



Calcitonin

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Calcitonin is a 32-amino acid polypeptide hormone of thyroid origin discovered by Copp in 1961 [1] who described it as regulating the plasma calcium concentration, or “tone.” Calcitonin is produced by the parafollicular “C” cells of the thyroid [1], which originate in the neural crest. Immunoreactive calcitonin has been found in many tissues [1].

Calcitonin secretion is stimulated by high plasma calcium levels. Calcitonin does not play a significant role in the regulation of calcium in normal individuals. No skeletal disease has been ascribed to calcitonin deficiency [2].

Calcitonin’s ability to lower serum calcium concentrations is associated with an inhibition of osteoclastic activity. Calcitonin binds to osteoclast receptors. After exposure to calcitonin *in vitro*, osteoclasts undergo flattening of their ruffled border and withdraw from sites of bone resorption [3]. In the continued presence of calcitonin, escape from the inhibitory action occurs in animal models, possibly due to downregulation of calcitonin receptors [4] or development of antibodies [5].

Calcitonin is FDA approved in the treatment of hypercalcemia of malignancy, Paget disease of bone, and postmenopausal osteoporosis in women more than 5 years postmenopausal [6].

Injectable calcitonin in postmenopausal osteoporosis

Effects on bone mineral density

Injectable calcitonin was approved by the FDA in 1984 based on radioactive calcium kinetics and neutron activation analysis data showing

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positive calcium balance with treatment [7–10]. Injectable calcitonin given daily or every other day at 50 IU to 100 IU intramuscularly or subcutaneously was found to increase lumbar spine bone mass in late postmenopausal women in three small, randomized controlled trials [11–14]. The effects of injectable calcitonin on hip bone mineral density (BMD) is not known. The use of injectable calcitonin is limited by side effects of nausea with or without vomiting, local reactions at the injection site, flushing of the face and hands [15], and the inconvenience of injection. Side effects are usually mild, and the severity of side effects is dose dependent.

Effects of injectable calcitonin on fracture

Data on the efficacy of injectable calcitonin in the reduction of vertebral fractures is limited to two studies. In a retrospective cohort study, the Mediterranean Osteoporosis Study, study Kanis [16] examined the rate of hip fracture in patients taking injectable calcitonin compared with patients on calcium alone. Patients taking calcitonin had a reduction in rate of hip fracture (relative risk [RR] 0.69), which was modestly but not significantly lower than that of patients taking calcium alone (RR 0.75).

Injectable calcitonin at 100 IU given 10 days per month was shown by Rico to significantly reduce the risk of vertebral fracture in a small, randomized, single-center study of 72 postmenopausal women with more than one vertebral fracture. The incidence of vertebral fractures was 0.07 per patient year in the group receiving injectable calcitonin and calcium 10 days each month and 0.45 per patient year in the calcium-only group ($P < 0.001$) [14].

Nasal spray salmon calcitonin

Nasal spray calcitonin has been available since 1995 in the United States. The bioavailability of nasal calcitonin is about 25% or less of the administered dose as compared with the intramuscular or subcutaneous preparation, which is 70% bioavailable [17]. An average dose of 200 IU nasal spray calcitonin is thus equivalent to about 50 IU of injectable calcitonin or less.

Efficacy of nasal calcitonin in postmenopausal osteoporosis

Effect on BMD

There are eight published randomized clinical trials on the efficacy of nasal calcitonin on BMD [18–25]. The trials were limited in that the numbers were small and the trials were mostly single-center trials.

Overgaard [18] randomized 37 late postmenopausal women with a history of previous forearm fractures to 200 IU nasal spray calcitonin daily

or placebo. All patients received 500 mg calcium daily. Valid completers who received 200 IU nasal spray calcitonin had a significant increase in lumbar spine BMD of 3.2% compared with the placebo group, which decreased 0.4% ($P = 0.04$). There was a nonsignificant loss of bone at the total skeleton and at the distal and proximal forearm.

In a second study, Overgaard [19] studied 208 women between the ages of 68 and 72 with low forearm bone density who were randomized to placebo nasal spray or 50, 100, or 200 IU calcitonin nasal spray daily for 2 years. All patients received 500 mg of calcium daily. Valid completers ($n = 41$) who received 200 IU nasal spray calcitonin had a significant increase in lumbar spine BMD of 3.0% (confidence interval [CI] 1.8–4.2) versus completers assigned to calcium only who had a mean increase of 1% (CI –0.1–1.5). The treatment group was significantly different from placebo at 6 months ($P < 0.05$). In addition, there was a dose response seen in the lumbar spine BMD.

