Drugs for Diabetes

Part 2

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VI. INCRETIN MIMETICS

- Oral glucose results in a higher secretion of insulin than occurs when an equal load of glucose is given IV. This effect is referred to as the “incretin effect” and is markedly reduced in type 2 diabetes.

- The incretin effect occurs because the gut releases incretin hormones, notably glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, in response to a meal.

- Incretin hormones are responsible for 60% to 70% of postprandial insulin secretion.

- Exenatide and liraglutide are injectable incretin mimetics used for the treatment of type 2 diabetes.

VI. INCRETIN MIMETICS

- **Mechanism of action:** The incretin mimetics are analogs of GLP-1 that exert their activity by acting as GLP-1 receptor agonists.

- These agents improve glucose-dependent insulin secretion, slow gastric emptying time, reduce food intake by enhancing satiety, decrease postprandial glucagon secretion, and promote **β**-cell proliferation.

- Consequently, weight gain and postprandial hyperglycemia are reduced, and HbA1c levels decline.

- **Pharmacokinetics:** Exenatide and liraglutide must be administered subcutaneously.

- Liraglutide is highly protein bound and has a long half-life, allowing for once-daily dosing without regard to meals.

- Exenatide is eliminated mainly via glomerular filtration and has a much shorter half-life. Because of the short duration of action, exenatide should be injected twice daily within 60 minutes prior to morning and evening meals.

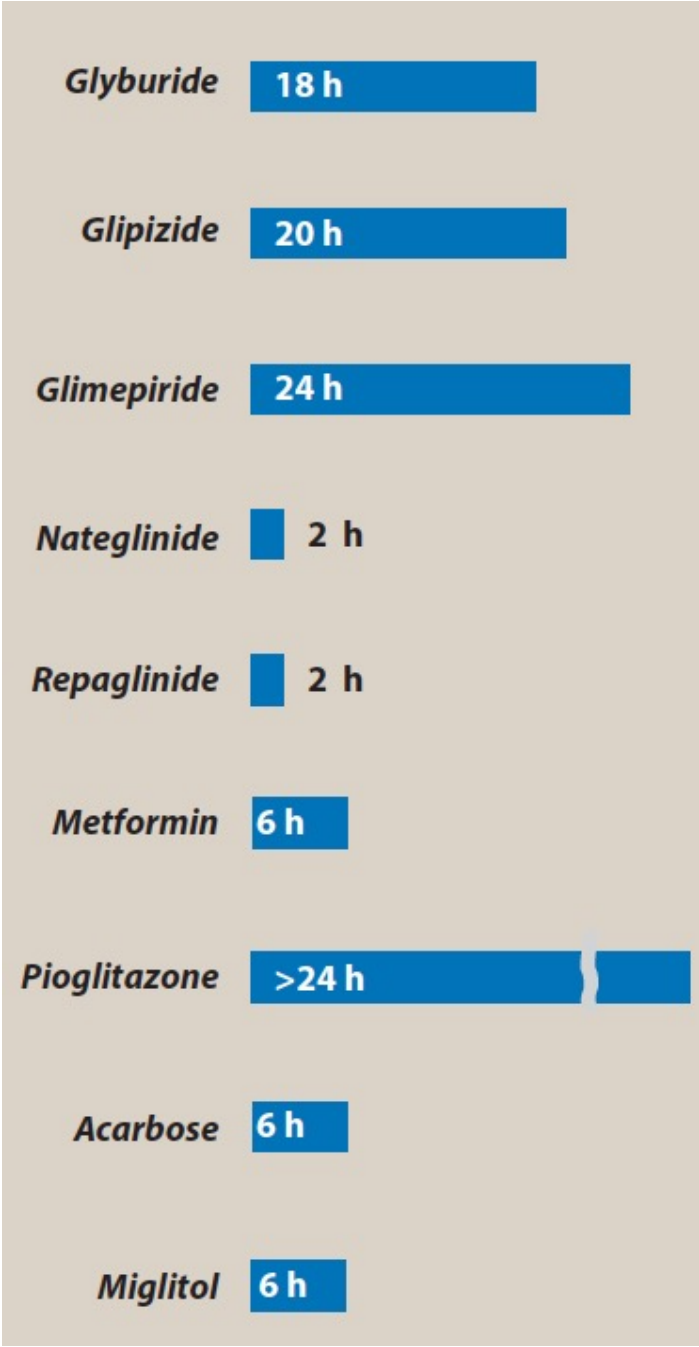
- A once-weekly extended-release preparation is also available. Exenatide should be avoided in patients with severe renal impairment.

VII. ORAL AGENTS

- Oral agents are useful in the treatment of patients who have type 2 diabetes that is not controlled with diet.

- Patients who developed diabetes after age 40 and have had diabetes less than 5 years are most likely to respond well to oral glucose-lowering agents.

- Patients with long-standing disease may require a combination of oral agents with or without insulin to control hyperglycemia.



A. Sulfonylureas

- These agents are classified as insulin secretagogues, because they promote insulin release from the B2 cells of the pancreas.

- The primary drugs used today are the second-generation drugs, ***glyburide, glipizide, and glimepiride***.

- **Mechanism of action:** Block ATP-sensitive K^+ channels, resulting in depolarization, Ca^{2+} influx, and insulin exocytosis.

- In addition, sulfonylureas may reduce hepatic glucose production and increase peripheral insulin sensitivity.

- The duration of action ranges from 12 to 24 hours.

B. Glinides

- This class includes ***repaglinide and nateglinide***. Glinides are also considered insulin secretagogues.

