CHAPTER IV
LITERATURE ON DRUG INVESTIGATED

4.1 ANTIDIABETIC DRUGS: AN OVERVIEW

Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration – hyperglycaemia (fasting plasma glucose greater than 7mmol./lit., or plasma glucose greater than 11.1 mmol./lit., 2hrs after a meal) – caused by insulin deficiency, often combined with insulin resistance. Hyperglycaemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis. When the renal threshold for glucose reabsorption is exceeded, glucose spills over into the urine (glycosuria) and causes an osmotic diuresis (polyuria), which in turn, results in dehydration, thirst and increased drinking. Insulin deficiency causes wasting through increased breakdown and reduced synthesis of proteins. Diabetic ketoacidosis is an acute emergency. It develops in the absence of insulin because of accelerated fat breakdown.

Various complications developed as a consequence of the metabolic derangements in diabetes, often over many years. Many of these are the result of disease of blood vessels, chronic renal failure.

There are two main types of diabetes mellitus

1. Type 1 diabetes (previously known as insulin dependent diabetes mellitus (IDDM) or juvenile onset diabetes).

2. Type 2 diabetes (previously known as non-insulin dependent diabetes mellitus (NIDDM) or maturity onset diabetes.)
In Type 1 diabetes, there is an absolute deficiency of insulin resulting from autoimmune destruction of β-cells. Without insulin treatment such patients will ultimately die with diabetic ketoacidosis. Main reason of causing disease is genetic factor, viral infection.

Type 2 diabetes is accompanied both by insulin resistance (which precedes over disease) and by impaired insulin secretion, each of which are important in its pathogenesis. Such patients are often obese and usually present in adult life, the incidence rising progressively with age as β-cells function declines. The treatment is initially dietary although oral hypoglycemic drugs usually become necessary and about one-third of patients ultimately requires insulin treatment.

**Oral hypoglycemic agents (OHA)**

Use of oral hypoglycemic agents (OHA) is now established in the management of diabetic state. In 1942, Janbon and coworkers discovered that p-aminobenzenesulfonamide – isopropyl thiazole (a sulfonamide) induced hypoglycemia. Loubatieres subsequently found that the compound was showing not any hypoglycemic activity when used in pancreatectomized animals. He, therefore, suggested that the hypoglycemic action was the result of stimulation of the pancreas to secrete insulin. At a latter date a drug called Tolbutamide found its place in therapeutic armamentarium and it became popular for the management of certain diabetic patients. Tolbutamide is a member of the class of drugs referred to as sulphonylureas.
Advantages of oral therapy in diabetes

1. Patient acceptability
2. Ease of administration
3. No need of exogenous insulin – hence decreased insulin antigenicity
4. Insulin – being endogenous – physiological major action on liver and less at periphery
5. Less frequent and less severe hypoglycemia when compared to insulin therapy

Disadvantages

1. Less of medical supervision
2. Disinclination towards potential dangers of diabetes
3. Drug interactions
4. Toxic reactions – though rare could be serious
5. Limitations of dosage and inflexible dosage
6. Increased incidence of therapeutic failure with the passage of time

Drugs used as oral hypoglycemic agents

1. Sulphonylureas
   a) First generation sulphonylureas
      Ex: Tolbutamide, Chlorpropamide, Acetohexamide, Tolazamide
   b) Second generation sulphonylureas
      Ex: Glibenclamide, Glipizide, Gliclazide
   c) Third generation sulphonylureas
      Ex: Glimepiride
2. **Biguanides**
   
   Ex: Buformin, metformin, Phenformin

3. **L – Glucosidase inhibitor**
   
   Ex: Acarbose, Meglitol

4. **Thiazolidinediones**
   
   Ex: Pioglitazone, Rosiglitazone

5. **Short acting insulinotropic agents (or) Meglitinide agents**
   
   Ex: Repaglinide, Nateglinide

**Mechanism of action of Sulphonylureas**

The principle action of sulphonylureas is on β-cells. Stimulating insulin secretion and thus reducing plasma glucose. High affinity receptors for sulphonylureas are present on the $K_{ATP}$ channels in β-cell plasma membrane and the binding of various sulphonylureas parallels their potency in stimulating insulin release. The drugs reduce the $K^+$ permeability of β-cells by blocking $K_{ATP}$ Channels, causing depolarization, calcium ions and thus insulin is released.
4.2 GLIPIZIDE – A PROFILE

Chemically glipizide is 1-cyclohexyl-3-[[p-(2-(5-methyl) pyrazine carboxamido) ethyl] phenyl] sulfonylurea.

