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Controversies of Pioglitazone in the Management of Diabetes Mellitus

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ABSTRACT

Type II-diabetes mellitus (T2DM) is a chronic metabolic disorder which is treated with oral hypoglycaemic agents including pioglitazone. The present work is aimed to collect a brief profile of pioglitazone, belonging to the thiazolidinedione class and controversies surrounding its use. Pioglitazone which was marketed in 1999 acts on the nuclear peroxisome proliferator-activated receptor γ PPAR-γ in adipose tissue, skeletal muscles and liver. Pioglitazone is safe, potent, insulin sensitizing gene activator and regulate blood sugar level when administered orally alone or combination with sulphonyl ureas or metformin. India is one of the leading T2DM patients country and most patients are using pioglitazone because of its efficacy and economy. Even though it is a safe drug for diabetics, it was observed that it causes adverse effects like hepatotoxicity, cardiac failure, osteoporosis and urinary bladder cancer and hence pioglitazone was suspended in India in June 2013 for a brief duration by the Indian government. There are over 30 lakh people in India using this drug and there is no strong evidence to show that the drug has serious life threatening side effects in patients in India and also using Pioglitazone is less expensive than other drugs. By considering the safety, efficacy, potency and economy, health ministry of India revoked the earlier suspension on the diabetic patients and has allowed the manufacture and prescription of Pioglitazone and its formulation with several conditions. Hence, there is a lot of debate about benefit to risk ratio of this drug. Our study presenting brief information about pioglitazone and its controversies for diabetic mellitus in India.

INTRODUCTION

Noninsulin dependent diabetes mellitus (NIDDM) is a range of dysfunctions described by hyperglycemia and resulting from the inadequate insulin secretion or resistance to insulin action or redundant glucagon secretion [1]. It is a multifaceted serious illness involving endocrine pancreas with multiple complications and affecting more than 285 million people worldwide and is considered one of the three leading causes of death in the world [2]. Diabetes mellitus is treated with Sulfonylureas, Biguanides, Meglitinide, α Glucosidase inhibitors and Thiazolidinediones. Among the oral antidiabetic drugs, Pioglitazone has been widely used in India to treat Type 2 diabetic patients. Apart from potent anti-hyperglycaemic action by improving insulin sensitivity, it also has positive effects on lipid metabolism and endothelial function [3]. There are several issues against the pioglitazone therapy for diabetic patients in India and globally with regard to risk of bladder cancer. Hence, recently pioglitazone was banned in India, but again ban was revoked for its use with special precautions. So, it is very essential to know about the pioglitazone and its controversies in India for the management of hyperglycemia and our study discusses a current detailed profile of pioglitazone with its controversies in clinical practice for Diabetes mellitus Type 2.

History of thiazolidinediones

Due to Safety problems and improper clinical effectiveness, number of new antidiabetic drugs introduced in the last decade faces an uncertain future. Targeting insulin resistance and/or hepatic glucose production was first made possible with the introduction of Biguanide metformin. Metformin has been available worldwide since 1957 and was introduced into the U.S. market in 1995 [4]. Subsequently thiazolidinediones were introduced about a decade ago. With the invention of glitazones (thiazolidinediones), the control of type 2 diabetes mellitus took a giant leap forward as this is the only class of drugs, other than metformin, to address the main pathophysiological defect in insulin resistance diabetes mellitus. Oral hypoglygemic agent's glitazones have desirable properties beyond their blood glucose lowering effects [5]. The glitazones are peroxisome-proliferator-activated receptors agonists improve glycemic control by increasing insulin sensitivity in fat, liver, and muscle, and may have a role in β cell protection [6].

Hence, right from the beginning, thiazolidinediones was mired in controversy because of their adverse effect profile due to which most drugs in this class have gone off the therapeutic armamentarium at some stage or the other. Troglitazone, the first molecule of pioglitazone, was launched in the USA in March, 1997 which became an instant success, particularly in the United States. It reached Europe later that year, only to be withdrawn within weeks on the from the USA market in March 2004 because of its liver toxicity [7,8]. Subsequently another two pioglitazones namely rosiglitazone and pioglitazone were launched in the USA in 1999. However, both rosiglitazone and pioglitazone had their own spectrum of adverse effects like weight gain, decrease in hematocrit values, edema, cardiac failure and possible worsening of diabetic macular edema [9]. Due to their remarkable oral ant diabetic efficacy, they became popular and were widely used globally in spite of these side effects. Research shown that rosiglitazone was a potent hypoglycemic drug with the adverse effect of myocardial infarction [10]. But, this coronary artery disease side effect was never decisively confirmed, the media hype and subsequent studies recommending that there could be a minor increase in coronary artery disease rates, eventually led to an extreme decline in the use of this drug, ending in it being banned in several countries including India [11]. In July 2010, the Health Ministry of India ordered Glaxo Smith Kline to suspend human studies being conducted in 19 sites across India. Subsequently, in October 2010, the Drug Controller General of India (DCGI) proposed to the Health Ministry to ban rosiglitazone [12]. Other drugs in the class darglitazone and englitazone have been discontinued from clinical development or withdrawn from the market. This left pioglitazone as the solitary agent in the thiazolidinedione class to regulate hyperglycemia.