Ellerington [20] compared the efficacy over 2 years of daily and intermittent (3 days weekly) use of 200 IU nasal spray calcitonin in 72 women who were in early and late postmenopause. No calcium supplementation was given. There was a nonsignificant increase in lumbar spine BMD in patients who took 200 IU nasal calcitonin on an intermittent dosing schedule. However, a significant increase in lumbar spine BMD after 2 years was found in late postmenopausal women treated with nasal calcitonin daily.

Effect of nasal spray calcitonin on prevention of bone loss in early menopause

It has not been established whether calcitonin is effective in preventing bone loss in early menopause. In a small, single-center study, injectable calcitonin was comparable to estrogen/progesterone in reducing lumbar bone loss [20]. Nasal calcitonin was effective in preventing lumbar spine bone loss but not radial bone loss in studies up to 3 years [18,23,24,26]. However, other multicenter studies [27] have not found calcitonin to be protective of early postmenopausal lumbar spine or radial bone loss. Nasal spray calcitonin at 200 IU thus may not be sufficient to inhibit bone resorption in the years immediately menopausal in all women. If nasal salmon calcitonin is effective in reducing bone loss in the early menopausal period, it is more effective in spine (trabecular bone) than cortical bone (hip and radius). Nasal calcitonin has therefore not been FDA approved for prevention.

Effect of nasal spray calcitonin on fracture

There are only two studies of the effect of nasal calcitonin on fracture. Overgaard [19] used pooled data from 50, 100, and 200 IU. Compared with

placebo, nasal calcitonin reduced the rate of vertebral fractures significantly to about one third of the rate seen in patients taking calcium alone (RR 0.23, CI 0.07–0.77) ($P = 0.046$).

The Prevent Recurrence of Osteoporotic Fracture (PROOF) study [27] was a large, 5-year, multicenter, double-blind, randomized study of the efficacy of nasal spray salmon calcitonin of patients with 1 to 5 previous vertebral fractures and low vertebral bone mass (t score < -2.0). Of the original 1255 postmenopausal women (mean age 68 years) who were randomized by investigators in the United States and the United Kingdom, 817 had 1 to 5 prevalent vertebral fractures with follow-up radiographs. Patients were randomized to placebo nasal spray or one of three doses of salmon calcitonin nasal spray daily: 100, 200, or 400 IU. All patients received supplements of 1000 mg elemental calcium and 400 IU vitamin D daily plus usual dietary calcium for a mean total calcium intake of 1800 mg. Baseline variables were similar across each of the four arms. A higher than expected discontinuation rate of 59% was seen, but this was similar across treatment groups and time. Sixty-two percent of the patients were valid completers of 3 years of the trial.

An intent-to-treat analysis of all randomized patients with 1 to 5 prevalent vertebral fractures at baseline and follow-up radiographs revealed significant 36% vertebral fracture reduction in the 200-IU group with a RR compared with placebo of 0.64 ($P = 0.03$) and a 45% reduction in the number of patients with multiple new vertebral fractures [28]. These reductions were seen only in the 200-IU group. When all patients who did not have prevalent fracture but who had follow-up radiographs are included in the analysis, there is a significant 33% reduction ($P = 0.03$) in the risk of vertebral fracture. Significant vertebral fracture reduction was seen with the 200-IU dose by Year 3 and was sustained through Year 5.

Lumbar vertebral bone density increased 1.2% in the 200-IU group in the first year, which was a significant change compared with control only at 1 year. There was no further increase in lumbar BMD after 1 year. There was a mean reduction in serum CTX from baseline of 25% at 12 months, which was sustained at 20% throughout the 5 years in the 200-IU group and in the 400-IU group [28].

