Late-Onset Psychosis and Risedronate Treatment for Osteoporosis: A Case Report

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Abstract

As women age and enter menopause, they are sometimes more susceptible than men to certain physical and mental disorders such as osteoporosis and late-onset schizophrenia. Risedronate (Actonel©) is a bisphosphonate used for the treatment of osteopenia. Early initiation of pharmacotherapy for osteopenia is recommended to prevent greater bone loss. The most common side effects of risedronate include fever and flu-like symptoms, hypocalcemia, bone and joint pain, peripheral edema, fatigue, change in bowel movements, osteonecrosis of the jaw, and atrial fibrillation. Though reports in the professional literature of psychotic reactions to risedronate are scant, there have been FDA reports as well as patient discussions of psychiatric side effects from this medication on popular websites. We report the case of M, age 59, who was treated with risedronate for osteoporosis, and was subsequently diagnosed with atypical psychosis after other organic causes were excluded. Though it is conceivable that age-related psychosocial and physical factors triggered late-onset schizophrenia, the temporal relationship between the termination of treatment with risedronate and the improvement in her mental state suggests that the risedronate might have triggered a psychotic reaction that resolved following cessation of treatment.

Key Words: Risedronate, Osteoporosis, Atypical Psychosis, Psychotic Reaction

Introduction

As women age and enter menopause, they are sometimes more susceptible than men to certain physical and mental disorders. For example, osteoporosis is most prevalent in women over the age of 50 as the hormonal influence of estrogen on bone health dissipates with the onset of menopause (1). It is also possible that menopause might be a risk factor for schizophrenia, since it has been observed that nearly 37% of women with schizophrenia develop their illness after age 45, the so-called "second-peak," presumably due to the fading effect of estrogen around menopause (2).

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Submitted: January 6, 2013; Revised: February 21, 2013; Accepted: February 28, 2013

Risedronate (Actonel©) is a bisphosphonate used for the treatment of osteopenia. It inhibits bone resorption via actions on osteoclasts or osteoclast precursors, leading to an increase in bone mineral density. Early initiation of pharmacotherapy for osteopenia is recommended to prevent greater bone loss (3). The most common side effects of risedronate include fever and flu-like symptoms, hypocalcemia, bone and joint pain, peripheral edema, fatigue, change in bowel movements, osteonecrosis of the jaw, and atrial fibrillation (4). Risedronate is available in various forms administered either once a day, weekly, biweekly or monthly.

Absorption of risedronate administered orally is relatively rapid (Tmax 1 hour). There is no evidence of systemic metabolism of risedronate; 80% of the drug is excreted with urine and 20% is absorbed by bone. Bioavailability of risedronate sodium is poor (0.54–0.75%) and the half-life of the reported form of administration is 480 hours. Approximately half of the absorbed dose is excreted in urine within 24 hours (4).

Risedronate and Psychosis

Reports of severe psychiatric side effects of bisphosphonates in general—and risedronate in particular—such as psychosis or depression are scant. Psychiatric side effects of risedronate as reported in Micromedex (5) include anxiety and depression. During a study that compared risedronate 5 mg daily and 35 mg weekly for the treatment of osteoporosis in postmenopausal women (n=965), the incidence of anxiety was 0.6 and 2.7%, respectively. The relationship of the treatment to the adverse event was not reported (6).

FDA Report ISR 5580350 (7) includes a physician report from Germany on December 17, 2007 that described a 77-year-old female patient diagnosed with osteoporotic fracture who was treated with Actonel© 35 mg/w for 33 days. After the drug was administered, the patient experienced acute psychosis, cardiac discomfort, chest discomfort, depression, dizziness, ear pain, formication, headache and influenza-like illness. During the same period, the patient was treated with levothyroxine, and antihypertensives. The patient was hospitalized and recovered.

Reports of severe psychiatric side effects of bisphosphonates in general—and risedronate in particular—such as psychosis or depression are scant.