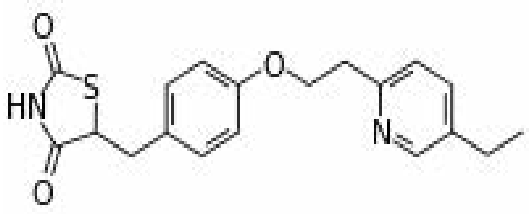
Pioglitazone

Pioglitazone is widely prescribed oral hypoglycaemic thiazolidinediones and selectively stimulates the nuclear peroxisome proliferator-activated receptor gamma (PPAR-γ) and to a lesser extent PPAR-α [13,14]. PPAR-γ enhances the transcription of the several insulin-responsive genes involved in the control of glucose and lipid metabolism in the muscle, adipose tissue, and the liver. It tends to increases transcription of glucose transporter-4 (GLUT 4). As a result, pioglitazone reduces insulin resistance in the liver and peripheral tissues; increases the expense of insulin-dependent glucose, decreases withdrawal of glucose from the liver and reduces quantity of glucose in the bloodstream. Improved glycemic control results in lowering of circulating HbA1C and insulin levels in type 2 DM patients. Apart from potent anti-hyperglycemic action by reducing insulin resistance, it also lowers serum triglyceride level and raises HDL level without much change in LDL level, probably because it acts on PPAR-α as well. Hence, on one side there is supporting ground of cardio-protective role of pioglitazone [15]. Whereas some studies showed its adverse effect of urinary bladder cancer. So there is a lot of debate about benefit to risk ratio of this drug.

Pharmacokinetics

Pioglitazone is administered as a single daily oral dose, reaches peak concentration in 2 h and attains steady state in 4-7 days. Bound to serum albumin, it is metabolized in the liver by both CYP2C8 and CYP3A4. Most of the drug is excreted into the bile and eliminated through faeces, while 15-30% is recovered in urine. The half-life of pioglitazone is 5-6 h, while the half-life of its active metabolites is 16-23 h [16] .

Pioglitazone



Efficacy

The efficacy of pioglitazone is well documented as monotherapy and in combination with both oral antidiabetics and insulin [17]. Pioglitazone exerts its effect on both fasting and post prandial blood glucose, thus lowering HbA1c by 1.3 to 1.6%, and the drug is equipotent to biguanide metformin and sulfonylureas.

Cardiovascular health

Pioglitazone has been reported to have a cardioprotective effect. Pioglitazone significantly decreased the progression of Carotid Intima-Media Thickness (CIMT), improvement in cardiovascular risk factors such as diabetes, obesity, and hyperlipidemia and prevention of arteriosclerosis [18,19].

Nonalcoholic steatohepatitis

Studies show that pioglitazone, a new diabetes medicine, on decreasing insulin resistance and improving hepatic disease in patients with nonalcoholic steatohepatitis (NASH). NASH is a chronic liver disease with unknown cause that involves fat accumulation and inflammation in the liver, leading to liver cirrhosis in 10 to 15% of patients and significant liver scarring in another 30%. It is most often seen in patients with insulin resistance. Pioglitazone decreases insulin resistance and improves blood lipid levels, so that it may improve liver disease in NASH [20] .

Adverse effects

Pioglitazone can cause fluid retention and peripheral edema, congestive heart failure [6], osteoporosis, Weight gain and urinary bladder cancer [21-23].

Brand names

Pioglitazone is marketed as trademarks Actos (USA, Canada, UK and Germany), Glustin (Europe), Glizone and Pioz (India).

Controversies

A bridge between bladder cancer and pioglitazone first appeared in preclinical studies in US in 1999 but initial experimental pharmacological studies suggested that this might be a rat-specific phenomenon [24]. Unfortunately this urinary bladder cancer has now been reported in human clinical studies also. Piccinni et al. analyzed association between anti-diabetic drugs and bladder cancer through adverse event recording. They reported 31 cases of bladder cancer in Pioglitazone users with significant ROR above 13 [25].

