

Anti-Diabetic Agents

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Drug Class: Biguanides

Introduction

The biguanide metformin is the drug of choice as initial therapy for a newly diagnosed patient with type 2 diabetes as an adjunct to diet and exercise. Metformin is contraindicated in certain patients to prevent lactic acidosis, a rare but serious side effect. It is often used in combination with other oral antidiabetic agents and/or insulin in patients who do not reach glycemic goals on those therapies. HbA1c reductions with metformin are generally between 1.5% and 2%.

Mechanism of Action for the Drug Class

Improves glucose tolerance by lowering both basal and postprandial plasma glucose. Decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

■ Metformin

Brand Names

Fortamet, Glucophage, Glucophage XR, Glumetza, Riomet

Generic Names

Metformin, metformin extended-release

Dosage Forms

Tablets, extended-release tablets, oral solution

Usage

- Type 2 diabetes mellitus*, PCOS, antipsychotic-induced weight gain.

Dosing

- Initial dose:
 - 500 mg twice daily with morning and evening meals, 850 mg once daily with a meal, or 500 mg extended release once daily with a meal

- Maintenance dose:
 - 2000–2550 mg daily in divided doses, or 2000 mg extended-release once daily
- Renal dosage adjustment:
 - Not recommended in patients with renal dysfunction (see Contraindications below)

Adverse Reactions: Most Common

- Diarrhea, vomiting, dyspepsia, flatulence, metallic taste, weight loss

Adverse Reactions: Rare/Severe/Important

- Lactic acidosis, megaloblastic anemia

Major Drug Interactions

Drugs Affecting Metformin

- Alcohol potentiates effect on lactate metabolism
- Iodinated contrast media can lead to acute renal failure and metformin toxicity

Contraindications

- Renal disease (males: SrCr \geq 1.5 mg/dl; females: SrCr \geq 1.4 mg/dl), heart failure requiring pharmacologic therapy, acute or chronic metabolic acidosis, active liver disease

Counseling Points

- Discontinue immediately and promptly notify health-care practitioner if unexplained myalgia, malaise, hyperventilation, or unusual somnolence because these are symptoms of lactic acidosis

Key Points

- Temporarily withhold in patients undergoing radiologic procedures involving the parenteral administration of iodinated contrast media because it may result in acute alteration of renal function. Do not restart for at least 48 hours or until renal function appears adequate.

Drug Class: Di-Peptidyl Peptidase-4 Inhibitor

Introduction

Sitagliptin is the first di-peptidyl peptidase-4 (DPP-4) inhibitor available. It inhibits the breakdown of active GLP-1 to inactive GLP-1 through the inhibition of the enzyme DPP-4. Active GLP-1 is released from the α cells of the pancreas in response to food intake. GLP-1 plays a role in regulating blood glucose by increasing the secretion of insulin from the pancreas in a glucose-dependent manner. GLP-1 also helps regulate glucagon secretion and decreases hepatic glucose production. Sitagliptin is used as monotherapy as an adjunct to diet and exercise or in combination with other oral antidiabetic agents in patients who do not reach glycemic goals. Average HbA1c reductions are between 0.7% and 1%.

Mechanism of Action for the Drug Class

Inhibition of DPP-4 enhances the activity of active GLP-1, thus increasing glucose-dependent insulin secretion and decreasing levels of circulating glucagon and hepatic glucose production.

Members of the Drug Class

In this section: Sitagliptin

Other: Saxagliptin

■ Sitagliptin

Brand Name

Januvia

Generic Name

Sitagliptin

Dosage Forms

Tablets

Usage

- Type 2 diabetes mellitus

Dosing

- 100 mg once daily with or without food
- Renal dosage adjustment:
 - 50 mg once daily: CrCl \geq 30 to <50 ml/minute
 - 25 mg once daily: CrCl <30 ml/minute

Adverse Reactions: Most Common

- Nasopharyngitis, nausea, diarrhea, vomiting, hypoglycemia, weight loss

Adverse Reactions: Rare/Severe/Important

- Acute pancreatitis, rash (Stevens–Johnson syndrome)

Major Drug Interactions

Sitagliptin's Effect on Other Drugs

- Digoxin: Increased levels

Counseling Points

- Discontinue immediately and promptly notify health-care practitioner if unexplained persistent nausea and vomiting occur (signs of acute pancreatitis)

