THE NORTHERN HOSPITAL

SITAGLIPTIN

"A Classical Maiden", oil on canvas, circle of John William Godward. "A Classical Study", oil on canvas, William Blake Richmond....The Praetorian guards were attached to the youth of Alexander. They loved him as a tender pupil whom they had saved from a tyrant's fury, and placed on the Imperial throne..

...as Alexander was a modest and dutiful youth, of only seventeen years of age, the reins of government were in the hands of two women, of his mother Mamaea and Maesa, his grandmother. After the death of the latter, who survived but a short time the elevation of Alexander, Mamaea remained the sole regent of her son and of the empire.

In every age and country, the wiser, or at least the stronger of the two sexes, has usurped the power of the state, and confined the other to the cares and pleasures of domestic life. In hereditary monarchies, however, and especially in those of modern Europe; the gallant spirit of chivalry, and the law of succession, have accustomed us to allow a singular exception; and a woman is often acknowledged the absolute sovereign of a great kingdom, in which she would be deemed incapable of exercising the smallest employment, civil or military. But as the Roman Emperors were still considered as the

generals and magistrates of the republic, their wives and mothers, although distinguished by the name of Augusta, were never associated to their personal honours and a female reign would have appeared an inexplicable prodigy in the eyes of those primitive Romans, who married without love, or loved without delicacy and respect. (...Metellus Numidicus, the censor, once acknowledged to the Roman people in a public oration, that had kind Nature allowed us to exist without the help of women, we should be delivered from a very troublesome companion; and he could recommend matrimony only as the sacrifice of private pleasure to public duty)....

The substance not the pageantry of power was the object of Mamaea's manly ambition. She maintained an absolute and lasting empire over the mind of her son, and in his affection the mother could not book a rival....the general tenor of her administration was equally for the benefit of her son and of the empire. With the approbation of the Senate, she chose sixteen of the wisest and most virtuous senators as a perpetual council of state, before who every public business of moment was debated and determined....As soon as they had purged the city from foreign superstition and luxury, the remains of the capricious tyranny of Elagabalus, they applied themselves to remove his worthless creatures from every department of public administration, and to supply their places with men of virtue and ability. Learning and the love of justice, became the only recommendations for civil offices; valour, the love of discipline, the only qualification for military employments. But the most important care of Mamaea and her wise councillors was to form the character of the young Emperor, on whose personal qualities the happiness of misery of the Roman world must ultimately depend....An excellent understanding soon convinced Alexander of the advantages of virtue, the pleasure of knowledge, and the necessity of labour. A natural mildness and moderation of temper preserved him from the assaults of passion, and the allurements of vice. His unalterable regard for his mother, and his esteem for the wise Ulpian, guarded his inexperienced youth from the poison of flattery.

The simple journal of his ordinary occupations exhibits a pleasing picture of an accomplished emperor and with some allowance for the difference of manners , might well deserve the imitation of modern princes....The exercises of the body succeeded to those of the mind; and Alexander, who was tall, active, and robust, surpassed most of his equals in the gymnastic arts. Refreshed by the use of the bath and a slight dinner, he resumed, with a new vigour, the business of the day; and, till the hour of supper, the principal meal of the Romans, he was attended by his secretaries, with whom he read and answered the multitude of letters, memorials, and petitions that must have been addressed to the master of the greatest part of the world. His table was served with the most fugal simplicity; and whenever he was at liberty to consult his own inclination, the company consisted of a few select friends, men of learning and virtue, amongst whom Ulpian was constantly invited. Their conversation was familiar and instructive; and the pauses were occasionally enlightened by the recital of some pleasing composition, which supplied the place of dancers, comedians and even gladiators so frequently summoned to the tables of the rich and luxurious Romans. The dress of Alexander was plain and modest; his demeanour courteous and affable; ay the proper hours his palace was open to all his subjects, but the voice of a crier was heard, as in the Eleusinian mysteries, pronouncing the same salutary admonition, "Let none enter those holy walls, unless he is conscious of a pure and innocent mind".

