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REVIEW

A review of minodronic acid hydrate for the treatment of osteoporosis

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Abstract: Minodronic acid hydrate was the first bisphosphonate developed and approved for osteoporosis treatment in Japan. With regard to inhibition of bone resorption, minodronic acid hydrate is 1000 times more effective than etidronic acid and 10–100 times more effective than alendronic acid. Clinical trials conducted to date have focused on postmenopausal female patients suffering from primary osteoporosis. In these trials, 1 mg of oral minodronic acid hydrate was administrated once daily, and a significant increase was observed in lumbar-spine and hip-joint bone density 1–2 years after administration. All markers of bone metabolism urinary collagen type 1 cross-linked N-telopeptide, urinary free deoxypyridinoline, serum bone alkaline phosphatase, and serum osteocalcin were decreased. The incidence rate of new vertebral and nonvertebral fractures was also decreased. Therefore, effectiveness in fracture prevention was confirmed. A form of minodronic acid (50 mg) requiring once-monthly administration has been developed and is currently being used clinically. A comparative study between this new formulation and once-daily minodronic acid (1 mg) showed no significant differences between the two formulations in terms of improvement rates in lumbar-spine and hip-joint bone density, changes in bone metabolism markers, or incidence of side effects. This indicates the noninferiority of the monthly formulation. Side effects such as osteonecrosis of the jaw or atypical femoral fractures were not reported with other bisphosphonates, although it is believed that these side effects may emerge as future studies continue to be conducted. On the basis of studies conducted to date, minodronic acid hydrate is considered effective for improving bone density and preventing fractures. We anticipate further investigations in the future.

Keywords: osteoporosis, minodronic acid hydrate, treatment, bisphosphonate

Introduction

Osteoporosis is defined as a disease that weakens bone structure and increases the risk of fractures.[1,2] It is becoming a serious issue in our aging society because sufferers are likely to sustain fractures of the vertebrae or femoral neck.[3,4]

Bone remodeling of osseous tissues comprises a dynamic repetition of bone resorption by osteoclasts and bone synthesis by osteoblasts, and this process is regulated to ensure that a balance is maintained.[5] If bone resorption increases relative to synthesis, bone mass decreases, and this is believed to lead to the onset of osteoporosis.

Bisphosphonates are structural analogs of inorganic pyrophosphate, and their basic structure comprises the substitution of the P–O–P bonds in pyrophosphates with P–C–P bonds, which have greater stability in vivo. These medications suppress bone resorption, maintain bone mass, and prevent bone fractures.[6] First-generation bisphosphonates inhibit calcification and bone resorption. Second-generation bisphosphonates have a

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P–C–P bond as their basic structure, with a nitrogen atom in the side chain. These medications show a significant difference in the extent of inhibition of calcification and bone resorption when compared with the first generation.[7]

Third-generation bisphosphonates, including minodronic acid hydrate, contain an amino group in the imidazole ring and are even more powerful inhibitors of bone resorption.[8]

With regard to inhibition of bone resorption, minodronic acid hydrate is 1000 times more effective than etidronate and 10–100 times more effective than alendronic acid.[9] Following administration, minodronic acid hydrate specifically accumulates in the bone. It is then separated from the bone by acid released by osteoclasts during the bone resorption process and selectively taken up by osteoclasts. Conventional bisphosphonates were believed to inhibit bone resorption through the induction of osteoclast apoptosis after being taken up by these cells.

Previous reports have indicated that when minodronic acid hydrates were administrated to rat models with type II collagen-induced arthritis, the number of osteoclasts decreased without the induction of osteoclast apoptosis. These results suggest that minodronic acid hydrate has a metabolic pathway different to that of the existing bisphosphonates.[10] Because farnesyl diphosphate synthase was also inhibited in the mevalonic acid metabolic pathway, bone resorption may be inhibited through the geranylgeranylation of the low-molecular-weight guanosine triphosphate-binding protein in osteoclasts, leading to decreased osteoclastic activity.[11] Because of this powerful suppression of bone resorption, this medication has been used clinically in Japan since 2009. In this study, we reviewed the results of previously published studies in which minodronic acid hydrate was administered for osteoporosis treatment.

Materials and methods

We searched for previous clinical reports on minodronic acid hydrate using Medline and Embase. The search keywords included minodronic acid hydrate, osteoporosis, trauma, older age, and treatment, and the search language was English. Papers without abstracts were excluded.

We searched for papers published between January 1, 2000 and April 1, 2012, targeting studies that investigated the effectiveness of minodronic acid hydrate in fracture prevention and bone-density improvement and with >1-year follow-up for patients.

