A Retrospective Evaluation of the use of Thiazolidinediones in Patients with Diabetes Mellitus in a Private Hospital in Ras Al Khaimah.

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ABSTRACT

Diabetes Mellitus is a major public health problem affecting around 800,000 people of United Arab Emirates (about 19.2 per cent of the population). Thus the country is ranked as the 10th worldwide in terms of highest prevalence rate as per the latest reports of the International Diabetes Federation. Thiazolidinediones (Rosiglitazone and Pioglitazone) are a group of antidiabetic drugs which are commonly used in United Arab Emirates among diabetic patients. There are reports about the cardiovascular risks and hepatotoxic effects of thiazolidinediones. Hence the present study was undertaken. The aim of the study was to determine the incidence of thiazolidinedione usage, its adverse drug reactions, efficacy and safety in diabetic patients. The present study was undertaken after the approval of the Research and Ethics Committee of RAK Medical and Health Sciences University. This was a retrospective study conducted in the outpatient clinic of the Department of Endocrinology and Diabetes of a private hospital in Ras Al Khaimah, United Arab Emirates, between January to December 2008. The required data was collected from the selected patients and entered into specific patient proforma. The data was analyzed for the following parameters like incidence of usage of thiazolidinediones, its efficacy and adverse drug reactions. A total of 143 patients with diabetes were enrolled in the study, out of which 54 patients were on Thiazolidinediones- 48 on Rosiglitazone and 6 on Pioglitazone- in the beginning of the study. At the end, 73 patients were on Rosiglitazone and 17 were on Pioglitazone. The most commonly observed adverse effect was pedal edema. No cardiovascular risks were observed in any of the patients who were on either Rosiglitazone or Pioglitazone. Though there are reports of cardiovascular risks with Thiazolidinediones, throughout our study, none of the patients reported any cardiovascular risk.

Keywords: Diabetes Mellitus, Thiazolidinediones, Adverse drug reactions, Utilization evaluation.

INTRODUCTION

Diabetes mellitus is the most common of the endocrine disorders. It is a chronic condition, characterized by hyperglycemia due to impaired insulin secretion with or without insulin resistance[1]. It is being recognized as a global epidemic, with the potential to cause a worldwide healthcare crisis. It is estimated that currently diabetes affects some 200 million people worldwide. According to estimates by the International Diabetes Federation, this figure is set to increase to 333 million by the year 2025[2].

Diabetes is a major public health problem in UAE[3]. Surveys released by the International Diabetic Federation (IDF) in the year 2011, showed that 19.2 % or 800,000 -people in the UAE live with diabetes leading to UAE being ranked as the 10th worldwide in terms of highest prevalence rate. It has been reported that 17.9% nationals and 13.4% expatriates are affected with this condition in UAE[4].

Type 2 diabetes patients, due to their progressive beta cell function and increasing insulin resistance usually require two or three drugs to maintain control before ultimately requiring insulin. Thiazolidinediones (TZDs) have established a significant role in Type 2 diabetes mellitus therapy[5]. They are known to increase insulin sensitivity by stimulating Peroxisome Proliferator Activated Receptor Gamma (PPAR-γ). Currently only one glitazone, i.e. pioglitazone is available in the UAE market following the removal of rosiglitazone in 2010[6].

There have been several studies reporting the cardiovascular risks associated with thiazolidinediones[7,8].

Studies related to these are lacking in the UAE population. More studies are required to know the adverse effects of these medications for a proper and safe usage as these are frequently prescribed to patients. Hence, the present study was undertaken.

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The main objectives of this study were to find out

- The incidence of usage of Thiazolidinediones in diabetic patients
- The incidence of cardiovascular and hepatic adverse effects with the use of Thiazolidinediones
- To compare the efficacy and safety of the commonly used Thiazolidinediones in UAE.

MATERIALS AND METHODS

Study site:

The study was carried out at the Endocrine department of a secondary care hospital in Ras al Khaimah, UAE.

Study duration:

Duration of the study was for one year ranging between January to December 2008.

Study type:

This was a retrospective study.

Study material:

Data collection form was prepared to enter the details of the patients enrolled in the study. (Appendix)

Study method:

The study protocol was approved by the RAK Medical and Health Sciences University, Ethics Committee, Approval letter dated 25th June, 2009. All the diabetic patients who visited the outpatient department of the hospital for treatment during the study period were included in the study.

The data was evaluated for

- Incidence of usage of thiazolidinediones
- Adverse effects associated with the use of thiazolidinediones
- Comparison of the different thiazolidinediones for their safety and efficacy

RESULTS

Total number of diabetic patients included in the study was 143. In the beginning of the study, 54 patients were on Thiazolidinediones of which 48 were on rosiglitazone and 6 on pioglitazone. At the end of the study, 73 patients were on rosiglitazone and 17 were on pioglitazone (fig. 1). At the beginning of the study 18 patients were on rosiglitazone and metformin combination and 30 patients were on Metformin and Sulphonylureas (Glibenclamide, Glimepride, Gliclazide) combination along with rosiglitazone. At the end of the study, 27 patients were on rosiglitazone and metformin combination. There were 34 patients with a combination of rosiglitazone , metformin and Sulphonylureas (Glibenclamide, Glimepride,Gliclazide) and 12 patients on a combination of rosiglitazone with Metformin, Sulphonylureas and Dipeptidyl Peptidase-4 Inhibitors (DPP4I) (fig.2).