Such a uniform tenor of life, which left not a moment for vice or folly, is a better proof of the wisdom and justice of Alexander's government, than all the trifling details preserved in the compilation of Lampridius. Since the accession of Commodus, the Roman world had experienced, during a term of forty years, the successive and various vices of four tyrants. From the death of Elagabalus it enjoyed (A.D 222-235) an auspicious calm of thirteen years. The provinces, relieved from the oppressive taxes invented by Caracalla and his pretended son, flourished in peace and prosperity, under the administration of magistrates, who were convinced by experience, that to deserve the love of the subjects was their best and only method of obtaining the favour of the sovereign. While some gentle restraints were imposed on the innocent luxury of the Roman people, the price of provisions and the interest of money, were reduced, by the paternal care of Alexander , whose prudent liberality, without distressing the industrious, supplied the wants and amusements of the populace. The dignity, the freedom, the authority of the senate were restored; and every virtuous senator might approach the person of the Emperor, without fear...The Praetorian guards were attached to the youth of Alexander. They loved him as a tender pupil whom they had saved from a tyrant's fury, and placed on the Imperial throne. That amiable prince was sensible of the obligation; but as his gratitude was restrained within the limits of reason and justice; they soon were more dissatisfied with the virtues of Alexander, than they had ever been with the vices of Elagabalus.

....The circumstances of his death are variously related. The writers, who suppose he died in ignorance of the ingratitude and ambition of Maximinus, affirm that after taking a frugal repast in the sight of the army, he retired to sleep, and that, about the seventh hour of the day, a part of his own guards broke into the Imperial tent, and with many wounds assassinated their virtuous and unsuspecting prince....His mother Mamaea...perished with her son.

Edward Gibbon, "The History of the Decline and Fall of the Roman Empire", volume 1, 1776.

The Empire had enjoyed thirteen years of peace and prosperity, unprecedented since the days of the Pax Romana, although the concept of "peace" for the Empire, had always been a relative one. After the chaos of the reign of Elagabalus all Romans were grateful indeed. The Emperor Alexander Severus was an intelligent, studious and mild mannered youth, who through extraordinary circumstances, had gained the Imperial throne in 222 A.D at the age of just 13 years. Of course a youth of that age, let alone one of Alexander's pleasing but timid demeanour could not have realistically been expected to rule the greatest Empire that had ever existed. A regent would be required, at least until Alexander had achieved adulthood, and this regent would be one of the most extraordinary figures in the history of Imperial Rome - his mother, Julia Mamaea. No woman would ever be Empress of the West, but occasional strong willed women did attain and wield great power and influence behind the charades of their "Emperor" husbands. Julia Mamaea became, in all but name, the Emperor of Rome. This did not matter in the least to Alexander, who idolized his mother and was always happy to seek her council. Alexander's rule was seen as wise and benevolent. He was loved by the Romans who admired his intelligence, love of learning and virtuous character. Julia was

similarly loved for her just and enlightened rule. But Rome's security and great prosperity did not only depend on its beloved rulers.

Out of sight and mostly out of the mind of most Romans, the distant borders of the Empire were protected from vast, savage and pre-literate hordes that inhabited the unknown and forbidding frozen forests beyond the Rhine and the Danube. Rome's toughest, battled hardened and most elite legions patrolled the great northern rivers; and by dint of savage and endemic warfare they shielded the Empire from barbarian invasion. For over two centuries the northern legions, had protected the empire, but by 235 A.D a crisis had been reached. The barbarian incursions had become so widespread and so constant that it was clear that a good deal more legions would be necessary to defend the Empire. It was at this juncture that the Emperor himself was urgently summoned by the generals of the north to attend in person. What they saw of the Emperor shocked them - a young boy, with pleasant manners, but dominated by his mother who had also arrived. These were two totally different worlds, neither having any understanding of the other - the cultured and civilized metropolis and the rough camps of soldiers on the front lines.