On 9th June, 2011 the French Agency for the Safety of Health Products concluded to withdraw pioglitazone in regards to high side effect of bladder cancer [26]. The European Medicines Agency ("EMA") [27] acknowledged in a statement on June 9, 2011 that: "While review of pioglitazone is ongoing, the Committee for Medicinal Products for Human Use (CHMP) is not recommending any changes to the use of pioglitazone-containing medicines". On June 10, 2011 Germany's Federal Institute for Drugs and Medical Devices also directed doctors not to prescribe the medication until further investigation of the bladder cancer risk had been conducted [28]. On June 15, 2011 the U.S. FDA announced that pioglitazone use for more than one year may be associated with an increased risk of bladder cancer, and that the information about this risk will be added to the Warnings and Precautions section of the label for pioglitazone-containing medicines.

The ministry of health and family welfare of India has suspended the manufacture and sale of pioglitazone under Section 26A of the Drugs and Cosmetics Act, 1940 with immediate effect, through a notification issued on June 18, 2013. The suspension had caught physicians, patients and pharmaceutical companies by surprise, following which there were hi-decibel protests and submissions to the Ministry. In a country full of diabetics, the ban came as a shock to both doctors and 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 following consultation with diabetes experts, with certain conditions including that the manufacturers carry warnings on the packing including a box warning in "bold red letters", product insert and promotional literature. The drug should not be used as a first line of therapy to treat diabetes and it 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 six monthly reviews and under pharmacovigilance watching, the notification added.

Need of pioglitazone in India over its controversies until safe alternative

In June 18, 2013, the Indian government suspended the popular anti-diabetic drug pioglitazone, over safety concerns only to revoke the suspension on July 31, 2013. While the oral hypoglycemic controversial drug, which has been linked to urinary bladder cancer, is back on the Indian market with warnings. Though pioglitazone produces urinary bladder cancer in diabetic patients, a numerous beneficial positive characters with pioglitazone will support the need and continuous use of this safe drug in India for diabetic patients instead of be banned until alternative available. Pioglitazone figures as an acceptable oral anti diabetic drug in all international guidelines and recommendations. There are complicated and controversial aspects against pioglitazone and its urinary bladder cancer. Patients with pioglitazone therapy cause urinary bladder cancer after a long treatment only and this adverse effect are not only by pioglitazone, and may be with other combined drug or genetic variation including various factors. Hence, PPARγ stimulation not only progress cancer and also inhibits cancer. Dose dependent cumulative cancer by pioglitazone also not possible in Indian patients because of low dose, i.e., 30 mg/day as a single dose is used unlike other countries 40 mg/day [29]. The cardiovascular and other complications produced by diabetic mellitus are more lethal than pioglitazone induced cancer.

India suffers from a growing diabetes epidemic particularly with insulin sensitive Type 2 diabetes mellitus. Insulin resistance is more common in Asian Indians and hence glitazones have been very popular in India [30,31].

Pioglitazone is grossly overused in India. As per the Monthly Index of Medical Specialities (MIMS) information, pioglitazone has annual sales of around INR8 billion (£84 million) in India. Annual sales of fixed-dose combinations of pioglitazone with metformin and glimepiride are around INR5 billion. India is predicted to have 101 million people suffering from diabetes by 2030. Pioglitazone is a Rs. 700 crore plus market in India and several companies including USV, Sun Pharma and Ranbaxy make the medicine. The sales data show that fixed-dose combinations of pioglitazone with other anti-diabetics are top-selling in the country. On the basis of above said background the pioglitazone is a safe drug for diabetic patients in India and should not be exempted from anti-diabetic therapy in India until safety drug discovery. Awareness and counseling of the patient using Pioglitazone is very important, which should include information to contact the prescriber in case of excessive weight gain, swelling feet, breathlessness, or passing of bloody urine [32]. Asymptomatic hematuria should be investigated with urological investigations promptly. It is important to recognize the benefits of pioglitazone and use it judiciously in appropriate patients who would benefit from the use of this drug.

CONCLUSION

Pioglitazone is a safe, and effective, oral anti-diabetic agent who has great potential in the management of diabetes mellitus Type 2 in India. Diabetic patients treating with pioglitazone should be insisted to report signs and symptoms of bladder cancer like blood in urine, pain during micturition, supra-pubic and back pain. Clearly more studies are needed, probably focused on the Indian population. Our study presenting brief information about pioglitazone and its controversies for diabetic mellitus in India.

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