Matin Ahmad Khan et al. / International Journal of Preclinical & Pharmaceutical Research. **2016; 7(1): 16-23.**

e-ISSN 2249-7552
Print ISSN 2229-7502

International Journal of
Preclinical & Pharmaceutical Research

Journal homepage: www.preclinicaljournal.com

PIOGLITAZONE AND RISK OF BLADDER CANCER: MYTH OR REALITY?

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ABSTRACT

Pioglitazone, an important armory in the basket to combat Diabetes mellitus has been liptop in the sense that first it was implicated to have caused bladder cancer in diabetes resulting into its ban and later on ban being lifted .As per FDA till Nov, 9, 2015: 3,101 people reported to have side effects when taking Pioglitazone. Among them, 57 people (1.84%) have Renal Failure. This paper examines both sides of the coin and leaves to the audience to take a stand. An extensive list of references has been incorporated to help the readers to refer to make the decision themselves.

Key Words: Pioglitzone, Bladder cancer, Diabetes mellitus.

INTRODUCTION

Changes in human behavior and lifestyle over the last century have resulted in a dramatic increase in the prevalence of type 2 diabetes and in addition to "diabesity" and the "metabolic syndrome". The risk of developing type 2 diabetes mellitus (T2DM) is particularly high among South Asians, which comprise one-fifth of the total world's population obese individuals, both diabetic and nondiabetic, are characterized by insulin resistance and compensatory hyperinsulinemia, in as a consequence of beta cell dysfunction. Metformin and thiazolidinediones (TZDs) are commonly used agents in diabetes management. Metformin, a partial insulin-sensitizing agent, is the gold standard first-line treatment for type 2 diabetes. This recommendation is based on data from the UKPDS that showed that metformin can improve cardiovascular outcomes in overweight patients with type 2 diabetes. Pioglitazone is a TZD that acts mainly via peroxisome proliferator-activated receptor gamma to improve insulin sensitivity and is licensed for use in combination with metformin in obese patients. Combining a TZD with metformin should enable additive clinical effects to be achieved through their different mechanisms of action.

Recently, however the safety of pioglitazone, an oral anti-diabetic agent in the thiazolidinedione class, has been controversial. Although pioglitazone is effective at reducing glycated haemoglobin (HbA_{1c}) levels and may decrease the risk of cardiovascular events, it has also been associated with weight gain and an increased risk of congestive heart failure and there have been contradictory reports of a probable association between pioglitazone use and bladder cancer.

A study by Lewis et al did not observe a statistically significant increase in risk of bladder cancer among patients treated with pioglitazone for <2 years. However, the analyses addressing increasing exposure to pioglitazone observed a weak increased risk with long-

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term therapy. In another study Tseng] reported that there was an insignificant 30% overall increase in bladder cancer risk among pioglitazone users. However, all bladder cancers occurred within 2 years of the start of therapy and no patients with a cumulative dose >28,000 mg developed bladder cancer, suggesting that there was no direct cause and effect relationship could be established on pioglitazone and bladder cancer. This study was undertaken to assess a link, if any, on glitazones as a cause of bladder cancer in the Indian population

MATERIALS & METHODS

In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial, the reported incidence of bladder cancer was higher among participants randomised to pioglitazone than among those randomised to placebo (14 *v* 6 cases), although this failed to reach statistical significance (P=0.069). However, it was later reported that one case in the placebo group showed benign histology, and the exclusion of this case resulted in a statistically significant increased risk of bladder cancer (14 *v* 5 cases, relative risk 2.83, 95% confidence interval 1.02 to 7.85) With respect to observational studies, a signal was observed in the US Food and Drug Administration adverse event reporting system. Furthermore, an interim analysis of an ongoing US cohort did not find an association between pioglitazone and bladder cancer overall but found a 40% increased risk in patients who used the drug for more than 24 months. In contrast, a modest increased risk was observed overall in a French cohort. Based on these findings, France decided to suspend the sale of pioglitazone, whereas Germany and Luxembourg recommended that doctors should not start new patients on this drug. After carrying out a review of the safety of pioglitazone, the European Medicines Agency decided to maintain the marketing authorization of the drug, whereas the FDA and Health Canada added warnings of a possible increased risk of bladder cancer in the product monograph Two subsequently published Taiwanese studies found no statistically significant association between pioglitazone and bladder cancer.

