overview of pharmacologic agents used in the management of DIABETES

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OBJECTIVES

1. List the different classes of diabetes medications, including the newer sodium-glucose co-transporter 2 inhibitors.
2. Describe the basic mechanism of action for each medication class.
3. Discuss potential adverse effects and safety concerns with the different agents.

Overview

• Oral Agents
  – Biguanides
  – Sulfonylureas
  – Meglitinides
  – TZDs
  – DPP-4 inhibitors
  – SGLT-2 inhibitors
  – α-glucosidase inhibitors
  – Misc.

• Injectable Agents
  – GLP-1 agonists
  – Insulin
    • Rapid
    • Regular
    • Intermediate
    • Long acting
    • Concentrated
Diabetes Overview

- **Type I**
  - Insulin dependent as the pancreas does not produce insulin normally

- **Type II**
  - Progressive disease over time
  - Involves "insulin resistance"
  - Pancreas typically produces insulin at first, but may decrease over time and patients may become dependent on insulin

ORAL AGENTS

Biguanides

- Metformin (Glucophage®)
- Metformin ER (Glucophage XR®, Fortimel®, Glumetza®)

- Mechanism of Action:
  - Decrease hepatic release of glucose
  - Increase sensitivity to insulin action in fat & muscle tissues
Biguanides

• Other effects/concerns:
  - Not recommended for use in renal failure or in combination with nephrotoxic agents (contrast dyes) due to potential for lactic acidosis
  - Typically held for 48 hours after procedure
  - Does not cause hypoglycemia on its own
  - Diarrhea/nausea common adverse effects

Sulfonylureas

Glipizide (Glucotrol®)
Glimepiride (Amaryl®)
Glyburide (Diabeta®)

• Mechanism of Action:
  - Stimulate insulin secretion from pancreatic β-cells

Sulfonylureas

• Adverse effects/concerns:
  - Weight gain (average 2.31kg)
  - Hypoglycemia is primary adverse effect of concern as insulin is being secreted
  - Typically well tolerated by patients with a “sulfa” allergy, as the structure does not contain a true sulfonamide component
### Meglitinides

**Repaglinide (Prandin®)**  
**Nateglinide (Starlix®)**

- **Mechanism of Action:**  
  - Similar to sulfonylureas, stimulate insulin secretion in the pancreatic β-cells  
  - Very short acting

- **Major adverse effect is hypoglycemia**

### Thiazolidinediones (TZDs)

**Rosiglitazone (Avandia®)**  
**Pioglitazone (Actos®)**

- **Mechanism of Action:**  
  - Increase tissue sensitivity to insulin  
  - Stimulates transcription of genes that transport glucose into muscle & fat  
  - Increase storage of free fatty acids, decrease breakdown of fatty acids

### Thiazolidinediones (TZDs)

- **TZD safety concerns and adverse effects:**  
  - Rosiglitazone (Avandia®) only available through REMS program due to potential for increased heart attack risk  
  - TZDs are contraindicated in patients with heart failure  
  - Potential for hepatotoxicity (other members of this class withdrawn from the market – troglitizone)
Thiazolidinediones (TZDs)

- TZD safety concerns and adverse effects (continued):
  - Weight gain
  - Increased risk of fractures in women
  - Potential increased risk of bladder cancer (higher in men) that may be related to duration of therapy

DPP-4 Inhibitors

- Sitagliptin (Januvia®)
- Linagliptin (Tradjenta®)
- Alogliptin (Nesina®)
- Saxagliptin (Onglyza®)

- Mechanism of Action:
  - Inhibits the breakdown of GLP-1, a naturally occurring hormone which stimulates insulin secretion only when glucose is present and inhibits glucagon

DPP-4 Inhibitors

- Other effects/concerns:
  - Weight neutral to slight weight loss
  - Some patients have decreases in blood pressure
  - Don’t see the GI adverse effects as with GLP-1 agonists
SGLT-2 Inhibitors

Canagliflozin (Invokana®)
Dapagliflozin (Farxiga*)

- **Mechanism of Action:**
  - Inhibit the sodium glucose co-transporter in the kidney to decrease blood sugar by excreting sugar in the urine

