Comparative evaluation of miglitol versus repaglinide on postprandial hyperglycemia and glycosylated haemoglobin in Type-2 diabetes mellitus patients

Naser Ashraf Tadvi, Mirza Shiraz Baig, Deepak Sadashiv Bhosle, P. R. Gade, P. N. Khandelwal

Dept. of Pharmacology, Govt. Medical College, Aurangabad, India

AIM: To assess the effect of miglitol versus repaglinide on postprandial hyperglycemia and glycosylated hemoglobin in Type-2 diabetes mellitus. **METHODOLOGY:** This open-labeled randomized parallel group prospective clinical trial of 16-week duration included 60 patients of Type-2 diabetes randomly assigned to receive miglitol 25 mg thrice a day for four weeks followed by 50 mg thrice a day for 12 weeks or repaglinide 0.5 mg thrice a day for four weeks followed by 1 mg thrice a day for 12 weeks. Glycosylated hemoglobin, fasting and postprandial plasma glucose levels were assessed at the start and end of the study. **RESULTS:** The mean glycosylated hemoglobin, postprandial plasma glucose levels as well as fasting plasma glucose decreased significantly in miglitol as well as repaglinide group ($P<0.001$). There was no significant difference in the reduction of glycosylated hemoglobin between miglitol (1.14%) versus repaglinide group (1.45%, $P=0.32$). The postprandial glucose reduction in miglitol group (88.5 mg%) was not different from repaglinide (101.2 mg%, $P=0.23$). Similarly reduction in fasting glucose between miglitol (45.6 mg%) and repaglinide (40.86 mg%) was not significantly different ($P=0.73$). **Conclusion:** Miglitol and repaglinide are equally efficacious in reducing postprandial glucose levels, fasting glucose levels as well as glycosylated hemoglobin.

KEY WORDS: Glycosylated hemoglobin, postprandial hyperglycemia, miglitol, repaglinide.

Introduction

Diabetes mellitus is the single most important metabolic disease recognized worldwide as one of the leading causes of death and disability.[1] Recent studies have shown that postprandial hyperglycemia may be a more accurate predictor of HbA_{1C} levels and cardiovascular mortality than fasting hyperglycemia.[2-4] This information has focussed attention on postmeal glycaemic control.

Currently two oral group of drugs i.e. alpha glucosidase inhibitors and meglitinide analogs (nonsulfonylurea secretagogues) are available that specifically target postprandial hyperglycemia. Alpha glucosidase inhibitors are being widely used in the treatment of type-2 diabetes. They delay the absorption of carbohydrates from small intestine and thus have a lowering effect on postprandial blood glucose and insulin levels.[5] Miglitol is the first pseudomonosaccharide alpha glucosidase inhibitor which has similar efficacy to acarbose even at lower therapeutic doses and additionally has the advantage of being non hepatotoxic.[6] Miglitol is a useful first line agent for treatment of Type-2 diabetes patients who are insufficiently controlled by diet alone and has been approved for monotherapy as well as combination with other antidiabetic drugs.[7]

Meglitinide analogues are a new family of nonsulfonylurea insulin secretagogues that stimulate insulin release by inhibiting ATP sensitive potassium channels of the β-cell membrane via binding to a receptor distinct from that of sulfonylureas. Meglitinide analogues have a rapid onset and shorter duration of action; as a result insulin secretion is stimulated to a greater extent within the first few minutes of their administration, hence they are effective in controlling postprandial surge of blood glucose levels.[8]

Repaglinide is a meglitinide analogue more efficacious than nateglinide and has been approved for monotherapy as well as in combination with other antidiabetic agents for the treatment of Type-2 diabetes mellitus.[9,10]

Correspondence to **Dr. Mirza Shiraz Baig,** Dept. of Pharmacology, Govt. Medical College, Aurangabad, India.
E-mail: shirazdoctor@yahoo.com

Studies carried out by Drent *et al*[11] and Chiasson *et al.*[12] reported that treatment with miglitol in Type-2 diabetes patients produced a significant reduction in blood glucose level and HbA_{1C}. Studies carried out by Jovanovic *et al*[13] and Goldberg *et al* [14] reported that treatment with repaglinide in Type-2 diabetes produces a significant reduction in blood glucose level and HbA_{1C}.

