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Review Article

ADME of Glyburide, Metformin and Nutrition for Management of Gestational Diabetes

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Abstract

Metformin and Glyburide are generally recommended for the treatment of gestational diabetes. These oral hypoglycemic agents are the best alternatives for Insulin treatment. Metformin and Glyburide have longer shelf life, less expensive and convenient for patients as compared to insulin. Glyburide and Metformin have different drug metabolism and pharmacokinetics characteristics during pregnancy. Glyburide and its metabolites cross the placental barrier, so does Metformin. Absorption, Distribution, Metabolism and Pharmacokinetics (ADME) of Glyburide and Metformin are crucial for the potency of these drugs in the treatment of pregnant patients. Hence the present review is focused on the metabolism and pharmacokinetics of Glyburide and Metformin and its impact on the treatment of Gestational Diabetes.

Keywords: Hyperglycemia; Gestational diabetes; Glyburide; Metformin; Nutrition

Introduction

Gestational diabetes

Gestational diabetes is due to high blood sugar levels during pregnancy [1]. Gestational diabetes is prevalent in 4% to 10% of all pregnancies and identified in women with no previous history of diabetes. Most often, gestational diabetes is deciphered after the child's birth. Women diagnosed with gestational diabetes are more prone to incur Type-II diabetes after pregnancy [2]. Historic data suggests that many women diagnosed with gestational diabetes develop Type-II diabetes after 10 to 12 years.

During pregnancy, hormonal changes occur in the body and few women are resistant to insulin. Specialized cells in the pancreas secrete insulin. Insulin is a hormone that metabolizes glucose for later usage as energy for proper function of the human body. In women diagnosed with gestational diabetes insulin levels were identified to be very low because pancreas cannot secrete insulin, resulting in high glucose levels in the blood [3-5]. Diabetes is classified as Type-I and Type-II diabetes. Type-I is referred as Insulin Dependent Diabetes Mellitus (IDDM) and Type-II is attributed to Non Insulin Dependent Diabetes Mellitus (NIDDM). Few of the patients suffering from gestational diabetes might incur Type-II diabetes at later stage but not Type-I diabetes.

Function of insulin to regulate blood glucose level

Beta cells identified as small clusters in the pancreas secrete insulin. These beta cells are called islets of langerhans. Produced insulin is delivered to the blood stream, disseminated throughout the body and is responsible for several activities in the body [6]. Major activities of insulin are synergized by biotransformation of sugars, starches, lipids, proteins and other carbohydrates in the body. Thus, insulin is crucial for the body's utilization of glucose as energy.

Generally, blood glucose levels are regulated by insulin, and it reduces the blood glucose level. When the blood glucose raises (after consuming food), insulin is delivered from the pancreas to regularize the glucose level by boosting the intake of glucose into body cells.

Resistance of Insulin occurs, when the effects of insulin have no effect on the body [6,7]. To compensate this, pancreas secretes more insulin and reaches a stage when it cannot produce insulin to meet the demands of the body. At this juncture, blood glucose level increases drastically in the body resulting in diabetes. Insulin resistance occurs in reaction to the insulin generated within the body (endogenous) or insulin injected in to the body (exogenous). Insulin resistance always takes precedence over the development of Type-II diabetes. Insulin level either reduces or it is found below optimum level in the patients diagnosed with diabetes. Several of these aspects result in high blood glucose level called as hyperglycemia.

Treatments available for gestational diabetes

Insulin injections are the standard care for the treatment of diabetes. However, due to shorter shelf life and inconvenience to patients during injections, alternative to insulin was always in search. Many oral antidiabetic drugs were tested for Gestational Diabetes as well. Oral antidiabetic drugs [8,9] such as Sulfonylurea drugs, biguanides, glitazones and gliptins were prescribed by Physicians to Patients to control diabetes. While many drugs are available to treat Type-II diabetes, treatment options for gestational diabetes are only few. Oral medications such as Glumetza, Glucophage, Micronase, Glynase, Diabeta and Fortamet are the medicines prescribed for Type-II diabetes, but all these medications are not approved by Food and Drug Administration to treat gestational diabetes.

