CHAPTER II

REVIEW OF GLIBENCLAMIDE

1. <u>Physicochemical Properties</u> (Florey, ed., 1981; Moffat, ed., 1986; Budavari, ed., 1989)

The chemical name of glibenclamide is 1-{4-[2-(5-chloro-2-methoxybenzamido) ethyl] benzenesulfonyl} -3-cyclohexylurea. It was synthesized in 1966. The chemical structure of glibenclamide is similar to acetohexamide, a first generation oral sulfonylurea hypoglycemic agent. However replacement of the acetyl group on the acetohexamide molecule results in much more potent hypoglycemic action. This potency is thought to be related to the exact distance between the two nitrogen atoms in the compound. (Figure 1)

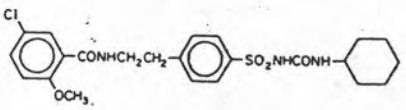

Figure 1 Chemical structure of glibenclamide

Empirical formula : $C_{23}H_{28}ClN_3O_5S$

Molecular weight : 494.0

Synonym : Glybenzcyclamide, Glyburide, HB419, U-26452

Appearance : A white odourless crystalline powder

Solubility : Practically insoluble in water, ether; slightly soluble in ethanol (96%) and in methanol; sparingly soluble in chloroform

Acidity : Glibenclamide is a weak acid

$pK_a = 5.3 \pm 0.1$

2. Pharmacology

Glibenclamide is a second generation oral sulfonylurea antidiabetic agent. The drug is effective only in non-insulin dependent diabetes mellitus (type II diabetes mellitus). Diabetes is clinically classified to two groups in term of absolute requirement of exogenous insulin. Patients with such an insulin requirement, primarily juvenile onset diabetics are referred as insulin-dependent diabetes mellitus (type I). The majority of patients previously known as adult onset diabetics are insulin resistance rather than insulin deficiency are referred as non-insulin dependent diabetes mellitus (type II). Unlike type I diabetics, type II diabetics exhibit some exogenous insulin secretion. Current evidence indicates that metabolic lesion in type II diabetics involves defects in pancreatic beta cell function and in cellular activity at the target tissues (Skyler, 1984)

To understand the mechanisms of therapeutic actions of glibenclamide, its effects must be considered in view of underlying metabolic lesion in non-insulin dependent diabetes mellitus and physiology of insulin secretion.

Physiology of Insulin Secretion (Czech, 1981 ; Beck-Nielsen, 1984)

Insulin is synthesized in pancreatic beta cells and released into blood stream upon an adequate stimulation especially by glucose. There are two phases of insulin secretion. The first or rapid phase, insulin secretion lasts for about 5-10 minutes followed by the second or slow phase that lasts for about 60 minutes or until the stimulation ceases. Insulin exerts its actions on many organs such as liver, adipose tissues and muscle by reversibly binding with insulin receptor on surface of cell membrane and forming a complex. Consequently intracellular metabolism of carbohydrate, lipid and protein are stimulated. Insulin stimulates glucose transportation into cells and decreases gluconeogenesis. The overall actions of insulin is essentially anabolic, i.e., it promotes net synthesis of glycogen, protein and triglyceride.

Metabolic Lesions in Type II Diabetics

Abnormal glucose metabolisms in type II diabetics involve the three major abnormalities : peripheral insulin resistance, increased hepatic glucose production and impaired insulin secretion. The peripheral insulin resistance and impaired insulin secretion serve to restrict insulin mediated glucose uptake. This decrease in uptake which is the prominent in patients with non-insulin dependent diabetes mellitus is the major cause of postprandial hyperglycemia. Fasting hyperglycemia is due to an increased basal rate of entry of glucose into the circulation from the liver. This increase in hepatic glucose production closely correlate with the degree of fasting hyperglycemia and is the predominant factor causing increased basal glucose levels (Beck-Nielsen, 1984; Olefsky, 1985)

Criteria for Diagnosis of Diabetes (Skyler, 1981)

1. Classic symptoms of dibetes mellitus (such as polyuria, dehydration, polydipsia, polyphagia, weight loss) with unequivocal hyperglycemia (> 200 mg./dl.)

2. Fasting venous plasma glucose greater than or equal to 140 mg./dl. on more than one occasion

3. Sustained venous plasma glucose greater than or equal to 200 mg./dl. during an oral glucose tolerance test

2.1 Mechanisms of Action

2.1.1 Pancreatic Mechanism

Glibenclamide, similar to other sulfonylurea, potentiates the release of insulin from the pancreatic beta cells in normal and type II diabetic patients in response to stimulation by glucose. The mechanism of this enhanced insulin secretion is not clearly understood. Possibly, it may act by increasing intracellular level of cyclic AMP (Sharp, 1979) since sulfonylureas are known to potentiate adenyl cyclase and inhibit phosphodiesterase. A direct effect of depolarization of the beta cell membrane with calcium flux into the cells has been postulated (Henquin, 1980).

2.1.2 Extrapancreatic Mechanism

In some observations, fasting serum insulin concentrations are normal or even slightly elevated in some type II diabetics suggest that there are insulin resistance actions at the peripheral cellular levels. A number of theories involving extrapancreatic effect have been developed to explain insulin resistance (Prendergast, 1984). These can be summarized as enhanced hepatic synthesis of glucose, impaired hepatic extraction of glucose and impaired peripheral tissue uptake of glucose. The latter can be subdivided into decreased binding to the insulin receptor on the cell wall (pre-receptor defect) and decreased intracellular glucose metabolism

(post-receptor defect).

