THE NORTHERN HOSPITAL

LIRAGLUTIDE

Heloderma suspectum (The Gila Monster)

"...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".

Edward O Wilson.

On the first part of the journey

I was looking at all the life
There were plants and birds and rocks and things
There was sand and hills and rings
The first thing I met was a fly with a buzz
And the sky with no clouds
The heat was hot and the ground was dry
But the air was full of sound

I've been through the desert on a horse with no name
It felt good to be out of the rain
In the desert you can remember your name
Cause there ain't no one for to give you no pain
La, la

After two days in the desert sun
My skin began to turn red
After three days in the desert fun
I was looking at a river bed
And the story it told of a river that flowed
Made me sad to think it was dead

You see I've been through the desert on a horse with no name
It felt good to be out of the rain
In the desert you can remember your name
Cause there ain't no one for to give you no pain
La, la

After nine days I let the horse run free
Cause the desert had turned to sea
There were plants and birds and rocks and things
There was sand and hills and rings
The ocean is a desert with its life underground
And a perfect disguise above
Under the cities lies a heart made of ground
But the humans will give no love

You see I've been through the desert on a horse with no name
It felt good to be out of the rain
In the desert you can remember your name
Cause there ain't no one for to give you no pain
La, la

Dewey Bunnell, America; "Horse with No Name", 1971

Though no one at the time in 1971, had any idea what the international hit "Horse with No Name", by America was about, it was nonetheless extremely popular, and remains so even today. It gave a strong sense of the sounds, heat, the feel of being in the New Mexico, Arizona desert. Some radio stations banned it on account of allegations that it

was actually about drugs, "horse" being one colloquialism at the time for heroin. But really this was a total misunderstanding of the song.

Lee Martin "Dewey" Bunnell the British-American musician, singer, guitarist, and songwriter, best known as a member of the folk rock band America, and who wrote its most famous song, "Horse with No Name", years later related that he had simply been, jamming away for his own amusement. He had been feeling a bit down being trapped in a dull rainy England, when he began to reminisce about his childhood days in the bright sunny New Mexico and Arizona deserts.

He related "I had spent a good deal of time poking around in the high desert with my brother when we lived at Vandenberg Air Force Base in California. And we'd drive through Arizona and New Mexico. I loved the cactus and the heat. I was trying to capture the sights and sounds of the desert, and there was an environmental message at the end. But it's grown to mean more for me. I see now that this anonymous horse was a vehicle to get me away from all the confusion and chaos of life to a peaceful and quiet place".

Though the exact meaning of the odd words were unclear, the imagery struck a powerful and universal chord of the sheer sereneness of the wide hot untamed desert - a place very far from "civilization", where one can escape the mad bustle of modern city life, and be at one with nature, and actually stop to reflect on life - to even just "remember your our name" again.

One of the most iconic images of the New Mexico deserts is that of the Gila Monster, one of only two known venomous lizards in North America. Though somewhat poisonous the creature is not aggressive at all, peacefully living out its existence on sunny desert rocks. However, it traditionally had a fearsome reputation of being aggressive and able to kill by its bite or even simply by its breath!

But Dr. Ward, of the Arizona Graphic, wrote of its placidness on September 23, 1899: "I have never been called to attend a case of Gila monster bite, and I don't want to be. I think a man who is fool enough to get bitten by a Gila monster ought to die! The creature is so sluggish and slow of movement that the victim of its bite is compelled largely to help it in order to get bitten!"