- **Mechanism of action:** similar to sulfonylureas.

- In contrast to the sulfonylureas, the glinides have a rapid onset and a short duration of action.

- They are particularly effective in the early release of insulin that occurs after a meal and are categorized as postprandial glucose regulators.

- Glinides should not be used in combination with sulfonylureas due to overlapping mechanisms of action. This would increase the risk of serious hypoglycemia.

- Glinides should be taken prior to a meal and are well absorbed after oral administration.

C. Biguanides

- ***Metformin***, the only biguanide, is classified as an insulin sensitizer.

- It increases glucose uptake and use by target tissues, thereby decreasing insulin resistance.

- Unlike sulfonylureas, metformin does not promote insulin secretion. Therefore, hyperinsulinemia is not a problem, and the risk of hypoglycemia is far less than that with sulfonylureas.

- **Mechanism of action:** The main mechanism of action of metformin is reduction of hepatic gluconeogenesis.

- Metformin also slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization.

- Weight loss may occur because metformin causes loss of appetite.

C. Biguanides

- The ADA recommends metformin as the initial drug of choice for type 2 diabetes.

- Metformin may be used alone or in combination with other oral agents or insulin.

- Hypoglycemia may occur when metformin is taken in combination with insulin or insulin secretagogues, so adjustment in dosage may be required.

- Other uses: Metformin is effective in the treatment of polycystic ovary disease. Its ability to lower insulin resistance in these women can result in ovulation and, possibly, pregnancy.

D. Thiazolidinediones or glitazones

- **Pioglitazone and rosiglitazone** are also insulin sensitizers.

- Although insulin is required for their action, the TZDs do not promote its release from the β-cells, so hyperinsulinemia is not a risk.

- **Mechanism of action:** The TZDs lower insulin resistance by acting as agonists for the peroxisome proliferator–activated receptor-γ (PPAR-γ), a nuclear hormone receptor.

- Activation of PPARγ regulates the transcription of several insulin responsive genes, resulting in increased insulin sensitivity in adipose tissue, liver, and skeletal muscle.

D. Thiazolidinediones or glitazones

- The TZDs can be used as monotherapy or in combination with other glucose-lowering agents or insulin.

- The dose of insulin may have to be lowered when used in combination with these agents.

- The ADA recommends pioglitazone as a second- or third-line agent for type 2 diabetes.

- **Pharmacokinetics:** No dosage adjustment is required in renal impairment.

- These agents should be avoided in nursing mothers.

- **Adverse effects:** Potential increased risk of myocardial infarction and death from cardiovascular causes with rosiglitazone. As a result, use of rosiglitazone was limited to patients enrolled in a special restricted access program. After a further review of safety data, the restrictions on rosiglitazone use were subsequently lifted.

- **Other uses:** As with *metformin,* the relief of *insulin* resistance with the TZDs can cause ovulation to resume in premenopausal women with polycystic ovary syndrome.

E. α-Glucosidase Inhibitors

- ***Acarbose*** and ***miglitol*** are orally active drugs used for the treatment of patients with Type 2 diabetes.

- **Mechanism of action:** Located in the intestinal brush border, α-glucosidase enzymes break down carbohydrates into glucose and other simple sugars that can be absorbed.

- *Acarbose* and *miglitol* reversibly inhibit α-glucosidase enzymes. When taken at the start of a meal, these drugs delay the digestion of carbohydrates, resulting in lower postprandial glucose levels.

- Since they do not stimulate *insulin* release or increase *insulin* sensitivity, these agents do not cause hypoglycemia when used as monotherapy.

- However, when used with *insulin* secretagogues or *insulin,* hypoglycemia may develop.

- Adverse effects limit the use of these agents in clinical practice.

F. Dipeptidyl peptidase-4 inhibitors (DPP-4)

- ***Alogliptin, linagliptin, saxagliptin, and sitagliptin*** are orally active dipeptidyl peptidase-4 (DPP-4) inhibitors used for the treatment of type 2 diabetes.

- **Mechanism of action:** These drugs inhibit the enzyme DPP-4, which is responsible for the inactivation of incretin hormones such as GLP-1. Prolonging the activity of incretin hormones increases insulin release in response to meals and reduces inappropriate secretion of glucagon.

- DPP-4 inhibitors may be used as monotherapy or in combination with sulfonylureas, metformin, TZDs, or insulin.

- Unlike incretin mimetics, these drugs do not cause satiety, or fullness, and are weight neutral.

- **Pharmacokinetics:** Food does not affect the extent of absorption.
- All DPP-4 inhibitors except **linagliptin** require dosage adjustments in renal dysfunction.

G. Sodium–glucose cotransporter 2 inhibitors (SGLT-2i)

- ***Canagliflozin and dapagliflozin*** are the agents in this category of drugs for type 2 diabetes.

- **Mechanism of action:** The sodium–glucose cotransporter 2 (SGLT2) is responsible for reabsorbing filtered glucose in the tubular lumen of the kidney. By inhibiting SGLT2, these agents decrease reabsorption of glucose, increase urinary glucose excretion, and lower blood glucose. Inhibition of SGLT2 also decreases reabsorption of sodium and causes osmotic diuresis.

- **Pharmacokinetics:** These agents are given once daily in the morning.

- Canagliflozin should be taken before the first meal of the day.

- These agents should be avoided in patients with renal dysfunction.

- **Adverse effects:** female genital mycotic infections (for example, vulvovaginal candidiasis), urinary tract infections, and urinary frequency.


Thank
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