9. Calcitonin in the treatment of osteoporosis

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Abstract • Résumé

Objective: To describe potential therapeutic uses of calcitonin in the prevention and treatment of osteoporosis.

Options: Parenterally and intranasally administered calcitonin (eel, salmon or human).

Outcomes: Fracture, fracture pain and loss of bone mineral density in osteoporosis; increased bone mass, prevention of fractures, reduction of pain and improved quality of life associated with calcitonin treatment.

Evidence: Relevant clinical studies and reports were examined, with an emphasis on recent randomized, placebo-controlled trials. In vitro and in vivo studies of osteoclast activity were also considered.

Values: Reducing fractures and fracture pain, increasing bone mineral density and minimizing side effects of treatment were given a high value.

Benefits, harms and costs: Calcitonin reduces acute pain associated with osteoporotic fractures and has been found useful in treating chronic back pain following vertebral fractures in spinal osteoporosis. It can prevent bone loss and may be effective in preventing fractures. Side effects are dose related and generally mild; they include gastrointestinal, vascular and dermatologic conditions that can be treated symptomatically or by varying the dosage. Side effects are much rarer with nasal administration than with injection. True allergic reactions are rare.

Recommendations: Calcitonin in both intramuscular and intranasal forms can reduce the pain of acute osteoporotic vertebral fractures and may be effective in treating that associated with chronic vertebral osteoporotic fractures. Calcitonin may also prevent postmenopausal bone loss and increase bone density in those with established osteoporosis. Current evidence for long-term prevention of fractures is limited and does not support the use of calcitonin as a first-line treatment for established osteoporosis. Most side effects can be avoided with nasal administration. Further trials are needed to assess fracture prevention and effective dose ranges for treating pain and increasing bone mineral density and to determine the long-term efficacy of calcitonin in secondary osteoporosis, in premenopausal women, in men and in elderly people.

Validation: These recommendations were developed by the Scientific Advisory Board of the Osteoporosis Society of Canada at its 1995 Consensus Conference.

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Calcitonin, a 32-amino-acid polypeptide discovered in 1962, is produced in humans by the parafollicular cells of the thyroid gland. It has an important although as yet incompletely defined role in calcium homeostasis. One of its major physiologic roles in bone metabolism is to suppress the activity of osteoclasts, thereby decreasing bone resorption. Calcitonin from animal species has been used for many years in the treatment of various metabolic bone diseases, especially Paget's disease. Because osteoporosis results partly from an imbalance between rates of bone resorption and formation, calcitonin has been an obvious candidate as a therapeutic agent for the prevention and treatment of osteoporosis. Parenterally administered calcitonin and, more recently, intranasal calcitonin are available in a number of countries around the world. The purpose of this paper is to describe potential therapeutic uses of calcitonin in the prevention and treatment of osteoporosis.

Calcitonin preparations

Several molecular forms of calcitonin are available for therapeutic use. The first commercially available calcitonin was extracted from salmon. This calcitonin, as well

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as that extracted from other fish (e.g., eels), is more potent than human calcitonin and acts over a longer period. More recently, synthetic salmon, human and eel calcitonin have become available. The traditional route of administration has been via subcutaneous or intramuscular injection. Although injectable calcitonin has proved to be safe, the parenteral route has limited its acceptability to patients. Newer formulations for intranasal administration have become popular in some countries. Calcitonin has also been given rectally, but data on this route of administration are limited.

Treatment of fracture pain

Osteoporotic vertebral fractures may be asymptomatic and detected only on radiologic investigation. In many cases, however, vertebral fractures can produce significant pain and debility, which can persist for many months following the fracture. Calcitonin has been used to treat pain associated with a number of bone conditions, including Paget's disease and metastatic bone disease, as well as for the pain from vertebral fractures that occur as a result of osteoporosis. In each condition, pain relief begins within the first several days following initiation of therapy, in many cases before significant alteration in bone metabolism can be demonstrated. This suggests that the pain-relieving action of calcitonin is not primarily a result of its modulation of bone turnover. Although the exact mechanism of acute pain relief is not known, calcitonin is thought to act, at least in part, by stimulating the endogenous opioid system.

A number of early, uncontrolled studies reported a role for calcitonin in relief of the pain of acute osteoporotic vertebral fracture.[1-4] The natural course of pain following such fractures is gradual improvement over several weeks to months. Thus the benefits demonstrated in such uncontrolled studies are only suggestive of a possible therapeutic effect. Comparison with placebo is necessary to demonstrate the efficacy of any agent used for fracture pain relief. At least three randomized, placebo-controlled studies have been reported using calcitonin in acute vertebral fracture cases.[5-7] Assessment of efficacy has been based on

- reports by patients of spontaneous pain at rest or in various positions,
- reports by patients of induced pain,
- physician assessment of the degree of patient pain,
- the degree of limitation of activities and
- doses of analgesics used by patients.