The PROOF study was not powered to detect nonvertebral fracture reduction. However, there was a nonsignificant 46% reduction in hip/femur fractures in the 200-IU group compared with placebo (9 of 305 in the placebo group and 5 of 315 in the 200-IU group) and a 28% nonsignificant reduction in humerus/wrist fractures [28]. A post hoc pooled analysis of the two marketed doses 100 IU and 200 IU showed a significant hip fracture reduction of 72% at Year 3 and 68% at Year 5 ($P < 0.05$) [29]. A multicenter study to examine the efficacy of nasal salmon calcitonin in improving function and pain after distal forearm fracture is planned.

A post hoc stratification analysis of the PROOF study has been done in elderly women by Silverman [29,30]. Nasal spray calcitonin reduced risk of

new vertebral fracture by 53% in women over age 60 in the PROOF study and by 59% in women over age 75 in the PROOF study using categorical analysis. Nasal calcitonin was well tolerated in these elderly women [29,30].

Strengths of the PROOF study

The PROOF study confirms that the FDA-approved daily dose of 200 IU nasal spray salmon calcitonin daily safely reduces the risk of new vertebral compression fractures in postmenopausal women with established osteoporosis with prevalent vertebral fractures. Reduction in vertebral fracture risk was independent of baseline variables previously noted to influence fracture risk and response to calcitonin, such as age, years since menopause, number of prevalent fractures, bone markers, and spinal BMD [31].

Limitations of the PROOF study

There are two limitations of the PROOF study. The first is that the discontinuation rate of 59% for the 5 years of the study was high although within the range seen with other approved osteoporosis therapies. Second, a dose-response curve of nasal calcitonin for fracture reduction was not seen. Although there was significant reduction in serum CTX and a significant increase in lumbar spine BMD compared with the control group in Year 1 and Year 2 in the 400-IU group, there was no significant fracture reduction in the 400-IU group [28] using intent to treat analysis. Both the 200 IU and 400 IU had similar effects on fracture efficacy at 3, 4, and 5 years using a complete analysis.

Effect of nasal spray calcitonin on bone markers

Nasal spray calcitonin modestly reduces urine and serum markers of bone turnover within 4 to 8 weeks [32,33]. The response is dependent on continued treatment with nasal calcitonin. After cessation of treatment, all markers return to baseline over a 12-week period. It has been suggested that patients with a higher bone turnover may have a greater response to injectable calcitonin in terms of BMD [34]. In the PROOF study, patients with higher levels of bone turnover had the greatest response to treatment in terms of bone marker reduction (D. Baylink, personal communication, 2001), although all patients responded to nasal spray calcitonin in terms of fracture efficacy irrespective of tertiles of baseline bone markers (urine N telopeptide, serum alkaline phosphatase, or osteocalcin).

Mechanism of effect of nasal spray calcitonin on fracture reduction

The effect of nasal calcitonin on BMD and bone markers is modest, but a significant fracture reduction with 200 IU was observed in the PROOF

study. The degree of vertebral fracture reduction was similar to raloxifene, a selective estrogen receptor modulator, whose vertebral fracture reduction has also been found to be associated with modest increases in lumbar BMD. Recent analyses by Cummings [35] and Sarkar [36] have shown that increases in BMD after treatment explain only 16% and 4% of the fracture reduction seen with alendronate and raloxifene, respectively. It has therefore been hypothesized that nasal spray salmon calcitonin improves bone strength by factors other than BMD, such as improved microarchitecture, decreased bone turnover leading to decreased trabecular perforation, or other unknown factors. It is possible that, with calcitonin, BMD changes are not a valid surrogate for bone quantitative changes. A study of the quantitative effects of salmon calcitonin (QUEST) has examined the effects of salmon calcitonin on bone quality as measured by newer imaging techniques [37]. The study showed presentation of microarchitecture in patients receiving nasal calcitonin (Chesnut, personal communication, 2002).

Use of salmon calcitonin nasal spray in men with idiopathic osteoporosis

Up to 20% of symptomatic vertebral fractures and 30% of hip fractures occur in men. Only alendronate has been shown to be effective in male idiopathic osteoporosis. Lyritis [38] studied the efficacy of 200 IU nasal salmon calcitonin in a 1-year, randomized, double-blind, placebo-controlled study of 28 men with idiopathic osteoporosis ranging in age from 27 to 74 years (mean 52.4 years). All the men received a daily supplement of 500 mg calcium. There was a significant increase from baseline in lumbar spine BMD of $7.1\% \pm 1.7\%$ in the group receiving calcitonin compared with an increase of $2.4\% \pm 1.5\%$ in the placebo group ($P < 0.05$). There was a non-significant increase versus placebo in the femoral neck. Therapy was well tolerated. Nasal salmon calcitonin may be an alternative therapy in men with idiopathic osteoporosis.

