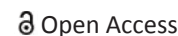




REVIEW ARTICLE



Thiazolidinediones and their drug interactions involving CYP enzymes

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ABSTRACT

Background: Thiazolidinediones (TZDs) include pioglitazone and rosiglitazone and they are indicated in the treatment of type 2 diabetes mellitus. They are insulin sensitizers and are metabolized primarily by the CYP2C8 enzyme. The drugs inhibiting or inducing CYP2C8 enzyme may result in pharmacokinetic drug interactions of TZDs. The probability of drug interactions is higher in type 2 diabetic patients as they administer many medications to manage blood glucose and to treat other diseases. Clinically significant drug interactions of TZDs are discussed in this review.

Methods: The literature review was done in databases like Medline/PubMed/PMC, Science Direct, Google Scholar, Directory of Open Access Journals, and reference lists to identify relevant articles.

Results: The drugs inhibiting the CYP2C8 enzyme such as gemfibrozil, clopidogrel, trimethoprim, ketoconazole, and rifampicin have been identified to affect the pharmacokinetics of TZDs.

Conclusion: The clinicians need to be aware of adverse drug interactions of TZDs to prevent negative outcomes.

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Introduction

Diabetes is a global health burden and it has been estimated that the number of patients affected by diabetes would reach around 552 million in the year of 2030 [1] and 642 million by 2040 [2]. Decreased secretion of insulin, action of insulin or both causes diabetes, which is characterized by hyperglycemia [3]. Type 1 diabetes and type 2 diabetes are considered as major classes of diabetes. Insulin resistance and inadequate insulin secretion cause type 2 diabetes [4]. Oral antidiabetic drugs, including metformin, sulfonylureas, meglitinides, thiazolidinediones (TZDs), etc., are indicated to treat type 2 diabetic patients.

TZDs are insulin sensitizers and they are employed in the treatment of type 2 diabetes mellitus. They include pioglitazone and rosiglitazone [5]. They bind to peroxisome proliferator-activated receptors gamma (PPAR γ) of adipose tissue, liver, and skeletal muscle cells. The glucoregulatory molecules are induced and the insulin sensitivity is enhanced by the activation of PPAR γ receptors [6,7].

The pleiotropic effects of TZDs include improved cardiovascular risk factors, such as dyslipidemia [8], blood pressure [9], endothelial function [10], inflammation markers [11], and delayed atherosclerosis progression [12,13]. In addition, TZDs are useful to improve diabetic complications, such as diabetic nephropathy [14]. Polycystic ovary syndrome might be treated by using TZDs [15]. Though TZDs exert many beneficial effects they must be monitored for peripheral edema and precipitation or exacerbation of congestive heart failure (CHF) [16–18].

Polypharmacy and drug interactions are common among type 2 diabetic patients since they receive many drugs to treat diabetes and co-morbidities [19]. Drug interaction is defined as the alteration of effects of one drug by the concomitantly administered drug, food, supplement, or alcohol [20]. Diminished therapeutic efficacy or enhanced toxicity resulting from a drug interaction is termed “Adverse drug interaction” [21,22]. Moreover, the drug interactions are categorized

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mainly as pharmacokinetic and pharmacodynamic interactions. As the number of concomitant medications increases, the probability of drug interaction would also be raised [23].

Methods

The articles related to the terms “Thiazolidinediones,” “drug interactions,” “pharmacokinetic drug interactions of Thiazolidinediones,” “Rosiglitazone,” “Pioglitazone,” CYP2C8, and CYP2C9 were searched in Medline/PubMed/PMC, Google Scholar, Directory of Open Access Journals, Science Direct, and reference lists.

Results and Discussion

Cytochrome P450 (CYP) enzymes are involved in the metabolism of TZDs. Pioglitazone is metabolized mainly by the CYP2C8 enzyme and by the CYP3A4 enzyme to a lesser extent [24] and the drugs inhibiting CYP2C8 enzymes play a major role in the pharmacokinetic drug interactions of pioglitazone. Rosiglitazone is also metabolized principally by the CYP2C8 enzyme; it is also metabolized by the CYP2C9 enzyme slightly [25] and few CYP2C8 inhibitors determine the pharmacokinetic drug interactions of rosiglitazone.