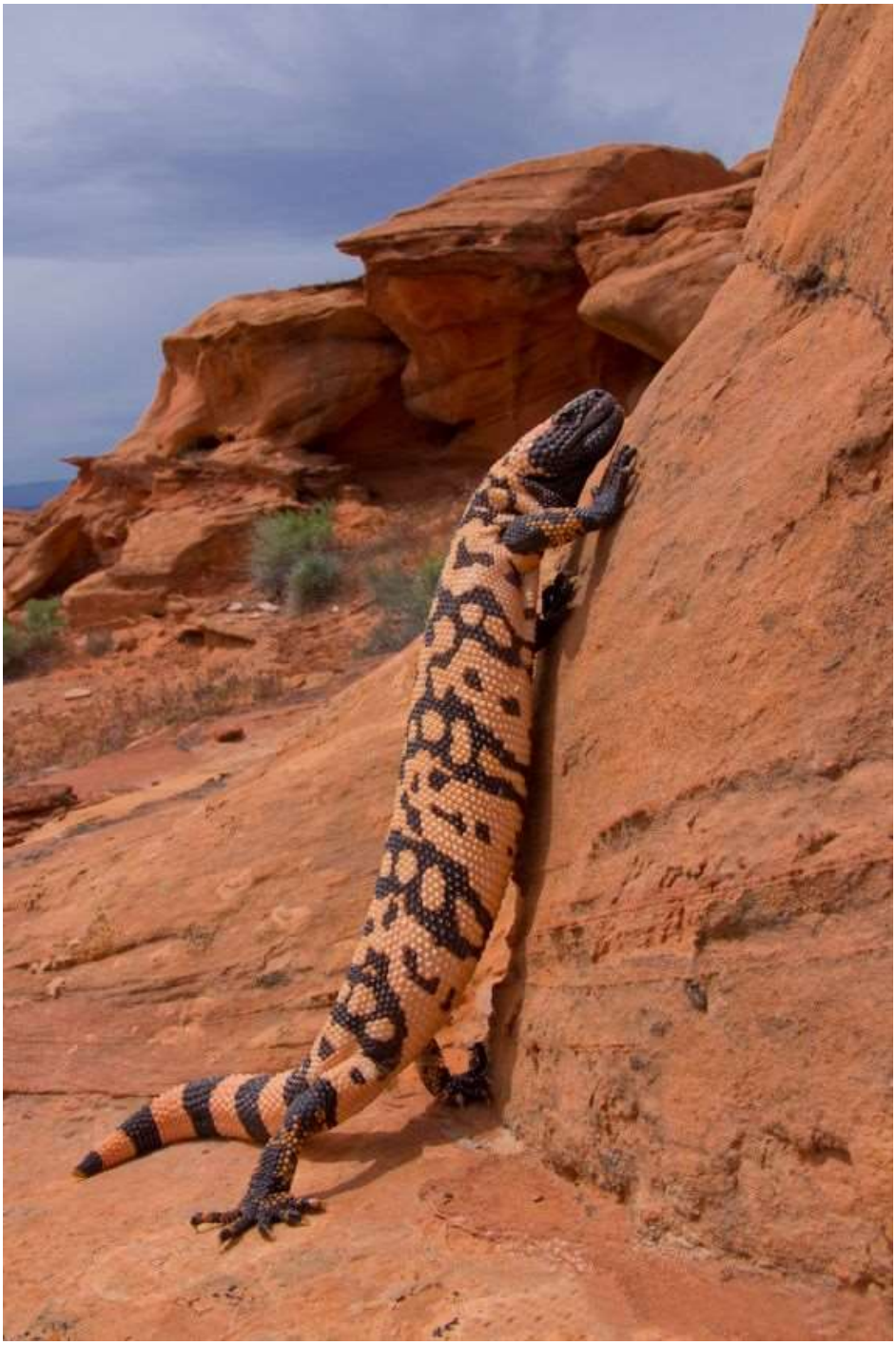
Fear of the harmless and very attractive creature led to its constant killing to the point that today it is approaching endangered species status, and now it is an officially protected species. May ignorant people however simply shrug their shoulders and exclaim, "why should a poisonous lizard be protected?"

The answer, quite apart from a respect for life on planet Earth, and being a beautiful creature in its own right, is that its venom contains a protein from which scientists developed a whole new class of medicine to treat type II diabetes, known as GLP-1 receptor agonists.

The magisterial Edward O. Wilson once wrote "...I will argue that every scrap of biological diversity is priceless, to be learned and cherished, and never to be surrendered

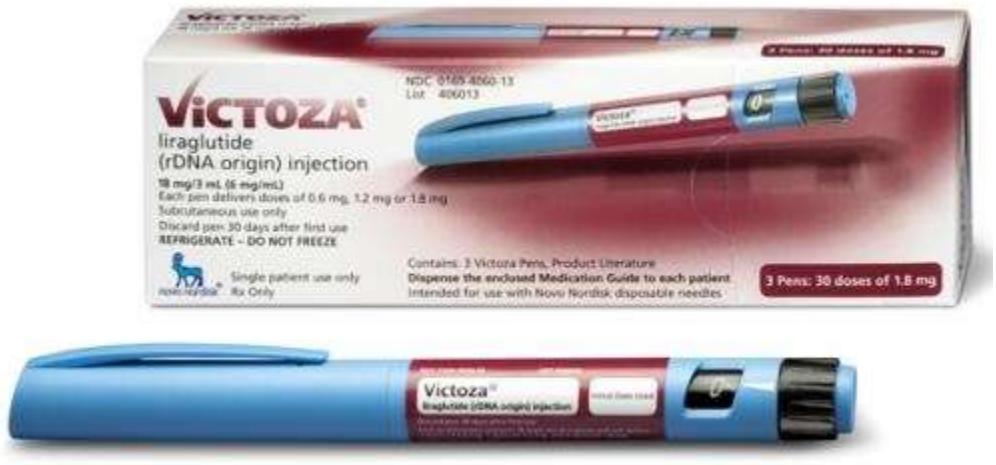
without a struggle….We should preserve every scrap ….while we learn to use it and come to understand what it means to humanity".