In addition, there are a number of patient reports of psychiatric side effects of risedronate on popular websites (e.g., EHealthMe; Drugs-Real World Outcomes) (8).

Later onset of schizophrenia among women and over representation of women among late-onset cases have been reported (9). It is conceivable that aging-associated psychosocial factors such as physical disability, retirement, financial difficulties, bereavement and deaths of peers may contribute to the precipitation of the symptoms of schizophrenia in later life (9). Premorbid educational, occupational, and psychosocial functioning is less impaired in late-onset than early-onset schizophrenia.

Case Report

We present the case of a female patient (Ms. M) who was treated with risedronate. A few months prior to her admission to our facility, her risedronate treatment was switched to the long-acting drug (monthly dosage). Reasons for switching to the long-acting form of the medication were not reported in her case notes. Soon after, she developed a severe psychotic state. M was admitted for compulsory hospitalization at Sha'ar Menashe Mental Health Center in October 2011 by court order owing to a severe psychotic state accompanied by dangerous behavior to herself and to others.

M was 59-years-old, married with two children. She had no known psychiatric history and no history of psychopathology in her family. She was born in the Ukraine and immigrated to Israel in 1990; birth and early development were unremarkable. She graduated from nursing school, married at age 20 and had two children. She worked as a nurse in a geriatric center until about one year prior to her admission. Her medical history included a hysterectomy (1998), hyperlipidemia and hypertension since 2003, and severe osteoporosis that emerged in 2004. In 2004 one lobe of her thyroid was removed because of goiter. She is in endocrinologic follow-up since 2005 for diffuse nontoxic goiter. In 2005 she began to suffer from back pain that stemmed from osteoporosis and, as a result, M retired at age 58. M is allergic to penicillin. She was regularly treated with risedronate 35 mg/week from May 2006 through July 2011, and then administration was changed to monthly dosages of 150 mg from 07.2011–10.2011, atorvastatin, vitamin D, and amlodipine prior to her admission to our hospital. Since she began treatment in 2006 with risedronate 35 mg/w she began to suffer from exacerbation of back pain and began to suffer from side effects such as severe constipation that did not respond to treatment, gastrointestinal complaints, heartburn with esophageal pain, and muscle pains in her limbs and chest. She also began to suffer from conjunctivitis and urinary tract infections.

After the administration of risedronate was switched to monthly dosages of 150 mg, M began to experience severe dizziness and loss of balance, and was ultimately hospitalized for non-specific dizziness and chest pains. She was in a general hospital for two days and discharged as per her request, with no clinical improvement.

Two weeks later there was a sharp change in her mental state; she became extremely restless, very frightened, threw out various objects from her home and turned on water faucets claiming that she was, thus, saving the world. She became aggressive and violent toward her family. She was examined by a psychiatrist in the emergency room of a general hospital, who diagnosed a stormy and violent psychotic state, including disorganized behavior, delusions of war and nuclear attacks, and disorders of perception. She claimed that "father is talking to me from the grave and instructing me to protect myself from war." She underwent a brain CT without contrast that was normal. A compulsory hospitalization order was issued by the court, and she was admitted to Sha'ar Menashe Mental Health Center.

At the beginning of her hospitalization she cooperated only partially. She had psychomotor restlessness, was tense, suspicious, fearful, irritable, had a blank look, did not make eye contact, was negativistic, had a low threshold, and physically shoved those around her, threw objects, was confused, tried to throw other patients from her room claiming that she was in a hotel and wanted a private room. She had disorganized thoughts with significant associative looseness. Even after the confusional state passed, her thought content revealed delusions with apocalyptic content: she claimed that there was a nuclear attack, war with Assad and Sadam Hussein, and she was terribly afraid of radiation following explosions like in Chernobyl. She sometimes behaved strangely; stripped in public and stereotypically turned on the faucets. Because the delusional content remained even after the confusional state passed, we arrived at the conclusion that the psychosis was substance induced. Because of her unpredictable and dangerous behavior, she was physically restrained a number of times. Cognitive impairments with a decline in concentration, memory and orientation were prominent. It should be noted that M was treated by a Russian-speaking psychiatrist, so that cultural and language barriers did not play a role in her clinical presentation.