Interactions with CYP2C8 Inhibitors

Many drugs have been identified to inhibit CYP2C8, *in vitro*. The potent CYP2C8 inhibitors include montelukast, zafirlukast, candesartan cilexetil, clotrimazole, felodipine, and mometasone furoate. In addition, the drugs such as

ketoconazole, fenofibrate, loratadine, simvastatin, lovastatin, ritonavir, levothyroxine, oxybutynin, nifedipine, salmeterol, raloxifene, tamoxifen, quercetin, ethinyl estradiol, and spironolactone were identified to be moderate CYP2C8 inhibitors [26]. However, montelukast has been identified as the most potent CYP2C8 inhibitor which exerted negligible inhibitory activity on pioglitazone metabolism, *in vivo* [27].

The drugs such as gemfibrozil and trimethoprim inhibit the CYP2C8-mediated metabolism of pioglitazone and rosiglitazone and increase their concentration-dependent adverse effects (Fig. 1).

Gemfibrozil

Gemfibrozil is a fibrate and it is an effective and safe drug indicated in the treatment of hypertriglyceridemia in type 2 diabetic patients [28]. The glucuronide metabolite of gemfibrozil (Gemfibrozil 1-O- β -glucuronide) can inhibit the CYP2C8 enzyme strongly [29–32]. Gemfibrozil inhibits the CYP2C8-mediated metabolism of pioglitazone and elevates its plasma concentrations [33,34]. The risk of dose-related adverse effects of pioglitazone may be enhanced by the concomitant use of gemfibrozil with pioglitazone [35] (Fig. 2). The blood glucose of patients taking gemfibrozil and pioglitazone concomitantly should be monitored carefully and the dose of pioglitazone may be reduced if necessary [36].

The plasma levels of rosiglitazone can also be enhanced by the co-administration of gemfibrozil, through the inhibition of the CYP2C8 enzyme, which may result in an elevated risk of adverse effects of

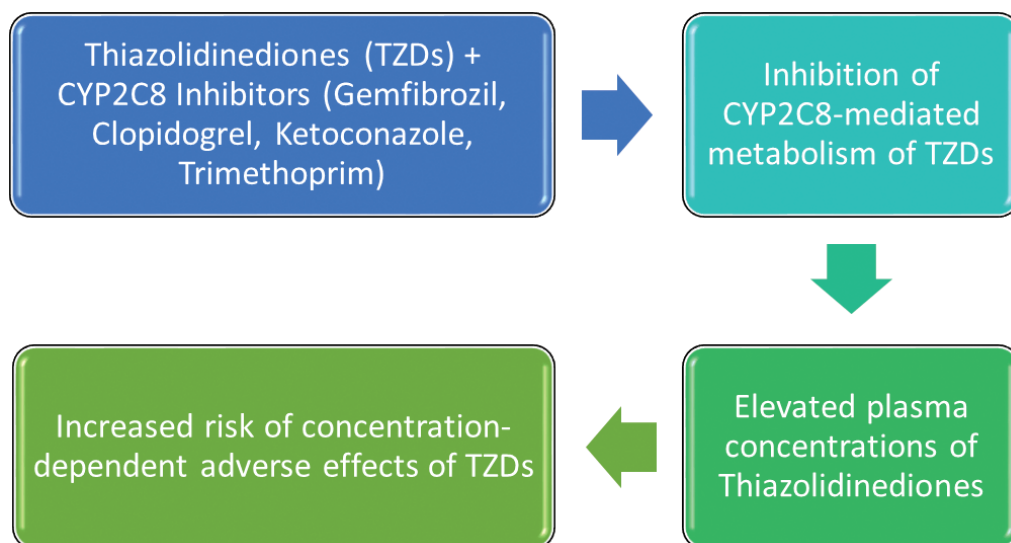


Figure 1. Interactions with CYP2C8 Inhibitors.

rosiglitazone [37]. It was reported that co-administration of fenofibrate with rosiglitazone may cause myopathy [38] and decreased HDL levels [39–42].

