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A REVIEW ON CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE OF METFORMIN

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ABSTRACT

Metformin is classified as a biguanide oral hypoglycemic agent used in first line treatment of type 2 diabetes mellitus. Metformin hydrochloride is a white crystalline compound having molecular formula of C4H11N5.HCl and a molecular weight of 165.63. It is freely soluble in water and is practically insoluble organic compounds like acetone, ether, and chloroform. Metformin has an oral bioavailability of 50-60% and exhibits slow absorption, bound to plasma proteins, approximately 90% of the absorbed drug is eliminated through renal route and half life is 6.2 hours. Metformin diminishes hepatic glucose production, and decrease intestinal absorption of glucose, and improve insulin sensitivity. It is available in the market under various trade names such as Glucophage, glumetza, formet, glucophage XR, obimet, gluformin, formin. Metformin can be prescribed with other anti diabetic drug medications such as glipizide, glimepiride, rosiglitazone, pioglitazone, to improve patient compliance and achieve the glycemic control. Metformin used to treat type 2 diabetes mellitus, prediabetes, polycystic ovarian syndrome, female infertility, gestational diabetes. Metformin drug interacts with furosemide, nifedipine, cationic drugs and less interact with highly plasma protein bound drugs. The most common adverse effect of Metformin includes diarrhea, cramps, nausea, vomiting, and increased flatulence, lactic acidosis, vitamin B_{12} deficiency. It is contraindicated in people with risk of lactic acidosis, kidney disorders and liver disease. It is prescribed with other oral hypoglycemic drugs thereby improve patient compliance and

maintaining the controlled levels of blood glucose levels to prevent the development of diabetic complications.

KEYWORDS: Metformin hydrochloride, bioavailability, insulin sensitivity, type 2 diabetes mellitus, lactic acidosis.

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders in which the blood glucose is higher than normal range due to deficiency of insulin release causes abnormal glycemic levels may exhibit symptoms of polyuria, polydipsia and polyphagia among diabetic patietns. It will help to renovate the body response to insulin and decrease the amount of blood sugar levels and to prevent diabetic complications. Metformin possesses good efficacy and safety profile and having beneficial cardiovascular and metabolic effects and is used to treat type 2 diabetes mellitus patients. According to the American Diabetes association guidelines recommends that metformin is used as a first-line drug treatment regimen for diabetic patients.

Metformin and sulfonylureas

Clinically combination of metformin and sulfonylurea drugs were most commonly prescribing showed a greater reduction in HbA1c. The glimepiride/metformin combination exhibited greater reduction of HbA1c levels and also cardiovascular complications when compared to other combinations.[1-3]

Metformin and insulin

Metformin prescribed with insulin regimens shown to maintain the controlled blood sugar levels.

Metformin combination therapy

Monotherapy with an oral hypoglycemic agent is often initially effective. It can be prescribed with other glycemic agents to control the glycemic levels.

Table 1: Metformin drug combinations.

1	Amaryl-M Forte (1-2mg/ 1000mg)	Glimepiride 1-2mg + Metformin 1000mg
2	Asoformin-P (15mg/ 500mg)	Pioglitazone 15mg + Metformin 500mg
3	Claz-M-OD (30mg/ 500mg)	Gliclazide 30mg + Metformin 500mg
4	Dianorm-M OD (60mg/ 500mg)	Gliclazide 60mg + Metformin 500mg
5	Galvus - MET	Metformin, Vidagliptin, Rosiglitazone
6	GLITENLY-M	Teneligliptin 20mg + Metformin 500mg
7	Glymep (5mg/ 500mg)	Glibenclamide 5mg + Metformin 500mg
8	Metformin, Vidagliptin	Voglibose 0.2mg + Metformin 500mg

Effects on cardiovascular mortality

Diabetic patients are at high risk of cardiovascular events, particularly of coronary heart disease. Type 2 diabetic patients without a previous history of heart diseases develop the same risk of coronary artery disease. This has led the National Cholesterol Education Program to consider diabetes as a coronary heart disease risk equivalent.[4-9]

Effects on the inflammatory pathway

Metformin can act as an inhibitor of pro-inflammatory responses include it will inhibit the NF-kB by blocking the PI3K– Akt pathway.

Effects on lipid profile

Metformin is associated with improvements in lipoprotein metabolism, including decreases in LDL-C and free fatty acids.

