A Single Infusion of Zoledronate Prevents Bone Loss After Stroke

Kenneth E.S. Poole, BM, PhD, MRCP; Nigel Loveridge, PhD; Collette M. Rose; Elizabeth A. Warburton, MA, DM, MRCP; Jonathan Reeve, DM, DSc, FRCP

Background and Purpose—Stroke is a major risk factor for hip fracture. Patients with intermediate rather than severe or mild stroke deficits at the time of hospital discharge have the most fractures. This proof-of-concept study evaluated the efficacy of a single infusion of zoledronate, an intravenous bisphosphonate, in preserving hip bone density after stroke.

Methods—In a 1-year randomized, double-blind, placebo-controlled, clinical trial, 27 newly hemiplegic patients (6 females, 21 males) with acute stroke were assigned to receive 4 mg of the intravenous zoledronate (n = 14) or placebo (n = 13) within 35 days. Strict inclusion criteria were followed-up to ensure recruited patients were likely to have residual functional impairment. Both groups received calcium and vitamin D supplementation. The primary outcome measure was the change in bone mineral density (BMD; Lunar Prodigy) at the hemiplegic hip during the year of investigation.

Results—The treatment was generally well tolerated. Mean total hip BMD was unchanged in the hemiplegic hip of the zoledronate group (mean 0.0% change), whereas in the placebo group the total hip BMD changed by −5.5%, with the greatest bone loss observed in the trochanteric subregion (mean, −8.1%). On the unaffected side the mean change in total hip BMD was +1.0% with zoledronate versus a mean change of −2.7% without. Repeated measures ANOVA confirmed the significance of the differences between groups at both hips (hemiplegic, P < 0.001; unaffected, P = 0.002).

Conclusions—Stroke patients were protected from the deleterious effects of hemiplegia on hip bone density for at least 1 year after a single infusion of zoledronate. (Stroke. 2007;38:1519-1525.)

Key Words: bone loss ■ hip fractures ■ randomized controlled trials ■ rehabilitation ■ stroke

Stroke patients are prone to falls, particularly onto the hemiplegic side. Hemiplegia and subsequent immobility predispose these patients to bone loss, resulting in a rapid reduction in bone mineral density (BMD) in the hemiplegic hip. These factors lead to a substantial increase in hip fractures in both sexes and across all age ranges after stroke.1 Most hip fractures after stroke are on the paretic side,2 with 84% caused by accidental falls.3 Early studies suggesting that those with moderate residual functional impairment were at heightened risk of subsequent fracture4 were confirmed in a large cohort study, showing that patients discharged with intermediate (rather than mild or severe) impairment had the highest risk of fracture after stroke.5 Several prospective studies6–9 have reported a steep decline in hip BMD after stroke. During 1 year, bone loss of the greatest magnitude occurred in the hemiplegic hip of those functionally impaired subjects who remained unable to walk 1 week after stroke.6,7

Recent randomized studies appeared to show that in women with acute stroke (with very mild impairment) and in men with chronic stroke (mean, 90 days after stroke), daily oral risedronate reduced hip fractures during 12 to 18 months of treatment, also preventing loss of BMD in the hand bones.10,11 However, more than half of patients are unable to swallow safely in the acute phase of stroke,12 when greatly increased osteoclastic resorption is already evident.13 Existing studies have not evaluated acute interventions in the group known to be at the highest subsequent fracture risk, ie, patients with intermediate functional impairment.5 Zoledronate, a potent intravenous bisphosphonate, has a short administration time, is well-tolerated, and has long-lasting effects on hip BMD in postmenopausal women.14 We proposed that zoledronate therapy might prevent bone loss and hip fractures after stroke,15 and could be administered in acute stroke units, irrespective of swallowing ability.16 The aim of the present study was to prove that a single dose of intravenous zoledronate in patients admitted to an acute stroke unit could prevent bone loss in the hemiplegic hip.

