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RESEARCH ARTICLE

METFORM IN EXTENDED RELEASE FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS: A RETROSPECTIVE STUDY IN SOUTH INDIA

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ABSTRACT

Diabetes mellitus is a chronic and progressive condition among the most common metabolic diseases in general medical practice. Intensive lifestyle intervention and metformin can prevent or delay progression to diabetes. Over the past decade, lifestyle interventions have been translated across various settings, but little is known about the translation of evidence surrounding metformin use. The purpose of this study is to evaluate the effect of metformin extended release formulation on the glycemic control gastrointestinal tolerability and patient satisfaction.

Design: Retrospective analysis over a 1-year period. We examined data from August 2016 to July 2017 from *ESIC hospital Peenya, Bangaluru* using a retrospective analysis of metformin prescription among adults. Data were analyzed in 80 patients with type 2 diabetes not well controlled by diet (glycated hemoglobin [HbA1c] .7.0% and 8.5%). Patients were given metformin XR (Metadoze IPR® BIOCON) for a period of 4 months at the maximum tolerated dose. We evaluated, HbA1c, fasting, postprandial glucose and body weight. Moreover, at the baseline and after 4 months, we also validated the patients by SF 16 questionnaire to assess patients' satisfaction toward treatments. After 4 months, metformin XR gave a greater improvement in glycemic control. A reduction in total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol was observed with metformin XR.

Conclusion: Metformin XR formulation seems to be more effective in improving glyco-metabolic control, lipid profile in patients with type 2 diabetes mellitus. Fewer gastrointestinal side effects and a greater sense of well being and satisfaction were seen with this medication.

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INTRODUCTION

Type 2 Diabetes Mellitus is a chronic metabolic disorder demands in intense management from diagnosis and through the progression of the disease (American Diabetes Association, 2008; EASD, 2007). Lifestyle modification and the use of pharmaceutical management are considered pivotal to achieving good glycaemic control and other cardiovascular risk factors (Gaede *et al*., 2008). Metformin been recommended in various International Guidelines (IDF, 2006; Nathan *et al*., 2009) as first line therapy due to its favourable profile on metabolic indices of glucose, lipid and weight control (Bailey *et al*., 2007) as well as offering protection from life threatening complications and premature mortality (UKPDS, 1992; Holman *et al*., 2008).

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Standard metformin suffers from the limitations of having to be administered twice or thrice daily and risk of triggering gastrointestinal symptoms affecting 25% of the individuals (Bailey *et al*., 1996; Garber, 1997). American Diabetes Association (ADA) and the European Society for the study of Diabetes (EASD) identify these difficulties and advices on how to improve poor compliance with standard metformin (Nathan *et al*., 2009). Compliance is major issue for all chronic diseases (Wu, 2006) and poor tablet adherence is a particular concern in managing individuals with diabetes due to the pill burden (Cramer, 2004; Donnan *et al*., 2002). In the 5 point plan for introducing metformin, the ADA/EASD diverted the attention to the extended release metformin. (Metformin XR). Extended-release formulations of metformin were developed to allow a more gradual release of the drug into the upper GI tract to improve tolerability and reduce the frequency of dosing.[18] *Metadoze IPR: Immediate and Patterned release* floating-delivery type matrix also ensures longer retention of tablet in the small intestine.

MATERIALS AND METHODS

Study design

This observational trial was conducted in individuals with diabetes. Suitable patients were contacted by the investigators in person or by telephone. All patients provided informed consent. We enrolled 80 patients with type 2 diabetes not well controlled by diet, glycated hemoglobin [HbA1c] > 7.0% and 8%), aged ≥18 years of either sex.

Patients were excluded if they had a history of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy; impaired hepatic or renal function; or severe anemia. Patients with serious cardiovascular disease (CVD) or cerebrovascular conditions within 6 months before were also excluded. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded. Patients were administered on metformin XR (Metadoze IPR® BIOCON) for a period of 4 months at the maximum tolerated dose (considering the onset of gastrointestinal adverse events as a sign of maximum tolerated dose. Maximum tolerated dose being 850mg±500mg.

Diet and exercise

Individuals began a controlled diet based on the Dietician recommendations.

Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination and vital signs. At the baseline and after 4 months, we evaluated the following parameters: HbA1c, fasting glucose, postprandial glucose, lipid parameter and body weight were assessed. Moreover, at the baseline and after 4 months, we administered patients the SF-36 Health Survey questionnaires. These analyses were performed using the statistical package for the social sciences (SPSS, version 13.0). Values were expressed as mean (± SD) or median (minimum/maximum).