The Gila Monster, like Dewey Bunnell's "Horse with No Name" was much misunderstood. Every life form on planet Earth is the result of countless eons of evolution and each has its own wondrous genetic secrets, miracles of DNA, that could be lost to us forever before we even understand the potential benefit to humanity these may hold.



A Gila monster, in the Utah desert

LIRAGLUTIDE



Pre-filled autoinjector, Liraglutide 6 mg/mL, in 3 mL

Introduction

Liraglutide, (pronounced lyra - glutide), (trade name "**Victoza**", among others) is an **injectable** antidiabetic agent, used in the treatment of **type II diabetes mellitus.**

It is **not** an insulin

It is a **glucagon-like peptide-1 analogue** that acts by:

1. Increasing insulin secretion.
2. Reducing glucagon secretion.
3. Causing a small reduction in appetite.
4. Slowing gastric emptying.

Liraglutide is recommended for use in patients with type 2 diabetes mellitus with:

1. Metformin and/or a sulfonylurea when these are inadequate
2. Basal insulin, with or without metformin when these are inadequate

History

Work on **exendin-4,** a protein found in the saliva of the **Gila monster lizard,** led to the development of a novel class of antidiabetic agents, known as the **Incretin-based therapies**

The exendin-4 protein is somewhat homologous with GLP-1, but it has a considerably longer half-life.

It binds to the intact human Glucagon-like peptide-1 receptor (GLP-1R) in a similar way to the human peptide glucagon-like peptide-1 (GLP-1) and produces similar actions.

Exendin-4 was first isolated by endocrinologist **Dr. John Eng** in 1992 while working at the Veterans Administration Medical Center, New York.

Chemistry

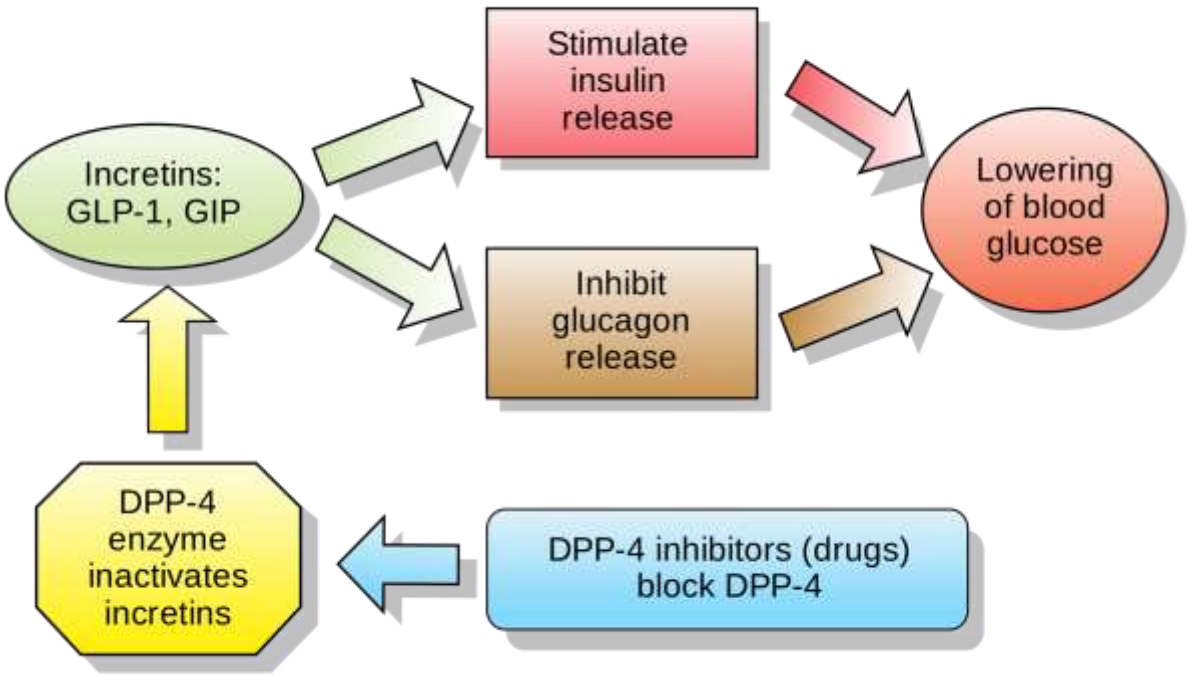
Liraglutide is a human glucagon-like peptide-1 (GLP-1) analogue that binds to and activates the GLP-1 receptor.