Use of calcitonin in glucocorticoid-induced osteoporosis

Several studies using injectable and nasal calcitonin have suggested a potential role for salmon calcitonin in the prevention and treatment of lumbar spine bone loss in patients treated with glucocorticoids. No data on reduction in fracture risk are available. Ringe [39] and Luengo [40] found calcitonin to increase or maintain lumbar spine BMD in patients treated with glucocorticoids. Montemurro [41] found calcitonin to prevent lumbar spine bone loss in glucocorticoid-treated patients. In a randomized, controlled trial comparing calcitonin and calcitriol plus calcium, calcitriol plus calcium, and placebo plus calcium over 2 years, Sambrook [42] found that calcitonin and calcitriol in the second year of study prevented lumbar spine bone loss in patients with glucocorticoid-induced osteoporosis, whereas calcitriol alone did not.

In summary, a few small studies demonstrate that nasal calcitonin may maintain lumbar spine BMD in patients in treatment with glucocorticoids. Data on nasal calcitonin are conflicting with regard to bone loss prevention. No data on fracture reduction are available. No hip BMD data are available. Fracture reduction data are available for the two marketed bisphosphonates (risedronate and alendronate). Until fracture reduction data are available, nasal spray calcitonin should not be considered a first-line agent for the treatment of glucocorticoid-induced osteoporosis.

Analgesic effects of calcitonin

The analgesic effects of salmon calcitonin have been recently reviewed by Silverman [44]. Salmon calcitonin has been found in human brain. Using ¹²⁵I-labeled salmon calcitonin, binding sites have been found in the human CNS. Significant binding has been found in the hypothalamus but also in the periaqueductal grey and dorsal horn, which are neuroanatomical structures involved in nociception. Exogenous salmon calcitonin crosses the blood-brain barrier in rabbits but has not been confirmed to cross the blood-brain barrier in humans.

Central or intracerebro-ventricular (ICV) administration of salmon calcitonin has been observed to have an analgesic effect in preclinical rodent and rabbit models [43]. Intramuscular or nasal salmon calcitonin has been proven to be analgesic for the acute pain of vertebral fracture [44–46], the chronic pain after vertebral fracture [47], the pain of tumor bony metastases [48], and Paget disease [49]. Calcitonin has also reduced the extraskelatal pain of complex regional pain syndrome 1 [50]. The analgesic effect of salmon calcitonin was noted at 1 week or less by visual analog scale (VAS) pain and by a decrease in analgesic consumption by Day 3. Increased mobilization was noted by Week 1 [44]. Salmon calcitonin may have a potential role in reducing the pain of acute vertebral fracture, decreasing immobilization, and reducing analgesic dependence.

The mechanism of bone pain relief by calcitonin is not known but seems to be a central effect [43]. Possible explanations include increases in circulating beta endorphins, inhibition of prostaglandin synthesis, interference with calcium flux, involvement of the cholinergic or serotonergic systems, a direct action on CNS receptors, a neuromodulator effect, or effects on prostaglandins [43]. Intramuscular calcitonin increases endorphins more rapidly in serum, whereas nasal spray (NS) calcitonin increases endorphins more rapidly in CSF [50]. The analgesic effect of calcitonin seems to operate through opioid and nonopioid mechanisms [43]. The analgesic effect of calcitonin may be additive to morphine [43].

Further studies are needed to understand the analgesic effect of calcitonin. The Calcitonin and Pain (CAP) study has been designed to address some of the important basic and clinical questions. In the CAP

study, radiolabeled salmon calcitonin will be administered to primates to confirm that it crosses the blood-brain barrier and CNS binding sites defined by PET scan. The CAP study will also define time of onset of analgesia after a variety of nociceptive stimuli.

Administration and side effects of nasal calcitonin

The recommended dose of calcitonin nasal spray is 200 IU daily administered intranasally in alternating nostrils. Nasal calcitonin may be taken at any time of day and may be taken without regard to timing of meals. Patients should take adequate calcium every day (1000 to 1500 mg calcium) and 400 to 800 IU vitamin D. The medication should be refrigerated until opened and then kept at room temperature and covered to avoid evaporation and condensation on the glass surface of the bottle.

