TREATMENT OF TYPE 2 DIABETES WITH GLICLAZIDE MODIFIED RELEASE 60MG IN THE PRIMARY CARE SETTING OF INDIA

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ABSTRACT

The majority of Indian type 2 diabetic patients are treated in the primary care setting, and not more than one quarter attain recommended glycemic control targets. This study examines whether substituting twice daily gliclazide 80mg with once daily gliclazide modified release (MR) 60mg achieves better control of type 2 diabetes in the primary care setting.

In a prospective multicentre study, medication with twice daily gliclazide 80mg in the treatment regimen of uncontrolled type 2 diabetic patients was substituted with once daily gliclazide MR 60mg, without changing any other antidiabetic drugs or their doses for 14 weeks. The primary outcome was the number of patients achieving glycemic control.

101 investigators recruited 162 patients distributed throughout India. On intention to treat analysis, 64.8% (57.4 to 72.2%) of patients achieved fasting blood glucose of less than 130 mg/dl, and there were 4.3% fewer hypoglycaemic episodes. Mean (95% confidence interval) fasting plasma glucose decreased by 73.3 (69.5 to 87.1, P< 0.01) mg/dl, total cholesterol by 20.2 (13.4 to 27.0, P< 0.01) mg/dl; low density lipoprotein cholesterol by 13.2 (7.8 to 18.6, P< 0.01) mg/dl; and total triglycerides by 21.5 (10.7 to 32.3, P< 0.01) mg/dl. Mean compliance was 96.9% with gliclazide MR 60mg.

Once daily gliclazide MR 60mg is more effective than twice daily gliclazide 80mg in glycemic control and causes less hypoglycemia, both in monotherapy and in combination with other agents. Gliclazide MR is a useful once daily sulphonylurea formulation for the management of type 2 diabetes in primary care.

KEYWORDS: Type 2 diabetes, Gliclazide modified release, Glycemic control; Primary care

INTRODUCTION

The prevalence of type 2 diabetes is about 12% in urban India (1), and it is estimated that the country has the largest number of these patients in the world (2). The majority are treated by physicians in the setting of primary care, with a strategy that includes diet, exercise, and blood sugar monitoring, with control of blood sugar, blood pressure and dyslipidemia. Surveys indicate that this strategy is effective in maintaining American Diabetes Association control targets in about 27% of patients in the community (3). Among the several reasons for this low rate of glycemic control are an inadequate compliance with oral antidiabetic drugs due to multiple dosage frequency, and side effects such as hypoglycemia. It has been reported that type 2 patients on monotherapy who convert from a multiple dose regimen to a once daily formulation increase their adherence to medication by 23%, and that this is reflected in lower HbA_{1c} levels (4). There is therefore a need for once daily oral antidiabetic drugs that are clinically effective and acceptable to patients.

Gliclazide is one of the most frequently used sulphonylureas for the treatment of type 2 diabetes. The original formulation required twice daily administration. A new once daily gliclazide modified release (MR) formulation has been recently introduced (Diamicron MR 60, Serdia, India). In a large randomised study on type 2 diabetic patients, once daily gliclazide MR 30-120mg was as effective as twice daily gliclazide 80-320mg in reducing HbA_{1c}, with fewer side effects and less risk of hypoglycemia (5). However, it is not clear from these results, based on a strict adherence to the randomised protocol, whether the expected improvement in compliance and less hypoglycemia with once daily gliclazide MR, translates into more effective glycemic control under conditions of primary care practice. Such information could be useful to physicians in selecting a gliclazide formulation and help increase glycemic control rates in the community.

The objectives of this study were to examine the clinical, biochemical, and adverse effects of substituting twice daily gliclazide 80mg with once daily gliclazide MR 60mg in the treatment regimen of patients with type 2 diabetes, under the primary care conditions of India.

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MATERIALS AND METHODS

The Research Society for the study of Diabetes in India had 3304 members in 2003. A simple 4% random sample of these physicians identified 132 potential investigators distributed throughout urban India, who were invited to participate in the study. Of these, 101 physicians accepted the study protocol for implementation. Each investigator identified consecutive type 2 diabetic outpatients of any age and either sex, who were receiving twice a day gliclazide 80mg as monotherapy or in combination with other antidiabetic drugs. Of these, patients with a fasting plasma glucose (FPG) of more than 150mg/dL (6), in whom the twice daily gliclazide could be replaced with the equivalent once daily gliclazide MR 60mg, without changing other antidiabetic drugs or their dose in the treatment regimen for the next 14 weeks, were selected for the study.