Results

Using the above criteria, we found four research papers. Three of them involved the once-daily formulation, whereas the remaining one involved the monthly formulation. All were prospective studies (Table 1).

The earliest clinical report investigating minodronic acid hydrate was by Hagino et al.[12] This was a randomized, active-controlled, double-blind, multicenter study. The subjects were 135 postmenopausal females aged ≥ 45 years who received 1 mg of minodronic acid hydrate daily for 12 months. The results of this group were compared with those of a group comprising 135 patients receiving 5 mg of alendronic acid daily.

Table 1 Clinical studies of minodronate acid hydrate in osteoporosis

Author and year of publication	Hagino et al[12] (2009)	Matsumoto et al[13] (2009)	Ito et al[14] (2010)	Okazaki et al[15] (2012)
Study population	n = 270 Minod n = 135 Alend n = 135	n = 704 Minod n = 359 Placebo n = 345	n = 103	n = 692 Minod (1) n = 203 Minod (30) n = 209 Minod (50) n = 229
Patients	≥45 years Postmenopausal	>55 years Postmenopausal	>45 years Postmenopausal	51–89 years Postmenopausal women and men
Follow-up (months)	12	24	12	12
Assessment	Bone mineral density Lumbar spine: hip Bone turnover marker	Vertebral fractures Bone turnover marker	Bone mineral density Lumbar spine: hip Bone geometry Bone-strength indices: femur	Bone mineral density Lumbar spine: hip Vertebral fractures Nonvertebral fractures
Drug	Minod 1 mg daily	Minod 1 mg daily	Minod 1 mg daily	Minod 50 mg monthly
Comparators	Alend 5 mg daily	Placebo	–	Minod 1 mg daily Minod 30 mg/month

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Abbreviations: Minod, minodronate hydrate acid; Alend, alendronate acid.

The study investigated bone density (proximal femur and lumbar vertebrae), bone metabolism markers (urinary collagen type 1 cross-linked N-telopeptide [NTx], urinary free deoxypyridinoline [DPD], and serum bone alkaline phosphatase [BAP]), and the presence or absence of adverse events.

After administration for a year, lumbar vertebral bone density increased by 5.86% with minodronic acid hydrate and 6.29% with alendronate. Femoral bone density increased by 3.47% and 3.27%, respectively.

In terms of bone metabolism markers, urinary DPD decreased more significantly in the minodronic acid hydrate group than in the alendronate group after administration for 6 months. Urinary NTx decreased significantly in the minodronic acid group at both 1 month and 9 months after administration. Serum osteocalcin and serum BAP did not show any differences between the two groups.

The main adverse events were gastrointestinal symptoms, with no significant difference in incidence between groups.

Matsumoto et al[13] conducted a randomized, active-controlled, double-blind study on 359 menopausal patients aged ≥ 55 years with decreased bone density. One milligram of oral minodronic acid hydrate was administrated daily for 24 months. The incidence of new vertebral fractures after administration was investigated and compared with that in a placebo group (n = 345). The levels of bone metabolism markers were designated as the outcome.

The incidence of new vertebral fractures decreased, irrespective of the presence or absence of existing vertebral fractures. The bone metabolism markers (serum BAP, serum osteocalcin, urinary DPD, and urinary NTx) showed a decrease at 6 months after administration, and this decrease was maintained until the end of the follow-up period.

Ito et al[14] conducted a study on 103 postmenopausal female patients aged ≥ 45 years, wherein the patients received 1 mg of oral minodronic acid hydrate daily for 12 months. The outcomes were designated as structural changes in the femoral neck and levels of bone metabolism markers. From 3 to 6 months after administration, bone density, bone strength, and proximal femoral (femoral neck, subtrochanteric region, and shaft) geometry showed improvement. All bone metabolism markers were significantly decreased at a year after administration.