Historical perspective of metformin

In the 20th century, scientific researchers isolated a compound from *G.* officinalis called guanidine can lower blood glucose levels. Researchers found that it can be prepared by bonding two guanidines together and forms biguanide compound. Metformin is one such biguanide, first synthesized in 1929 and then clinically developed in the late 1950s by the French physician Jean Sterne, who gave it its first trade name, Glucophage.[10-15]

- 1772 Galega officinalis used to treat symptoms of diabetes
- 1844–1861 Identification and synthesis of guanidine
- 1878–1879 Synthesis of biguanide
- 1922 Synthesis of dimethylbiguanide
- 1926–1928 Galegine and synthalin lower blood glucose in animals and humans
- 1929 Metformin and other biguanides lower blood glucose in animals
- 1957 Jean Sterne publishes use of metformin to treat diabetes

- 1968 First large prospective comparator trial of metformin
- 1994–1995 Metformin approved (1994) and introduced (1995) in the USA
- 1995–1996 Key publications confirm favorable benefit: risk ratio of metformin in the management of type 2 diabetes mellitus.
- 1998 UKPDS reports long-term metabolic effects of metformin and reduced cardiovascular risk with treated patients.
- 2000–2002 Extended-release formulation and fixed-dose combination drugs with metformin as the primary active ingredient are approved in the USA.
- 2002 Metformin reduced progression of 'pre-diabetes' (IGT and/or IFG) to T2D in the DPP
- 2005 The IDF recommends metformin as an initial glucose-lowering pharmacotherapy for T2D. Other guidelines adopt metformin as an initial glucose-lowering agent.
- 2011 Metformin included in WHO's essential medicines list

Metformin classification

Metformin is classified as a biguanide, a group of anti-diabetic drugs that lowers blood sugar. Biguanides originate from a lilac bush preparation that has long been used in herbal medicine. In 1957, a French doctor named one biguanide 'Glucophage,' which means 'glucose eater.' Metformin slows the release of glucose from the liver, slows blood glucose uptake from the intestine, and increases insulin sensitivity. Since metformin's worldwide spread for over 50 years, numerous studies concerning other potential indications have emerged, which showed that metformin can also be used as an anticancer agent, an antiaging agent, a cardiovascular protective agent, a neuroprotective agent or an optional drug for polycystic ovary syndrome. Metformin is primarily used for the treatment of type 2 diabetes mellitus, particularly in obese patients [16-20]. Metformin has been shown to reduce diabetes mortality and complications by thirty percent compared to insulin, glibenclamide and chlorpropamide.

Physicochemical properties of Metformin

Metformin Hydrochloride is the hydrochloride salt of the biguanide metformin with antihyperglycemic and potential antineoplastic activities.

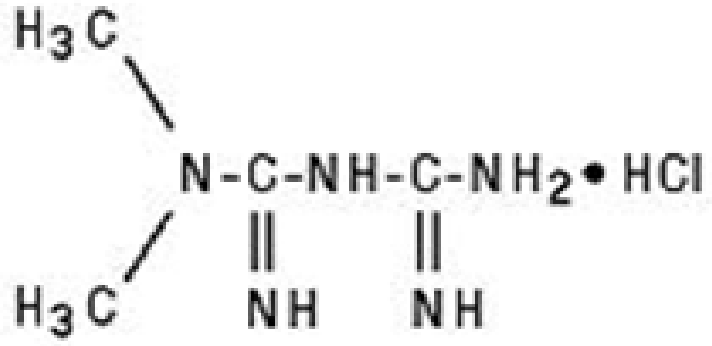

Fig. 1: Chemical structure of Metformin.

Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of C4H11N5 • HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

Chemical class

A Hydrochloride obtained from the reaction of Metformin with one molar equivalent of hydrogen chloride.

Chemical and Physical Properties

Appearance: crystalline solid

Melting Point: 223-226℃

Boiling Point: 224.1 °C at 760 mmHg

Vapour: 0.0929mmHg at 25°C

Flash Point: 89.3 °C

Solubility: Soluble in water, 95% alcohol and insoluble in organic solvents such as ether, chloroform.

Biological activity: Antidiabetic agent; lowers plasma glucose levels and improves insulin sensitivity. It inhibits hepatic gluconeogenesis via activation of the LKB1/AMPK pathway.

