Salmoncal

Salmon calcitonin 100 I.U.

Product Monograph

INDEX

INTRODUCTION

INTRODUCTION

Osteoporosis is the most common bone disorder seen in clinical practice and has become a major public health issue. It exists in all population and has been so since prehistoric time (1). Early diagnosis is difficult because osteoporosis is not noticed until it advances enough the bone strength of the patient to the point at which clinical symptoms appear. The major causes of bone loss and clinical associations are listed in table 1.

Postmenopausal osteoporosis constitutes a major portion of the osteoporotic patients. It was over 50 years since Albright postulated the loss of ovarian function in pathogenesis of postmenopausal osteoporosis (2). Since then, many studies in different ways have confirmed this link. In man, the decline in bone mass with age results largely from decreased bone formation whereas in women, postmenopausal bone loss appears to be due to increased bone resorption (3). Some, but probably not all, postmenopausal women lose trabecular bone disproportionately.

Therefore, they are more at risk of fracture of

Table 1. The major causes of bone loss

1. Causes Unknown	2 Causes known	3. Associated with osteomalacia
A. Age related bone loss • Postmenopausal • Elderly	**A. Immobility - general or local**	Celiac disease Partial gastrectomy Renal osteodystrophy Liver disease
B. Not related to age • Osteoporosis of pregnancy • Idiopathic juvenile osteoporosis • Osteoporosis in young adults.	**B. Endocrine** • Hypogonadism including oophorectomy • Cushing's syndrome - spontaneous or iatrogenic • Thyrotoxicosis • Hypopitutarism	
	C. Chromosomal (Turner's syndrome)	
	D. Others • Rheumatoid arthritis • Heparin and cytotoxic drugs • Scurvy • Organ transplant Inherited • Osteogenesis imperfecta • Homocystinuria	

the vertebral bodies and distal radius as these predominantly contain trabecular bone (4). Osteoporosis, however, should not be considered a gender-related problem, though in male, it is less well investigated. Recent data suggest that male osteoporosis may be a larger problem than was originally presumed like any other ethnic group osteoporosis is widely prevalent in India. Even though kyphosis, a sign of advanced osteoporosis is common and taken as characteristic of an elderly, the exact prevalence of osteoporosis is not known due to,

I. Non availability of bone densitometry
II. Attempt to avoid use of medical care facilities or hospital admissions in management of osteoporotic vertebral and/or hip fractures,
III. Indian male are more likely to seek medical attention than Indian female, thereby distorting the sex prevalence, and
IV. Use of WHO criteria (Table2) may not correctly identify the Indian population at risk for osteoporosis as the normal values for the peak bone density in the Indian population has not been established.

During the past couple of years, awareness of osteoporosis and interest in this disorder has grown considerably. Data from few organized centers in India, indicate that,

1 About 44% men and women above age of 50 years have osteopenia with no significant difference in the rate of bone loss (6% per decade after third decade of life).

Table 2.
WHO criteria for assessing osteoporosis

WHO Criteria for Assessing Disease Severity	
Diagnostic Criteria*	**Classification**
T= 0 to -1 SD	Normal
T= -1 to -2 SD	Osteopenia
T $\leq$ 2.5 SD	Osteoporosis
T $\leq$ 2.5 SD + fragility fractures	Severe osteoporosis

*Measured in "T scores," ie, the number of standard deviations Below or above the peak bone mass in a young adult reference population of the same sex; SD=standard deviation.

2. The average age of osteoporotic hip fracture in Indian population is 56 - 58 years as compared to 71 - 76 years in the western population.
3. Osteoporotic hip fracture occurs more commonly in Indian men (50 - 76%) as compared to the western male population (11 - 37%) (5).

Structural failure, either as fracture or vertebral body collapse, represents the end stage of osteoporosis. Therefore, the emphasis is on prevention of osteoporosis. For preventive treatment to be effective, it has to be instituted before the stage of structural failure is reached. It implies identification of those at risk by measurement of bone mass. Though there are many techniques available for measurement of bone mass including DEXA, their main use is as research tools to assess effectiveness of treatments. (Table3). They are unsuitable as a screening procedure and in ordinary clinical practice one is usually restricted to plain x-

Table 3. Bone mineral density-measuring techniques		
Bone Measurement Techniques		
Technique	**Precision (%)**	**Significant change (%)**
Spine DEXA	1	3
Hip DEXA	1.5	4
Q-CT	3	8
p-DEXA	2	5
Ultrasound	4	11

Table 4. The most common risk factors

- Female
- Age 50 or older
- Post menopause
- Prolonged sex hormone deficiencies
- Ovaries removed or menopause before age 45
- Not enough calcium in diet
- Limited exposure to sunlight or insufficient Vit. D in diet
- Not enough physical activity
- Family history of osteoporosis
- Thin, "small-boned"
- White or Eurasian ancestry (mixed European and Asiatic ancestry)
- Smoker
- Caffeine (consistently more than three cups a day of coffee, tea, cola)
- Alcohol (consistently more than two drinks a day)
- Excess use of certain medications (cortisone, prednisone, anti-convulsants, thyroid hormone, aluminium containing antacids)

rays. Risk factor identification is another means to identify patient at risk. It also offers basis for interventions aimed at the primary prevention of osteoporosis. (Table 4).The primary and the secondary prevention or treatment of osteoporosis in men and women involves attention to risk factors influencing peak bone mass, rate of bone loss.

Weight bearing excercises maintains general bone mass and may increase total body calcium as well as lumbar vertebral density in postmenopausal women (6,7). However, the osteogenic response to biomechanical stress is greater in young individuals hence its benefits are more if started while skeleton is growing and carried on through out later life. Avoidance of sedentary life style, with maintenance of mobility, flexibility and speed of movement may also reduce the incidence and severity of falls and thus contribute in reducing the fracture rate, the final arbiter of osteoporosis control.

During the phase of bone loss, there is no evidence that calcium supplements cause gain in bone mass. Intakes of 1.5 to 2g calcium daily has been shown to be not effective (8) as well to be effective in reducing cortical bone loss (9,10). There is little correlation between current calcium intake and cortical bone mass in postmenopausal women and increase in peak bone density with calcium supplementation has not been found in men.

Increasing the total bone mass or total body calcium does not automatically result in strengthening of the skeleton. Skeletal calcium is closely correlated with its compressive strength (11). And population with higher peak adult bone mass is at less risk from fractures of the femoral neck (12). However, once the internal architecture of bone has been disrupted by osteoporosis, subsequent increases in bone mass may merely increase the size of remnant structure without restoring the resistance to compressive forces (13).

In spite of common practice to prescribe vitamin D or its more potent analogues (calcitriol, alfacalcidol) in prevention and treatment of osteoporosis, there is no conclusive evidence for its efficacy in management of uncomplicated osteoporosis. In studies of combined treatment regimens, the vitamin D groups often did worse, with increased calcium loss and increased vertebral compression. Hypercalcemia was frequent and toxicity was a common problem. However, in most of the elderly individuals subclinical vitamin D deficiency may exist and these will be benefited by daily intake of 10 -20 mcg (400 -800 IU) vitamin D intake. In such cases serum calcium and alkaline phosphatase should be monitored during vitamin D treatment to prevent complications of toxicity (14, 15).

Alcohol abuse and smoking have been shown to be risk factors both for low bone mass and for fractures, in both men and women. While the relation to alcohol is uncertain, the relation to smoking appears to increase with exposure. In one study, alcohol and smoking effects were shown to be additive (15). Therefore, avoidance of tobacco and excessive alcohol use are reasonable approaches to prevention of osteoporosis in both the sexes.

