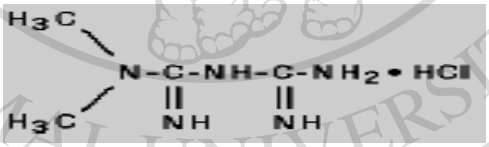
CHAPTER 2

LITERATURE REVIEW

Physicochemical Properties

Metformin HCl (*N,N*-dimethylimidodicarbo nimidic diamide hydrochloride) is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$ • HCl and a molecular weight of 165.63. It is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pK_a is 12.4 and the pH of a 1% aqueous solution is 6.68. Metformin tablets contain 500 mg, 850 mg, or 1000 mg of metformin HCl. Each tablet contains the inactive ingredients; povidone and magnesium stearate. In addition, the coating for the 500 mg and 850 mg tablets contains hypromellose and the coating for the 1000 mg tablet contains hypromellose and polyethylene glycol (17).



The chemical structure of metformin HCl

Mechanism of Action

Metformin improves glucose tolerance in patients with type 2 DM by lowering both basal and postprandial plasma glucose (7). Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Unlike sulfonylureas, treatment with metformin alone does not produce hypoglycemia in patients with type 2 DM or in normal subjects (hypoglycemia during intense exercise has been reported, but is extremely rare) and does not cause hyperinsulinemia (18, 19). With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease. The glucose lowering effect of metformin is mainly a consequence of reducing hepatic

glucose production (primarily through inhibition of gluconeogenesis and to a lesser extent glycogenolysis) (18-22). Since the patient with type 2 DM has three times the normal rate of gluconeogenesis, metformin treatment reduces this by over one third and results in reducing plasma glucose level (23).

The exact mechanism through which metformin reduces hepatic glucose production remains unclear, but its primary site of action appears to be in hepatocyte mitochondria, where it disrupts respiratory chain oxidation of complex I substrates (for example, glutamate). Inhibition of cellular respiration decreases gluconeogenesis (24) and may induce expression of glucose transporters, therefore, glucose utilization (25). Metformin also facilitates insulin induced suppression of gluconeogenesis from several substances, including lactate, pyruvate, glycerol, and amino acids, and opposes the gluconeogenic actions of glucagon. It has been suggested that biguanides bind specifically and competitively to divalent cation sites on proteins, thus interfering with intracellular handling of calcium especially in the mitochondria (24). In several tissues, including skeletal muscle and adipocytes, metformin facilitates trafficking of glucose transporters 4 and 1 to the plasma membrane. Moreover, metformin may increase the glucose transport capacity of glucose transporter 4, and to some extent, glucose transporter 1. The effects of metformin on peripheral insulin-sensitive tissues require the presence of insulin for its full action. It enhances most of the biological actions of insulin, including glucose transport and glycogen and lipid synthesis. The drug also increases insulin-stimulated glucose uptake in skeletal muscle and adipocytes. In persons with preexisting insulin resistance, it facilitates glucose transport in cultured skeletal muscle in the absence of insulin (25). Metformin activates insulin and tyrosine kinase activity in insulin-like growth factor-1 receptor of vascular smooth-muscle cells independently of insulin action. The drug activates tyrosine kinase in *Xenopus* oocytes, with subsequent stimulation of inositol 1, 4, 5-triphosphate production and glycogen synthesis (26). Thus, metformin has metabolic effects on insulin-sensitive tissues that may contribute to its glucose-lowering effect.

Metformin has been shown to reduce free fatty acid oxidation by 10% to 30% (21-23). Elevated levels of free fatty acids contribute to increased hepatic glucose production and development of insulin resistance. Increased fatty acid oxidation

inhibits key enzymes of the glycolytic pathway by accumulation of acetyl coenzyme A and citrate, by-products of free fatty acid oxidation (27). Increased glucose 6-phosphate concentrations, in turn, inhibit the hexokinase enzyme, resulting in reduced glucose uptake and oxidation. By decreasing free fatty acid levels, metformin not only improves insulin sensitivity but also helps correct impaired insulin secretion by beta-cell. Metformin has no direct effect on beta-cell function, but it can improve insulin secretion that has been altered by long-term exposure to free fatty acids or hyperglycemia (glucose toxicity) (27). The drug may also improve hyperglycemia by attaining high concentrations in the small intestine and decreasing intestinal absorption of glucose (28), an action that may contribute to a decrease in postprandial blood glucose levels. It has been speculated that increased glucose consumption in the small intestine of metformin-treated patients may prevent further glucose transport to the hepatic circulation. In conclusion, metformin decreases hepatic glucose production, improves peripheral insulin sensitivity, decreases gastrointestinal glucose absorption and indirectly improves pancreatic beta-cell response to glucose by reducing glucose toxicity and free fatty acid levels.