By these criteria, calcitonin has been shown to produce significant alleviation of the acute pain that occurs as a result of osteoporotic vertebral fracture. The effects of pain reduction persist for at least the first month of administration. Only salmon calcitonin has been used in controlled trials, although data suggest that all forms by all routes may be active. One study demonstrated a beneficial effect in glucocorticoid-induced osteoporotic vertebral fractures.[6]

Chronic back pain can develop following vertebral fractures in spinal osteoporosis. The mechanisms are unclear but may include persistent injury to the vertebrae, degenerative changes subsequent to the fracture and pain originating from paraspinal tissues resulting from abnormal anatomical positioning and spinal malalignment. One randomized, placebo-controlled study[8] has demonstrated that calcitonin may provide pain relief in this chronic state. Pain relief may occur if calcitonin is instituted anytime within the first year after fracture, although data suggest that the benefit is greater the earlier the drug is administered. Pain relief continues for at least 4 months of administration. In the reported study, synthetic human calcitonin was administered subcutaneously at doses of 0.125 or 0.25 mg three times per week.[8]

Most studies of pain relief in osteoporotic vertebral fractures have assessed only postmenopausal women. One report[7] included a small number of male patients, but no separate analysis is available to determine whether their response rates are different from those of postmenopausal women. Data are also limited on the use of calcitonin for relief of pain following fracture at nonvertebral sites or in secondary osteoporosis.

Role of calcitonin in the prevention of fractures

The effects of calcitonin on bone can be considered in three areas: biochemical markers of bone turnover, bone density and fracture rate.

Biochemical markers of bone turnover

In-vitro and in-vivo studies show that calcitonin is effective in inhibiting osteoclast activity, thereby reducing bone resorption. The biochemical markers of bone resorption, such as urinary hydroxyproline and pyrodinolines, are decreased. However, demonstration of reduction in the biochemical parameters of bone turnover in the short term does not necessarily indicate long-term improvements in bone mass or reduction in fracture prevalence.

Bone density

A large number of uncontrolled studies, often of short duration, using different preparations of calcitonin have shown that bone density increases significantly during the course of observation. However, as randomized, placebo-controlled studies are considered necessary to assess this effect of calcitonin, only this type of study will be considered further. The majority of such studies have demonstrated greater bone density in calcitonin-treated patients compared with controls.[8-24] In some cases, controls were given only placebo, in others, both treatment and control groups received calcium or calcium and vita-

min D supplements. Differences in bone density have been demonstrated as early as 3 months following institution of calcitonin treatment, and benefits have been reported to persist for up to 3 years and, in one small study, 5 years. In some studies, bone density did not increase; it was merely maintained, compared with a loss of bone density in the control group. In other studies, bone density increased by as much as 5% to 10% over 2 years of therapy. This is similar to the increase in bone density seen with the bisphosphonates, another class of drugs that inhibits bone resorption.

This implies that the increase in bone density associated with calcitonin treatment is another example of improvement secondary to filling in the resorption space. Because calcitonin is primarily an antiresorptive agent, it may be most effective in situations where bone resorption is increased. In one well-conducted study,[25] calcitonin was most effective in preventing further bone loss and modestly increasing bone mass in patients with increased bone turnover, compared with a low turnover group in whom little significant effect of calcitonin was observed. Only one controlled study[21] has included male patients, but no separate analysis is available to determine whether their response differs from that of postmenopausal women. The same report studied glucocorticoid-induced osteoporosis and demonstrated a beneficial effect of calcitonin on bone density. Controlled data on the use of calcitonin in other forms of secondary osteoporosis are limited.

Several studies,[11,12] mostly of short duration (1 to 2 years), have demonstrated the efficacy of both parenteral and intranasal calcitonin in preventing bone loss in the early postmenopausal period. On the basis of these data, it has been suggested that calcitonin might be a useful alternative for those who cannot or will not take estrogen.

Beneficial effects on bone density have been demonstrated for virtually all forms of calcitonin over a wide range of dosages, although formal dose-ranging and dose-response studies are limited. Intermittent dosing schedules have also been studied and appear to be effective,[15] but long-term confirmatory evidence is required.

Long-term effects of calcitonin on bone density are not known, as most controlled studies report data for only 1 to 2 years of therapy; the longest controlled study is 3 years of treatment.[20] Uncontrolled studies have suggested that bone density either reaches a plateau or may actually begin to decrease after several years of calcitonin therapy.

Antibodies to calcitonin, particularly to fish calcitonin, develop in a significant proportion of patients receiving long-term treatment. There is some concern that these antibodies may diminish the efficacy of calcitonin, but the extent to which they interfere with calcitonin action remains unresolved. Measurement of calcitonin antibodies is a research tool and is not indicated for patient monitoring or treatment decisions.

