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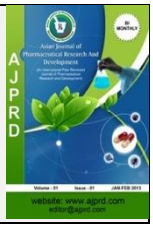

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Research Article

A Retrospective Assessment of The Safety Profile of Pioglitazone in T2dm Patients

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A B S T R A C T

Background: Pioglitazone is a drug that belongs to the category of thiazolidinedione (TZD) and is used for its hypoglycemic activity that is very-well associated with some serious adverse drug reactions (ADR). Previous studies have dealt with country-specific pharmacovigilance databases to assess the ADR profile of pioglitazone but none of them utilized a scholarly literature database.

Objective: This study was conducted to assess the safety profile of pioglitazone in terms of expectedness, causality, and the seriousness of ADR by using a literature database.

Methods: The published literature cases of pioglitazone-induced ADR from the PubMed database (between 1993 and 2020) were retrieved by using Medical Subject Headings (MeSH) terms.Only the valid cases (as per the ICH validity criteria) were analyzed. Following this, valid cases were further assessed for the expectedness of ADR by using the "Summary of Product Characteristics" document of Takeda Pharmaceuticals UK Ltd. Seriousness criteria of WHO for ADR were used for assessing the seriousness of ADR while the Naranjo's scale was used for causality assessment.

Results: A total of 871 results were found of which only 26 valid ICSRs cases were found. Of the total 168 ADRs, a total of 131 (77.97%) and 37 (22.02%) unexpected and expected ADRs were found. Only two of the events were found to be non-serious and they were Iatrogenic lipomatosis and Angioneurotic edema. 1 (32.5 %), 24 (77.4 %), 6 (19.35 %) reactions were serious due to death, important medical event, and hospitalization, respectively. There were, in total, 7 (27 %) and 19 (74 %) cases that belonged to a possible and probable category, respectively.

Conclusion: It is worth mentioning that pioglitazone is associated with the risk of heart failure and edema besides causing bladder cancer. The patient should be evaluated for the possible adverse effects of proper monitoring and follow-ups.

Keywords: Bladder Cancer, Macular Edema, ICH, Pharmacovigilance, Urinary Tract Infection

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INTRODUCTION

It is evaluated that diabetes influences around 150 million individuals around the world, and this figure is expected to be multiplied in the next 20 years. Around 90-95% of all North American instances of diabetes are type 2 diabetes mellitus (T2DM), and about 20% of the populace beyond 65 years old has T2DM [1-3]. Around 5-10% of the aggregate social insurance spending plan has

been utilized for T2DM in numerous nations. The pathophysiology of T2DM focuses on the 3 key defects that are decreased insulin production from beta cells, increased hepatic glucose production, and the increased insulin resistance [4-6]. Apart from hyperglycemia, it leads to inordinate urination, compensatory thirst, obscured vision, unexplained weight reduction, torpidity, and changes in energy metabolism. T2DM may bring about serious chronic complications that are renal pathologies, slow healing wounds, and blood vessel disorders. Of all the three, insulin resistance plays a major role in the T2DM pathology that is responsible for less peripheral insulin uptake by body tissues like adipose, liver, and muscle tissue [7,8].The possible mechanisms for insulin resistance incorporate hereditary or acquired cell defect, autoantibodies to insulin, and quickened insulin degradation. Given that glucose and lipid metabolism relies upon mitochondria to create energy in cells; the dysfunction of mitochondria has been assumed to play a substantial role in the advancement of insulin resistance. Treatment of type 2 diabetes depends on the interaction of patient qualities, hyperglycemia severity, and accessible remedial alternatives [9,10]. Metformin, sulfonylureas (SU) and thiazolidinediones (TZD) are the most concentrated of the oral medications utilized around the world. They assume a noticeable beginning role in the T2DM as suggested by the European Diabetes Association for the Study of Diabetes (EASD) and by the American Diabetes Association (ADA) [11].Metformin is viewed as a first-line treatment except if not endured or contraindicated. This drug reduces the blood glucose level by decreasing the hepatic glucose production, increasing insulin sensitivity, and decreasing glucose absorption from the intestine [12]. The second most used drug that increases insulin sensitivity is the pioglitazone which is the only TZD that is still being marketed in various countries including India but countries like France and Germany have banned this drug due to its potential to cause the bladder cancer [13]. In India, this drug was also banned but after 2 months, the ban was revoked as there were not enough individual case safety reports (ICSR) regarding adverse drug reaction (ADR) due to pioglitazone [13-15]. The term, ICSR refers to the adverse event report of an individual patient that serves as a very important role in phase-4 clinical studies whose important source of information is spontaneous reporting of ADR by patients or health care professionals followed by other sources like literature [16]. Pharmacovigilance is defined by the WHO as the "science and activities that are concernedwith the detection, understanding, assessment, and prevention of adverse effects due to drug and other drug-related problem and it is very important to monitor the drug for its risk till it is in the market [17].There are only a few studies in the literature that have addressed the ADR due to pioglitazone through the assessment of ICSR. Berthet S et al., conducted a study to rule out the profile of ADR and the risk factors for ADR due to pioglitazone and rosiglitazone in T2DM patients by using the French pharmacovigilance database [18]. They reported that with TZD, there is an increased risk for heart failure and edema than any other ADR. Piccini C et al., assessed the association between the urinary bladder cancer and pioglitazone by using spontaneous case reports of the United States adverse drug event reporting system and estimated a substantial link between bladder cancer and pioglitazone [19]. These studies have investigated the ADR due to pioglitazone in T2DM by using pharmacovigilance databases containing the ICSR of patients but no study has investigated the profile of ADR of pioglitazone by using the academic database that also serves a very important source of information (ICSR) about the ADR in the pharmacovigilance and if the literature article has an identifiable reporter (authors), suspected ADR, suspected drug, and an identifiable patient, then it becomes a valid ICSR [20,21].

