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Case Report / Olgu Sunumu

Stroke following zoledronic acid infusion: effect of treatment or coincidence?

Zoledronik asit infüzyonu sonrası gelişen inme: Tedavinin yan etkisi mi tesadüf mü?

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ABSTRACT

Zoledronic acid is a parenteral aminobisphosphonate which is administered annually in the treatment of osteoporosis. It is an alternative to oral bisphosphonates, particularly in elderly patients with multiple comorbidities, because of its efficacy and intravenous route of administration. The most common side effects include post-dose reaction, renal dysfunction, and mild to moderate hypocalcemia. In this article, we report a 67-year-old male case of stroke during osteoporosis treatment of zoledronic acid within a day. Stroke development may be a coincidence, as the patient had stroke history and other risk factors for recurrent stroke. This case report highlights the possibility of zoledronic acid infusion-induced stroke with unusual side effects in geriatric patients.

Keywords: Osteoporosis; stroke; zoledronic acid.

ÖZ

Zoledronik asit, osteoporoz tedavisinde yıllık olarak uygulanan parenteral bir aminobisfosfonattır. Özellikle birden fazla komorbiditesi olan yaşlı hastalarda, etkinliği ve intravenöz yolla uygulanmasından dolayı oral bifosfonatlara alternatiftir. En sık görülen yan etkileri doz sonrası reaksiyon, böbrek fonksiyon bozukluğu ve hafif ila orta şiddette hipokalsemidir. Bu yazıda zoledronik asit ile osteoporoz tedavisi sırasında bir gün içinde inme gelişen 67 yaşında bir erkek olgu sunuldu. Hastanın inme öyküsü ve tekrarlayan inme için diğer risk faktörleri olduğundan, inme gelişimi bir tesadüf olabilir. Bu olgu, geriatrik hastalarda olağan dışı yan etkiler ile zoledronik asit infüzyonuna bağlı inme olasılığına dikkat çekmektedir.

Anahtar sözcükler: Osteoporoz; inme; zoledronik asit.

Osteoporosis is a disease characterized by low bone mineral density (BMD) and poor bone quality that results in reduced skeletal strength and increased risk of fracture.[1] Osteoporosis and osteopenia are common conditions and affect approximately 200 million people worldwide.[2] Although osteoporosis can occur at any age, it becomes more common with aging, predisposing many older individuals to fractures.[1]

Oral bisphosphonates are often the first-line therapy for most patients with osteoporosis and widely used for the prevention and treatment of osteoporosis. They have proven efficacy in BMD gains and future fracture risk reduction.[3,4] Zoledronic acid is the most recent potent aminobisphosphonate to be approved for the treatment of osteoporosis in doses of 5 mg intravenous (i.v.) annually. The relatively long duration of action of zoledronic acid is attributable to its high binding affinity for bone mineral matrix, its potent inhibition of the osteoclastic key enzyme farnesyl pyrophosphate synthase translate and slow release from bone.[5]

The parenteral route of administration overcomes the poor compliance associated with oral dosing of bisphosphonates which is further complicated by the need for pre- and post-dose fasting, posture requirements and potential gastrointestinal side effects.[5-7] The use of once yearly iv zoledronic acid

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also offers the potential to improve clinical efficacy by providing 100% bioavailability, eliminating concern of malabsorption of oral bisphosphonates due to intestinal disease or incorrect administration.[8] Therefore zoledronic acid is a reasonable option for elderly patients with comorbidities and those who do not tolerate or absorb oral bisphosphonates.

In this article, we report a patient with osteoporosis who developed stroke after the administration of zoledronic acid infusion. We review his history and comorbidities; discuss potential mechanisms and precautions to reduce serious side effects.

CASE REPORT

A 67-year-old man admitted to hospital with weakness on right side of the body and diagnosed as ischemic type cerebrovascular disease four years ago. Diffusion magnetic resonance imaging (MRI) revealed infarct area in the left middle carotid artery territory. The patient had a history of seizures that had developed one year after the stroke and carbamazepine treatment was started by the neurology clinic. He participated in three rehabilitation programs. He did not have an epileptic episode for several months under the current therapy. He was admitted to emergency department with symptoms of eye deviation and loss of consciousness four months ago and hospitalized with seizure diagnosis. After the attacks of epilepsy were under control, the patient was taken over to our clinic for a rehabilitation program. He had a history of hypertension, ischemic type stroke and epilepsy. He was taking his drugs regularly. He was a non-smoker and had no alcohol consumption. A written informed consent was obtained from the patient.