- **Other effects/concerns:**
  - Low hypoglycemia risk
  - Slight decrease in body weight
  - Increased genitourinary tract infections

α-glucosidase Inhibitors

Acarbose (Precose®)
Miglitol (Glyset®)

- **Mechanism of Action:**
  - Inhibit action of α-glucosidase enzymes that break down complex carbohydrates, resulting in decreased intestinal absorption

- **Adverse Effects:**
  - Bloating, gas, other GI symptoms
Bile Acid Sequestrants

Cholesevelam (WelChol®)

• Mechanism of Action:
  – Mostly unknown

• Other effects/concerns:
  – GI disturbances
  – Decreased absorption of vitamins A, D, E, & K
  – Many drug interactions, must separate from drugs such as warfarin, phenytoin, levothyroxine, and more

Dopamine Agonist

Bromocryptine (Cylcoset®)

• Mechanism of Action:
  – Stimulates dopamine receptors, which is thought to have a role in insulin resistance

• Other effects/concerns:
  – Nausea, dizziness/hypotension
  – Not for use in nursing women due to increased stroke risk

Amylin Analogue

Pramlintide (Symlin®)

• Mechanism of Action:
  – Synthetic version of the naturally occurring hormone; works by slowing gastric emptying, decreasing caloric intake
  – Used in combination with insulin for Type I or II DM

• Other effects/concerns:
  – Nausea
  – Not for use in patients with gastroparesis
INJECTABLE AGENTS

GLP-1 Agonists

Exenatide (Byetta®)
Exenatide ER (Bydureon®)
Liraglutide (Victoza®)

• Mechanism of Action:
  – Mimics action of naturally occurring GI hormones
  – Helps restore normal insulin secretion after food intake

• Other effects/concerns:
  – Usually associated with weight loss of 2-4 kg
  – 30-60% of patients have GI adverse effects
  – No causal relationship found for pancreatitis
  – May slow down GI tract & should not be used in patients with gastroparesis
Insulin

- Available in short, intermediate, and long acting formulations
- Major concern is hypoglycemia
  - High risk medication!

Short Acting Insulin

- Aspart (Novalog®)
- Glulisine (Apidra®)
- Lispro (Humalog®)
- Regular (Humulin R®/Novolin R®)

- Fastest onset (10-30 minutes) and shortest duration, dosed with meals
- Also used in IV infusions

Concentrated Regular Insulin

U-500

- Allows decreased volume for extremely insulin resistant patients requiring large doses of insulin (>200 units per dose)
- Has longer duration of action than standard concentrations; timing more similar to NPH
- Huge safety concern → use extra caution!
  - Should always be prescribed in exact units
  - Patients need to be aware of syringe amounts
NPH Insulin
Isophane (Humulin N®/Novolin N®)
• Intermediate onset and duration, can be used as lower cost alternative to long acting insulins
• Cloudy appearance
  – Patients are to gently roll insulin to mix prior to use
  – If mixing with short acting insulin, patient should draw up short acting (clear) insulin first to avoid contamination

Mixed Insulin
Humalog 75/25, 50/50
Novolog 70/30
• Pre-mixed insulin combining short acting and intermediate acting insulins
  – Typically dosed twice daily with meals

Long Acting Insulin
Detemir (Levemir®)
Glargine (Lantus®)
• Long acting insulins provide a “baseline” level of insulin throughout the day
• May be dosed once or twice daily
• Don’t have to be timed around meals
Use in Type I Diabetes

- Insulin is the cornerstone of therapy
  - Pancreas does not produce sufficient insulin

- Other agents (metformin, pramlintide, etc.) may be used to improve efficacy, but there are no substitutes for insulin!

Use in Type II Diabetes

- Metformin is the cornerstone of therapy
  - Good efficacy and safety profile

- Other agents added depending on patient specific factors
  - Fasting vs post-prandial high blood sugars
  - Co-morbidities (i.e. heart failure)
  - Cost

- Can use pretty much any combination

SUMMARY

1. There are a number of different classes of diabetes medications, with both oral and injectable agents available.

2. Various mechanisms for each class of medication allow providers to choose agents best suited to each individual patient.

3. It is important to be aware of safety concerns associated with diabetes medications.

REFERENCES