Recent researches in osteoporosis have improved understanding of osteoporosis and have laid foundation for introduction of potent drugs for management of the disease. These drugs have been shown to increase bone mineral density with reduction in fracture rates.

Among various drugs, calcitonin is probably the first drug used successfully for treatment of various forms of osteoporosis. Its physiological role in control of calcium metabolism forms the basis of therapeutic use. Development of synthetic process for production facilitated the use of calcitonin in therapeutic doses.

SALMON CALCITONIN

I. BIOCHEMISTRY

Table 5. Regulation of secretion

Stimulant	Suppressant
High Ca, Str., Ba, Mg.	Low Ca, high Mg. In pts. With thyroid Ca
Gastrin. Glucagon, CCK Beta agonists	Beta blockers, alpha stimulants & dopamine
Estrogens	Somatostatin

Calcitonin is a 32 amino acid polypeptide mainly secreted by parafollicular thyroid C cells, which originate from the ultimobranchial body in the embryo.

This peptide hormone has a molecular weight of approximately 3500.

The structures of at least twelve types of calcitonins have been determined. Common characteristics of the molecule from different sources are:

1. A disulfide bond between amino acid 1 and 7, forming a ring of 7 terminal amino acids.
2. Glycine in position 28, and,
3. A proline amide group at the carboxy terminal end (16).

According to their primary structure, calcitonins from various sources are grouped into three categories:

1. Artiodactyl - porcine, ovine and bovine calcitonin
2. Primate/rodent - human and rat calcitonin
3. Teleost/avian - salmon, eel and chicken calcitonin.

The order of potency of calcitonin from the above sources is as follows:

Teleost > Artiodactyl > Human

Studies have shown that the ring structure appears to protect and stabilize the molecule though the linear analogue retain hypocalcemic activity and ability to activate adenylate cyclase, the proline amide group located at the carboxy terminal end is essential for the biological activity, but changes in positions 8 -22 are tolerated without affecting the biological activity. The general conclusion is that maintaining the tertiary structure is more important for biological potency than the length of the chain per se (16).

Four types of calcitonins are used for therapeutic purposes in human. They are:

Group I: Salmon calcitonin, Aminosuberic analogue of Eel calcitonin, Elcatonin.

Table 6. Relative Potency

Species	Activity (units/ml)	Activity (mg/unit)
Salmon I * Salmon II Chicken Asu[1,7] eel	4000 - 6000	0.00017 - 0.00025
Salmon III Eel	2000 - 4000	0.00025 - 0.0005
Rat	-400	-0.0025
Ox Sheep Pig Man	100 - 200	0.005 - 0.01

Group II: Human calcitonin, Porcine calcitonin.

The biological activity of the first group calcitonins are 20 - 40 times greater than that of the second group calcitonin (16). This is because of their,

I. Greater resistance to metabolic breakdown and

Ii. High degree of intrinsic activity on the receptors.

Since its discovery, structural organization of salmon calcitonin is fully elucidated. This has led to development of technology to synthesize this peptide molecule by assembling the structural amino acids in their proper places as present in the calcitonin from the natural source. This fully synthesized calcitonin, called, "Synthetic Salmon Calcitonin", is the most commonly used calcitonin for therapeutic purposes.

The Synthetic salmon calcitonin is prepared by a complex peptide synthesis process. Initially two separate fragments corresponding to 1 - 10 and 11 - 32 amino acid sequence of the salmon calcitonin is synthesized separately. Subsequently these are coupled to obtain complete molecule of the salmon

Table 7. Comparative summary I

Metabolism (degradation) • Plasma / serum	SCT = ECT < HCT < PCT
• Liver	SCT = ECT < HCT < PCT
• Kidney	SCT = ECT < HCT < PCT
Elimination • MCR in normal subjects	SCT = ECT < HCT (2x) < PCT (3x)
• MCR in renal insufficiency	3-5 times lower for SCT than in normal
• Main organ involved	Kidney (SCT, ECT , HCT) Liver PCT
Analgesic effect	SCT = ECT > HCT < PCT
Anti-inflammatory effect	SCT = ECT > HCT < PCT
cAMP production • Plasma /kidney	SCT = ECT > HCT > PCT
Diuretic effect	SCT = ECT > HCT = PCT
Electrolytes • Blood /urine levels	SCT = ECT > HCT = PCT
Alkaline phosphatase inhibition	SCT = ECT > HCT = PCT

(SCT = Salmon calcitonin, ECT = Elcatonin, HCT = Human calcitonin, PCT = Porcine calcitonin)

calcitonin. Confirmation that the synthesized polypeptide is structurally exactly same as the natural salmon calcitonin is carried out using tests like elemental analysis, amino acid analysis, infrared (IR), nuclear magnetic resonance (NMR), ultraviolet (UV), mass spectroscopy (MS), high performance liquid chromatography (HPLC) and high performance capillary electrophoresis (HPCE). Appropriate bioassays are carried out to confirm its biological activity.

The synthetic salmon calcitonin is a white puffy powder, freely soluble in water, has melting point near 150 degree Celcius with decomposition.

The pure synthetic salmon calcitonin has peptide content of >80% and the biological activity ranging from 4000 - 7000 IU/mg of dry weight (17).

Table 7. Comparative Summary II

Chemical stability	
• In solution	SCT = ECT > HCT = PCT
• Oxidation sensitivity	SCT = ECT < HCT > PCT
Biological activity	
• Units /mg	4000+6000 (SCT, ECT) 100+200 (HCT, PCT)
• 50% loss of activity in	6 h (SCT, ECT) 2 h(HCT) 1 h(PCT)
• Intrinsic activity at receptor level	SCT = ECT > HCT > PCT
• Duration of hypocalcaemic activity	SCT = ECT > HCT > PCT
• Affinity for receptor	SCT = ECT > HCT > PCT

Table. 8: Contents of Salmon Calcitonin

Aspartic acid	2
Threonine	5
Serine	4
Glutamic acid	3
Proline	2
Glycine	3
Cysteine	2
Valine	1
Leucine	5
Tyrosine	1
Histidine	1
Lysine	2
Arginine	1

II. PHARMACOLOGY

Mechanism of Action

1. Effects on Bone

Both in vivo and in vitro studies have shown that calcitonin has a direct inhibitory effect on bone resorption. However, there is no evidence that calcitonin increases calcium uptake by bone (16).

The main effect of calcitonin is to inhibit bone resorption by inhibition of osteoclasts, mediated through activation of calcitonin receptor (18). The receptor activation is associated with an increased production of cAMP and increase in cytosolic calcium in osteoclast due to activation of phospholipase C. Binding of calcitonin with the receptors on osteoclast leads to marked decrease in activity and recruitment of these cells. The morphology of osteoclast changes rapidly on exposure to calcitonin. These multinuclear cells decrease in size and their ruffled borders, responsible for bone resorption, recede from the resorptive surface (19). In addition, calcitonin inhibits formation of osteoclast by inhibiting fusion of mononuclear cells to form multinuclear osteoclast (20).

Table 9. Systemic effects
Lower plasma Ca & PO4 through action on bone and kidney.
Effect on gut, liver , pancreas and other organs unrelated to its hypocalcemic properties.

