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Pharmacokinetic interactions between topiramate and pioglitazone and metformin

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Summary
Objective: To investigate potential drug—drug interactions between topiramate and metformin and pioglitazone at steady state.
Methods: Two open-label studies were performed in healthy adult men and women. In Study 1, eligible participants were given metformin alone for 3 days (500 mg twice daily [BID]) followed by concomitant metformin and topiramate (titrated to 100 mg BID) from days 4 to 10. In Study 2, eligible participants were randomly assigned to treatment with pioglitazone 30 mg once daily (QD) alone for 8 days followed by concomitant pioglitazone and topiramate (titrated to 96 mg BID) from days 9 to 22 (Group 1) or to topiramate (titrated to 96 mg BID) alone for 11 days followed by concomitant pioglitazone 30 mg QD and topiramate 96 mg BID from days 12 to 22 (Group 2). An analysis of variance was used to evaluate differences in pharmacokinetics with and without concomitant treatment; 90% confidence intervals (CI) for the ratio of the geometric least squares mean (LSM) estimates for maximum plasma concentration (C_{max}), area under concentration—time curve for dosing interval (AUC_{12} or AUC_{24}), and oral clearance (CL/F) with and without concomitant treatment were used to assess a drug interaction.
Results: A comparison to historical data suggested a modest increase in topiramate oral clearance when given concomitantly with metformin. Coadministration with topiramate reduced metformin oral clearance at steady state, resulting in a modest increase in systemic metformin exposure. Geometric LSM ratios and 90% CI for metformin CL/F and AUC_{12} were 80%

Abbreviations: ANOVA, analysis of variance; AUC_{12}, area under concentration—time curve over dosing interval of 12 h; AUC_{24}, area under concentration—time curve over dosing interval of 24 h; BID, twice daily dosing; CI, confidence interval; CL/F, oral clearance; C_{max}, maximum observed plasma concentration; ECG, electrocardiogram; LC/MS—MS, liquid chromatography with tandem mass spectroscopy; LSM, least squares mean; QD, once daily dosing; SD, standard deviation; TEAE, treatment—emergent adverse event; t_{max}, time to maximum observed peak concentration.

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(75%, 85%) and 125% (117%, 134%), respectively. Pioglitazone had no effect on topiramate pharmacokinetics at steady state. Concomitant topiramate resulted in decreased systemic exposure to pioglitazone and its active metabolites, with geometric LSM ratios and 90% CI for AUC_{24} of 85.0% (75.7%, 95.6%) for pioglitazone, 40.5% (36.8%, 44.6%) for M-III, and 83.8% (76.1%, 91.2%) for M-IV, respectively. This effect appeared more pronounced in women than in men. Coadministration of topiramate with metformin or pioglitazone was generally well tolerated by healthy participants in these studies.

Conclusions: A modest increase in metformin exposure and decrease in topiramate exposure was observed at steady state following coadministration of metformin 500 mg BID and topiramate 100 mg BID. The clinical significance of the observed interaction is unclear but is not likely to require a dose adjustment of either agent. Pioglitazone 30 mg QD did not affect the pharmacokinetics of topiramate at steady state, while coadministration of topiramate 96 mg BID with pioglitazone decreased steady-state systemic exposure to pioglitazone, M-III, and M-IV. While the clinical consequence of this interaction is unknown, careful attention should be given to the routine monitoring for adequate glycemic control of patients receiving this concomitant therapy. Concomitant administration of topiramate with metformin or pioglitazone was generally well tolerated and no new safety concerns were observed.

Introduction

Topiramate has been approved for use as an anticonvulsant worldwide for more than a decade, and its broad spectrum efficacy as monotherapy or adjunctive therapy for the management of epilepsy in adult and pediatric (2 to 16 years) patients is well established (Lyseng-Williamson and Yang, 2007). In addition, topiramate is currently indicated for migraine prophylaxis in adults (Linde et al., 2013) and adolescents (TOPAMAX®, 2014).

Diabetes is one of the most common non-communicable diseases worldwide, affecting an estimated 371 million people globally in 2012 (approximately 8.3% of the adult population), according to the International Diabetes Federation (2012). There is some support for an increased risk of seizures or epilepsy in patients with diabetes. McCorry et al. (2006) reported that the prevalence of type 1 diabetes was 4 times higher among patients with idiopathic generalized epilepsy, and Adelöw et al. (2011) found a nearly 2-fold higher risk of developing unprovoked seizures after initial hospitalization for diabetes. In a population-based study in the United Kingdom, the prevalence ratio of diabetes in patients diagnosed with epilepsy was 1.57% higher than that in the age- and sex-controlled general population without epilepsy (Gaitatzis et al., 2004).

Drug therapy is an important part of the management strategy for diabetes (Guthrie, 2012), epilepsy (French et al., 2004a,b), and migraine prophylaxis (Dodick and Silberstein, 2007). As such, it is important to understand potential interactions between drugs commonly used in treating each of these conditions, specifically, whether coadministration of such agents results in any change in the exposure to either (or both) agents that could possibly reduce effectiveness or pose an increased safety risk. This paper presents findings from two clinical pharmacology studies investigating the potential for an interaction between topiramate at doses of approximately 200 mg/day and the antidiabetic drugs, metformin and pioglitazone. Although, the outcomes of these studies (conducted in 1998—1999 and in 2001, respectively) are important components of the prescription information of topiramate, these studies to date have not been published. Dissemination of these data will enable physicians and health care providers to better understand the pharmacokinetics of topiramate and accordingly make appropriate treatment decisions in their patients with epilepsy or recurrent migraines who have concurrent diabetes.

Topiramate has linear and predictable kinetics at recommended doses and a long plasma elimination half-life of approximately 21 to 24 h. It is primarily excreted unchanged in the urine, with known metabolites contributing <20% of the total drug excreted (Johannessen, 1997; Shank and Maryanoff, 2008). While topiramate is only minimally bound to plasma albumin and does not undergo appreciable hepatic metabolism, its propensity to interact with other drugs is comparatively greater than that of other newer antiepileptic drugs (Landmark and Patsalos, 2010). Specifically, topiramate has been shown to affect the clearance of drugs that are metabolized via CYP3A4 and to reduce the clearance of drugs that are primarily eliminated in the urine (Bialer et al., 2004), although the propensity for drug interactions with topiramate and other agents appears to be less at doses of 200 mg/day or lower (Bialer et al., 2004; Shank and Maryanoff, 2008). The recommended dose of topiramate for migraine prophylaxis is 100 mg/day (TOPAMAX®, 2014), and the target dose for topiramate monotherapy in most types of epilepsy prevention is 100 to 200 mg/day, which is lower than the maximum dose of 400 mg/day recommended in the labeling. These lower doses of topiramate as monotherapy or adjunctive therapy for epilepsy have been shown to be equi-effective to higher doses with better tolerability (Guberman et al., 2002; Peeters et al., 2003; Silberstein et al., 2005).

Metformin, is currently one of the most widely used medications for the treatment of diabetes (Mahmood et al., 2013), and is recommended as first-line therapy for type 2 diabetes along with lifestyle and dietary changes (Nathan et al., 2009). Metformin has an absolute oral bioavailability of 40% to 60%, is rapidly distributed following absorption, and does not bind to plasma proteins. Metformin is