

Oral and Injectable Medication Options for Diabetes Treatment

Presented by:
Dr. Daphne E. Smith, Pharm.D., CDE
Clinical Assistant Professor/Clinical Pharmacist-University of Illinois at Chicago College of Pharmacy

Learning Objectives

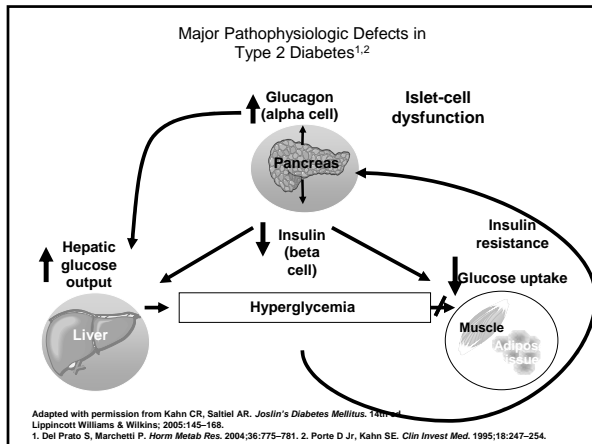
- Identify the various classifications of oral and injectable medication currently used in the treatment of diabetes mellitus
- Describe the mechanism of action, pharmacokinetics, dosing, adverse effects and drug interactions of each class of diabetes medications

Pathophysiology

Diabetes Mellitus:

Metabolic disorder characterized by hyperglycemia

- Impaired pancreatic insulin secretion
- Increased hepatic glucose production
- Decreased peripheral glucose uptake



- ### Diabetes Treatment
- Meal planning
 - Physical Activity
 - Self Monitoring of Blood Glucose
 - Education
 - Oral Medications
 - Insulin
 - Other injectable medications

- ### Oral medications for diabetes treatment
- Insulin secretagogues
 - Action on pancreatic beta cells
 - Insulin sensitizers
 - Improve target cell response to the liver and peripheral tissues
 - Alpha-glucosidase inhibitors
 - Slow digestion of carbohydrates
 - DPP-4 inhibitors
 - Enhance incretin system

Insulin Secretagogues

Sulfonylureas

Mechanism of Action (MOA): Stimulate insulin secretion from pancreatic beta cells, reduces glucose output from liver, improves insulin sensitivity in periphery

Second Generation Sulfonylureas

- Glyburide (Micronase, Diabeta)
- Glyburide Micronized (Glynase PresTab)
- Glipizide (Glucotrol, Glucotrol XL)
- Glimepiride (Amaryl)

Sulfonylureas

- | | |
|---|---|
| <ul style="list-style-type: none">■ Kinetics• Onset: <60 minutes• Peak: 2-4 hours• Duration: 12-24 hrs. | <ul style="list-style-type: none">■ Adverse effects➢ Hypoglycemia➢ Photosensitivity➢ Dizziness➢ Thrombocytopenia➢ Gastrointestinal Disturbances➢ Allergic skin reactions➢ Disulfiram-type reaction |
|---|---|

Sulfonylureas

Drug Interactions

Increased Hypoglycemia

- Anticoagulants
- Salicylates
- Sulfonamides
- MAO Inhibitors
- Tricyclic antidepressants
- Azole antifungals

Drug Interactions

Decreased Action

- Beta Blockers, Diuretics, Ca²⁺ Blockers
- Corticosteroids, Estrogens, Thyroid Hormones
- Sympathomimetics, Phenothiazines
- Isoniazid, Phenytoin, Nicotinic Acid

Sulfonylureas

Precautions

Caution in elderly
Severe allergy to sulfonamides

Administration

Once daily-Twice daily dosing

Insulin Secretagogues

Meglitinides

MOA: Stimulate insulin release from
pancreas

Products:

Repaglinide (Prandin)

Nateglinide (Starlix)

Meglitinides

- | | |
|----------------------|-------------------------------|
| ■ Kinetics | □ Adverse effects |
| • Onset: <30 minutes | ➢ Hypoglycemia (Repaglinide) |
| • Duration: 2-3 hrs | ➢ Headache |
| | ➢ Upper respiratory infection |
| Dosing: With meals | ➢ Dizziness |
| | ➢ Diarrhea |