The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose dependent insulin secretion from the pancreatic beta cells.

Liraglutide exhibits 97% homology to human GLP-1. In liraglutide, the lysine at position 34 has been replaced with arginine, and a palmitic acid has been attached via a glutamoyl spacer to lysine at position 26.

Liraglutide is produced by recombinant DNA technology using *Saccharomyces cerevisiae*, a species of yeast

Physiology



Incretins are a group of hormones that:

- Stimulate insulin release
- Inhibit glucagon release

The two principal incretin hormones are:

1. Glucose - dependent insulinotropic polypeptide (GIP) - (*formerly and less correctly known as Gastric inhibitory polypeptide*).
    - It is synthesized by K cells, which are found in the mucosa of the duodenum and the jejunum of the gastrointestinal tract.
    - It stimulates the production of insulin from the beta cells of the pancreas.
2. Glucagon-like peptide - 1 (GLP -1):
    - It is synthesized by L cells which are primarily found in the ileum and large intestine.
    - It stimulates the production of insulin from the beta cells of the pancreas in response to rising glucose, while also suppressing glucagon secretion from the alpha cells of the pancreas.

The incretin hormones are part of an endogenous system involved in the physiological regulation of glucose homeostasis.

Incretin hormones are released by the **intestinal tract** in response to an oral **glucose load.**

Type 2 diabetics are less responsive to GIP and have lower levels of GIP secretion after a meal when compared to non-diabetics.

Classification

There are currently 6 classes (6 oral and one injectable within the Incretin-based therapies) of non-insulin hypoglycemic agents available in Australia:

The two principle classes are:

1. **The Biguanides**:

    These agents act by reducing hepatic glucose production (i.e. gluconeogenesis) and increasing the peripheral utilization of glucose.

    Examples include:

    - Metformin

2. **The Sulphonylureas**:

These agents act by increasing pancreatic insulin secretion and also possibly by enhancing peripheral sensitivity to insulin:

Examples include:

First generation:

- Tolbutamide (no longer used)

Second generation, (more potent, lower doses):

- Glibenclamide
- Gliclazide
- Glipizide

Third generation:

- Glimepiride

Other newer agents with less clinical experience include:

3. **Incretin-based therapies**:

Dipeptidyl peptidase - 4 inhibitors (i.e. **DPP - 4 inhibitors** or "**Gliptins**"):

These agents increase the concentrations of incretin hormones (GLP-1 and GIP) that are produced in the gut following ingestion of food; GLP-1 stimulates insulin release, and reduces glucagon secretion.

Examples include:

- Alogliptin
- Linagliptin
- Saxagliptin
- Sitagliptin
- Vildagliptin

Glucagon-like peptide-1 (GLP-1) receptor agonists:

These agents are synthetic analogues of GLP-1; they increase insulin secretion and reduce glucagon secretion and also cause a small reduction in appetite.

Examples include:

- Exenatide
- **Liraglutide**
- Dulaglutide

4. **Glucosidase inhibitors**:

These agents reduce the breakdown of complex carbohydrate in the gut, thereby reducing absorption of carbohydrate and hence insulin requirements

Examples include:

- Acarbose.

5. **Thiazolidinediones (or "Glitazones")**:

These agents reduce peripheral insulin resistance and hence insulin requirements

Examples include:

- Pioglitazone
- Rosiglitazone

6. **Sodium-glucose co-transporter 2 (or SGLT-2) inhibitors (or "Gliflozins")**:

These agents reduce glucose reabsorption in the kidneys.

Examples include:

- Dapagliflozin
- Empagliflozin
- Ertugliflozin

Preparations

Liraglutide as:

Ampoules:

- 6 mg/mL, in 3 mL

Mechanism of Action

It is a **glucagon-like peptide-1 analogue** that acts by:

1. Increasing insulin secretion.
2. Reducing glucagon secretion.
3. Causing a small reduction in appetite.
4. Slowing gastric emptying.

Pharmacodynamics

Liraglutide improves glycaemic control through the immediate and sustained effects of lowering both postprandial and fasting glucose concentrations in patients with type 2 diabetes.

