Assessing the Association of Pioglitazone Use and Bladder Cancer Through Drug Adverse Event Reporting

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OBJECTIVE—To analyze the association between pioglitazone use and bladder cancer through a spontaneous adverse event reporting system for medications.

RESEARCH DESIGN AND METHODS—Case/noncase bladder cancer reports associated with antidiabetic drug use were retrieved from the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) between 2004 and 2009 and analyzed by the reporting odds ratio (ROR).

RESULTS—Ninety-three reports of bladder cancer were retrieved, corresponding to 138 drug-reaction pairs (pioglitazone, 31; insulin, 29; metformin, 25; glimepiride, 13; exenatide; 8; others, 22). ROR was indicative of a definite risk for pioglitazone (4.30 [95% CI 2.82-6.52]), and a much weaker risk for gliclazide and acarbose, with very few cases being treated with these two drugs (6 and 4, respectively).

CONCLUSIONS—In agreement with preclinical and clinical studies, AERS analysis is consistent with an association between pioglitazone and bladder cancer. This issue needs constant epidemiologic surveillance and urgent definition by more specific studies.

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Author's Osler cancer first appeared in preclinical studies and was first reported on the U.S. pioglitazone label in 1999, but experimental studies recently suggested that it might be a rat-specific phenomenon (1). In the large PROactive (PROspектив pioglitAzone Clinical Trial In macroVascular Events) study, 14 bladder cancers occurred in the pioglitazone arm (0.5%) versus 6 in the placebo arm (0.2%) (2,3), and in September 2010, the U.S. Food and Drug Administration (FDA) announced an ongoing investigation on the possible risk in humans (4). Accordingly, the drug manufacturer is conducting a 10-year observational study to address the long-term risk of bladder cancer associated with pioglitazone (4).

Very recently, the European Medicines Agency (EMA) suspended the marketing authorization of rosiglitazone (5), and the FDA largely restricted its use because of an increased cardiovascular risk (6). These measures will increase the prescription of pioglitazone; thus, the definition of its benefit/risk profile becomes all the more pressing.

Our aim was to contribute to defining the safety profile of pioglitazone, focusing on cases of bladder cancer recorded in the FDA Adverse Event Reporting System (AERS) database associated with antidiabetic drug treatment.

RESEARCH DESIGN AND METHODS—The reports recorded in FDA AERS from January 2004 to December 2009 were downloaded from the FDA website. The system contains all reports of adverse drug events spontaneously reported by health care professionals, manufacturers, and consumers from the U.S. and serious and unlabeled spontaneous reports from non-U.S. countries. The adverse events are codified by Medical Dictionary for Regulatory Activities (MedDRA) terminology. Reports concerning antidiabetic drugs were selected, provided that age, sex, and event date were available. Duplicates and multiple records, a well-known drawback of FDA AERS (7), were excluded by a semiautomated multistep process (8).

The association between antidiabetic drugs and bladder cancer was analyzed by the case/noncase methodology (9). Cases were the reports retrieved under the MedDRA high-level term “bladder neoplasms” for any given drug; noncases were all of the other reports related to the same drug. The association between the drug and bladder cancer was calculated by the adverse drug reaction reporting odds ratio (ROR) as a measure of disproportionality. The ratio cases/noncases for each drug were compared with the ratio of cases/noncases for all other antidiabetic drugs. Stratified analyses weighed the influence of male sex and old age. The possible effect of notoriety bias was tested by a year-by-year analysis. Epi Info software (Centers for Disease Control and Prevention, Atlanta, GA) was used for statistical analyses.

RESULTS—From 2004 to 2009, 86,987 reports involving antidiabetic drugs were recorded in FDA AERS, corresponding to 599,085 drug-reaction pairs (obtained by splitting comedinations and multiple reactions reported for each case), with 37,841 reports concerning pioglitazone. Overall, 93 reports of bladder cancer were retrieved, corresponding to 138 drug-reaction pairs, with 31 concerning pioglitazone; 29 insulin; 25 metformin; 13 gliclazide; 8 exenatide; 6 glimepiride; 5 glipizide; 4 sitagliptin; acarbose and rosiglitazone; 3 glibenclamide; 2
Pioglitazone and bladder cancer risk

for gliclazide and acarbose (Table 1). Among the 31 cases of bladder cancer re-
ported in pioglitazone users (mean age, 70 years; range 53–84), 23 occurred in
men (3.86 [2.37–6.26]; Supplementary Table A1) and 8 were in women (5.19
[2.15–12.11]). When stratified by age (cutoff, 65), ROR for pioglitazone was
only significant in older patients (5.10
[1.4–8.23]). Four cases of bladder can-
cer were reported in 2004, three in 2005,
nine in 2006, five in 2007, six in 2008,
and four in 2009 (ROR not statisti-
cally significant in 2005 and 2009;
Supplementary Table A2).