METHODS

Data Collection using Pub Med

Data Collection will be done in two steps. First, the abstract and the title of each case report from Jan 2001 to December 2019 were reviewed to identify a list of potentially relevant cases and in the second step; the full text of each case was reviewed to check the validity. The criteria for a valid case were taken from the ICH (International Council for Harmonization) E2D guidelines.The keywords used for searching the PubMed were medical subject headings (MeSH) terms that were(Adverse drug reactions OR Adverse drug events AND "Pioglitazone" AND Diabetes mellitus). The articles were searched from Jan 01 2000 to Dec 31 2019. No other filter was used. All the articles that were valid ICSRand were following the following criteria were included.

1. The article had the author's name listed for the purpose of identifiable reporters.
2. The article had information about the individual patient and not as group information like in observational studies.
3. The article in which pioglitazone was acting like a suspected drug and not a concomitant medication.

Expectedness Assessment

All the ADR whose severity or the nature was not consistent with the applicable product information that is the reference document was regarded as unexpected ADR otherwise they were classified as expected ADR [22]. In this study, Summary of Product Characteristic (SmPC) document was used as a reference document. The rationale for using was that it contains the information about the ADR from different pharmaceutical companies marketing the pioglitazone. On the basis of Expectedness, if anyone of the ADR was considered to be unexpected, then, the overall assessment of the case was Unexpected while if all the ADR were expected, then, the overall assessment on the basis of Expectedness was noted down to be expected. All the expected and unexpected ADR terms were taken from the medical dictionary for drug regulatory activities

Assessment of Causality

The causal association between the event and the drug was established by using the Naranjo's scale [23]. The extent of the association was classified according to the scores given on the scale of Naranjo. Accordingly, the relationship was categorized as "Certain" or 'Probable" or "Possible" or "Doubtful".

Seriousness Assessment

The seriousness of the event was determined by using the criteria of seriousness given in the ICH guidelines. The reactions were then either differentiated into serious or non-serious events [22].

Statistical Analysis

The descriptive analysis that is frequencies and percentages were used to express the results.

RESULT

A total of 311 articles were found of which only 26 articles were estimated as valid which is represented in **Table 1**.

