THE NORTHERN HOSPITAL

SAXAGLIPTIN

Two views of "Mary Cassatt at the Louvre" pastel on paper, 1885, Edgar Degas.

Of all the oeuvre of Edgar Degas' work, it is his series of female bathers that created the greatest controversy, even scandal. These works on the whole drew applause from most, but from a vocal minority they drew the heated accusation of "misogynist". Even a century after this death debate continues. Adherents to the misogynist theory have

pointed to the fact that Degas never married, however besides this and a subjective dislike for certain of his works there is no other evidence whatsoever, that Degas disliked women. Indeed the facts of his work and of his life tell exactly the opposite story. After around 1870, virtually all his works depict women, not only in his paintings but also in the sculptures he produced towards the end of his life. In regard to why he never married he once remarked, "Why I never married? Well I was always afraid that my wife might look at one of my paintings and say: "Mmm, very nice dear"...There's love and there's painting. And we have only one heart".

If Art was Degas's first mistress, then a very close second was the American Impressionist, Mary Cassatt, who became his intimate Artistic collaborator. To say that they were merely friends is to misunderstand their relationship, they were the deepest of soul-mates from the moment they met in 1874 until Degas' death forty years later in France's darkest hour of the First World War in 1917. Most Art historians assume their relationship was purely platonic, though, surprisingly, either by accident or design, no letters between them or personal diaries have survived and so it is impossible to know for certain the true nature of their relationship. In her novel "I Always Loved You", author Robin Oliveira imagines a passionate scene between Edgar Degas and Mary Cassatt; "...nobody knows what goes on in their neighbor's house, let alone what happened between two artists 130 years ago", she once explained. True enough of course, particularly for two Artists so passionate about each other's work!

Mary Cassatt first met Degas in 1877, she was 33 years old, he, ten years her senior. Mary was a gifted Artist, and she was studying in Paris at the time, learning the style of Academic Art, that was thought most appropriate for exhibition at the great Salons. But even before she met Degas, he had had a profound effect on her. She once recounted how she had seen one of his iridescent pastels in a storefront window and was electrified by the what she had seen. As she came to know more of his work, she knew that this radically new and modern style was where she wanted to go. Edgar Degas, in no small part, helped to create the first great American Impressionist. But Artistic influence did not go in just one direction. Degas himself was enthralled by Mary's works when he eventfully saw them. From the moment they met, they fell in love, if not literally, then at least professionally!

There is evidence that Degas and Cassatt collaborated on certain works. Mary Cassatt commented once that Edgar had assisted her on one of her best known works, "Little Girl in a Blue Armchair", 1878. It is known that the girl was a child of one of Degas' acquaintances. She sits awkwardly in a large armchair, seemingly bored at proceedings, eyeing off the small dog on the adjacent chair, which she no doubt would rather be playing with. Art Conservator Ann Hoenigswald has used magnified X-ray and infrared imaging to examine an area of the rear window that appears stylistically different from Cassatt's work. Interestingly it showed sharp, small, quick brush strokes that are not seen anywhere else, perhaps confirming the hand of Degas. Mary Cassatt was the first to use metallic paints on canvas; ordinarily these were used for the decorating crafts. Degas used unusual mixtures of media in many of his works; including pastels, oils, gouache and metallic paints. It is possible that he was inspired to use metallic paints, and other media by the work of Mary Cassatt.

Degas worked tirelessly to promote Mary's work, just as Mary worked no less tirelessly to promote his. But Mary was not the only female Artist, Degas helped to promote. In an age when it was near impossible for female Artists to gain the recognition they deserved, he was instrumental in organizing a major retrospective of 300 of the Impressionist, Berthe Morisot's paintings at the Galeries Durand-Reul. He personally hung Berthe's paintings, with some help from his friend Auguste Renoir, all hardly the actions of a supposed rabid misogynist!

Degas sketched and painted Mary Cassatt many times, but his deep admiration for her is best demonstrated in a series of beautiful pastels he made of her in 1879 - 80, during visits to the Louvre. They spent many hours admiring the great masters, or at least Mary did, Edgar spent many hours admiring Mary. Mary a striking woman, is seen standing, examining the paintings. She has an air of sophistication and confidence about her. Another figure notices Mary as she passes by, and turns to look at her. She is dressed in a smart tight fitting jacket, large felt hat, and a long elegant skirt. She leans nonchalantly on her umbrella, as if it were a gentleman's walking cane, her slim corseted waist accentuating the graceful curves of her body. Degas used his sketches of Mary in the Louvre to produce a number of beautiful pastels.

Though their styles diverged over the years, and they saw less of each other, they always remained close. Even in old age when Degas had lost most of his vision, as would Mary in her old age, and could no longer paint, he continued to take an interest in Mary's work. By the end of his life he owned more works by her than any other contemporary artist including the noted collectors, Pissarro, Manet and Gauguin. Edgar Degas and Mary Cassatt had half a life time of passionate collaboration. Each helped the other in their professional development and careers, devoted muses to each other in equal measure.