Table 10. Effects on bone tissue
Completely inhibits osteoclastic bone resorption in 15 min. & reaches peak at 1hr. after administration
Inhibits calcium efflux from pool of labile bone Ca by lowering cytosolic Ca in bone cells
Inhibits resorption of the organic phase of bone
Stimulates osteoblastic bone formation

2. Effects on the G. I. Tract

The gut is not necessary for the hypocalcemic

Table 11. Action of calcitonin on osteoclast
Disappearance of brush border of osteoclast leading to detachment from bone resorption surface
Effect is dose related and occurs within 30 min. of administration
Affects internal structure leading to restricted cytoplasmic motility of cell, reduction in life span & number
Suppresses recruitment of osteoclasts (BMU & bone resorption)
Does not interfere with the recruitment of new BMU

Table 12. Effects of calcitonin on the G. I. Tract
Decreases gastrin & gastric acid secretion
Increases small bowel secretion of Na, K, Cl & H_2O
Seen only at supraphysiological levels
Probably has no major effect on intestinal absorption of Ca

effect of calcitonin. It has no effect on absorption of calcium. At supraphysiological concentration, it increases intestinal secretion of sodium, potassium, chloride and water and affects G.I. calcium flux. It also inhibits gastric emptying, gastrin and insulin secretion as well as gastric acid secretion.

4. Effects on the Kidney

Calcitonin has two distinct effects on the kidneys. It enhances excretion of sodium, potassium, calcium, magnesium and phosphate and this effect is probably mediated via cAMP. Calcitonin also enhances the renal production of 1,25-dihydroxycholecalciferol.

5. Other effects

The calcitonin receptors are not only confined to the bone tissue. They are widely distributed in the body (Table 14). They may be responsible for many of the non-skeletal effects of calcitonin (Table 15), which may have therapeutic potential. These are listed in the table 14 below.

Parenteral or intranasal administration of salmon calcitonin decreases bone resorption and inhibit bone loss in animal models of postmenopausal osteoporosis as well as corticosteroids- or heparin- induced osteoporosis. In healthy volunteers single parenteral doses of 50 - 100 IU salmon calcitonin are associated with reduction in urinary elimination of hydroxyproline and cross

Table 13.
Effects of calcitonin on the kidneys

Calcitonin decrease renal tubular resorption of Ca, PO4, Na, K, & Mg.
Binds to specific renal receptors and activates adenylate cyclase
Deficiency of calcitonin doesn't disturb renal handling of Ca, Na or Po4

Table 14. Distribution of calcitonin receptors in the body

Bone	Osteoclasts and some marrow cells
Kidney	• Proximal and distal convoluted tubules. • Ascending limb of the loop of Henle. • Cortical segment of the coll ecting tubule.
CNS and pituitary	• High density of receptors • Hypothalamus • Preoptic nucleus and nucleus accumbens • Amygdaloid nucleus. • Zona incerta. • Interpedundal nucleus • Nucleus griseus periventricularis • Reticular formation
CNS and pituitary Other sites	• Average or low density • Arcuate nucleus and nucleus supramammillaris • Substantia nigra • Pituitary (pars intermedia and anterior lobe) • Spinal cord • Leydig cells • Lymph cells (man) • Mammary and bronchial tumor cells

links of pyridinolines, an increase in cAMP and a decrease in serum calcium concentration. Similar findings have been reported in women with postmenopausal osteoporosis, given single dose of 50 - 400 IU salmon calcitonin, intranasally. The highest doses of salmon calcitonin (200 - -400 IU) are associated with reduction in the serum concentrations of total calcium, ionic calcium and phosphate with pronounced increase in urinary calcium, sodium and phosphate concentration. The hypocalcemic effect of single dose lasts for upto 6 hours.

Inhibition of bone resorption by salmon calcitonin depends on the drug binding to the specific calcitonin receptors on osteoclasts. This drug receptor interaction reduces the activity and recruitment of the cells responsible for the for bone resorption.

Some studies suggest that exogenous calcitonin also acts on osteoblastic cell lines and administration of calcitonin may have beneficial effects on microarchitecture and biomechanical performance of the bone (21). The clinical significance of these findings has not been fully explored.

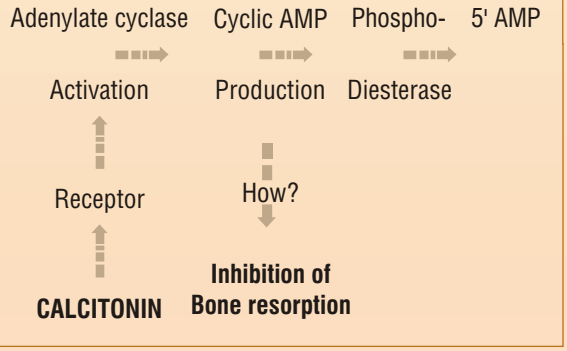
Administration of salmon calcitonin does not appear to modify the serum levels of vitamin D metabolites, parathormaone or endogenous calcitonin. It does not have any direct on the adenohypophysis (16).

The analgesic effect of calcitonin has been shown in patients with great variety of diseases. Administration of salmon calcitonin to post menopausal women with osteoporotic fracture have been shown to reduce pain, and lower analgesic intake (22) The analgesic effect of calcitonin is independent of its effect on bone resorption. The exact mechanism of the analgesic effect of calcitonin is not fully understood.

Table 15. Non-skeletal effects of calcitonin

Kidney	Mild diuretic effect
Gastrointestinal tract and associated organs	Inhibition of secretary activity of stomach and pancreas
Cardiovascular system	Vasodilatation Sympathomimetic activity
Central nervous system	Analgesia Neuromodulation
Other effects	Peripheral analgesia Anti-inflammatory effects

Figure 1. Calcitonin receptors in bone



Suggested mechanisms are (16),

A. Increased levels of endogenous beta-endorphins,
B. Direct effects on specific receptors in the CNS,
C. Decreased synthesis of prostaglandins and other humoral factors,
D. Involvement of serotoninergic and monoaminergic pathways, and
E. Changes in the intracellular calcium in CNS.

Long term treatment with heterogeneous calcitonin may lead to formation of neutralizing antibodies, but true clinical significance of this phenomenon is not known. Some studies have reported sustained significant efficacy in reducing the risk of further vertebral fractures despite formation of neutralizing antibody. On the other hand, development of resistance, plateau phenomenon or reduced efficacy in patients with high antibody titers, have also been reported (16). However, down regulation of calcitonin receptors in the bone cells following prolonged administration of calcitonin may also be responsible for the above mentioned escape phenomenon (23).

Table 16.

Analgesic effect due to stabilizing or augmenting bone mass
Skeletal blood flow changes, stimulation of endogenous endorphin production
Direct action on pain centres in the brain
Inhibition of PG synthesis
Modulation of 5-HT pathways & monaminergic pathways
Pain relief seen from second day

Table 17. Pain syndromes in which calcitonin has analgesic effects

Non-skeletal	Skeletal
Headache (migraine)	Paget's disease of bone
Phantom limb pain	Algodystrophy (Sudeck)
Postoperative pain	Metastatic bone disease
Electrical stimulation of teeth pulp	Primary and secondary osteoporosis

Pharmacokinetics

Calcitonins are rapidly inactivated when administered orally. On parenteral administration, calcitonin is quickly metabolized, mainly in the kidneys and excreted in urine. Calcitonin is absorbed through the nasal and rectal mucosa. Following subcutaneous administration salmon calcitonin is rapidly absorbed with an absorption half-life of 23.4 minute. Attainment of peak plasma concentration and elimination is relatively fast with elimination half-life of 87 minutes. **Generally the peak levels of intranasally administered salmon calcitonin is lower than those administered subcutaneously or intramuscularly. Intranasal administration provides approximately 25 - 50% of biological activity compared to parenteral administration. Thus, intranasal dose, two to four times the**

Table 18. Calcitonin pharmacokinetics	
Peak plasma concentration 16-39 min (I.M. / S.C.)	
Cmax	69 - 97 ng / ltr
T ½	Human - 10 min Salmon - 43 min
AUC 78	155 ng/ ltr.hr
Clearance rate 8.4 ml/kg/min	
Renal excretion accounts for total clearance rate. Sal Cal. least metabolized	

intramuscular or subcutaneous dose show equivalent biological effects (16).