Clopidogrel

Clopidogrel is an antiplatelet drug and it belongs to the second generation thienopyridine group [43]. The glucuronide metabolite of clopidogrel (Clopidogrel acyl- β -d-glucuronide) is an inhibitor of the CYP2C8 enzyme [44]. Co-administration of clopidogrel and pioglitazone may result in increased plasma levels of pioglitazone and the

risk of fluid retention, which can worsen the symptoms of CHF and other adverse effects of pioglitazone (Fig. 3). Caution is advised in patients taking this combination [45].

Ketoconazole

The patients with diabetes have higher rates of fungal infections [46]. Ketoconazole is an effective antifungal agent, which belongs to the imidazole group [47]. Ketoconazole inhibits CYP2C8 enzyme moderately [48] and CYP2C9 enzyme weakly [49]. Hence, the concomitant use of ketoconazole and

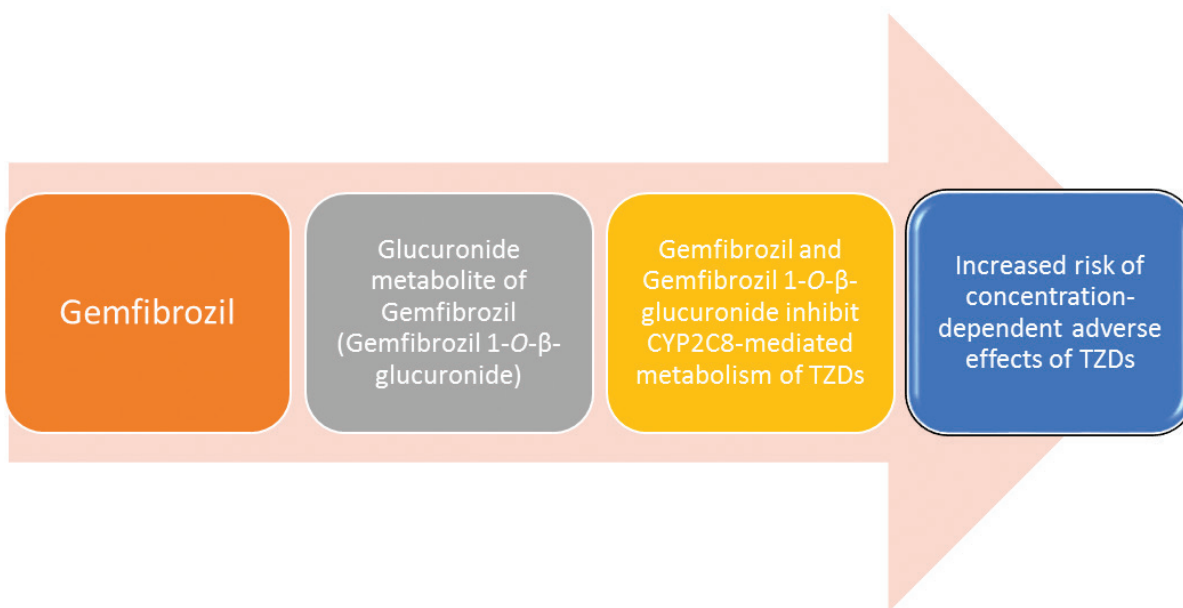


Figure 2. Interactions between gemfibrozil and TZDs.