Drug Class: Insulin

Introduction

The hormone insulin is endogenously released from the β cells of the pancreas. Patients with type 1 diabetes mellitus have an absolute deficiency of insulin, and patients with type 2 diabetes mellitus may also have a decreased production of endogenous insulin. Insulin is required in all type 1 diabetic patients as a lifelong treatment. Insulin is commonly used in type 2 diabetic patients as either adjunct therapy to oral antidiabetic agents or as monotherapy as the disease progresses. Various substitutions on the insulin molecule and other modifications have led to multiple types of insulins. These are characterized and administered based on their pharmacodynamic and pharmacokinetic characteristics such as onset, peak, and duration of action. Most significantly, they are classified as rapid-acting, short-acting, intermediate-acting, or long-acting types of insulin.

Mechanism of Action for the Drug Class

Insulin lowers blood glucose by stimulating peripheral glucose uptake, especially in skeletal muscle and fat, and by inhibiting hepatic glucose production.

Usage for the Drug Class

- Type 1 diabetes mellitus*, type 2 diabetes mellitus*, hyperkalemia, DKA*/diabetic coma

Dosing for the Drug Class

- Initial dose:
 - 0.5 to 1 unit/kg per day Sub-Q (high interpatient variability)
- Maintenance dose:
 - Adjust doses to achieve premeal and bedtime blood glucose levels of 80–140 mg/dl

- Renal dosage adjustment:
 - CrCl 10–50 ml/minute: Administer 75% of normal dose
 - CrCl <10 ml/minute: Administer 25–50% of normal dose; monitor closely

Adverse Reactions for the Drug Class: Most Common

- Hypoglycemia (anxiety, blurred vision, palpitations, shakiness, slurred speech, sweating), weight gain

Adverse Reactions for the Drug Class: Rare/Severe/Important

- Severe hypoglycemia (seizure/coma), edema, lipatrophy or lipohypertrophy at injection site

Major Drug Interactions for the Drug Class *Drugs Affecting Insulin (Decreased Hypoglycemic Effect)*

- Acetazolamide
- Diuretics
- Oral contraceptives
- Albuterol
- Epinephrine
- Phenothiazines
- Asparaginase
- Estrogens
- Terbutaline
- Corticosteroids
- HIV antivirals
- Thyroid hormones
- Diltiazem
- Lithium

Drugs Affecting Insulin (Increased Hypoglycemic Effect)

- Alcohol
- Fluoxetine
- Anabolic steroids
- Lithium
- β -Blockers
- Sulfonamides
- Clonidine

Contraindications for the Drug Class

- Use during severe hypoglycemia
- Allergy or sensitivity to any ingredient of the product

Counseling Points for the Drug Class

- Follow a prescribed diet and exercise regularly
- Rotate injection sites to prevent lipodystrophy
- Insulin requirements may change during times of illness, vomiting, fever, and emotional stress
- Wear diabetic identification
- Insulin stored at room temperature will be less painful to inject compared to refrigerator-stored insulin
- Mild episodes of hypoglycemia may be treated with oral glucose or carbohydrates

Members of the Drug Class

In this section: Insulin glulisine, insulin lispro, insulin NPH, Insulin (R), insulin glargine, insulin detemir, insulin aspart; various mixtures are also available

Types of Insulin

■ Insulin Glulisine

Brand Name

Apidra

Generic Name

Insulin glulisine (rapid-acting insulin)

Dosage Forms

Injection 100 units/ml (10-ml vial and 3-ml cartridge for pen use)

Dosing

- Administer Sub-Q 15 minutes before or immediately after starting a meal

■ Insulin Lispro

Brand Name

Humalog

Generic Name

Insulin lispro (rapid-acting insulin)

Dosage Forms

Injection 100 units/ml (10-ml vial and 3-ml cartridge for pen use)

Dosing

- Administer Sub-Q 15 minutes before or immediately after starting a meal

■ Insulin NPH

Brand Names

Humulin N, Novolin N

Generic Name

Insulin NPH (intermediate-acting insulin)

Dosage Forms

Injection, suspension, 100 units/ml (10-ml vial and 3-ml cartridge for pen use)

