T3182

Population Pharmacokinetics/Pharmacodynamics of Antidepressant R,R(-) and S,S(+) Reboxetine (RBX)

A.J. Xiao,[1] J. Fiedler-Kelly,[1] M. Redman,[1] J.C. Fleishaker[2]

[1]Cognigen Corporation, Buffalo, NY and [2]Pharmacia Corporation, Kalamazoo, MI

ABSTRACT

Purpose. To develop a population pharmacokinetic model describing the disposition of each enantiomer of antidepressant reboxetine and a pharmacodynamic model relating plasma concentrations and adverse effects.

Methods. Data for analysis were from a double-blind, placebo-controlled, multi-center trial. 198 patients received oral doses of 1, 2, or 4 mg b.i.d. reboxetine and 80 patients received placebo. Population PK models for R,R(-) and S,S(+) reboxetine were developed separately in NONMEM®. A PD model on pulse variation was also developed using NONMEM® and a logistic regression analysis was performed on the risk of selected adverse events during treatment with reboxetine using SAS® software.

Results. One-compartment models with first-order absorption best described the PK of both R,R(-) and S,S(+) reboxetine. Clearance and steady-state volume of distribution of R,R(-) and S,S(+) reboxetine were estimated as 2.36 L/hr, 59.2 L, 4.45 L/hr and 102 L, respectively. Gender and weight were observed to affect clearance of R,R(+) reboxetine, with a 24.3% reduction for females and about 0.012 L/hr reduction for every 1 kg gain in weight. None of the concomitant medications explored was found to significantly influence R,R(-) reboxetine PK. Neither demographic characteristics nor concomitant medications were found to significantly affect S,S(+) reboxetine PK. Reboxetine doses were found to be significantly related to the risk of the combined adverse events with an odds ratio (95% CI) of 1.52 (1.26, 1.83). The time course of change in pulse rate from baseline is best represented by a sigmoid model. Reboxetine treatment was observed to increase pulse rate by about 8 beats/minute on average, not significantly varying with doses, demographics, or concomitant medications.

Conclusions. No demographic factors were identified in this analysis which affect the pharmacokinetics of reboxetine enantiomers to a clinically significant degree. No clear relationship between reboxetine exposure and specific adverse events was observed.

INTRODUCTION

Reboxetine (RBX) is a unique selective noradrenaline reuptake inhibitor that exhibits antidepressant activity in adult patients with major depression. Oral absorption of reboxetine is rapid and unaffected by food, with at least 90% of absorbed drug being plasma protein bound. Reboxetine is a racemic mixture of the R,R(-) and S,S(+) enantiomers, and plasma concentrations of the R,R(-) enantiomer are typically twice those of the S,S(+) enantiomer. In healthy volunteers, the elimination half-lives of the enantiomers were similar (approximately 11-13 hours) and not substantially affected by dose level after single oral reboxetine doses of 1.5-4.5 mg. Reboxetine is eliminated primarily by hepatic metabolism, principally by the CYP3A4 isoenzyme. Elimination is slowed, and systemic exposure increased in elderly patients and those with renal or hepatic impairment. Reboxetine can cause side effects typical of enhanced noradrenergic tone such as dry mouth, constipation, and increased heart rate, although these effects were less common when directly compared with imipramine or desipramine. Although qualitative analysis of reboxetine adverse effects has been reported, the relationship between adverse effects and reboxetine dose or plasma concentrations has not been described. The present population pharmacokinetic and pharmacodynamic analysis was performed using available R,R(-) and S,S(+) reboxetine plasma concentrations from a double-blind, placebo-controlled, multi-center clinical trial of reboxetine in patients with major depression.

OBJECTIVES

- Develop a population pharmacokinetic model to describe the disposition of each enantiomer following oral administration of reboxetine.
- Describe inter- and intra-subject variabilities in the pharmacokinetic parameters.
- Develop a pharmacodynamic model to evaluate reboxetine-related adverse events.
- Evaluate the influence of patient covariates and concomitant medications on the pharmacokinetic and pharmacodynamic relationships.

