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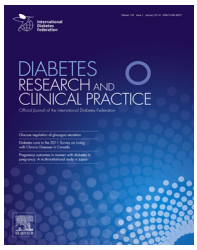

Comparative risk of severe hypoglycemia among concomitant users of thiazolidinedione antidiabetic agents and antihyperlipidemics

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ABSTRACT

We conducted high-dimensional propensity score-adjusted cohort studies to examine whether thiazolidinedione use with a statin or fibrate was associated with an increased risk of severe hypoglycemia. We found that concomitant therapy with a thiazolidinedione + fibrate was associated with a generally delayed increased risk of severe hypoglycemia.

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1. Introduction

Dyslipidemia is a major, yet modifiable, risk factor for cardiovascular disease. While glycemic control improves the lipid profile of persons with diabetes, treatment with antihyperlipidemics is often indicated. Co-prescribing of antidiabetic and antihyperlipidemic agents, though, may not be without risks. In particular, thiazolidinediones (TZDs)—peroxisome proliferator-activated receptor (PPAR) γ agonists which increase insulin sensitivity—are metabolized primarily by hepatic cytochrome P450 (CYP) 2C8 [1]. This isozyme can be inhibited by some antihyperlipidemics, most notably fibrates [2], leading to higher concentrations of TZDs. In addition, the PPAR α activity of fibrates may itself have effects on glucose homeostasis [3]. Some statins may also affect glucose metabolism [4]. These mechanisms might result in enhanced glucose lowering effects in concomitant users of TZDs and certain antihyperlipidemics. While these effects may be desirable for some patients, drug interactions might also increase the risk of severe hypoglycemia—a major clinical and public health problem. We therefore examined severe hypoglycemia risk among concomitant users of TZDs and antihyperlipidemics.

2. Methods

We conducted two high-dimensional propensity score-adjusted cohort studies of adult users of pioglitazone and rosiglitazone, respectively, using Medicaid data from five large states. Each cohort consisted exclusively of person-time concomitantly-exposed to the TZD plus one of eight antihyperlipidemics: atorvastatin; fenofibrate; fluvastatin; gemfibrozil; lovastatin; pravastatin; rosuvastatin; or simvastatin. The day on which the subject was first co-exposed served as the cohort entry date. Exposure was defined by the antihyperlipidemic active upon cohort entry. The primary outcome was a validated diagnosis-based algorithm for severe hypoglycemia within 30 days of cohort entry. Please see *Supplemental Materials* for details on: the data source; defining the study cohorts; exposure, covariate, and outcome ascertainment; and statistical analyses.

3. Results

3.1. Pioglitazone

Characteristics of pioglitazone users are presented in Table 1. Unadjusted and adjusted hazard ratios (HRs) for severe hypoglycemia within 30 days are presented in Table 2 and Fig. 1, respectively. Unadjusted and adjusted HRs for severe hypoglycemia within 180 days are presented in Table 2. Time-specific association measures for concomitant use of pioglitazone and fibrates are presented in Fig. 2. No time-course effects were evident for concomitant use with statins. See *Supplemental Materials* for results from sensitivity analyses.

3.2. Rosiglitazone

See *Supplemental Materials*.

4. Discussion

We examined potential drug–drug interactions between TZDs and antihyperlipidemics. While we found no increased risk of severe hypoglycemia during the first month of concomitant pioglitazone and antihyperlipidemic therapy, the risk was elevated and increased monotonically with time during later months of concomitant therapy with a fibrate. Pioglitazone + -fenofibrate was associated with an increased risk of severe hypoglycemia as much as 2.3-fold during 60–180d post-initiation of concomitant therapy, and pioglitazone + gemfibrozil as much as 2.6-fold during 30–180d. For rosiglitazone, we found no increased risk of severe hypoglycemia during the first 30d of concomitant use with a statin, but use of rosiglitazone + gemfibrozil was associated with a 1.6-fold increased risk. Subsequently, the risk of severe hypoglycemia peaked during 30–59d—1.8-fold for rosiglitazone + fenofibrate and 2.5-fold for rosiglitazone + gemfibrozil—and returned to the null by 180d.

This is first pharmacoepidemiologic investigation of these potential drug interactions. The presumptive mechanism underlying prior pharmacokinetic- and laboratory science-based work was that fibrates inhibited CYP2C8, the major metabolic pathway for TZDs. Yet, even if inhibition by fibrates significantly raises serum concentrations of TZDs, it is not generally thought that TZDs cause severe hypoglycemia [5]. However, we found that severe hypoglycemia occurs at a rate of ~2.5 per 100 p-y among TZD users even in the absence of concomitant insulin or sulfonylureas. Further, Bron et al. reported that TZDs are associated with a small but significant increased risk of moderate or severe hypoglycemia, especially within the first year of therapy [6]. This raises the possibility that TZDs, while clearly less associated with hypoglycemia than insulin or sulfonylureas, may cause severe hypoglycemia in certain circumstances. That being said, the mechanism seems more complex than elevated TZD serum concentrations caused by CYP2C8 inhibition. Arguments against a lone, major role for CYP2C8 inhibition include: some statins also inhibit CYP2C8 [7], yet we did not find elevated HRs for statins; and the inhibition and inactivation of CYP enzymes occurs rapidly [8], yet we generally found delayed rather than rapid-onset increases in the risk of severe hypoglycemia. This latter point could also be explained by the delayed onset of action of TZDs, whose effects may peak at one month [9,10].

A more plausible explanation for our findings may be driven by expected actions of fibrates. The PPAR α agonist effects of fibrates beneficially impact lipid and lipoprotein metabolism. Lipid and glucose homeostasis is interrelated [11] and lowering free fatty acids ameliorates insulin resistance [12,13] via protection of pancreatic islets [14]. Alternatively, or in addition, fibrates may induce fatty acid-binding protein and stimulate β-oxidation in skeletal muscles [15]. Regardless of potential mechanism, improvements in insulin resistance and glycemic control have been reported in users of gemfibrozil [16] and fenofibrate [13,17]. Further, some fibrates also act at PPAR γ [18], the site of action of TZDs. Of further interest are