Materials and Methods
This was a randomized, double-blinded, placebo-controlled trial of zoledronate (Zometa 4 mg; Novartis) in newly hemiplegic patients with acute stroke. Patients were randomized to receive a single infusion of zoledronate or placebo within 35 days of stroke. The study population consisted of patients admitted to the Lewin Stroke
TABLE 1. Exclusion Criteria for the RCT

<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>Patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient not walking independently before stroke or previous stroke causing hemiplegia</td>
<td>44</td>
</tr>
<tr>
<td>2. Stroke not affecting the lower limb OR (Functional Ambulatory Category &gt;1 at assessment 7 days after stroke)</td>
<td>149</td>
</tr>
<tr>
<td>3. Unconsciousness or terminal illness</td>
<td>13</td>
</tr>
<tr>
<td>4. Pre-existing dementia or cognitive impairment</td>
<td>32</td>
</tr>
<tr>
<td>5. Aphasia/significant language impairment</td>
<td>45</td>
</tr>
<tr>
<td>6. Renal/hepatic impairment</td>
<td>12</td>
</tr>
<tr>
<td>7. Aged &lt;40 and &gt;89</td>
<td>35</td>
</tr>
<tr>
<td>8. Known or baseline osteoporosis or prior treatment with a bisphosphonate, corticosteroids, or unilateral bone disease affecting BMD; prior hip fracture or prosthetic material at the hip</td>
<td>26</td>
</tr>
<tr>
<td>9. Unable to randomize and give infusion within 35 days of stroke, eg, tertiary referrals from another hospital</td>
<td>37</td>
</tr>
<tr>
<td>10. Current treatment with an aminoglycoside antibiotic</td>
<td>0</td>
</tr>
</tbody>
</table>

*Renal impairment was added as a protocol amendment, see Discussion. The first reason for exclusion was recorded for each subject.

Unit at Addenbrooke’s Hospital between October 2001 and July 2004. Men and women aged 40 to 89 were approached after admission with their first-ever strokes, which were defined using the Oxford Community Stroke Project Classification. Patients were eligible if they were previously walking independently, had clinical evidence of stroke (either hemorrhagic or ischemic on the basis of computed tomography), were unable to walk 1 week after stroke (Functional Ambulatory Category [FAC]; 0 or 1), and could give written informed consent. Exclusion criteria are shown in Table 1. Consent was obtained in accordance with the Second Helsinki Declaration. The study was approved by the regional committee for research ethics. Power calculations were performed using estimates of bone loss from a prospective study. The flow of patients through the trial is shown in Figure 1.

The primary outcome measure (determined before the start of the trial) was the change in BMD at the hemiplegic hip during the year of investigation. Eligible patients underwent dual energy x-ray absorptiometry scanning of both hips and were randomized immediately afterward unless they had existing osteoporosis (an exclusion criterion). BMD was measured with narrow-angle fan-beam dual energy x-ray absorptiometry (Lunar Prodigy, enCORE V6.8; Lunar, Wis). Scans of both hips were performed at baseline and 6 and 12 months (after randomization) by a single operator to minimize positioning errors. The “copy region of interest” function was used to ensure duplicate region of interest placement. The “total hip,” “femoral neck,” and “trochanter” regions were determined automatically. The short-term coefficient of variation (determined by repeated measurements of 3 stroke patients with repositioning in between) was 1.03% (hemiplegic total hip) and 1.12% (femoral neck). Longitudinal drift assessed by phantom measurements was <1%.

Serum vitamin D (25OHD) was assessed immediately after consent. Patients received daily calcium (1g) and vitamin D (800 IU) for the study duration. If baseline 25OHD was <25 nmol/L, a single oral dose of ergocalciferol (100 000 IU) was given (protocol amendment, see Discussion) with calcium and vitamin D thereafter. Central randomization was used, with random numbers generated and the code sealed and kept centrally by a designated trials pharmacist who, after receiving notification of a study participant by the trial team, was responsible for preparing the colorless drug or placebo infusion in 50-mL coded sachets (according to the random number sequence) on the day of infusion. The trial team then collected the coded 50-mL sachet from a receptionist. The infusion was administered over 15 minutes, followed by a single bag of 250 mL of 0.9% sodium chloride solution over 2 hours. The administering team, receptionist, and the patients were blinded to the treatment allocation and preparation procedure.

The physical dependency of the patient was assessed at 0, 6, and 12 months (Barthel index18). Stroke severity was assessed using the Scandinavian Stroke Scale. The FAC assessed the assistance required for ambulation. Serum parathyroid hormone, 25OHD, calcium, phosphate, urea, creatinine, and liver function tests were measured before infusion. Further serum samples were taken on days 1 to 5 and on day 10 after infusion. Fourteen patients (5 drug, 9 placebo) further consented to trans-iliac bone biopsy at a mean of 10.4 weeks (±1.9) after stroke, and histomorphometry was performed on undecalciﬁed sections to assess bone remodeling responses to hemiplegia and zoledronate. Sections were stained with Von Kossa and toluidine blue. Histomorphometric measurements of cancellous, endocortical, and cortical bone were made using light microscopy, a digitizing pad, and image analysis software. Osteoclasts and their precursors were identiﬁed on frozen sections using tartrate-resistant acid phosphatase staining.

