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Review Article

IMPORTANCE OF METFORMIN WITH REPAGLINIDE IN THE TREATMENT OF TYPE II DIABETES MELLITUS: A DECADEL REVIEW

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ABSTRACT

Objectives of this work is to summarize the consequent development of dosage form from clinical evidence to market and its combination to control the both, insulin deficiency and resistance, to achieve the minimal hypoglycemia, repaglinide shows that no cardiac and vascular effect, antioxidant effect, no increase in blood pressure and improved lipid profile. Also shows glucose concentration dependent response, combination to exert additive/synergistic effect to achieve near normal glycemia.

Key words: Combination therapy, Metformin, Repaglinide.

INTRODUCTION

From the last two decades history of diabetic patients, most of the monotherapeutic treatments for type 2 diabetes mellitus fail to achieve normal glycemia. The targets of normal glycemia are achieving HbA_{1c} levels less than 7% or 6.5% [1, 2]. These targets are used to evaluate the therapeutic treatment strategies to attain normal HbA_{1c} levels.

Most of the patients are with stimulated insulin deficiency and insulin resistance. The former can manifest the post prandial hyperglycemia and later as fasting hyperglycemia. Higher failures are from long term monotherapies and uncontrolled post prandial glucose excursions in progression of microvascular complications. Metformin monotherapy[3] can reduce fasting plasma glucose levels by approximately 1.5% and gradual deterioration of glycemic control is commonly observed due to progressive ß cell failure. To overcome such failures of monotherapy, a combined therapy of oral anti-diabetic agents should be considered, the recently used oral anti-diabetic agents are sulphonylureas, biguanidines & thiazolidinediones and non-sulphonylureas. The former three categories were mainly target the fasting hyperglycemia and had a limited effect on post prandial glucose levels. Later one can control both fasting plasma glucose and post prandial glucose levels.

Metformin, N, N-dimethylimido dicarbonimidic diamide hydrochloride, a biguanidines derivative, is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents has been used in the treatment of type2 diabetes for nearly 50 years as insulin sensitizer, lowers fasting plasma glucose but increase in use of metformin results in lactic acidosis can occurs by accumulation of metformin. May be the factors are renal impairment, old age doses more than 2g per day. The secondary reason may be due to metformin excreted unchanged in the urine was decreased. The chronic impairment associated with acute dehydration, shock and tissue hypoxia, acute myocardial infarction, pulmonary embolism, cardiac failure and chronic liver disease. Between 1985& 2001, total 48 cases of lactic acidosis with metformin were reported to Australian adverse drug reactions advisory committee (ADRAC). The dose of the metformin should be significantly reduced under these circumstances.

MECHANISM OF ACTION OF METFORMIN

Metformin improves glucose tolerance in patients with type 2 diabetes; its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Without doubt, metformin is the drug of choice for most of the patients with type 2 diabetes mellitus. The combination therapies can correct the metabolic defects. Long term monotherapies lost the early phase of insulin secretion, leads to increased post prandial glucose and increased insulin resistance also frequently occurs in people, who are obese and associated with metabolic syndrome. For example good treatments are achieved by only about 25% of patients treated with monotherapies such is metformin monotherapy with a mean baseline HbA_{1c} of 8.2 to 8.4[4,5].

Most of oral anti-hyperglycemic agents were mainly to reduce fasting plasma glucose, but controlling of both post prandial and fasting glycemia are important for improvement of metabolic disorder. Most of the studies did not mention about post prandial glycemia and glycosylated haemoglobin (HbA_{1c}) was found to be a strong predictor of major cardiovascular events.

Sulphonylureas provide optimal efficiency and few side effects at low dosages but apart from their tendency to cause hypoglycemia. £-glucosidase inhibitors can reduce the post prandial hyperglycemia but gastrointestinal side effects limits their use in combination. The best example for insulin sensitizer is metformin. Addition of acarbose to metformin, patients inadequately control decreases the post prandial glucose levels but however the complications are git side effects, bloating, abdominal discomfort, diarrhorea and flatulence.