Physical examination revealed that the patient was in good physical condition. He had no cardiac and pulmonary symptoms. His vital signs were within normal limits and stable. The patient was evaluated for range of motion, strength, bed mobility, transfers from bed to wheelchair, balance, and gait. Brunnstrom stages for upper extremity, hand and lower extremity were 3, 2, and 3 respectively. He had disturbed sitting balance. Range of motion, progressive-resistive, relaxation, balance and breathing exercises were performed. With the assistance of the physical therapist, the patient practiced sitting balance and learned transfers. Then he started to practice standing up in the parallel bars with the assistance of a physical therapist. He had risk factors for osteoporosis and falls such as stroke, epilepsy, anticonvulsant medication, poor balance and impaired mobility-transfers. Therefore he was evaluated for osteoporosis by dual energy X-ray absorptiometry which revealed osteoporosis with T scores of -3.1 for total lumbar spine and -2.5 for femur neck. On admission serum calcium (Ca) level was 8.59 mg/dL (8.6-10.2), serum phosphorus (P) level 3.55 mg/dL (2.5-4.5), alkaline phosphatase level 82.1 U/L (40-129), blood urea nitrogen (BUN) level 17.9 mg/dL, serum creatinine level 0.8 mg/dL, estimated glomerular filtration rate 97.4 and serum 25-hydroxyvitamin D level 7.8 ng/L (25-80). Since the patient had chronic immobilization and disturbed sitting balance due to hemiplegia, zoledronic acid infusion was planned for the osteoporosis treatment. Electrocardiography (ECG) was in sinus rhythm prior to drug administration. The patient was hydrated prior to administration of zoledronic acid. Following intramuscular 150,000 IU vitamin D3 supplement, 5 mg of zoledronic acid was infused iv in 15 minutes. Although he had bladder control he suffered from urine incontinence nine hours after infusion. The next day the patient had a fever up to 38 degrees, became sleepy and confused. His control neurological examination revealed Brunnstrom stages for upper extremity, hand and lower extremity as 2, 2, and 2 respectively. Laboratory evaluation revealed mildly reduced calcium level of 8.04 mg/dL and phosphorus level was in normal range. Electrocardiography reading was regular sinus rhythm. Blood glucose, serum electrolytes, BUN and serum creatinine levels were in normal ranges. His vital signs were stable and within normal limits. Supplementation with 1,200 mg of calcium carbonate and 800 IU of vitamin D per day were started.

Due to his current status, brain diffusion MRI was performed in order to check out the occurrence of a new cerebrovascular event and an acute infarct area was detected in the right cerebellum hemisphere. The patient was transferred to the neurology clinic for early acute stroke management.

DISCUSSION

Zoledronic acid, represents a highly potent aminobiphosphonate that is effective in various benign and malignant metabolic bone diseases. Its annually parenteral route of administration maintains a high level of patient compliance and persistence with therapy which is particularly important in patients who do not adhere to or tolerate oral biphosphonates.[9] The efficacy of once-yearly zoledronic acid in the treatment and prevention of osteoporosis has been evaluated and described in different studies. The most common side

effects of zoledronic acid therapy include post-dose reaction, hypocalcemia, and renal toxicity.[10-12]

We report a case of stroke developed in association with the administration of zoledronic acid for osteoporosis. Both osteoporosis associated fractures and stroke are major public health problems associated with significant morbidity and mortality resulting in a substantial personal and economic burden to individuals.[8,13] Moreover, due to progressive aging of the population, the absolute number of stroke and osteoporosis are expected to increase.[13,14] In addition to demographic factors, various medical conditions and lifestyle factors have considerable impact on an individual's risk of stroke. Atrial fibrillation (AF) is one of the independent risk factors for stroke and transient ischemic attack (TIA).[15]

