THE NORTHERN HOSPITAL

EMPAGLIFLOZIN

"Eve", oil on canvas, 1885, Anna Lea Merritt

Paradise and the test of free will:

…Now the Lord God had planted a garden in the east, in Eden; and there he put the man he had formed. The Lord God made all kinds of trees grow out of the ground - trees that were pleasing to the eye and good for food. In the middle of the garden were the tree of life and the tree of the knowledge of good and evil…

And the Lord God commanded the man, "You are free to eat from any tree in the garden; but you must not eat from the tree of the knowledge of good and evil, for when you eat from it you will certainly die…

The Fall:

Now the serpent was more crafty than any of the wild animals the Lord God had made. He said to the woman, "Did God really say, 'You must not eat from any tree in the garden?....You will not certainly die…For God knows that when you eat from it your eyes will be opened, and you will be like God, knowing good and evil."

When the woman saw that the fruit of the tree was good for food and pleasing to the eye, and also desirable for gaining wisdom, she took some and ate it. She also gave some to her husband, who was with her, and he ate it. Then the eyes of both of them were opened, and they realized they were naked; so they sewed fig leaves together and made coverings for themselves…

Genesis 2:8 - 3:1-7

The exact nature of the "forbidden fruit" of Eden has been the topic of fierce scholarly debate for millennia. In Christian, Islamic and Jewish traditions alike, it has usually been depicted as the apple - its sweetness providing the greatest of temptation, too much in fact for Eve to resist. Whatever fruit it was, the actual meaning of the story has been the topic of even fiercer scholarly debate. Perhaps it was Dante in the Fourteenth century who came closest to giving theological purpose to it. In the Inferno we inexplicably find the Greek hero Ulysses, burring in the fires of the Eighth Circle of Hell! Learned scholars who have studied the Divine Comedy over a professional life time, tell us that it was Ulysses' questioning of his place in the world that got him damned in the eyes of Dante! After the conclusion of the Trojan war, Ulysses' duty was clear. He should return to his family in Greece, but instead in his unquenchable thirst for knowledge he forgoes his duty to explore the world…

....not tenderness for a son, nor filial duty
toward my aged father, nor the love I owed
Penelope that would have made her happy,

could overcome the fervour that was mine
to gain experience of the world
and learn about man's vices, and his worth.
...and so I set forth on the open deep...

To the medieval mind, any questioning of one's place in the Universe was an anathema. The answer was simply "God's plan" as revealed by received religious dogma, and any questioning of this was heresy punishable by the eternal flames of Hell. Little wonder in the West at least, this belief sustained a dark age that lasted close on eight centuries. In other words to eat of the tree of knowledge was an attempt to understand the mind of God, which in turn meant an attempt to be like God. Such blasphemy led swiftly to perdition. Indeed Milton in "Paradise Lost" explored the same terrible dichotomy - the thirst for knowledge versus a blind and unquestioning obedience - but in the end to question God's word meant eternal damnation.

Much of Christian and Islamic theology has roots that can be traced to even more ancient traditions, the origins of the story of Noah's flood for example greatly predates both these religions. In classical Greek mythology we see the apple presented as a symbol of impending disaster. Eris, the goddess of discord, uses a golden apple to create jealousy between Hera, Athena and Aphrodite. This leads to the fateful Judgment of Paris, which in turns leads to the Trojan War. We see other examples where the apple is presented as symbol of great temptation. King Eurystheus of Mycenae so craved the golden apples of the Hesperides that for Heracles' eleventh labour he demanded that he steal them from under the nose of the god Atlas! Atalanta was the greatest female athlete in all of Greece. Her father insisted that she marry, but she refused. She compromised with her father by agreeing that if any of her suitors could outrun her in a footrace she would marry them. Those who lost however would be killed! Hippomenes was in love with Atalanta and he sought the help of the goddess Aphrodite in his quest to marry her. Aphrodite gave him three golden apples to temp Atalanta, in the race he would have to have to win her. During the race whenever Atalanta got ahead Hippomenes would throw an apple in front of her. Atalanta unable to resist would stop to pick it up, thus allowing Hippomenes to win.

By the Seventeenth century the apple took on an entirely different symbolism. It became a symbol of science in the age of the Enlightenment. Isaac Newton maintained that he underwent an epiphany when a falling apple struck him on the head, (though modern scholars now insist that this never happened (….they would). There are however a number of accounts that survive to say that he did at least conceive of his theory via a theoretical analogy with an apple falling to the ground.