In the last decade, the newer agents are become available for therapy of type2 diabetes mellitus. Repaglinide is the first of the non-sulphonylureas derivative, it is an active S (+) enantiomer of 2-ethoxy-4(2-((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid, a carbamoyl benzoic acid derivative.

MECHANISM OF ACTION OF REPAGLINIDE

Repaglinide differs structurally form the sulphonylureas[6]. The main effect of repaglinide is the inhibition of ATP sensitive K^+ channels in the membrane of the pancreatic B-cell causing depolarization and influx of calcium ions, increasing intracellular concentration and stimulation of excursions[7]. Repaglinide not promote insulin exocytosis directly[8]. The drug is rapidly absorbed after oral administration but is also rapidly metabolized with half-life approximately 30 min[9, 10]. The drug acts rapidly to stimulate post prandial insulin secretion but has a short duration of action and hence a low risk of inducing hypoglycemia. Hatrop V et al[11] stated that pharmacokinetics of repaglinide in young and elderly are same. No significant differences in pharmacokinetics parameters either after single oral administration or after pre-prandial administration of repaglinide 2mg TID for 7 days.

The S-enantiomer of repaglinide was 100 times more potent than the R-enantiomer[12]. The insulinotropic effect of repaglinide was depending on glucose concentration available[13]. Repaglinide is more potent at stimulating insulin secretion than glibenclamide in the

presence of 10mmol/l glucose. A dose dependent reduction of blood glucose was achieved with minimum dose of 0.01mg/kg; the response was 18 times greater than glyburide and 25 times than glibenclamide[14].

TOXICOLOGICAL STUDIES

Repaglinide has little or no toxicological effects at doses up to 100 folds greater than maximum therapeutic doses in humans (2mg/kg/day). No carcinogenic effect has been shown up to 60 mg/kg/day[15]. There were no significant clinical changes observed under single centre, open label, phase I trial, 6 healthy male volunteers received 2 mg of repaglinide 4 times a day for 13 days[16]. Repaglinide is metabolized predominantly in the liver by cytochrome p450 enzymes, 90% of repaglinide was recovered in faces and 8% in urine, the biotransformation processes were initializing from oxidative opening of piperidine ring 7 glucuronidation of the aromatic carboxlic acid group, the dicarboxylic acid metabolites are in urine, major metabolite in the feces.

Repaglinide is bound to human serum albumin and £$_1$-acid glycoprotein. In vitro protein binding was approximately 98.5%. The order of repaglinide and its metabolites by concentration in the feces was M2> unknown metabolite M1> repaglinide> M4> M5> M6> M7. In vitro protein binding studies are showing that repaglinide replaced by warfarin, furosemide, and tolbutamide. Fibric acid derivatives, statins and ACE inhibitors increase the repaglinide metabolism.

Repaglinide was rapidly absorbed after oral administration in the fasting state, t_{max} Was 0.6hr, independent of dose bioavailability was 63%, and half-life of repaglinide is 1.0-1.4 hr in type2 diabetes patients.

Repaglinide is suitable as first line monotherapy in the management of type 2 diabetic patients who have failed to respond adequately to diet alone. It shows synergistic activity with metformin in obese patients because of rapid absorption and sort duration of action repaglinide can intensifies the blood glucose control an insulin secretogoggue.