Meglitinides- Drug Interactions (CYP3A4, CYP2C9)

- Increased effect
 - Azole Antifungals
 - NSAIDs, Salicylates
 - Sulfonamides
 - Thyroid Hormones
 - Oral Contraceptives
- Decreased effect
 - Rifampin
 - Barbiturates
 - Carbamazepine

Insulin Sensitizers

Biguanide-Drug of choice for Type 2 diabetes

MOA:

- Decreases hepatic glucose production
- Decreases intestinal absorption of glucose
- Increases peripheral glucose uptake and utilization

Biguanide

Products:

Metformin (Glucophage, Glucophage XR, Riomet)

Kinetics:

Half-life:4-6 hrs

Duration: 6-24 hours

Excreted unchanged in urine

Dosage: Once daily-
Three times daily

Adverse effects:

- Diarrhea
- Nausea, vomiting
- Heartburn
- Flatulence, Abdominal bloating
- Metallic taste
- Anorexia

Biguanide

Drug Interactions: (Increased effects)

- Cationic drugs (e.g. Digoxin, Amiloride, Morphine, Procainamide, Quinidine)
- Cimetidine
- Iodinated Contrast Material
- Alcohol
- Nifedipine

Biguanide

Contraindications:

- Renal disease (Cr >1.5 mg/dl Men, >1.4 mg/dl Women)
- CHF requiring pharmacologic treatment
- Radiologic studies involving use of iodinated material
- Acute or chronic metabolic acidosis

Insulin Sensitizers

Thiazolidinediones

MOA:

- Improve insulin sensitivity
- Enhance glucose uptake in muscle and adipose tissue
- Inhibit gluconeogenesis
- Delayed onset of action (up to 12 weeks)
- Metabolized to active and inactive metabolites

Products:

Rosiglitazone (Avandia)
Pioglitazone (Actos)

Thiazolidinediones

Precautions:

CARDIAC: Black box warning for increase in myocardial ischemic events

Hepatotoxicity:

- Monitor LFTs at start of therapy
- Monitor LFTs periodically thereafter
- Do not initiate if ALT >2.5x ULN

Adverse effects: Edema, weight gain, change in lipids, upper respiratory infection

Dosing:

- Pioglitazone: Once daily
- Rosiglitazone: Once or twice daily

Drug Interactions

Increased effect: gemfibrozil, ritonavir

TZDs may increase effect of: amiodarone, amphetamines, SSRIs, certain beta blockers

Decreased effect:

Carbamazepine, phenobarbital, phenytoin, rifampin

Alpha-Glucosidase Inhibitors

MOA:

- ❑ Delay absorption of carbohydrates
- ❑ Inhibit metabolism of sucrose to glucose and fructose

Products:

Acarbose (Precose)
Miglitol (Glyset)

Kinetics:

Onset: Immediate

Half-life: 2 hours

Duration: up to 6 hours
(Acarbose)

Metabolism

Acarbose: GI tract

Miglitol: Not metabolized

Alpha-Glucosidase Inhibitors

Side Effects:

Flatulence
Abdominal pain
Diarrhea

Lab disturbance:

Elevated AST, ALT
(Acarbose)

Drug Interactions

Decreased effect:
Digestive enzymes
Intestinal absorbents

May decrease Digoxin,
Glyburide,
Propranolol and
Ranitidine
concentrations

Alpha-Glucosidase Inhibitors

Contraindications

- Inflammatory Bowel Disease
- Colonic Ulceration
- Intestinal Obstruction
- Chronic Intestinal Diseases

Monitoring: LFTs every 3 months (Acarbose)

Dosing: Three times daily with first bite of each meal

DPP-4 Inhibitors

- New drug class affecting Dipeptidyl peptidase (DPP-4)
- Sitagliptin (Januvia)
- Enhances the incretin system
- Increases insulin release, reduces glucagon
- Dosed once daily
- Available in combination with metformin (Janumet)
- Drug interaction: May increase concentration of digoxin
- Adverse effects
 - Headache
 - Upper respiratory infection
 - Nasopharyngitis