Power calculations based on limited published data7 indicated that 15 patients per group were required to have a probability of at least 0.8 (at the 5% level of significance) of rejecting the null hypothesis (that the change in BMD would be the same in both groups) if the total hip BMD in the populations differed by 10% at 12 months. Data were analyzed with JMP software (v 4.0, SAS). A fixed-effects repeated-measures ANOVA model was fitted with time as the repeated measure and drug treatment as the between-subjects factor. The model was used to assess the effects of treatment and the covariate age, baseline 25OHD, time from stroke to infusion,
Scandinavian Stroke Scale, Barthel index, and FAC (as well as the nominal covariates sex, smoking, and stroke type) on hip BMD in the hemiplegic and unaffected sides. The functional scales (Scandinavian Stroke Scale, Barthel index, and FAC) were added to the model separately because of their expected interdependence. The significance of any postinfusion symptoms was determined by comparing the proportions of patients from each group with the symptoms and testing the difference. The paired t statistic was used to compare change scores in calcium between groups. A planned interim analysis was conducted involving 16 patients who had completed the protocol at the end of the second year.

Results
Baseline characteristics are summarized in Table 2. The mean time to randomization (days) was 14±8 (zoledronate) and 14±8 (placebo). The number of days between randomization and the second scan was 189 (18) versus 192 (14), and between randomization and the third scan was 369 (21) versus 365 (12). There was a high prevalence of vitamin D insufficiency. BMD was similar at baseline in the 2 groups. In untreated patients, BMD declined in both the hemiplegic and unaffected hips by 6 months, with the hemiplegic hip showing further reductions over the next 6 months (Figure 2). After 12 months, patients in the placebo group had a 5.5% change in calcium with zoledronate from 9.08 (0.4) mg/dL versus placebo group 5.62 (2.8). The greatest bone loss was observed in the trochanteric region (7.6, 1.3). One patient died (of pneumonia) in the treatment group, and the remaining patients survived and were fracture-free throughout the study.

There was only one significant interaction term in the repeated-measures ANOVA of the hemiplegic side BMD: treatment with zoledronate (P<0.001, Greenhouse-Geyser correction). The other nominal and continuous covariates had insignificant effects. The same was true for the unaffected side BMD (P=0.002, unadjusted). Mean functional status and stroke severity scores improved over time in both groups, but did not differ significantly between groups at the study end point. These changes in functional scales tracked the changes in BMD poorly and functional recovery did not predict change in BMD in either group. Although no bone turnover markers were available in this study, trans-iliac bone biopsy samples taken 10 weeks after stroke were examined for histomorphometric indices of bone remodeling. These samples showed significantly lower numbers of tartrate-resistant acid phosphatase-positive cells in zoledronate-treated patients, consistent with an inhibitory effect of the drug on osteoclasts and their precursors (K.E.S.P., unpublished data, 2006).

Falls and Fractures
There were no fractures during the study. Falls from a standing height or less occurred in 72% (11/13 placebo and 10/14 zoledronate). The median number of falls per patient was 2 (range, 0 to 17).

Adverse Events
The treatment was generally well-tolerated. Postinfusion events that were significantly more common in the zoledronate-treated group were: serum calcium <8.4 mg/dL (7 treated versus 0 placebo; P<0.001) and serum phosphate <3.2 mg/dL (10 versus 0; P<0.001). The mean serum calcium changed with zoledronate from 9.08 (0.4) mg/dL.

| TABLE 2. Baseline Characteristics of Stroke Patients |
|----------------------------------|----------------|----------------|----------------|----------------|
| Measurement                      | Zoledronate*  | Placebo*       | Placebo*       |
|                                  | (Completed)   | (Completed)    | (All Patients) |
| Demographics                     |               |                |                |
| Age, years                       | 66.9 (11.7)   | 72.9 (10.4)    | 73.6 (9.5)     |
| N (females, males)               | 14 (4, 10)    | 13 (2, 11)     | 16 (5, 11)     |
| Hemorrhage                       | 2             | 3              | 4              |
| Infarction                       | 12            | 10             | 12             |
| Biochemistry                     |               |                |                |
| 250HD, nmol/L                    | 36.1 (15.9)   | 35.1 (15.7)    | 37.9 (20.3)    |
| Baseline total hip BMD           |               |                |                |
| Hemiplegic, g/cm²                | 1.03 (0.2)    | 1.01 (0.2)     | 0.99 (0.2)     |
| T score                          | -0.2 (1.4)    | -0.5 (1.2)     | -0.6 (1.1)     |
| Unaffected, g/cm²                | 1.05 (0.2)    | 0.97 (0.2)     | 0.98 (0.2)     |
| T score                          | -0.1 (1.6)    | -0.6 (1.1)     | -0.7 (1.1)     |
| Functional parameters            |               |                |                |
| Baseline Stroke Severity Scale, /48 | 27.4 (6.6)  | 27.1 (6.5)    | 23.6 (7.1)     |
| Baseline Barthel, /100           | 43.9 (19.2)   | 42.7 (19.2)    | 30.0 (21.6)    |

