**Abstract**

Troglitazone (TGZ) caused life-threatening drug-induced liver injury (DILI) in diabetic patients, whereas the risk in class, pioglitazone (PGZ), has rarely been associated with DILI. Inhibition of bile acid transport, which may result in accumulation of toxic bile acids in hepatocytes, is one proposed mechanism of TGZ-mediated hepatotoxicity. However, PGZ is a more potent inhibitor of the bile salt export pump (BSEP) than TGZ based on in vitro microtome vesicle transport studies. In the current study, the hepatotoxic potential of TGZ and PGZ due to interference with bile acid homeostasis was investigated using DILysim®, a systems pharmacology model of DILI. Experimentally measured inhibition constants of TGZ, TGZ sulfite (TS), and pioglitazone (PGZ) for multiple bile acid transport proteins were employed to simulate the altered bile acid disposition and subsequent DILI in humans.

**Introduction**

- Drug-induced liver injury (DILI) is one of the primary reasons for the failure of pharmaceutical agents during drug development as well as withdrawal of approved drugs from the market.
- Troglitazone (TGZ) caused delayed and life-threatening DILI and was withdrawn from worldwide markets. TGZ and its major metabolite, TGZ sulfate (TS), are potent inhibitors of hepatic bile acid homeostasis.
- Pioglitazone (PGZ) has also been associated with DILI, but its mechanism remains unclear.

**Objectives**

- To determine the relative liver safety of PGZ compared to TGZ.
- To assess the impact of bile acid transporters on the hepatotoxic potential of TGZ and PGZ.
- To predict the relative liver safety of PGZ.
- To identify the critical transporters that mediate DILI.

**Methods**

- Physiologically based pharmacokinetic (PBPK) model development of TGZ and pioglitazone (PGZ) and pioglitazone (PGZ) was developed using in vitro and in vivo pharmacokinetic data available from the literature (see reference for details).
- Human virtual populations (SimPops®) were used to model the incidence and delayed hepatotoxicity associated with TGZ and PGZ.

**Results**

- Troglitazone hepatotoxicity is sensitive to transporter inhibition constants. Pioglitazone is not likely to exert acid mediated hepatotoxicity in humans.

**Conclusions**

- Mechanistic modeling based on bile acid effects adequately predicted the incidence and delayed presentation of troglitazone hepatotoxicity, and the relative liver safety of pioglitazone.
- Systems pharmacology models integrating physiological and experimental data can evaluate DILI mechanisms and may be useful to predict hepatotoxic potential of new drug candidates.

**References**

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