Modest weight loss (2-3 kg) has been observed, but long term effect on weight is currently unknown.

Unlike native GLP-1, liraglutide has a pharmacokinetic and pharmacodynamic profile in humans suitable for **once daily** administration.

Liraglutide stimulates insulin secretion in a glucose dependent manner and improves beta-cell function.

Simultaneously, liraglutide lowers inappropriately high glucagon secretion, also in a glucose dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, during hypoglycaemia liraglutide diminishes insulin secretion and does not impair glucagon secretion

Pharmacokinetics

Absorption:

- Liraglutide is administer by SC injection

Distribution

- Protein binding is high at > 98%
- The apparent volume of distribution after subcutaneous administration is 11-17 Liters.
- It is unknown if liraglutide crosses the human placenta.

- It is likely that liguratide is distributed into human breast milk.

Metabolism and excretion:

- Liraglutide is endogenously metabolised in a similar manner to large proteins without a specific organ as major route of elimination.
- Elimination half-life is around 13 hours.

Indications

Indications include:

Patients with type 2 diabetes, with:

1. Metformin and/or a sulfonylurea when these are inadequate
2. Basal insulin, with or without metformin when these are inadequate

Contra-indications/precautions

These include:

1. Known hypersensitivity to liraglutide
2. Renal impairment:
    - Contraindicated if CrCl <30 mL/minute.
    - Elimination may be reduced possibly increasing the risk of adverse effects.
3. Severe GI disease:
    - e.g. gastroparesis, dumping syndrome: avoid use due to effects on the GIT.
4. History of pancreatitis (contraindicated).
5. Gall bladder disease:
    - GLP-1 analogues *may* increase the risk of gall bladder disease and the need for cholecystectomy.

Pregnancy

Liraglutide is a category B3 drug with respect to pregnancy.

Category B3 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 have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

There is very limited information available describing the use of liraglutide during pregnancy.

A single case report of exposure to liraglutide during the first trimester has described healthy pregnancy and neonatal outcomes.

However, due to potential adverse effects, dietary modification and insulin should be considered as alternative therapies to liraglutide during pregnancy.

Follow-up and monitoring of both maternal and fetal wellbeing by a multidisciplinary team is recommended to ensure optimal glycaemic control and fetal growth .

Breast feeding

Published reports describing the use of liraglutide during breastfeeding have not been located.

Transfer of liraglutide into breast milk is likely to be limited due to the high molecular weight of the medicine.

However, due to potential adverse effects in the breastfed infant, consider an alternative treatment or avoid breastfeeding while undergoing liraglutide therapy.

Adverse Effects

These include:

1. Hypersensitivity or allergic reactions:
    - Including anaphylaxis
    - Injection site reactions:
        - ♥ Injection site reactions have been reported in approximately 5 % of subjects receiving exenatide in long-term (26 weeks or longer) controlled clinical trials.

          These reactions have usually been *mild* and usually did not result in discontinuation of exenatide.

2. GIT upset:

- GIT upset is **common** and may include, nausea and/or vomiting diarrhoea, constipation, dyspepsia

- Symptoms usually improve however with continued treatment.

3. Hypoglycaemia:

   - Hypoglycaemia is *unlikely* unless GLP−1 analogue is used with a **sulfonylurea** or **insulin**

4. Antibodies:

   - **Anti-liraglutide antibodies** develop in approximately 9% of patients.

     They do not appear to be associated with decreased efficacy or an increased risk of adverse effects.

5. Cholelithiasis / cholecystitis

6. Renal impairment.

7. Pancreatic complications:

   - This is an area of uncertainty. There is some concern over subclinical pancreatitis and more importantly pancreatic cancer

     GLP-1 analogues have been implicated with pancreatic adverse effects: however most studies suggest the risk of acute pancreatitis is likely to be very low, (data collection is ongoing).

Dosing

For Type 2 diabetes, usual dosing is:

Adults:

- SC, initially 0.6 mg once daily, at about the same time each day.

  After > 1 week, increase to 1.2 mg once daily.

  Maximum 1.8 mg daily

Note that there is limited information available on *long-term* safety and efficacy of the GLP-1 analogues

Dewey Bunnell (America) on Dutch television,1972

References

1. eTG - March 2020.

2. Liraglutide in Australian Medicines Handbook Website, January 2020

3. Liraglutide in MIMs Website, 1 March 2018.

4. Liraglutide in RWH Pregnancy & Breastfeeding Guidelines; 15 January 2019.

Dr J. Hayes
Reviewed March 2020.