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Nasal Calcitonin

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Nasal calcitonin is a newly approved treatment for established osteoporosis that increases lumbar spine bone mass, is safe, and well tolerated. Fracture efficacy data is not yet available, although preliminary results are promising. The dose for established osteoporosis is 200 IU. The dose for prevention of postmenopausal osteoporosis has not been established. Nasal calcitonin may be analgesic to bone and may be of benefit in glucocorticoid-induced vertebral osteoporosis. Nasal spray calcitonin may be of benefit to the symptomatic patient with acute vertebral fracture, the complex patient, or the patient with established osteoporosis who is intolerant of bisphosphonates or estrogen.

Key Words: Calcitonin; osteoporosis therapy.

Mode of Action of Nasal Calcitonin

Nasal calcitonin is an antiresorptive agent. Its major action is to decrease osteoclast activity in vitro *(1)* and this appears to be its major mechanism in vivo. In addition, it has been suggested that calcitonin may have an anabolic osteoblastic effect on bone *(2)*, which could improve bone quality *(3)* and reduce incidence of bone fracture *(4,5)*.

Efficacy of Nasal Calcitonin

Three randomized studies suggest the efficacy of nasal calcitonin in increasing lumbar spine bone mass. These studies suggest that nasal spray calcitonin increases lumbar spine bone mass 2–3% as compared to placebo over 2 yr when given at a dose of 200 IU daily in late postmenopausal women.

Overgaard *(6)* in an initial pilot study randomized 40 late postmenopausal women with a history of prior forearm fractures to either 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 bone mineral density (BMD) of 3.2% compared with the placebo group who decreased 0.4% ($p = 0.04$). The results were identical for both the intent to treat group and valid completers. There was no statistically significant difference between nasal spray calcitonin and placebo in both distal and proximal forearm bone mineral content (BMC) or total body bone mineral content among valid completers.

Overgaard in 1992 *(4)* studied 208 females between the ages of 68 and 72 with low forearm bone density in a dose-ranging study. Patients were randomized to placebo or 50, 100, or 200 IU calcitonin nasal spray daily for 2 yr. All patients received 500 mg of calcium daily. Valid completers who received 200 IU nasal spray calcitonin had a significant increase in lumbar spine BMD of 3.0% (CI 1.8–4.2%) in the 24 mo of study vs calcium only who had a mean increase of 1% (CI–0.1–1.5%). The treatment group was significantly different from the placebo group by 6 mo ($p < 0.05$).

Not all patients in the 1992 Overgaard study were responders to nasal spray calcitonin. In a later analysis of this study, 76% (31/41) of valid completers who were treated with 200 IU nasal spray responded to treatment as defined by an increase in bone mass relative to baseline, whereas only 38% of the placebo patients responded *(7)*. Patients who received lower doses of nasal spray calcitonin did not significantly increase bone mass.

Ellerington *(8)* compared the efficacy of 200 IU nasal spray calcitonin to placebo in a 2-yr study. He also compared both early and late postmenopausal women and daily vs intermittent (three times weekly) dosing schedules. This study is of interest in that no calcium supplementation was given. There was a significant increase in lumbar spine BMD in the late postmenopausal women as early as 6 mo ($p = 0.021$). At the end of 2 yr in the late postmenopausal patients using 200 IU daily of calcitonin group, there was a significant increase in lumbar spine bone mass of 1.38% vs placebo, which lost 1.73% ($p = 0.007$). There was no significant increase in lumbar spine BMD in the group taking calcitonin three times weekly (–2.4%, $p < 0.001$). Whereas bone loss in the daily calcitonin group was insignificant at the proximal femur, bone loss was significant in the placebo or intermittent dose group.

Reginster *(9)* studied the efficacy of long-term (5 yr) intermittent nasal spray calcitonin given 5 d weekly in the prevention of lumbar spine bone mass in a randomized study. Bone density increased significantly in the calcitonin group as compared to baseline up to 42 mo (+2.5% ± 0.7%) ($p < 0.01$), but was unchanged statistically at completion of the trial (+1.1 ± 1.1%) [not statistically significant (NS)]. The calcium only group has a significant decrease in

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bone mass after 6 mo, which remained significant at the end of the trial (–6.6 + 1.0%) ($p < 0.01$).

There have been two single center studies showing promising early results that calcitonin may reduce rate of vertebral fracture. Rico *(5)* studied the fracture efficacy of injectable calcitonin in 72 postmenopausal women with more than one vertebral fracture. Rico compared 36 patients given 100 IU of injectable calcitonin plus 500 mg of calcium for 10 d each mo to 36 patients only given calcium for 10 d per month for 24 mo. The incidence of vertebral fractures was 0.07 per patient year in the calcitonin group and 0.45 in the calcium only group ($p < 0.001$). There is a suggestion that injectable calcitonin may reduce hip fracture in the Mediterranean Osteoporosis Study (MEDOS), a nonrandomized epidemiology study *(10)*. The only study to examine fracture efficacy of nasal spray calcitonin was the 1992 study of Overgaard mentioned earlier. In this study, the rate of patients with new fractures was reduced significantly in valid completers in all groups taking nasal spray calcitonin to about one third of the rate seen in the women taking calcium. These results will need to be confirmed with a multicenter study. A 5-yr, multicenter fracture study with nasal spray calcitonin is currently underway.

