Risedronate Sodium Therapy for Prevention of Hip Fracture in Men 65 Years or Older After Stroke

Yoshihiro Sato, MD; Jun Iwamoto, MD; Tomohiro Kanoko, PhD; Kei Satoh, MD

Background: There is a high incidence of hip fractures in patients after hemiplegic stroke. Bone mineral density is decreased on the hemiplegic side in patients after stroke, correlating with the immobilization-induced bone resorption, the degree of paralysis, and hypovitaminosis D. The purpose of this study is to evaluate the effectiveness of risedronate sodium, an inhibitor of bone resorption, on osteoporosis and the risk of hip fractures in men 65 years or older after stroke.

Methods: We conducted an 18-month randomized double-blind trial. Of 280 male patients 65 years or older who were poststroke, 140 received a daily dose of 2.5 mg risedronate sodium and the other 140 received placebo. Incidence of hip fractures in the 2 groups was compared.

Results: Ten patients sustained hip fractures in the placebo group, and 2 hip fractures occurred in the risedronate group. The relative risk of hip fracture was 0.19 (95% confidence interval, 0.04-0.89). The number of patients needing the treatment was 16 (95% confidence interval, 9.32). Bone mineral density increased by 2.5% in the risedronate group and decreased by 3.5% in the placebo group (P < .001). Urinary deoxypyridinoline, a bone resorption marker, decreased by 58.7% in the risedronate group and by 37.2% in the placebo group.

Conclusion: Treatment with risedronate increases bone mineral density and reduces hip fractures in elderly men who are poststroke.

Arch Intern Med. 2005;165:1743-1748

This study compared the occurrence of fractures in male patients after stroke who were administered risedronate or placebo. Study subjects were 280 consecutive ambulant men who were poststroke, recruited at the Mitate Hospital, Tagawa, Japan, from April 2003 to May 2003 and followed up until December 2004. Inclusion criteria were age of 65 years or older, first stroke occurring at least 3 months before the study began, and being in a convalescent stage with hemiplegia. Exclusion criteria were...
history of fractures; impairment of hepatic, renal, cardiac, or thyroid function; other known causes of osteoporosis, such as primary hyperparathyroidism, renal osteodystrophy, and familial osteoporosis; and use of any drug known to alter bone metabolism for 3 months or longer during the preceding 12 months. We excluded patients with esophageal problems and with swallowing problems resulting from stroke. Diagnosis of stroke was based on clinical evaluation, magnetic resonance imaging brain scans, and magnetic resonance imaging angiography.

At baseline evaluation, we determined each patient’s Barthel index (BI), a functional independence score. The clinical severity of the hemiplegia was evaluated according to the Scandinavian Stroke Scale. Patients who had fallen at least once in the 3 months before recruitment and during the study period were defined as “fallers.” The study was approved by the local ethics committee, and written informed consent was obtained from all control and research subjects.

Patients were assigned to 1 of 2 groups by computer-generated random numbering. Random allocation sequence was implemented using numbered containers, and the sequence was concealed until interventions were assigned. Patients were randomized to the 2 groups using a permuted block size of 4. No other restrictions were used in the randomization procedure. Although risedronate has not yet been shown to reduce hip fractures in a general population of men, increased bone resorption following a stroke has been reported in both sexes. Risedronate therapy may reduce bone resorption in male patients after stroke and may be effective in reducing hip fractures, particularly if this therapy is initiated during the first year following a stroke.

Patients received a 2.5 mg oral risedronate sodium tablet (Actonel; Aventis Pharma, Tokyo, Japan) or a placebo (n=140) daily for 18 months. (In Japan, 2.5 mg/d is the maximal dose approved by the government-financed insurance system.) Because this study was undertaken to address the effect of risedronate alone, vitamin D and calcium supplements were not administered.

Patients were instructed to take the tablet with water (180 mL) 30 to 60 minutes before breakfast. They were not allowed to take any other drugs that could affect bone and calcium metabolism. Adherence to study medication was assessed by pill count of returned tablets. One physician (Y.S.), who was blind to treatment assignment, performed follow-up assessment of the patients.