*Mean (SD).
before infusion to 8.52 (0.8) 5 days after infusion ($P=0.03$). In the placebo group it was unchanged: 9.2 (0.4) mg/dL to
9.28 (0.4; $P=0.21$). Baseline 25OHD did not predict hypocalcaemia in the zoledronate-treated patients. In 4 subjects, “acute phase” symptoms of postinfusion malaise and pyrexia were observed (3 zoledronate, 1 placebo; $P=0.114$). In addition, a subject with pre-existing moderate chronic renal impairment had prolonged asymptomatic hypocalcaemia after zoledronate, as well as a transient increase in urea and creatinine. All biochemical parameters returned to baseline levels. In response to this outcome, the study inclusion criteria were amended to exclude patients with renal impairment according to an updated product schedule (Novartis SPC, 2003).

**Figure 2.** Percentage change in main outcome variables with time. Significance of time–treatment interaction by repeated measures ANOVA: total hip BMD (A) $**P=0.0003$; (B) $**P=0.002$; femoral neck BMD (C) $^P=0.139$; (D) $^P=0.216$; trochanteric BMD (E) $^P=0.003$; (F) $^P=0.013$ (*unadjusted F test, **adjusted test).
Discussion

Zoledronate therapy prevented BMD loss from the vulnerable hemiplegic hip. A single intravenous dose administered within 5 weeks of admission effectively prevented bone loss in patients with hemiplegia who were unable to walk unaided 1 week after stroke. This is the first study to demonstrate the efficacy of intravenous bisphosphonates in preventing the substantial loss of bone that can occur in the hemiplegic hip during the first year. In the total hip region, the mean BMD declined in the placebo group by −5.5% and in the trochanteric region by −8.1%, despite calcium and vitamin D supplementation (Figure 2). The individual patient responses are shown in Figure 3. This study has important implications for the bone health of stroke patients because they have a propensity for injurious falls toward the hemiplegic side. In one large series, 82% of stroke patients admitted with a subsequent hip fracture had sustained the fracture on the hemiplegic side. We confirmed the trend for falling, with 72% of patients falling within 12 months but no fractures occurred in either group. Although there are no equivalent studies for comparison in stroke patients, osteoporotic women given a single injection of zoledronate had a mean increase in femoral neck BMD of +2.5% at 12 months. In contrast, we show that the mean femoral neck BMD on the hemiplegic side of zoledronate-treated stroke patients remains stable at 12 months, with +0.1% change (95% CI, −2.5, +2.7). Thus, zoledronate given in the acute stroke unit acts as an effective countermeasure by preventing bone loss at the hemiplegic hip.

Zoledronate is a potent long-acting inhibitor of osteoclastic resorption and, in keeping with this, histomorphometric analysis of trans-iliac biopsy samples from our hemiplegic patients confirmed significantly lower numbers of osteoclasts and their precursors in the zoledronate group. Bone biomarker data are not available for our study patients. In other studies, biomarkers have shown that osteoclastic resorption is substantially increased within 1 week of an acute stroke, remaining elevated 1 year later.

The greatest loss of bone we observed using serial dual energy x-ray absorptiometry was from the trochanteric region (Figure 2E and 2F); changes in femoral neck BMD (Figure 2C and 2D) occurred later than changes at the trochanter. This may be explained by the higher rate of remodeling in the trochanteric cancellous bone compared with the predominantly cortical bone of the femoral neck, as well as altered physiology resulting from reduced tensile forces acting through the muscles attached to the trochanter in hemiplegics. Despite a wide range of BMD responses in the present study, functional status indices did not explain the variance in BMD response in either group. There appear to be unmeasured factors that determine the magnitude of bone loss in moderate to severely affected stroke patients. One possible determinant of bone loss is the duration of unloading of the hemiplegic leg (which was the sole predictor of bone loss in a study of unilateral bone loss after lower limb fractures), but this is difficult to define accurately in stroke patients. Another possibility is autonomic nervous system dysfunction and altered bone blood flow affecting hip BMD on the hemiplegic side.