METHODS

Pharmacokinetic Analysis

Subjects and data collection

- Data were collected from patients enrolled in a double-blind, placebo-controlled, European multi-center, multi-national clinical trial investigating RBX for major depression.
- Patients were randomized to receive placebo or a total daily dose of 2, 4, or 8 mg of oral reboxetine for 6 weeks (b.i.d.).
- Blood samples were collected from each patient on study days 7, 14, 28, and 42. Plasma concentrations of both the R,R(-) and S,S(+) enantiomers were quantified.

Pharmacostatistical modeling

- NONMEM® version V (with FO estimation method)[1] was used to fit the model to the data.
- The R,R(-) and S,S(+) RBX concentration-time data were separately fit to one- and two-compartment models with first-order absorption and elimination.
- Interindividual variability in CL, V, and k_a were modeled using an exponential error model.
- Residual variability: three error models were evaluated (proportional error, additive error, and combined additive plus constant coefficient of variation error model).

Patient covariate analysis

- Covariates: weight, age, gender, tobacco use (none, light, heavy), and creatinine clearance (CrCL, calculated using the Cockroft and Gault equation[2]).
- Concomitant medications:
  - estrogens and oral contraceptives
  - nonbarbiturate sedatives and hypnotics (excluding doxylamine and doxylamine succinate)
  - lorazepam, oxazepam, and other antianxiety medications which undergo conjugation or glucuronidation
  - alprazolam, diazepam, and other antianxiety medications which undergo oxidation or hydroxylation

Statistical analysis

- For univariate analyses using the forward selection procedure, statistical significance was defined as a change in the minimum value of the objective function of at least 3.84 ($\alpha = 0.05$, 1 degree of freedom) for the addition of a single parameter.
- Interaction effects between covariates were evaluated for significance using the same criteria.
- For multivariable backward elimination, a change of least 10.83 ($\alpha = 0.001$, 1 degree of freedom) was used to define statistical significance for the deletion of a single covariate.

Pharmacodynamic Analysis

Adverse event analysis

- Adverse events (AEs) were grouped and evaluated together as described below:
  - constipation and dry mouth
  - palpitations and tachycardia
  - increased/decreased urinary frequency, impaired urination, and urinary retention
  - all of these adverse events combined
- Logistic regression was used (SAS® software, version 6.12[3])to evaluate the risk of selected AEs and the effect of RBX exposure, patient covariates, and concomitant medications on that risk.
- Independent variables evaluated for influence on the risk of adverse events:
  - Measures of reboxetine exposure: dose and predicted R,R(-) and S,S(+) RBX 12-hour trough concentrations
  - Demographic characteristics (as specified previously)
  - Concomitant medications (as specified previously)

Heart rate and systolic/diastolic blood pressure change analyses

- Model-based analyses with NONMEM® were used to describe the time course of changes from baseline as a function of the independent predictor variables listed above. Statistical significance for covariate analyses was as defined previously.

RESULTS

Pharmacokinetic Analysis and Modeling

Data

- 630 R,R(-) reboxetine plasma concentrations and 628 S,S(+) reboxetine plasma concentrations from 198 patients were available for pharmacokinetic model development.