Ten cases occurred during clinical
studies. The length of drug use, which
was recorded in 15 cases, was 6 months
in 6 patients, 6–24 months in 5, and
24 months in 4. Antiplatelet agents (e.g.,
apirin and clopidogrel), antihypertensive
drugs (e.g., ACE inhibitors and diuretics),
lipid-lowering agents (e.g., statins), other
antidiabetic drugs (e.g., glimepiride, met-
formin, and acarbose), and glucocorticoid
steroids (fluticasone and mometasone) were
the cotreatments most frequently recorded
(24 patients). One patient was being treated
with cytotoxic therapy (infliximab
and methotrexate for psoriatic arthrop-
yth), and one was treated with interferon-
β-1 for multiple sclerosis.

CONCLUSIONS—Bladder cancer is
the fourth most common cancer and the
ninth leading cause of cancer death,
among U.S. men (10). Cigarette smoking,
urinary tract infections, occupational
exposure to aromatic amines and polycy-
clic aromatic hydrocarbons, and drugs (e.g.,
cyclophosphamide) are risk factors for the
disease, as might be the systematic use of
glucocorticoids (11).

We found a definite signal for bladder
cancer associated with pioglitazone use.
The demographic characteristics of the
selected cases were consistent with blad-
ner cancer epidemiology (male sex, old-
age) (10). A weaker signal was also asso-
ciated with gliclazide, and a much weaker
signal was associated with acarbose. Of
note, the occurrence of fewer than five
events, although resulting in a statistically
significant ROR, may be considered clini-
cally meaningless because it is too sus-
ceptible to reporting biases (12).

Although notoriety bias may have
contributed to part of the association
between pioglitazone use and bladder
cancer (13), we also observed a significant
relationship in 2004, which preceded
publication of the PROactive study (2)
and label revision. Therefore, we do not
believe that our findings can be explained
by notoriety bias alone. A greater use of
pioglitazone could also have influenced
this result (14).

Preliminary data found an increasing
risk of bladder cancer with pioglitazone
exposure, with statistical significance af-
after 24 months (4). This issue could not be
confirmed by our analysis, with only four
cases of bladder cancer occurring in pa-
ients exposed to pioglitazone for more
than 2 years and several missing data. In
general, the association with bladder
cancer does not seem to derive from con-
comitant drug use or comorbidity, with
only two patients receiving treatments
potentially favoring carcinogenesis and
five patients receiving glucocorticoids.

The ROR analysis has several limi-
tations: generic under-reporting, over-
reporting generated by notoriety bias,
dependence on the drug marketing pe-
(Weber effect), missing or misspelled
data (7,13,15), and lack of information on
patients’ habits (smoking) or occupa-
tional risks. Despite limitations, the
higher-than-expected reporting of blad-
ner cancer for pioglitazone users com-
pared with users of other antidiabetic
drugs should stimulate specific case–con-

control studies aimed at verifying the magni-
tude of the hazard: until the final data of
the FDA investigation are available, physi-
cians should pay careful attention to this
possible risk.

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reviewed and edited manuscript. E.P. re-
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pioglitazone in high-risk patients with
type 2 diabetes: an overview of data from
4. Food and Drug Administration. FDA Drug
Safety Communication: ongoing safety re-

Table 1—ROR of bladder cancer for antidiabetic drugs

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Cases*</th>
<th>All ADR</th>
<th>ROR 95% CI</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td>31</td>
<td>37,841</td>
<td>4.30 2.82–6.52</td>
<td>.001</td>
</tr>
<tr>
<td>Insulin</td>
<td>29</td>
<td>124,873</td>
<td>1.01 0.06–5.15</td>
<td>.961</td>
</tr>
<tr>
<td>Metformin</td>
<td>25</td>
<td>138,900</td>
<td>0.73 0.46–1.15</td>
<td>.158</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>13</td>
<td>35,388</td>
<td>1.66 0.89–3.01</td>
<td>.080</td>
</tr>
<tr>
<td>Exenatide</td>
<td>8</td>
<td>100,946</td>
<td>0.30 0.14–0.64</td>
<td>.001</td>
</tr>
<tr>
<td>Acarbose</td>
<td>4</td>
<td>3,479</td>
<td>5.12 1.61–14.33</td>
<td>.001</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>4</td>
<td>44,096</td>
<td>0.38 0.12–1.05</td>
<td>.045</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>3</td>
<td>38,214</td>
<td>0.03 0.08–1.06</td>
<td>.043</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>2</td>
<td>4,994</td>
<td>1.75 N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>2</td>
<td>6,060</td>
<td>1.44 N.A.</td>
<td>N.A.</td>
</tr>
</tbody>
</table>
Phenformin & 1 & 65 & 68.30 & N.A. & N.A. & \\
Voglibose & 1 & 2,938 & 1.48 & N.A. & N.A. & \\
Other antidiabetic drugs & 0 & 7,367 & N.A. & N.A. & N.A. & \\
Total & 138 & 599,085 & & & & \\

ADR, adverse drug reaction; N.A., not available. *Cases of bladder cancer. † Mantel–Haenszel corrected.


AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

Q1: According to the FDA Web site, “System” is part of the acronym; should be AERS rather than AER System.

Q2: The title of ref 5 has been adjusted to match the title of the PDF that is cited in the reference. Please check.

Q3: Trademarked items generally require the supplier and location. Please check for EpiInfo. Note name changed per CDC Web site.

Q4: Check that the conflict of interest information for each author is presented in full in the Acknowledgments section.