The study of Defronzo, Ferrannini and Koivisto (1983) showed that during long term therapy with glibenclamide, carbohydrate metabolism and insulin sensitivity were significantly enhanced. Kolterman et al. (1984), who from the results of an 18-month study of 17 patients with type II diabetes treated with glibenclamide, concluded that basal hepatic glucose output was reduced significantly, which correlated well with the reduction seen in the fasting blood glucose. Another conclusion from this study was that glibenclamide enhanced the peripheral effect of insulin by acting primarily at the post-receptor sites.

3. Pharmacokinetics

3.1 Absorption

Following oral administration of a single 5 mg. dose of glibenclamide, the drug appears in plasma within 15-60 minutes. Average peak plasma concentration approximately 140-350 ng./ml., usually are attained within 2-6 hours (Pearson, 1985; McEvoy, 1989). Study in healty volunteers demonstrates that food does not affect the absorption of the drug (Sartor et al., 1980).

3.2. Distribution

The apparent volume of distribution has been reported to range from 9 to 40 litres (Prendergrast,

1984). Glibenclamide has been shown to be more than 99% bound to plasma albumin. Unlike the plasma protein binding of some other first generation sulfonylurea antidiabetic agents (e.g., acetohexamide, chlorpropamide, and tolbutamide) but like that of glipizide, the protein binding of glibenclamide is pricipally non-inonic (Jackson and Bressler, 1981; Asmal and Marble, 1984; Pearson, 1985; McEvoy, 1989).

3.3 Elimination

Glibenclamide is almost completely metabolized in the liver to two hydroxy derivatives and one unidentified metabolite. The drug is metabolized at cyclohexyl ring principally to 4-trans-hydroxyglibenclamide and a minor to 3-cis-hydroxyglibenclamide, having 0.25% and 2.5% of the hypoglycemic activity of the parent compound following oral administration in rabbits, respectively (Prendergast, 1984; McEvoy, 1989). The drug is excreted as metabolites in urine and feces in approximately equal proportions (Fucella, Tamassia and Valzelli, 1973). Following oral administration, urinary excretion occurs within 6-24 hours and fecal excretion occurs more slowly. A single oral dose of the drug is completely excreted in the urine and feces within 3-5 days in healthy individuals (McEvoy, 1989).

4. Clinical Use and Efficacy

Glibenclamide is used for the treatment of type II diabetes mellitus in patients who remain hyperglycemia after an adequate trial of diabetic dietary management and exercise program. Many variables, including duration of diabetes, obesity, dietary compliance and age influence the response to glibenclamide therapy (Asmal and Marble, 1984; Feldman,1985).

Owens et al. (1980) demonstrated the effect of glibenclamide treatment in type II diabetic patients whose hyperglycemia were not controlled by diet alone. They indicated that glibenclamide when administered orally to type II diabetic patients, as a single dose achieved a rapid and satisfactory lowering of blood glucose for a period of 24 hours following its first administration. A similar response was observed after six months of therapy employing the same single dosage.

In a non-blind crossover study involving a prior dietary period, Sonksen et al. (1981) found that hyperglycemia of type II diabetic patients was markedly reduced by four months of glibenclamide therapy. In the subsequent four months of placebo treatment, hyperglycemia returned, demonstrating that glibenclamide is clearly an effective hypoglycemic agent.

5. Adverse Effects (Asmal and Marble, 1984)

Glibenclamide is generally well tolerated when administered in the recommended doses. Although the most common adverse effects that may rarely occur are minor gastrointestinal disturbances (e.g. nausea, vomiting, dyspepsia) and dermatological reactions (e.g. pruritus, urticaria, erythema).

6. Drug Interactions

Drug interactions with glibenclamide therapy has been reported less frequently than the first generation sulfonylureas. Since glibenclamide is bound to plasma proteins by non-ionic forces or van der Waal forces, it is less susceptible displacement from the binding sites by acidic or anionic drugs (e.g. salicylates, warfarin, phenylbutazone) than are the first generation agents. First generation sulfonylureas are more easily displaced because their binding involves ionic forces (Feldman, 1985; McEvoy, 1989). In addition to protein binding, other drugs may interact indirectly to potentiate or antagonize the hypoglycemic action of glibenclamide. Beta-adrenergic blocking agents can mask the symptomatic signs of hypoglycemia (e.g. tachycardia, tremor) and prevent the patients from recognizing the onset of hypoglycemic episodes. The concurrently ingestion of alcoholic beverages with glibenclamide therapy should be avoided because ethanol inhibits gluconeogenesis which

can result in profound hypoglycemia. Drugs that may enhance the hypoglycemic effect of glibenclamide include chloramphenicol, probenecid and monoamine oxidase inhibitors. On the other hand, drugs such as thiazide diuretic (e.g. furosemide), corticosteroids, estrogen, rifampin may antagonize the hypoglycemic effect of the drug (Jackson and Bressler, 1981).

7. Contraindication (Asmal and Marble, 1984)

1. Patients with insulin-dependent diabetes mellitus
2. Diabetes during pregnancy
3. Hypersensitivity to glibenclamide
4. Patients with severe hepatic or renal diseases

8. Dosage and Administration (Asmal and Marble, 1984)

The usual starting dose of glibenclamide is 2.5 mg. to 5 mg. as a single daily dose, given each morning before breakfast. Dosage adjustment should be made in increments of 2.5 mg. to 5 mg. at weekly intervals, as determined by plasma glucose response. Some patients, particularly those who require more than 10 mg. daily dose, may have a more satisfactory response when glibenclamide is administered in two divided dose. For maintenance dose, the usual daily dose is 1.25 mg. to 20 mg.