بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Endocrine Pharmacology | FINAL 7

Insulin and Oral Hypoglycemic Drugs Pt.2

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Synthetic Amylin Analog

Pramlintide

- Is a synthetic amylin analog **(WHAT is Amylin??!)** **amylin is a hormone created and secreted from the pancreas, function is to work together with insulin! (Like when u eat breakfast, the food will stimulate insulin AND amylin secretion), amylin goal is to Dec blood glucose lvl by two mechanism:**

1. Delays gastric emptying (slows GI motility and delays absorption of glucose to decrease blood glucose)(the glucose in the stomach will take a long time to reach the intestines)(major site of absorption)
2. Decreases postprandial glucagon secretion (glucagon elevates blood glucose, so amylin inhibits it)

3. Amylin does not act on insulin; it works together (co-secreted) with insulin to regulate blood glucose levels.

- Indicated as an adjunct to **mealtime** insulin therapy in Type 1 or advanced stage 2 diabetes.
- Is administered by subcutaneous injection inhibits
- Should be injected immediately prior (before) to meals. **(WHY?!)**

Pramlintide

- Pramlintide is an amylin analog prescribed for patients with **type 1 diabetes mellitus** and patients with **advanced-stage type 2 diabetes mellitus** who have a high level of glycosylated hemoglobin (HbA1c). It is **administered in combination with insulin**, as both drugs have complementary effects that improve glycemic control.

- Pramlintide has two main mechanisms of action. First, it **slows gastric emptying**, which delays the absorption of glucose from the intestine and consequently reduces the amount of glucose entering the bloodstream, particularly after a meal. Second, it **inhibits the release of glucagon**, which normally increases blood glucose levels by promoting glucose production by the liver. Therefore, inhibition of glucagon secretion also contributes to lowering blood glucose levels.

Pramlintide

- – Pramlintide is administered **subcutaneously** immediately before a meal, together with mealtime insulin. Because the combination increases the risk of hypoglycemia, **the dose of mealtime insulin should be reduced when pramlintide is started.** The patient should eat immediately after taking pramlintide to reduce the risk of hypoglycemia.

- – As an amylin analog, pramlintide is **contraindicated** in patients with **gastroparesis**, a condition characterized by delayed gastric emptying, because pramlintide further slows gastric emptying and may worsen the condition.

Synthetic Amylin Analog

Pramlintide

- When pramlintide is initiated, the dose of rapid- or short-acting insulin should be decreased by 50% prior to meals **(WHY?!)** to avoid a risk of severe hypoglycemia.

- Adverse effects are **mainly gastrointestinal** and consist of nausea, anorexia, and vomiting.
- **Should not be given to patients with:**

1. Diabetic gastroparesis (delayed stomach emptying)
2. History of hypoglycemic unawareness.

Because amylin is obtained from human sources, it is difficult to produce it as a medication; therefore, a synthetic analog called pramlintide is developed for therapeutic use.

- After studying the drugs that mimic the actions of insulin in the previous lecture, we can now discuss another group of drugs called **adjunctive drugs**, which are not insulin in their structure and are mainly **administered orally**. Instead, they assist the release and function of insulin and therefore help in controlling blood glucose levels.

- The first group is **sulfonylureas**. The chemical structure of these drugs is clinically important because it raises the possibility of **crossallergenicity** with other drugs that contain a sulfonamide group. These include sulfonamide antibacterial drugs, which inhibit folic acid synthesis in bacteria, as well as some diuretics, such as furosemide (Lasix). Therefore, when prescribing a sulfonylurea, it is important to ask the patient about any previous allergic reactions to sulfonamide-containing drugs, particularly antibiotics or certain diuretics.