All of the aforementioned studies included prevalent users of antidiabetic drugs, which may have underestimated the strength of the association between pioglitazone and bladder cancer. As available data on the reported association between pioglitazone and bladder cancer are limited, additional studies are needed to inform regulatory agencies, doctors, and patients on its long term safety. We carried out a population based study to determine if pioglitazone is associated with an increased risk of bladder cancer in people with type 2 diabetes.

A recent observational study using the Kaiser Permanente Northern California diabetes registry data found that, among 193,099 diabetic patients who were ≥40 years old, use of pioglitazone at any time (n = 30,173) was not associated with the risk of bladder cancer (adjusted HR: 1.2; 95% CI: 0.9–1.5). However, long-term use of pioglitazone (>24 months of therapy) was associated with an increased risk of bladder cancer (adjusted HR: 1.4; 95% CI: 1.03–2.0). More recent data from observational studies show relative risks (RRs) ranging from 1.12 to 1.33 when diabetic patients receiving pioglitazone are compared with diabetic patients receiving other antidiabetic medicines but not exposed to pioglitazone Two studies have been reported from England: one suggested an association between pioglitazone and the risk of bladder cancer while the other did not [6]. Two subsequently published Taiwanese studies and one Korean study found no significant association between pioglitazone and bladder cancer Thus, this relationship remains controversial. Only one study in Japan investigated the risk of bladder cancer with pioglitazone use. In our hospital, half of the patients with type 2 diabetes mellitus (T2DM) were treated by pioglitazone to prevent cardiac or cerebral vascular events. Most pioglitazone was prescribed by cardiologists. Therefore, it seems that this situation facilitated an assessment of the relationship between pioglitazone and bladder cancer. Therefore, the data of diabetic patients treated at Teikyo Chiba Medical Center were retrospectively analyzed.

The new 10-year findings, from three large database analysis, were published July 21 in the Journal of the American Medical Association by James D Lewis, MD, of the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, and colleagues.

Pioglitazone is currently used by up to a quarter of diabetes patients in the United States. In a large, 10-year study, The lead investigator Assiamira Ferrara, section chief for Women's and Children's Health and research scientist with the Kaiser Permanente Northern California Division of Research, Oakland found no statistically significant association between the use of pioglitazone and the increased risk of bladder cancer, which should be reassuring to clinicians and patients.. A small increased risk of bladder cancer could not be excluded. Their study was able to examine 4 years or more of pioglitazone use, but they were not able to address bladder-cancer risks associated with longer-term use.

Pioglitazone helps people with type 2 diabetes to make better use of insulin. Like all drugs for diabetes and all medications, there will always be risks and benefits, .The decision to use pioglitazone is dependent on the balance of these factors for any individual. This study can help doctors and patients with diabetes to better understand the risks of pioglitazone, allowing a better understanding when choosing treatments

Balancing Risk

The new findings represent 10 years of observational follow-up requested by both the US Food and Drug Administration (FDA) and European Medicines

Agency (EMA). A 5-year interim analysis had shown a small but significant 1.4-fold elevated risk of bladder cancer among patients receiving pioglitazone for longer than 2 years. In response, both the FDA and EMA revised the drug's label but allowed for continued marketing, pending the current results.

In one of two accompanying editorials, Joshua M Sharfstein, MD, of Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, and Aaron S Kesselheim, MD, JD, of the division of pharmaco-epidemiology and pharmaco-economics, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, cite the pioglitazone case as an example of the need for the FDA to develop a standardized framework for regulatory decisions about drug safety in situations of uncertainty.

