Oral Hypoglycemic Drugs

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Diabetes is one of the most common metabolic disorders of the world and is a major cause of morbidity in the elderly population. The treatment of diabetes has gone into a number of refinements, and currently, the majority of people who are suffering from the disease can be treated with the help of oral hypoglycemic drugs. These drugs form the first line of pharmacological treatment for patients with type 2 diabetes mellitus, whereas, in patients with type 1 diabetes mellitus, the first line of treatment is insulin. This article discusses in detail the various oral hypoglycemic drugs, which are currently available on the market.

Outline of the Pharmacological Treatment

The various classes of drugs available for the treatment of diabetes mellitus include:

- Biguanides
- Sulfonylurea
- Meglitinide
- Thiazolidinedione
- Dipeptidyl peptidase IV inhibitors
- Alpha-glucosidase inhibitors

Each class of drugs has its own pros and cons and is valuable in their own ways. These groups of drugs are generally classified on the basis of their effects on insulin. One group contains **insulin secretagogues**, which function by increasing the secretion of insulin.

Another is the **insulin sensitizers**, which function by means of increasing the sensitivity to already present insulin.

Although the general consensus is to initially try **modifying a person's lifestyle,** studies have shown the beneficial effect of the early initiation of the pharmacotherapy.

Biguanides

Classification and mechanism of action

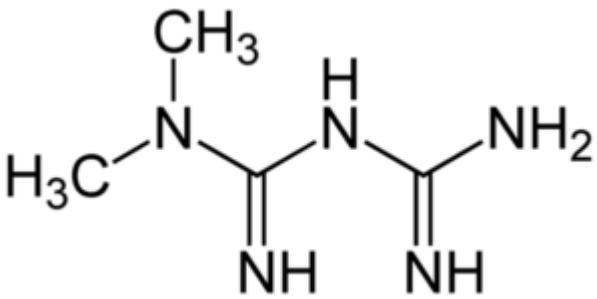

Image: "Chemical formula of metformin" by Jü – Own work.
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This class of drugs comes under insulin sensitizers, with the most important being **metformin**.

The mechanism of action of metformin includes decreasing the production of glucose in the liver (**gluconeogenesis**), decreasing the absorption of glucose from the intestine and increasing the sensitivity to the insulin. The increase in sensitivity is achieved by increasing the peripheral utilization and uptake of glucose. The proposed mechanism of action for decreasing the insulin resistance is by increasing the **AMP-activated protein kinase** (**AMPK) signaling,** a master regulator of cellular energy homeostasis.

Although metformin is one of the most effective drugs in the treatment of diabetes, there is an important drawback: requirement of the **beta-cell function** for its effect to occur. Progressive **beta-cell failure** causes its effectiveness to reach a plateau phase.

Pros & cons and a main indication of biguanides

Metformin is one of the preferred drugs for **monotherapy** in the treatment of diabetes mellitus, and it is recommended by the guidelines of the American Diabetes Association. However, caution needs to be undertaken to look out for the **contraindication** of giving metformin (listed below). Metformin is also preferred in **combination therapy**.

The biguanides group is very effective in **overweight and obese** patients because it has beneficial effects on the **low-density lipoprotein level** of the body and also decreases the **triglyceride** concentration. The advantage of this group of drugs is that there is **no weight gain problem,** and **the risk of hypoglycemia decreases**.

Though the observational data have shown a reduction in the incidence of **cancer** with the usage of metformin, the same results did not arise with the meta-analysis of the random control trials.

In the UKPDS and other trials, metformin has shown to have a reduction in cardiovascular events.

Adverse and side effects related to biguanides

The main disadvantage of biguanides is the gastrointestinal side effects.
There is increased risk of lactic acidosis; though rare, it has a very high case fatality rate. That's why this drug is contraindicated in patients with:

- Renal disease and impaired kidney function
- Liver disease
- Alcoholic abuse
- Acute and chronic heart failure
- Pulmonary decompensation in the acute phase.

As there is an elevated chance of developing lactic acidosis, the administration of metformin is contraindicated.

The drug causes an increased risk of **vitamin B12 deficiency**. Vitamin B12 is required for the normal nerve functions, and deficiency of the same leads to **neuropathy**. The risk of neuropathy precedes that of **megaloblastic anemia**.