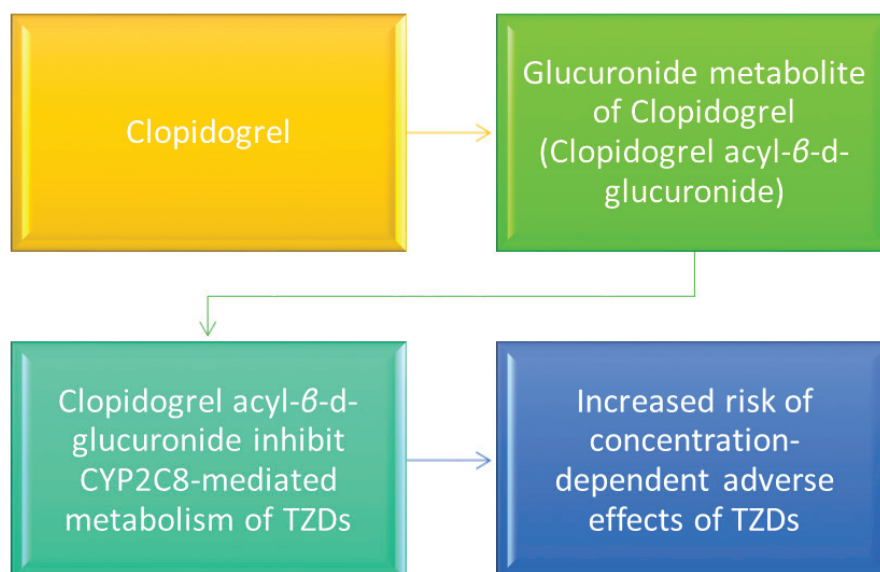


Figure 3. Interactions between clopidogrel and TZDs.

rosiglitazone enhance the risk of adverse effects of rosiglitazone [50] (Fig. 4).

Ketoconazole is also expected to interact with pioglitazone significantly since it is the substrate of CYP2C8 and CYP3A4 enzymes [50].

Trimethoprim

Trimethoprim is a synthetic antibacterial drug, which helps to treat infections occurring in the urinary tract, respiratory tract, skin, and others [51]. Trimethoprim can inhibit CYP2C8 enzyme moderately [52]. Concurrent use of pioglitazone and trimethoprim can result in moderate elevation of plasma concentrations of pioglitazone [53] (Fig. 5).

Co-administration of trimethoprim and rosiglitazone also resulted in increased exposure of rosiglitazone through the inhibition of CYP2C8-mediated metabolism [54]. Caution is advised while adding trimethoprim therapy in type 2 diabetic patients taking rosiglitazone, to avoid concentration-dependent adverse effects of rosiglitazone [55].

Interactions with CYP2C8 Inducers

The drugs including rifampicin, phenobarbital, cyclophosphamide, paclitaxel, hyperforin (an ingredient of St. John's wort), etc., have been found to induce CYP2C8 enzyme, in experimental *in vitro* studies [56]. However, rifampicin has decreased

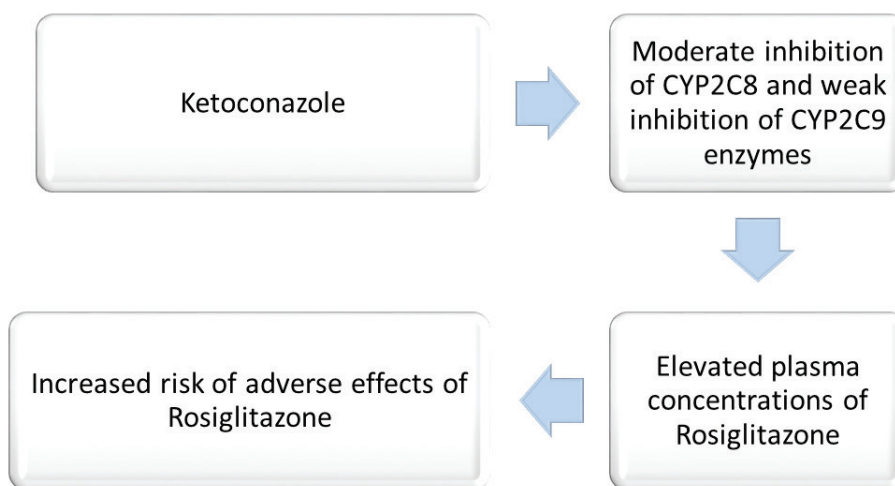


Figure 4. Interactions between ketoconazole and TZDs.

