World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Review Article

Spotlight on pharmacology of a noble oral hypoglycaemic agent: Metformin

Neerjesh P[1], Vipender Singh Chopra [2], Rajkishor Singh[4], Kavita Dhar[3], Sanjay Kumar Singh[1], Dharti N[5]

[1]Lecturer, Motilal Nehru Medical College, Allahabad
[2]Professor, [3]Assistant Professor, Santosh Medical College, Ghaziabad
[4]Assistant Professor, B.R.D Medical College, Gorakhpur
[5]Ex- Resident Pacific Dental College& Hospital, Udaipur, India

Received: 09-10-2015 / Revised: 17-11-2015 / Accepted: 01-12-2015

ABSTRACT

The management of T2DM requires aggressive treatment to achieve glycemic and cardiovascular risk factor goals. In this setting, metformin, an old and widely accepted first line agent, stands out not only for its antihyperglycaemic properties but also for its effects beyond glycemic control such as improvements in endothelial dysfunction, hemostasis and oxidative stress, insulin resistance, lipid profiles, and fat redistribution. These properties may have contributed to the decrease of adverse cardiovascular outcomes otherwise not attributable to metformin's mere antihyperglycaemic effects. Metformin's negligible risk of hypoglycemia in monotherapy and few drug interactions of clinical relevance give this drug a high safety profile. The tolerability of metformin may be improved by using an appropriate dose titration, starting with low doses, so that side-effects can be minimized or by switching to an extended release form. We reviewed the role of metformin in the treatment of patients with type 2 diabetes and describe the additional benefits beyond its glycemic effect. We also discuss its potential role for a variety of insulin resistant and pre-diabetic states, obesity, metabolic abnormalities associated with HIV disease, gestational diabetes, cancer, and neuroprotection.

KEY WORDS; Metformin, Type 2 Diabetes mellitus, Oral hypoglycemia, Reduced glucose output, Protective effect.

INTRODUCTION

Metformin hydrochloride is an oral antihyperglycaemic drug used in the management of type 2 diabetes. Metformin hydrochloride [N, N-dimethylimidodicarbonimidic diamide hydrochloride] is not chemically or pharmacologically related to any other classes of oral antihyperglycaemic agents [1]. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of C4H11N5•HCI and a molecular weight of 165.63. The discovery of metformin began with the synthesis of galegine-like compounds derived from Gallega officinalis, a plant traditionally employed in Europe as a drug for diabetes treatment for centuries [1].

Clinical pharmacology

Mechanism of Action: Metformin is an antihyperglycaemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycaemic agents [1].

Metformin acts primarily at the liver by reducing glucose output and, secondarily, by augmenting glucose uptake in the peripheral tissues, chiefly muscle. These effects are mediated by the activation of an upstream kinase, liver kinase B1 [LKB-1], which in turn regulates the downstream kinase adenosine monophosphatase co-activator, transducer of regulated CREB protein [1] [TORC2], resulting in its inactivation which consequently down regulates transcriptional events that promote synthesis of gluconeogenic enzymes [2]. Inhibition of mitochondrial respiration has also been proposed to contribute to the reduction of gluconeogenesis since it reduces the energy supply required for this process [2]. Metformin's efficacy, security profile, benefic cardiovascular and metabolic effects, and its capacity to be associated with other antidiabetic agents makes this drug the first glucose lowering agent of choice when

***Corresponding Author Address: Dr. Neerjesh P,** Lecturer, Motilal Nehru Medical College, Allahabad**, India; E-mail:** dr.neerjesh@rediffmail.com*

treating patients with type 2 diabetes mellitus [TDM2] [1].

Pharmacokinetics

Absorption and Bioavailability: The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin tablets of 500 mg and 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak concentration [Cmax] and 25% lower area under the plasma concentration versus time curve [AUC], and a 35 minute prolongation of time to peak plasma concentration [Tmax] following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown [1].

Indications & Usage: Metformin hydrochloride tablets, as monotherapy, are indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes [1]. Metformin is used concomitantly with sulfonyl urea to improve glycemic control in adults.

