THE NORTHERN HOSPITAL

SALCATONIN

"Salmon Fishing on the Cascapediac River" oil on canvas, Albert Bierstadt, *(1830 -1902)*

"When I reflect that all this grand portion of our Union, instead of being in a state of nature, is now more or less covered with villages, farms, and towns....that the woods are fast disappearing under the axe by day, and the fires by night....when I see the surplus population of Europe coming to assist in the destruction of the forest and the transplanting of civilization onto its darkest recesses - when I remember that these extraordinary changes have all taken place in the short period of twenty years, I pause, wonder, and although I know all to be fact, can scarcely believe in its reality".

Jean-Jacques Audubon, November 1829.

So wrote the great naturalist and ornithological artist, Jean-Jacques Audubon in 1829. He could scarce believe his own eyes how in just the space of barely twenty years, vast tracts of the pristine American wilderness had been ripped down and converted into towns, roads, and villages. Yet all this took place in the first years of the Nineteenth century. The pace of destruction of nature and the environment would be trivial compared to what would come over the ensuing years of the Nineteenth century, and throughout the Twentieth century. One wonders what Audubon would have thought of his adopted homeland in the 21st century. It is an arresting thought to consider what the vast North and South American continents must have been like when European seafarers first set foot in the New World in the late Fifteenth century. Virtually half the land surface of the planet in a pristine state of Eden.

With the ever accelerating destruction of the natural habitats of the world, comes a fearful a secondary cost. The loss of beauty is one thing, but the permanent loss of the Earth's biodiversity, in both plants, animals, and even in the microscopic world unseen is quite another matter all together. It is biodiversity that drives evolution. This is what natural selection acts on. Without biodiversity, natural disasters will result in catastrophic extinction, without hope of recovery or renewal. Audubon was incredibly prescient for his age. He was the first to correctly recognize that the unabated destruction of natural habitat would lead to eventual catastrophe. To keep this in the context of his times, this was a pre-Darwinian age when many learned naturalists did not even believe that extinctions of species occurred! The animal and plant world was a truly vast inexhaustible resource, that Genesis said was specifically for the benefit of humanity. There was no concept at this time that natural resources could be finite! In 1841 Audubon, alarmed by the changes he saw going on everywhere he cared to look, approached Daniel Webster, the Secretary of State, with an impassioned plea to urgently "...establish a Natural History Institution to advance our knowledge of natural science...". His request was met with uncomprehending indifference. In 1847 he became ill, losing his eyesight and he could no longer paint his beloved birds. His general health then rapidly deteriorated and he died in 1851. Today Audubon's name has come to symbolize not only a love of birds and nature but also the conservation of the natural environment, a noble and enlightened legacy he would have been well pleased with.

Amoung the biodiversity of the Earth lies a vast trove of untapped, unknown biochemical wonders. It is to these wonders that humanity may look to new medicines. Cures to ancient human scourges, such as quinine and the more recently discovered artemisinins, or penicillin from a humble fungus, have been found. Many more in all probability lie as yet undiscovered. But with the increasing loss of habitat, biodiversity is being lost at a catastrophic rate and along with it untold eons of wondrous biochemical substances are lost with it; lost without humanity ever having been aware of their existence. The magisterial Edward O. Wilson, wrote "…I will argue that every scrap of biological diversity is priceless, to be learned and cherished, and never to be surrendered without a struggle….We should preserve every scrap ….while we learn to use it and come to understand what it means to humanity".

The humble salmon, is a source of a most powerful calcitonin. The very fact that fish, mammals, birds and reptiles all produce variants of this chemical shows the deep evolutionary kinship of all life on Earth. The salmon seems to us today an inexhaustible resource, yet the sad story of the once teeming, "inexhaustible", Atlantic Cod, driven to the very brink of extinction, by massive factory sized Twentieth century trawlers should remind us that ***no*** *species of the planet's seas or rivers are immune to extinction at the hands of humanity.*

SALCATONIN

Introduction

Salcatonin is a synthetic polypeptide hormone structurally identical to **salmon calcitonin.**

In the ED it is used to treat **severe hypercalcaemia.**

In acute life-threatening situations, it is used to achieve a more rapid effect than saline rehydration and pamidronate.

Its efficacy however wanes after several days

History

Calcitonin was isolated in 1962 by **Copp** and **Cheney**

Chemistry

Salcatonin consists of a 32 amino acid linear sequence with a disulphide bridge at positions one and seven.

Physiology

Naturally occurring calcitonin is a 32-amino acid linear polypeptide hormone synthesised by the **parafollicular** cells (also known as C-cells) in the **thyroid gland** of mammals

Calcitonin is a natural hormone involved in calcium regulation and bone metabolism.

The secretion and biosynthesis of calcitonin in both animals and humans are regulated by the **concentration of calcium** in plasma. When the calcium concentration is high the amount of the hormone increases in response in order to reduce calcium levels back towards normal.

Calcitonin has also been found in other *non-mammalian* species including fish, reptiles, and birds. It is produced in the **ultimobranchial gland** of **birds and fish.**

Its importance in humans has not been as well established as its importance in other animals, as its function is usually insignificant in the regulation of normal calcium homeostasis in humans.

Preparation

Salcatonin as:

Ampoules:

- 50 units/mL, 1 mL
- 100 units/mL, 1 mL

Mechanism of Action

Salcatonin acts to **lower blood calcium**, opposing the effects of parathyroid hormone (PTH).

It lowers calcium levels by:

1. Inhibiting osteoclastic bone resorption:

    - Salcatonin is effective in diminishing hypercalcaemia in patients with hyperparathyroidism, vitamin D intoxication as well as osteolytic bone metastases.