Table 1: Selected Valid Cases with Reference

Article/Case	Reference
Hepatocellular injury in a patient receiving Pioglitazone	24
Pioglitazone induced reversible pancytopenia	24
Mixed-hepatocellular cholestatic liver injury after Pioglitazone therapy	26
Peroxisome-proliferator activated gamma in thyroid eye disease: Contraindication for thiazolidinedione use	27
Thiazolidinedione-induced edema	28
Pioglitazone induced heart failure despite normal left ventricular function-1st case	29
Pioglitazone induced heart failure despite normal left ventricular function-2nd case	29
Severe decrease in serum HDL-cholesterol during combination therapy of bezafibrate and pioglitazone	30
Fatal liver failure associated with Pioglitazone	31
Leukopenia and thrombocytopenia caused by thiazolidinedione	32
Second generation thiazolidinedione and hepatotoxicity	33
Massive bilateral pleural effusion associated with the use of Pioglitazone	34
Thiazolidinedione associated congestive heart failure and pulmonary edema	35
Suspected suppression of INR by thiazolidinedione: Interaction between warfarin and TZD	36
Treatment with pioglitazone induced significant, reversible mitral regurgitation	37
Angioneurotic edema as a side effect of Pioglitazone	38
Thiazolidinedione and heart failure: the potential to precipitate the irreversible cardiac dysfunction	39
Reversible mitral and aortic regurgitation due to Pioglitazone	40
Severe macular edema induced by pioglitazone in a diabetic retinopathy patient: a case study	41
Pioglitazone-induced acute rhabdomyolysis	42
Pioglitazone induced heart failure in a patient with restrictive cardiomyopathy and metabolic myopathy	43
Letter: Iatrogenic Lipomatosis: a rare manifestation of treatment with a PPAR gamma	44
Severe but reversible cholestatic liver injury after Pioglitazone therapy	45
Pioglitazone associated fulminant hepatic failure	46
Thiazolidinedione-associated congestive heart failure and pulmonary edema	47

Seriousness Assessment

Following the criteria of seriousness, it was evident that most of the adverse drug reactions were serious as they were important medical events. This was followed by hospitalization and death, respectively**. Fig. 1** is depicting the total number of serious and non-serious cases. The events (based on the major diagnosis) leading to death, hospitalization, and the events that were medically significant are given in **Table 2**. Only two of the events were found to be non-serious and they were Iatrogenic lipomatosis and Angioneurotic edema. 1 (32.5 %), 24 (77.4 %), 6 (19.35 %) reactions were serious due to death, important medical event, and hospitalization respectively.

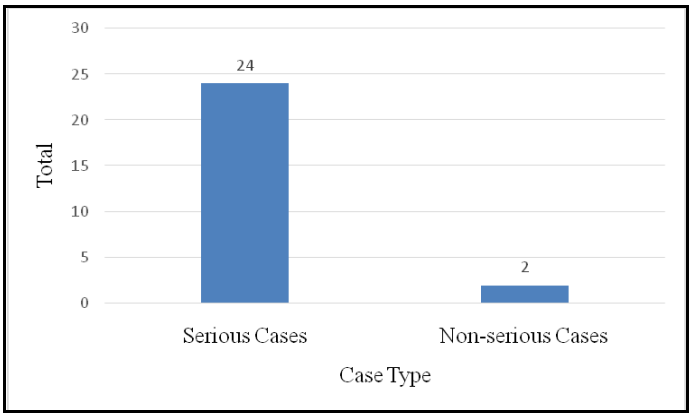

Figure 1: A depiction of total number of serious and non-serious cases

Table 2: Different Serious Reactions Based on the Diagnosis

Death	Congestive Heart Failure
Hospitalization	Pulmonary Edema, HDL cholesterol decreased, Bilateral Pleural effusion, Sinus tachycardia, Rhabdomyolysis, Aspartate amino transferase increased.
Important medical events	Hepatocellular injury, Fulminant hepatic failure, Mixed hepatocellular cholestatic liver injury, Cholestatic liver injury, Graves' disease, Pretibial myxedema, Infarction with peri-infarct ischemia, Congestive heart failure, Hepatotoxicity, Orthopnea, Heart Failure, Leukopenia, Thrombocytopenia, International normalized ratio decreased, Dilated cardiomyopathy, Mitral regurgitation, Diabetic macular edema, Red blood cell sedimentation rate increased, Anemia, Thrombocytopenia, Peripheral arterial disease, Anemia, Pancytopenia, Aortic regurgitation

Causality assessment

The causal relationship between drugs and events of different cases has been depicted in **Fig. 2**. There were in total of 7 (27 %) and 19 (74 %) cases that belonged to possible and probable category respectively.

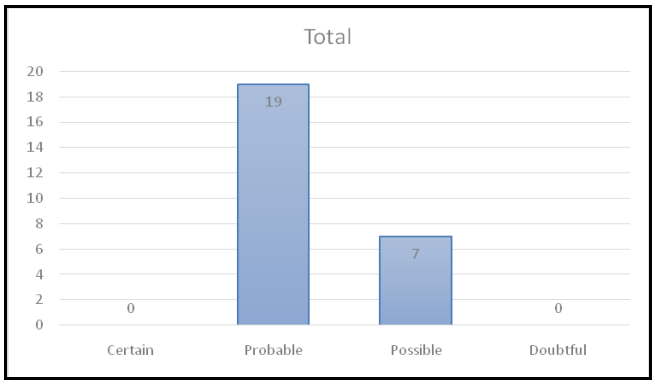

Figure 2: Different cases pertaining to causal relationship

Expectedness Assessment

After the assessment, all the 26 cases were found to be Unexpected. None of the cases belonged to Expected while there were 131 unexpected adverse drug events and 37 expected adverse drug events. **Table 3** shows different Expected and Unexpected adverse events of 26 cases. Descriptive analysis showed that a total of 131 (77.97 %) and 37 (22.02 %) were unexpected and the expected reactions respectively.