- However, cross-allergenicity is not inevitable; having an allergy to a sulfonamide-containing drug does not necessarily mean that the patient will develop an allergic reaction to a sulfonylurea. The possibility of a reaction should therefore be considered based on the patient's previous history and the specific drug involved

- The mechanism of action of sulfonylureas is similar to the **physiological effect of glucose on pancreatic β-cells**, as they stimulate the release of insulin. Sulfonylureas block ATP-sensitive K^+ channels (KATP channels) on the membrane of pancreatic β-cells. This causes a decrease in K^+ efflux, leading to membrane depolarization. Depolarization then opens voltage-gated Ca^{2+} channels, resulting in an influx of Ca^{2+} into the βcell. The increased intracellular Ca^{2+} concentration triggers the exocytosis of insulin - containing vesicles, leading to increased insulin secretion.

- Sulfonylureas(Amaryl) are **not used in patients with type 1 diabetes mellitus** because they depend on the presence of functional pancreatic β-cells to stimulate insulin secretion. In type 1 diabetes, the pancreatic β-cells are destroyed by the autoimmune process, resulting in an **absolute deficiency of insulin**. Therefore, there are insufficient functional β-cells for sulfonylureas to act on, making these drugs ineffective in type 1 diabetes

- As we become **older**, **insulin** secretion may **decrease**, and in a patient with **type 2** diabetes who still has functioning pancreatic β-cells, a sulfonylurea can be used to stimulate the release of endogenous insulin. For example, if a patient previously had normal insulin secretion but their β-cell function has declined, **sulfonylureas can stimulate the remaining functional β-cells to increase insulin secretion.**

- When using sulfonylureas, we are particularly concerned about two important adverse effects. The first is **hypoglycemia**, because these drugs stimulate insulin secretion and can continue to do so even when blood glucose levels are low. Therefore, taking an excessive dose can cause severe hypoglycemia, which can potentially be life-threatening. For example, a patient who takes two tablets before going to a party expecting to eat a meal containing sweets such as knafeh, may develop severe hypoglycemia if the dose is excessive or the food intake does not match the increased insulin secretion.

- The second important adverse effect is **weight gain**, because insulin is an **anabolic hormone**. Increasing insulin secretion promotes anabolic processes and can consequently contribute to weight gain.

Oral Agents: Insulin Secretagogues

Sulfonylureas

- Promote insulin release from the β cells of the pancreas.

- Mechanisms of action:

1) stimulation of insulin release from the β cells by blocking the ATP-sensitive K+ channels, resulting in depolarization and Ca2+ influx >>> may cause hypoglycemia
2) Reduction in hepatic glucose production
3) Increase in peripheral insulin sensitivity.

- Sulfonylureas are classified into two generations. The first-generation sulfonylureas, such as **tolbutamide**, are less potent and generally require higher doses. The secondgeneration sulfonylureas, such as **glimepiride**, were developed to be more potent and can be used at lower doses. Some second-generation agents also have a lower risk of prolonged hypoglycemia compared with certain firstgeneration agents.

- a patient with advanced-stage type 2 diabetes mellitus who has a high level of glycosylated hemoglobin (HbA1c) and still has functioning pancreatic β-cells, a second-generation sulfonylurea such as glimepiride may be used to stimulate insulin secretion. If the patient does not achieve adequate glycemic control despite an appropriate dose, the treatment should be reassessed and another appropriate antidiabetic therapy may be added or substituted rather than simply switching to a first-generation sulfonylurea because it is considered “stronger.”

Oral Agents: Insulin Secretagogues

Sulfonylureas

- **First generation:** tolbutamide (shortest action)

2nd generation derivatives are: (longer duration of action)

1. Glyburide (is reasonably safe alternative to insulin therapy for diabetes in pregnancy)
2. Glipizide
3. Glimepiride.

For pregnant women with gestational diabetes, **insulin** is considered the safest treatment option when medication is needed.

Oral Agents: Insulin Secretagogues

Sulfonylureas

Adverse effects:

1. Weight gain
2. Hypoglycemia
3. Renal impairment is a particular problem in agents metabolized to active compounds, such as glyburide.