In one of the meta-analyses, it was demonstrated that the combination of metformin and **glibenclamide** is associated with increased **Charlson comorbidity index** and an increase in the mortality when compared with other insulin secretagogues.

The **Charlson comorbidity index** predicts the one-year mortality for a patient who may have a range of **comorbid** conditions, such as heart disease, AIDS, or cancer (a total of 22 conditions). Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one.

Sulfonylurea

Classification and mechanism of action of sulfonylurea

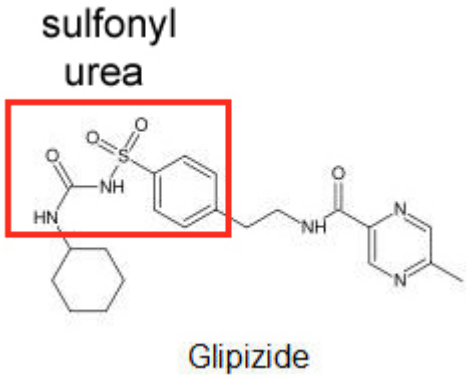

Image: "Sulfonyl urea – functional group emphasized by bounding box and label" by Togmv232 – Own work.
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This group of drugs consists of **insulin secretagogues** as their function is to increase the secretion of insulin by means of closing the **potassium ATP channel** of the pancreatic beta cells. This induces depolarization of the membrane potential with activation of voltage-gated calcium channels, and thus the calcium-dependent release of insulin. Naturally, these drugs require the effective functioning of the beta cells of the pancreas for any action to occur.

There are two generations of agents in this class of drugs. The most prominent drugs in the first generation are **tolbutamide** and **chlorpropamide**. In the second generation, the most prominent drugs are **glipizide**, **glibenclamide**, **glimepiride,** and **gliclazide**.

Pros & cons and main indication of sulfonylurea

One of the advantages of this group of drugs is the **low cost of treatment** along with attaining a **rapid reduction in the fasting plasma glucose level**. The drug is mainly targeted in patients who are recently diagnosed with diabetes mellitus, especially in the initial span of 5 years.
Treatment with sulfonylurea has been reported to be associated with a decline in the function of the beta cells, which occurs progressively over the period of time in a linear fashion. This might end up in **beta-cell failure**.

Adverse and side effects related to sulfonylurea

The main disadvantage of this group of drugs is the problem of **weight gain** (due to the anabolic effect of the increase in the insulin concentration) along with the **increased risk of hypoglycemia** (due to the insulin release even when the glucose level is normal).
The hypoglycemia generally manifests as **sweating along with giddiness,** and if not properly corrected, it would lead to **unconsciousness**.

Meglitinide

Classification and mechanism of action of meglitinide

Image: “Repaglinide, antidiabetic drug” by Norbora – Own work. License: CC BY-SA 3.0

The group of drugs under this class includes **repaglinide** and **nateglinide**. They also cause an increase in the production of insulin and are specifically referred to as short-acting secretagogues.

Their mechanism of action occurs by inhibiting the potassium channels and thereby causing the secretion of insulin. Their binding site is different from that of the sulfonylurea class of agents.

Pros & cons and main indication of meglitinide

They typically help in maintaining **postprandial blood glucose,** especially after a meal. One more advantage of this class of drugs is their **short-acting nature** and that dosing can be easily adjusted according to food intake.

Adverse and side effects related to meglitinide

As common to all secretagogues, there is a **risk of hypoglycemia and weight gain** (the mechanism of both side effects is almost similar to that of sulphonylurea).

Thiazolidinedione

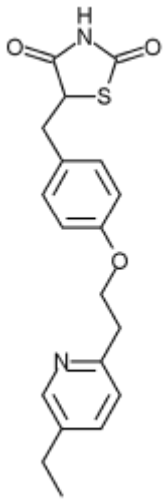

Image: “Structural Formula of pioglitazone” by Pngbot. License: CC BY-SA 3.0

Classification and mechanism of action of thiazolidinedione

This class of drugs belongs to the insulin sensitizer family, which includes **pioglitazone** and **rosiglitazone**.