Repaglinide has shown equal efficacy to pioglitazone, glimepiride, glibenclamide and metformin.[15-18] But the studies comparing miglitol with repaglinide are limited and no clinical studies comparing repaglinide and miglitol in a head to head comparison have been reported. With the above background and the clinical data available to date, the present study was planned to compare and evaluate, head to head the effect of miglitol versus repaglinide on postprandial blood sugar level and glycosylated hemoglobin (HbA_{1C}) in patients of Type-2 diabetes mellitus.

Methodology

This study was randomized, parallel group, comparative, prospective study in patients of Type-2 diabetes mellitus. Sixty patients (n = 60) with uncontrolled blood glucose levels, defined as postprandial plasma glucose levels more than 200 mg % and glycosylated haemoglobin more than 7% at visit one were included in the study provided they were ready to give written informed consent and had a history of Type-2 diabetes mellitus for six months or longer, not controlled by dietary measures and exercise. The exclusion criteria for patients were presence of type 1 diabetes or requirement of insulin for diabetic control, known allergy to study drugs, deranged liver function tests or kidney function tests, patients with history of myocardial infarction or anaemia, pregnant and lactating females, unwillingness to give written informed consent, history of antidiabetic medication during the past three months, presence of gastrointestinal diseases like inflammatory bowel disease, large hernias, intestinal obstruction, active ulcers, chronic pancreatitis and patients taking any other concomitant medication effecting glucose homoeostasis like corticosteroids. Approval of the institutional ethics committee was taken prior to the start of study. 60 subjects were enrolled in the study after satisfying the inclusion and exclusion criteria. Included patients were explained in detail about the study pattern and related hazards. Those included went under all baseline investigations like complete blood count, liver function tests, kidney function tests, blood sugar level and glycosylated Hb, at the start of the study and at the end of the study. Enrolled patients were divided into two groups of thirty each by computer generated randomization chart (calculated from True Epistat, Standard version 1999). Group-1 patients received Tab. Miglitol 25 mg T.D.S with first bite of major meals for duration of four weeks and 50 mg T.D.S with first bite of major meals for another twelve weeks. Group 2 patients received Tab Repaglinide 0.5 mg T.D.S fifteen minutes before each major meal for a period of four weeks followed by 1 mg T.D.S fifteen min before each major meal for a period of another 12 weeks. Each patient in respective group was provided free medications for fifteen days and was asked to visit the diabetic clinic for follow up and for collection of drugs. At each follow-up visit, patients were assessed for glycemic control (blood glucose level); history pertaining to adverse drug effect was asked. All patients were given advice about diet and exercise. The study population was not allowed to take other antidiabetic drugs during the study period.

The primary efficacy measures for the study were change in postprandial blood glucose level from baseline to end of study (16 weeks) and change in glycosylated hemoglobin (HbA_{1C}) from baseline to end of study. The secondary efficacy measure was change in fasting blood glucose from baseline to end of study. For comparing the effect of miglitol and repaglinide on blood sugar level and HbA_{1C} before and after therapy paired 't' test was carried out. For comparison among groups unpaired 't' test was carried out.