Clinical experience has shown the side effects with nasal calcitonin to be minimal [51]. In the PROOF study, the largest study with salmon calcitonin to date, there was only a significant increase in rhinitis and a significant decrease in headache [28].

Resistance to calcitonin

Calcitonin is a biological agent for osteoporosis, as opposed to bisphosphonates, which, as inorganic agents, bind directly to bone. Because calcitonin is a biological agent, concerns have been raised about the potential for clinical resistance caused by the presence of antibodies or downregulation.

Patients may develop antibodies to calcitonin under treatment [43,44]. Binding antibodies with titers of greater than 1:1000 were observed in approximately 20% of patients in the PROOF study [28]. The presence of these antibodies did not seem to effect fracture efficacy.

Organ culture experiments have suggested the downregulation of osteoclast calcitonin receptors with prolonged exposure to calcitonin with escape from calcitonin effect [4]. Calcitonin receptors return after a calcitonin holiday, suggesting the need for studies of intermittent use of the medication to avoid clinical resistance and potentially to lower costs.

The best way to identify patients who are resistant is not known. Stepan [52] has suggested the use of a loading dose followed by serum CTX measurement.

Use of calcitonin in combination therapy

There are little data on the combination of salmon calcitonin and other anti-resorptives or anabolic agents for osteoporosis. Meschia [53] combined

eel calcitonin and hormonal replacement therapy and observed a significant 10% gain in lumbar spine bone mass at 1 year. Hodsmen [54] found that the increase in bone density with sequential therapy with calcitonin and PTH was no better than cyclic parathyroid hormone alone.

Role of calcitonin in the therapy of postmenopausal osteoporosis

Calcitonin is FDA approved for the treatment but not the prevention of postmenopausal osteoporosis. Nasal spray is the most commonly used delivery system. Calcitonin use is very safe. Its efficacy is considered less robust than estrogen replacement therapy or a bisphosphonate such as alendronate. Calcitonin has been found to reduce risk of vertebral fracture by 36% in patients with prevalent vertebral fracture, similar to the effect of selective estrogen receptor modulators such as raloxifene, which reduces risk 30% [44]. Calcitonin has not been shown to significantly reduce the risk of hip fracture.

Nasal spray calcitonin should be considered one of the options for the treatment of the late menopausal patient with established osteoporosis who may not be tolerant of alendronate or risedronate. Other options include estrogen and raloxifene.

Nasal spray calcitonin should be considered for patients with established osteoporosis who have a history of estrogen-dependent neoplasia, thromboembolic disease, or a history of active gastrointestinal problems such as gastritis, duodenitis, ulcer, or motility problems. Nasal spray calcitonin should also be considered for patients with renal impairment, multiple medications, a rigid lifestyle, or for the institutionalized older patient who is unable to stay upright for 30 minutes after taking a bisphosphonate.

Nasal spray calcitonin should be considered as one of the options for initial treatment of the symptomatic patient with osteoporotic vertebral fracture because of its potential analgesic effect.

Calcitonin is not FDA approved for the prevention of osteoporosis in women at the time of menopause because of the absence of data showing efficacy. Raloxifene and alendronate are available as estrogen alternatives.

Summary

Calcitonin is FDA approved for the treatment of postmenopausal osteoporosis but not for prevention. The preferred delivery system is nasal. Nasal calcitonin is safe and well tolerated. The vertebral fracture efficacy of calcitonin is less robust than the two approved bisphosphonates (alendronate and risedronate) but is similar to raloxifene in the treatment of established osteoporosis. Calcitonin has not been demonstrated to reduce hip fracture risk, although a post-hoc pooled analysis suggests potential effectiveness of nasal calcitonin. Calcitonin produces small increments in

bone mass of the spine and modestly reduces bone turnover in women with osteoporosis. Calcitonin may have analgesic benefit in patients with acute painful vertebral fractures. Treatment with calcitonin should be considered for older women with osteoporosis with painful vertebral fractures and for women who fail to respond to or cannot tolerate bisphosphonates. Calcitonin may also be indicated for women who are unable to take bisphosphonates because of impaired renal function.

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