Clinical Pharmacokinetics of Gabapentin After Administration of Gabapentin Enacarbil Extended-Release Tablets in Patients With Varying Degrees of Renal Function Using Data From an Open-Label, Single-Dose Pharmacokinetic Study

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ABSTRACT

Background: Gabapentin enacarbil, a transported acyloxyalkylcarbamate prodrug of gabapentin, provides predictable and dose-proportional gabapentin exposure (AUC). Gabapentin is cleared via renal excretion, and its elimination is proportional to creatinine clearance (CrCL); CrCL can, therefore, be used as a predictor of gabapentin renal clearance. Gabapentin produced from hydrolysis of gabapentin enacarbil is also eliminated via the renal clearance pathway. It was, therefore, anticipated that the pharmacokinetics of gabapentin derived from gabapentin enacarbil would also be affected by renal function.

Objective: The objective of this study was to describe a population pharmacokinetic analysis of gabapentin enacarbil in patients with varying degrees of renal function, using data from an open-label study of gabapentin enacarbil in patients with renal impairment (XenoPort, Inc. protocol XP066), to determine whether dosage adjustments are necessary in patients with renal impairment.

Methods: Men and women >18 years of age with a body mass index ≤34 kg/m^2 and who were, in general, healthy with the exception of renal impairment were enrolled All patients received a single 600-mg gabapentin enacarbil extended-release tablet under fed conditions. After dosing, plasma, urine, and dialysate samples were analyzed. Safety profile evaluations included adverse events, vital signs, ECGs, and laboratory values. Pharmacokinetic data were compared with those from Phase I–III studies in subjects with normal renal function to evaluate the relationship between gabapentin oral clearance (CL/F) and CrCL.

Results: Fifteen patients (11 men and 4 women) were enrolled. One patient had moderate renal impairment (CrCL 30–59 mL/min), 7 patients had severe renal impairment (CrCL <30 mL/min), and 7 patients had end-stage renal disease (CrCL <15 mL/min). Ten patients were white, 4 were African American, and 1 was American Indian or Alaskan Native. Their mean (range) age was 55 (28–76) years, weight was 85.6 (62–134) kg, and body mass index was 28.3 (22–34) kg/m^2. Mean maximum plasma gabapentin concentration was 5.77 μg/mL in patients with moderate and severe renal impairment, and 5.59 μg/mL in patients with end-stage renal disease who were undergoing hemodialysis. Based on the population pharmacokinetic analysis, gabapentin CL/F after administration of gabapentin enacarbil was proportionally related to CrCL, with an approximately 1.6-fold decrease in CL/F for every 2-fold decrease in CrCL. The most frequent adverse event was dizziness (4 of 15 patients). Other adverse events that were assessed as possibly or probably related to treatment were defecation urgency, extremity pain, feeling of relaxation, and muscle weakness; each occurred in 1 patient only. All events were mild or moderate and resolved without sequelae.

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Conclusions: The data suggest that dosage adjustment for gabapentin enacarbil is necessary in patients with impaired renal function. Gabapentin enacarbil, 600 mg, seemed to be well tolerated in this small selected population. (*Clin Ther*. 2012;34:201–213)

Key words: end-stage renal disease, gabapentin enacarbil, population pharmacokinetics, renal impairment, restless legs syndrome.

INTRODUCTION

Gabapentin, a structural analogue of γ-aminobutyric acid, is marketed in the United States for treatment of post-herpetic neuralgia[1–3] and as adjunctive therapy for partial seizures in adults and children with epilepsy.[4–8]

Absorption of gabapentin is mediated by a low-capacity nutrient transporter (an L-type amino acid transporter) located in a narrow region of the small intestine.[9,10] The extent of gabapentin absorption in an individual is a function of the transit time of the drug through the small intestine and the level of expression of the gabapentin transporters. Gabapentin absorption is saturated at therapeutic doses.[9] As a result, gabapentin exhibits dose-dependent bioavailability and highly variable exposure between patients, which may limit its clinical use.[9,11–14]

Gabapentin enacarbil is a transported acyloxyalkylcarbamate prodrug of gabapentin that is stable in gastrointestinal contents.[15] It is absorbed throughout the large and small intestines by high-capacity nutrient transporters and is hydrolyzed to gabapentin after oral absorption.[15–17] The extended-release formulation of gabapentin enacarbil provides sustained dose-proportional gabapentin exposure (AUC).[17,18] Gabapentin enacarbil has been approved for treatment of moderate to severe primary restless legs syndrome (RLS),[19,20] a neurologic condition characterized by an urge to move the legs and by uncomfortable sensations in the limbs.[21] Gabapentin enacarbil doses of 600 to 1200 mg are effective in relieving the symptoms of moderate to severe RLS[19,20]; these doses correspond to 312 to 625 mg released gabapentin, respectively. After oral administration, gabapentin is excreted in the urine without further metabolism.[13,22]

Renal clearance of gabapentin (CL_R) correlates well with creatinine clearance (CrCL), which can be used as a predictor of CL_R.[22] In patients with anuria, gabapentin can be effectively removed via dialysis.[23] Gabapentin produced from hydrolysis of gabapentin enacarbil is also eliminated via the renal clearance pathway.[16,17] The pharmacokinetic properties of gabapentin derived from gabapentin enacarbil are, therefore, expected to be similarly related to renal function, and as a result, it was anticipated that it may be necessary to recommend dosage adjustment of gabapentin enacarbil in patients with renal impairment. The US Food and Drug Administration *Guidance for Industry on Pharmacokinetics in Patients with Impaired Renal Function*[24] allows use of pharmacokinetic data from patients with severe renal impairment together with population pharmacokinetic data from healthy subjects in lieu of a complete renal impairment study. The present study was, therefore, conducted to assess the pharmacokinetic properties and tolerability of gabapentin enacarbil in patients with severe renal impairment (CrCl <30 mL/min) and in patients with end-stage renal disease (ESRD) undergoing hemodialysis. The resulting pharmacokinetic data were used in conjunction with Phase I data and population pharmacokinetic data from the Phase II and III studies to establish the dosing recommendations for patients with various degrees of renal impairment.

The present study assessed the pharmacokinetic properties and tolerability of a single 600-mg gabapentin enacarbil extended-release tablet in patients with various degrees of renal function. The study included patients with renal impairment and patients with ESRD who were undergoing hemodialysis.

PATIENTS AND METHODS

Study Design

An open-label, single-dose, renal impairment study in patients with moderate to severe renal impairment (Study No. XP066; sponsored by XenoPort, Inc., Santa Clara, California) was performed between January and November 2007 in 2 centers (Orlando Clinical Research Center, Orlando, Florida, and Prism Research, St. Paul, Minnesota), and the resulting pharmacokinetic data were combined with population pharmacokinetic data from healthy patients. The study was approved by the institutional review boards of the participating institutions and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki (1996).[25] This Phase I study was initiated in January 2007, at which time the International Committee of Medical Journal Editors policy on trials reg-