It may not be feasible for the FDA to reconcile all competing interests and opinions about complex questions of drug safety. A more realistic goal is a rigorous, fair, and transparent framework that will make drug safety less a recurrent crisis and more just another difficult task facing a very important agency.

In another editorial, JAMA declare that the journal stated that it will continue to review studies evaluating the potential relationship between drugs, devices, or vaccines and adverse outcomes. Each manuscript will be considered based on its scientific validity, as well as the importance of the results and merits of the main study message.

By publishing the results of these studies, the JAMA will continue to provide information physicians can use in discussions with patients and regulatory bodies can use in policy decisions about the benefits and risks of various therapies.

10-Year Results Reassuring, but Risk Can't Be Ruled Out

The three studies were a cohort analysis of 193,099 people with diabetes aged 40 years and older, a nested study of 464 bladder-cancer patients compared with 464 matched controls, and a separate cohort study of 236,507 individuals with diabetes, that analyzed the risk of 10 additional cancers based on-use vs non-use of pioglitazone. All data were from Kaiser Permanente Northern California.

Of the 193,099 adults with diabetes, 34,181 received pioglitazone during follow-up and 1261 (0.65%) received a diagnosis of bladder cancer.

The crude incidence of bladder cancer was 89.8 and 75.9 per 100,000 person-years in pioglitazone users and nonusers, respectively. Cancer stage did not differ between pioglitazone users and nonusers. After adjustment for potential confounders, there was no association between ever use of pioglitazone and bladder cancer, with a hazard ratio (HR) of 1.06. Use of other diabetes medications was also not associated with bladder cancer risk. Results were similar in the case-control analysis, which included adjustments for self-reported race/ethnicity, smoking history, occupations associated with bladder cancer, frequency of urinary-tract infections, and HbA_{1c}. In this analysis, the odds ratio for ever use of pioglitazone was a non-significant 1.18 (95% confidence interval [CI], 0.78 – 1.80).

In the third analysis, 16% (38,190) of 236,507 individuals had ever used pioglitazone and 6.8% (15,992) had received a diagnosis of some type of cancer. Pioglitazone use was associated with an increased risk of prostate cancer, with a crude incidence of 453 vs 449 per 100,000 person-years (HR, 1.13; 95% CI, 1.02 – 1.26), and pancreatic cancer (81 vs 48 per 100,000 person-years; HR, 1.41; 95% CI, 1.16 – 1.71). Other cancers were not significantly related to pioglitazone use.

However, the authors note that other diabetes medications were also associated with pancreatic cancer, which suggests reverse causality, because hyperglycemia is an early manifestation of pancreatic cancer. This explanation is supported by the observation that risk of pancreatic cancer lowered with time since initiation.

The increased prostate and pancreatic cancer risks associated with ever use of pioglitazone merit further investigation to assess whether the observed associations are causal or due to chance, residual confounding, or reverse causality,. Bladder cancer is the 5th most common cancer in the United States the 7th most common cancer worldwide and the 9th most common cancer in Japan

Known risk factors include age, sex (male), ethnicity/race (white), smoking, and several occupations, particularly those involving exposure to aromatic amines Evidence is accumulating that diabetes may be related to the risk of several cancers, including a reduced risk for prostate cancer [14] and increased risks for cancers of the pancreas, liver, colon, and breast but the evidence is not as clear for bladder cancer. A meta-analysis published in 2006 suggested that diabetic patients had a slightly elevated risk of bladder cancer relative to non-diabetic patients One meta-analysis in 2013 found that diabetic patients had a slightly elevated risk of bladder cancer.

