Case Report

Profound Muscle Weakness and Pain after One Dose of Actonel

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The World Health Organization (WHO) defines osteopenia as a bone density between 1 and 2.5 standard deviation (SD) below the bone density of a normal young adult [1]. Osteoporosis is defined as 2.5 SD or more below that reference point [1]. Bisphosphonates are a group of medications used to treat osteoporosis, Paget's disease of bone, and osteopenia. We report a woman who developed profound muscle weakness and pain after one dose of Risedronate (Actonel).

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1. Introduction

Risedronate (Actonel) is a bisphosphonate used for the treatment of osteopenia that inhibits bone resorption via actions on osteoclasts or osteoclast precursors, leading to an increase in bone mineral density. Pharmacologic therapy for osteopenia is recommended as early as possible to prevent the greater bone loss [1]. 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 [2]. We describe a case report of severe weakness as a potential new side effect of Risedronate in a woman with osteopenia.

2. Case Report

A 53-year-old Caucasian woman presented with diffuse muscle weakness and pain. Past medical history was notable for gastroesophageal reflux disease, diverticulitis, intermittent lower back pain, and osteopenia. She took one dose of Risedronate, 35 mg for osteopenia. Within 15 hours, she developed severe aching muscle pain (10/10 on Visual Analog Scale) throughout the body with fevers, sweats, chills, tingling throughout the body, and loss of bladder control. In the Emergency Room, she was told she had a drug reaction from Risedronate and prescribed oxycodone for pain management. Evaluation included normal complete blood counts and electrolytes. Potassium and creatinine were mildly low at 3.4 mEq/L, and 0.5 mg/dL, respectively. The CO2 was elevated at 31.4 mEq/L (normal range 22.0–29.0 mEq/L), Calcium, creatine phosphokinase (CPK) and ESR were normal. Neurological examination in the emergency room was notable for decreased strength in proximal lower extremities graded at 4+/5 using the Medical Research Council (MRC) scale. Deep tendon reflexes were normal. The only medications patient was taking at the time of the event were Nexium 40 mg per day and Posture D vitamins.

Over the next three weeks, she developed severe muscle cramps, bilateral lower extremity edema, and progressive muscle weakness and could not raise her arms above her head. She had several falls and became wheelchair bound. Diffuse pain (8/10 on VAS) in the bones and muscles of her limbs and back was present.

She underwent electromyography (EMG) testing which demonstrated mild bilateral median neuropathies bilaterally and active denervation (fibrillations and positive sharp waves) only in the right deltoid muscle. MRI of cervical spine was normal. Methylprednisolone, 24 mg with a six day taper was prescribed without clinical benefit.

One month post dose, she had proximal weakness in the upper and lower extremities with bilateral deltoid graded at MRC 3+/5, hip flexors at 3–4/5, and hamstrings at 4/5. Proximal muscle weakness was evident on gait testing. She was admitted to an outside hospital. During her stay, the work up for following differential diagnosis
was done: multiple myeloma, Gullian-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, Systemic Lupus Erythematosus, Waldenstrom’s macroglobuline-

mnia, Cushing disease, myasthenia gravis, hyperparathy-
roidism, and polymyalgia rheumatica. Work up included
an MRI of brain with and without gadolinium, a lumbar
puncture for cerebrospinal fluid analysis, and a whole
body positron emission tomography scan, all which were
normal. MRI of the muscle was not performed. Results
of a second EMG study were similar to the previous test
with the exception that the active denervation changes in
right deltoid were absent. A muscle biopsy was considered
at the beginning of the hospitalization, but was deferred
because her aldolase and repeat CPK tests were normal. She
started a program of physical and occupational therapy, and
acupuncture.

The pain and weakness began to slowly subside approx-
imately four months after the dose. By six months postdose,
she improved to the point that she no longer needed a cane
to ambulate. One year postdose, she reports easy fatigability,
severe pain (7/10 on VAS) in the left biceps and back,
and mild weakness in her legs. She has difficulty going up
the stairs and standing from a lying position. Neurological
examination was notable for mild proximal lower extremity
and hand weakness with MRC grades of 4+ iliopsoas, 5−
abductor policis brevis, 4+ abductor digiti minimi, and
4+ first dorsal interosseous bilaterally with some weakness
on the finger extensions. No atrophy or fasciculations
were seen.