Alexander's solution was negotiation with the barbarians rather than crushing them with overwhelming military might. This strategy so disgusted the battle hardened legions that they then and there proclaimed a particularly brutal general of giant stature, said to be part barbarian by the name of Maximinus as their new Emperor, without any consultation or the slightest regard of the Senate and People of Rome. The first act of the new Emperor was the slaying of a terrified Alexander and Julia, mother and son in each other's arms, begging for mercy as they were brutally cut down. Thus ended the Severan dynasty. Maximinus "ruled" for three years, never setting foot in Italy, let alone Rome. He was respected only out fear feared by his troops, but he was never loved by them. As soon as convenient he too would be cut down, by his own men. The next fifty years were a Roman dark age, characterized by great barbarian invasions and soldier - Emperors who fought each other as much as the enemy. The empire would disintegrate into three parts and would not be reunited for half a century when two truly remarkable soldier - Emperors, Claudius Gothicus and Aurelian would restore the Empire to its former unity and glory.

Just as Julia Mamaea brilliantly and cleverly controlled the Roman Empire indirectly via the agency her much loved son, so we may brilliantly and cleverly control type II diabetes indirectly via by the agency of gliptin drugs, such sitagliptin.

Silver denarius of the Emperor Severus Alexander. Obv.: IMP SEV ALE-XAND AVG, laureate head right. Rev.: VICTO-R-IA AVG, Victory advancing left, holding wreath and palm. Struck 228-231 AD. RIC. 180. C. 563 (Author's collection).

SITAGLIPTIN

Introduction

Sitagliptin (trade name in Australia, "**Januvia"**) 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 agent increases 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

Sitagliptin phosphate monohydrate as:

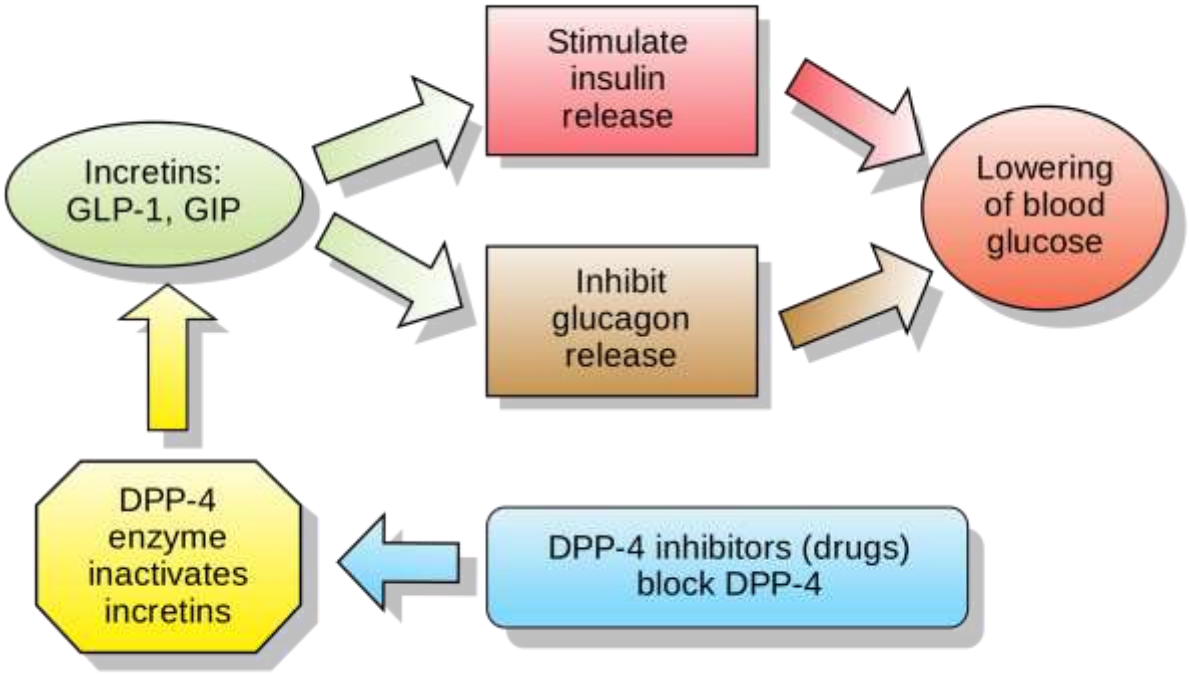
Tablets:

- 25 mg, 50 mg, 100 mg.