At the beginning of the study, there was 1 patient on Pioglitazone, 2 on combination with metformin and 3 patients on a combination of pioglitazone, Metformin and Sulphonylureas .At the end of the study, there was 1 patient on Pioglitazone, 6 on combination with metformin ,7 patients on a combination of pioglitazone, metformin and Sulphonylureas (Glibenclamide, Glimepride, Gliclazide) and 3 patients on a combination of pioglitazone, Metformin, Sulphonylureas and DPP4I (fig. 3).

Both the Thiazolidinediones were well tolerated by all the patients except one who developed pedal edema and facial puffiness with the use of Rosiglitazone and the drug was withdrawn. No other cardiovascular adverse effects were observed in any of the patients who were on either

Fig.1: Type of Thiazolidinediones prescribed

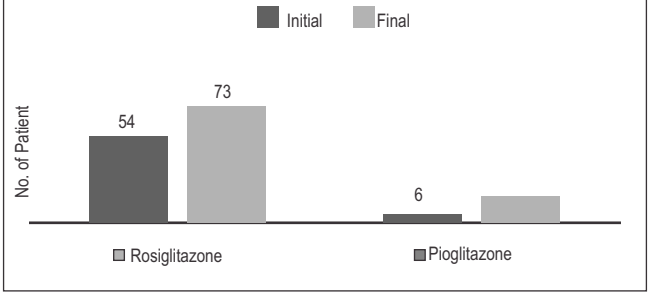


Fig.2: Combination Therapy-Rosigkitazone

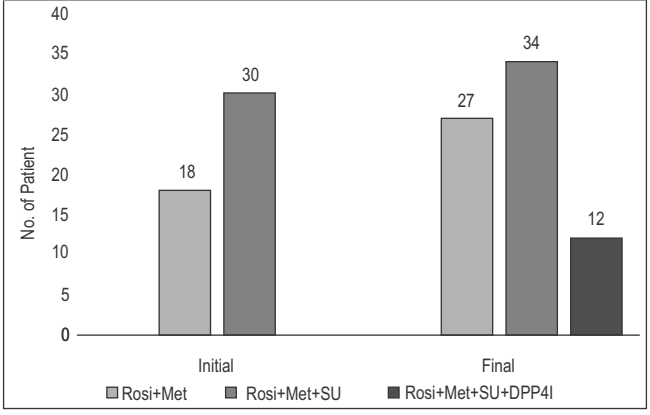
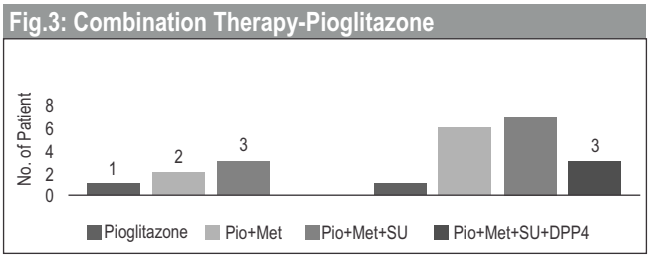


Fig.3: Combination Therapy-Pioglitazone



Rosiglitazone or Pioglitazone. The hepatic transaminases of the patients before and towards the end of the study were within the normal range (Table 1). Efficacy wise Rosiglitazone was able to bring down the HbA1c % compared to Pioglitazone (Table 2).

Table1: Hepatic Adverse drug reactions of Thiazolidinediones

PARAMETER	ROSIGLITAZONE	PIOGLITAZONE
ALT (SGPT) IU/L		
Initial	39.06 ±25.75 (n - 84)	46.61±39.78 (-15)
6 Months	39.91 ±24.45 (n - 45)	40.42±31.69 (-11)
AST (SGOT) IU/L		
Initial	31.52±17.17 (n-31)	32.91±30.40 (n-8)
6 Months	32.67±21.10 (n-11)	22.55±2.89 (n-2)

ALT- Alanine aminotransferase, SGPT- serum glutamic pyruvic transaminase , AST- Aspartate amino transferase, SGOT- serum glutamic oxaloacetic transaminase

Table2: Safety and Efficacy of Thiazolidinediones

PARAMETER	ROSIGLITAZONE	PIOGLITAZONE
HbA1c %		
– Initial	7.82±1.94	7.66±1.56
At the End	6.92±0.99	7.74±1.86
FBS		
Initial	168.72±55.33	188.26±67.47
At the End	142.84±34.71	142.93±13.29