After giving their written informed consent, patients were assessed at baseline for demographic, clinical, treatment and biochemical characteristics shown in Table 1. They were then instructed to discontinue twice daily gliclazide 80mg, and prescribed gliclazide MR 60mg to be taken once a day after breakfast with no other change in their treatment regimen. Treatment of associated disease was allowed at the discretion of the physician. All medications were purchased by patients from the market. Patients were followed up and reassessed after 2, 6, 10, and 14 weeks of treatment. At each follow-up visit, FPG, weight and blood pressure were measured, and patients were asked about the frequency of hypoglycemic episodes and side effects since the previous visit. Compliance with gliclazide MR 60mg was assessed by tablet count (proportion of tablets ingested out of those prescribed). Biochemical tests done at baseline were repeated at the end of the study at 14 weeks.

Statistical Analysis: The primary outcomes were the number of patients achieving glycemic control (FPG < 130mg/dL) on an intention to treat basis, and mean change in FPG from baseline after substituting twice daily gliclazide 80mg with once daily gliclazide MR 60mg for 14 weeks. Other outcomes were the mean change in weight, plasma lipids, frequency of hypoglycemic episodes, and compliance with gliclazide MR 60mg medication. Changes in continuous variables were tested for significance by the standard error of difference in means. Categorical data were expressed as percentages with their 95% confidence intervals (CI). Significance was defined as a P value of less than 0.05.

RESULTS

The 101 investigators recruited 162 uncontrolled type 2 diabetic patients distributed throughout urban India who were undergoing treatment that included twice daily gliclazide 80mg, and which could be substituted with once daily gliclazide MR 60mg, with no other change in the antidiabetic treatment regimen. At baseline (Table 1), patients were of either sex, and most were middle aged, hypertensive, not obese, and under treatment for type 2 diabetes for about 7 years. More than 70% were receiving antidiabetic treatment with twice daily gliclazide 80mg as monotherapy or in combination with metformin, 11.1% complained of hypoglycemic symptoms, and compliance with the twice daily gliclazide medication was 89.3%. During the 14 weeks of study, 12(7.4%) were lost follow up. No patients withdrew because of side effects.

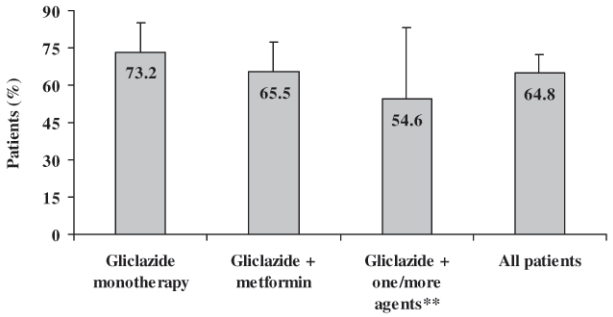
Table 1: Baseline Characteristics of Uncontrolled* Type 2 Diabetic Patients Receiving Treatment that included Twice Daily Gliclazide 80mg.

Patient Characteristics	N=162
Age (years)	52.7 ± 10.9
Males	83(51.2)
Females	79(48.8)
Duration of diabetes (years)	7.0 ± 4.5
Treatment	
Gliclazide monotherapy	56(34.6)
Gliclazide + metformin	62(38.3)
Gliclazide + glitazones	4(2.5)
Gliclazide + acarbose	4(2.5)
Gliclazide + insulin	2(1.2)
Gliclazide + more than one agent	34(21.0)
Side effects	
Hypoglycemia	18(11.1)
Weight gain	1(0.6)
Compliance with treatment	89.3 ± 8.3
Associated disease	
Hypertension	108(66.7)
Dyslipidemia	3(1.8)
Body mass index (kg/m^2)	26.9 ± 4.4
Systolic blood pressure (mmHg)	150.7 ± 82.8
Diastolic blood pressure (mmHg)	89.5 ± 11.5
Fasting plasma glucose (mg/dL)	201.9 ± 52.5
Plasma lipids (mg/dL)	
Total cholesterol	219.1 ± 33.6
Total triglycerides	179.9 ± 57.6
Low density lipoprotein	129.8 ± 26.3
High density lipoprotein	48.3 ± 42.2
Serum creatinine (mg/dL)	1.0 ± 0.7

**FPG >150mg/dL. Plus minus values are means ± standard deviation, all other values are numbers of patients followed in parentheses by percentages of the group.*