Table 3: Different expected and unexpected adverse drug reactions

Study/Year	Expected Adverse Events	Unexpected Adverse Events
(Maeda, 2001)	ALT (Alanine transaminase)	Bilirubin increased, AST (Alanine aspartate) abnormal, ALP (Alanine phosphatase) increased, GGT (Gamma glutamyl transferase) abnormal
(Chase &Yarze, 2002)	ALT increased	Jaundice, Hepatic encephalopathy, Serum bilirubin increased, Direct bilirubin increased, Prothrombin time increased, ALP increased, AST abnormal
(May et al., 2002)	ALT increased, Loss of weight, nausea	Mixed hepatocellular cholestatic injury, Anorexia, Upper abdominal discomfort, AST increased, ALP increased, direct bilirubin increased, Cholestasis intrahepatic, Scleral icterus, Acholic stool,
(Neimeyer& Janney, 2002)	Edema	Kidney failure acute, Respiratory failure, Pulmonary failure, Apnea, Pleural effusion, Respiratory distress, Pulmonary venous congestion
(Pinto, Cummings &Chalasini, 2002)	ALT increased, diarrhea	Jaundice, Intrahepatic cholestasis, Liver Injury, AST increased, Stool discoloured, Discoloration urine, Itching, Pedal edema, Periportal edema, Bile duct proliferation, Apoptosis
(Starkey et al, 2003)	No expected event found	Pretibial myxedema, Graves disease
(Karmani& Garg, 2003)	No expected event found	Respiratory distress, Pleural effusion, Cardiomegaly, severe edema
(Cheng &Fantus, 2004)	Weight gain, Congestive Heart Failure	Exertional dyspnea, Orthopnea, Paroxysmal nocturnal dyspnea, Pulmonary edema, Diastolic dysfunction, Infarction with Peri-infarct ischemia, sleep apnea, hypokinesia.
(Jamieson &Abousleiman, 2004)	Congestive heart failure, Dyspnea	Acute pulmonary edema
(Marcy, Britton, & Blevins, 2004)	Loss of appetite, Fatigue	Urine color abnormal, Shortness of breath, Orthopnea, Hepatotoxicity
(Farley-hills, Shivasankar& Martin, 2004)	Liver Failure	Encephalopathy, Prothrombin time increased, Fibrosis Liver, Steatohepatitis, Acidosis
(Shah, Kolandaivelu&Fearon, 2004)-1st case	Peripheral edema, Fluid retention, Pitting edema	Paroxysmal nocturnal dyspnea, Bibasilar crackles, creatinine level increased, Heart Failure
(Shah, Kolandaivelu&Fearon, 2004)-2nd case	Pitting edema, Edema	Jugular venous distention, Bilateral rales, Heart Failure
(Digman, Klein & Pittas, 2005)	Hematocrit decreased	Thrombocytopenia, White Blood Cell (WBC) decreased
(Hoffman et al., 2006)	No expected event	International normalized ratio decreased
(Senba, Kawano & Kawakami, 2006)	Diarrhea, Nausea, Appetite loss,	Triglyceride increased, High Density Lipoprotein(HDL)decreased, Blood Urea Nitrogen (BNP) increased
(Iqbal, 2008)	No expected events	Exertional dyspnea, Orthopnea, Acute pulmonary edema, Left ventricular systolic dysfunction, Left bundle branch block, Cardiomegaly, Dilated cardiomyopathy, Systolic dysfunction
(Dorkhan, Dencker&Frid, 2008)	Weight gain, Hemoglobin decreased	BNP increased, Mitral regurgitation, Ejection fraction abnormal, atrial enlargement, Left ventricular end diastolic pressure increased
(Chen et al, 2008)	Dyspnea	Blood pressure reading high, Heart rate increased, Breathing rate increased, Anasarca, Breath sound decreased, Sinus tachycardia, Ejection fraction abnormal, Pulmonary hypertension, Bilateral pleural effusion