Animal models and some post-marketing studies have suggested elevated risk for bladder cancer in pioglitazone users. Now, researchers present three studies in which pioglitazone use was assessed in patients who developed bladder cancer (in two studies) and other cancers (in the third study). All studies were conducted at a large integrated healthcare system in California In a cohort analysis of 193,099 patients with diabetes (18% treated with pioglitazone for a median 3 years), unadjusted bladder cancer incidence did not differ significantly between those who did and did not use pioglitazone (90 and 76 per 100,000 person-years, respectively). In a case-control analysis that involved 464 patients with incident bladder cancer and 464 matched controls, pioglitazone use did not differ significantly between those with bladder cancer and

controls. In a cohort analysis of 193,099 patients with diabetes (18% treated with pioglitazone for a median 3 years), unadjusted bladder cancer incidence did not differ significantly between those who did and did not use pioglitazone (90 and 76 per 100,000 person-years, respectively). In a case-control analysis that involved 464 patients with incident bladder cancer and 464 matched controls, pioglitazone use did not differ significantly between those with bladder cancer and controls. Finally, to assess risk for 10 other cancers (e.g., prostate, pancreatic, breast, colon) in pioglitazone users versus nonusers, researchers performed a cohort analysis of 236,507 patients with diabetes (16% treated with pioglitazone). During mean follow-up of about 6 years, risks for prostate cancer and pancreatic cancer were elevated significantly in pioglitazone users (adjusted hazard ratios, 1.13 and 1.41, respectively).The evidence on the association between pioglitazone use and bladder cancer is contradictory, with many studies subject to allocation bias. The cumulative use of pioglitazone or rosiglitazone was not associated with the incidence of bladder cancer in this large, pooled multipopulation analysis.

India's ministry of health and family welfare has revoked the ban that it placed on the anti-diabetes drug pioglitazone just within six weeks because of the drug's association with bladder cancer.

The Drug Technical Advisory Board, through the Gazette of India, recommended revoking the ban after reviewing the evidence, and imposed various conditions for the use of pioglitazone. It recommends, for example, that pioglitazone should not be used as a first line treatment for diabetes.

The ban and the subsequent reversal of the policy have caused a media storm in India, with many commentators demanding clear processes for drug licensing that are based on scientific evaluation of the evidence.

The whole process of banning first and revoking later was shocking. This shows how incompetent the system is. Drug control authorities in India are hardly aware about evidence based medicine and seem to rely mostly on [the] personal opinions of some clinicians

The ban on pioglitazone was apparently triggered by a letter after a noted Indian diabetologist and Padmashree awardee (the fourth highest civilian award in India) wrote to the prime minister's office detailing the risk of bladder cancer with pioglitazone use.

Clinicians were also puzzled about the clinical safeguards imposed by the drug control agency. These require prescribers to review the safety of pioglitazone every three to six months and to keep only those patients who are deriving a benefit from the drug on it.

The prescribers expected to order a cystoscopy every three months to screen for bladder cancer Also, pioglitazone is often given in combination with other oral hypoglycaemic (drugs) so it would be difficult to decide on whether to continue or discontinue pioglitazone solely based on the patient's overall blood sugar control as one may not know for sure which of the drugs (pioglitazone or metformin or sulfonylurea) are actually working

The requirement for manufacturers to mention various safeguards on their package insert and promotional literature of the drug is also being questioned.

Clinical decisions regarding drug prescription in India mainly depend on information about the drug given by medical representatives. No medical representative is going to focus on things mentioned in the Gazette. Clinicians in India are usually poor at assessing evidence and don't have much time and interest in prescribing drugs based on guidelines or box warnings so this Gazette is going to have limited implications."

The guidelines mentioned in the gazette are unrealistic and it may not be possible to maintain safeguards by either CDSCO (the drug control agency in India) or the treating physician."

The Health Ministry has revoked its earlier suspension on the diabetes drug, and has allowed the manufacture and prescription of pioglitazone and its formulations, but with several riders - including a box warning in "bold red letters" to caution patients.

The suspension had caught doctors, patients and drug companies by surprise, following which there were hi-decibel protests and submissions to the Ministry. Doctors said that the drug was best suited for Indian patients. Lacing its notification with much caution, the Health Ministry said that it was aware that the drug was risky and safer alternatives were available.

