Efficacy and Tolerability of Calcitonin in the Prevention and Treatment of Osteoporosis

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Abstract

Calcitonin in general, and, more specifically, salmon calcitonin (salcatonin), has been known for 30 years to be a specific inhibitor of bone resorption. Studies have confirmed its efficacy in metabolic bone diseases characterised by excessive bone resorption, such as osteoporosis. Most randomised studies in which salcatonin and oral calcium were administered for 1 to 5 years to recently postmenopausal women for the prevention of osteoporosis have shown that bone mineral density or bone content of the lumbar spine increased significantly, compared with a reduction among women receiving calcium only. Prospective studies have shown that salcatonin is effective in the treatment of established osteoporosis, reducing significantly the relative risk of new vertebral fractures.

The benefits of salcatonin nasal spray therapy were observed in the majority of women studied, and it has been shown to be an effective alternative for osteoporotic women more than 5 years postmenopausal who refuse estrogens, or for whom estrogens are contraindicated. Finally, in established osteoporosis, nasal calcitonin possesses a potent analgesic effect. The well-demonstrated effects of nasal calcitonin permit it to be considered a well tolerated and efficient approach for prevention and treatment of postmenopausal osteoporosis.
1. Pharmacological Properties

Since its discovery more than 30 years ago, calcitonin has been extensively tested both in animals and humans. In humans, calcitonin is mainly produced by the C cells of the thyroid[1] and is a polypeptide containing 32 amino acid residues.

1.1 Relative Activity

There are several differences in the amino acid composition of the calcitonins from different species, and these are associated with different potencies.[2] The biological activity of different calcitonins is expressed in MRC (Medical Research Council) units, also called IU (International Units).[3] It is measured through induction of hypocalcaemia at 1 hour after injection in a standardised model using young rats. The mass corresponding to 1 unit of calcitonin differs widely from species to species. Eel and salmon calcitonins have the highest activity/weight ratio. Pig and human calcitonins have a weaker effect for the same weight. An assessment of the relative potencies of various calcitonins reveals that calcitonins from teleostean fish are 50 to 100 times more potent than those from mammals, and also have a longer duration of hypocalcaemic activity.

1.2 Endogenous Calcitonin

Secretion of endogenous calcitonin is modulated by many factors. These include blood calcium level, which is the main physiological factor regulating calcitonin secretion. Calcitonin inhibits bone resorption and thereby lowers plasma calcium. Calcitonin is a calcium-regulating hormone with a negative feedback mechanism. Calcitonin also seems to belong to the neuro-endocrine system. Receptors to calcitonin have been found in the central nervous system.

1.3 Exogenous Calcitonin

Because of its anti-osteoclastic and analgesic properties, calcitonin is a first line choice in the treatment of several bone diseases characterised by absolute or relative bone resorption.

1.3.1 Effects on Bone

All calcitonins have an anti-osteoclastic property. Osteoclasts possess specific receptors that bind calcitonin. Administration of calcitonin causes the brush border of the osteoclasts to disappear and the osteoclasts to move away from the bone resorption surface. Calcitonin radically alters the internal structure of isolated osteoclasts, inhibiting cytoplasmic mobility, which is essential for bone resorption. Finally, calcitonin reduces the lifespan and number of osteoclasts, probably by decreasing their rate of formation by blocking the fusion of mononuclear marrow cells, the committed progenitors of the osteoclasts that are known to possess calcitonin receptors.

Zimolo et al.[4] demonstrated a quantifiable pharmacological effect of calcitonin on single osteoclasts. They were able to show in animal models that Na+-independent acid extrusion is stimulated by osteoclast attachment to bone and is virtually absent when osteoclasts are treated with salcatonin.

1.3.2 Routes of Delivery

For many years, it was necessary to administer calcitonin parenterally, by either intramuscular or subcutaneous injection. With respect to the prevention and treatment of postmenopausal osteoporosis, the chronic nature of the disease and the subsequent long duration of the pharmacological intervention required uncomfortable repetitive long term administration. New routes of administration have therefore been developed. Rectal administration is very efficient, but does not seem to be well accepted from a social or personal standpoint. Oral administration of polypeptide hormones is precluded because of gastrointestinal digestion; at present, the most promising delivery method is that of nasal spray. In a recent review,[5] it was concluded from comparative studies evaluating the effects of intranasal and parenteral salcatonin in healthy volunteers that equivalent biochemical effects are obtained when the intranasal dosage is approximately 2 to 4 times that of the parenteral dosage, although full dose-response curves are not concurrently available for the 2 routes of administration.