Dosing

- NPH should only be mixed with regular insulin
- Draw regular insulin into the syringe first; then add the NPH insulin to the syringe

■ Insulin Regular

Brand Names

Humulin R, Novolin R

Generic Name

Insulin regular (short-acting insulin)

Dosage Forms

Injection 100 units/ml (10-ml vial and 3-ml cartridge for pen use)

Dosing

- Administer Sub-Q 30 minutes before a meal
- Caution: A concentrated 20-ml vial containing 500 units/ml is available

■ 70% NPH and 30% Regular Insulin Mixture

Brand Names

Humulin 70/30, Novolin 70/30

Generic Name

70% NPH and 30% regular insulin mixture

Dosage Forms

Injection, suspension, 100 units/ml (10-ml vial and 3-ml cartridge for pen use)

■ 50% NPH and 50% Regular Insulin Mixture

Brand Name

Humulin 50/50

Generic Name

50% NPH and 50% regular insulin mixture

Dosage Forms

Injection, suspension, 100 units/ml (10-ml vial and 3-ml cartridge for pen use)

■ 75% Intermediate-Acting Lispro Suspension and 25% Rapidacting Lispro Solution

Brand Name

Humalog Mix 75/25

Generic Name

75% intermediate-acting lispro suspension and 25% rapid-acting lispro solution

Dosage Forms

Injection 100 units/ml (10-ml vial and 3-ml cartridge for pen use)

■ Insulin Glargine

Brand Name

Lantus

Generic Name

Insulin glargine (long-acting insulin)

Dosage Forms

Injection 100 units/ml (10-ml vial and 3-ml cartridge for pen use)

Dosing

- When changing to insulin glargine from once-daily NPH, the initial dose of insulin glargine should be the same. When changing to insulin glargine from twice-daily NPH, the initial dose of insulin glargine should be reduced by 20% and adjusted according to patient response.
- Administer once daily
- Starting dose in a type 2 diabetic patient is 10 units at bedtime and titrate according to patient response

■ Insulin Detemir

Brand Name

Levemir

Generic Name

Insulin detemir (long-acting insulin)

Dosage Forms

- Injection 100 units/ml (10-ml vial and 3-ml cartridge for pen use)

Dosing

- Indicated for once-daily or twice-daily dosing
- Once daily is dosed Sub-Q with the evening meal or at bedtime
- Twice daily is dosed every 12 hours

■ Insulin Aspart

Brand Name

NovoLog

Generic Name

Insulin aspart (rapid-acting insulin)

Dosage Forms

Injection 100 units/ml (10-ml vial and 3-ml cartridge for pen use)

Dosing

- Administer Sub-Q 15 minutes before or immediately after starting a meal

TABLE 2-1

Comparison of Insulin Products

Product	Onset, hours	Peak, hours	Duration, hours	Appearance
Rapid-Acting				
Insulin Aspart (NovoLog)	0.25	1-2	3-5	Clear
Insulin Glulisine (Apidra)	0.25	1	3-4	Clear
Insulin Lispro (Humalog)	0.25	0.5-1.5	3-4	Clear
Short-Acting				
Regular Insulin (Humulin R, Novolin R)	0.5-1	2-3	3-6	Clear
Intermediate-Acting				
NPH Insulin (Humulin N, Novolin N)	2-4	6-10	10-16	Cloudy
Long-Acting				
Insulin Detemir (Levemir)	4	N/A	12-24	Clear
Insulin Glargine (Lantus)	4	N/A	24	Clear

70% Intermediate-Acting Insulin Aspart Suspension and 30% Rapid-Acting Aspart Solution

Brand Name

NovoLog Mix 70/30

Generic Name

70% intermediate-acting insulin aspart suspension and 30% rapid-acting aspart solution

Dosage Forms

- Injection 100 units/ml (10-ml vial and 3-ml cartridge for pen use)

Comparison of Insulin Products

Refer to Table 2-1.

Drug Class: Sulfonylureas

Introduction

The sulfonylureas are used as adjuncts to diet and exercise in patients with type 2 diabetes mellitus. Although periodically used as monotherapy, sulfonylureas are more commonly used in combination with other oral antidiabetic agents in patients who do not reach glycemic goals, sometimes in the same formulation. General dosing guidelines are to start with a low dose and titrate upward according to patient response while monitoring for signs and symptoms of hypoglycemia, which is a common adverse effect. Use caution in patients with renal or hepatic impairment. HbA1c reductions are between 1% and 2%.