Studies of Gonnelli revealed that the speed of sound (SOS), broadband ultrasound attenuation (BUA), and the bone Stiffness Index measured with an Achilles ultrasound unit all improved significantly in 78 osteoporotic women ($p < 0.001$) treated with the salmon calcitonin nasal spray (200 IU/d, 1 mo on and 1 mo off for 2 yr). Vertebral BMD had also increased significantly by 1.99% in this study *(11)*. These studies may prove consistent with earlier results of the MEDOS study *(10)* since ultrasound appears to discriminate patients with hip fractures equally well as dual energy X-ray absorptiometry and independently of BMD *(12)*.

The efficacy of calcitonin may be dependent on the degree of bone turnover. Patients with a higher bone turnover have a greater response *(13)*.

Nasal calcitonin did not prevent bone loss in patients with endometriosis treated with gonadotropin-releasing hormone agonists at doses of 200 IU daily *(14)*.

Effect on Bone Markers

The findings of Overgaard that not all patients respond to nasal calcitonin raise the issue of monitoring response with either bone density or bone markers. Kraenzlin *(15)* studied the effect of nasal calcitonin at 100 IU twice daily on bone turnover in postmenopausal women. By 8 wk, he found a decrease of 26% in urine pyridinoline, a 32.7% decrease in urine deoxypyridinoline, a 32.7% decrease in hydroxyproline, and a 24.1% decrease in urine *N*-telopeptide. The reduction in each of these four bone markers of resorption was significant. There was a significant decrease in osteocalcin of 14.4%, but there was no significant decrease in C-terminal procollagen type I peptide. After 8 wk, all resorption markers showed a plateau and a trend to increase. After cessation of treatment at 12 wk, both formation and resorption markers rapidly returned to baseline.

Overgaard studied the correlation of bone marker response to nasal spray calcitonin to incidence of fracture using urinary C telopeptide in the 208 women in his 1992 study *(16)*. In women who fractured during the 2-yr period, the urine C telopeptide remained unchanged at 6 to 9 mo whereas decreases of 30% were seen in women who did not fracture. This may suggest that biochemical markers may be useful to determine nonresponders to nasal calcitonin.

Use in Steroid-Induced Osteoporosis

Nasal calcitonin may be a treatment for glucocorticoid-induced osteoporosis *(17–20)*. Ringe *(17)* found that injectable calcitonin increased lumbar spine bone density in patients with glucocorticoid-induced osteoporosis. Montemurro *(18)* studying a group of patients with glucocorticoid-induced osteoporosis with nasal calcitonin found no bone loss at 2 yr in the treated group as opposed to the control that lost 15%. Luengo *(19)* in a randomized, placebo-controlled study of 44 patients with steroid-dependent asthma found nasal spray calcitonin to be effective in preventing bone loss. Calcitonin at 200 IU every other day increased spinal bone mass in the first year and maintained bone mass in the second year. There was no effect on vertebral fracture rate. Sambrook *(20)* in a 2-yr study compared treatment with calcitriol (1,25 dihydroxy vitamin D3), calcium, and nasal calcitonin. In the second year, there was no lumbar spine bone loss in the group treated with calcitonin and calcitriol, whereas there was lumbar spine bone loss in the groups treated with calcium or calcitriol alone. A large multicenter study of the efficacy of calcitonin nasal spray in glucocorticoid-induced osteoporosis is currently ongoing.

Use in Early Postmenopausal Women

Nasal spray calcitonin at doses up to 200 IU may not be sufficient to inhibit bone resorption in the lumbar spine in some women in the immediate postmenopausal years. Campodarve *(21)* in a dose ranging study in early postmenopausal women using 200, 100, and 50 IU nasal calcitonin found no significant increases in lumbar spine bone mass at either lumbar spine and radius. A dose response effect in early postmenopausal women was suggested by Reginster *(9)*. A multicenter dose-ranging early postmenopausal prevention study which includes a dose arm of 400 IU nasal is ongoing.

Analgesic Effects of Calcitonin

Salmon calcitonin has an analgesic effect *(22)*. It can relieve both bone pain caused by tumor metastases, Pagets, or osteoporosis as well as pain caused by migraine, pancreatitis, and posthysterectomy. The mechanism of pain relief

is not known, but potential explanations include increases in circulating beta endorphins, inhibition of PGE2 synthesis, interference with calcium flux, involvement of the cholinergic or serotoninergic systems, a direct action on CNS receptors or a neuromodulator effect *(22,23)*.

