Pharmacokinetic/Pharmacodynamic Analysis of Amantadine for Levodopa-Induced Dyskinesia: Correlation of Therapeutic Plasma Concentrations from Multiple Species with Humans

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Background

Epidural is a common motor complication associated with the use of levodopa to treat Parkinson’s disease. While the progressive loss of dopaminergic neurons in the substantia nigra is the hallmark of Parkinson’s disease and its progression to end-stage human motor disability, animal models of parkinsonian-like disease and motor dysfunction exist in rodents, non-human primates, and human.

Numerous animal studies in mice, rats, and non-human primates (NHP) have demonstrated that the NMDA receptor antagonist, amantadine, reduces the expression of dyskinesia in models of levodopa-induced dyskinesia (LID) in a dose-dependent manner. These findings support the use of amantadine in the treatment of dyskinesia in patients with Parkinson’s disease without levodopa-induced dyskinesia (LID).

Objective

To evaluate the pharmacokinetic/pharmacodynamic (PK/PD) relationship between amantadine plasma concentrations and anticytokine efficacy across multiple species in order to define optimal therapeutic dosing in patients with Parkinson’s disease treated with levodopa to provide evidence to these animal models for binding novel drugs to treat dyskinesia.

Methods

The PK/PD analysis was undertaken in 2016 (ch guarded, shares owned by 0.5% of the market at 1123/125 mg). All endpoints were 0.01% measured by the following domains: % with 12.5, 30, and 50 mg/kg (±2.5%) for the first order rate constant receiving levodopa-based therapy.

Mouse PK/PD

• Systemic doses were administered daily on oral 210 mg, with 15 mg/kg levodopa introduced into sodium acetate buffer, pH 5.0) or amantadine HCl (22.5, 45, or 83 mg/kg/day). During the amantadine treatment period, all animals received a single oral dose of amantadine and were used to simulate plasma concentrations for other dose levels used in the literature to which appropriate plasma concentrations for other dose levels used in the literature to which appropriate

• The efficacy of amantadine in reducing LID was assessed in Parkinson’s disease models (6-OHDA rat and MPTP macaque).

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• Development of LID in the MPTP-macaque model followed our previously described methods.1

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• 3-weeks after surgery rats received once-daily oral levodopa (10 mg/kg with 15 mg/kg benserazide) to induce stable AIMs.

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• A single oral dose of amantadine resulted in a dose-dependent decrease in dyskinesia in MPTP-macques, with up to 75% reduction in median levels of AIMs occurring at 8 mg/kg amantadine.

• PK/PD relationship in MPTP macaque using calculated plasma concentrations and published disease data on AIMs is model results in an EC50 of 1055 ng/mL.

• Amantadine plasma concentrations were dose-proportional between 1 and 30 mg/kg and were used to simulate plasma concentrations for the dose range used in published mouse studies.

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Clinical Data (EASED Study)

• In clinical studies where plasma levels were determined, doses that resulted in significant reduction in dyskinesia resulted in plasma concentrations spanning 50-90 ng/mL.

• These results are in agreement with the non-clinical PK/PD relationship and provide validation that the animal models are predictive of clinical relationship.

Conclusions

• Collectively, these data show good correlation across species between amantadine plasma concentrations and reduction in dyskinesia, highlighting an EC50 of approximately 1400 ng/mL (17 µM) as an efficacious target plasma concentration. These data are consistent with the mean plasma amantadine concentrations observed in patients with Parkinson’s disease (~1500 ng/mL) treated with ADS-5102 at doses that demonstrated a statistically significant reduction in dyskinesia.

• Further support for the efficacy of this range of concentrations is provided by the study in the rat-DJ-1 model showing a substantial IC50 reduction of amantadine. Significant reductions in AIMS compared with vehicle were produced in the group with average amantadine plasma concentrations of 3237 ng/mL. No significant effect on AIMS was observed in the dose groups resulting in average amantadine plasma concentrations below 900 ng/mL.

• These results also correlate well with the range of 50% inhibitory drug concentration values reported for amantadine in the NMDA receptor (~1-10 µM).

• These findings demonstrate that the animal models are predictive of a relationship between plasma amantadine concentration and reduction in dyskinesia in humans and support the involvement of the NMDA receptor and the glutamatergic pathway in mediating the expression of dyskinesia and motor complications in Parkinson’s disease.

References


Acknowledgment

The authors would like to acknowledge the contribution of Ken Van for his vital support in study conduct and data preparation.

 rims are of the placebo, 210-mg, 274-mg, and 338-mg groups, respectively. Doses are represented as freebase. Source: Parikh H, et al. Mov Disord Clin 2015; 9:789-793.

Table 1. List of Studies

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<th>Reference</th>
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Continuous Infusion of Amantadine in 6-OHDA LID rat

• Amantadine infused at 80 mg/kg/hr, which gives plasma levels above the EC50 (2000 ng/mL), significantly reduced dyskinesia.

• Amantadine plasma concentrations that result in plasma concentration below 100 ng/mL did not significantly impact dyskinesia.