Mechanism of Action for the Drug Class

Lowers blood glucose by stimulating insulin release from the β cells of the pancreatic islets.

Usage for the Drug Class

- Type 2 diabetes mellitus*

Adverse Reactions for the Drug Class: Most Common

- Hypoglycemia, GI distress, dizziness

Adverse Reactions for the Drug Class: Rare/Severe/Important

- SIADH (most commonly with chlorpropamide); disulfiram-like reactions

Major Drug Interactions for the Drug Class

Drugs Affecting Sulfonylureas

- Anticoagulants, azole antifungals, gemfibrozil-enhanced hypoglycemic effects
- β -Blockers: Decreased hypoglycemic effects; also may mask signs and symptoms of hypoglycemia

Sulfonylurea Effects on Other Drugs

- Digoxin: Increased levels

Contraindications for the Drug Class

- Diabetes complicated by ketoacidosis, with or without coma
- Type 1 diabetes mellitus
- Diabetes complicated by pregnancy

Counseling Points for the Drug Class

- Monitor glucose as directed and be aware of the signs and symptoms of hypoglycemia

Members of the Drug Class

In this section: Glimepiride, glipizide, glyburide

Others: Acetohexamide, chlorpropamide, tolazamide, tolbutamide

■ Glimepiride

Brand Name

Amaryl

Generic Name

Glimepiride

Dosage Forms

Tablets

Dosing

- Initial dose:
 - 1–2 mg once daily at breakfast
- Maintenance dose:
 - 1–8 mg once daily

■ Glipizide

Brand Names

Glucotrol, Glucotrol XL

Generic Names

Glipizide, glipizide extended-release

Dosage Forms

Tablets, extended-release tablets

Dosing

- Initial dose:
 - Glucotrol: 2.5–5 mg once daily 30 minutes before breakfast
 - Glucotrol XL: 5 mg extended release once daily with breakfast
- Maintenance dose:
 - Glucotrol: 10–40 mg daily (>15 mg/day should be divided)
 - Glucotrol XL: 5–20 mg extended-release once daily

■ Glyburide

Brand Names

DiaBeta, Micronase, Glynase PresTab

Generic Name

Glyburide

Dosage Forms

Tablets

Dosing

DiaBeta and Micronase

- Initial dose:
 - 1.25–5 mg once daily with breakfast
- Maintenance dose:
 - 1.25–20 mg once daily; may give as single or divided doses

Glynase PresTab

- Initial dose:
 - 1.5–3 mg once daily with breakfast
- Maintenance dose:
 - 1.5–12 mg once daily; may give as single or divided doses

Drug Class: Thiazolidinediones

Introduction

The thiazolidinediones, pioglitazone and rosiglitazone, decrease insulin resistance by enhancing insulin-receptor sensitivity. They are used as adjuncts to diet and exercise in patients with type 2 diabetes mellitus. Although periodically used as monotherapy, thiazolidinediones are more frequently used in combination with other oral antidiabetic agents and/or insulin in patients who do not reach glycemic goals. Recent clinical data suggest that patients taking thiazolidinediones may be at an increased risk of myocardial infarction and death, and so they should be used with caution in patients with a history of previous cardiac disease. They are not recommended in patients with NYHA class III and IV heart failure. A structurally similar thiazolidinedione, troglitazone, was removed from the market due to cases of liver failure and death. It is

recommended to avoid use in patients with hepatic dysfunction. HbA1c reductions are between 1% and 1.5%.

Mechanism of Action for the Drug Class

Increase insulin sensitivity by affecting the peroxisome proliferator-activated receptor γ (PPAR γ). Acting as an agonist to these receptors, they decrease insulin resistance in adipose tissue, skeletal muscle, and the liver.