Pharmacokinetics

Absorption

The absolute bioavailability of metformin tablet given under fasting conditions is approximately 50% to 60% (29). C_{max} and T_{max} after a single oral dose 850-mg metformin in healthy adults are 1.60 $\pm$ 0.38 μg/mL and 2.75 $\pm$ 0.81 h, respectively. Studies using single oral doses of metformin 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to a saturable and incomplete absorption rather than an alteration in elimination (30). The reason may be due to its physicochemical properties that limit its permeability in the gastrointestinal tract where it is largely ionized and is nonlipophilic (31, 32). The extent of absorption of metformin is also influenced by food (33) and gastrointestinal transit time (34). Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean C_{max}, a 25% lower AUC and a 35-minute prolongation of T_{max} 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 food effects

is unknown. At the usual doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 h. The drug concentrations are generally less than 1 μg/mL and C_{max} does not exceed 5 μg/mL even at maximum doses (29, 30).

Distribution

The average apparent volume of distribution (V_d) of 850-mg metformin following a single oral dose is 654 ± 358 L. The drug is negligibly bound to plasma proteins (29), however, partitions into erythrocytes as a function of time most likely represents a secondary compartment of distribution (29, 35).

Metabolism and elimination

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion (29). Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 h, with a plasma elimination $t_{1/2}$ of approximately 4.0 – 8.7 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination $t_{1/2}$ is prolonged, leading to increased levels of metformin in plasma. In blood, the elimination $t_{1/2}$ is approximately 17.6 h, suggesting that the erythrocyte mass may be a compartment of distribution (35).

Indication and Dosage

Metformin monotherapy is indicated as an adjunct to diet and exercise in patients with type 2 DM, especially in overweight patients. It can be administered in combination with a sulphonylurea or insulin to improve glycemic control in adults (36). It is indicated in patients 10 years of age and older. There is no fixed dosage regimen for the management of hyperglycemia in patients with type 2 DM and dosage of metformin must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily doses of 2550 mg in adults (29). The drug should be given in divided doses with meals, started at a low dose, with gradual dose escalation, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the

patient. The usual starting dose of metformin for adults is 500 mg twice a day or 850 mg once a day, given with meals. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms. Dosage increases should be made in increments of 500 mg weekly or 850 mg every 2 weeks, up to a total of 2000 mg/day, given in divided doses.

In general, clinically significant responses are not seen at doses below 1500 mg/day. Patients can also be titrated from 500 mg twice a day to 850 mg twice a day after 2 weeks. For those patients requiring additional glycemic control, metformin may be given to a maximum daily dose of 2550 mg/day. Doses above 2000 mg may be better tolerated given three times a day with meals. During treatment initiation and dose titration, fasting plasma glucose should be used to determine the therapeutic response to metformin and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose (29).

Adverse Reactions

The common adverse effects of metformin include diarrhea, nausea/vomiting, flatulence, indigestion, and abdominal discomfort. Diarrhea led to discontinuation of study medication in 6% of patients, however, during long-term metformin administration, only 4.2% of patients discontinued therapy because of gastrointestinal side effects (11). Additionally, the following adverse reactions are reported in ≥ 1.0-≤ 5.0% of patients: hypoglycemia, myalgia, lightheaded, dyspnea, nail disorder, rash, sweating, taste disorder, chest discomfort, chills, flu-like syndrome, flushing, and palpitation. Lactic acidosis, a serious and potentially lethal metabolic condition, has occurred with all biguanides, but rarely with metformin. The mean incidence of lactic acidosis associated with metformin therapy is only about 0.03 cases per 1,000 patient-years (13). Strict observance of contraindications and prescribing precautions substantially reduces this risk.

Drug Interactions (17)

Glyburide

In a single-dose interaction study in type 2 DM patients, co-administration of metformin and glyburide does not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} are observed, but are highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide

A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrates that pharmacokinetic parameters of both compounds are affected by co-administration. When administered with metformin, the C_{max} and AUC of furosemide are 31% and 12% smaller, respectively, than when administered alone, and the terminal $t_{1/2}$ is decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrates that co-administration of nifedipine increases plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increases the amount of metformin excreted in the urine. T_{max} and $t_{1/2}$ are unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin has minimal effects on nifedipine.

Cationic drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single-and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There is no change in

elimination $t_{1/2}$ in the single-dose study. Metformin has no effect on cimetidine pharmacokinetics.

Other Drugs

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving metformin, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin, the patient should be observed closely for hypoglycemia.

Precautions and Contraindications (17)

Metformin is contraindicated in patients who are hypersensitive to the drug and in the patients with renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance) and acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.