

## Calcitonin in the Treatment of Osteoporotic Bone Pain

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Calcitonin has been observed to have an analgesic effect on painful bone conditions. A case illustrating the antinociceptive effect of calcitonin on bone pain caused by osteoporotic vertebral compression fracture is presented. There is increasing clinical evidence supporting this phenomenon, though few rigorously controlled studies exist. Calcitonin may have an advantage over

other analgesics in the treatment of bone pain resulting from an osteoporotic compression fracture, because, in addition to the observed analgesic effect, it is useful in treating the underlying disorder.

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Calcitonin, a natural hormone produced by the parafollicular "C" cells of the thyroid, has been investigated for its potential role in halting or reversing the progression of osteoporosis.<sup>1-5</sup> In humans, calcitonin is believed to inhibit osteoclastic bone resorption and to exert an analgesic effect on diseases associated with bone pain.<sup>6-16</sup>

The case report below illustrates the use of calcitonin in the reduction of pain caused by an osteoporotic compression fracture.

### Case Report

A 76-year-old woman was admitted to the hospital for progressively severe midback and flank pain of 6 weeks' duration. She was recovering from viral bronchitis with a stubborn cough when she first developed this pain. Initially, her symptoms were thought to be associated with bronchitis, but further investigation revealed that the pain was sharp and intermittent in nature, and was aggravated by even slight movements. Radiographs obtained 2 weeks before admission revealed a vertebral compression fracture of T-6. She became increasingly more uncomfortable despite the use of potent analgesics. Eventually, the pain prevented ambulation and she was admitted to the hospital.

The patient was a postmenopausal white woman of medium build. These factors increase the risk for os-

teoporosis. She was taking estrogen replacement and calcium supplementation. She had no history of smoking or alcohol use, and although she was active around the house, her activity had diminished owing to poor eyesight resulting from retinal degeneration.

A physical examination at the time of admission revealed an alert woman lying on her side, gripping the bed rail, and crying in pain. Findings on abdominal examination were normal except for slight left upper quadrant tenderness that produced the same pain that the patient felt in her back. No gross back deformity or spasm was found. Her back was tender from T-6 to L-5. She also had deep gluteal tenderness, which was greater on her left side. Knee and ankle reflexes were 1+ bilaterally, and tests for Babinski signs were negative. Manual motor strength testing and sensation were grossly intact. The patient was unable to stand because of pain. Rectal examination revealed normal tone.

Initial management included pain control and investigation into the cause of the fracture. Radiographs taken at the time of admission were remarkable only for the compression fracture previously seen at T-6. A subsequent bone scan revealed increased uptake at T-6, T-11, and T-12 (Figure 1). Multiple myeloma and malignancy were ruled out, and the compression fractures were determined to be secondary to osteoporosis. Pain control was attempted with ketorolac injections. Narcotics were avoided, as the patient had developed severe constipation while taking oxycodone before admission. Her pain did not respond well to ketorolac. Meperidine was then administered intramuscularly, which provided only minimal relief of her symptoms and aggravated her constipation.

Subcutaneous salmon calcitonin injections (100 IU

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Figure 1. Bone scan showing increased uptake at T-6, T-11, and T-12.

daily) were then begun in an attempt to relieve her symptoms and arrest further bone loss. The patient noticed pain improvement within 48 hours. Administration of meperidine was tapered off, and the patient began to ambulate. She was instructed on self-administering calcitonin injections, a procedure that she learned easily.

She was able to walk independently 1 week after starting calcitonin, and was discharged. Two days later she no longer required pain medications. Four weeks after being discharged, the patient no longer required muscle relaxants (Chlorzoxazone) and was able to perform most of her activities of daily living without pain.

## Discussion

Calcitonin was first discovered in 1962, but its exact physiologic role is still uncertain.<sup>17</sup> Its principal actions are inhibiting osteoclastic bone resorption, and, in higher doses, lowering serum calcium.<sup>17</sup> Calcitonin has been approved for treatment of osteoporosis, hypercalcemia, and Paget's disease because of this positive effect on bone mass.

Interest in using calcitonin to treat osteoporotic bone pain arose from clinical observations that it possessed analgesic qualities.<sup>6-16</sup> In several studies, pain relief induced by calcitonin preceded any significant effect on the skeletal disorder.<sup>15,16</sup> This suggests that calcitonin

possesses a primary analgesic property that is independent of its effect on bone.