Results

Sixty patients (n=60) of Type-2 diabetes completed the study [Table 1]. The mean post treatment glycosylated hemoglobin value decreased statistically in miglitol group (9.25 ± 1.96 to 8.1 ± 1.3, $P < 0.001$). Similarly the

Table 1: Comparison of glycemic control before and after the study

Group	HbA_{1C} (%) (Mean value ± SD)		Plasma glucose level (mg/dl %) (Mean value ± SD)			
			Before		After	
	Before therapy	After therapy	Fasting	Postmeal	Fasting	Postmeal
I	9.25 ± 1.96	8.1 ± 1.30*	138.53 ± 59.57	260.96 ± 75.41	96.26 ± 18.77*	162.46 ± 27.97*
II	9.74 ± 0.98	7.37 ± 0.79*	148.30 ± 38.30	258.66 ± 47.92	107.43 ± 38.26*	157.46 ± 24.41*

P< 0.001*: Statistically highly significant, Group I: Miglitol, Group II: Repaglinide

Table 2: Inter group comparison

Parameter	Baseline		After 16 weeks		Difference (16 weeks *vs* baseline)		*P* value for difference (16 wks *vs* baseline) between the 2 groups
	Group I	Group II	Group I	Group II	Group I	Group II	
FPG mg/dl (Mean + SD)	138.53+59.57	148.30+38.30	96.26+18.77	107.43+38.26	45.6±70.16	40.86±26.36	0.73
PPPG (mg/dl) (Mean + SD)	260.96+75.41	258.66+47.92	162.46+27.97	157.46+24.41	88.5±30.5	101.2±49.29	0.23
HbA_{1C} (%) (Mean + SD)	9.25+1.96	9.74+0.98	8.1+1.30	7.37+0.79	1.14±1.20	1.45±1.20	0.32

Group I: Miglitol, Group II: Repaglinide, BSL: Blood Sugar Level, FPG: Fasting plasma glucose, PPPG: Postprandial plasma glucose

Table 3: Adverse events during the study period

Adverse event	Group I		Group II	
	n	%	n	%
Any adverse event	8	26.66	5	16.66
Headache	1	3.33	3	10
Dizziness	1	3.33	2	6.66
Fatigue	0	0	1	3.33
Nausea	5	16.66	3	10
Flatulence	4	13.33	1	3.33
Diarrhea	3	10	1	3.33
Back pain	1	3.33	0	0

Group I: Miglitol, Group II: Repaglinide, n: number of patients

mean post-treatment value for HbA_{1C} in repaglinide group also decreased statistically (9.74 ± 0.98 to 7.37 ± 0.79, $P < 0.001$). The mean postprandial plasma glucose levels were significantly reduced when compared to baseline values in both the groups, miglitol (260.96 ± 75.41 mg / dl to 162.46 ± 27.97 mg / dl, $P < 0.001$) and repaglinide (258.66 ± 47.92 mg / dl, $P < 0.001$).

When mean fasting plasma glucose values were compared after the therapy significant decrease was seen in miglitol (138.53 ± 59.57 to 96.26 ± 18.77, $P < 0.001$) and repaglinide (148.30 ± 38.30 to 107.43 ± 38.26, $P < 0.001$) [Table 2].

Inter-group comparison between miglitol and repaglinide showed that mean reduction in glycosylated hemoglobin was more in repaglinide group (1.45 ± 1.20) as compared to miglitol (1.14 ± 1.20) but this value was not statistically significant ($P = 0.32$).

Similarly repaglinide also showed greater mean reduction in postprandial blood sugar level (101.2 ± 49.29 mg / dl) as compared to miglitol (88.5 ± 30.5 mg / dl) but this difference was not significant ($P = 0.23$).

However, the mean reduction for fasting plasma glucose level was more in miglitol group (45.6 ± 70.16 mg / dl) when compared to repaglinide (40.86 ± 26.36 mg / dl). This difference was also not significant ($P = 0.73$).

Adverse events were reported in 8 patients in miglitol group (26.66%) as compared to 5 patients (16.66%) in repaglinide group [Table 3]. The most common adverse events in miglitol group were gastrointestinal disturbances such as flatulence seen in four patients (13.33%), diarrhea in three patients (10%) and nausea in five patients (16.66%).