STRUCTURE

Mol. Formula: C\textsubscript{21}H\textsubscript{27}N\textsubscript{5}O\textsubscript{4}S  
Mol.Wt.: 445.55

Properties:

It is a white or almost white, odourless or almost odourless crystalline powder. Practically insoluble in water, sparingly soluble in actone, soluble in chloroform. It dissolves in dilute alkali hydroxide.

Absorption and Fate:

Glipizide is rapidly and completely absorbed from the gastrointestinal tract. It is extensively bound to plasma proteins and half-life\textsuperscript{1} of 3.4 ± 0.7 h. It is metabolized in the liver and excreted in the urine largely as inactive metabolites.

Pharmacokinetics:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral availability</td>
<td>95 %</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td>&lt; 5 %</td>
</tr>
</tbody>
</table>
Bound in plasma -- 98.4 %
Clearance -- 0.52 ± 0.18 ml/minute/kg
Volume of distribution -- 0.17 ± 0.02 L/Kg
Half-life -- 3.4 ± 0.7 h

**Adverse Effects, Treatment and Precautions:**

**Adverse Effects:**

Gastrointestinal disturbances such as nausea, vomiting, heartburn, anorexia, diarrhoea and metallic taste may occur with sulfonylurea and are usually mild and dose dependent. Increased appetite and weight gain may occur.

Hypoglycemia occurs with all hypoglycemic agents and may be severe, prolonged and sometimes fatal. Other severe effects may be manifestations of a hypersensitivity reaction. They include cholestatic jaundice, leucopenia, and thrombocytopenia, aplastic anaemia, erythema multiforme or the Stevens Johnson syndrome, exfoliative dermatitis and erythema nodosum.

**Treatment of Adverse Effects:**

In acute poisoning the stomach should be emptied by emesis or lavage. Hypoglycemia should be treated with urgency.

**Precautions:**

Glipizide use in non-insulin dependent diabetes mellitus is contraindicated in patients with ketoacidosis and in those with severe infection, stress and trauma.
Glipizide should not be given in severe impairment of renal or hepatic function because of increased risk of hypoglycemia.

**Packing and Storage:**

Preserved in tight containers and protected from light. Glipizide is marketed as 5 mg and 10 mg tablets. SR tablets containing 10 mg of glipizide are available commercially.

**Therapeutic Uses:**

Glipizide is used to control hyperglycemia in type-II diabetes. Usual initial dose in treatment of diabetes mellitus is 2.5 to 5 mg daily 3 or 4 times.

**Mechanism of Action:**

Glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependant upon functioning of beta cells in the pancreatic islets. The mechanism by which glipizide lowers blood glucose during long term administration has not been clearly established. Fasting insulin levels are not elevated even on long-term glipizide administration, but the post-prandial insulin response continues to be enhanced after at least 6 months of treatment.

**Pharmacokinetics:**

Gastrointestinal absorption of glipizide in man is uniform, rapid and essentially complete. Peak plasma concentrations occur 1-3 h after a single oral dose. The half-life of elimination ranges from 2-4 h in normal subjects, whether given intravenously or orally. The metabolic and excretory patterns are similar.
with the two routes of administration, indicating that the first pass metabolism is not significant. Glipizide does not accumulate in plasma on repeated oral administration. It has been reported that total absorption and disposition of an oral dose was unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes. Thus glipizide was more effective when administered about 30 minutes before, rather than with a test meal in diabetic patients. Protein binding was studied in serum and found to be 98-99 %, one hour after either oral or intravenous administration of glipizide.

The apparent volume of distribution of glipizide after intravenous administration was 11 L, indication of localization within the extra cellular fluid compartment.

Metabolism of glipizide is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and excreted mainly in the urine. Less than 10% unchanged glipizide found in the urine.

4.3 NEED FOR CONTROLLED RELEASE OF GLIPIZIDE

Oral hypoglycemic agents represent the most commonly practiced pharmacological approach to the treatment of NIDDM. Most of the physicians initially use sulphonylurea medications in the management of NIDDM, because they have a long history of proven efficacy and safety . Differences in the pharmacokinetic and pharmacodynamic characters of the various sulfonylurea compounds produce different therapeutic side effect profiles. Longer – acting agents like glyburide or chlorpropamide are efficacious but tend to produce more
sustained hyperinsulinemia and have higher rates of hypoglycemia during routine clinical use\(^8\text{-}^{10}\).