III. THERAPEUTIC USES

1. Paget's Disease of Bone

The characteristic features of Paget's disease are increased bone turnover and remodeling, primarily due to excessive osteoclastic resorption. Bijvoet and Jansen in 1967 demonstrated the beneficial effects of calcitonin. It is now recognized that calcitonin treatment regularly improves bone pain and other clinical features of the disease with improvement in the biochemical, histological and radiological features. It is well established that calcitonin is an effective agent in the treatment of Paget's disease. There are five situations like bone pain, immobilization hypercalcemia, repeated fractures or non-union, neurological complications and, before and after major orthopedic surgery, that warrants calcitonin treatment (29). Twice weekly subcutaneous injections of 100 IU is effective in most patients but thrice weekly or daily administration may be necessary if lower dose is ineffective.

Table 19. Indications for calcitonin use in Paget's disease
Bone pain, progressive deformities & neurological complications
Metabolic complications
Surgery on Pagetic bone

Inhibits increased osteoclastic resorption
Relieves bone pain
Lower skin temperature over involved bone
Decreases excessive cardiac output
Stabilize hearing impairment & improves neurological function
Appearance of bone to normal

2. Familial Idiopathic Hyperphosphatasemia (Juvenile Paget's Disease)

This condition is seen in infancy and early childhood and is extremely rare. Increased bone resorption by osteocyte, with multiple fracture due to minimal trauma is the characteristic of the disease. Woodhouse in 1972 showed that calcitonin treatment is highly beneficial, especially when therapy is started before gross deformities have developed (29).

3. Osteogenesis Imperfecta

Increased bone resorption seen in the various forms of this disease is the basis for calcitonin

treatment. Initial studies have shown some biochemical evidence of reduced bone turnover, but there is no convincing clinical improvement reported (29).

4. Algodystrophy (Sudeck's Atrophy)

This disease is characterized by a massive local increase in bone resorption occurring as a complication of orthopedic surgery. Many studies have shown clinical improvements with calcitonin treatment (29)

5. Osteoporosis

Osteoporosis may be due to decreased bone formation, increased bone resorption or both. It is the resorptive aspect of the disease, which is amenable to calcitonin treatment.

There is a large body of evidence that calcitonin treatment is effective prevention of postmenopausal osteoporosis. There is a sound theoretical ground for use of calcitonin for prevention and treatment of postmenopausal osteoporosis. Women by nature are relatively deficient in calcitonin compared to men. Loss of estrogen at the menopause exaggerates the age related calcitonin secretion. In such situations, calcitonin alone or along with estrogen may reduce resorption and restore the bone mass. Many studies have shown that calcitonin is effective in reducing the rate of bone resorption and maintaining the bone mineral density in patients of postmenopausal osteoporosis (29). Calcitonin is also reported to be effective in treatment of age related osteoporosis and corticosteroid induced osteoporosis (29).

Table 20. Calcitonin in osteoporosis
Used in the Rx of since 1984
• Primary action is inhibition of bone resorption rate by direct action on the osteoclasts
• A potential stimulatory effect on osteoblastic bone formation
• Very effective in immobilized, glucocorticoid & early post - menopausal high bone turnover osteoporosis
• Effective in older patient with established osteoporosis and fracture.
• Effective in young menopausal women with medical oopherectomy syndrome
• Useful in amenorrhoea athletes with low BMD
• Maximal effect in osteoporotics with high bone turnover syndrome (active osteoporosis)
• Prevention of bone loss in perimenopause needing higher dose

6. Acute Hypercalcemia

Table 21. Calcitonin in hypercalcemia
Used in the Rx of Hypercalcemia of malignancy
Life threatening or symptomatic cases
75 -90 % respond within few hrs. Reaching peak between 12 - 24 hrs after I.m. injection
Escape from hypocalcemic effect may occur after several days of therapy

In patients with hypercalcemia due to conditions like hyperparathyroidism, thyrotoxicosis, malignant hypercalcemia and metastatic hypercalcemia, calcitonin causes an acute fall in serum calcium. It can be used in conjunction with standard treatment such as fluid replacement and oral phosphate. As a continuous intravenous infusion, it can be safely given in doses in the order of 200 to >1000 IU 4- to 6- hourly.

Adverse Effects

The most frequently reported symptoms related to adverse effect with subcutaneous or intramuscular administration are feeling of warmth and nausea, burning sensation and irritation at the injection site leading to discontinuation in 5 -14% patients.

Dosage and Administration

In case of parenteral calcitonin, doses of 100 IU/day was the recommended dose initially However, evidence that lower doses are effective, has led to progressive decrease. Currently dosing regimen of 50 or 100 IU on alternate days are recommended (24).

Table 22. Calcitonin ADR profile
Nausea & Gastric discomfort 8 -10 %
Facial flushing & skin reactions 2 - 5 %
Pruritus at the site of injection 10 %
Epigastric fullness , increased urinary frequency and diarrhoea.

In case of intranasal calcitonin, the dose ranges from 50 - 400 IU/day have been used in various clinical practice.

However, the correct recommended dose to achieve effective bone mass with reduction of fracture, is 200 IU/day. Its efficacy is prolonged and is independent of major pretreatment risk factors (25).

Storage

Store at 2-80 C. Protect from light

Packing

Each 1ml ampoule of Salmoncal contains 100 I. U. Salmon Calcitonin.

5 such ampoules in a carton.

4 such cartons in a thermacol box with 2 coolants

Table 23. Calcitonin recommended dosage
Osteoporosis with pain - 100 IU s.c. daily
Osteoporosis without pain - 50 - 100 IU s.c. thrice weekly
Weekly therapy for 2 - 3 months followed by 1 month off / on intermittent therapy for 18 -24 months
Therapy reinstituted if BMD decreases by more than 3 - 4 % or presence of risk factors
Paget's disease - 50 - 100 IU / day
Hypercalcemia - 4 - 8 IU/kg every 6 - 12 hrs.

IV. CLINICAL STUDIES

As mentioned earlier, the structural failure, either as fracture or vertebral body collapse, represents the end stage of osteoporosis. For a 50 year old woman, the risk of experiencing an osteoporotic fracture some time in her life is 40% (27, 28). The most frequent fractures are those of the femur, radius and vertebrae. The femoral fracture is most important because it is associated with increased mortality risk (20% of patients die during the first year after the fracture). The other localizations, while not as prominent, do significantly reduce quality of life.

Therefore, in practical terms, treatment of osteoporosis is limited to primary prevention in patients known to be at risk and secondary prevention (i.e. prevention of recurrences) in those who have already identified themselves as osteoporotic by having sustained a fracture after minimal trauma. Efficacy of calcitonin in these areas has been proven by many investigators. The US FDA approved the use of salmon calcitonin as an injectable formulation for the treatment of osteoporosis in 1984. In 1995 intranasal calcitonin was approved for the treatment of osteoporosis.

The summary of the clinical evidences presented below is not exclusive but is aimed at providing key information on the drug's usefulness in management of osteoporosis and other related disorders.

Table 24.
Developmental history of calcitonin

Discovered in	1962
Paget's Disease	1975
Hypercalcemia	1980
Osteoporosis	1984
Cortic. Osteo	1989
Intranasal admin.	1995

A. Analgesic Activity

Analgesic Efficacy of Calcitonin for Vertebral Fracture Pain

Linsey A Blau The Annals of Pharmacotherapy: 2003 Vol. 37, No. 4, 564-570.