Each patient was given a general medical evaluation. Laboratory values were assessed on entry to obtain baseline values and at 6, 12, and 18 months. Members of the comparison group visited the clinic 6, 12, and 18 months after enrollment; 6 members dropped out. Data from the 2 patient groups were also analyzed at entry and at 6, 12, and 18 months later.

The clinical status of the 2 groups was assessed at baseline, and all research subjects were seen every 4 weeks in the outpatient clinic, at which times all fractures were recorded. Falls were registered on monthly “fall calendars.” The participants were instructed to complete the calendar daily, marking an “X” for each fall on the date it occurred. The 2 groups were evaluated for falls and possible hip fractures every 4 weeks. Falls were defined as incidents during which a patient fell because of an unexpected loss of balance.

Using a computed x-ray densitometer (Teijin, Tokyo, Japan), we measured the BMD of the second metacarpal in both hands of each patient. This method measures the BMD at the middle of the second metacarpal using a radiograph of the hand relative to an aluminum step wedge used as a standard (20 steps, 1 mm/step). The computer algorithm compares bone radiodensity with the gradations of the aluminum step wedge, calculating the bone thickness as aluminum equivalent (millimeters of aluminum) with the same x-ray absorption. Precision errors (coefficients of variation) of the computed x-ray densitometer method have ranged from 0.2% to 1.2%. The validity and accuracy of this method have been described elsewhere.

On the day of BMD evaluation, blood and urine samples were obtained after an overnight fast. Serum ionized calcium, intact PTH, 25-hydroxyvitamin D (25-OHD), and 1,25-(OH)2D were measured as described previously. Urinary deoxypyridinoline (D-Pyr) was measured using an enzyme immunoassay kit (Meta Biosystems Inc, Mountain View, Calif) and expressed relative to the urinary creatinine concentration (D-Pyr/creatinine, nanomoles per millimole).

To assess adverse events, each patient underwent physical examination every 4 weeks. We performed hematomatological and biochemical tests and collected information about adverse events. At the end of the study, each patient’s weekly exposure to sunlight during the preceding year was assessed by a questionnaire and graded as either less than 15 minutes per week or 15 minutes or more per week.

We estimated that in a study population of 280 patients, there would be a 10% incidence of hip fracture. We also estimated that we had an 80% probability of reducing that risk by 70% with risedronate treatment. Analyses were performed on the intent-to-treat population; all patients were randomized to treatment, received at least 1 dose of study medication, and provided data at baseline and at least 1 postbaseline assessment. The primary end point was defined as the incidence of a hip fracture. We calculated the relative risk and the number needed to treat (NNT). Values are given as mean ± SD unless otherwise indicated. We used the unpaired t test to determine the significance of differences between the 2 groups. Group differences in categorical data were assessed by using a x2 test. We used the paired t test to assess the significance of the differences in BMDs between the nonhemiplegic and hemiplegic sides. We calculated Spearman rank correlation coefficients to determine the relationship between BMD and other variables.

We used the Wilcoxon rank sum test to compare the laboratory values of the 2 stroke groups. We used the paired t test to assess the differences in BI and Scandinavian Stroke Scale or biochemical indices between baseline values and values after 6, 12, and 18 months. We computed the BMD measurements and the laboratory values and expressed them as a percentage change from the baseline. We compared both groups with respect to the BMD by Wilcoxon rank sum test. Values of less than .05 were considered significant.

RESULTS

There were 43 fallers in the risedronate group and 44 in the placebo group. A total of 269 falls occurred in the former group and 278 in the latter group during the study period, or 4.2 falls per patient and year for both groups. In the risedronate group, 28 (20%) of 140 patients fell at least once, and 15 (80%) fell twice or more; in the placebo group, 29 (21%) of 140 patients fell at least once, and 15 (79%) fell twice or more. The number of falls among fallers ranged from 1 to 12 in both groups.