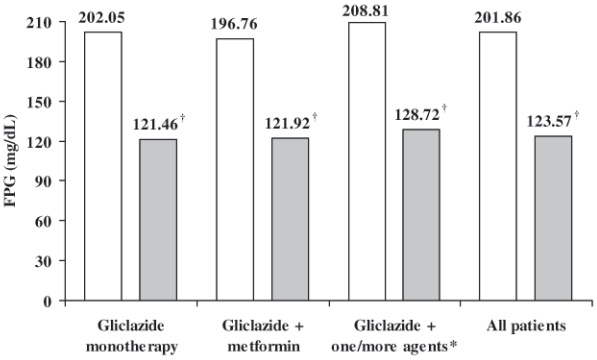
The number (%, 95% confidence interval(CI)) of patients achieving a FPG of less than 130mg/dL after substitution of twice daily gliclazide 80mg with once daily gliclazide MR 60mg for 14 weeks was, in all patients, 105 (64.8, 57.4 to 72.2); in the subgroups receiving gliclazide monotherapy, 41 (73.2, 61.6 to 84.8); receiving gliclazide plus metformin 40 (65.5, 53.7 to 77.3); and receiving gliclazide plus one or more of glitazones, acarbose, and insulin, 24(54.6, 25.8 to 83.4) (Fig. 1). Mean (95% CI) FPG decreased among all patients by 78.3 (69.5 to 87.1, P<0.01) mg/dL; in the subgroups receiving gliclazide monotherapy by 80.6 (66.0 to 95.2, P<0.01) mg/dL; receiving gliclazide plus metformin by 74.9 (61.6 to 88.2, P<0.01) mg/dL; and receiving gliclazide plus one or more of glitazones, acarbose and insulin by 80.1 (60.9 to 87.1, P<0.01) mg/dL (Fig. 2).

Figure 1: Patients Achieving Glycemic Control* after Substitution of Twice Daily gliclazide 80mg with Once Daily Gliclazide Modified Release 60mg.



The number (%) of patients complaining of hypoglycemic episodes decreased from 18(11.1) at baseline to 11(6.8) among all patients and to 3(1.9) in those achieving glycemic control (FPG<130mg/dL) after substitution of twice daily gliclazide 80mg with once daily gliclazide MR 60mg. Other adverse effects reported by patients with twice daily gliclazide at baseline, (nausea in 3, giddiness in 2 and vertigo in 1) did not occur with once daily GMR 60mg. Mean (95% CI) total cholesterol decreased by 20.9(13.4 to 27.0, P<0.01) mg/dL; low density lipoprotein cholesterol by 13.2(7.8 to 18.6, P<0.01) mg/dL; and total triglycerides by 21.5(10.7 to 32.3, P<0.01) mg/dL. The increase of 2.0mg/dL in high density lipoprotein was not significant. Body weight, blood pressure, and serum creatinine showed no significant change. Mean compliance with the once daily medication of gliclazide MR 60mg was 96.9%.

Figure 2: Change in Mean Fasting Plasma Glucose after Substitution of Twice Daily Gliclazide 80mg with Once Daily Gliclazide MR 60 in Type 2 Diabetic Patients.



DISCUSSION

In the setting of primary care, the replacement of twice daily gliclazide 80mg with once daily gliclazide MR 60mg in uncontrolled type 2 diabetic patients, without any other change in the treatment regimen for 14 weeks, resulted in substantial benefits. About 70% of patients were able to achieve glycemic control in monotherapy and 60% in combination with other antidiabetic agents, average FPG decreased significantly, and the frequency of patients complaining of hypoglycemia decreased by more than half.

In a previous prospective observational study on 151 uncontrolled type 2 patients under treatment with diet and gliclazide 80mg, switching to the equivalent gliclazide MR 30mg/day significantly reduced HbA_{1c} by nearly 10% after 27 weeks (7). However, the effect of such action on FPG, the proportion of patients achieving glycemic control, and the benefits of switching to the more usual dose of twice a day gliclazide 80mg with once a day gliclazide MR 60mg has not been reported. Although a 4 month double blind randomised study comparing the two formulations reported equivalent efficacy (5), the likely influence of differences in patient compliance under conditions of day to day primary care practice on efficacy is not known. The low frequency of hypoglycemic episodes with once daily gliclazide MR observed in this study is consistent with earlier reports (5).

The once daily gliclazide MR formulation is based on a specially developed hydrophilic polymer matrix tablet that has gastric dissolution characteristics,

which enable controlled release of the embedded gliclazide in relation to meal timings over 24 hours. When administered at breakfast, plasma concentration increases and plateaus from the 3rd to the 12th hour, which prevents post prandial hyperglycemia due to meals, and its gradual decrease thereafter minimizes risk of hypoglycemia during the remainder of the day (7). In a study on type 2 diabetic patients, plasma glucose was measured at 2 hourly intervals for 24 hours before and after 10 weeks treatment with gliclazide MR. After treatment, the mean decrease in plasma glucose from baseline was uniform throughout the 24 hours of assessment (8). Gliclazide MR is therefore suitable for once daily administration. It has a high bioavailability, which allows an effective dose that is half that of the previous formulation. These features may translate into better patient compliance because of once a day administration, and less hypoglycemia due to a lower dose, and serve to explain the useful results of this study in the primary care setting.

