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No link found between bladder cancer and use of pioglitazone or rosiglitazone, Avandia

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Some previous studies have linked the diabetes medication pioglitazone to bladder cancer. However a new study – including more than one million people in six populations worldwide – has found no link between either pioglitazone or rosiglitazone (also known as Avandia) and bladder cancer. The new study is published in *Diabetologia* (the journal of the European Association for the Study of Diabetes), and is by Dr Samira Bell, Professor Helen Colhoun and Mr Danny Levin, University of Dundee, UK, and colleagues from the International Diabetes and Cancer Research Collaboration.

Bladder cancer is the ninth most common cancer in the world, with 430,000 new cases diagnosed in 2012. Europe and North America have the highest incidence of bladder cancer, with an even higher incidence in people with diabetes.

Bladder tumours overexpress a natural part of the cell machinery, a transcription factor in the cell nucleus known as 'peroxisome proliferator-activated receptor gamma' (or PPARγ) that is found in the urothelium (the lining of the urinary tract). Both pioglitazone and rosiglitazone are part of the thiazolidinediones (TZDs) class of drugs, which act as PPARγ agonists, meaning they induce the same action as PPARγ. They are used in the treatment of type 2 diabetes, however their use, has been questioned owing to safety concerns, including preclinical studies showing male rats overexposed to pioglitazone were at increased risk of bladder cancer.

Observational studies in humans have observed an increased risk of bladder cancer in patients using pioglitazone, leading to withdrawal of the drug in France and Germany. The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have also advised that the drug not be used in patients with current or previous bladder cancer. However other studies have published contradictory results. The authors of this new work say that studies that showed an increased risk could be biased in certain ways, for example if those who were destined to be given pioglitazone were already at higher risk of bladder cancer (so-called allocation bias). The authors of this new study used a different approach that makes allocation bias very unlikely. Other possible explanations are that studies that detected an increased risk might have done so if those given pioglitazone were subsequently more likely to have bladder cancer detected, for example if their urine was tested more often (so-called detection bias).

In this new study, the authors aimed to address the limitations of previous observational studies by measuring the effect of exposure to pioglitazone on bladder cancer risk across several cohorts. They gathered prescription, cancer and mortality data from people with type 2 diabetes from six populations across the world: British Columbia (Canada); Finland, Manchester (UK), Rotterdam (Netherlands), Scotland, and the UK Clinical Practice Research Datalink (covering 566 general practices in the UK). Data from each centre were used to model the effect of cumulative drug exposure on bladder cancer incidence, and the data were then pooled for further analysis. Data were collated on 1.01 million persons over 5.9 million person-years. There were 3,248 cases of incident bladder cancer, with only 117 cases in those patients ever exposed to pioglitazone. The median duration of follow-up was 4.0 to 7.4 years.

Overall, the authors found no evidence for any association between cumulative exposure to pioglitazone and bladder cancer in men (rate

ratio [RR] per 100 days of cumulative exposure, 1.01) or women (RR 1.04) after adjustment for age, calendar year, diabetes duration, smoking and any ever use of pioglitazone. No association was observed between rosiglitazone and bladder cancer in men (RR 1.01) or women (RR 1.00). In this study, the authors were looking to see if there was a dose-response relationship between pioglitazone and risk of bladder cancer, and found that this risk did not increase with longer exposure in users of pioglitazone.

The authors say: "This analysis, to our knowledge, is the only one to use identical methodology across international centres involving a large number of diabetic patients."

They conclude: "In summary, our large international analysis does not support a causal effect of pioglitazone on bladder cancer, thus contradicting previous studies deemed to have proven this relationship. To fully resolve this controversy, future analyses are needed, involving longer follow-up of exposed persons and using methods to minimise allocation bias."

Provided by Diabetologia

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