Combination Products

- Glyburide/Metformin (Glucovance)
- Glipizide/Metformin (Metaglip)
- Rosiglitazone/Metformin (Avandamet)
- Pioglitazone/Metformin (Actoplus Met)
- Rosiglitazone/Glimepiride (Avandaryl)
- Pioglitazone/Glimepiride (Duetact)

Insulin

Insulin

- Very Rapid Acting
- Rapid/Short Acting
- Intermediate Acting
- Long Acting

Insulin

- **Very Rapid Acting (Analog)**
 - Differ from human insulin by 1 amino acid in B-chain
 - Insulin Aspart (Novolog)
 - Insulin Lispro (Humalog)
 - Insulin Glulisine (Apidra)
 - Onset: <15 minutes
 - Peak: 40 min-1.5 hours
 - Duration: 3-5 hours
 - Clear appearance

Insulin

Rapid/Short Acting

- Regular
 - Onset: 0.5-1 hr
 - Peak: 2-3 hours
 - Duration: 3-8 hours
 - Available 100 units/ml, 500 units/ml

Intermediate Acting

- NPH (Isophane Insulin Suspension)
 - Onset: 2-4 hrs, Peak: 4-10 hrs, Duration: 10-18 hrs
 - Cloudy appearance

Insulin-Long Acting

- Insulin Glargine (Lantus)
 - Onset: 2-4 hrs
 - No pronounced peak
 - Duration: 24 hrs
 - Clear acidic solution

- Insulin Detemir (Levemir)
 - Onset: 3-4 hrs
 - Peak: 6-8 hrs
 - Duration: dose dependent 6-23 hrs
 - Clear solution

Insulin Mixtures

- 70% NPH/ 30% Regular (*Humulin 70/30, Novolin 70/30*)
- 75% Lispro protamine/ 25% Lispro (*Humalog 75/25 insulin*)
- 70% Aspart protamine/ 30% Aspart (*Novolog 70/30 insulin*)
- 50% NPH/ 50% Regular (*Humulin 50/50 insulin*)
- 50% Lispro protamine/50% Lispro (*Humalog 50/50 insulin*)

New Injectable Products

- Exenatide (Byetta)
 - Incretin system
 - Increases insulin secretion
 - Slows gastric emptying
 - Increases beta cell growth
- Twice a day injection within 1 hour of meals
- Indicated for Type 2 Diabetes
- Available as prefilled pen for 5 mcg or 10 mcg dose
- Adverse Effects
 - Hypoglycemia
 - Nausea, vomiting, diarrhea
 - Dysgeusia-impaired taste
- May affect extent of absorption of oral medications
- Oral medications should taken 1 hour before injection

New Injectable Products

- Pramlintide (Symlin)
 - Amylin analog
 - Prolongs gastric emptying time
 - Reduces postprandial glucagon secretion
 - Reduces caloric intake through centrally mediated appetite suppression
- Injection administered three times a day with meals
- Dose in mcg (given in insulin syringe)
- Indicated for **type 1** diabetes **and** type 2 diabetes on insulin therapy
- Adverse effects
 - Nausea, vomiting, anorexia
 - Hypoglycemia

Pramlintide dosing

- Type 1**
 - Initial dose: 15 mcg (2.5 units) before each meal
 - Target dose: 30-60 mcg before each meal
- Type 2**
 - Initial dose: 60 mcg (10 units) before each meal
 - May increase to 120 mcg

Insulin dose is reduced by 50% to avoid hypoglycemia when initiating pramlintide

Pramlintide may delay absorption of other medications

Initiating treatment

- Type and duration of diabetes
- Current blood glucose and A1c measurement
- Concurrent disease state
- Cost/Insurance formulary
- Allergies or past intolerances of medication
- Barriers to adherence

Monitoring

- Blood glucose, A1c
- Blood pressure and lipids
- Electrolytes
- Renal and liver function
- Signs/symptoms of complications
- Adverse effects of medication
- Adherence