In 21st century we now question every aspect of reality. About us we see an alarming loss of biodiversity. It is through this biodiversity we are just beginning to understand life on Earth, our place in the Universe and our future destiny. The Malus sieversii is a wild apple species native to mountainous regions of Central Asia, including Kazakhstan, the Himalayas, Western China and Mongolia. DNA studies have shown this wild species to be the ancient common ancestor of most cultivars of the modern domesticated apple (Malus pumila). It was first described in 1833 by Carl Friedrich von Ledebour, a German naturalist who discovered it growing in the Altai Mountains. Malus sieversii has recently been cultivated by the United States Agricultural Research Service, in the hope of finding genetic information that may enable the development of disease resistant species that may help feed a exponentially rising human population. The variation in Malus sieversii's response to disease on an individual basis is a sign of its rich genetic diversity compared to the much impoverished diversity of its domesticated descendants.

The 21st century's response to the apple's ancient and ignorant symbolism as the "forbidden fruit", is best summed up by the magisterial Edward O. Wilson:

"…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".

EMPAGLIFLOZIN

Malus sieversii (by Flemming Thorninger)

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***The Malus sieversii** is a wild apple species native to mountainous regions of Central Asia, including Kazakhstan, the Himalayas, Western China and Mongolia. In 1835, French chemists isolated phlorizin from the bark of apple trees. This natural substance turned out to be the first known inhibitor of the SGLT symporter protein, critical in the cellular transport of glucose in mammalian cells.*

Introduction

Empagliflozin (trade name in Australia, "**Jardiance"**) is a novel oral antidiabetic agent used in the treatment of type II diabetes.

It is a reversible competitive inhibitor of the protein **sodium-glucose co-transporter 2 (SGLT-2**).

SGLT- 2 is the predominant transporter for the reabsorption of glucose from the glomerular filtrate back into the circulation.

The SGLT-2 inhibitors as a group reduce glucose reabsorption in the kidney and so increase its excretion in the urine.

These agents improve glycaemic control in patients with type II diabetes by reducing renal glucose reabsorption, thus lowering blood glucose levels.

Note that all patients taking a SGLT-2 inhibitor will show positive for glucose in the urine, and so this sign will not necessarily indicate poor glycemic control.

The glucosuria observed with SGLT-2 inhibitors such as empagliflozin is accompanied by *mild diuresis* which may contribute to a **sustained mild reduction of blood pressure**.

As there is there is no direct effect on beta islet cell function or insulin secretion or action, there is **low risk** for the development of hypoglycaemia with this agent.

History

In 1835, French chemists isolated **phlorizin** from the bark of the **apple tree.**

The German physician **Josef von Mering** (1849-1903) discovered the glycosuric effect of phlorizin in 1886

In August 1960, in Prague, the American biochemist **Robert Kellogg Crane** (1919 - 2010) discovered the sodium-glucose co-transport mechanism for intestinal glucose absorption.

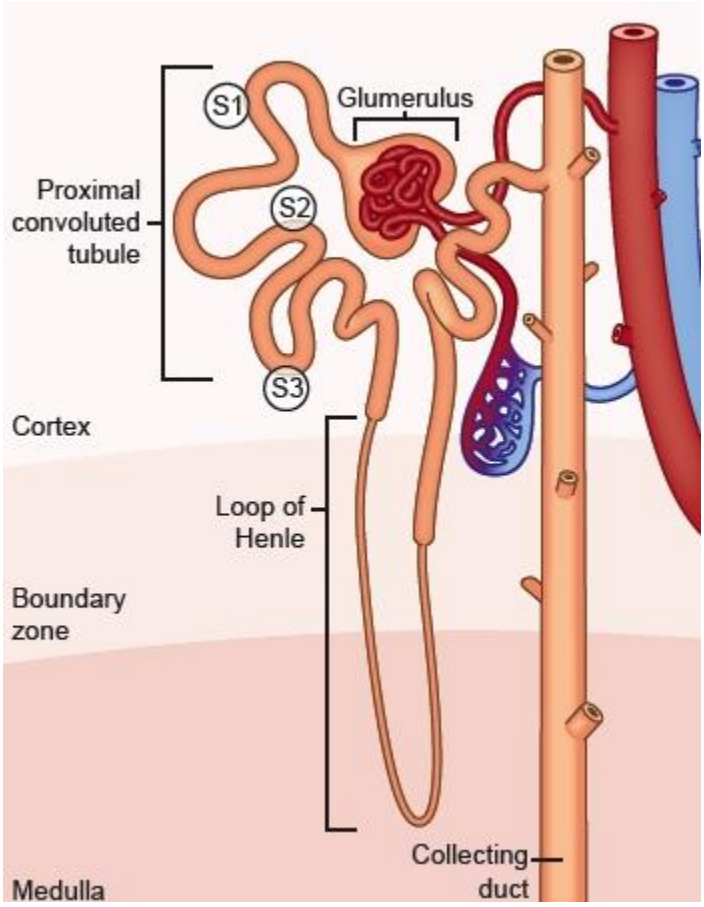
Subsequently it was discovered that the naturally occurring substance, **phlorizin**, was an SGLT inhibitor which *non-selectively* blocked both the SGLT-1 and SGLT-2 symporter proteins.