A hip fracture occurred in 10 patients in the placebo group and in 2 patients in the risedronate group during the study period, and the relative risk was 0.19 (95% confidence interval [CI], 0.04-0.89). All of these fractures occurred on the hemiplegic side. The NNT for hip fractures was 16 (95% CI, 9-32). The number of hip fractures per 1000 patient-years was 10 for the risedronate group and...
51 for the placebo group. Fractures other than hip fractures occurred in 2 patients in the risedronate group (1 fracture each at the wrist and ankle) and 6 patients in the placebo group (2 fractures each at the proximal femur and ribs, 1 each at the proximal humerus and pelvis).

DEMographic AND BAsIClE CLINICAL Characteristics OF STUDY SUBJECTS

Of 312 assessed subjects, 280 were randomized into the treatment groups (Figure 1). Six patients in the risedronate group and 7 in the placebo group dropped out or withdrew from the study due to noncompliance, lost to follow-up, intercurrent illness, or death. Thus, a total of 267 patients (134 in the risedronate group and 133 in the placebo group) completed the trial. The low dropout rate may be due to the fact that the subjects had relatively mild disabilities.

The Table lists the baseline characteristics of the participants. There were no significant differences between the placebo group and risedronate group in BI, degree of hemiplegia, number of fallers, type of stroke, BMD, or biochemical indices of bone metabolism. Although the values of BMD on both hemiplegic and nonhemiplegic sides were within the reference range compared with the elderly general Japanese population,\textsuperscript{22} BMD on the hemiplegic side was significantly reduced compared with that of the nonhemiplegic side, which agrees with previous reports.\textsuperscript{8,9,11} Compared with the reference range of the elderly general Japanese population,\textsuperscript{20} both groups of patients had high levels of serum ionized calcium and urinary D-Pyr and low serum concentrations of PTH, 25-OHD, and 1,25-(OH)\textsubscript{2}D at baseline. Serum 25-OHD was outside of the reference range in both groups: 114.6±10.0 nmol/L (45.9±7.7 nmol/L) in the placebo group and 114.6±16.7 ng/mL (45.9±6.7 nmol/L) in the risedronate group.

CHANGES IN CLINICAL AND BIOCHEMICAL MEASUREMENTS DURING FOLLOW-UP

In both groups of patients, BI and degree of hemiplegia improved from the baseline values during the first 6 months but remained virtually unchanged in the remaining 12 months of the study.

Serum ionized calcium and urinary D-Pyr concentrations decreased to reference range in the risedronate group after 6 months and remained within the reference range thereafter (Figure 2A and B). In the placebo group, these indices gradually decreased but still remained higher than the reference range even after 18 months (Figure 2A and D). Parathyroid hormone concentrations were enhanced throughout the study in the risedronate group but remained low in the placebo group during the 18 months of the study (Figure 2C). Serum 1,25-(OH)\textsubscript{2}D levels in the risedronate group continued to increase during the 18 months, whereas 1,25-(OH)\textsubscript{2}D levels remained low in the placebo group (Figure 2D). Serum 25-OHD levels were reduced in both groups: the average values after 18 months were 58.0±10.0 ng/mL (23.2±4.0 nmol/L) in the placebo group and 60.0±12.5 ng/mL (23.2±5.0 nmol/L) in the risedronate group.

The relationships among various indices after 6, 12, and 18 months were analyzed separately in the 2 groups. In the placebo group, BI correlated negatively with serum ionized calcium or urinary D-Pyr (r=−0.298 for calcium, r=−0.311 for D-Pyr after 6 months; r=−0.275 for calcium, r=−0.305 for D-Pyr after 12 months; r=−0.271 for calcium, r=−0.289 for D-Pyr after 18 months; P<.001), but these correlations were not observed in the risedronate group. The BI correlated positively with serum 25-OHD levels in both groups (r=0.269, P<.01 after 6 months; r=0.280, P<.001 after 12 months; r=0.654, P<.001 after 18 months) and with 1,25-(OH)\textsubscript{2}D only in the placebo group (r=0.380 after 6 months; r=0.323 after 12 months; r=0.302 after 18 months; P<.001). Parathyroid hormone correlated positively with ionized calcium or 1,25-(OH)\textsubscript{2}D concentrations in the placebo group (r=0.540 for calcium, r=0.323 for 1,25-(OH)\textsubscript{2}D after 6

