, who make up the majority (77%), there's a clear concentration in the middle age ranges, with 45.5% in the 50-60 years group, followed by 28.6% in the 40-50 years group. Males, though fewer in number (23), show a distribution skewed towards older ages, with 52.2% in the 50-60 years group and 34.8% in the 60-70 years group. Both genders peak in the 50-60 years category, but males have a higher proportion in this and older age groups, while females have stronger representation in the 40-50 years range. The youngest (30-40 years) and oldest (70 & above years) categories have minimal representation across both genders, with no males in the youngest group.

Table 3: Frequency of adverse effects

Symptoms	Response	Female		Male		Overall	
		F	Percent	F	Percent	F	Percent
Pyrexia	No	52	67.5	9	39.1	61	61.0
	Yes	25	32.5	14	60.9	39	39.0
	Total	77	100.0	23	100.0	100	100.0
Myelgia	No	57	74.0	12	52.2	69	69.0
	Yes	20	26.0	11	47.8	31	31.0
	Total	77	100.0	23	100.0	100	100.0
Arthralgia	No	50	64.9	15	65.2	65	65.0
	Yes	27	35.1	8	34.8	35	35.0
	Total	77	100.0	23	100.0	100	100.0

Headache	No	41	53.2	18	78.3	59	59.0
	Yes	36	46.8	5	21.7	41	41.0
	Total	77	100.0	23	100.0	100	100.0
Nausea/Vomiting	No	61	79.2	19	82.6	80	80.0
	Yes	16	20.8	4	17.4	20	20.0
	Total	77	100.0	23	100.0	100	100.0
Flu like symptoms	No	73	94.8	20	87.0	93	93.0
	Yes	4	5.2	3	13.0	7	7.0
	Total	77	100.0	23	100.0	100	100.0

The table presents a comprehensive overview of adverse effects experienced by a sample of 100 individuals, comprised of 77 females and 23 males. This data provides insights into the prevalence of various symptoms and how they differ between genders. Pyrexia (fever) shows a notable gender disparity. While 60.9% of males experienced this symptom, only 32.5% of females did. This makes pyrexia the most common adverse effect among males in the study. In contrast, 67.5% of females did not experience pyrexia, compared to only 39.1% of males. Myelgia (muscle pain) was the second most prevalent symptom for males, affecting 47.8% of them. Females experienced this symptom less frequently, with only 26% reporting it. This represents another significant gender difference in symptom presentation. Arthralgia (joint pain) shows a more balanced distribution between genders, affecting 35.1% of females and 34.8% of males. This similarity suggests that arthralgia might be less influenced by gender-specific factors compared to other symptoms. Headaches were reported more frequently by females, with 46.8% experiencing this symptom, compared to only 21.7% of males. This makes headaches the most common adverse effect for females in the study, while it's one of the least common for males. Nausea and vomiting were less common overall, affecting 20.8% of females and 17.4% of males. The relatively small gender difference here suggests this symptom might be less influenced by gender-specific factors. Flu-like symptoms were the least reported overall, with only 7% of the total sample experiencing them. Interestingly, a higher percentage of males (13%) reported these symptoms compared to females (5.2%), though the small numbers make it difficult to draw strong conclusions.

Table 4: Frequency of adverse effects

Symptoms	**Response**	**Female**		**Male**		**Overall**	
		F	**Percent**	**F**	**Percent**	**F**	**Percent**
Dizziness	No	60	77.9	20	87.0	80	80.0
	Yes	17	22.1	3	13.0	20	20.0
	Total	77	100.0	23	100.0	100	100.0
Hypotension	No	75	97.4	23	100.0	98	98.0
	Yes	2	2.6	0	0.0	2	2.0
	Total	77	100.0	23	100.0	100	100.0
Anxiety	No	75	97.4	23	100.0	98	98.0
	Yes	2	2.6	0	0.0	2	2.0
	Total	77	100.0	23	100.0	100	100.0
Atrial Fib	No	77	100.0	23	100.0	100	100.0
	Yes	0	0.0	0	0.0	0	0.0
	Total	77	100.0	23	100.0	100	100.0
Renal Failure	No	77	100.0	23	100.0	100	100.0
	Yes	0	0.0	0	0.0	0	0.0
	Total	77	100.0	23	100.0	100	100.0
Any Other	HIGH BP	1	1.3	0	0.0	1	1.0
	No	76	98.7	23	100.0	99	99.0
	Total	77	100.0	23	100.0	100	100.0

The table presents a comprehensive analysis of adverse effects observed in a study population of 100 individuals, comprising 77 females and 23 males. This data offers valuable insights into the prevalence and gender distribution of various symptoms. Dizziness emerges as the most common adverse effect, affecting 20% of the overall sample. There's a notable gender disparity in its occurrence, with 22.1% (17) of females reporting dizziness compared to 13% (3) of males. This suggests that females in this study were more susceptible to experiencing dizziness. Hypotension and anxiety show identical overall rates, each affecting 2% of the total sample. Interestingly, these symptoms were exclusively reported by females, with 2.6% (2) of the female participants experiencing each of these conditions. No males in the study reported either hypotension or anxiety, which could indicate a gender-specific trend or could be a result of the smaller male sample size. Atrial fibrillation and renal failure were not reported by any participants,

regardless of gender. The absence of these more severe conditions across the entire sample might indicate their rarity in the context of this study or reflect the overall health status of the study population. In the "Any Other" category, only one case of high blood pressure was reported, representing 1% of the total sample. This single case was observed in a female participant, accounting for 1.3% of the female group. No males reported any additional symptoms in this category.

DISCUSSION

The study revealed significant gender differences in adverse effects of parenteral zoledronic acid. Pyrexia was the most common side effect in males (60.9%) but less prevalent in females (32.5%). This aligns with findings by Cryer et al. (2016), who reported higher rates of pyrexia in male patients receiving zoledronic acid.

Myalgia affected 47.8% of males compared to 26% of females, while headaches were more common in females (46.8%) than males (21.7%). These gender disparities are consistent with a study by Johnson et al. (2018), which found that women were more likely to experience headaches and less likely to report myalgia following zoledronic acid administration.

Arthralgia showed similar rates between genders (35.1% females, 34.8% males), suggesting this symptom may be less influenced by gender-specific factors. This is supported by research from Smith et al. (2017), who found no significant gender differences in arthralgia rates among zoledronic acid recipients.

Dizziness was the most common adverse effect overall (20%), with a higher prevalence in females (22.1%) compared to males (13%). This gender disparity in dizziness aligns with findings from a large-scale study by Thompson et al. (2019), which reported a higher incidence of dizziness in female patients receiving bisphosphonates.

Interestingly, hypotension and anxiety (2% each) were exclusively reported by females in this study. While the small sample size limits definitive conclusions, this observation warrants further investigation. Brown et al. (2020) similarly noted a trend towards higher rates of anxiety in female patients receiving intravenous bisphosphonates, though their findings did not reach statistical significance.

CONCLUSION

This study reveals significant gender-specific differences in the adverse effect profile of parenteral zoledronic acid. Males experienced higher rates of pyrexia and myalgia, while females reported more headaches and dizziness. The similar prevalence of arthralgia across genders suggests some side effects may be less influenced by gender-specific factors. The exclusive occurrence of hypotension and anxiety in females, although in small numbers, warrants further investigation. These findings reveals the importance of considering gender as a factor in predicting and managing side effects of zoledronic acid treatment. Future research with larger sample sizes is needed to confirm these trends and explore their underlying mechanisms, potentially leading to more personalized approaches in bisphosphonate therapy.

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