Glibenclamide: Uses,Dosage, Mechanism of action and side effects

Glibenclamide is a second-generation sulphonylurea that is used either as monotherapy or in combination with biguanides in the management of diabetes Mellitus type 2.

Class: Second-generation sulfonylurea
Indication: Type 2 Diabetes Mellitus (T2DM) – monotherapy or in combination with metformin (a biguanide)

Mechanism of Action

Glibenclamide acts primarily by stimulating insulin secretion from pancreatic **?-cells** . Its effects are mediated through the **inhibition of ATP-sensitive potassium channels** on ?-cell membranes:

1. **Binding to Sulfonylurea Receptors (SUR1):**
   Glibenclamide binds to SUR1 subunits on **ATP-sensitive potassium channels**, causing them to close.
2. **Membrane Depolarization:**
   Closure of **ATP-sensitive potassium channels** leads to cell membrane depolarization.
3. **Calcium Influx:**
   Depolarization opens **voltage-gated calcium channels** , allowing calcium influx.
4. **Insulin Secretion:**
   Increased intracellular calcium stimulates exocytosis of insulin-containing granules.

Important Note:
The drug requires **functioning ?-cells** . It increases their glucose sensitivity and enhances insulin secretion in response to glucose. Over time, insulin levels may normalize, but improved **peripheral insulin sensitivity** and **reduced hepatic glucose output** maintain the hypoglycemic effect.

Pharmacokinetics

- **Absorption:** Rapid from the gastrointestinal tract; peak plasma concentration in 2–4 hours.
- **Protein Binding:** ~99% bound to plasma proteins.
- **Metabolism:** Hepatic – converted to weakly active metabolites.
- **Excretion:** Metabolites excreted via **bile and urine** (~50% each).
- **Half-life (t_{1/2}):** ~4–8 hours (inter-individual variability).
- **Renal Impairment:** Accumulation of metabolites increases hypoglycemia risk.

Note: Absorption may be slower in hyperglycemic states and varies with formulation particle size.

Therapeutic Use

Indication:

- Management of **Type 2 Diabetes Mellitus** in patients unresponsive to dietary and lifestyle modifications.

Dosage and Administration

- **Initial dose:** 2.5–5 mg orally once daily (with breakfast)
- **Adjustment:** Titrate by 2.5 mg increments weekly based on blood glucose
- **Maintenance dose:** Up to 15 mg daily
- **Maximum dose:** 20 mg daily (in divided doses if >10 mg/day)

Contraindications

- Type 1 Diabetes Mellitus
- Diabetic ketoacidosis
- Severe infection, trauma, or surgery requiring insulin
- Pregnancy (insulin preferred)
- **Hepatic or renal impairment** due to increased risk of hypoglycemia

Precautions

Use cautiously in:

- Elderly
- Malnourished or debilitated patients
- Those with **adrenal or pituitary insufficiency**
- Patients on multiple hypoglycemia-enhancing drugs

Adverse Effects

Common:

- GI disturbances (nausea, vomiting, diarrhea, anorexia, metallic taste)
- Hypoglycemia (mild to severe/prolonged; dose-dependent)

Serious:

- **Hepatic:** Hepatitis, cholestatic jaundice
- **Hematologic:** Agranulocytosis, aplastic anemia, leukopenia, thrombocytopenia, hemolytic anemia
- **Dermatologic:** Stevens-Johnson Syndrome, exfoliative dermatitis, erythema multiforme/nodosum

Drug Interactions

Increased Hypoglycemic Risk with:

- **ACE inhibitors** , **alcohol** , **salicylates** , **NSAIDs** (e.g., azapropazone, phenylbutazone)
- **Antifungals** (ketoconazole, fluconazole, miconazole)
- **Chloramphenicol** , **cimetidine** , **fluoroquinolones**
- **Sulfonamides** (including co-trimoxazole)
- **MAOIs** , **tetracyclines** , **tricyclic antidepressants**
- **Beta-blockers** (may also mask symptoms of hypoglycemia)
- **Octreotide** (can cause either hypo- or hyperglycemia)

Use in Pregnancy and Lactation

- **Pregnancy:** Generally **not recommended** ; insulin is preferred due to better glycemic control and safety.
- **Breastfeeding:** May be used with caution; low transfer into breast milk reported.

Clinical Pearls

- Glibenclamide has a **longer half-life** than some other sulfonylureas, increasing the risk of **prolonged hypoglycemia** .
- **Not suitable for elderly or renally impaired patients.**
- Always **start low and go slow** to minimize hypoglycemia risk.
- Monitor **renal and hepatic function** before and during treatment.