HbA1c- Glycated hemoglobin, FBS- Fasting blood sugar

DISCUSSION

The present study was aimed to find the incidence of use of Thiazolidinediones, any association of cardiovascular and hepatic risks and comparison of the efficacy and safety of different thiazolidinediones. It was observed during the study that majority of the patients were on rosiglitazone (n=73) compared to pioglitazone(n=17). A study conducted by Balkrishnan R comparing Rosiglitazone and Pioglitazone monotherapy has reported that introduction of rosiglitazone was associated with a decreased number of hospitalizations, emergency department visits, and total health care costs compared with pioglitazone[8]. In majority of the patients in our study, the thiazolidinediones were used in combination with other antidiabetic medications and it was found that rosiglitazone was more effective in bringing down the HbA_{1c} values when compared to pioglitazone when these drugs were used in combination with other antidiabetic drugs.No cardiovascular adverse events were observed in any of the patients. This could be related to the lower dose of drugs used (2-4 mg for rosiglitazone and 15-30 mg for pioglitazone) or due to the rational or appropriate usage of the drugs. During the study one patient developed pedal edema and facial puffiness with use of Rosiglitazone. Our findings support the study by Mudaliar S, who has also found that both pioglitazone and rosiglitazone have been associated with development of edema. The incidence of edema in these trials varied from 3.0 to 7.5% with the thiazolidinediones compared with 1.0 to 2.5% with placebo or other oral antidiabetic therapy. Available evidence suggests that edema is a class effect of the thiazolidinediones and is multifactorial in origin[9]. The study by Richard WN also supports our findings regarding edema with usage of thiazolidinediones. According to this study, the incidence of edema was 4.8% in the rosiglitazone group compared with 1.3% on placebo. When combined with metformin or sulfonylurea, edema was observed in 3 to 4% of patients compared with 1.1 to 2.2% on either comparator drug alone. These data suggest that edema is a side effect of the TZD drugs to a similar degree, either when used as monotherapy or when combined with other oral antidiabetes agents[10].

There were no significant hepatic adverse effects in any of the patients who were on Thiazolidinediones-neither Rosiglitazone nor Pioglitazone. Their liver enzymes were within normal range (Table 4). Our study thus is in agreement with study by Harold E L who stated that no evidence of hepatotoxic effects was observed in studies that involved 5,006 patients taking rosiglitazone as monotherapy or combination therapy for 5,508 person years. This is in keeping with hepatic data from clinical trials of another member of the class, pioglitazone[11].Only a few case reports of hepatotoxicity have been reported in patients treated with rosiglitazone until now, with a causal relationship remaining uncertain. Furthermore, no single case of severe hepatotoxicity has been reported yet with pioglitazone[12].

The present study showed a better efficacy with rosiglitazone (Table 2) in reducing HbA1c %. This finding was in contrast to the report of Ronald et al where both the glitazones showed similar efficacy. A study showed that rosiglitazone 8 mg daily and pioglitazone 45 mg daily brought about 1.5% improvement in HbA1c %, after 6 months of treatment. The glycemic lowering effect of these agents is slightly less than that reported with sulphonylureas or metformin, yet the durability of glycemic control is superior[13]. Pioglitazone showed better improvement in the FBS levels of the patients compared to Rosiglitazone. But the number of patients who were on Pioglitazone was comparatively less.

CONCLUSION

Our study concludes that thiazolidinediones were well tolerated in almost all the patients who were enrolled in the

study. There were no major cardiovascular or hepatic adverse effects observed during the study except one patient who developed edema which was reversible. Since there are reports on the cardiovascular and hepatic adverse effects of these drugs , a close monitoring of the patients is essential. Though there are many other ADRs which are common to Thiazolidinediones like weight gain and anaemia, we did not observe such ADRs in our study. This is an area which is still of concern among clinicians and other healthcare professionals since reporting of ADRs is very important. As the drug rosiglitazone has been banned from the UAE market, a study on pioglitazones for its adverse drug reactions can be done in a wider population. Since the study was done in a private hospital where majority of the patients were expatriates, a similar study can be conducted in the national population receiving these medications since diabetes prevalence is more in them compared to expatriates.

Appendix

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Data collection form

Name of the hospital :
Name of the treating doctor :
File number :
Contact no :
Ethnicity :
Occupation :
Age :
Sex :
Duration of diabetes :
Age of onset :
Family history of diabetes :
Height :
Weight :
BMI :
WC :
BP :
Marital status :
Lifestyle factors : sedentary/active
Exercise :
Diet : veg/ non-veg
Smoking :
Alcohol :
Co-morbidities :
DIAGNOSIS: ……

Investigations:	0	2	4	6	8	10	12
FBS							
PPBS							
HbA1c							
SGOT							
SGPT							
Uric acid							
Creatinine							
Urea							
Total Cholesterol							
Triglycerides							
HDL							
LDL							
HDL/LDL							
CPK							
Electrolyte K Na							
Hemoglobin							
Urine Micral A/C ratio							
Any other additional investigations							
<u>Treatment:</u>							
Diabetes							
Hypertension							
Dyslipidemia							
Others							

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