Oral Agents: Insulin Secretagogues

Meglitinide analogs

Skipped by the doctor

- Their action is dependent on functioning pancreatic β cells.

- **MOA:** They bind to a distinct site on the sulfonylurea receptor of ATP-sensitive K+ channels, initiating a series of reactions culminating in the release of insulin.(Same as sulfunylurea)

- The meglitinides have a rapid onset and a short duration of action than sulfonylurea >>>>> effective in the early release of insulin that occurs after a meal >>>> postprandial glucose regulators.

Oral Agents: Insulin Secretagogues

Meglitinide analogs **Skipped by the doctor**

- Hypoglycemia appears to be lower than sulfonylurea.
- Meglitinides should not be used in combination with sulfonylureas (WHY?!) >>> sever hypoglycemia
- **This class of agents includes:**

1. Repaglinide
2. Nateglinide

Oral Agents: Insulin Secretagogues

Meglitinide analogs

Skipped by the doctor

- Drugs inhibit CYP3A4 (ketoconazole, erythromycin, and clarithromycin) may enhance the effect of repaglinide >>>>
  They must be used with caution in hepatic impairment

- CYP3A4 inducers: barbiturates, carbamazepine, and rifampin, decreases the effect of repaglinide.

- Weight gain is of less problem than sulfonylureas.

Metformin (Glucophage):

- The second drug is **metformin (Glucophage)**,which is commonly used in the management of diabetes mellitus. Its anti-aging effect was initially observed in animal studies, where the administration of metformin was found to reduce some characteristics of aging, such as wrinkles. Based on these findings, it was subsequently used for the same purpose inhuman.

- The mechanism of action of metformin is primarily as an **insulin sensitizer**, meaning that it increases the sensitivity of tissues to insulin and enhances insulin signaling through its receptor.In **polycystic ovary syndrome (PCOS)**, women may develop insulin resistance; therefore, metformin can be prescribed for the management of PCOS rather than specifically for the treatment of diabetes mellitus.

Metformin (Glucophage):

- It is also important to note that metformin has significant **anti-inflammatory effects.** Our bodies can develop a condition known as low grade chronic inflammation, sometimes referred to asa “silent killer,” which may accumulate over time with aging. This chronic inflammation has been associated with the development of age-related conditions, such as hypertension, diabetes mellitus, and dementia.

- As we studied in the previous lecture, the increased prevalence of type 2 diabetes mellitus in obese patients is associated with the **accumulation of visceral fat,** where macrophages accumulate and release specific cytokines and other inflammatory mediators.These inflammatory mediators contribute to insulin resistance by reducing the sensitivity of tissues to insulin. To help overcome this problem , metformin may be administered due to its anti-inflammatory effects, which can help **reduced the release of inflammatory mediators and thereby improve insulin sensitivity.**

Metformin (Glucophage):

- **The major mechanism of action of metformin is its entry into the liver which is the site of action.** After administration, metformin is absorbed from the intestine into the bloodstream and then transported to the liver by organic cation transporters (OCTs), which facilitate its uptake into hepatocytes. Once inside the hepatocytes, metformin **inhibits gluconeogenesis**, which is the formation of glucose from non-carbohydrate sources. It also **inhibits lipogenesis**, which is the formation of lipids.

- Once metformin enters the hepatocytes, it reaches the mitochondria, where it reduces **ATP production**. This leads to an **increase in ADP-levels**, which contributes to the **inhibition of gluconeogenesis and lipogenesis.** As a result, patients taking metformin experience a reduction in hepatic glucose synthesis and lipid synthesis

Metformin (Glucophage):

- The most important point to remember is that metformin does not stimulate insulin release; therefore, it has a minimal risk of causing hypoglycemia . This is one of the reasons why some people without diabetes may take metformin for **weight loss**, as it has a **low risk of causing hypoglycemic shock.**

- Some people may misuse this drug because they want to experience a feeling of euphoria or.For example, a person may take an entire strip of-the medication and have a cup of coffee ready to help them feel more alert after experiencing the drowsiness caused by the drug. When such a patient presents to the clinic, dextrose may be administered as part of the management.