As where the most common adverse effect in repaglinide group were nausea and headache in three patients (10 %) and dizziness in two patients (6.66%).

Discussion

Diabetes is characterized by a high incidence of cardiovascular disease and related complications.[19] Poor control of hyperglycemia appears to play a significant role in the development of these complications in diabetes.[20] Recently, there has been increasing evidence that the postprandial state is an important contributing factor to the development of atherosclerosis and related complications.[21] In diabetes, the postprandial phase is characterized by a rapid and large increase in blood glucose levels and these postprandial "hyperglycaemic spikes" may be relevant to the pathophysiology of late diabetes complications, this concept is recently receiving much attention. Evidence that tight glycemic control helps to prevent complications in Type-2 diabetes is also accumulating.[22,23] Moreover, it appears that management of postprandial plasma glucose (PPG) levels, rather than fasting plasma glucose (FPG) levels, is important to prevent the complications associated with Type-2 diabetes.[3,6]

Unfortunately sulphonylureas and biguanides act principally to reduce fasting blood glucose levels. Postprandial blood sugar levels remain elevated in more than 60% of patients treated with these agents.[23] This has generated an interest for the search of agents which effectively reduce postprandial blood glucose levels.

Miglitol and repaglinide are novel drugs targeting mainly postprandial blood glucose levels.

The present study demonstrated that miglitol and repaglinide are equally efficacious and significantly reduce the postprandial plasma blood sugar levels, fasting plasma blood sugar levels as well as glycosylated hemoglobin levels In addition to the primary effect on postprandial glucose level alpha glucosidase inhibition by miglitol has several important secondary actions. This agent also decreases insulin resistance in peripheral tissues, which may in turn lead to a reduction in the fasting plasma glucose levels. Reduced glucose toxicity and increased late increase of glucagons like peptide-1 (GLP-1) are thought to contribute to the decrease in fasting plasma glucose levels associated with therapy of alpha glucosidase inhibitors.[24] The effect of repaglinide on fasting blood sugar level can be explained by the fact that repaglinide stimulated insulin secretion reverses much more slowly leading to lower glucose levels even long after the post prandial period has ended thus exhibiting the effect on fasting glucose levels in addition to the postprandial blood glucose levels.[25]

The adverse effects seen with the study drugs were minor and related to GI disturbances with Miglitol and headache and dizziness with Repaglinide.

Conclusion

Miglitol and repaglinide are very effective drugs in the management of Type-2 diabetes mellitus. These drugs not only have a dominant effect in reducing postprandial plasma glucose levels and glycosylated hemoglobin but also reduce the fasting plasma glucose levels. The results also conclude that miglitol as well as repaglinide are equally efficacious in reducing these parameters. Therefore these drugs may be preferred while treating the patients of Type-2 diabetes and especially in the management of postprandial hyperglycemia.