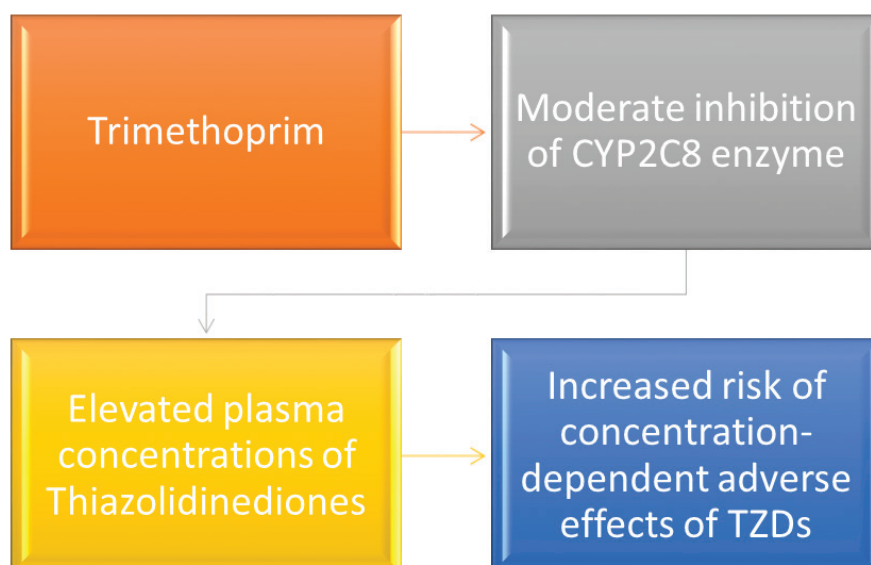


Figure 5. Interactions between trimethoprim and TZDs.

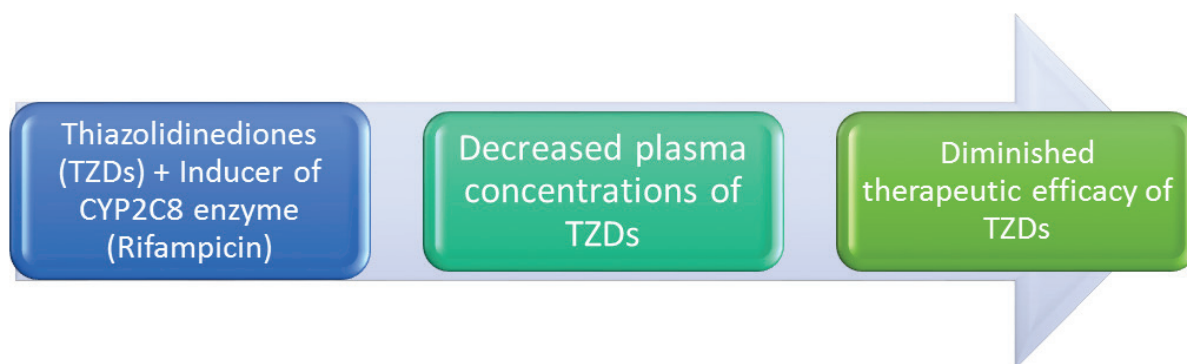


Figure 6. Interactions with CYP2C8 inducers.

the CYP2C8-mediated metabolism of substrates, in humans [54,57].

Rifampicin is an inducer of CYP2C8 enzyme and its co-administration with TZDs may result in decreased plasma concentration and therapeutic efficacy of TZDs (Fig. 6).

Rifampicin

Rifampicin is an antibiotic primarily used to treat mycobacterial infections, such as tuberculosis and leprosy. Rifampicin can induce both CYP2C8 and CYP3A4 enzymes [58], which metabolize pioglitazone. The plasma levels and therapeutic efficacy of pioglitazone might be decreased by the administration of rifampicin in patients taking pioglitazone [59].

The plasma concentration of rosiglitazone is also decreased by the concomitant use with rifampicin, which can induce CYP2C8 and CYP2C9 enzymes responsible for the biotransformation of rosiglitazone [60].

Conclusion

The patients with diabetes have more prevalence of drug interactions since polypharmacy is common among them. The type 2 diabetic patients may take oral antidiabetic drugs along with other medications to treat diabetes and other comorbidities like dyslipidemia, heart diseases, infections, etc. TZDs such as pioglitazone and rosiglitazone are useful oral antidiabetic drugs and are metabolized primarily by the CYP2C8 enzyme. The drugs inhibiting or inducing CYP2C8 enzyme determine some clinically significant drug interactions of them. The clinicians are required to be aware of the drugs interacting with TZDs, to prevent the risk of adverse consequences.

Funding

Nil.

Conflicts of interest

Nil.

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