Many clinical trials are still in progress to identify the right prescription for the pregnant patients. Insulin, Metformin, Glyburide (Figure 1) and combination of Glyburide and Metformin have been successful in clinical trials and patients were also comfortable taking these medications [10,11]. Patients of different background get adjusted to one of the above treatments along with regular exercise and diet. Even though insulin is preferred, pain caused during

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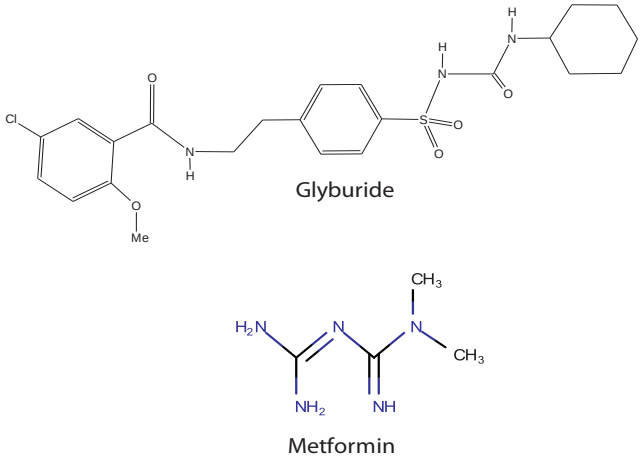

Figure 1: Structure of Glyburide and Metformin.

injection directs physicians to prescribe Metformin, Glyburide or Combination of Metformin and Glyburide for the treatment of gestational diabetes.

Glyburide lowers the blood glucose by stimulating the release of insulin from the pancreas. This is a mechanism dependent upon beta cells in the pancreas. With chronic administration in patients with type 2 diabetes, the blood glucose lowering effect continues despite a gradual decline in the insulin secretion with respect to the dose of glyburide. Extra pancreatic effects may also be involved in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

In patients with type-2 diabetes antihyperglycemic agent Metformin improves glucose tolerance by decreasing both basal and postprandial plasma glucose. Metformin improves insulin sensitivity by decreasing the absorption of glucose in intestine, reducing the production of hepatic glucose and increases utilization and peripheral glucose uptake.

Metformin and Glyburide – perspectives from metabolism studies

Metformin and Glyburide have two different chemical structures and their mechanism of action is also different (Figure 1). Metformin is metabolically very stable drug, but glyburide is highly metabolized. Until recently around ten major metabolites were identified. Metabolites of sulfonylurea drug glyburide were monohydroxylated metabolites [12], metabolite due to loss of cyclohexyl ring, dihydroxylated metabolites, metabolite due to monooxygenation and dehydrogenation [13-15]. Monohydroxylated metabolites were formed in very large quantities, whereas other metabolites were identified in very less quantity [16,17]. Potency and toxicity studies of monohydroxyated metabolites were studied extensively. Monohydroxylated metabolites are expected to be eliminated by urine due to its polar nature. Potency and toxicity studies of newly identified metabolites in scant quantities were not carried out in detail. Many of the patients were accustomed to the treatment of glyburide without complications. Some patients have reported few side effects that might be due to the scant quantity of the metabolites for which the studies are yet to be carried out.

Metabolism of Glyburide was also carried out in placental

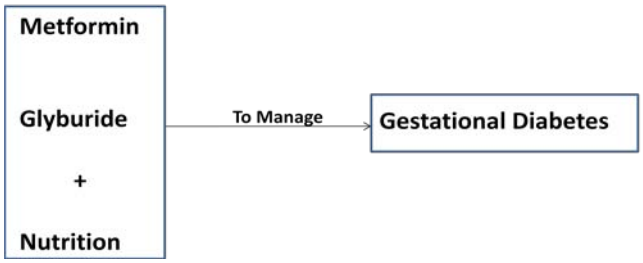

Figure 2: Management of Gestational Diabetes through Pharmaceutical Drugs and Nutrition.

microsomes and its results were compared with liver microsomes from human and baboon [12]. Many differences were identified. Most of the metabolites identified in liver microsomes were identified in placenta as well, but in different quantities. Hence, it is important to screen the compounds in both liver and placental microsomes. Generally, it was noticed that metabolite formation was high in liver as compared to that of placenta. Among the monohydroxylated metabolites, metabolite M1 was predominant in liver microsomes, but metabolite M5 was abundant in placental microsomes.