Phlorizin itself was not developed for use in humans because of its low oral bioavailability (around 15%) and its action on SGLT-1, which could result in GIT side effects, such as diarrhea.

Canagliflozin (no longer available) was the first SGLT-2 specific inhibitor to be developed for clinical use in 2013.

Empagliflozin was introduced into clinical practice in 2014. It was developed by Boehringer Ingelheim and Eli Lilly and Company.

Physiology



The 3 segments of the proximal convoluted tubule of the nephron

Sodium-glucose co-transporter (SGLT) is a transporter protein that transports both sodium and glucose across cell membranes. It is an example of a *symporter* transport membrane protein. It carries out a process of *secondary active transport*, whereby sodium ions are transported down a concentration gradient which takes glucose with it *against* its concentration gradient.

There are different isoforms of this enzyme including:

1. SGLT-1:

    - This is a high affinity, low capacity transporter that transports 1 glucose and 2 sodium molecules
    - It is found in the mucosa of the small intestine, and is the primary transporter of glucose in the gastrointestinal tract

2. SGLT-2:

- This is a low affinity, high capacity transporter that transports 1 glucose and 1 sodium molecule.

- It is found almost exclusively in the proximal tubules of nephrons.

In the kidneys, 100% of the filtered glucose in the glomerulus has to be reabsorbed along the nephron.

Reabsorption of glucose occurs in the **proximal convoluted tubule** of the nephron and is carried out by isoforms SGLT - 1 and SGLT - 2

SGLT-2 is located in the S1 and S2 segments of the proximal convoluted tubule and has a high capacity but low affinity for glucose transport. It reabsorbs about 90 % of filtered glucose.

SGLT-1 is located in the S3 segment of the proximal convoluted tubule and has a low-capacity, but high-affinity for glucose transport. It reabsorbs the remaining 10% of the filtered glucose.

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 SGLT-2) inhibitors (or "Gliflozins")**:

   These agents reduce glucose reabsorption in the kidneys.

   Examples include:

   - Dapagliflozin
   - **Empagliflozin**

Preparations

Empagliflozin as:

Tablets:

- 10 mg, 25 mg.

Fixed dose combination with metformin:

- Empagliflozin 5 mg + metformin 500 mg
- Empagliflozin 5 mg + metformin 1000 mg
- Empagliflozin 12.5 mg + metformin 500 mg
- Empagliflozin 12.5 mg + metformin 1000 mg

Mechanism of Action

The SGLT-2 inhibitors as a group reduce glucose reabsorption in the kidney and so increase its excretion in the urine.

Pharmacodynamics

Effects include:

1. Glycemic effects:

    - Empagliflozin improves both fasting and postprandial plasma glucose levels.

      Following the administration of empagliflozin to patients with type II diabetes, urinary glucose excretion increases immediately and is continued over an ensuing the 24 hour period.

      Excretion averages approximately 78 grams per day with an empagliflozin dose of 25 mg once daily.

      As there is there is no direct effect on beta islet cell function or insulin secretion or action, there is a **low risk** of for the development of hypoglycaemia with this agent.

2. Mild diuretic effects:

    - The glucosuria observed with SGLT- 2 inhibitors such as empagliflozin is accompanied by *mild osmotic diuresis.*

3. Mild blood pressure lowering effect:

    - Mild diuresis may contribute to a sustained mild reduction of **blood pressure**.

4. Weight loss:

    - Overweight and obese patients treated with SGLT - 2 inhibitors may achieve some modest weight loss (2 - 3 kilograms)

Pharmacokinetics

Absorption:

- Empagliflozin is administered orally.

  It is rapidly absorbed after an oral dose

- Peak blood levels are seen within 1.5 hours following ingestion.

Distribution

- Protein binding is around 86 %.

- The apparent steady-state volume of distribution is estimated to be around 73.8 liters
- It is not known if human placental transfer occurs
- It is not known if excretion into breast milk occurs.

Metabolism and excretion:

- Plasma concentrations decline in a biphasic manner with a rapid distribution phase and a relatively slow terminal elimination phase of around 12.4 hours
- About 50 % of a dose of empagliflozin is metabolized
- About 50 % of a dose of empagliflozin is excreted as unchanged drug in the urine.

Indications

Empagliflozin is indicated for:

1. Type 2 diabetes (either alone or in fixed-dose combination with metformin)
2. Diabetics with heart failure: [5]
    - Sodium-glucose co-transporter 2 (SGLT2) inhibitors *in general* are recommended in patients with type 2 diabetes mellitus associated with cardiovascular disease and insufficient glycaemic control despite metformin, to decrease the risk of cardiovascular events and decrease the risk of hospitalization for heart failure.

