A PHARMACOKINETIC SIMULATION-BASED COMPARISON OF VARYING ADHERENCE RATES FOR PALIPERIDONE ER AND RISPERIDONE IN PATIENTS WITH SCHizophrenIA

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BACKGROUND

• Medication adherence is important to successful management of patients with schizophrenia and related psychotic disorders; patient nonadherence is documented in numerous studies (e.g., 30–35% patient noncompliance).1,2
• Drug formulation affects the pharmacokinetic (PK) profile and plays an important role in maintaining therapeutic plasma concentrations.
• Paliperidone extended-release (ER) and risperidone have similar pharmacokinetic effects with regard to D2 receptor occupancy.2,3
• Compared with risperidone, however, paliperidone ER formulation has a longer elimination half-life and is peak-dose-to-trough fluctuations at steady state.

METHODS

• Data utilized were from three Phase 3 studies of paliperidone ER1,4 and four Phase 1 and three Phase 3 trials for risperidone1,5
• PK parameter estimates for paliperidone ER and risperidone were obtained from population models developed previously with the Mixed Effects Modeling Software1,6 used for dosing and biostatistical analysis.
• The PK simulation process is outlined in Figure 1.

RESULTS

• Plasma concentrations representative of 100% adherence are outlined in Figure 2.

Figure 2. Predicted Paliperidone ER and Risperidone Concentrations Following 100% Adherence.

• With 100% adherence, approximately 24% of the virtual paliperidone ER patients showed consistent plasma concentration levels in the target range compared with 5% of virtual risperidone patients (Table 3; Figure 3).
• With adherence rates of 67% and 33%, the effects on paliperidone ER plasma concentrations were less extensive compared with those of risperidone paliperidone concentrations; paliperidone ER demonstrated longer time within the target range.
• With 67% adherence rate, approximately 10% (virtual paliperidone ER patients) and 3% (virtual risperidone patients) were consistently within the target range (Table 3; Figure 3).

Figure 3. Percentage of Time Subjects Always Maintained Within Target Bounds for Paliperidone ER and Risperidone, Stratified by Adherence Rate.

DISCUSSION AND LIMITATIONS

• Adherence rates altered the drug plasma concentration levels and altered the amount of time during a dosage interval that either risperidone or paliperidone ER concentration was within a range associated with desirable dopamine receptor occupancy.
• Although the effects of drug dosage regimens that produce plasma concentrations outside of these occupancy ranges have not been extensively studied regarding their clinical consequences, available data suggest that formulation modifications (e.g., ER) should minimize fluctuations in drug concentration.
• The effects of decreased adherence rates had less influence on maintaining plasma drug concentrations within a target range for paliperidone ER than for risperidone.
• Although this study used a PK simulation-based approach to analyze the effects of adherence rates on plasma drug concentrations, a variety of patient factors also play a role in influencing outcomes in clinical practice.

CONCLUSIONS

• These results suggest that decreased adherence rates may have less of an effect on drug plasma concentrations of paliperidone ER versus risperidone.

The authors wish to acknowledge the writing and editing assistance of Matthew Gryczyn, PhD, and Paule Medical Communications (funding supported by Orto-Medico Jansen Scientific Affairs, LLC, Titusville, NJ, USA) in the development of this poster.

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Poster presented at the 21st US Psychiatric and Mental Health Congress; November 2-5, 2008; Las Vegas, NV.

Supported by funding from Orto-Medico-Jansen Scientific Affairs, LLC.
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- Drug formulation affects the pharmacokinetic (PK) profile and plays an important role in maintaining therapeutic plasma concentrations.4-6
- Paliperidone extended-release (ER) and risperidone have similar pharmacokinetic effects with regard to D2 receptor occupancy.7-9
- Compared with risperidone, however, paliperidone ER formulation has a longer elimination half-life and less peak-to-trough fluctuations at steady state.10

METHODS
- PK simulations using clinical study data provide a novel methodology to compare drug plasma concentrations following different adherence rates.
- PK simulations were performed to examine the impact of various adherence rates during chronic therapy with paliperidone ER and risperidone.