The mechanism by which these drugs reduce insulin resistance is quite novel. They activate the **Peroxisome Proliferator-Activated Receptors Gamma (PPAR-Gamma) variety in the fat and muscle cells**. Thus, the drugs increase the glucose uptake into these, while reducing the glucose level in the blood. PPAR-Gamma specifically regulate the storage of fatty acid and the metabolism of glucose.

Pros & cons and main indication of thiazolidinedione

This class of drugs is targeted in **overweight, obese and insulin-resistant patients**. It is also used in **combination therapy along with biguanide**. Since it is an insulin-sensitizing therapy, there is a low risk of causing hypoglycemia.

There are some reported beneficial effects on the lipid level with this drug (though the drug has been reported and confirmed for **cardiovascular morbidity**).

Adverse and side effects related to thiazolidinedione

This class of drugs also have the disadvantage of causing **weight gain** as well as

increasing the risk of causing **heart failure** (especially rosiglitazone).

One of the meta-analyses showed that the odds ratio of **myocardial infarction** and death is greater with rosiglitazone as compared to that of the control.

Though the drug is advocated for patients with obesity and increased resistance, its side effect causes an **increase in the LDL cholesterol and triglycerides level** and has been reported to be linked with the risk of causing **bladder cancer**.

This group of drugs also has the risk of **hepatotoxicity** and of causing **fractures of the long bones**, **edema** and **anemia**.

Alpha Glucosidase Inhibitor

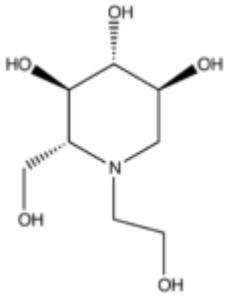

Image: “Structure of miglitol” by Louisajb (talk) 15:39, 12 December 2011 (UTC) – Own work. License: Public Domain

Classification and mechanism of action of alpha glucosidase inhibitor

The drugs under this category include **acarbose**, **voglibose,** and **miglitol**. Alpha-glucosidase is an enzyme which is present in the intestine and is responsible for the digestion of carbohydrates. This digestion of carbohydrates is required for the absorption of glucose in the intestine.

These drugs act by means of inhibiting the enzyme alpha-glucosidase, thus **reducing the absorption of glucose**, which in turn results in the reduction of the blood glucose level.

Pros & cons and main indication of alpha glucosidase inhibitor

This group of drugs is mainly used along with other drugs in **combination therapy**. As compared with the sulfonylurea, this is not associated with weight gain.

Adverse and side effects related to alpha glucosidase inhibitor

In addition to being **expensive**, the drug holds the risk of causing **GI disturbances** and

is the **least effective** drug among the oral hypoglycemics in lowering the **HBa1c levels**. (The level of HB a1c is the indirect prediction of the control of glucose over a range of months).

Another drawback is the side effects like **flatulence and bloating**. This causes discomfort to the patient as well as the surrounding persons.

Incretin-Based Therapies

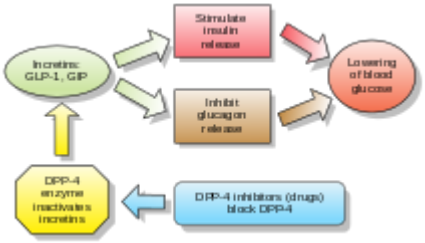

Image: "Mechanism of action of the DPP-4 inhibitors" by Clinical Cases, Ilmari Karonen – Drawn in Inkscape by Ilmari Karonen based on w:Image:Incretins and DPP 4 inhibitors.jpg from http://casesblog.blogspot.com/2006/11/dpp-4-inhibitors-for-treatment-of.html (uploaded by author). License: CC BY-SA 3.0

Gliptins, or DPP-4 inhibitors

This class of drugs is called **gliptins** and function by inhibiting the DPP-4 enzyme. Under this category fall **sitagliptin, vildagliptin, saxagliptin linagliptin**.

Incretin enzyme, which consists of **GLP-1 and GIP, stimulates glucagon release. Glucagon increases the blood glucose level. By inactivating that enzyme, the release of glucagon is inhibited**.

In addition to this, it also decreases the **gastric emptying time,** so there will be less time for absorption of glucose, thus reducing the blood glucose level.