Calcitonin has been studied for its analgesic properties. Fourteen double-blind, placebo-controlled trials that evaluated the analgesic efficacy of calcitonin for osteoporosis-related vertebral fracture pain were identified and reviewed. Thirteen of these studies demonstrated statistically significant improvement in pain or function in calcitonin-treated patients.

Calcitonin has proven efficacy in acute pain associated with osteoporosis-related vertebral fractures.

The analgesic role of calcitonin following osteoporotic fracture.

Silverman SL *Osteoporos Int - 01-NOV-2002; 13(11): 858-67*

Salmon calcitonin (SCT) is an anti-resorptive agent which has been shown to reduce the risk of vertebral fractures (by 36%) in postmenopausal women with osteoporosis and previous fractures, with a safety profile comparable to placebo over long-term use. Clinical evidence suggests that SCT (with either subcutaneous and intranasal delivery) is an analgesic for the acute pain following osteoporotic fracture. **Pain relief with SCT occurs after 1 week or less of treatment.** Associated with this pain relief, vertebral fracture patients receiving SCT have been observed to have earlier mobilization compared with those receiving a placebo. Both preclinical and clinical data suggest a central analgesic effect for SCT.

Analgesic effect of salmon calcitonin in osteoporotic vertebral fractures:

A double-blind placebo-controlled clinical study.

Lyritis GP *Calcif Tissue Int - 01-DEC-1991; 49(6): 369-72*

A new vertebral crush fracture gives rise to severe pain that immobilizes the patient and necessitates bedrest. In this double-blind controlled clinical trial, 56 patients who had recently (within the last 3 days) suffered an osteoporotic vertebral fracture were hospitalized for a period of 14 days. Salmon calcitonin (100 IU) or placebo injections were given daily. Pain was rated daily on a 10-point scale by the same observers. Blood and urinary parameters were also evaluated. The results showed a significant (P less than 0.001) difference in pain intensity between the calcitonin group and the placebo group. **This beneficial effect was generally apparent from the second day of treatment onward, and over the following 2 weeks, the patients were able to sit and stand, and gradually started to walk again.** A significant decrease in urinary hydroxyproline and urinary calcium was also noted in the calcitonin group. It is concluded that calcitonin exerts a beneficial effect on back pain following a vertebral crush fracture.

Pain killing with calcitonin in patients with malignant tumours.

Szántó J *Oncology - 01-JAN-1986; 43(2): 69-72*

The most essential role of Calcitonin, a 32-amino-acids peptide, is the preservation of osseal integrity. Based on this physiological fact it is assumed that this hormone may have a bone-regenerating effect in bone metastasis formation and sometimes in other malignancies. Though no considerable calcium incorporation could be revealed in our 58 patient treated with Calcitonin, a marked relief of pain was observed in 65.5% of the patients. For objectivation of the subjective pain sensation, the decrease in the quantity of other analgetics used daily, duration of pain and

changes of its intensity were studied. These figures were 35.4% on the average, from 12.5-6 h and 23.6%, respectively. The pain-killing character of Calcitonin is by following mechanisms:

A. it partially inhibits the synthesis of algogenous peptides;
B. With its possibly cytostatic effect it inhibits the cell proliferation in loco and normalizes the internal pressure of the destroyed region, and
C. By conversion into beta-endorphin it exerts its effect centrally.

Compared to the pain-killing effect, the simultaneous improvement of the quality of life seems to be even more essential. It has been proved earlier that a hormone physiologically present, when applied in a high dose, has an analgetic effect, i.e. by utilizing the endogenous substance of the organism, relief of pain can be achieved.

We should like to point out that **Calcitonin is the only analgetic agent capable of ensuring relief of pain with a simultaneous improvement of the quality of life.** Accordingly, the application of Calcitonin in patients suffering from malignant tumours is highly recommended.

Effect of calcitonin on the skeleton and bone pain in multiple myeloma

Fremiotti A *Curr.Ther.Res.1984; 86(4): 627-640*

In this study, the authors have treated 36 patients with multiple myeloma having osteolytic lesion and / or bone pain. Salmon Calcitonin was given at a dose of 1.5 to 2.0 units/kg / day, 2-3 times a week.

Authors observed that in all 36 patients, there was either an attenuation or disappearance of the ostalgia. **The pain relief was seen from 1-5 months following treatment.** Parallel to the pain relief, there was improvement in the mobility. The treatment was found to be well tolerated.

A double-blind controlled trial of salmon calcitonin in pain due to malignancy.

Cancer Chemother Pharmacol. 1982;9(2):71-4, Hindley AC, Hill EB, Leyland MJ, Wiles AE.

Thirty-two patients with established malignancy and associated pain participated in a randomised double-blind controlled trial. They received salmon calcitonin SC 200 IU or matching placebo 6-hourly for 48 h and were assessed by using a combination of a 20-point visual analogue scale (VAS), a 4-point physician's global pain scale, and ranking of the co-administered analgesics into 20 grades of potency. Twenty-five patients (13 calcitonin, 12 placebo) were evaluated. Seven patients (4 calcitonin, 3 placebo) were excluded either because the initial pain score was less than or equal to 5 on the VAS, or because there were

insufficient data (due to death occurring within the first week of the study or, in one patient, blindness preventing completion of the VAS). One week after commencing therapy there was improvement or marked improvement of pain in significantly more patients in the calcitonin group (5/13) than in the placebo group (0/12) (Fisher's exact two-tailed probability test, P = 0.0484). At the end of the second week three patients in the calcitonin group were still showing marked improvement.

Salmon calcitonin in metastatic bone pain. Demonstration of acute analgesia in tumor patients

Dtsch Med Wochenschr. 1984 Jun 15;109(24):944-7, Kleibel F, Schmidt G.

Infusion of 200 IU Calcitonin-Sandoz in 20 of 44 hospitalized patients with malignant tumor suffering from chronic severe pain due to bone metastases, reduced the intensity of pain and with it the need for analgesics for an average of 10 hours. The result points to an analgesic potential of salmon-calcitonin.

Calcitonin in the treatment of intractable pain from advanced malignancy.

Pharmatherapeutica. 1983;3(7):482-6, Allan E.

Clinical details are given of 8 patients who complained of severe pain from metastatic bone disease or from multiple myeloma. Four of the patients were included in a double-blind pilot trial designed to compare the effectiveness of salmon calcitonin (200 IU intramuscularly) and placebo given twice daily for 4 days. Two of these patients experienced pain relief and were found to have been given salmon calcitonin; the other 2 had no pain relief and had been given placebo. The other 4 of the 8 patients were treated with salmon calcitonin and also had relief of their pain. It would appear, therefore, that salmon calcitonin may be dramatically effective in the treatment of intractable pain from advanced malignancy and its use warrants further study.

Salmon calcitonin in cancer pain: comparison between two different treatment schedules.

Int J Clin Pharmacol Ther Toxicol. 1987 Apr;25(4):229-32., Schiraldi GF, Soresi E, Locicero S, Harari S, Scoccia S.

The analgesic effect of salmon calcitonin was evaluated in an open study of thirty-four patients with bone metastases of a lung cancer. Two different administration protocols were used: eighteen subjects received sCT 400 IU/day for three consecutive days, while the remaining sixteen were given sCT 200 IU/day for six consecutive days. In both protocols salmon calcitonin was diluted in saline and infused intravenously in one hour. Bone, visceral and neuritic pain were evaluated by means of Huskisson's visual analog scale and Keele's pain scale. The analgesic efficacy of salmon calcitonin was also evaluated on the basis of daily consumption of analgesic drugs.