Edgar's Degas' professional and loving relationship with the American Impressionist, Mary Cassatt in addition to his touching support of the French Impressionist Berthe Morisot, shows clearly that he was no misogynist. Degas never married, once explaining that he could only fully commit to one love, and that was his Art. Speculation was rife during his life-time that Mary Cassatt was his mistress, though as both destroyed all their correspondence between them, and we have no other contemporary corroboration, this must always remain speculation, unless some further information comes to light in the future. Apart from professional, whatever the exact nature of their more intimate relationship was, most Art historians agree that it was mysteriously enigmatic and most assuredly "complicated".

The oral anti-diabetic agent saxagliptin is one of a novel class of drugs known collectively as the "gliptins". Like the relationship between the famous Nineteenth century Impressionists, Edgar Degas and Mary Cassatt its exact mechanism of action is quite indirect and most complicated!

SAXAGLIPTIN

Introduction

Saxagliptin is an oral **antidiabetic agent** of the **dipeptidyl peptidase 4 (DPP - 4) inhibitor** or **"gliptin" class.**

They are indicated in **type II diabetes mellitus**, (including fixed dose combination preparations with **metformin**).

History

Sitagliptin was the first of the class of gliptin drugs.

It was introduced into clinical practice in the U.S in 2006.

Classification

There are currently 6 classes of oral 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

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:**

These agents reduce peripheral insulin resistance and hence insulin requirements

Examples include:

- Pioglitazone
- Rosiglitazone

6. **Sodium-glucose co-transporter 2 (or SGLT2) inhibitors (or "Gliflozins")**:

These agents reduce glucose reabsorption in the kidneys.

Examples include:

- Dapagliflozin
- Empagliflozin

Preparations

Saxagliptin as:

Tablets:

- 2.5 mg
- 5 mg

Fixed-dose combination with metformin:

- Saxagliptin 2.5 mg + metformin 1000 mg
- Saxagliptin 5 mg + metformin 500 mg
- Saxagliptin 5 mg + metformin 1000 mg

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):

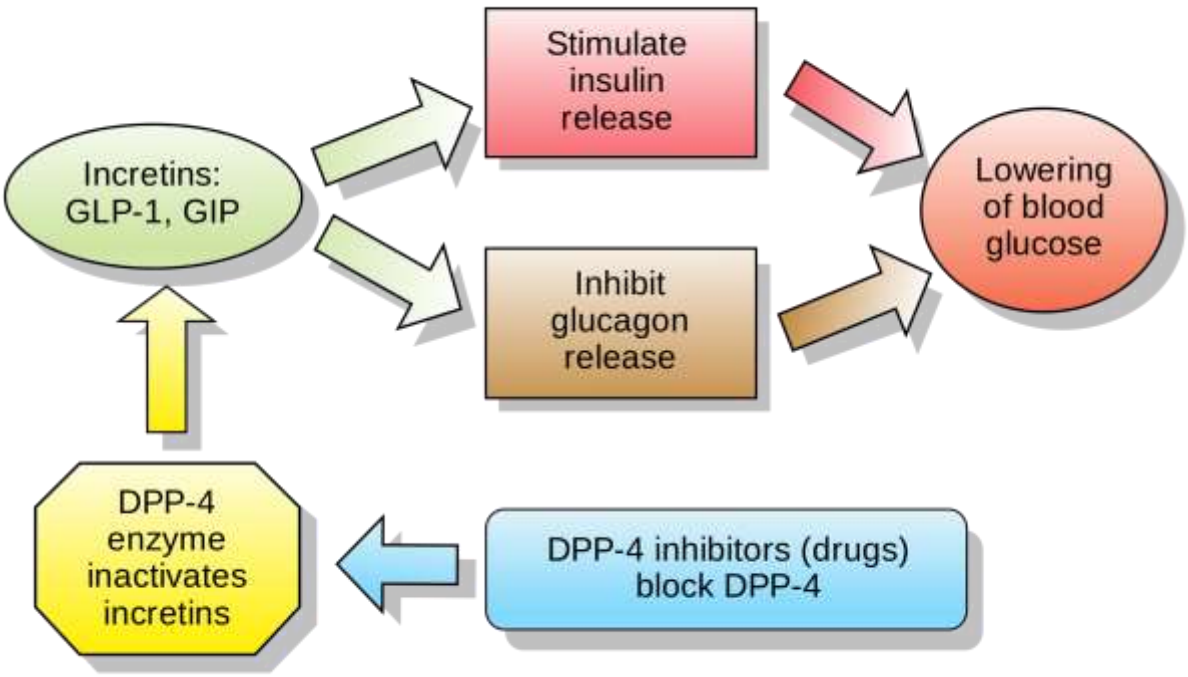
    - It is synthesized by L cells which are primarily found in the ileum and large intestine.