Short acting sulfonylurea such as glipizide is thought to be more efficacious in enhancing post-prandial insulin secretion and generally have a lower risk of hypoglycemia\(^{11\text{-}16}\). But glipizide is having short biological half-life 3.4 ± 0.7 h, need to be administered more than once a day, which increases the possibility of non-compliance and produce greater fluctuations in plasma drug levels both above and below therapeutic range \(^{17\text{-}18}\). The drug profile makes a glipizide a suitable candidate for formulating controlled release dosage form. This will reduce frequent dosage administration necessary to control hyperglycemia. It also maintains the optimum therapeutic drug concentrations with reduced adverse effects and finally will improve the patient compliance.

The physiology of NIDDM is associated with abnormalities in pancreatic insulin resistance. Since, insulin resistance and hyperinsulinemia have been observed as independent risk for clinical cardiovascular complications i.e., cardiomyopathy\(^{19\text{-}21}\). Excellent glucose control with lower circulating insulin levels is considered to be a goal of therapy of NIDDM. The control of plasma glucose in patients with NIDDM is likely to have benefits in reducing or preventing the long term complications such as diabetic nephropathy, diabetic cardiomyopathy, diabetic retinopathy, diabetic neuropathy and gangrene\(^{22\text{-}23}\).

The clinical reports on extended release glipizide indicated that it was significantly more effective than immediate release glipizide in reducing fasting glucose levels. Both formulations reduced post-prandial plasma glucose levels
equally; however, extended release glipizide extended its control in maintaining optimum therapeutic insulin and C – peptide levels. This suggests that controlled release of glipizide improves insulin sensitivity\textsuperscript{23}.

Controlled release of glipizide produces maximum therapeutic effect based on pharmacokinetic and pharmacodynamic relationships and it is much effective even in poorly controlled patients (those with fasting plasma glucose levels greater than 250 mg/dl). It was safe and well tolerated in a wide variety of patients with NIDDM and did not produce weight gain or adversely affect lipids\textsuperscript{24}. Cefalu \textit{et al}\textsuperscript{25}, also reported that glipizide extended – release preparation is effective in lowering glucose tolerance and improving insulin sensitivity without an increase in fasting insulin, weight gain, or change in abnormal fat composition.

Some of the adverse effects such as leucopenia, agranulocytosis, thrombocytopenia, hemolytic anaemia, aplastic anaemia, pancytopenia, hepatic porphyria, hyponatremia, syndrome of inappropriate antidiuretic hormone which are reported with usage of conventional dosage forms and other sulphonylureas, have not been observed with controlled release glipizide dosage forms\textsuperscript{26}. Controlled release formulations of glipizide will lower monthly drug acquisition costs and improves the patient compliance.

Controlled release formulations of glipizide will provide more stable therapeutic plasma drug concentrations over longer periods of time. This not only assists better glycemic control but also produce less fasting insulinemia. The incidence of hypoglycemia with controlled release formulations of glipizide is low (less than 3\%)\textsuperscript{27}.  

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4.4 PAST WORK ON CONTROLLED RELEASE OF GLIPIZIDE

Delivery of glipizide from asymmetric membrane capsules using encapsulated excipients was studied by Gibbes et al.\textsuperscript{28} An evaluation of bioadhesive glipizide spheres and compacts from spheres prepared by extruder/marumerizer technique was done by Ghaly et al.\textsuperscript{29} Development and evaluation of osmotically controlled oral drug delivery system of glipizide was done by Verma, R.K. and Garg, S.\textsuperscript{30} Cyclodextrin complex osmotic tablet for glipizide delivery was developed by Gan et al.\textsuperscript{31} A preliminary evaluation of glipizide spheres and compacts from spheres prepared by crosslinking technique was done by Garcia, J.G. and Ghlay, E.S.\textsuperscript{32} Characterization, \textit{in vitro} and \textit{in vivo} evaluation of mucoadhesive microcapsules of glipizide was made by Chowdary K.P.R. and Rao Y.S.\textsuperscript{33} Bioavailability assessment of immediate and extended release formulations glipizide in healthy volunteers was made by Dhawan et al.\textsuperscript{34} Development of a controlled release low dose class II drug glipizide was made by Jamjad, S. and Fassihi, R.\textsuperscript{35} Pharmacological evaluation of membrane moderated transdermal systems of glipizide was done by Mutalik, S. and Udapa, N.\textsuperscript{36} Formulation and evaluation of mucoadhesive glipizide microspheres was carried out by Patel et al.\textsuperscript{37}

REFERENCES