Monotherapy with Metformin & Treatment with Others

Metformin in the management of adult diabetic patients: Current guidelines from the American Diabetes Association/ European Association for the Study of Diabetes [ADA/EASD] and the American Association of Clinical Endocrinologists/American College of Endocrinology [AACE/ACE] recommend early initiation of metformin as a first-line drug for monotherapy and combination therapy for patients with T2DM. [5],[6]. Metformin's first-line position was strengthened by the United Kingdom Prospective Diabetes Study [UKPDS] observation that the metformin-treated group had risk reductions of 32% [p = 0.002] for any diabetes-related endpoint, 42% for diabetes-related death [p = 0.017], and 47% for all-cause mortality [p = 0.011] compared with the control group. The UKPDS demonstrated that metformin is as effective as sulfonylurea in controlling blood glucose levels of obese patients with type 2 diabetes mellitus. Metformin has been also been shown to be effective in normal weight patients. Metformin in combination therapy although monotherapy with an oral hypoglycemic agent is often initially effective, glycemic control deteriorates in most patients which requires the addition of a second agent. Currently, marketed oral therapies are associated with high secondary failure rates. Combinations of metformin and insulin secretagogue can reduce HbA1c between 1.5% to 2.2% in patients sub-optimally controlled by diet and exercise. The optimal second-line drug when metformin monotherapy fails is not clear. All noninsulin antidiabetic drugs when added to maximal metformin therapy are associated with similar HbA1c reduction but with varying degrees of weight gain and hypoglycemia risk. A meta-analysis of 27 randomized trials showed that thiazolidinediones, sulfonylureas, and glinides were associated with weight gain; glucagon-like peptide-1 analogs, glucosidase inhibitors, and dipeptidyl peptidase-4 inhibitors were associated with weight loss or no weight change. Sulfonylureas and glinides were associated with higher rates of hypoglycemia than with placebo. When combined with metformin, sulfonylureas and alphaglucosidase inhibitors show a similar efficacy on HbA1c.[3]

Metformin and sulfonylureas: The combination of metformin and sulfonylurea [SU] is one of the most commonly used and can attain a greater reduction in HbA1c [0.8–1.5%] than either drug alone.[4] The glimepiride/metformin combination results in a lower HbA1c concentration and fewer hypoglycemic events when compared to the glibenclamide/metformin combination. The use of metformin was associated with reduced all-cause mortality and reduced cardiovascular mortality. Metformin and sulfonylurea combination therapy was also associated with reduced all-cause mortality. Epidemiological investigations suggest that patients on SUs have a higher cardiovascular disease event rate than those on metformin. Patients who started SUs first and added metformin also had higher rates of cardiovascular disease events compared with those who started metformin first and added SUs. These investigations are potentially affected by unmeasured confounding variables.[5]

Metformin and insulin: Metformin as added to insulin-based regimens has been shown to improve glycemic control, limit changes in body weight, reduce hypoglycemia incidence, and to reduce insulin requirements [sparing effect], allowing a 15–25% reduction in total insulin dosage.[6] The addition of metformin to insulin therapy in type 1 diabetes is also associated with reductions in insulin dose requirement and HbA1c levels .

Metformin and Thiazolinediones: The addition of rosiglitazone to metformin in a 24-week randomized, double-blind and parallel-group study significantly decreased HbA1c concentration and improved insulin sensitivity and HOMA ß cell

function. However, in spite of preventing diabetes incidence, the natural course of declining insulin resistance may not be modified by a low dose of the metformin-rosiglitazone combination. The ADOPT study [A Diabetes Outcome Progression Trial] assessed the efficacy of rosiglitazone, as compared to metformin or glibenclamide, in maintaining long-term glycemic control in patients with recently diagnosed type 2 diabetes. Rosiglitazone was associated with more weight gain, edema, and greater durability of glycemic control; metformin was associated with a higher incidence of gastrointestinal events and glibenclamide with a higher risk of hypoglycaemia [8].

