THE NORTHERN HOSPITAL

DULAGLUTIDE

"Blond Bather", oil on canvas, 1881, Auguste Renoir.

"Try to take care of your health conscientiously.....and try to exercise a little. I worry that your fat will play nasty tricks on you. I'll admit that it isn't easy to lose weight, but I wouldn't want you to get sick before your time...Take care of yourself".

August Renoir, letter to his wife, Aline, June 1887.

I am very worried about my wife. She wrote to me that Doctor Journiac has discovered that she is suffering from albuminuria. I have been worried for a long time that this would happen to her and I think, or rather, I fear, that it is quite serious. I wrote to her that it was nothing, considering her difficult labour and delivery of Coco, but I do not believe a word of what I wrote".

August Renoir, letter to Jean Baudot, December 1903.

Aline Victorine Charigot was abandoned as a child, and was brought up by an Aunt and Uncle who neglected her education. She had no money and her future prospects looked uncertain if not bleak. In 1874 she rejoined her mother in Montmartre, Paris, where she took up dressmaking, scarce able to make a living. Around 1880 she met a poor Artist, who took a great liking to her and begged her to model for him. She liked the nervous but polite man despite his odd tics and working class accent and so she agreed to pose for him. The name of the Artist was Auguste Renoir and he would become one of the greatest Impressionist Artists of the Belle Epoch. Aline in turn would become not only his muse but also his wife, even though he was twenty years older than her, and she would feature in some of the greatest works of Art of the Nineteenth century, amoung them Luncheon of the Boating Party, 1881.

Although Renoir today is well known as the quintessential Impressionist, this is a simplification, and his style was much more complex than that and it changed over time. His magisterial biographer Barbara Ehrlich White describes his evolving styles in terms of a progression from Realism in 1866, to Impressionism in 1868, to "Realist Impressionism" in 1878, to "Classical Impressionism" in 1881, then to an "Ingres Impressionism" by 1884. Renoir strove his whole life to develop a unique style, never being entirely satisfied with his efforts. He loved and worked in the Impressionist style, but at the same time he also greatly admired the older and distinctly non-Impressionist lines of Neoclassical Art, in particular that of his idol Jean-Auguste-Dominique Ingres. He created many unique and beautiful works which combined hard classical (or Ingres) lines for his models set against the ethereal indistinctness of an Impressionist backdrop.

Barbara Ehrlich White identifies Auguste's earliest work of "Classical Impressionism", one that would define the direction of his future work, as the beautiful "Blond Bather" oil on canvas, 1881. The model is Aline. They had been travelling in Italy, where Auguste had been struck by the frescoes of Raphael in the Vatican which he compared to the ancient Roman frescos at Pompeii. "I prefer Ingres in oil painting" he wrote to his dealer Durand-Ruel, "but the Raphael frescoes, they are admirable in their simplicity and grandeur!" Auguste was inspired to emulate his figures in the classical manner, yet at the same time he retained his love of Impressionist light and colour. He resolved to stay on in Naples in order to develop his new direction. In February of 1882 he wrote to Mme Charpentier; "Thus I remain in the sun - not to paint portraits in the light - but

while warming myself and observing a lot, I think I will have gained that grandeur and simplicity of the ancient painters". The Blond Bather reflects the well defined lines of classical and Neoclassical Art. Aline at twenty-two years, is in the full bloom of her youth and beauty. She is generously curvaceous, without being overtly obese, just the perfect form not only for Auguste, but for the Rubensesque tastes of the time. She sits languorously in the warmth of the Naples sunshine, her deep blue "far away" eyes mirror the brilliant azure of a summer Mediterranean sea and cloudless sky. A faint sunburn superimposes upon her glowing red cheeks. Renoir captures a timeless image of a fleeting moment of carefree youth, health and beauty, as a classical form in an Impressionist dream.

For thirty years Auguste and Aline lived their lives happily but in abject poverty. But slowly things began to change as Impressionism progressed from derision and scorn - the term "Impressionism" itself was originally meant as derogatory - to grudging acceptance - to hyper-vogue. And following the stunning success of Auguste's works in America, around 1890, he became the most famous Impressionist of all - regaled as the greatest of all living French painters. Aline and Auguste would become comfortably wealthy, a privilege experienced by very few of his fellow Impressionists.