The pathophysiology of calcitonin's observed analgesic effect is not fully understood. Several animal studies support the phenomenon and provide theories explaining possible mechanisms. Calcitonin is found in portions of the central nervous system (CNS) and pituitary gland, and investigators have speculated that it may act as a neurotransmitter or neuromodulator.<sup>17-19</sup> Studies in rodents have found high concentrations of calcitonin receptors in the periaqueductal gray matter and mesencephalic reticular formation.<sup>20</sup> Furthermore, salmon calcitonin was found to have a significant analgesic effect when injected directly into the CNS.<sup>20,21</sup> The analgesia induced by calcitonin has been found to be both resistant to naloxone and reversible. Thus, in rodents calcitonin apparently produces its analgesic effect by interaction with both opiate and nonopiate receptors.

In humans a number of hypotheses explaining the mechanism of calcitonin's analgesic properties have been proposed. Studies using calcitonin on patients with osteolytic metastases and bone pain found that clinically significant analgesia was associated with an increase of circulating  $\beta$ -endorphin levels.<sup>8,11</sup> This led to the theory that calcitonin may potentiate the body's endogenous opiate system and thereby relieve pain.<sup>22</sup> Other theories suggest that calcitonin may act locally by reducing calcium, which in turn decreases pain receptor sensitivity, or by directly affecting local pain mediators.<sup>22,23</sup> Since some believe that osteoporotic bone pain may arise as a result of rapid bone resorption or destruction, another hypothesis is that the primary effect is due to the antiresorptive property of calcitonin.<sup>24</sup> In humans, calcitonin minimally crosses the blood-brain barrier. However, it produces significant analgesia when injected peripherally.<sup>22</sup> Therefore, the action of calcitonin on CNS receptors seen in rodents is difficult to extrapolate to humans. Clearly there is no consensus on the mechanism of calcitonin-induced analgesia, and further research needs to be done.

Though calcitonin has been observed to decrease the pain secondary to osteoporotic vertebral compression fractures, few clinical studies supporting this phenomenon exist. Generally these studies were not placebo controlled; therefore, the observed analgesic effect cannot be distinguished from that of spontaneous remission or a placebo effect.<sup>25,26</sup> Furthermore, these studies used subjective measures of pain relief and did not attempt to compare the analgesic effect of calcitonin with other analgesics. To date, only one double-blinded, placebo-controlled trial using calcitonin to treat the pain of vertebral compression fractures has been done. Pun and Chan<sup>24</sup> demonstrated that intranasal salmon calcitonin significantly reduced pain compared with placebo in 18

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patients with acute vertebral collapse secondary to osteoporosis. Improvement in pain control was evident both on a descriptive pain scale and by a decrease in the consumption of analgesic drugs.

Currently, several calcitonin preparations are commercially available in the United States. They are all synthetic polypeptides and are based on either human or salmon calcitonin. Salmon calcitonin is more potent than its human counterpart. Salmon calcitonin has a few possible adverse effects: flushing, nausea, vomiting, and local irritation. The current dose recommended for osteoporosis is 100 IU daily, given subcutaneously. Since few studies have been done investigating calcitonin's analgesic effect, no consensus on dosing or duration of treatment exists. In the United States it is currently only available in injectable form, but intranasal calcitonin is available in other countries.

The studies describing the analgesic effect of calcitonin in osteoporotic bone pain are consistent with our experience with this patient. Although it is possible that the patient experienced pain relief merely by the healing of her fractures over time, her recovery was more dramatic and sudden than would be expected solely by the natural healing process.

In summation, calcitonin has been observed to possess an analgesic effect in many painful bone conditions. Further research is needed to determine the precise role of calcitonin in the treatment of bone pain. However, based on the existing clinical evidence that calcitonin can slow or halt the progression of osteoporosis, calcitonin has an advantage over other analgesics in that it has minimal side effects and is useful in treating the underlying disorder. This successful use of calcitonin to relieve protracted bone pain further contributes to the body of clinical observations that calcitonin is an effective analgesic for severe osteoporotic bone pain.