    - 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.



Mechanism of Action

The dipeptidyl peptidase - 4 (DPP - 4) enzyme deactivates the incretins

The **gliptin** class of drugs (including **saxagliptin**) **inhibits the DDP-4 enzyme**, and so results in an increase in the level of the incretins - thereby increasing insulin release and decreasing glucagon levels in a *glucose dependent* manner, thus resulting in a lowering of blood glucose levels.

This *glucose dependent* mechanism is unlike the mechanism seen with sulfonylureas where insulin is released *even when glucose levels are low*, which can lead to hypoglycaemia in patients with type 2 diabetes and in normal subjects.

Pharmacodynamics

Saxagliptin improves glycaemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes

Although short-term trials have shown initial combination treatment with a DPP−4 inhibitor and metformin reduced HbA1c slightly more than monotherapy, starting diabetes treatment with combination therapy is not currently recommended.

Pharmacokinetics

Absorption:

- Saxagliptin is administered orally.

  It is well absorbed

- Peak blood levels are reached within 2 hours of administration.

- The absolute oral bioavailability of saxagliptin is approximately 50%

Distribution

- Saxagliptin has *negligible* protein binding.

  Changes in blood protein levels in various disease states (e.g. renal or hepatic impairment) therefore are not expected to alter the distribution of saxagliptin

- It is unknown if human placental transfer occurs.

- It is not unknown if saxagliptin is excreted into human breast milk

Metabolism and excretion:

- The metabolism of saxagliptin is primarily by the cytochrome P450 system (CYP3A4/5).

  The major metabolite of saxagliptin is also a reversible, competitive DPP-4 inhibitor, half as potent as saxagliptin.

- Half-life is around 2.5 - 3 hours

Indications

Saxagliptin is indicated for:

1. Type 2 diabetes, in combination with other antidiabetic drugs

2. Fixed-dose combination with metformin

Contra-indications/precautions

These include:

1. Known hypersensitivity

2. A history of pancreatitis

3. Renal impairment:

   - According to product information, dose adjustment in kidney impairment (creatinine clearance less than 50 mL/minute) is recommended for all DPP-4 inhibitors except linagliptin. [1]

4. Drug interactions:

   Sulphonylureas and Insulin:

   - Caution when used in combination with sulphonylureas or insulin, as hypoglycemia may occur.

   ACE Inhibitors:

   - **Vildagliptin** has been associated with an increased risk of ACE inhibitor-induced angioedema; caution is advised as it is possible that this may be a class effect and so other DPP−4 inhibitors may also have this effect.

Pregnancy

Saxagliptin 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.

Published reports describing the use of saxagliptin in human pregnancy have not been located.

Due to potential adverse effects, dietary modification and insulin should be considered as alternative therapies to saxagliptin in pregnant women.

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

Breast feeding

Reports describing the use of saxagliptin during breastfeeding have not been located.

Due to potential adverse effects in the breastfed infant, consider an alternative medicine in women who wish to breastfeed.

Adverse Effects

The gliptins as a group are generally well tolerated and are **not** associated with **weight gain** or **hypoglycaemia.**

Adverse effects include:

1. GIT upset

2. Allergic:

    - Including anaphylaxis, angioedema

3. Dermatological hypersensitivity reactions:

    - Including serious reactions such as Stevens-Johnson syndrome.

4. **Hypoglycaemia:**

    - Saxagliptin does not cause hypoglycemia in its own right, however when used in **combination** with a **sulfonylurea** or with i**nsulin**, hypoglycaemia may occur.

Therefore, to reduce the risk of sulfonylurea or insulin induced hypoglycaemia, reduction in the dose of these agents should be considered.

5. Pancreatitis (rare):

- Gliptins should therefore not be used in a setting of previous pancreatitis, and should be ceased if pancreatitis occurs.

Dosing

Usual dosing in adults is:

- Oral, 5 mg once daily.

Renal impairment:

- CrCl < 50 mL/minute, 2.5 mg once daily.

Fixed-dose combination with metformin:

- 1 tablet (of any strength) once daily

Or

- 2 tablets of 2.5 mg/1000 mg once daily.

Above: "Little Girl in a Blue Armchair", oil on canvas, 1878 Mary Cassatt (& Edgar Degas).

Left: Study for "Mary Cassatt at the Louvre", pastel on paper, c.1879 - 80, Edgar Degas.

References

1. eTG - June 2017

2. Saxagliptin in Australian Medicines Handbook Website Accessed June 2017.

3. Saxagliptin in MIMs Website, 1 February 2017.

4. Saxagliptin in RWH Pregnancy & Breastfeeding Guidelines; 18 May 2017

Dr J. Hayes
August 2017.