Metformin (Glucophage):

- According to statistics, metformin is one of the most commonly used drugs for weight loss inJordan. One reason is that metformin does not stimulate insulin secretion, so there is a lower risk of hypoglycemia when it is used alone. In addition, metformin inhibits lipogenesis, which may contribute to its effect on body weight. It can also cause gastrointestinal side effects, particularly nausea, due to irritation of the gastrointestinal tract. This irritation can make the patient feel nauseous and as if they may vomit, consequently reducing their appetite and food intake.

- Metformin is considered a relatively safe drug,and one indication for its use is weight management in some people without diabetes.It can also be used as a preventive measure in individuals who are at high risk of developing type 2 diabetes. For example, a person with a strong family history of diabetes, a sedentary lifestyle, an unhealthy diet, and high sugar intake may have several risk factors that increase the likelihood of developing diabetes. Therefore,metformin may be prescribed as prophylaxis in certain high-risk individuals.

Insulin Sensitizers: Biguanides

- The only drug member is Metformin
- Increases glucose uptake by target tissues, thereby decreasing insulin resistance.
- Metformin requires insulin for its action.
- It does not promote insulin secretion. (IMPORTANT)

The main mechanism of actions:

1. Inhibiting hepatic gluconeogenesis.
2. Slows intestinal absorption of sugars
3. Improves peripheral glucose uptake and utilization.
4. Reduces LDL, VLDL and increases HDL. These effects need 4 to 6 weeks of use.

- The patient often loses weight (WHY?!) because of loss of appetite.

Although some textbooks mention concerns regarding the cardiovascular safety of metformin, it can actually improve the lipid profile by decreasing LDL cholesterol and increasing HDL cholesterol, which may be beneficial for cardiovascular health

Insulin Sensitizers

Biguanides

- Metformin is recommended as the drug of choice for Type 2 diabetics.
- Not metabolized in the liver but excreted unchanged renally.
- Metformin is effective in the treatment of polycystic ovary disease (HOW?) Its ability to lower insulin resistance in these women can result in ovulation and, possibly, pregnancy.

Metformin (Glucophage):

- Metformin should also be used cautiously or avoided in patients with **significant renal impairment and certain hepatic conditions**.Although the liver is a major site of metformin action, the drug itself is **highly water-soluble** and exists in a charged form. Therefore, it does not require extensive hepatic metabolism and is eliminated primarily through the kidneys. Inpatients with impaired renal function, the elimination of metformin is reduced, which can lead to **accumulation of the drug in the blood.**

- Excessive accumulation of metformin can increase the risk of **lactic acidosis**. By impairing mitochondrial energy production and reducing ATP availability, metformin can increase the reliance on anaerobic metabolism, leading to increased lactate production. Although metformin associated lactic acidosis is uncommon , it is a serious and potentially life-threatening complication. Therefore, metformin should be avoided or carefully dose-adjusted inpatients with significant renal impairment to minimize this risk.

Metformin (Glucophage):

- One of the adverse effects of metformin is that it can **reduce vitamin B12 absorption**. Vitamin B12is important for normal nerve function, so long-term metformin use may increase the risk of vitamin B12 deficiency and associated neurological symptoms. In such cases, vitaminB12 supplementation may be required, and in some patients, it may be given by injection rather than orally

Insulin Sensitizers

Biguanides

- Adverse effects >>> GI disterbane.
- Metformin is contraindicated in

1. Renal and hepatic disease (WHY?!)
2. Acute MI and **CHF**
3. Severe infection
4. Diabetic ketoacidosis.

- Lactic acidosis has occurred.
- Long-term use may interfere with vitamin B12 absorption.
- Hypoglycemia is less than with sulfonylurea. (WHY?!)

Additional Resources:

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
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