Table. Demographic and Baseline Clinical Characteristics of the Patients With Hemiplegic Stroke at Study Entry*
months; $r = 0.498$ for calcium, $r = 0.521$ for $1,25-(OH)_2D$ after 12 months; $r = 0.589$ for calcium, $r = 0.511$ for $1,25-(OH)_2D$ after 18 months; $P < .001$], while significant negative correlations were observed between PTH and serum ionized calcium or $1,25-(OH)_2D$ in the risedronate group [$r = -0.529$ for calcium, $r = -0.402$ for $1,25-(OH)_2D$ after 6 months; $r = -0.514$ for calcium, $r = -0.418$ for $1,25-(OH)_2D$ after 12 months; $r = -0.602$ for calcium, $r = -0.457$ for $1,25-(OH)_2D$ after 18 months; $P < .001$]. There was a negative correlation between PTH and 25-OHD only in the risedronate group ($r = -0.81$ after 6 months; $r = -0.802$ after 12 months; $r = -0.854$ after 18 months; $P < .001$).

Reduced mobility may have prevented the patients from venturing outdoors during the study period, because 109 patients (83%) in the risedronate group and 107 patients (82%) in the placebo group had less than 15 minutes of sunlight exposure per week.

**RELATION OF BMD CHANGES TO OTHER FACTORS**

**Figure 3** shows percentage changes from the baseline in metacarpal bone mineral density (BMD) on (A) the hemiplegic side and (B) nonhemiplegic side after 6, 12, and 18 months in men 65 years or older after stroke in the risedronate and placebo groups. The differences in the percentage changes in the BMD on the hemiplegic side between the 2 groups were significant ($P < .001$ for all). Numbers in parentheses are the numbers of the subjects followed. On the nonhemiplegic side, the differences between the 2 groups were also significant ($P < .001$ for all).

for $1,25-(OH)_2D$ after 12 months; $r = -0.602$ for calcium, $r = -0.457$ for $1,25-(OH)_2D$ after 18 months; $P < .001$]. There was a negative correlation between PTH and 25-OHD only in the risedronate group ($r = -0.81$ after 6 months; $r = -0.802$ after 12 months; $r = -0.854$ after 18 months; $P < .001$).

Reduced mobility may have prevented the patients from venturing outdoors during the study period, because 109 patients (83%) in the risedronate group and 107 patients (82%) in the placebo group had less than 15 minutes of sunlight exposure per week.

**RELATION OF BMD CHANGES TO OTHER FACTORS**

**Figure 3** shows percentage changes from the baseline in metacarpal BMD. The changes in the BMD on the hemiplegic side were $+2.5\% \pm 0.1\%$ in the risedronate group and $-3.5\% \pm 0.2\%$ in the placebo group (Figure 3A; analysis of covariance, $P < .001$). The changes in the BMD on the nonhemiplegic side were $+3.3\% \pm 0.1\%$ in the risedronate group and $-2.0\% \pm 0.2\%$ in the placebo group (Figure 3B; analysis of covariance, $P < .001$). Thus, in both groups, BMD on the hemiplegic side was significantly lower than that on the nonhemiplegic side (risedronate group: $2.55 \pm 18$ vs $2.62 \pm 19$, $P < .001$; placebo group: $2.40 \pm 18$ vs $2.50 \pm 18$, $P < .001$), and this result agrees with
In previous studies, there were correlations between serum 25-OHD concentration and BMD on both sides, at the end point, in both stroke groups (risdonate group: hemiplegic side, \( r=0.173, P=0.04 \); nonhemiplegic side, \( r=0.183, P=0.03 \); placebo group: hemiplegic side, \( r=0.199, P=0.02 \); nonhemiplegic side, \( r=0.219, P=0.01 \)). As previously reported, BMD on the hemispheric side correlated with the degree of hand paralysis in both groups (risdonate group, \( r=0.181, P=0.03 \); placebo group, \( r=0.229, P=0.007 \)). Urinary D-Pyr in the placebo group correlated with BMD on both hemispheres (\( r=0.418, P<0.001 \)) and nonhemispheric sides (\( r=0.281, P=0.001 \)).