The study has limitations. The effect of substituting twice daily gliclazide 80mg with once daily gliclazide MR 60mg was not compared with other once daily sulphonylurea formulations using a randomised protocol. The results are over the short term, and the possible benefit of improved compliance due to the substitution on glycemic control over a longer period was not assessed. The majority of patients were on gliclazide monotherapy or in combination with metformin, and the effect of the substitution in patients on other anti diabetic drug combinations with gliclazide is less clear. However, the patients studied were recruited by randomly selected physicians distributed throughout urban India, representing type 2 diabetic patients seen in primary care, and the treatments were administered under conditions of actual clinical practice.

The results of this study suggest that in comparison to twice daily gliclazide 80mg, once daily gliclazide MR 60mg is more effective in achieving short term glycemic control with less hypoglycemic symptoms, both in monotherapy and in combination with other agents. Gliclazide MR is a useful once daily sulphonylurea formulation for the management of type 2 diabetes which will help in reducing the high frequency of uncontrolled patients in the Indian primary care setting.

ACKNOWLEDGEMENTS: I am indebted to Dr David Park, consultant epidemiologist; Dr Preeti Modi and Dr Aparna Kalsekar for assistance in organising the study, the following doctors who participated in the trial: Dr A Kulshrestha *(Agra)*; Dr D Dantara *(Ahmedabad)*; Dr V Agrawal, Dr A Mathur *(Allahabad)*; Dr V Jain *(Ambala)*; Dr V Apte, Dr R K Shah *(Aurangabad)*; Dr L Krishnamurthy, Dr H N Seshadri, Dr S Subramanyam *(Bangalore)*; Dr R S Meena, Dr A Shukla *(Bhopal)*; Dr V K Chhabra, Dr A Pahwa (*Chandigarh)*; Dr V T Bhaskaran, Dr M Chandrasekar, Dr S Chandrasekar, Dr M V Mohan, Dr S Nallaperumal, Dr V Parthasarathy, Dr D S Victor *(Chennai)*; Dr N Senthil Vel *(Coimbatore)*; Dr J K Panda *(Cuttack)*; Dr P N Daiv *(Dahanu)*; Dr R Bansal, Dr A Bhatia, Dr D S Chadha, Dr A R Choudhary, Dr M K Daga, Dr M L Goglani, Dr S K Gupta, Dr U Kansra, Dr A K Manchanda, Dr R Manocha, Dr V K Rastogi, Dr B K Tripathi *(Delhi)*; Dr H Mehta *(Ghaziabad)*; Dr M Abubaker, Dr M Idrees, Dr P Raghuramulu, Dr J Ramesh, Dr V Rao, Dr L Rodrigues, Dr B Rojanandam, Dr M Siraj *(Hyderabad)*; Dr N Batra, Dr G Devpura, Dr D K Jain, Dr P Saxena *(Jaipur)*; Dr C P Mathur *(Jodhpur)*; Dr V Kalyanarayanswamy *(Karaikudi)*; Dr S Kalra *(Karnal)*; Dr D P Banerjee, Dr G Banerjee, Dr P K Das, Dr S K Das, Dr N Mallik, Dr D Saha, Dr K N Sen, Dr U K Sengupta *(Kolkata)*; Dr V Balachandran *(Kollam)*; Dr A Agarwal, Dr A Sharma *(Lucknow)*; Dr P Khanna *(Ludhiana)*; Dr B D Rai, Dr A P Rao *(Mangalore)*; Dr E D'Mello *(Margao)*; Dr A Gautam, Dr N K Sharma *(Meerut)*; Dr V I Agera, Dr P Bhatia, Dr A Doshi, Dr S J Doshi, Dr A Ghongane, Dr A C Hattangadi, Dr H K Kundalia, Dr V Parvatkar, Dr D Patil, Dr S Pawar, Dr S Sahasrabudhe, Dr R S Tungare *(Mumbai)*; Dr N Furtado *(Panaji)*; Dr N Parameswaran *(Perambur)*; Dr L Gunalan *(Pondicherry)*; Dr V N Tiwari *(Ranchi)*; Dr M G Uvaraj *(Salem)*; Dr J J Rao *(Secunderabad)*; Dr J Antao *(Taleigao)*; Dr T Palanichamy *(Trichy)*; Dr R Nair *(Trivandrum)*; Dr D P Singh *(Udaipur)*; Dr D T Gaikwad *(Ulhasnagar)*; Dr W A Ansari, Dr M K Jaiswal *(Varanasi)*; Dr V Phadke *(Vasai)*; Dr D Prabhu *(Vasco da Gama)*; Dr K Annamalai *(Vellore)*; Dr M Kumar, Dr Y Sivakumar *(Vijayawada)*; Dr N Sivaprakash, Dr K A V Subramanyam *(Vizag)*; and Miss Kinnari Gandhi for secretarial assistance.

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