Okazaki et al[15] performed a randomized, active-controlled, double-blind study to evaluate the efficacy of the 50 mg monthly minodronic acid hydrate formulation. A total of 692 patients, including males and postmenopausal females aged 51–89 years, were randomized into three groups: one received a 50 mg monthly oral dose of minodronic acid hydrate (n = 229), one received a 30 mg monthly oral dose of minodronic acid hydrate (n = 209), and one received a 1 mg daily oral dose of minodronic acid hydrate (n = 203). The administration period was 12 months. The outcomes were designated as lumbar vertebral bone density; femoral bone density; levels of bone metabolism markers (serum BAP, serum osteocalcin, urinary DPD, and urinary NTx), serum Ca, and parathyroid hormone (PTH); and frequency of both vertebral and nonvertebral fractures. At the 12-month follow-up, lumbar vertebral and femoral bone density had improved significantly, with no significant differences among the three groups. Bone metabolism markers decreased significantly after administration, with no significant differences among groups. Bone density and bone metabolism markers showed significant improvement at the 12-month follow-up when compared with baseline values in all groups. Serum Ca and serum PTH showed no significant changes, with no significant differences between groups at 24 months after administration. These findings indicated that the efficacy of the 50 mg monthly formulation of minodronic acid hydrate was almost equivalent to that of the 1 mg daily formulation. Most side effects were gastrointestinal symptoms, with no significant differences among groups.

Discussion

The incidence rates of osteoporosis are known to be different between individuals of differing ethnicity.[16] Minodronic acid hydrate was originally developed in Japan, and its usefulness was also verified there;[17,18] therefore, it has been used clinically to treat osteoporosis in Japan since 2009. Minodronic acid hydrate shows the strongest inhibition of bone resorption among all the bisphosphonates used for osteoporosis treatment in Japan. The 1 mg daily formulation of minodronic acid hydrate was the first to be marketed in 2009. Monthly oral administration was investigated thereafter, and no differences were observed in improvement of bone density between 30 and 50 mg monthly oral administrations of minodronic acid hydrate.[15] The 50 mg monthly formulation of oral minodronic acid hydrate has been available since 2011 in Japan.

Our review indicated that bone density increased in both the lumbar vertebrae and proximal femur, verifying an improvement rate equivalent to that observed with alendronate. Strengthening of the proximal femur following minodronic acid hydrate administration was also verified, indicating sufficient efficacy in the enhancement of bone density.

Okazaki et al investigated the effectiveness of minodronic acid hydrate in the prevention of nonvertebral fractures.[15]

In previous studies, minodronic acid hydrate was shown to be effective in the prevention of vertebral fractures; however, there were no reports regarding the prevention of nonvertebral fractures. Okazaki et al demonstrated that the incidence of nonvertebral fractures decreased in the minodronic acid hydrate group compared with that in the placebo group, indicating that the medication may have contributed to the decreased incidence.

Bone resorption markers were also decreased at a relatively early stage, and these findings were sustained for 1–2 years, suggesting that the inhibition of bone resorption occurs at an early stage.

Mori et al[19] investigated the inhibitory effect of minodronic acid compared with risedronic acid alendronic acid on bone resorption in the pit assay using bone cells and in the rat ovariectomized model. This report concluded that minodronic acid hydrate inhibits bone resorption at lower doses compared to risedronic acid and alendronic acid in the pit-formation assay and in the rat model of postmenopausal osteoporosis.

We considered that minodronic acid hydrate has the inhibitory effect of bone resorption risedronic acid and alendronic acid, at least in clinical studies.

The adverse events reported with minodronic acid hydrate were mainly gastrointestinal symptoms, which are the same as those reported with first- and second-generation bisphosphonates. Although the incidence of adverse events was low with minodronic acid hydrate, there were a few cases in which the medication had to be discontinued following the appearance of gastrointestinal symptoms.

On investigation of alendronic acid, there were no significant differences in the incidence of gastrointestinal symptoms between monthly and daily oral administrations.[20,21] In addition, no significant differences in gastrointestinal symptoms related to administration method or concentration were reported by Okazaki et al.[15] It is important to consider the possibility of gastrointestinal symptoms while administering minodronic acid hydrate. In recent years, intravenous alendronate has become available for osteoporosis treatment in order to prevent gastrointestinal symptoms. Although not yet available, intravenous minodronic acid hydrate should also be considered in the future.

To date, no reports have documented osteonecrosis of the jaw and atypical femoral fractures, which have recently been regarded as adverse events. The administration of high concentrations of zoredronic acid, a third-generation bisphosphonate, has been associated with a high risk of osteonecrosis of the jaw.[22] Future reports may show higher incidences of this adverse event.

Minodronic acid hydrate was developed in Japan; therefore, studies conducted to date have been restricted to a comparatively small number of Japanese subjects, many of whom were postmenopausal females. In addition, some studies involved concomitant administration of Ca formulations or oral administration of active vitamin D, whereas others did not. Therefore, the pharmacological efficacy of minodronic acid hydrate monotherapy cannot be systematically analyzed or generalized for the overall population. Further detailed investigations with larger and more heterogeneous samples will be required to confirm the effectiveness of this medication.

Disclosure

The authors report no conflicts of interest in this work.

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