Metformin and Glifozins: Dapagliflozin, a highly selective inhibitor of SGLT2, has demonstrated efficacy, alone or in combination with metformin, in reducing hyperglycemia in patients with type 2 diabetes.Studies are in development for assessing the safety and efficacy of this combination. Metformin and α glicosidase inhibitor Acarbose reduces the bioavailability of metformin [9].However, it has been reported that the association of acarbose to metformin in sub-optimally controlled patients reduced HbA1c by about 0.8-1.0% [10].

Metformin and incretin-based therapies DDPIV prolongs the duration of active glucagon-like peptide 1 [GLP-1] by inhibiting DPPIV peptidase, an enzyme which cleaves the active form of the peptide. This action results in an improvement of insulin secretion as a physiological response to feeding. The mechanism of DPPIV inhibitors is complementary to that of metformin which improves insulin sensitivity and reduces hepatic glucose production, making this combination very useful for achieving adequate glycemic control. Metformin has also been found to increase plasma GLP-1 levels, probably by either direct inhibition of DPPIV or by increased secretion, leading to reduced food intake and weight loss. Saxagliptin added to metformin led to clinically and statistically significant reductions in HbA1c from baseline versus metformin/placebo in a 24-week randomized, double-blind, placebo-controlled trial. Saxagliptin at doses of 2.5, 5, and 10 mg plus metformin decreased A1 by 0.59%, 0.69%, and 0.58%, respectively, in comparison to an increase in the metformin plus placebo group [+0.13%]; $p < 0.0001$ for all comparisons [12].

A meta-analysis of 21 studies examined incretin-based therapy as an add-on tometformin in patients withT2DM for 16–30 weeks; 7 studies used a short-acting GLP-1 receptor agonist [exenatide BID], 7 used longer acting GLP-1 receptor agonists [liraglutide or exenatide LAR], and 14 examined DPP-IV inhibitors. Long-acting GLP-1 receptor agonists reduced HbA1c and fasting glucose levels to a greater extent than the other therapies [13].

Effects of metformin on vascular protection

Effects on cardiovascular mortality: Diabetic patients are at high risk of cardiovascular events, particularly of coronary heart disease by about 3-fold.[14] It has been stated that type 2 diabetic patients without a previous history of myocardial infarction have the same risk of coronary artery disease [CAD] as non-diabetic subjects with a history of myocardial infarction.[15] This has led the National Cholesterol Education Program to consider diabetes as a coronary heart disease risk equivalent.[16] Although there is no doubt that there is an increased risk of CAD events in diabetic patients, there is still some uncertainty as to whether the cardiovascular risk conferred by diabetes is truly equivalent to that of a previous myocardial infarction [17].

Effects on the inflammatory pathway: The benefits of metformin on macrovascular complications of diabetes, separate from its conventional hypoglycemic effects, may be partially explained by actions beyond glycemic control, particularly by actions associated with inflammatory and atherothrombotic processes.[18] Metformin can act as an inhibitor of pro-inflammatory responses through direct inhibition of NF-kB by blocking the PI3K– Akt pathway. This effect may partially explain the apparent clinical reduction of cardiovascular events not fully attributable to metformin's anti-hyperglycemic action [18].

Effects on oxidative stress: Oxidative stress is believed to contribute to a wide range of clinical conditions such as inflammation, ischemic perfusion injury, diabetes, atherosclerosis, neurodegeneration, and tumor formation. Metformin has antioxidant properties which are not fully characterized. It reduces reactive oxygen species [ROS] by inhibiting mitochondrial respiration and decreases advanced glycosylation end product [AGE] indirectly through reduction of hyperglycemia and directly through an insulin-dependent mechanism [19].

There is some evidence that metformin also has a beneficial effect on some components of the antioxidant defense system. It can upregulate uncoupled proteins 2 [UCP2] in adipose tissue and can also cause an increase in reduced glutathione [20].

Effects on endothelial function: Type 2 diabetes is associated with a progressive and generalized

impairment of endothelial function that affects the regulation of vasomotor tone, leucocyte adhesion, hemostasis, and fibrinolysis. These effects are probably direct and not related to decreases in hyperglycemia [21].