## References

- MacIntyre I, Stevenson JC, Whitehead MI, Wimalawansa SJ, Banks LM, Healy MJ. Calcitonin for prevention of postmenopausal bone loss. *Lancet* 1988; 1:900-2.
- Reginster JY, Denis D, Albert A, et al. 1-Year controlled randomized trial of prevention of early postmenopausal bone loss by intranasal calcitonin. *Lancet* 1987; 2:1481-3.
- Overgaard K, Hansen MA, Nielsen VA, Riis BJ, Christiansen C. Discontinuous calcitonin treatment of established osteoporosis: effects of withdrawal of treatment. *Am J Med* 1990; 89:1-6.
- Gruber HE, Ivey JL, Baylink DJ, et al. Long-term calcitonin therapy in postmenopausal osteoporosis. *Metabolism* 1984; 33:295-303.
- Mazzuoli GF, Passeri M, Gennari C, et al. Effects of salmon calcitonin in postmenopausal osteoporosis: a controlled double-blind clinical study. *Calcif Tissue Int* 1986; 38:3-8.
- DeRose J, Singer FR, Avramides A, et al. Response of Paget's disease to porcine and salmon calcitonins: effects of long-term treatment. *Am J Med* 1974; 56:858-66.
- MacIntyre I, Evans IM, Hobitz HH, Joplin GF, Stevenson JC. Chemistry, physiology, and therapeutic applications of calcitonin. *Arthritis Rheum* 1980; 23:1139-47.
- Roth A, Kolaric K. Analgetic activity of calcitonin in patients with painful osteolytic metastases of breast cancer. Results of a controlled randomized study. *Oncology* 1986; 43:283-7.
- Altman RD, Collins-Yudiskas B. Synthetic human calcitonin in refractory Paget's disease bone. *Arch Intern Med* 1987; 147:1305-8.
- Schiraldi GF, Soresi E, Locicero S, Harari S, Scoccia S. Salmon calcitonin in cancer pain: comparison between two different treatment schedules. *Int J Clin Pharmacol Ther Toxicol* 1987; 25:229-32.
- Szanto J, Jozsef S, Rado J, Juhos E, Hindy I, Eckhardt S. Pain killing with calcitonin in patients with malignant tumours. *Oncology* 1986; 43:69-72.
- Serdengecti S, Serdengecti K, Derman U, Berkarda B. Salmon calcitonin in the treatment of bone metastases. *Int J Clin Pharmacol Res* 1986; 6:151-5.
- Ricevuti G. Effects of human calcitonin on pain in the treatment of Tietze's syndrome. *Clin Ther* 1985; 7:669-73.
- Hindley AC, Hill EB, Leyland MJ, Wiles AE. A double-blind controlled trial of salmon calcitonin in pain due to malignancy. *Cancer Chemother Pharmacol* 1982; 9:71-4.
- Cohn SH, Dombrowski W, Hauser W, Klopfer J, Atkins HL. Effects of porcine calcitonin on calcium metabolism in osteoporosis. *J Clin Endocrinol Metab* 1971; 33:719-28.
- Milhaud G, Talbot JN, Coutris G. Calcitonin treatment of postmenopausal osteoporosis. Evaluation of efficacy by principal components analysis. *Biomedicine* 1975; 22:223-32.
- Austin LA, Heath H 3d. Calcitonin: physiology and pathophysiology. *N Engl J Med* 1981 29; 304:269-78.
- Welch SP, Dewey WL. The activity of several peptide fragments of parathyroid hormone, alone and in combination with salmon calcitonin and morphine, in antinociceptive tests in the mouse. *J Pharmacol Exp Ther* 1990; 252:140-6.
- Adams ML, Brase DA, Welch SP, Dewey WL. The role of endogenous peptides in the action of opioid analgesics. *Ann Emerg Med* 1986; 15:1030-5.
- Fabbri A, Fraioli F, Pert CB, Pert A. Calcitonin receptors in the rat mesencephalon mediate its analgesic actions: autoradiographic and behavioral analyses. *Brain Res* 1985; 343(2):205-15.
- Welch SP, Cooper CW, Dewey WL. Antinociceptive activity of salmon calcitonin injected intraventricularly in mice: modulation of morphine antinociception. *J Pharmacol Exp Ther* 1986; 237:54-8.
- Gennari C, Avioli LV. Calcitonin therapy in osteoporosis. In: *The osteoporotic syndrome 2*. Philadelphia: Grune & Stratton, 1987; 121-42.
- Guidobono F, Netti C, Sibilia V, Olgiati VR, Pecile A. Role of catecholamines in calcitonin-induced analgesia. *Pharmacology* 1985; 31:342-8.
- Pun KK, Chan LW. Analgesic effect of intranasal salmon calcitonin in the treatment of osteoporotic vertebral fractures. *Clin Ther* 1989; 11:205-9.
- Maresca V. Human calcitonin in the management of osteoporosis: a multicentre study. *J Intern Med Res* 1985; 13:311-6.
- Pontioli AE, Pajetta E, Calderara A, et al. Intranasal and intramuscular human calcitonin in female osteoporosis and in Paget's disease of bones: a pilot study. *J Endocrinol Invest* 1991; 14:47-51.