RESULTS
- Plasma concentrations representative of 100% adherence are outlined in Figure 2.

Figure 2. Predicted Paliperidone ER and Risperidone Concentrations Following 100% Adherence.

- With 100% adherence, approximately 24% of the virtual paliperidone ER patients showed consistent plasma concentration levels in the target range compared with 5% of virtual risperidone patients (Table 3, Figure 3).
- With adherence rates of 67% and 33%, the effects on paliperidone ER plasma concentrations were less extensive compared with those of risperidone plasma concentrations; paliperidone ER demonstrated longer time within the target range.
- With 67% adherence rate, approximately 10% (virtual paliperidone ER patients) and 3% (virtual risperidone patients) were consistently within the target range (Table 4, Figure 3).

CONCLUSIONS
- These results suggest that decreased adherence rates may have less of an effect on drug plasma concentrations of paliperidone ER versus risperidone.

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DISCUSSION AND LIMITATIONS
- Adherence rates altered the drug plasma concentration levels and altered the amount of time during a dosing interval that either risperidone or paliperidone ER concentration was within a range associated with desirable dopamine receptor occupancy.
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- The effects of decreased adherence rates had little influence on maintaining plasma drug concentrations within a target range for paliperidone ER than for risperidone.
- Although this study used a PK simulation-based approach to analyze the effects of adherence rates on plasma drug concentrations, a variety of patient factors also play a likely to influence outcomes in clinical practice.

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Figure 3. Percentage of Time Subjects Always Remained Within Target Bounds for Paliperidone ER and Risperidone, Stratified by Adherence Rate.

Figure 4. A PHARMACOKINETIC SIMULATION-BASED COMPARISON OF VARYING ADHERENCE RATES FOR PALIPERIDONE ER AND RISPERIDONE IN PATIENTS WITH SCHIZOPHRENIA

Figure 5. Time Above, Between and Below Target Concentration Ranges Using Pooled Clinical Trial Data.

Randomly Generated Plasma Concentration Time Series for Paliperidone ER and Risperidone Using Pooled Clinical Trial Data for Clinical Study Population

Portfolio Models
- Paliperidone: 10-17 ng/mL
- Risperidone, Stratified by Adherence Rate.
- Paliperidone: 10-17 ng/mL
- Risperidone: 10-17 ng/mL

Abbreviations
- ER: Extended-Release
- CYP2D6: Cytochrome P450 2D6
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- Drug formulation affects the pharmacokinetic (PK) profile and plays an important role in maintaining therapeutic plasma concentrations.
- Paliperidone extended-release (ER) and risperidone have similar pharmacologic effects with regard to D2 receptor occupancy.4-5

RESULTS
- Plasma concentrations representative of 100% adherence are outlined in Figure 2.
- With 100% adherence, approximately 24% of the virtual paliperidone ER patients showed consistent plasma concentration levels in the target range compared with 15% of virtual risperidone patients (Table 3, Figure 3).
- With adherence rates of 67% and 33%, the effects on paliperidone ER plasma concentrations were less extensive compared with those of risperidone plasma concentrations; paliperidone ER demonstrated longer time within the target range.
- With 67% adherence rate, approximately 10% (virtual paliperidone ER patients) and 3% (virtual risperidone patients) were consistently within the target range (Table 4, Figure 3).

DISCUSSION AND LIMITATIONS
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- The effects of decreased adherence rates had less influence on maintaining plasma drug concentrations within a target range for paliperidone ER than for risperidone.
- Although this study used a PK simulation-based approach to analyze the effects of adherence rates on paliperidone plasma concentrations, a variety of patient factors also contribute to influence outcomes in clinical practice.

CONCLUSIONS
- These results suggest that decreased adherence rates may have less of an effect on drug plasma concentrations of paliperidone ER versus risperidone.
- This novel approach links medication adherence rate to comparative drug pharmacokinetics and potentially may be applied to other antipsychotic agents.