Salmon calcitonin proved of extreme efficacy in the treatment of intractable pain from advanced malignancy. A higher and earlier analgesic activity was observed with sCT at the 400 IU daily dosage.

Analgetic activity of calcitonin in patients with painful osteolytic metastases of breast cancer. Results of a controlled randomized study.

Oncology. 1986;43(5):283-7., Roth A, Kolaric K.

The analgesic effect of salmon calcitonin was tested by a double-blind clinical randomized controlled trial in 40 female patients with painful osteolytic metastases. Twenty patients were administered (daily) 100 IU of salmon calcitonin subcutaneously over 28 days, while the other 20 were administered identical ampoules containing 2 ml of physiological solution over the same period of time. The basic treatment (chemotherapy, hormone therapy) was not changed during the trial, and had to be stabilized for a minimum of 3 months prior to the trial. The effect of calcitonin was monitored with respect to daily analgesic consumption, duration of pain, patient's functional capacity, patient's own assessment of pain, and assessment of efficacy by the investigator. Statistically significant differences were established in terms of reduced analgesic consumption, shorter duration of pain and the patient's subjective assessment of pain duration and intensity; the difference was not statistically significant with regard to patient's functional capacity. The objective assessment of the analgesic effect of calcitonin by the investigator showed the drug to be extremely useful in 3 patients and moderately useful in 11 patients; 3 instances of 'moderately useful' were observed in the placebo group. No changes were observed in serum calcium levels; there were likewise no skeleton changes as established by X-rays and bone scintiscans before and at the end of treatment. The trial has shown calcitonin to produce a pronounced analgesic effect in breast cancer patients with painful osteolytic metastases.

B. Osteoporosis Prevention

Prevention of corticosteroid-induced osteoporosis with salmon calcitonin in sarcoid patients.

Montemurro L, Calcif Tissue Int - 01-AUG-1991; 49(2): 71-6

The aim of this study was to evaluate the usefulness of salmon calcitonin (sCT) in preventing corticosteroid-induced osteoporosis. Three groups of patients with sarcoidosis requiring long-term steroid therapy were followed for 2 years with yearly evaluations of vertebral cancellous mineral content (VCMC) by quantitative computed tomography. The first group (n = 18) was treated with intramuscular (i.m.) sCT for the 2-year study period; the second (n = 11) with i.m. sCT for the first 4 months and then with sCT

nasal spray for 20 months; the third (n = 35) received no sCT. It was observed a large mineral loss in the third group but a very slight drop of VCMC in the two groups receiving sCT. The action of sCT appeared extremely useful, especially in the first year of steroid therapy when corticosteroid-induced mineral loss was maximal. **SCT is a good tool for preventing corticosteroid-induced osteoporosis.**

Effects of salmon calcitonin on the bone loss induced by ovariectomy.

Mazzuoli GF, Calcif Tissue Int - 01-OCT-1990; 47(4): 209-14

In this study the results of a 12-month clinical study assessed the effects of synthetic salmon calcitonin (sCT) on a group of fertile white women who had undergone ovariectomy for uterine fibromatosis. The study was performed to verify whether CT can prevent the loss of bone mass and the changes in calcium-phosphorus metabolism associated with acute estrogen deficiency. The study consisted of an initial double-blind phase of 6 months, followed by a 6-month open period. Treated patients were given 100 MRC U of synthetic salmon CT injected i.m. in the morning, every other day, starting on the 7th day after the operation and continued for 12 months. Control patients received a placebo injection for the first 6 months; subsequently, they too were treated with sCT i.m. every other day for 6 months at the same dose as the 12 month-treated group. All patients received 500 mg of elementary calcium p.o., b.i.d. Bone mineral content (BMC) was measured at the extreme distal radius of the nondominant arm by a dual photon bone densitometer which utilizes two radio nuclides, 241 Am and 125 I, with energies of about 60 and 30 KeV. Biochemical parameters of the calcium-phosphorus metabolism were also measured. **After 12 months of study, no significant changes of BMC were observed in the 12 months sCT treated group,** while control patients, treated 6 months after the ovariectomy, showed a significant decrease in BMC values.

Salmon calcitonin in the therapy of corticoid-induced osteoporosis.

Ringe JD, Eur J Clin Pharmacol - 01-JAN-1987; 33(1): 35-9

There is uncertainty about the best treatment for steroid-induced osteoporosis. Thirty-six patients with steroid-dependent, chronic obstructive lung disease and associated steroid osteoporosis have been studied, of whom 18 were treated with salmon calcitonin and the other 18 served as controls. Treatment lasted for 6 months and consisted of 100 I.U.s.c. every other day. In the controls there were significant decrements of 1.4% and 3.5%, respectively, in cortical and cortical and trabecular bone mineral content, whereas in subjects on calcitonin there were increments of 2.6% and 2.7%, respectively. Additional evidence of positive effect of calcitonin was derived from the **reduced incidence of new fractures occurring during the observation period.**

A significant reduction in back pain was a further consequence of the hormone therapy.

Effects of salmon calcitonin in postmenopausal osteoporosis: a controlled double-blind clinical study.

Mazzuoli GF, Calcif Tissue Int - 01-JAN-1986; 38(1): 3-8

In this study 12-month double-blind clinical multicenter study assessing the effects of synthetic salmon calcitonin (CT) administration in a group of white postmenopausal osteoporotic women were compared. Treated patients were given 100 MRC units of synthetic salmon CT injected i.m. in the morning every other day. Control patients received a placebo injection. All patients received 500 mg of elementary calcium p.o., b.i.d. Bone mineral content (BMC) was measured at the extreme distal radius of the nondominant arm by a dual photon bone densitometer which utilizes two radionuclides, 241Am and 125I, with energies of about 60 keV and 30 keV respectively. Biochemical parameters of calcium-phosphorus metabolism were also measured. After 12 months of treatment a significant mean increment of BMC and nondialyzable OHPr/creatinine values and a significant decrease of total OHPr/creatinine values were observed in the treated group, while controls showed a significant decrease in BMC values. These results, together with the observation that in some patients the decrease in total OHPr/creatinine values was not accompanied by an increment of BMC, show that **long-term salmon CT treatment may be of benefit in postmenopausal osteoporosis** and that the **effects of CT on bone mass may be due not only to the inhibition of bone resorption but also to the stimulation of bone formation.**

C. Osteoporosis- Treatment

Total and regional bone mineral content and fracture rate in postmenopausal osteoporosis treated with salmon calcitonin: a prospective study.

Rico H, Calcif Tissue Int - 01-MAR-1995; 56(3): 181-5

Seventy-two postmenopausal osteoporotic women having more than one nontraumatic vertebral crush fracture were studied. Thirty-six of them, aged 68.8 +/- 1.2 years (18 +/- 4 YSM-years since menopause), were treated with 100 IU/day of salmon calcitonin i.m. plus 500 mg of elemental calcium for 10 days each month. The remaining 36 patients, aged 69.6 +/- 1.4 years (19 +/- 3 YSM), were given only 500 mg of elemental calcium for 10 days each month. All patients underwent clinical and analytical evaluation every 3 months. Radiological evaluation, assessment of vertebral deformities, and metacarpal radiogrammetry were done every 6 months. Densitometric measurements of total and

regional bone mass were made every 12 months. At 24 months, the calcitonin group showed a 60% reduction in the number of new fractures and the group receiving only calcium had a 45% increase ($P < 0.001$). The incidence of vertebral fractures was 0.07 per patient-year in the group treated with calcitonin and 0.45 per patient-year in the group treated with calcium ($P < 0.001$). At 2 years, the calcitonin group showed a 12% increase in cortical bone mass on metacarpal radiogrammetry, a 16% increase in the axial skeleton on trunk densitometry, a 3.5% increase in total body bone mineral content, a 30.7% increase in pelvic bone mineral content, and a 6.2% increase in arm bone mineral content (all $P < 0.001$). In the group treated with calcium alone there was a loss of bone mass in every region. These findings suggest that **salmon calcitonin is effective in the treatment of osteoporosis and show that it acts on cortical and trabecular bone.**

Effect of calcitonin on vertebral and other fractures.