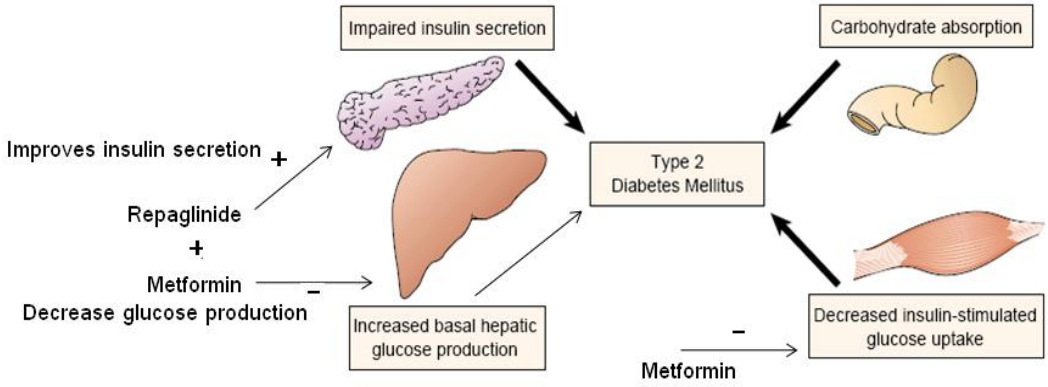

Figure 1: Combination of Metformin and Repaglinide

MONOTHERAPY OF REPAGLINIDE

One year comparison study for repaglinide Vs glyburide and repaglinide Vs Glipizide showed that repaglinide is effective as monotherapy for the treatment of type2 diabetes and shows superior efficacy to Glipizide[17, 18, 19]. A 10 week study of 4mg repaglinide given in breakfast and dinner results in significant reductions were achieved pre-prandial repaglinide dosing reduces both fasting blood glucose and post prandial glucose concentration[20]. In 18 week placebo controlled study in 99 patients received repaglinide 0.25-8.0mg before each main meal, the treated patients had a significance reductions in postprandial glucose, mean fasting glucose and HbA_{1c}concentrations compared with placebo[21].

Improvement of glycemic control is unrelated to meal frequency. Repaglinide treated patients had constituency in decrease in $HbA_{1c}$and fasting blood glucose regardless of number of meals per day. Repaglinide controlled post prandial glucose levels more efficiently in sulphonyl urea –naïve patients. The repaglinide treated patients has equal efficiency in reducing fasting plasma glucose and HbA_{1c} levels.

K_{ATP} channels are composed of two different type protein sub units: an inwardly rectifying potassium channel (kir 6.x) and a sulphonylureas receptor (SUR) [22, 23, 24]. K_{ATP} channel is an octamer, assembled from four SUR subunits and four Kir 6: x subunits[25, 26, and 27]. Kir 6.2 sub unit serve as the pore of the K_{ATP} channel in beta cells, heart, skeletal; muscle and some types of smooth muscle. The sulphonyl urea sub units are SUR1 in beta cells, SUR 2A in cardiac and skeletal and SUR 2B in smooth muscle [28, 29, 30]. SUR 2A and SUR 2 B both are different in only in their last 42 amino acids.

The gliclazide and tolbutamide inhibit Kir 6.2 /UR 1(beta cell) but not Kir 6.2/ SUR A (cardiac type) or Kir6.2/SUR 2B (smooth muscle type) channels with high potency, while glibenclamide and benzoic acid derivatives block all three types of channels with similar potency[31, 32]. Repaglinide is a carbamoyl benzoic acid derivative that has been shown to be effective in blocking beta cell K_{ATP} and stimulating insulin release from islets and isolated perfused pancreas[33, 34].It also enhances insulin secretion in type II diabetic patients and hereditarily diabetic rats[35, 36].

There is no species differences in repaglinide affinity repaglinide block all three types of K_{ATP} Channel with similar affinity and they share common binding site at concentrations 8nmol/lt. Gribble FM et al[32] studied that tolbutamide blocks K_{ATP} channels containing SUR1, but not

SUR 2A or SUR 2B.Meglitinide blocks all three types of cloned K_{ATP} channel.

Glibenclamide contains both sulphonyl urea and benzamido derivatives interact with both sites on SUR1 but only on single site on SUR 2.

So, the repaglinide can interact with cardiac and smooth muscle type of K_{ATP} channel. Cross-reactivity does not result in cardiovascular side effects[37]. An in vitro study of effect of fibrates and Rifampicin studied by laur I.kajosaari[38] on recombinant cyp2C8 and recombinant cyp3A4 metabolized repaglinide at similar rates quercetin (25 µm) and itraconazole (3µm) inhibited the metabolism of 0.02µm repaglinide by 58% and 71%.