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ABSTRACT

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• Paliperidone extended-release (ER) and risperidone have similar pharmacokinetic profiles with regard to D2 receptor occupancy.2•

METHODS

• PK simulations using clinical study population data provide a novel methodology to compare drug plasma concentrations following different adherence rates.
• PK simulations were performed to examine the impact of various adherence rates during chronic therapy with paliperidone ER and risperidone.
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• With 67% adherence rate, approximately 10% (virtual paliperidone ER patients) and 3% (virtual risperidone patients) were consistently below target bounds.

CONCLUSIONS

• These results suggest that decreased adherence rates may have less of an effect on drug plasma concentrations of paliperidone ER versus risperidone.

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Figure 3. Percentage of Time Subjects Always Remained Within Target Bounds for Paliperidone ER and Risperidone, Stratified by Adherence Rate.

• These results suggest that decreased adherence rates may have less of an effect on drug plasma concentrations of paliperidone ER versus risperidone.

• The PK modeling approach links medication adherence rates to comparative drug pharmacokinetics and potentially may be applied to other antipsychotic agents.

DISCUSSION AND LIMITATIONS

• Adherence rates altered the drug plasma concentration levels and altered the amount of time during a dosing interval that either risperidone or paliperidone ER concentration was within a range associated with desirable dopamine receptor occupancy.
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125

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• Medication adherence is important to successful management of patients with schizophrenia and related psychotic disorders; patient nonadherence is documented in numerous studies (e.g., 30%–35% patient noncompliance). 1–3

• Drug formulation affects the pharmacokinetic (PK) profile and plays an important role in maintaining therapeutic plasma concentrations. 4

• Paliperidone extended-release (ER) and risperidone have similar pharmacokinetic effects with regard to D2 receptor occupancy. 5

• Compared with risperidone, however, paliperidone ER formulation has a longer elimination half-life and less peak-to-trough fluctuations at steady state. 6

• PK simulations using clinical study population data provide a novel methodology to compare drug plasma concentrations following different adherence rates.

• PK simulations were performed to examine the impact of various adherence rates during chronic therapy with paliperidone ER and risperidone.

Methods

• Data utilized were from three Phase 3 studies of paliperidone ER and four Phase 1 and three Phase 3 trials for risperidone. 6–8

• PK parameter estimates for paliperidone ER and risperidone were obtained from population models developed previously with the mixed-effects computer modeling algorithm NONMEM (Nonlinear Mixed Effects Modelling Software) 9 using pooled clinical trial data.

• The PK simulation process is outlined in Figure 1.

Figure 1. PK Simulation Flow Chart.

PK Models

• Risperidone: two-compartment model (developed using NONPHARM data) with zero-first-order absorption, a mixed model that accounted for CYP2D6 polymorphic metabolizer and covariate effects of carboxyesterase cleavage (CYP2A6 induction).

• Paliperidone ER: two-compartment model (developed using 21,163 plasma drug concentrations) with zero-first-order input, first-order absorption and elimination, and covariate effects for renal function (creatinine clearance) and lean body weight.

• Data from Phase 3 paliperidone ER and risperidone studies were utilized to develop population pharmacokinetic (PK) models. 6,7

• Data from other paliperidone ER and risperidone studies were utilized to develop a mixed-effects population PK model. 6-8

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• Adherence rates altered the drug plasma concentration levels and altered the amount of time during a dosage interval that either risperidone or paliperidone ER concentration was completely within a range associated with desirable dopamine receptor occupancy.

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- Data utilized were from three Phase 3 studies of paliperidone ER3 and four Phase 1 and three Phase 3 trials for risperidone.4
- PK parameter estimates for paliperidone ER and risperidone were obtained from population models developed previously with the mixed-effects computer modeling algorithm NONMEM (Nonlinear Mixed Effects Modeling Software)5 using pooled clinical trial data.
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RESULTS

Figure 1. PK Simulation Flow Chart.

Table 1. Summary Parameter Estimates

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