Fixed combination preparations:

- Sitagliptin and metformin standard release:
  - Sitagliptin 50 mg and metformin 500 mg
  - Sitagliptin 50 mg and metformin 850 mg
  - Sitagliptin 50 mg and metformin 1000 mg
- Sitagliptin and metformin controlled release:
  - Sitagliptin 50 mg and metformin (controlled release) 1000 mg
  - Sitagliptin 100 mg and metformin (controlled release) 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 found in 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 **sitagliptin**) **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

In patients with type 2 diabetes with **hyperglycaemia**, the changes in insulin and glucagon levels lead to:

1. Lower fasting and postprandial glucose concentrations.

2. Lower haemoglobin A1c (HbA1c) levels:

    - DPP−4 inhibitors however appear to be less effective in reducing HbA1c than metformin, sulfonylureas or thiazolidinediones

In patients with type 2 diabetes, administration of single oral doses of sitagliptin leads to inhibition of DPP-4 enzyme activity for a 24 hour period.

It results in a 2 to 3 fold increase in circulating levels of active GLP-1 and GIP, increased plasma levels of insulin and C-peptide, decreased glucagon concentrations, reduced fasting glucose, and reduced glucose levels following an oral glucose load or a meal.

Pharmacokinetics

Absorption:

- Sitagliptin is rapidly absorbed orally

Peak blood levels are reached in 1 - 4 hours of ingestion.

- The absolute bioavailability of sitagliptin is approximately 87%.

Distribution

- The mean volume of distribution at steady state following a single 100 mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters.

- Reversible binding to plasma proteins is low at around 38 %.

Metabolism and excretion:

- Sitagliptin is primarily eliminated **unchanged in urine**, (about 80 %).

- About 20 % of sitagliptin is metabolized by the liver primarily by the CYP3A4, system with a lesser contribution from the CYP2C8 system.

- Half-life is around 12.4 hours

Indications

The gliptins as a class are indicated in **type II diabetes mellitus**, (including fixed dose combination preparations with **metformin**).

Specific indications include: [3]

The treatment of diabetes mellitus type 2 in persons 18 years of age and older who have failed dietary measures and exercise:

- As monotherapy

- As an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus, when **metformin cannot be used**

- As dual combination therapy with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.

- As triple combination therapy with metformin and a sulfonylurea when combination therapy with both agents does not provide adequate glycaemic control.

- As add-on combination therapy with insulin (with or without 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

Sitagliptin 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 information describing sitagliptin use during pregnancy has not been located.

Due to potential adverse effects, dietary modification and insulin should be considered as alternative therapies to sitagliptin in pregnant women. [4]

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

Breast feeding

Reports describing the use of sitagliptin 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. [4]

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:**

    - Sitagliptin 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

Sitagliptin can be administered with or after food.

Usual adult dosing is: [2]

- **100 mg once daily.**

In patients with renal impairment

- Cr Cl 30 - 50 mL/minute, 50 mg once daily.

- Cr Cl < 30 mL/minute, 25 mg once daily.

For Fixed-dose combination with **metformin:**

- Usual initial dose is sitagliptin 100 mg daily with the current daily metformin dose.

    - ♥ Conventional tablet, 1 tablet (of any strength) twice daily.

    - ♥ Controlled release tablet, 1 tablet of 100 mg/1000 mg or 2 tablets of 50mg/1000 mg once daily.

Julia Avita Mamaea, (birth unknown - 235 A.D), marble bust, Roman 2nd Century A.D, British Museum.

References

1. eTG - July 2016.

2. Sitagliptin in Australian Medicines Handbook, Accessed October 2016.

3. Sitagliptin in MIMs Website, 1 October 2016

4. Sitagliptin in RWH Pregnancy & Breastfeeding Guidelines, 17 February 2016.

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