Kanis JA, QJM - 01-MAR-1999; 92(3): 143-9

Kanis JA, Centre for Metabolic Bone Diseases (WHO Collaborating Centre), University of Sheffield Medical School, UK

Incidence of vertebral and non-vertebral fractures in published randomised clinical trials using calcitonin by parenteral injection or intranasal spray were examined. Trials were reviewed that compared calcitonin with placebo, no therapy, or calcium with or without vitamin D, and that mentioned fracture as an outcome. Studies that compared the effect of calcitonin with other active treatments were excluded. Fourteen trials with 1309 men and women were identified. In the calcitonin and the control groups, vertebral and non-vertebral fractures were summed and divided by the number of individuals originally allocated to the treatment groups. The relative risk of any fracture for individuals taking calcitonin versus those not taking calcitonin was 0.43 (95% CI 0.38-0.50). The effect was apparent for both vertebral fracture (RR 0.45; 95% CI 0.39-0.53) and non-vertebral fractures (RR 0.34; 95% CI 0.17-0.68). When studies identifying patients with fracture, rather than numbers of fractures were pooled, the magnitude of effect was less (RR 0.74; 95% CI 0.60-0.93), and the separate effects on vertebral and non-vertebral fractures was of borderline significance. Treatment with **calcitonin is associated with a significant decrease in the number of vertebral and non-vertebral fractures.**

A randomized controlled trial of salmon calcitonin to prevent bone loss in corticosteroid-treated temporal arthritis and polymyalgia rheumatica

Healey J.H, Calcif. Tissue Int.1996; 58:71-80.

This study was a randomized; double blind placebo controlled to evaluate effect of Salmon Calcitonin in corticosteroid induced osteoporosis.

The patients were chronic corticosteroid users suffering from different connective tissue disorders. The patients were stratified according to diagnosis and randomized into 1 of the 2 treatment,

One group received Salmon Calcitonin 100 IU subcutaneous thrice weekly, while the other group was put on placebo injections. All received 1500mg of calcium. The study was for a period of 2 years.

The authors found that the **mean change in the lumbar spine bone density in Salmon Calcitonin group over 2 years period** was 0.001gm/cm^2, while that in placebo group was 0.011gm/cm^2.

The density at the femoral neck in Salmon Calcitonin group was 0.027 gm/cm^2 compared with 0.53 gm/cm^2. The rate of vertebral fracture incidence in Salmon Calcitonin group was 11% while in the placebo group was 14% over a period of 2 years.

Bone turnover in postmenopausal osteoporosis. Effect of calcitonin treatment.

Civitelli R, J Clin Invest - 01-OCT-1988; 82(4): 1268-74

The effectiveness of calcitonin treatment of postmenopausal osteoporosis in relation to bone turnover was investigated in 53 postmenopausal osteoporotic women before and after one year of therapy with salmon calcitonin (sCT), at the dose of 50 IU every other day. Baseline evaluation revealed that 17 (32%) patients had high turnover (HTOP), and 36 (68%) normal turnover osteoporosis (NTOP) as assessed by measurement of whole body retention (WBR) of 99mTc-methylene diphosphonate. The two groups did not differ in terms of bone mineral content (BMC) measured by dual photon absorptiometry at both lumbar spine and femoral diaphysis. However, HTOP patients had higher levels of serum osteocalcin (OC) and urinary hydroxyproline excretion (HOP/Cr). Multivariate regression analysis showed no correlation between parameters of bone turnover (WBR, OC, HOP/Cr) and both femoral and vertebral bone density; the latter being negatively correlated only with the years elapsed since menopause (R2 = 0.406). Treatment with sCT resulted in a significant increase of vertebral BMC in the 53 patients taken as a whole group (+/- 7%, P less than 0.001). When the results obtained in HTOP and NTOP were analyzed separately, only those with HTOP showed a marked increment of spinal BMC (+22%, P less than 0.001), NTOP subjects neither gained nor lost bone mineral during the study. Femoral BMC decreased in the whole group after sCT therapy (-3%, P less than 0.003). However, HTOP patients maintained initial BMC values, whereas those with NTOP lost a significant amount of bone during the study period (-5%, P less than 0.001). The increase of vertebral bone mass was associated with a marked depression of bone turnover detectable in both subsets of patients and in the whole group. In conclusion:

(a) assessment of bone turnover cannot help predict the severity of bone loss in postmenopausal osteoporosis; (b) **calcitonin therapy appears to be particularly indicated for patients with high-turnover osteoporosis,** resulting in a net gain of bone mineral in the axial skeleton and a slowing of bone loss in the appendicular bones.

Long-term calcitonin therapy in postmenopausal osteoporosis.

Gruber HE, Metabolism - 01-APR-1984; 33(4): 295-303

Results are presented from a 2-year controlled study evaluating the efficacy of 100 units synthetic salmon calcitonin/d in the treatment of postmenopausal osteoporosis. All patients received 400 units D2 po qd and 1200 mg CaCO3 po qd. The 21 control and 24 treated patients (mean age 65) were not statistically different at baseline. Although mean total body calcium (TBCa) was not significantly different between treated and control patients throughout the study, mean differences in the change in TBCa from baseline (treated minus control) were significant at 12, 18, and 26 months. The mean slope of TBCa for treated patients, but not for controls, was significantly positive through 18 months. Iliac crest bone biopsies showed (1) a significantly **greater percent total bone area in treated compared to control patients at 2 years, and (2) a significantly decreased percent resorbing surface in treated patients** when evaluated by paired difference from baseline. At 4 months, serum calcium values were significantly lower in treated patients than in controls (mean difference, treated minus controls), but were not statistically different from controls at study completion. Urine calcium increased significantly for the first 4 months in treated subjects and then declined to baseline levels. Since urinary calcium increased, the increase in TBCa was probably associated with an increase in net intestinal calcium absorption.

Long term calcitonin therapy in Post menopausal osteoporosis

Metabolism 1984; 33(4): 295-303.

In this study, 24 post menopausal osteoporotic women aged 51-75 were treated with 100 units of Salmon Calcitonin injected IM or subcutaneously for a period ranging from 24-30 months. 21 women served as controlled group. All patients received 400 units of Vitamin D daily and 1200 mg of Calcium Carbonate daily by oral route. In the bone studies, it was found that the percent total bone area was significantly greater in the treated patients than in the controlled patients (18.7% versus 14.4%). Throughout the study, there was no significant difference in the radial bone mass.

The results of this study show that **Calcitonin is relatively free from serious side effects.**

Calcitonin treatment of post-menopausal osteoporosis. Evaluation

of efficacy by principal components analysis.

Milhaud G, Biomedicine - 01-MAY-1975; 22(3): 223-32

The efficacy of long term treatment of senile osteoporosis by low doses of calcitonin was established using five parameters of calcium kinetics and a quantitative pain scale. Under treatment the calcium balance improved, due predominantly to a **decrease in bone resorption associated with an increase in bone accretion and intestinal absorption of calcium. In addition, the hormone had a marked analgesic effect, which increased with the length of the treatment.** Principal components analysis enables to establish the value of a therapeutic agent for the management of a progressive disease with period of regression like osteoporosis, for which the eficacy of previously advocated treatments had never been proven.

