BIGUANIDES

FLAME LECTURE: 3

MOHIUDDIN. 8.22.18

LEARNING OBJECTIVES

- To describe the mechanism of action of Metformin
- To counsel the patient regarding the benefits, risks, and uses for Metformin
- Prerequisites:
  - NONE
- See also – for closely related topics
  - FLAMEs on Type 2 DM / Medications for treatment of DM

OVERVIEW

- Biguanides are oral agents used in the management of Type 2 DM
  - Metformin (Glucophage) is currently the only agent in this antidiabetic class available in this country
- **First-line monotherapy**
- Proven to **reduce mortality rates** in patients with Type 2 DM

MECHANISM OF ACTION

- Major effect is to decrease hepatic glucose output by **inhibiting gluconeogenesis**
  - Inhibits enzyme (glycerophosphate dehydrogenase) which is an enzyme in the gluconeogenic pathway
- Metformin **increases insulin sensitivity**
  - Increases insulin-mediated glucose utilization in peripheral tissues (such as muscle and liver), especially after meals
- Anti-lipolytic effect that lowers serum free fatty acid concentrations (which also serves to further decrease substrate availability for gluconeogenesis)

INDICATIONS & BENEFITS

- Target diabetic population
  - Overweight/obese
  - Insulin resistant
- Favorable cost
- Generally tolerable - relatively mild side effect profile
- Hypoglycemia is rare
  - Because Metformin does not affect insulin secretion, it is not associated with hypoglycemia when used as a monotherapy
- Promotes weight loss
  - Metformin is unique among oral hypoglycemic therapy because is does NOT cause weight gain, but may even cause weight loss in some overweight patients

ADVERSE EFFECTS

- Most common = **GI side effects**
  - Metallic taste, GI discomfort, Nausea/diarrhea
  - Most of these S/E's are transient and commonly seen only when starting treatment
  - Taking Metformin with meals can also lessen the severity of GI side-effects
- **B12 deficiency**
  - Metformin reduces the absorption of B12 in the ileum
- **Lactic acidosis** is a rare but serious potential adverse effect
  - Usually only seen in patients with underlying renal disease
  - Due to inhibition of gluconeogenesis, NADH builds up in the cytosol leading to decreased conversion of lactate to pyruvate, which when paired with renal disease can precipitate lactic acidosis

CONTRAINDICATIONS

- Metformin is contraindicated in patients with factors predisposing to lactic acidosis
  - **Impaired renal function**
    - Strict C/I with GFR < 30 mL/min
    - Evaluate in patients with GFR 30-45 mL/min
  - Active or progressive **liver disease**
  - Active alcohol abuse
  - Unstable or acute heart failure
- **Hold prior to surgery or contrast**
  - Serum creatinine should be assessed 2-3 days following contrast administration

REFERENCES

1. Metformin in the Treatment of Adults with Type 2 Diabetes Mellitus (https://www.uptodate.com/contents/metformin-in-the-treatment-of-adults-with-type-2-diabetes-mellitus)
2. Oral Agents in the Management of Type 2 DM (https://www.aafp.org/afp/2001/0501/p1747.pdf)
3. Management of Blood Glucose in Type 2 DM (https://www.aafp.org/afp/2009/0101/p29.html)