Metformin; Uses, Mechanism of action, Dosage, Side effects and Interactions

Metformin hydrochloride is an oral antidiabetic drug that belongs to a class of biguanides. This agent is given orally in the management of type 2 diabetes mellitus.
Metformin does not stimulate insulin release and requires some insulin to be present in order to exert its antidiabetic effect.

Brand Name: Glucophage, Glucophage XR, Fortamet, Glumetza, Riomet.

Indications /Uses of Metformin

Metformin is usually the first line therapy in the management of type 2 diabetes mellitus.

Metformin is used as a monotherapy in the management of type 2 diabetes mellitus as an adjunt to diet, exercise and lifestyle changes such as weight loss to improve glycemic (blood sugar) control in adults with type 2 diabetes. .

It is uses in obese patients with type II diabetes (with insulin resistance).

It may be used in combination with sulphonylureas, thiazolidinediones and insulin to improve glycemic control in adults with whom oral monotherapy is inadequate

Advantages:

Its use is not associated with any risk of hyperinsulinemia or hypoglycemia or weight gain (anorexia).

Because metformin is an insulin-sparing drug (insulin sensitizer), its use does not increase body weight nor provoke hypoglycemia,

Mechanism of action

The possible mechanisms of action of metformin is by reduction of hepatic glucose production through activation of the enzyme AMP-activated protein kinase (AMPK).

It also works by delaying absorption of glucose from the gastrointestinal tract, increasing insulin sensitivity and glucose uptake into the cells and tissues (tissue glycolysis), increasing glucose to lactate conversion by enterocytes, inhibiting in hepatic gluconeogenesis, and reduction of plasma glucagon levels.

Metformin does not require functioning B cells nor does it stimulate insulin release.

It also reduces low density lipoproteind (LDL) and very low density lipoproteins (VLDL) and increased high density lipoproteins (HDL).

Metformin does not produce hypoglycemia in either of the normal subjects or patients with type 2 diabetes mellitus, due to this reason, metformin and other biguanides are more appropriately termed “euglycemic” agents.

It does not lead to hyperinsulinemia.

Metformin like other biguanides does not depend on functioning pancreatic beta cells.

Individuals with type 2 diabetes mellitus have considerably less fasting hyperglycemia as well as lower postprandial hyperglycemia after administration of biguanides;

Pharmacokinetics

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract, the absolute bioavailability of a single 500 mg dose is about 50-60% although this is reduced somewhat if taken with food.

Following absorption, ,Metformin is not bound to plasma proteins, is not metabolized therefore it is excreted unchanged by the kidneys to urine as the active compound.

Metformin has a half-life of 1.5–3 hours

The plasma elimination half life ranges from 2-6 hours after oral administration

Due to metformin’s blockade of gluconeogenesis, its use may impair the hepatic metabolism of lactic acid. In patients who have a renal insufficiency, metformin may accumulate in the body and eventually increase the risk of lactic acidosis.

Dosage and administration

Children 10 years and over and adolescents

The usuall starting dose is 500-850 mg once daily. the maximum dose is 2000 mg taken as 2-3 divided doses with the lowest effective dose being recommended.

Treatment of choldren between 10-12 years of age is only recommended on specific advice from a physician and its use for this age group is limited.

Adults

The usual starting dose is 500 mg 2-3 times a day daily or 850 mg 1-2 times a day. the maximum dose is 2-3 grams taken in divided doses with the lowest effective dose being recommended.

Administration

Metformin can be initiated as a once-daily dose (OD) at bedtime or before a meal depending on whether the primary abnormality is fasting hyperglycemia or postprandial hyperglycemia,

For fasting hyperglycemia, a single 500-mg tablet at bedtime for a week or more is recommended. If hyperglycemia persists and no associated gastrointestinal comfort then, a second 500-mg tablet may be added with the evening meal.

If further dose increases are required, an additional 500-mg tablet can be added and taken with breakfast or the midday meal. Alternatively an 850-mg tablet can be taken twice daily or even three times daily if required.

Metformin should be taken in divided because an ingestion of more than 1000 mg at any one time may provoke a significant gastrointestinal adverse effects.

Dosage Modifications

Hepatic (liver) impairment: Avoid use; risk of lactic acidosis.

Renal (kidney) impairment

- Obtain eGFR before starting metformin
- eGFR less than 30 mL/min/1.73 m^2: Contraindicated
- eGFR 30-45 mL/min/1.73 m^2: Not recommended to initiate treatment
- Monitor eGFR at least annually or more often for those at risk for renal impairment (e.g., elderly)
- If eGFR falls below 45mL/min/1.73 m^2 while taking metformin, health risks and benefits of continuing therapy should be evaluated
- If eGFR falls below 30 mL/min/1.73 m^2: while taking metformin, discontinue the drug

Polycystic Ovary Syndrome (Orphan)

Orphan designation for treatment of pediatric polycystic ovary syndrome

Contraindications

Metformin use is contraindicated in;

- Patients with renal disease or renal dysfunction
- Patients with known hylersensitivity to metformin
- Acute or chronic metabolic acidosis with or without coma
- Patients with liver disease
- Alcoholism or
- Conditions predisposing a person to tissue anoxia such as chronic cardiopulonary dysfunction

Remember that diabetic ketoacidosis should only be treated with insulin.

Side effects of metformin

The common side effects associated with metformin use are gatrointestinal adverse effects such as anorexia, nausea, vomitting, and diarrhea and abdominal discomfort that usually occur at the

onset of therapy, and are often transient.

Patients may experience metallic taste and there may be some weight loss

Absorption of some substances such as vitamin B12 may be impaired during long-term metformin therapy, therefore an annual screening of serum vitamin B12 levels and RBC parameters is recommended to determine the need for vitamin B12 supplementation injections

Lactic acidosis, sometimes fatal may occur in presence of hypoxia and renal insufficiency.

Precautions

Biguanides are innapropriate for patients with diabetic coma and ketoacidosis or for those with severe infection, trauma or other severe condition where a biguanide in unlikely to control the hyperglycemia. insulin should be administered in such situations.

Metformin should not be administered to patients with heart faulure, recent myocardial infarction, dehydration, alcoholism or any other condition that is likely to predispose to lactic acidosis.

Overdosage

Acute poisoning or development of lactic acidosis calls for intesnive supportive therapy.

Interactions

The se of metformin with other drugs that lower blood glucose concentration increases the risk of hypoglycemia while drugs that increase blood glucose levels may reduce the effectiveness of metformin.

One needs close lood glucose levele monitoring when using metformin and;

- Diuretics
- Beta 2 agonisnts such as salbutamol or tebutaline
- Corticosteroids
- Contrast media (iodinated)

Alcohol may increase the risk of developing lactic acidosis as well as hypoglycemia.

Care should also be taken when administerig metformin together with drugs that may impaire normal renal function

Pregnancy and lactation

Metformin is not recommended for use in lactating or breastfeeding mothers.