Antipsychotic treatment with haloperidol (10 mg/d) was initiated and led to extrapyramidal side effects. Haloperidol was stopped after 4 days and olanzapine treatment (20 mg/d for 15 days) was initiated, but was then gradually titrated down and stopped after 3 weeks. Ten days after her admission to the hospital she refused and, therefore, did not receive risedronate 150 mg/m on schedule. Her mental state began to improve. She became calmer and more organized in her behavior and her thoughts, and her auditory and visual hallucinations ceased. The delusions passed.

Before the onset of illness, M had graduated nursing school and was employed as a nurse; thus, it can be assumed that her mental functioning was normal at that time. There are no records of IQ evaluations prior to her admission to our facility. Nineteen days after admission, the patient was evaluated by a neurologist who noted very low mental functioning (Mini-Mental State examination score 21/30). There were no focal signs, a brain CT with contrast was recommended, as well as an abdominal ultrasound. These tests were performed and were normal.

Repeat blood work including blood counts, electrolytes, liver and kidney functions, thyroid function, vitamin B12 and folic acid levels revealed no unusual results. Calcium and phosphate levels were within normal ranges (9.2–9.7 mg/dl and 3.95–4.32 mg/dl, respectively), so hypoparathyroidism was ruled out as a cause for psychosis. The carotid duplex was normal. EEG was normal. Three weeks later, she was transferred to an open ward. At this point, her clinical picture reflected a decline in her mood, high levels of anxiety, psychomotor reduction, decline in concentration and short-term memory. Her main complaints were somatic such as weakness and fatigue, dizziness, severe constipation, burning during urination, back pains and insomnia.

The organic work-up revealed no cause for her psychosis, and led us to search for alternate causes, and raised the suspicion that the administration of risedronate was responsible for her psychosis. It was decided not to renew treatment with risedronate. Treatment with citalopram 10 mg/d did not lead to improvement and anxiety increased, so citalopram therapy was stopped. Because the psychosis was drug induced—rather than an expression of schizophrenia—dosages of antipsychotic agents were relatively low. Her pharmacotherapy was changed to quetiapine 50 mg/day, clonazepam 0.5 mg/d and mirtazapine 15 mg/d (administered as a sleep aid). With that treatment she became more relaxed, anxiety declined, and her mood improved. Cognitive functioning returned to pre-hospitalization levels. The patient had a number of home visits, functioned well, and her family felt that "she was back to herself."

The temporal relationship between the termination of treatment with risedronate and the improvement in her mental state suggests that the risedronate might have triggered a psychotic reaction that resolved following cessation of treatment.

M was discharged two months after her compulsory admission. She was stable and was discharged with recommendations to continue the following treatment regimen: quetiapine 25 mg/d, clonazepam 0.5 mg/d and mirtazapine 15 mg/d as a sleep aid.

Discussion

Though reports in the professional literature of psychotic reactions to risedronate are scant, there are a number of patient reports of psychiatric side effects of this medication on popular websites (e.g., EHealthMe; Drugs-Real World Outcomes) (8). M was diagnosed with atypical psychosis after other organic causes were ruled out.

However, considering her psychosocial and medical history of hysterectomy and severe osteoporosis that accounted for physical disability and early retirement, comorbidity with late-onset schizophrenia should be considered.

However, there was a temporal connection between the change in the type of administration of risedronate and the emergence of the complaints that led to admission to a general hospital and the subsequent development of psychosis. The temporal relationship between the termination of treatment with risedronate and the improvement in her mental state suggests that the risedronate might have triggered a psychotic reaction that resolved following cessation of treatment.

Acknowledgment

The authors thank Rena Kurs for assistance in preparation of the manuscript.

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