Stroke patients have a wide spectrum of initial neurological deficits, and varying patterns of motor recovery, weight bearing, and walking function. We carefully selected a group of patients with lower limb hemiplegia because our aim was to target those patients with residual functional impairment who are considered to be at high risk for subsequent bone loss and hip fracture, although the small group size is acknowledged as a limitation. Our study subjects were unable to walk independently 1 week after stroke. Such patients were previously shown to sustain greater bone loss (using hip BMD at 7 and 12 months) than those who could walk 1 week after stroke. This focused approach could be criticized on the basis that the results may not be applicable to the entire stroke population.

![Individual BMD responses (Hemiplegic hip)](image)
population. However, emerging data suggest that focused intervention in particular groups of stroke patients with the greatest risk of subsequent bone loss and fracture may be the key to preventing hip fractures in stroke. It is acknowledged that in a small trial baseline imbalances may still be large enough to influence outcomes. In this trial there was a baseline imbalance in age (treatment group younger), sex (more women in placebo group), and lower severity in treatment group which (although extremely unlikely, given the magnitude of the treatment effect) could partly explain the differences in BMD seen. Finally, we evaluated changes in hip BMD but acknowledge that vertebral BMD responses would also have been of interest in the study population.

Declining hip BMD is one of several factors thought to predispose stroke patients to hip fracture after a fall. However, fall dynamics in recovering hemiplegics may result in falls of greater force, without the usual protective reflexes (such as an outstretched hand) to absorb the impact. To verify that the early protection of hip bone density with zoledronate leads to a reduction in hip fractures, a fracture prevention study evaluating zoledronate or a similar drug in an acute stroke population would be needed. However, with forthcoming studies of zoledronate after hip fracture and in postmenopausal osteoporosis, such a trial may pose ethical problems in light of current guidelines, unless it can be argued that stroke patients have a different mode of fracture or response to zoledronate. Which patients should be targeted is also an immediate challenge to the design of such a trial. Epidemiological studies have shown the greatly increased risk of hip fractures after stroke (with the highest relative risk in younger stroke patients, but higher absolute risk in the elderly) and their timing (highest fracture risk within 1 year of stroke). A high risk of hip fracture in patients with intermediate functional ability was recently shown in a large stroke cohort study that also showed patients with more or less severe disability at discharge did not appear to have a greatly increased risk of fracture.

The most common reasons for ineligibility for our study were a mild functional stroke deficit (able to walk at 1 week) or absent lower limb involvement (38%). Two recent randomized controlled trial evaluated daily oral risedronate in female stroke patients with very mild functional deficits and male chronic stroke patients (mean, 90 days after stroke). There appeared to be a significant reduction in hip fractures (1 versus 7 hip fractures during 12 months in females, 2 versus 10 during 18 months in males). Patients in our study had lower functional scores at baseline; our study patients had mean (SD) Barthel index for placebo and bisphosphonate groups of 33.9 (22.2) and 43.9 (19.2), respectively, (in the “intermediate” range) compared with the 78 (24) and 77 (24) baseline Barthel index (in the “mild” range) reported in the female risedronate study. Thus, there may be several approaches available to the stroke unit physician: early intervention with intravenous bisphosphonates in those with moderate to severe stroke (FAC 0 or 1) or oral bisphosphonates in those with mild strokes, if safe and effective swallowing function and the ability to remain upright during administration can be demonstrated.

Although zoledronate was generally well-tolerated, 2 issues arose from its administration in stroke patients. First, there was an unexpectedly high prevalence of baseline vitamin D insufficiency. Recent reports highlight the risks of intravenous bisphosphonates in patients with vitamin D insufficiency. Our study protocol was amended to allow high-dose vitamin D repletion in those with very low vitamin D, but only 1 patient (from the 11 randomized after the amendment) required this. Second, a prolonged hypocalcemic episode in 1 study patient prompted a protocol amendment excluding patients with renal impairment (pre-existing or acquired), although in future clinical usage a simple dosage adjustment may be used to avoid excluding such patients. Even in those without established renal impairment, we would recommend regular assessment of renal function and hydration status in stroke patients selected for intravenous bisphosphonate treatment.

Conclusion
In acute stroke units and during subsequent stroke recovery, falls and hip fractures are increasingly recognized as costly and devastating complications. A single dose of intravenous zoledronate effectively prevented bone loss after stroke in patients with lower limb hemiplegia. It is the first agent shown to attenuate bone loss at the hip after stroke.

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Disclosures
None.

References


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