Double blind randomized placebo-controlled parallel study of efficacy and safety (body weight &hypoglycemia) of repaglinide in a flexible meal time dosing regimen in every day clinical practice of total 408 patients poorly controlled by diet, receives 0.5mg at meal times for 16weeks on one meal-one dose and no meal-no dose principle. Significantly improves glycemic control to base line by reducing 1.45 HbA_{1c} on independent of meal pattern and degree of obesity and no significant increment in body weight[39].

COMBINATION THERAPY

Cho et al[58] studied that the efficacy and safety of giving mitiglinide to patients with inadequate glycemic control with metformin monotherapy mitiglinide effectively decreased HbA_{1c} levels. Addition of mitiglinide improved both fasting and post prandial hyperglycemia and did not increase adverse events compared with placebo. Other members of the meglitinide family with metformin can be comparable. Metformin and repaglinide effect can see in figure 1.

Metformin suppresses glucose production in the liver[40]And improves insulin resistance in skeletal muscle through the activation of AMP-activated protein kinase [41, 42]. Metformin monotherapy is reduces FPG by 2.0mol/l and HbA_{1c} by 1.5%[43, 44].

The gradual deterioration in glycemic control is commonly observed in subjects receiving metformin monotherapy relative to B-cell failure[45]. This may be due to loss of early phase insulin release [46, 47, 48]. Mitiglinide family can restore early phase insulin release from B-cell more effectively than sulphonylureas[49, 50, 51, and 52]

This is important in that the early phase insulin release after meals inhibits endogenous glucose production and plays a critical role in the maintenance of post prandial glucose homeostasis. Therefore the combination of repaglinide and metformin would be a good treatment option for better glycemic control.

Controlling of post prandial hyperglycemia with mitiglinide family shows the improvement of oxidative stress and inflammation, which are pathological mechanisms of cardiovascular diseases in diabetic patients. Comparison of hypoglycemia greater rate observed for repaglinide /metformin FDC (fixed dose combination) than for thiazolidinediones with metformin

Repaglinide /metformin treatment had minimal effects on lipid profiles, whereas rosiglitazone/ metformin treatment increased HDL, LDL & non-LDL cholesterol levels it has showed 14.1% increment in LDL and 11.4% in HDL for base after 26 weeks of treatment.

Raskin et al stated that, incidence of adverse events like peripheral edema was absent for repaglinide /metformin therapy. These events are occasional; of rosiglitazone/metformin FDC therapy[58]

Comparison the effect of repaglinide with metformin and monotherapy of each drug on glycemic control: a total of 83 patients had inadequate glycemic control (HbA_{1c} >7.1%) 27 out of 83 patients continued with prestudy dose metformin with addition of repaglinide , repaglinide dose alone for 29 patients for 4-8 weeks titration and continued for 3 months maintenance period. In the combined therapy: HbA_{1c} was reduced by 1.4±0.2%. From 8.3 to 6.9% and fasting plasma glucose by 2.2mmol/l. no significant changes were observed in subject treated with repaglinide or metformin monotherapy in HbA_{1c} 0.4 and 0.3% decreases respectively, Combined metformin and repaglinide therapy resulted in superior glycemic control compared with repaglinide or metformin monotherapy in patients with type 2 diabetes mellitus whose glycemia had not been well controlled by metformin monotherapy.

A open labeled parallel randomized multicenter trails to compare efficacy and safety of repaglinide versus Nateglinide with metformin on 192 patients whose uncontrolled glycemic levels HbA_{1c} >7% and ≤12% previous treatment with sulphonylureas and patients randomized to addition of repaglinide (n=96) or Nateglinide (n=96) for 16 weeks the final HbA_{1c} levels were lowered for repaglinide (7.1vs7.5%) significantly. Medium final doses were 5.0 mg/day for repaglinide and 360mg/day for repaglinide and 360mg/day for Nateglinide.

The addition of repaglinide to metformin therapy resulted in reductions of HbA_{1c} and FPG values that were significantly greater than the reductions observed for Nateglinide.

CONCLUSION

Combination therapy with metformin and repaglinide is safe and effective for the treatment of type2 diabetic patients, who show inadequate glycemic control with metformin monotherapy. More clinical studies needed to examine the side effects.

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