Effects on body weight: Metformin may have a neutral effect on body weight of patients with T2DM when compared to diet [7] or may limit or decrease the weight gain experienced with sulfonylureas [7], TDZ [22], insulin, HAART, and antipsychotics drugs.

Modest weight loss with metformin has been observed in subjects with IGT, However, a meta-analysis of overweight and obese non-diabetic subjects, found no significant weight loss as either a primary or as secondary outcome. The mechanisms by which metformin contributes to weight loss may be explained through the reduction in gastrointestinal absorption of carbohydrates and insulin resistance48, reduction of leptin and ghrelin levels after glucose overload [21], and by induction of a lipolitic and anoretic effect by acting on glucagon–like peptide 1[11].

Effects on lipid profile: Metformin is associated with improvements in lipoprotein metabolism, including decreases in LDL-C , fasting and postprandial TGs, and free fatty acids [22].

ADVERSE EFFECTS

The most common adverse effects of metformin relate to the gastrointestinal tract, including watery diarrhea, nausea, abdominal pain, abdominal bloating, flatulence, dyspepsia, metallic taste, and anorexia. These effects occur in 10–50% of patients receiving metformin therapy, but resolve within a few days to weeks after the initiation of therapy. Their severity can be lessened by employing a gradual titration schedule, taking metformin with food, and/or temporarily lowering the dosage [1].
Metformin should be initiated at a dose of 500 mg once daily with the largest meal, and the dose should be then increased weekly in 500 mg steps if required [maximum 2500–2550 mg/day in three divided doses with meals]. If nausea or diarrhea occurs at a given dose, that dose is either maintained or decreased by 500 mg/day for 2–4 weeks until the symptoms abate. When diarrhea, attributed to an alteration in the absorption of bile salts, does not resolve, discontinuation of the medication may be necessary [1].

Metformin therapy can cause malabsorption of vitamin B12 in the distal ileum in 10–30% of patients. Proposed mechanisms by which metformin affects vitamin B12 absorption involve altered small bowel motility, bacterial overgrowth, and direct effects on mucosal cell and intracellular handling of calcium. In patients treated with metformin, an increased risk of vitamin B12 deficiency has been associated with increasing patient age, current dose, and duration of metformin use. The presenting symptoms of vitamin B12 deficiency may be indistinguishable from those of peripheral neuropathy, while hematological repercussions may also occur. Nevertheless, only a small number of metformin-associated megaloblastic anemias have been reported in the literature.Vitamin B12 deficiency may also evoke hyperhomocysteinemia, which is linked with adverse cardiovascular effects. Therefore, during metformin therapy plasma levels of vitamin B12 should be measured, and patients should be monitored for clinical signs and symptoms of vitamin B12 deficiency [1].

Lactic acidosis is a rare, potentially fatal metabolic condition described as a biguanide class effect. Lactic acidosis can occur whenever substantial tissue hypoperfusion and hypoxia exist. However, the two biguanides, metformin and phenformin, influence lactate metabolism in different ways. Metformin binds with a much lower affinity than phenformin to mitochondrial membranes and does not adversely affect mitochondrial lactate oxidation, unless plasma concentrations of metformin are excessive [1].

Lactic acidosis has been rarely reported with the use of metformin, mostly in patients with contraindications to the drug or in cases of intoxication after drug overdosage.1

Contraindications for metformin include renal dysfunction [a serum creatinine level 01.4 mg/dl], hepatic dysfunction, severe congestive heart failure, or a history of alcohol abuse. However, in the absence of contraindications, the increased risk of lactic acidosis is either zero or negligible [1].

TOLERABILITY

Gastrointestinal side-effects are common with the use of metformin of standard release and are usually associated with rapid titration and high-dose initiation of metformin. These effects are generally transient, arise early in the course of treatment, and tend to subside over time [23]. The gastrointestinal side-effects can be addressed by taking the agent with meals, reducing the rate of dose escalation, or transferring to a prolonged-release formulation [24]. Some studies point to a dose-related relationship of the incidence of side-effects, whereas other evidence gives no support for a dose-related effect of metformin on the gastrointestinal system [24].

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