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Pharmacokinetics of topiramate in patients with renal impairment, end-stage renal disease undergoing hemodialysis, or hepatic impairment

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Summary
Purpose: Topiramate is primarily renally excreted. Chronic renal and hepatic impairment can affect the clearance of topiramate. Therefore, the objective was to establish dosage guidelines for topiramate in chronic renal impairment, end-stage renal disease (ESRD) undergoing hemodialysis, or chronic hepatic impairment patients.
Methods: In 3 separate open-label, parallel group studies ($n = 5$—7/group), in patients with mild—moderate and severe renal impairment (based on creatinine clearance), ESRD requiring hemodialysis, or moderate—severe hepatic impairment (based on Child—Pugh classification) and matching healthy participants, pharmacokinetics of a single oral 100 mg topiramate was determined.
Results: Compared with healthy controls, overall exposure ($AUC_{0-\infty}$) for topiramate was higher in mild—moderate (85%) and severe renal impairment (117%), consistent with significantly ($p < 0.05$) lower apparent total body clearance (CL/F) and renal clearance (CL_R), leading to longer elimination half-life. Both CL_R and CL/F of topiramate correlated well with renal function. CL/F was comparable in ESRD and severe renal impairment. Half of usual starting and maintenance dose is recommended in moderate—severe renal impairment patients, and those

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with ESRD. Hemodialysis effectively removed plasma topiramate with mean dialysis clearance approximately 12-fold greater than CL/F (123.5 mL/min versus 10.8 mL/min). Compared with healthy matched, patients with moderate—severe hepatic impairment exhibited small increase (29%) in topiramate peak plasma concentrations and $AUC_{0-\infty}$ values, consistent with lower CL/F (26%). Topiramate was generally well tolerated.

Conclusion: Half of usual dose is recommended for moderate—severe renal impairment and ESRD. Supplemental dose may be required during hemodialysis. Dose adjustments might not be required in moderate—severe hepatic impairments; however, the small sample size limits generalization.

Introduction

Topiramate (Topamax®, Johnson & Johnson Pharmaceutical Research & Development, LLC, Titusville, NJ, USA), a second-generation broad-spectrum antiepileptic drug (AED) is approved as monotherapy or adjunctive therapy for the prevention of different types of epileptic seizures in both adults and children (Topamax prescribing information, 2012). It is also approved for the prophylactic treatment of migraines in adults. Absorption of topiramate from the gastrointestinal tract is rapid and peak plasma levels are attained in 2—4 h and the pharmacokinetics of topiramate are linear (Doose et al., 1988; Easterling et al., 1988). It exhibits a long plasma half-life (~19—23 h) (Easterling et al., 1988). The bioavailability (81—95%) is not significantly affected by food and it is minimally bound to blood proteins (9—17%) (Doose et al., 1992; Nayak et al., 1994; Perucca, 1997). In healthy volunteers, 50—80% of topiramate is excreted unchanged by the kidneys, indicating that urinary elimination is the major route of elimination (Britzi et al., 2005; Doose et al., 1996; Shank and Maryanoff, 2008). However, this largely renal excretion of topiramate could pose a significant risk in patients with chronic kidney disease, as topiramate pharmacokinetics can be altered. In patients with compromised kidney status, inappropriate dosage of drugs in general can lead to toxicity or ineffective therapy (Munar and Singh, 2007; Zand et al., 2010).

In addition to renal excretion, topiramate is also eliminated by hepatic clearance via hydroxylation and hydrolysis metabolic pathways (Perucca, 1997). In patients who receive concurrent enzyme (cytochrome P450) inducing AEDs such as phenytoin, barbiturates, or carbamazepine, hepatic clearance plays an important role in the elimination of topiramate (Britzi et al., 2005; Perucca, 2006; Sachdeo et al., 1996). In patients co-medicated with topiramate and carbamazepine, a shortening (~70%) of topiramate half-life, and a decrease in fraction of the dose excreted unchanged in urine as compared with that in non-comedicated patients (32% versus 56%) occurred (Sachdeo et al., 1996; Shank and Maryanoff, 2008). In addition, total oral clearance and nonrenal clearance was increased by two-to-three fold as compared with results from topiramate monotherapy. As topiramate is predominantly excreted unchanged renally, considerable changes in topiramate pharmacokinetics are not expected in patients with chronic hepatic impairment. However, renal clearance in patients with severe hepatic impairment may also be affected. There is limited information to aid in dosage adjustment in patients with chronic kidney disease and chronic hepatic impairment. In this report, we describe three phase 1, open-label studies conducted to help provide dosage guidelines for topiramate in patients with chronic renal impairment, end-stage renal disease (ESRD) undergoing hemodialysis, or chronic hepatic impairment.

Although, the outcomes of these studies (conducted in 1993) are important components of the prescription information of topiramate, these studies have never been published. However, dissemination of this historical 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 who have renal or hepatic impairment.

Materials and methods

Participants

Renal impairment study

Eligible participants were aged 18—75 years, of any race who met pre-defined criteria from sub-categorization according to renal function based on creatinine clearance (CL_{CR}) estimated by the Cockcroft—Gault method (Cockcroft and Gault, 1976). Patients with CL_{CR} from 30 to 69 mL/min/1.73 M^2 were categorized to be in the mild—moderate renal impairment group; while, patients with CL_{CR} from <30 mL/min/1.73 M^2 were categorized to be in the severe renal impairment group. Except for their renal function, all patients were in good health with clinical laboratory tests, physical examination, neurological examination, and an electrocardiogram within normal limits or clinically acceptable (other than laboratory tests expected to be out of the reference range for patients with renal impairment). Healthy participants with normal renal function were matched to patients with the renal impairment with respect to age (±10 years), sex, and body weight (±20 lbs).

End-stage renal disease study

Eligible patients with ESRD that required hemodialysis had clinical laboratory test within normal limits (other than for tests expected to be out of the normal range for patients with ESRD), and were free of clinical significant diseases, except when related to the patient's renal disease and comorbid conditions.

Hepatic impairment study

Eligible participants were with moderate to severe hepatic impairment, aged 18—75 years, of any race. Other than