When compared to baboon, major differences were noticed in the quantity of the metabolites formed in liver compared to that of humans. Similar metabolites were identified in both humans and baboons, but major differences in quantity were observed. Metabolite M4 was present abundantly in baboon, whereas metabolite M1 was present in high quantity in human. Differences were noticed in placental microsomes of humans and baboons as well.

Thus two different species humans and baboons as well as two organs liver and placenta showed major differences in the quantity of the metabolites formed.

Later studies were extended to other species such as Rat, Mouse and Dog [18,19]. Here as well many differences were noticed in terms of quantities of the metabolites formed. Kinetics of the metabolism of glyburide suggests that baboons were very close to humans in terms of metabolism [20]. Thus *in vitro* metabolism studies confirm that sulfonyl urea drug Glyburide is safe for treatment of gestational diabetes. Most of the identified metabolites were not toxic, but two of the monohydroxylated metabolite was found to have potency similar to that of parent drug Glyburide. This could be the reason in some of the patients that both glyburide and two of the monohydroxylated metabolites were active to bring down the blood sugar level leading to hypoglycemia where the concentration of glucose reduced drastically [21,22]. Hypoglycemic conditions also lead to discomfort in some of the patients. Overall sulfonylurea drug glyburide is safe to treat patients suffering from gestational. Some patients who are not comfortable with glyburide treatment respond well for Metformin treatment and vice versa. Hence, combination therapy of Metformin along with Glyburide is also suggested to treat gestational diabetes.

Absorption, distribution and pharmacokinetics of Glyburide

Pharmacokinetics studies have confirmed the absorption of Glyburide in an hour and have maximum drug concentration for about 4 hours. After 24 hours, only traces of Glyburide have been detected in many studies. Glyburide distribution is influenced by its

affinity towards serum albumin (99 percent bound), and clearance of the glyburide is observed to be biliary and renal routes [23-25].

Absorption, distribution and pharmacokinetics of Metformin

Metformin absorption gets completed in 6 hrs after oral dose followed by rapid distribution. Metformin do not bind to plasma or hepatic proteins and do not undergo metabolism, hence the risk of lactic acidosis is less. Oral bioavailability of metformin is about 40 to 60% and plasma elimination half-life occurs between 4 to 8 hrs [26,27].

Nutrition and Gestational Diabetes Mellitus

Nutrition plays an important role in pathogenesis as well as in management of gestational diabetes mellitus. Nutrition therapy in tandem with medications and suitable physical activity can help improve the glycemic control and overall health. Studies indicate use of medical nutrition therapy to ensure adequate pregnancy weight gain and fetus growth while maintaining euglycemia and avoiding ketones [28]. Simple measures like changing dietary patterns, consuming foods with low glycemic load, dividing carbohydrates into three major meals and three snacks can contribute significantly to control blood glucose in Gestational Diabetes Mellitus [29,30]. In low-income settings where women have a low intake of micronutrient-rich foods, improving dietary micronutrient quality by increasing intake of green leafy vegetables, fruits, and/or milk may have an important protective effect against the development of Gestational Diabetes Mellitus [31]. Nutrition thereby provides a window of opportunity to prevent the complications and existing problems associated with Gestational Diabetes Mellitus not only in the case of mother but also for the unborn generation.

Conclusion

Metformin and Glyburide along with appropriate nutritious diet are good alternatives for insulin to control gestational diabetes. Insulin is the first line treatment for Gestational Diabetes. Insulin is not preferred by many patients due to inconvenience. Absorption, Distribution, metabolism and pharmacokinetics of metformin and glyburide suggests that appropriate dosage for a particular patient is necessary. Eventhough metformin, glyburide and its metabolites are permeable through placenta, yet there is no major risk for fetus. Optimal therapy for managing glucose levels depends on the characteristics of a specific patient. More studies have to be performed with both oral anti diabetic drugs and nutrition to manage the gestatational diabetes in both mother and fetus.

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