But fate is often pitiless

Just as they began to enjoy the fruits of their immense labours, around 1890 their health began to deteriorate alarmingly. In Auguste's case he was struck down with a horrifying and relentlessly progressive rheumatoid arthritis. In an age before any effective drugs were available for this condition, he wasted away, eventually becoming wheelchair bound. But most devastating of all was the destruction of his hands. Photographs of Renoir show the end stage deformities that today's medical students appreciate only in old textbooks. Despite this he continued to paint with the aid of an assistant who had to place his brushes into his withered hands for him. In cruel juxtaposition, while Auguste degenerated into a living skeleton, Aline grew enormously obese and would develop type II diabetes as a consequence. This was also age before any effective anti-diabetic agents where available. While Auguste could do nothing about the progression of his rheumatoid arthritis, Aline in fact had one option available to her. To lose weight. She struggled with her weight all her life. While at the age of 22, she was seen as beautiful and derisible, Auguste warned her that she walked a fine line. Just six years after "The Bather" he became alarmed at the size Aline was becoming, and time and again he would gently urge her to think about dieting, as he had begun to fear for her health. But Aline had had a difficult childhood of abandonment and poverty, and now that they were financially comfortable and able to support a family - she bore three children - as well as own their own house and a country retreat for good measure...well she wasn't about to hold back on the good life now! She simply ignored her weight problem. By 1903 she had developed the kidney and heart failure that would incapacitate her final years. She died in 1915.

Auguste's last years were equally sad. He was widowed, lonely and his two elder sons were badly wounded on the Western Front. And yet despite living in terror of the war then raging just barely outside of Paris, he retained to the very end the joie de vivre of a Gilded Age, a Belle Epoch, that he and his fellow Impressionists recorded for posterity.

Aline Victorine Renoir, died of the complications of obesity and type II diabetes just seven years before Charles Best and Frederick Banting produced life saving insulin. Even if effective modern anti-diabetic agents had been available to Aline, however, one suspects that her compliance with dieting and medication would still have been somewhat .....uncertain. In this regard the useful adjunctive agent, dulaglutide, would have been a good option for Aline. Not only does it assist in weight loss, its once weekly administration is most helpful for compliance in those more concerned with the good life than with tedious medications!

"The Luncheon of the Boating Party", oil on canvas, 1881, Auguste Renoir. This is one of the greatest and most delightful works of the Nineteenth century genre of Impressionism. The model for the young woman playing with her beloved dog in the left foreground, was Aline Victorine Charigot, Renoir's muse and wife.

DULAGLUTIDE

Introduction

Dulaglutide (trade name in Australia, "Trulicity") is a novel **injectable** antidiabetic agent, used in the treatment of **type II diabetes mellitus.**

It is **not** an insulin.

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

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

Exenatide is recommended as an adjunct in patients with type 2 diabetes mellitus with:

1. Metformin and/or a sulfonylurea, when these are inadequate.
2. Metformin and a basal insulin, when these are inadequate.

A great advantage of dulaglutide in regard to compliance is that it is given as a **once weekly** SC injection.

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.

Dulaglutide was introduced into clinical practice in the US in 2014.

It was introduced into clinical practice in Australia in 2018.

Chemistry

Dulaglutide is a genetically engineered **GLP-1 analogue**.