Usage for the Drug Class

- Type 2 diabetes mellitus*

Adverse Reactions for the Drug Class: Most Common

- Weight gain, edema, hypoglycemia (when used with insulin or other oral antidiabetic drugs that may cause hypoglycemia)

Adverse Reactions for the Drug Class: Rare/Severe/Important

- Hepatic failure, heart failure, anemia, ovulation in anovulatory premenopausal women, bone loss

Major Drug Interactions for the Drug Class

Drug Affecting Thiazolidinediones

- Gemfibrozil: Increased levels
- Rifampin: Decreased levels

Thiazolidinedione Effects on Other Drugs

- Oral contraceptives: Decreased efficacy

Contraindications for the Drug Class

- Patients with NYHA class III and IV heart failure
- Active liver disease (alanine aminotransferase [ALT] >2.5 times the upper limit of normal)
- Concurrent insulin or nitrate use with rosiglitazone

Counseling Points for the Drug Class

- Report signs and symptoms of liver dysfunction and/or shortness of breath immediately

Members of the Drug Class

In this section: Pioglitazone, rosiglitazone

■ Pioglitazone

Brand Name

Actos

Generic Name

Pioglitazone

Dosage Forms

Tablets

Dosing

- Initial dose:
 - 15–30 mg once daily without regard to meals
- Maintenance dose:
 - 15–45 mg once daily

■ Rosiglitazone

Brand Name

Avandia

Generic Name

Rosiglitazone

Dosage Forms

Tablets

Dosing

- Initial dose:
 - 4 mg once daily as a single or divided dose
- Maintenance dose:
 - 4–8 mg once daily

Review Questions

- Which oral antidiabetic drug works primarily in the pancreas to increase the secretion of insulin?
 - Avandia
 - Glucophage
 - Micronase
 - Actos
- What is the correct dose of sitagliptin in a patient with type 2 diabetes and moderate renal dysfunction (CrCl ~40 ml/minute)?
 - 100 mg once daily
 - 50 mg once daily
 - 25 mg once daily
 - Not recommended in patients with moderate renal dysfunction
- Which of the following insulins should be administered 15 minutes prior to a meal?
 - Insulin NPH
 - Insulin glargine
 - Insulin detemir
 - Insulin aspart
- Which antidiabetic medication has the potential to cause the rare but serious side effect of lactic acidosis?
 - Metformin
 - Rosiglitazone
 - Glyburide
 - Sitagliptin
- Which of the following is a contraindication to the use of Glucophage?
 - Osteoporosis
 - Obesity
 - Hyperkalemia
 - Renal disease
- Which diabetes medication is contraindicated in patients with NYHA III or IV heart failure?
 - Sitagliptin
 - Rosiglitazone
 - Glimepiride
 - Insulin lispro

7. Which class of drugs is indicated for both type 1 and type 2 diabetes mellitus?
 - A. Biguanide
 - B. Sulfonylurea
 - C. Insulin
 - D. Thiazolidinedione
8. What is the maximum daily dose of Actos?
 - A. 8 mg once daily
 - B. 12 mg daily
 - C. 45 mg once daily
 - D. 2550 mg daily
9. What is the average HbA1c reduction expected with sitagliptin?
 - A. 0.7–1%
 - B. 1–1.5%
 - C. 1–2%
 - D. 1.5–2%
10. What is the only insulin suspension (cloudy) that is on the market?
 - A. Insulin glulisine
 - B. Insulin regular
 - C. Insulin NPH
 - D. Insulin glargine
11. Which oral antidiabetic medication should you temporarily withhold in patients undergoing radiologic procedures involving the parenteral administration of iodinated contrast media?
 - A. Pioglitazone
 - B. Glyburide
 - C. Sitagliptin
 - D. Metformin
12. Which antidiabetic medication has the potential to cause acute pancreatitis?
 - A. Glucophage
 - B. Januvia
 - C. Levemir
 - D. Amaryl
13. Which medication is available by the brand names DiaBeta, Glynase, and Micronase?
 - A. Glimepiride
 - B. Glipizide
 - C. Glyburide
 - D. Metformin
14. Which of the following is used to treat diabetic ketoacidosis?
 - A. Metformin
 - B. Insulin
 - C. Glipizide
 - D. Rosiglitazone
15. Which medication works to increase insulin sensitivity by affecting the peroxisome proliferator-activated receptor γ (PPAR γ)?
 - A. Insulin lispro
 - B. Metformin
 - C. Pioglitazone
 - D. Sitagliptin