Pun *(24)* studied the analgesic effect of nasal salmon calcitonin in the treatment of vertebral fractures caused by osteoporosis. Patients with vertebral fractures were treated with either nasal spray calcitonin at 200 IU per d or placebo. Pain was graded by visual analog scale. There was a significant decrease in bone pain observed after 7 d. There was a statistically significant reduction in the consumption of analgesic drugs by 7 d after treatment.

Administration and Side Effects of Nasal Calcitonin

Nasal spray calcitonin is generally well tolerated. Overall adverse events of nasal spray calcitonin are similar to placebo nasal spray (26). Nasal symptoms have been most frequently reported for both nasal spray calcitonin and placebo nasal spray (31 and 30%, respectively). The incidence of nasal adverse events was similar between nasal spray calcitonin and placebo *(26)*. There have been no reports of serious nasal side effects such as nasal ulceration *(26)*. The incidence of gastrointestinal upset (<1.8%) and flushing (<1.0%) with nasal spray calcitonin are lower than that seen with injectable calcitonin (gastrointestinal upset 10%, flushing 2–5%) *(25)*. For all other organ systems, side effects are 1% or less.

Since calcitonin is a protein, systemic allergic reactions are possible, although no allergic or anaphylactic reactions have been reported with nasal spray calcitonin.

The recommended dose of calcitonin nasal spray is 200 IU daily administered intranasally in alternating nostrils. Approximately 3% (range 0.3–30.6%) of a nasally administered dose is bioavailable compared with the same dose administered by intramuscular injection *(9)*.

Nasal spray calcitonin can be administered at any time without regard to meals. In addition to calcitonin, patients should take adequate calcium every day (1000–1500 mg calcium) and 400 to 800 IU vitamin D. The medication should be refrigerated until opened, but then kept at room temperature and covered to avoid evaporation and condensation.

Resistance to Calcitonin

Antibody formation against salmon calcitonin has been reported in patients receiving continuous therapy with injectable calcitonin. The clinical significance is controversial since the occurrence of antibodies is not correlated with resistance *(27)*. In the Kraenzlin study *(15)* discussed earlier, only 1 of 10 patients developed antibodies during the 12 wk of study. This patient was fully responsive to nasal calcitonin and had similar decreases in markers of bone turnover. This confirms earlier reports of Reginster *(28)* that antibody formation to calcitonin was not correlated with the skeletal response in patients with Paget's disease receiving nasal calcitonin.

Because of receptor downregulation, a resistance to the hormone may occur after 10 to 12 mo of treatment, which may be avoided or delayed by cyclic administration *(29)*.

Use of Combination Therapy

Combination therapy with estrogen and eel calcitonin not only prevented postmenopausal bone loss, but resulted in a 11.2% gain in lumbar spine bone mass in the first year and 9.2% after 2 yr *(30)*. There have been no studies on the combination of nasal calcitonin with other agents.

Use of Nasal Calcitonin in the Therapy of Postmenopausal Osteoporosis

The author uses nasal spray calcitonin as the agent of choice for the initial treatment of the symptomatic patient with osteoporotic fracture. Nasal calcitonin has a dual role in that it increases lumbar spine bone mass and has an analgesic effect on the pain of acute vertebral fracture. Hopefully, this dual effect helps break the cycle of vertebral fracture by preventing immobility which results in further bone loss.

Patients receiving nasal calcitonin should be followed with an annual bone density measurement of the lumbar spine. Bone markers may be of value in determining which patients are responders to nasal calcitonin. Nasal spray calcitonin should be continued in patients showing a positive effect.

Nasal spray calcitonin should be considered for the asymptomatic late postmenopausal patient with established osteoporosis who may not be tolerant of, or has contraindications to, estrogen or alendronate. This would include the patient with a history of estrogen-dependent neoplasia or a contraindication to estrogen such as a history of pulmonary embolus. Complex patients with active gastrointestinal problems such as gastritis, duodenitis, or ulcer, or patients on high-dose nonsteroidal anti-inflammatory drug (NSAID) therapy should be considered for nasal calcitonin. Patients with renal impairment, complex patients on multiple medications or with a rigid lifestyle, or older patients who are unable to stay upright for 30 min after taking alendronate should also be considered for nasal calcitonin.

Nasal spray calcitonin should also be considered for the younger patient because of its short half-life in bone and calcitonin's long-term safety record. This would include the premenopausal woman with significant osteopenia, athletic amenorrhea, or a child with steroid-induced osteoporosis.

There is insufficient information about efficacy or dosing to recommend nasal spray calcitonin as an estrogen alternative in the immediate postmenopausal years at this time.

In conclusion, nasal spray calcitonin should be considered a safe treatment for established osteoporosis. At doses of 200 IU/d, nasal spray calcitonin prevents and may reverse bone loss in the lumbar spine. Nasal spray calcitonin may be analgesic to bone. Data with regards to fracture efficacy is promising but awaits confirmation from an ongoing multicenter trial.

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