Fracture rate

Several early, controlled studies designed to look at changes in bone density in response to calcitonin therapy also reported on fracture incidence. The relative risks calculated from these data are contradictory. However, none of these studies was designed to look at fracture rates, and patient numbers were too small to produce statistically significant risk assessments. There have been at least two controlled, randomized studies,[24,26] both of 2 years' duration, that have produced statistically significant reductions in vertebral fracture rates in calcitonin-treated postmenopausal women. One of these[24] also found a decrease at all fracture sites.

In one study,[26] patients were given salmon calcitonin intramuscularly for only 10 days per month at a dose of 100 IU/d, along with a calcium supplement. The other study[24] gave 50, 100 or 200 IU/d of salmon calcitonin intranasally along with calcium. The design of this study[24] is better, and it shows a convincing small but statistically significant sustained increase in lumbar vertebral bone mineral density in elderly postmenopausal women with established osteoporosis. In addition, despite the small number of patients (particularly as only the 200 IU/d dose was consistently efficacious), there was a significant reduction in the prevalence of fractures.

This study[24] was not specifically powered to look at fracture rates; thus, it was fortuitous that the authors were able to detect a significant difference among the groups given the small sample size. Despite the fact that initial fracture rates were low (fewer than 10% to 15% of participants had vertebral fractures at baseline), the small number of patients and other methodological problems, this trial demonstrates a statistically significant increase in bone mineral density resulting from 200 IU/d of calcitonin administered nasally over 2 years.

Data on hip fractures from prospective, controlled studies are limited. A single case–control study[27] of postmenopausal women demonstrated a significant reduction in hip fractures in calcitonin-treated patients compared with controls. Although suggestive, this finding is limited by the inherent selection biases and weaknesses of case–control methods. There are no control data on fracture risk in men, in premenopausal women or in secondary osteoporosis. There is no information on whether apparent benefits are sustained beyond 2 years of calcitonin treatment.

Side effects

Side effects in patients receiving intramuscular or subcutaneous calcitonin are dose related and generally inconvenient rather than serious, but can occur in up to 80% of patients on high doses. The most common side effects are gastrointestinal and consist of anorexia, nausea, vomiting, a metallic taste or, rarely, diarrhea. Vascu-

lar phenomena, such as flushing or shivering, are the next most common, followed by dermatologic changes, including a local rash at the injection site, a generalized rash and pruritus. These skin changes are usually not immunologic in origin. True allergic reactions, consisting of urticaria and anaphylaxis are rare. In the past, a test dose of calcitonin with medical monitoring was recommended to detect individuals with an acute allergic reaction. This approach is probably not necessary because of the rarity of anaphylaxis and because anaphylaxis may occur only after multiple doses. Headache and diuresis may also occur in some patients.

Side effects of nasal calcitonin are similar to those occurring with the injected drug, but are much less common. Local skin reactions do not occur as they are sequelae of the injection method, but nasal irritation may occur. Anaphylaxis has not been reported.

Specific side effects may be treated with medications that relieve the symptoms. Alternatively, because most side effects are dose related and decrease in severity with duration of use, the calcitonin dose may be reduced and gradually increased as tolerated. Even with these measures, up to a third of people using injected calcitonin will discontinue therapy. Only a small fraction will stop using the much better tolerated nasal calcitonin.

Conclusions

- Calcitonin can be an effective therapy for the pain of acute osteoporotic vertebral fractures and should be instituted as early as possible. Both intramuscular and intranasal forms are effective. Therapy should be adjusted according to response and may be effective for at least 1 month.
- Calcitonin may provide relief of back pain in patients with chronic vertebral osteoporotic fractures and can provide benefit for several months in those who respond.
- Calcitonin given either parenterally or intranasally has been shown to prevent bone loss in the early postmenopausal period and in women with established osteoporosis.
- The evidence for efficacy of calcitonin for long-term prevention of fractures is limited; therefore, it is not possible to provide an accurate estimate of the degree of fracture risk reduction. Although data suggest that calcitonin can reduce fracture incidence, current evidence does not provide strong support for the use of calcitonin as a first-line treatment for established osteoporosis.
- Calcitonin is a safe drug, but it can produce a wide range of usually mild side effects in a significant proportion of patients when injected. Side effects are much less common with the nasal route of administration.
- Further randomized, controlled clinical trials of calcitonin therapy — particularly assessing fracture prevention and effective dose ranges for treating pain and improving bone mineral density — are necessary to delineate more fully the role of calcitonin in osteoporosis therapy. Studies are also needed to determine specifically the long-term efficacy of calcitonin in secondary osteoporosis, in premenopausal women, in men and in elderly people.

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