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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A link between pioglitazone and bladder 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 (PROspective 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 3.4.3-2007 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 comedications 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 glimepiride; 8 exenatide; 6 gliclazide; 5 glipizide; 4 sitagliptin, acarbose and rosiglitazone; 3 glibenclamide; 2 nateglinide and repaglinide; and 1 phenformin and voglibose.

The ROR of bladder cancer was significantly >1 for pioglitazone (ROR 4.30 [95% CI 2.82–6.52]; $P < 0.001$) as well as

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for gliclazide and acarbose (Table 1). Among the 31 cases of bladder cancer reported 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 [3.14–8.23]). Four cases of bladder cancer were reported in 2004, three in 2005, nine in 2006, five in 2007, six in 2008, and four in 2009 (ROR not statistically 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., aspirin and clopidogrel), antihypertensive drugs (e.g., ACE inhibitors and diuretics), lipid-lowering agents (e.g., statins), other antidiabetic drugs (e.g., glimepiride, metformin, and acarbose), and glucocorticoid (fluticasone and mometasone) were the cotreatments most frequently recorded (24 patients). One patient was being treated with cytotoxic therapy (infliximab and methotrexate for psoriatic arthropathy), and one was treated with interferon-β-1α 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 polycyclic 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 bladder cancer epidemiology (male sex, old age) (10). A weaker signal was also associated 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 clinically meaningless because it is too susceptible 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 after 24 months (4). This issue could not be confirmed by our analysis, with only four cases of bladder cancer occurring in patients 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 concomitant drug use or comorbidity, with only two patients receiving treatments potentially favoring carcinogenesis and five patients receiving glucocorticoids.

The ROR analysis has several limitations: generic under-reporting, over-reporting generated by notoriety bias, dependence on the drug-marketing period (Weber effect), missing or misspelled data (7,13,15), and lack of information on patients' habits (smoking) or occupational risks. Despite limitations, the higher-than-expected reporting of bladder cancer for pioglitazone users compared with users of other antidiabetic drugs should stimulate specific case–control studies aimed at verifying the magnitude of the hazard; until the final data of the FDA investigation are available, physicians should pay careful attention to this possible risk.

Table 1—*ROR of bladder cancer for antidiabetic drugs*

Active substance	Cases*	All ADR	ROR	95% CI	*P*†
Pioglitazone	31	37,841	4.30	2.82–6.52	<0.001
Insulin	29	124,873	1.01	0.06–1.55	0.961
Metformin	25	138,900	0.73	0.46–1.15	0.158
Glimepiride	13	35,388	1.66	0.89–3.01	0.080
Exenatide	8	100,946	0.30	0.14–0.64	0.001
Gliclazide	6	7,560	3.56	1.42–8.39	0.001
Glipizide	5	34,816	0.61	0.22–1.54	0.272
Sitagliptin	4	11,638	1.51	0.48–4.22	0.416
Acarbose	4	3,479	5.12	1.61–14.33	<0.001
Rosiglitazone	4	44,006	0.38	0.12–1.05	0.045
Glibenclamide	3	38,214	0.33	0.08–1.06	0.043
Nateglinide	2	4,994	1.75	N.A.	N.A.
Repaglinide	2	6,060	1.44	N.A.	N.A.
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.

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