GLP-1 receptor agonists

This group of drugs is similar in structure to GLP-1 but was modified to **resist breakdown** by the enzyme DPP-4. The drugs under this category include **exenatide** and **liraglutide**.
These drugs are given **subcutaneously** because they are not orally active.
Unlike sulfonylureas, incretin-based therapies stimulate insulin secretion only when there is a glucose "trigger"; when the level of glucose in the blood is normal, insulin secretion is not increased. Therefore, this group of drugs does not cause hypoglycemia.

SGLT2 Inhibitors

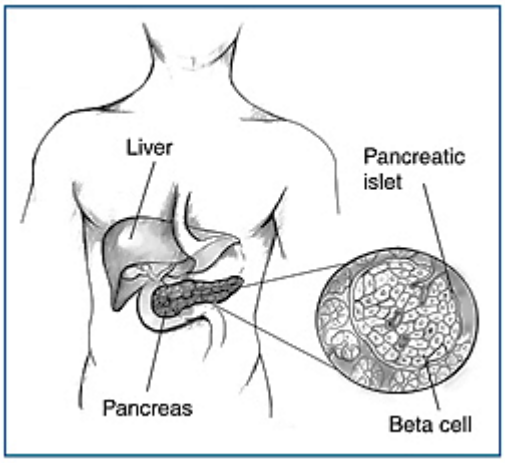

Image: “Insulin is produced in beta cells within the Islets of Langerhans in the pancreas.” by United States Department of Health and Human Services: National Diabetes Information Clearinghouse (NDIC) – http://diabetes.niddk.nih.gov/dm/pubs/diagnosis/. License: Public Domain

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are considered a new promising class of oral hypoglycemic medications because of their therapeutic effect without causing hypoglycemia and stimulating weight loss. Secondly, this is an **insulin-independent mechanism** of action, and thus, it would be effective even in case of the low reserve of the pancreatic beta-cell.

Dapagliflozin, canagliflozin, and empagliflozin are the drugs that fall under this category.

Mechanism of action of SGLT2 inhibitors

Urine glucose is routinely excreted in very small amounts, as most of the glucose is actually reabsorbed. This **reabsorption** involves the **sodium-glucose cotransporter**, which is located at the **proximal renal tubules of the nephrons** present in the kidney. The kidney has a set threshold, until which the glucose will be completely absorbed. When the filtered glucose level exceeds the threshold, glucose is excreted in the urine.

This group of drugs acts by **blocking the sodium-glucose cotransporter** (more specifically, on the SGLT2 located in the S1 and S2 segment of the proximal renal tubules, along the brush border of the epithelial cells) and **inhibiting the reabsorption of glucose**. In addition, the **renal threshold is also reduced**, hence shifting the kidney to excrete glucose even at the lower level of glucose in the filtered fluid.

Adverse and side effects related to SGLT2 inhibitors

Due to the excretion of glucose in the urine as part of the mechanism, there occurs increase in the risk of **fungal infection of the urinary tract (Vulvovaginal Candidiasis)**, increase in the **frequency of urination** and increase in the potassium concentration in the blood (**hyperkalemia**).

One of the serious adverse effects is **acute kidney injury** in patients who are treated with canagliflozin and dapagliflozin. Therefore, the drug should be avoided in patients with predisposing factors for acute kidney injury, and appropriate dose adjustments need to be made in **renal impairment patients**.

There is an increased risk of **venous thromboembolism** and **hemoconcentration** consequent to the volume depletion, which occurs with this group of drugs.

Combination of Oral Hypoglycemic Drugs

Combination therapy is preferred when the blood glucose level of the patient is not typically controlled by treatment with a single monotherapy agent.

Some of the recognized combination therapies administered to the patient include:

- Biguanide plus sulfonylurea
- Biguanide plus alpha-glucosidase inhibitors
- Biguanide plus thiazolidinediones
- Biguanide plus meglitinide.

In addition to the double combination therapy, in uncontrolled patients, even the **triple combination therapy** can be given. Some of the recognized combinations include:

- Biguanide plus sulfonylurea plus thiazolidinediones
- Biguanide plus sulfonylurea plus alpha-glucosidase inhibitors.

An alternative option for patients who do not respond to a single agent or dual therapy is the **addition of insulin** into the treatment regimen. However, this decision falls in the hands of the physician.

The details about the various insulin regimens and their pros and cons have been discussed in detail in the alternate topic.

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