Editorial

Pioglitazone: A prudent prescription

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All substances are poisons: There is none which is not a poison. The right dose differentiates a poison and a remedy"

- Paracelsus (1493-1541)

What is common between the oral contraceptives (OCs), metronidazole, and tamoxifen as drugs? What do alcoholic beverages, tobacco and diesel exhaust fumes have in common? OCs, metronidazole (in diabetic foot) and tamoxifen are used routinely in endocrine clinics; While alcohol, tobacco and diesel exhaust are an integral part of our life, something that cannot be wished away (even if we want to do so). Both these disparate groups provide succour (in differing manners, though) to the ill and needy and continue to be used, despite being carcinogens.

Background

The last few decades have witnessed an upsurge in the diabetes pandemic, matched by an equally explosive rise in the number of drugs and modalities available to manage the condition. While very few molecules complete the research journey from the laboratory bench to the patient bed side, those which do reach clinical use are subject to intense scrutiny. The chosen ones are expected to be efficacious without compromising the safety of patients significantly. In today's era of evidence based medicine, the use and disuse of a therapeutic agents is based on information supporting or refuting the claims. Drugs seem to rise and fall with amazing regularity, in a manner similar to that of governments and empires. Apart from aspirin crossing a century, insulin marching confidently towards the hundred mark, and metformin having scored a half-century, other metabolic drugs seen to be on a sticky wicket. The older sulfonylureas face a threat to their place of pride, while rosiglitazone, phenformin, sibutramine and rimonabant have exited the therapeutic field.

This editorial, studies the case of pioglitazone, an oral hypoglycemic agent with undoubted efficacy, now embroiled in a controversy regarding its safety.

Points to Ponder

Numerous papers have been published related to the purported association of pioglitazone and bladder cancer. To understand this phenomenon, we need to read the fine print of these reports. Was the evidence generated from prospective randomized controlled trials (RCTs) or meta-analysis of homogenous RCTs? or the evidence is from the relatively weaker sources as case control studies, case series or retrospective data? When a rare outcome, such as bladder cancer, is reported, do authors control for confounding factors? Do these reports base their findings upon pre-planned data analysis, or upon post-hoc statistical jugglery? Do they report an association, or actually prove causality?

From a clinician's perspective, we also need to understand a few basic principles of pharmacology and pharmaco-epidemiology. Each and every drug that we use in practice is a foreign entity, the use of which comes with certain risks. Within endocrinology, hormone supplementation and hormone replacement too are linked with adverse risks. These adverse effects are an accepted part of modern medicine, provided their benefit is greater than the potential risk.

The Controversy

A controversy arose because of the publication of a longitudinal cohort study, which reported increased risk of bladder cancer with pioglitazone, in 2011.[1] These results were echoed by authors of a population-based cohort study

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nested case- control study, and metanalysis.[2-4] At the same time, another cohort study made a case for higher risk of bladder cancer only with longer duration of therapy.[5] A retrospective analysis from Japan, reported no statistical difference between pioglitazone users and non-users with respect to occurrence of bladder cancer. The same study reported a higher prevalence of bladder cancer only in patients with >24 months exposure, which is difficult to explain.[6]

Such alarmist publications have been criticized for their inherent methodological limitations and selection bias.[7] Unfortunately, they seem to have received more attention as compared to other, better designed studies, which show no added risk with pioglitazone. One such propensity score matched (which is required to balance covariates in observational studies) analysis was done in a large cohort of 2,07,714 patients, age ≥40 years, with type 2 diabetes, enrolled in the General Practice Research Diabetes (GPRD), United Kingdom. Of these patients, 23,548 had been exposed to pioglitazone. No difference in risk of bladder cancer was observed between the pioglitazone-exposed and pioglitazone non-exposed groups. (80.2 and 81.8 per 1,00,000 person years respectively). As compared to other antidiabetic drugs, pioglitazone did not increase the risk of bladder cancer (hazard ratio 1.16).[8] In the follow-up of the ProActive study, in fact, bladder cancer cases were numerically [though not statistically] less in pioglitazone – treated subjects as compared to those on placebo.[9]

Pre Clinical Cues

A review of preclinical animal studies conducted on pioglitazine show that rats developed bladder tumours only at dose equivalent to 14 times the maximum human dose (45 mg), with male rats being more predisposed, mice were immune to this effect, suggesting species-specific toxicity.

The authors propose a urolithiasis-mediated hypothesis for the increased propensity of bladder tumours in male rats, in whom there is a predilection for cancer at the ventral dome. They suggest acidification of urine as a means of preventing cancer, and caution against cross-species extrapolation of data. The differences in the anatomical orientation of the bladder between quadrupedal rats and bipedal humans may be a reason for rat- specific carcinogenesis pathway.[10]

Prescribe with Prudence

Experts opine that pharmacovigilance is the only way to ensure patient safety. However, we can take cues from animal data, and can put in place prudent prescription policies to help us manage patients with a maximal benefit: Risk ratio.

Pioglitazone is associated with proven glycemic and extra-glycemic effects. A few alarmist publications should not make us overlook these benefits, and withhold them from people with diabetes, by completely stopping usage of this drug. If this were to be accepted, insulin especially glargine, sulfonylureas and glinides should all be withdrawn because of associations with cancer. An extremist viewpoint would be that diabetes be classified and managed as an oncological disease, by oncologists, in view of its link with malignancies!

Additionally, the whole issue comes down to risk: Benefit. Had pioglitazone not been prescribed to patients with diabetes, how many additional deaths would have occurred because of complications of uncontrolled hyperglycemia. The risk: Benefit is tilted heavily in favor of pioglitazone. The number of patients required to be exposed to pioglitazone to cause one bladder cancer following use of pioglitazone is too high when compared to the number of deaths prevented by its prescription.

What is the way forward? *Prescribe pioglitazone, with prudence*. Use pioglitazone where indicated, when indicated, as per guidelines. Watch for conditions which predispose to urolithiasis, such as high urinary solids (including proteinuria). Watch for other conditions which predispose to bladder cancer, e.g., smoking, be alert for the symptoms, signs and laboratory markers that lead one to suspect bladder cancer. Use low dose pioglitazone (7.5-15 mg/day), which has been tested for efficacy in many countries across the world.[11,12] Focus on stringent glycemic control, as diabetes itself predisposes to cancer. Individualize therapy, choosing what is right for each patient.

Do not throw the baby out with the bath water!

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