References

1. Zimmet PZ. Diabetes epidemiology as a tool to trigger diabetes research and care. Diabetologia 1999;42:499-518.
2. Avignon A, Radauceanu A, Monnier L. Non fasting plasma glucose is better marker of diabetic control than fasting plasma glucose in type 2 diabetes. Diabetes care 1997;20:1822-6.
3. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, *et al.* Risk factors for myocardial infarction and death in newly detected NIDDM: The Diabetes Intervention Study, 11-year follow-up. Diabetologica 1996;39:1577-83.
4. Nihalani KP, Shembalkar JP. New modalities in treatment of diabetes. Diabetes Update. June 1999. p. 12-7.
5. Adiyodi JR. Acarbose: Revolutionising treatment of NIDDM. Diabetes update. June 1999. p. 18-22.
6. Scott LJ, Spencer CM. Miglitol: A review of its therapeutic potential in type II diabetes mellitus. Drugs 2000;59:521-49.
7. Fehmann HC. The alpha glucosidase inhibitor miglitol for the treatment of type 2 diabetes mellitus in doctor's office. Fortschr Med Orig 2001;119:55-61.
8. Landgraf R. Meglitinide analogues in the treatment of type 2 diabetes mellitus. Drugs Aging 2000;17:411-25.
9. Rosenstock J, Hassman DR, Madder RD, Brazinsky SA, Farrell J, Khutoryansky N, *et al.* Repaglinide versus nateglinide monotherapy: A randomized multicenter study. Diabetes Care 2004;27:1265-70.
10. Mississippi Medicaid Pharmacy and Therapeutics committee Preferred drug list Drug Classification Reviews. Antidiabetic Agents: American hospital formulary service (AHFS) class 68:20.
11. Drent ML, Tollefsen AT, Van Heusden FH, Hoenderdos EB, Jonker JJ, Van der Veen EA. Dose-dependent efficacy of miglitol, an alphaglucosidase inhibitor, in type 2 diabetic patients on diet alone: Results of a 24-week double-blind placebo-controlled study. Diabetes Nutr Metab 2002;15:152-9.
12. Chiasson JL, Naditch L; Miglitol Canadian University Investigator Group. The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes. Diabetes Care 2001;24:989-94.
13. Jovanovic L, Dailey G 3rd, Huang WC, Strange P, Goldstein BJ. Repaglinide in type 2 diabetes: A 24-week, fixed-dose efficacy and safety study. J Clin Pharmcol 2000;40:49-57.
14. Goldberg RB, Einhorn D, Lucas CP, Rendell MS, Damsbo P, Huang WC, *et al.* A randomized placebo-controlled trial of repaglinide in the treatment of type 2 diabetes. Diabetes Care 1998;21:1897-903.
15. Jovanovic L, Hassman DR, Gooch B, Jain R, Greco S, Khutoryansky N, *et al.* Treatment of type 2 diabetes with a combination regimen of repaglinide plus pioglitazone. Diabetes Res Clin Pract 2004;63:127-34.
16. Derosa G, Mugellini A, Ciccarelli L, Crescenzi G, Fogari R. Comparison between repaglinide and glimepiride in patients with type 2 diabetes mellitus: A one-year, randomized, double- blind assessment of metabolic parameters and cardiovascular risk factors. Clin Ther 2003;25:472-84.
17. Landgraf R, Bilo HJ, Muller PG. A comparison of repaglinide and glibenclamide in the treatment of type 2 diabetic patients previously treated with sulphonylureas. Eur J Clin Pharm 1999;55:165-71.
18. Moses R, Slobodniuk R, Boyages S, Colagiuri S, Kidson W, Carter J, *et al.* Effect of repaglinide addition to metformin monotherapy on glycaemic control in patients with type 2 diabetes. Diabetes Care 1999;22:119-24.
19. Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes. Diabetes 1999;48:937-42.
20. Bonora E, Muggeo M. Postprandial blood glucose as a risk factor for cardiovascular disease in type II diabetes: The epidemiological evidence. Diabetologia 2001;44:2107-14.
21. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, *et al.* The UK Prospective Diabetes Study Group: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. BMJ 2000;321:405-12.
22. Gaster B, Hirsch IB. The effects of improved glycaemic control

on complications in type 2 diabetes. Arch Intern Med 1998;158:134-40.
23. Savage PJ. Cardiovascular complications of diabetes mellitus: What we know and what we need to know about their prevention. Ann Intern Med 1996;124:123-6.
24. Alpha glucosidase inhibitors in the treatment of diabetes. Rupp M, Leroith D, Taylor SI, Olefsky JM. Diabetes mellitus: A fundamental and clinical text. 3rd ed. 2004. p. 1151-9.
25. Glinides, Foley JE, Khemlani LS, Leroith D, Taylor SI, Olefsky JM. Diabetes mellitus: A fundamental and clinical text. 3rd ed 2004. p. 1163-74.

Source of Support: Nil, **Conflict of Interest:** None declared.