Contra-indications/precautions

These include:

1. Renal impairment:
    - Efficacy is reduced in renal impairment (CrCl <45 mL/minute) as efficacy is dependent on renal function.

      Note that empagliflozin may be used with caution, however, the SGLT-2 agent, dapagliflozin is specifically contraindicated in these patients.
2. Elderly:
    - The elderly are at increased risk of adverse effects related to volume depletion such as hypotension and syncope

3. Drug reactions:

    - Caution when combined with other diuretic agents due to an increased risk of volume depletion.

4. Contraindicated in pregnancy and breast feeding (see below)

5. Surgery:

    - Consider withholding SGLT- 2 inhibitors due to perioperative risks such as dehydration, UTI and renal impairment and the potential for an increased risk of euglycaemic ketoacidosis, (see below).

Pregnancy

Empagliflozin is a category D class drug with respect to pregnancy.

Category D drugs are those drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.

Published information describing the use of empagliflozin during pregnancy has not been located.

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

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 empagliflozin 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

These include:

1. Volume depletion:

    - SGLT- 2 inhibitors have a mild osmotic diuretic effect and when used in combination with other diuretics

2. Hypoglycemia:

- Although the risk of hypoglycemia is low with the SGLT-2 inhibitors, hypoglycemia may occur if used in combination with other hypoglycemic agents, in particular with sulfonylureas or insulins.

  Dosages may need to be reduced when combination therapies are used.

3. UTI:

   - Glucosuria can lead to an increased risk of urinary tract infections

4. Local candidiasis:

   - Glucosuria can lead to an increased risk of local candidiasis, balanitis/ vulvovaginitis.

     Maintaining good hygiene is important to reduce the chance of local candidiasis.

5. Renal impairment may occur with prolonged diuresis

6. Euglycaemic ketoacidosis:

   - Euglycaemic ketoacidosis has been associated with the use of SGLT-2 inhibitors.

     The risk appears to be greatest under conditions where ketosis occurs, such as acute serious illness or prolonged fasting.

     If a high anion gap metabolic acidosis occurs, consider SGLT- 2 inhibitor's potential causative role and look for ketosis.

Dosing [2]

Usual adult dosing is:

- Initially 10 mg orally once daily.

Then

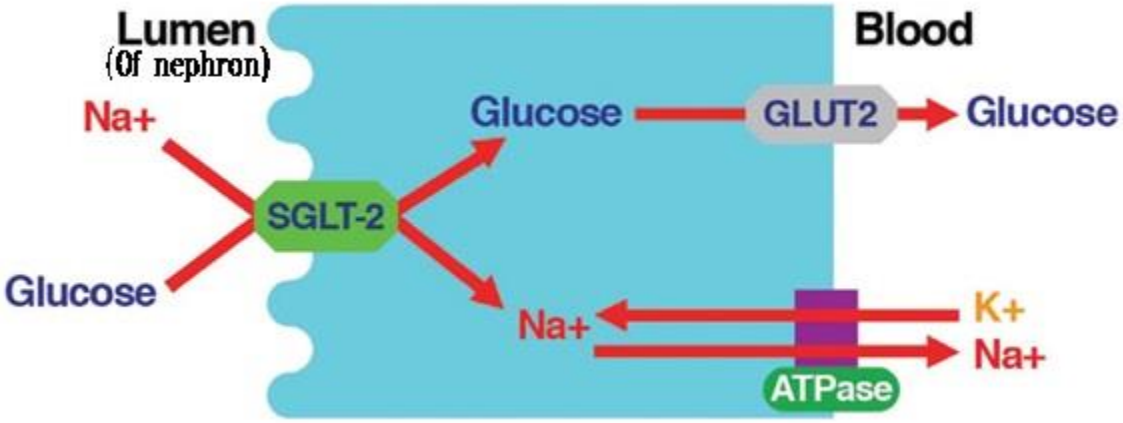
- As necessary, increase up to 25 mg once daily.

Fixed-dose combination with metformin:

- 1 tablet (of any strength) twice daily.

Appendix 1

The SGLT-2 Symporter system:



SGLT-2 mediates glucose reabsorption in the kidney. It catalyzes the active transport of glucose (against a concentration gradient) across the luminal membrane by coupling it with the downhill transport of Na+.

The inward Na+ gradient across the luminal epithelium is maintained by active extrusion of Na+ across the basolateral surface into the intracellular fluid. Glucose diffuses out of the cell down a concentration gradient via the basolateral facilitative transporter GLUT-2.

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