Atrial fibrillation adverse events (AEs) were observed more in patients receiving zoledronic acid in Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT). Several potential factors have been postulated for increased risk of AF, including drug-induced electrolyte imbalances and inflammatory cytokines however no temporal connection was revealed between the timing of infusion and the incidence of AF in HORIZON-PFT.[16] However, the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly–Recurrent Fracture Trial (HORIZON-RFT) did not confirm the observation of more AF and arrhythmias AEs with zoledronic acid treatment. Although the patient had risk factors for stroke development like hypertension, previous stroke history and advanced age, during hospitalization blood pressure was under control and he was receiving his drugs regularly including antiplatelet medication. He did not have cardiovascular disease history. Electrocardiography on admission and after his new neurological symptoms started, showed sinus rhythm. Because of the known causal relationship between AF and stroke-related events, the potential association between bisphosphonate therapy and AF is a cause for concern. No apparent relationship between AF AEs and stroke-related AEs was found in either HORIZON-PFT or HORIZON-RFT.[16] HORIZON studies had not shown a significant increase in stroke.[10-12] In HORIZON PFT extension study, none of the strokes occurred within 30 days of infusion, excluding TIAs. Unlike these studies, our patient developed stroke within one day of zoledronic acid infusion. To our knowledge this is the first report in published literature. Because of the risk factors of our patient, the development of stroke after zoledronic acid treatment could be just coincidence.

Zoledronic acid inhibits osteoclast-mediated bone resorption and due to its mechanism lowers serum calcium in both normal and hypercalcemic individuals.[17] Although asymptomatic hypocalcemia is common with administration of zoledronic acid, symptomatic hypocalcemia after its use is rarely reported.[18] Hypocalcemia can be a risk factor for arrhythmias causing stroke. The patient's baseline calcium level was in the lower limit of normal reference range and he developed asymptomatic hipocalcemia after treatment. Therefore, careful clinical and biochemical evaluation before and after of the patient zoledronic acid administration is essential.

Stroke patients are prone to falls, particularly onto the hemiplegic side. Hemiplegia and subsequent immobility predispose these patients to bone loss. Reduced PTH and active vitamin D may contribute to suppression in bone formation. These factors lead to a substantial increase in fractures after stroke.[19] Poole et al.[20] investigated early effects of stroke and zoledronic acid on bone structure and remodeling and found that stroke patients had higher resorption indices and lower bone forming surfaces, consistent with uncoupling of bone remodeling. In addition, zoledronic acid treatment was associated with a reduction in osteoclastic cell numbers consistent with its known mode of action in bone.

Zoledronic acid's adverse effects, such as the increased risk for atrial fibrillation and arrhythmias may be partially counteracted by the benefits of bisphosphonates in preventing ischemic stroke. Kang et al.[13] explored the effect of bisphosphonate treatment on stroke using a large population cohort study and they found that patients who received bisphosphonate therapy after suffering osteoporotic fractures had significantly lower risk of stroke during a two-year follow-up period bisphosphonates have a high affinity for the minerals in the bones and their half-life in the skeleton may reach 10 years. It has been shown that a small part of these drugs may be concentrated in the liver, the spleen, and the artery walls.[21] Both atherosclerosis and vascular calcification are linked with osteoporosis.[22]

Although several mechanisms regarding the anti-atherosclerotic effects of bisphosphonates have been proposed from animal studies,[13] the data regarding the protective effects of bisphosphonates against atherosclerosis in humans are still limited and conflicting. Delibası et al.[23] reported no significant

change of carotid artery intima-media thickness which is an early marker of atherosclerosis, in postmenopausal women receiving bisphosphonate therapy. However, Celiloglu et al.[21] showed that alendronate sodium significantly decreased intima-media thickness in the carotid artery during a one-year follow-up.

The patient had chronic medical conditions that favored a parenteral therapy over an oral biphosphonate. As with all drugs, the clinician's decision to prescribe must be based on careful assessment of the benefits and risks for the individual patient. Since zoledronic acid is a good choice in elderly patients with comorbid diseases and limited ambulation we should pay attention to some points during administration. Drug should be administered over no less than 15 minutes. Patients should be hydrated prior to administration of zoledronic acid. Patients should receive adequate intake of calcium and vitamin D. Careful clinical and biochemical evaluation before and after zoledronic acid administration is also essential.

In conclusion, we report a rare case of stroke following zoledronic acid infusion used for osteoporosis. This case report raises concerns for stroke following zoledronic acid therapy. Further investigations are needed for the administration and side effect profiles of zoledronic acid in elderly patients. Physicians should be aware of this entity and patients with a documented stroke should be monitored more closely.

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