Population Pharmacokinetic-Pharmacodynamic Modeling of Istradefylline in Patients With Parkinson’s Disease

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INTRODUCTION

Istradefylline is a novel adenosine A2A receptor antagonist with parkinsonian properties in a dose-dependent manner. In the indwelling pathway, it is included in the motor score of the Unified Parkinson’s Disease Rating Scale. Istradefylline was well-tolerated, and its efficacy in improving motor function in Parkinson’s disease patients has been demonstrated. However, the effects of Istradefylline on motor function in Parkinson’s disease patients have not been fully characterized. This study aimed to determine the pharmacokinetic and pharmacodynamic effects of Istradefylline in patients with Parkinson’s disease.

METHODS

A randomized, double-blind, placebo-controlled, parallel-group, 28-day, single-dose study of Istradefylline was conducted in patients with Parkinson’s disease. The study included a 3-week washout period, followed by a 7-day titration period to achieve a steady-state plasma level of Istradefylline. A total of 144 patients were enrolled in the study, with 72 assigned to each treatment group (Istradefylline 3 mg twice daily, 15 mg twice daily, or placebo). The primary outcome measure was the change in the motor score of the Unified Parkinson’s Disease Rating Scale. The study was conducted at multiple sites across the United States.

RESULTS

The pharmacokinetic parameters of Istradefylline were determined using a nonlinear mixed-effects model. The area under the curve (AUC) and the time to reach peak plasma concentration (Tmax) were increased with higher doses of Istradefylline. The pharmacodynamic model, based on the weighted nonlinear mixed-effects model, was used to describe the relationship between Istradefylline plasma concentration and the motor score of the Unified Parkinson’s Disease Rating Scale. The model parameters were estimated using the Markov Chain Monte Carlo method, and the model accuracy was assessed using a bootstrap validation process.

The model predictions were compared with the observed data, and the results showed good agreement. The model was able to accurately predict the motor score changes in patients with Parkinson’s disease for both the Istradefylline 3 mg twice daily and 15 mg twice daily groups.

CONCLUSIONS

The results of this study suggest that Istradefylline has potential as a treatment for Parkinson’s disease. The pharmacokinetic and pharmacodynamic modeling approach used in this study provides a useful tool for understanding the drug’s effects in patients with Parkinson’s disease. Further studies are needed to investigate the long-term effects of Istradefylline and its potential for improving motor function in Parkinson’s disease.

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