Therapeutic uses: Metformin is indicated in patients with type 2 diabetes to control hyperglycemia that cannot be controlled by diet management, exercise, or weight reduction, or when insulin therapy is not required or feasible. It is used as monotherapy or as an adjunct

to sulfonylureas or insulin when either alone does not achieve adequate glycemic control.[21-26]

Indications

- Polycystic Ovaries Syndrome
- Type 2 Diabetes Mellitus
- Prediabetes
- Gestationsl diabetes

Pharmacodynamics

Metformin is an oral antihyperglycemic agent that improves glucose tolerance in patients with NIDDM, lowering both basal and postprandial plasma glucose. Metformin is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with NIDDM or healthy subjects and does not cause hyperinsulinemia. Metformin does not affect insulin secretion.[27-32]

Mechanism of action

Metformin decreases blood glucose levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects are mediated by the initial activation by metformin of AMP-activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats. Activation of AMPK is required for metformin's inhibitory effect on the production of glucose by liver cells. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors. Metformin administration also increases AMPK activity in skeletal muscle. AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose uptake [33-34]. The rare side effect, lactic acidosis, is thought to be caused by decreased liver uptake of serum lactate, one of the substrates of gluconeogenesis.

Pharmacokinetics of metformin

Absorption

Absorbed over 6 hours, bioavailability is 50 to 60% under fasting conditions. Administration with food delays the absorption [35]. Oral dose of GLUMETZA after a meal, the time to reach

maximum plasma metformin concentration is achieved at approximately 7 - 8 hours.

Distribution

Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. The volume of distribution following IV administration is 63-276 L, likely due to less binding in the GI tract.[36-37]

Protein binding

Metformin is negligibly bound to plasma proteins.

Metabolism and Excretion

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism. Approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours.[38]

Half life: 6.2 hours.

Drug interactions

Clinically metformin interacts with some cationic agents such as amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin may participate with metformin for elimination. The simultaneous administration of cimetidine, furosemide, or nifedipine may increase the concentration of metformin. These drugs include the thiazides diuretics, corticosteroids, phenothiazines, thyroid products, oral contraceptives, phenytoin, calcium channel blocking drugs, and isoniazid enhances hyperglycemia.[39] Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid.

Synonyms of metformin

- Apophage
- Diaformin
- Fornidd
- Glucoformin
- Glucophage
- LA 6023

- Melbin
- Orabet
- Riomet
- Walaphage

Overdose

It can be occurred with prescribing metformin hydrochloride dose is greater than50 grams. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Hemodialysis may be useful for removal of accumulated drug from patients.

Contraindications

It is contraindicated in patients with:

- Renal disease, acute myocardial infarction, and septicemia.
- Hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

Storage

It should be stored at 20° to 25°C and excursions permitted to 15° to 30°C (59° to 86°F). It is stored in tightly closed (protect from moisture). Protect from light. Avoid excessive heat and humidity.

Adverse effects of metformin

It includes

- Abdominal pain
- Cough
- Decreased appetite
- diarrhea
- Breathlessness
- Fever
- Muscle pain
- Painful urination
- Sleepiness
- Lactic acidosis

CONCLUSION

Metformin is a biguanide oral hypoglycemic drug used in initial therapy to treat type 2 diabetes mellitus. It is the most commonly prescribed drug in diabetic treatment due to safety profile, low cost. Metformin acts directly on the hepatic cells and lower the glucose production and thereby increase the gut glucose secretion. Metformin can reduce the macro vascular complications and improve glycemic control. It is prescribed with other oral hypoglycemic drugs thereby improve patient compliance and maintaining controlled glycemic levels. The drug represents a useful therapeutic tool for treating type 2 diabetes mellitus, prediebtes, PCOS, gestational diabetes. It is contraindicated with renal diseases, acute metabolic acidosis. Metformin with fixed dose combinations can effectively reduce the glycemic levels in the practice [40-42]. Early identification of adverse effects and drug interactions can promote the treatment outcomes and reduce disease complications. Metformin can decrease insulin levels, reduction in the weight, improving lipid profiles and also increase the function of endothelial cells, inhibit the inflammatory condition and reduces the progression of diabetic severity in the community.

Conflict of interest: Authors declare no conflict of interest.

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