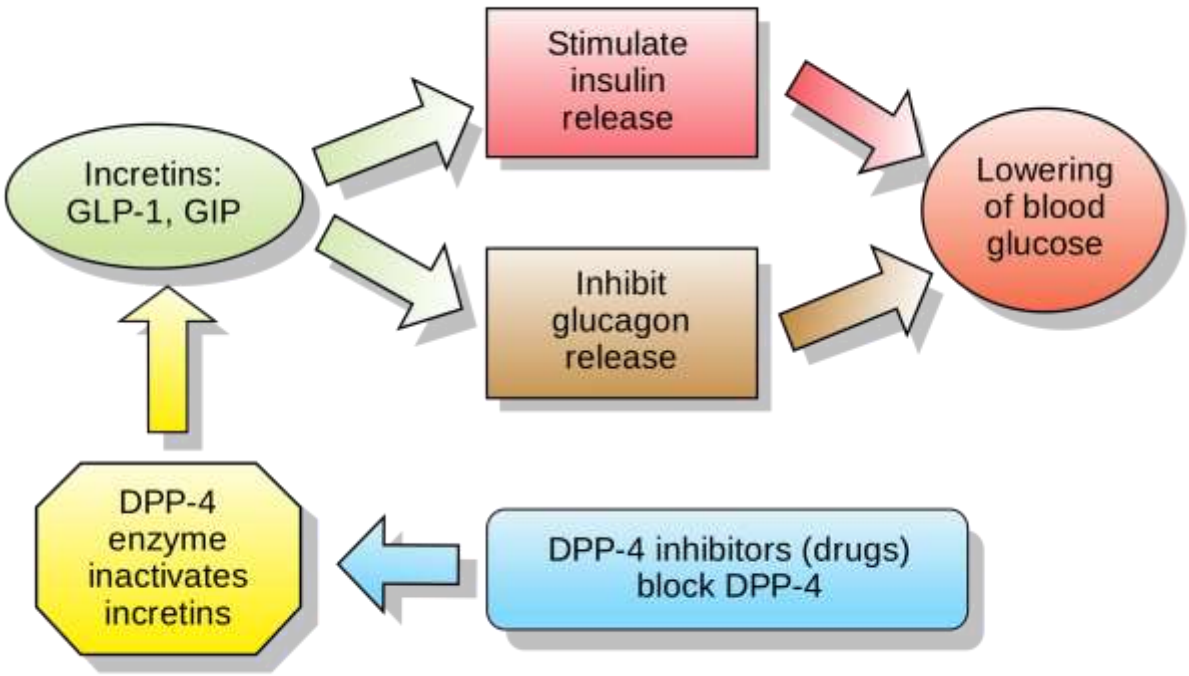
It is a **long-acting** human GLP-1 receptor agonist.

The molecule consists of two identical, disulfide-linked chains, each containing an N-terminal GLP-1 analog sequence covalently linked to a modified human immunoglobulin G4 Fc heavy chain by a small peptide linker.

In contrast to native (i.e natural) GLP-1, **dulaglutide** is resistant to degradation by dipeptidyl peptidase-4. It also has a large size that slows absorption and reduces renal clearance.

These engineered features result in a soluble formulation and a prolonged half-life of about 5 days, making it suitable for once-weekly subcutaneous administration.

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

Dulaglutide as:

Preloaded injector:

- **1.5 mg / 0.5 mL solution**.

Mechanism of Action

Dulaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist that acts by:

1. Increasing insulin secretion

2. Reducing glucagon secretion

3. Causing a small reduction in appetite.

4. Slowing gastric emptying.

Pharmacodynamics

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

The effect is sustained for **1 week**.

There seem to be few differences between the GLP-1 analogues.

Dulaglutide appears to have a greater effect on HbA1c than exenatide and is non-inferior compared to liraglutide (which must be given once daily). [4]

Although the absolute differences are small, dulaglutide appears to reduce weight more than exenatide, but less than liraglutide. [4]

Pharmacokinetics

Absorption:

- Dulaglutide is administered by **S.C** injection.

  Dulaglutide should **not** be administered IV or IM.

  Following subcutaneous administration to patients with type 2 diabetes, dulaglutide reaches peak plasma concentrations in 48 hours

Distribution

- The mean volume of distribution after subcutaneous administration of dulaglutide 1.5 mg to steady state in patients with type 2 diabetes mellitus is approximately 17.4 L.

- It is unknown if exenatide crosses the human placenta.

- It is unknown if exenatide is distributed into human breast milk.

Metabolism and excretion:

- Dulaglutide is presumed to be degraded into its component amino acids by general protein catabolism pathways.

Indications

Dulaglutide is indicated for the treatment of type II diabetes as:

- Monotherapy

Or

- In combination with the following oral glucose-lowering medications:
    - ♥ Metformin
    - ♥ Metformin and sulfonylurea
    - ♥ Metformin and a thiazolidinedione

Or

- In combination with prandial insulin, with or without metformin.

Contra-indications/precautions

Contra-indications / precautions to the GLP-1 receptor agonists as a class include:

1. Known hypersensitivity to the agent.
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

Limited data; use should be avoided in pregnancy and replaced with insulin therapy.

Breast feeding

There is no human data; but dulaglutide is unlikely to be absorbed by the child.

Adverse Effects

Adverse effects to the glucagon-like peptide‑1 analogues as a class include:

1. Hypersensitivity or allergic reactions:
    - Including anaphylaxis
    - Injection site reactions (usually mild)
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:
    - Antibody development has been observed with exenatide and liraglutide.

      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

Usual adult dosing is:

- **1.5 mg S.C once a week**.

It can be administered once weekly, at any time of day, and independently of meals

References

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