2. Increasing urinary excretion of calcium (and phosphate).

    - By decreasing their tubular reabsorption.

Calcitonin/Salcatonin is not thought to have any major effects on the *intestinal* absorption of calcium.

Pharmacodynamics

The pharmacological actions of salmon calcitonin is the same as that of mammalian calcitonin.

In humans, data on relative potency are sparse, but salcatonin is thought to be at least 10 - 40 times as potent by weight as human calcitonin in its ability to produce hypocalcaemia.

This is thought to be due to its *greater affinity* for receptor binding sites in bone and kidney, as well as its slower rate of metabolism compared to humans.

The onset of action is immediate after intravenous administration. [3]

It occurs in about 15 minutes following intramuscular or subcutaneous administration, with peak plasma levels being attained within one hour.

After subcutaneous administration, peak plasma levels are reached in about 30 minutes.

Pharmacokinetics

Absorption:

- Salcatonin can be administered by **SC, IM** or **IV** routes.it may also be given as a **continuous IV infusion**.

  It cannot be administered orally, due to the action of intestinal proteases which inactivate the drug.

- The bioavailability of salcatonin is about 70% following both IM or SC administration.

Distribution:

- Protein binding is around 30 - 40%.
- The Vd is 0.15 - 0.30 liters / kg.
- In animal studies, calcitonin salmon does not cross the placental barrier. It is uncertain if salcatonin crosses the *human* placenta. [4]
- It is unknown if salcatonin is excreted into human breast milk

Metabolism and excretion:

- Salcatonin is metabolised to inactive metabolites primarily in the kidneys, but also in the blood and peripheral tissues.
- The metabolic clearance rate of salcatonin appears to be lower than human calcitonin.
    - Up to 95% of salcatonin and its metabolites are excreted by the kidney, of which less than 2% is unchanged drug.
- The apparent biological half-life is several hours.

Indications

In the ED:

1. Severe/ symptomatic hypercalcaemia
    - In acute life-threatening hypercalcaemia, salcatonin can be given for a more rapid effect that that achieved by saline rehydration and pamidronate.

Outside the ED:

2. Active Paget's disease of bone (but only *rarely* used for this)

Contraindications/ Precautions

Hypersensitivity to salcatonin (rare)

Pregnancy

Salcatonin is categorized as a B2 drug with respect to pregnancy.

Category B2 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

In animal studies, calcitonin salmon does not cross the placental barrier.

Reports of an association between calcitonin salmon use during pregnancy and an increased risk of congenital malformations or adverse pregnancy outcomes have not been located.

There has been one case report of the use of cinacalcet and calcitonin for the treatment of hyperparathyroidism in the third trimester of pregnancy. While calcium levels were reduced in the mother, the outcome of the pregnancy was not documented.

Due to the limited information available and concerns of potential fetal toxicity, consider an alternative therapy during pregnancy if possible.

Breast feeding

Infants exposed to calcitonin salmon via breast milk are unlikely to experience adverse effects, as the transfer of calcitonin salmon into the breast milk is limited by the high molecular weight of the medicine.

While there are no reports describing the use of calcitonin salmon during breastfeeding, consider an alternative treatment as animal studies have suggested that calcitonin may suppress lactation.

Adverse Effects

These may include:

1. Flushing

2. GIT upset: Nausea/ vomiting

3. Antibody development:

    - Antibodies may develop after *prolonged* treatment.

    - While the development of resistance to calcitonins is not uncommon, *antibody-mediated* resistance to treatment is rare.

4. Hypersensitivity reactions:

    - Being a polypeptide, salcatonin may give to localized hypersensitivity reactions or to generalized anaphylactoid/ anaphylactic type reactions, although these are *rare.*

Dosing

For hypercalcaemia:

In acute life-threatening hypercalcaemia, salcatonin can be given for a more rapid effect than that achieved by saline rehydration and pamidronate.

Its efficacy however wanes after several days.

Salcatonin can be given by **SC, IM** or **IV** routes. It may also be given by **continuous IV infusion.**

For SC or IM dosing:

- 100 IU (*or 5- 10 IU / kg*) SC or IM, **6 - 12 hourly**.

  Use multiple injection sites if the *volume* is more than 2 mL.

For IV dosing:

- Inject **100 IU** *(or 5- 10 IU / kg)* **slowly** over **3 - 5 minutes** every **6 - 12 hourly**.

For continuous IV infusion:

- Intravenous infusion may be the most effective method of administration in severe cases of hypercalcaemia.

  Dilute 100 IU *(or 5- 10 IU / kg)* **of salcatonin in 500 mL sodium chloride 0.9% and infuse over at least 6 hours.** [2]

"Still Life with Salmon", oil on canvas, 1866-1869, Edouard Manet

Wild salmon flesh is generally a deep orange to red. This is on account of its diet in the wild. Some salmon have white flesh however, (as Edouard Manet showed us in his "Still Life with Salmon" of 1869). The orange coloration, is due to a mechanism akin to the pink colour of the flamingo, or the yellow colour of some canaries - its diet. Many salmon feed on krill and other tiny shellfish and it is from these food sources they obtain the carotenoids, (astaxanthin and to a lesser extent canthaxanthin), that gives them their distinctive orange coloured flesh. "Consumers", do not care for white salmon - it's not really salmon, is it! Farmed salmon are therefore given artificial colorants in their diets, to make them look like "real" salmon! But Edouard Manet's white salmon, with lemons and white wine looks just fine all the same!

References

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4. Calcitonin salmon (salcatonin) in RWH Pregnancy & Breastfeeding Guidelines, 18 May 2017.

5. Salcatonin in Australian Injectable Handbook, Website Accessed April 2019.

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