Two and a half years after taking one pill of Risedronate,
the patient continues to improve. She reports some weakness
of her shoulders, difficulty carrying heavy things, and some
shortness of breath with exertion. Recently, she underwent
quantitative muscle testing (QMT) to assess her muscle
weakness [3]. Isometric strength of ten muscle groups
was measured bilaterally. Her percent of predicted strength
values indicated extensive weakness throughout, with muscle
strength of different muscle groups ranging from 31.5% to
76.4%, with the mean strength 50.5%.

A MedWatch form was filed with the FDA.

3. Discussion

We describe a 53-year-old woman who developed a severe
pain and weakness after taking one pill of Risedronate for
treatment of osteopenia. The side effect of medication was so
profound that patient lost ability to ambulate and two and a
half years later is still not completely recovered.

According to 2004 Surgeon General report on bone
health and osteoporosis, 33.6 million individuals over age 50
have low bone mass or osteopenia of the hip and are at risk of
osteoporosis and its potential complications. The prevalence
of osteoporosis and low bone mass is expected to increase to
12 million cases of osteoporosis and 40 million cases of low
bone mass among individuals over the age of 50 by 2010, and
to nearly 14 million cases of osteoporosis and over 47 million
cases of low bone mass in individuals over that age by 2020
[4]. Bisphosphonates are approved for treatment of Paget’s
disease of bone, osteoporosis, and osteopenia.

Absorption of Risedronate after the oral dose is relatively
rapid (Tmax 1 hour). There is no evidence of systemic
metabolism of Risedronate with 80% of the drug excreted
with urine and 20% absorbed by bone. Bioavailability of
Risedronate sodium is poor (0.54%–0.75%) and half-life is
480 hours. Approximately half of the absorbed dose is
excreted in urine within 24 hours [2].

Risedronate was used in the treatment of the patient pre-

sented in this case report. The FDA has received six serious
adverse event reports of severe bone, joint, or muscle pain
for this medication [5]. Pain (described as “incapacitating,”
“disabling”) and loss of ability to climb stairs, ambulate, and
perform the usual activities were reported as side effects of
different bisphosphonate, Alendronate (Fosamax), which
may suggest a possible class effect [5]. According to the
FDA article published in 2006, many patients underwent
numerous diagnostic tests with mostly normal findings [5,
6]. Details on the exact number of patients and the names
of diagnostic tests patients performed are not provided.
There have not been other reported cases of proximal muscle
weakness after Risedronate use.

Symptoms experienced by the patient described in this
case report (rise in temperature and accompanying flu-
like symptoms) resemble an acute phase response. The
mechanism for this response in general appears to be
associated with the release of tumor necrosis factor (TNF)α,
interferon γ (INF-γ), interleukin 1 (IL1), and interleukin 6
(IL-6) although the effector cells that release these cytokines
and the mechanism of action remains not completely under-
stood [7]. Aminobisphosphonates (including Risedronate)
increase serum levels of proinflammatory cytokines [8].
Therefore, it is possible that patient’s muscle weakness
might be an inflammatory response to the drug toxicity.
Such hypothesis cannot be supported by patient’s levels of
proinflammatory cytokines because they were not measured
during the course of the disease. Muscle biopsy was not
performed in this case, however will be an essential test
to perform in similar cases to better assess etiology of
symptoms. Pain and muscle weakness as adverse events of
Risedronate may be underreported and not taken into con-
sideration because of the subjective nature of pain, confusion
with the pain from osteoporosis, and attribution of the loss of
ambulation to pain. Combined with normal diagnostic
tests, it may result in failure to recognize this potential side
effect and a delay in stopping the bisphosphonate. Four
of the bisphosphonates are listed in the Top 200 Brand
Drugs By Units in 2007 accounting for almost 31 million
prescriptions [9]. Given the number of patients receiving
bisphosphonate therapy and the paucity of reports, the
incidence of the complex of symptoms is assumed to be
relatively low. However, the formal reporting of adverse drug
events is known to underestimate their true incidence [10, 11].

For each patient, decisions regarding the therapy must
also take into consideration the long period of treatment,
substantial costs, and potential side effects. At this point, the
risk factors and incidence of the incapacitating muscle pain
and profound muscle weakness are unknown. Additional
studies are needed to investigate the possible mechanism of
pain, muscle weakness, and edema following bisphosphonate
treatment. Even if low, the awareness of these side effects is very important because of the serious nature of the problem.

References


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