(Oshitari et al, 2008)	Face oedematous, Weight gain,	Retinal detachment, Visual acuity reduced, Diabetic macular edema
(Finsterer&Stollberger, 2009)	Hemoglobin low, Leg edema, Myalgia	Blood sedimentation increased, Creatine kinase increased, Thrombocytopenia, Creatinine increased, Crackles lung, Prohormone brain natriuretic peptide increased, Bilateral atrial enlargement, Ptosis, Weakness of upper extremities, Tendon reflex absent, Hypoesthesia, Peripheral sensorimotor polyneuropathy, Motor dysfunction, White matter lesion
(Slim et al, 2010)	Myalgia, AST increased	Muscle weakness, tenderness, Creatine phosphokinase serum increased, Myoglobin blood increased, Creatinine increased, Rhabdomyolysis
(Kota et al, 2012)	No expected event	Pancytopenia
(Karakurt, Kargii&Kasapoglu, 2010)	Hemoglobin low	Mitral regurgitation, Pedal edema, Aortic regurgitation, exertional dyspnea, Ejection fraction abnormal, Atrial enlargement, Weight decrease, Brain natriuretic peptide decreased
(Shadid& Jensen, 2002)	Pharyngitis	Swelling lips, Swelling of tongue, Angioneurotic edema
(Femia& Klein, 2010)	No expected event	Lipomatosis

DISCUSSION

Pioglitazone, a member of the PPAR-gamma-mediated lowering agent, has been used for decades to lower the blood glucose level in type-2 diabetes mellitus patients. This drug like the other members of the thiazolidinedione is not devoid of adverse effects. Most of the reports that are individual case safety reports implicate adverse events and almost all of them correspond to a link with the drug. According to a Product monograph of "Actos", whose main constituent is pioglitazone, it is not always possible to estimate the causal link between the drug and the event because the ICSR comes from the population of non-certain size [48]. In many reports, causality is not established to know the extent of the causal relationship between drug and the event found out. In this study, most of the reactions, after assessing the cases, belonged to the probable followed by the possible category as evident in **Fig. 2**.

The product monograph of Actos of 2018 stated that it's very rare that these reports have included liver failure with or without the fatal outcome and have not included the causal relationship [48]. Saravanan et al., (2011) found most of the adverse drug reactions due to pioglitazone in a tertiary care hospital to study the adverse drug reactions due to antidiabetic drugs. Pioglitazone caused non-serious adverse drug reactions like hypoglycemia (major), followed by diarrhea, edema, and headache [49]. In this work, only two reactions were non-serious and that were angioneurotic edema and lipomatosis. Other reactions were serious that led to either death or hospitalization or were important medical events. In the majority of cases, congestive heart failure and hepatotoxicity were the most common reactions. Expectedness assessment showed that a majority of reactions were unexpected despite being an old molecule. The reference safety information like Summary of product characteristic and United States Prescribing Information (USPI) should be updated.

This drug causes many serious adverse drug reactions. This study has involved the scholar database, PubMed that is the major limitation of the study. There are many other paid databases like Embase and EBSCO's database, *Biotechnology Source* that robustly helps to monitor the literature for the adverse drug events more efficiently [50,51].

This was a retrospectively assessed study involving the published individual cases or the info of adverse drug reactions. Underreporting, lack of follow-up data, lack of data regarding concomitant drugs are some of the other important limiting factors that hinder the assessment of ADR of pioglitazone.

CONCLUSION

The thiazolidinedione class of drugs is full of conflicts and tragedies to date. Pioglitazone has faced terrible uncertainties due to safety issues but still, it is the only drug that is being marketed in a country like India, although it is banned in countries like Germany and the country France. This drug is associated with some tortuous serious adverse drug reactions that if not taken cautiously, can lead to death. Although this drug has been associated with some expected adverse events like weight gain, edema, heart failure, decreased hemoglobin but the unexpected adverse drug reactions found are such that they seem to outweigh the benefits of drugs. The fluid retention that is the most common adverse effect can aggravate the pre-existing heart failure or it can also worsen the condition in the patient suffering from left ventricular dysfunction. The concomitant medicines used with this drug should be very cautiously used as it can become a possible causative factor for an adverse reaction.

To summarize, every patient taking pioglitazone, especially those taking multiple medications, geriatrics, a patient

suffering from chronic heart and renal disease, should be evaluated for the possible adverse effects by proper monitoring and follow-ups. The serious and unexpected adverse drug reactions found in this study could be very useful for generating new signals and further enrich the pharmacovigilance research related to Pioglitazone.

CONSENT FOR PUBLICATION

Not applicable

CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest in relevance to this review article.

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