Nevertheless, it proceeds to say that the Drugs Technical Advisory Board recommended the revocation of the suspension of pioglitazone, with certain conditions including that the manufacturers carry warnings on the packing, product insert and promotional literature. The drug should not be used as a first line of therapy to treat diabetes. It would carry the warning in bold red letters and also would carry advice for healthcare professionals, the notification said.

Further, it added, that the drug not be given to patients with a history of bladder cancer, be restricted to the elderly and prescribed after knowing the patients history. Those prescribed with the drug would also be put through 6 monthly reviews, the notification added. Pioglitazone is a Rs. 700-crore plus market in India, and several companies including USV, Sun Pharma and Ranbaxy make the medicine.

The drug is banned in France, restricted to existing prescriptions in Germany and sold with patient and doctors warnings in the US and the EU. An extremely large database study across more than a million people found no increased risk of bladder cancer with the diabetes drug pioglitazone. The drug, along with similar agent rosiglitazone, had been implicated as potentially increasing the risk of bladder cancer in previous work.

Indian Scenario

A retrospective study on finding correlation of pioglitazone and incidences of bladder cancer in the Indian population by V Balaji et al (2014) [1] found that he number of diabetic patients on pioglitazone with bladder cancer was fewer than the diabetic patients on other medications with the disease. Further, no link could be established between any specific drug use and bladder cancer. Least number of patients with bladder cancer was on pioglitazone, suggesting that pioglitazone alone cannot be considered a cause for increased incidence of bladder cancer in diabetic patients.

This retrospective cohort study aimed to analyze the probable link between antidiabetic agents and incidence of bladder cancer in a cancer patient cohort. The study also analyzed the other potential risk factors of cancer in these patients. In this study, the number of diabetic patients on pioglitazone with bladder cancer was the lowest as compared with patients on other antidiabetic agents, including metformin, sulphonylureas, DPP 4 inhibitors, and insulin.

These results are consistent with other recently published studies in which an association between pioglitazone use and bladder cancer has not been found. In the study by Song et al. a relationship between pioglitazone use and incidence of bladder cancer was not observed in Korean diabetic patients.

In another study by Wei et al., 66 and 803 new cases of bladder cancer occurred in the pioglitazone and other antidiabetic drug group respectively, suggesting that pioglitazone may not be significantly associated with an increased risk of bladder cancer in patients with type 2 diabetes.

In the light of the above results, key issues relating to bladder cancer and cancer risk associated with a medication needs to be viewed in the appropriate perspective. Bladder cancer incidence differs among different ethnicities, with men consistently showing a higher risk than their female counterparts within the same ethnicities, and a higher incidence of bladder cancer in Caucasians as compared with blacks and Asians. The incidence of bladder cancer must also be viewed keeping in mind that pioglitazone is usually a second- or third-line antidiabetic agent, and the users may be elderly, with longer diabetes duration, poorer glycemic control, and higher rates of complications and comorbidities.

On the contrary, there are increasing data on benefits of pioglitazone both in diabetes prevention and in diabetes management as well as in long-term cardiovascular morbidity and mortality as seen from the results of PROACTIV.

Results of several studies including our own indicate that pioglitazone does not appear to raise the risk of bladder cancer in diabetic patients, any more than other antidiabetic agents. The benefits offered by pioglitazone are far higher than the alleged risk. It has been suggested that it would be ideal to use pioglitazone where indicated, when indicated, as per guidelines, preferably at lower doses of 7.5-15 mg. In our study too, patients were on this dosage

CONCLUSION

The FDA's current recommendation on pioglitazone does include a warning that use of the drug for more than 1 year could be associated with an increased risk of bladder cancer. The large international analysis does not support a causal effect of pioglitazone on bladder cancer, thus contradicting previous studies deemed to have proven this relationship It not appear to be associated with an increased risk of bladder cancer, as had been previously suggested, but new data indicate a possible increased risk of prostate and pancreatic cancer Although available data are limited, there is now some evidence suggesting that pioglitazone may be associated with an increased risk of bladder cancer.

ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST: None

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