ADVERSE EFFECTS

In the risdonate group, 2 patients had esophagitis and 1 experienced abdominal pain, but these resolved with appropriate therapy without discontinuation of the treatment.

COMMENT

In previous studies of patients after stroke, we found second metacarpal BMD by computed x-ray densitometer to correlate with risk of hip fractures. Therefore, reduced second metacarpal BMD in patients after stroke may reflect a decrease throughout the appendicular skeleton.

Risdonate has been demonstrated to increase BMD in hemiplegic limbs and prevent hip fractures in women who are poststroke, and the present study examined the effect of risdonate in men following stroke. Hip fracture risk was extremely low in the risdonate group compared with the placebo group. A previous study demonstrated that risdonate reduced the incidence of nonvertebral fractures (NNT = 20) in postmenopausal women and hip fractures in elderly women after stroke (NNT = 29). In the present study, NNT for hip fractures was calculated as 16; the higher NNT value in elderly women is explained by other factors such as postmenopausal osteoporosis. The rate of hip fractures in a reference population of Japanese men between 75 and 79 years old is reported to be 2.0 per 1000 patient-years. Although the ages of the subjects in our study were within this range, the fracture rate even in the risdonate group was far higher than the reference value. This may be attributable to frequent falls and osteoporosis due to deficiency of 25-OHD, increased bone resorption, reduced mobility due to hemiplegia, and inhibition of renal synthesis of 1,25-(OH)\(_2\)D associated with immobilization-induced hypercalcemia. Because the number of falls was similar in the 2 groups, risdonate may prevent hip fractures despite frequent falls.

Little is known about calcium metabolism in men who are poststroke. At baseline, we found high levels of serum calcium and low serum concentrations of PTH, 25-OHD, and 1,25-(OH)\(_2\)D; the indices of bone metabolism were normal. Also, decreased exposure to sunlight after stroke is probably an important factor for the low 25-OHD concentrations in patients who are recovering from stroke. In the present study, immobilization-induced bone resorption may account for the increased serum calcium and urinary D-Pyr in the placebo group as evidenced by the correlations between BI and serum calcium or urinary D-Pyr. Hypercalcemia, in turn, may inhibit the compensatory PTH that otherwise would occur in response to hypovitaminosis D; there was a correlation between serum calcium and PTH concentrations in both groups. This inhibition would then decrease renal 1,25-(OH)\(_2\)D production. After 18 months, these abnormalities were still observed in the placebo group.

In conclusion, decreased urinary D-Pyr following risdonate therapy is consistent with the inhibition of bone resorption, which leads to normalization of hypercalcemia. This may have reversed the inhibition of the renal synthesis of 1,25-(OH)\(_2\)D and the subsequent increase in serum PTH. Risdonate is shown to increase BMD in postmenopausal women. This study also demonstrates that it is effective, despite other deleterious factors such as 25-OHD insufficiency and immobility after stroke. Because serum 25-OHD is one of the major determinants of BMD during the convalescent stage after stroke, therapy with vitamin D and risdonate may be more suitable for hemiplegic patients. However, calcium supplementation with vitamin D should be avoided, since such therapy may further increase hypercalcemia.

Accepted for Publication: April 17, 2005.

Correspondence: Yoshihiro Sato, MD, Department of Neurology, Mitate Hospital, 237 Yugeta, Tagawa 826-0041, Japan (y-sato@ktarn.or.jp).

REFERENCES