Responses to salmon calcitonin in chronic renal failure: relation to histological and biochemical indices of bone turnover.

Eur J Clin Invest. 1981 Jun;11(3):177-84., Cundy T, Heynen G, Gaspar S, Earnshaw M, Bartlett M, Paton S, Kanis JA.

Twenty-one patients with chronic renal failure and bone disease or hypercalcaemia were studied before and following single (twenty patients) or repeated (fourteen patients) intravenous injection of synthetic salmon calcitonin. Significant correlations were noted before treatment between bone surfaces occupied by osteoblasts or osteoclasts and plasma levels of immunoreactive parathyroid hormone, alkaline phosphatase and hydroxyproline. Following a single injection of 2--200 IU salmon calcitonin, plasma levels of calcium and phosphate fell for 6--8 h, but rose subsequently to pre-injection levels at 24 h. The magnitude and duration of the hypocalcaemic response was not clearly dose-dependent, but correlated with measured indices of bone cell activity. Repeated administration of calcitonin (10--200 IU thrice weekly for up to 2 months) lowered plasma calcium in the majority of patients and restored plasma calcium to normal in four previously hypercalcaemic patients. Mean levels of alkaline phosphatase increased but no significant changes in plasma phosphate, immunoreactive parathyroid hormone and calcitonin, or hydroxyproline occurred. Calcium absorption (six studies) did not change during treatment. We conclude that **synthetic salmon calcitonin is an effective short-term inhibitor of bone resorption in patients with chronic renal failure. Its use as a possible treatment for hypercalcaemia and hyperparathyroid bone disease in chronic renal failure** is discussed.

REFERENCES

1. *Woolf AD and Dixon ASJ. Osteoporosis; An Update on Management. Drugs 1984; 28:565-576.*

2. *Albright F, Bloomberg E and Smith PH. Postmenopausal osteoporosis. Trans. Assoc. Am. Phys. 1940; 55:298-305.*

3. *Nordin BEC, Aaron J, Speed R and Crilly RG. Bone formation and resorption as the determinants of trabecular bone volume in postmenopausal osteoporosis. Lancet, 1981; 2:277-279.*

4. *Riggs BL Wahner HW, Seeman E, Offord KP, Dunn WJ, Mazes RB, Johnson KA and Melton LJIII. Changes in bone mineral density of proximal femur and spine with aging. J Clin. Invest. 1982; 70:716-723.*

5. *Gupta A. Osteoporosis in India, The Nutritional Hypothesis. Nat. Med. J. Ind. 1996; 9(6): 268-274.*

6. *Aloia JF, Cohn H, Ostuni JA, Cane R and Ellis K. Prevention of involutional bone loss by exercise. Ann. Intern. Med. 1978; 89:356-358.*

7. *Krolner B, Toft B, Nielsen SP, and Tondevold E. Physical exercise as prophylaxis against involutional vertebral bone loss; A controlled trial. Clin. Sci. 1983; 64:541-546.*

8. *Christensen C, Christensen MS, McNair P, Hagen C, Stocklund E and Transbol I. Prevention of early menopausal bone loss: Controlled two year study in 315 normal females. Eu. J. Clin. Invest. 1980; 10:273-279.*

9. *Riggs BL, Seeman E, Hodgson SF, Taves DR and Otslon WM. Effects of the fluoride/calcium regimen on vertebral fracture occurrence in postmenopausal women. Comparison with conventional therapy. N. Eng. J. Med. 1982; 306:446-450.*

10. *Epstein O, Kato Y, Dick R and Sherlock S. Vitamin D, hydroxyapatite and calcium gluconate in treatment of cortical bone thinning in postmenopausal women with primary biliary cirrhosis. Am. J. Clin. Nutr. 1982; 36:426-430.*

11. *Bartley MH, Arnold JS, Haslam RK and Webster SSJ. The relationship of bone strength and bone quality in health, disease and ageing. J. Gerontol.1966; 21:517-521.*

12. *Matkovic V, Kostial K, Simonovic I, Buzina R, Brodarec A and Nordin BEC. Bone status and fracture rates in two regions of Yugoslavia. Am. J Clin. Nutr. 1979; 32:540-549.*

13. *Kanis JA. Treatment of osteoporotic fracture. Lancet, 1984; 1:27-33.*

14. *Woolf AD and Dixon A st J. Osteoporosis: An update on Management. Drugs, 1984; 28:565-576.*

15. *Heaney RP. Bone mass, nutrition, and other lifestyle factors. Am. J Med., 1993; 95(suppl. 5A): 29s-32s.*

16. *Torres MM and Raya PM. Calcitonin. Drugs of Today, 2000; 36(suppl D): 1-11.*

17. *Calcitonin Chemistry. Data on file. Amadeus Biotech and Pharmaceuticals Pvt. Ltd., 2001.*

18. *Overgaad K, and Christiansen C. Long term treatment of established osteoporosis with intranasal calcitonin. Calcif Tissue Int. 1991; 49(suppl): s60-s63.*

19. *Gennari C, Agnusdei D and Camporeale A. Long term treatment with calcitonin in osteoporosis. Horm Metab Res. 1993; 25:484-485.*

20. *Nielsen NM von der Recke P Hansen, Ma et. al. Estimation of effects of salmon calcitonin in established osteoporosis by biochemical bone marker. Calcif. Tissue Int. 1994; 55:8-11.*

21. *Guesens P, Boonen S, Nijs J et. al. Effect of salmon calcitonin on femoral bone quality in adult ovariectomized ewes. Calcif Tissue Int., 1996; 59; 315-320.*

22. *Foti R, Martorana U Broggini M Long term tolerability of nasal spray formulation of salmon calcitonin. Curr. Ther. Res., 1995; 56:429-435.*

23. *Takahashi S, Goldring S and Katz M. Down-regulation of calcitonin receptor mRNA expression by calcitonin during human osteoclast-like cell differentiation. J Clin. Invest. 1995; 95:167-171.*

24. *Civitelli R. Calcitonin. In: Marcus R Feldman D and Kelsey J (Eds). Osteoporosis. Academic Press: San Diego, 1996; 1235-1258.*

25. *Stuart L, Silverman SL, Chesnut C., et. al. Salmon calcitonin nasal spray (NS-CT) reduces risk of vertebral fracture (VF) in established osteoporosis and has continuous efficacy with prolonged treatment: Accrued 5 year worldwide data of the PROOF study. 2ND Joint Meet Am Soc. Bone Mineral Res., (San Francisco 1998).*

26. *Chesnut C, Silverman SL, Adriano K., et.al. Salmon calcitonin nasal spray (NS - CT) reduces the rate of new vertebral fractures independently of known major pre-treatment risk factors: Accrued 5 year analysis of the PROOF study. 2nd Joint Meet. Am. Soc. Bone Mieral Res. (San Francisco, 1998).*

27. *Alexandre C. Diagnosis and treatment of osteoporosis. Curr. Opin. Rheumatol. 1995; 7:240-242.*

28. *Melton LJ, Chrichilles EA Cooper C, et. al. Perspective How many women have osteoporosis. J. Bone Miner Res. 1992; 7:1005-1010.*

29. *Stevenson JC and Evans IMA Pharmacology and therapeutic use of calcitonin. Drugs 1981; 21:257-272*

SHREYA

SHREYA LIFE SCIENCES PVT. LTD.
Shreya House, 301/A, Pereira Hill Road, Andheri (East), Mumbai 400099