RESULTS

Study sample

A total of 80 patient's data were available from the completed study. After 4 months, metformin XR gave a greater reduction in HbA**1c**, PPG, and FPG compared with baseline (P<0.01).

Lipid profile

A reduction in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) was observed with metformin XR (P<0.05). A decrease in triglyceride (Tg) was observed with metformin XR (P<0.05). No variations in high-density lipoprotein (HDL) were recorded

Adverse events

Adverse events were less common with metformin XR after 4 months (P <0.01 vs metformin XR). A total of 73 patients (91.2%) were asymptomatic, with the remainder reporting symptoms of diarrhoea (n =4), nausea (n = 2) and epigastric pain (n = 1)

Table 1. Characteristics of enrolled patients treated with Metformin-XR

Characteristics	Metformin-XR Baseline	Metformin- XR 4month
n	80	80
Sex (M/F)	46/34	46/34
Age (years)	55.±10.3	55.±10.3
Weight (kg)	73.8±5.8	74.5±5.4
BMI(kg/m^2)	27.2±2.4	26.9±1.8
HbA_{1c} (%)	7.5±0.5	7.0±0.4*
FPG(mg/dL)	156.3±19.5	137.9±17.1*
PPG(mg/dL)	182.7±23.2	162.7±15.2
TC(mg/dL)	188.7±33.9	180.7±24.4
LDL-C(mg/dL)	125.2±19.3	120.3±16.7
HDL-C(mg/dL)	41.8±5.7	42.1±5.7
Tg (mg/dL)	108.4±47.2	101.6±42.9

Questionnaires

Regarding the SF-36 Health Survey questionnaire, there was an increase in the score of the two questions related to general health perception (question 1: "In general, would you say your health is good?" and question 2: "Compared to 4 months ago, how would you rate your health in general now?", with a higher score, meaning a better health perception, after the introduction of metformin XR. No other significant differences were recorded for the other questions. The results of the patient satisfaction questionnaire indicated that 70 patients (87.5%) felt better on metformin XR.

DISCUSSION

Metformin is recommended as a core therapy in diabetes management worldwide at diagnosis and is seen as being complementary to lifestyle change either alone or in combination with other oral antidiabetic therapies or insulin (Nathan *et al*., 2009). In our study, we recorded a better effect of metformin XR in improving glycemic control. The same can be said about lipid profile. We recorded an improvement in TC and LDL-C with metformin XR. The positive effects of metformin on lipid profile have been already shown in various studies and we confirmed them in this human study. At a first glance, the improvement in glycemic factor in the case of metformin XR could be due to the constantly better control of blood sugar levels. Better or improved lipid and other levels may be the consequence of glycemic levels. Moreover, also a better patients' compliance could partially explain the better effect of metformin XR.

A majority of patients treated with metformin are GI symptom free but upwards of 25% of patients experience dose limiting side effects though discontinuation can be in the order of 5% (Garber *et al*., 1997). In the Juliana Levy etal study, over 77% of patients were GI symptom free on completion of 6 months continuous therapy on extended release metformin showing similar to our study showing 91.2% asymptomatic (Juliana, 2010). These data should not surprise, in fact, one of the factors that affect glycemic control is patient's compliance to therapy. Patients' compliance is correlated with the complexity of the treatment, to the total number of tablets taken daily, to the size of the tablets, to the difficulty in swallowing, to the side effects, and to the cost of therapy. A limitation of this study is that we used different doses of metformin XR in each

patient, according to the patients' gastrointestinal tolerability; however, considering all the samples, metformin XR were used at an average dose ±50% of the dose. Metformin XR led to a greater sense of well being and patient satisfaction. These findings have the potential to lead to better adherence with therapy. Donnelly and colleagues from Dundee have reported greater adherence in patients switched from standard metformin to an extended release (Donnelly, 2009; Fujioka, 2003).

Moreover, in the same study glycaemic control was reported to improve by almost 1% but small numbers prevented the change becoming significant. Transfer from standard metformin to the extended release metformin XR tablet is associated with a neutral outcome on cardiovascular risk factors. No detrimental changes were reported for measures of glycaemia, blood pressure, body weight or anthopometric indices and this has been confirmed by others. Measures of tolerability and patient satisfaction were recorded using simple questionning techniques. Adherence and better compliance lead to fewer long termer complications with sustained release formulation of metformin XR.

Conclusion

Metformin XR formulation seems to be more effective in improving glyco-metabolic control, lipid profile and treatment satisfaction in patients with type 2 diabetes mellitus. Fewer gastrointestinal side effects and a greater sense of well being and satisfaction were seen with this medication.

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