Table 1: Demographic Characteristics and Concomitant Medication Usage of Patients Included in Pharmacokinetic Analysis (N=198)

Age (yrs)	Mean (SD) Median Min-Max	41.38 (10.41) 41 18 - 65
Creatinine Clearance (mL/min)	Mean (SD) Median Min-Max	110.77 (30.97) 106.08 44.20 - 212.16
Weight (kg)	Mean (SD) Median Min-Max	68.69 (13.58) 65.55 43 - 110
Gender Male Female	N (%) N (%)	59 (29.8%) 139 (70.2%)
Smoking Status None Light Heavy	N (%) N (%) N (%)	120 (60.61%) 24 (12.12%) 54 (27.27%)
Concomitant Medications Estrogens Sedatives/Hypnotics Benzo[1]-Conjugated Benzo[1]-Oxidated	N (%) N (%) N (%) N (%)	31 (15.66%) 12 (6.06%) 90 (45.45%) 1 (0.51%)

[1]Benzo = benzodiazepine

Final equation for computing apparent oral clearance of R,R(-) RBX:

$$CL_i = \left[\Theta_{CL}^{0} \bullet \left(1 + \Theta_{CL}^{SEXF} \bullet SEXF_i\right) + \Theta_{CL}^{WTKG} \bullet (WTKG_i - 68.5)\right] \bullet e^{\eta_{2i}}$$

Final equation for computing apparent oral clearance of S,S(+) RBX:

$$CL = \Theta_{CL}^{0} \bullet e^{\eta_{2i}}$$

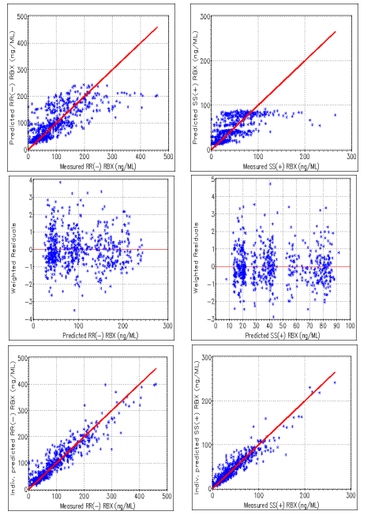
Table 2: Comparison of R,R(-) and S,S(+) RBX Parameter Estimates from the Final Pharmacokinetic Models

Parameters	R,R(-)		S,S(+)	
	Final Estimate	%SEM	Final Estimate	%SEM
Clearance, (L/hr) Θ_{CL}^{0}	2.36	5.3	4.45	3.3
Gender effect on CL, Θ_{CL}^{SEXF}	-0.243	20.7	NE	NE
Weight effect on CL, Θ_{CL}^{WTKG}	-0.0119	39.7	NE	NE
Volume of Distribution, (L) Θ_{V}^{0}	59.2	19.4	102.0	16.2
Absorption Rate Constant, (1/hr) Θ_{ka}^{0}	0.904	28.3	0.761	23.7
Inter-individual variability in CL, (%CV) η_{CL}	35.1	13.3	42.7	18.2
Inter-individual variability in V, (%CV) η_{V}	38.6	291.9	NE	NE
Residual variability (%CV)	29.2	10.8	29.2	11.3

NE = Not Estimated

- Inter-individual variability in V was modeled only for the R,R(-) enantiomer.
- The proportional residual error model was used in both PK models.

Figure 1: Goodness-of-Fit of the PK Models for R,R(-) and S,S(+) Reboxetine



Pharmacodynamic modeling

Combined adverse events analysis

- Because no clear relationship between RBX exposure and specific AEs was observed, only the overall grouping of combined events was explored using logistic regression analysis.
- The final model describing risk of combined adverse events is a function of only RBX dose.

Table 3: Parameter Estimates from Logistic Regression Analysis of Risk of the Combined Adverse Events

Parameter	Final Estimate	Standard Error	*p*-value	Odds Ratio (95% CI)
Intercept	-1.3209	0.2298	0.0001	
Dose	0.4189	0.0954	0.0001	1.520 (1.261, 1.832)

Table 4: Observed vs. Predicted Frequencies of AEs by Dose

	Placebo	1mg bid	2mg bid	4mg bid
Observed Frequency (%)	12.1	41.1	41.2	54.4
Model-based Predicted Probability (%)	21	29	38	59

Heart rate and blood pressure analysis

- Overall, observed systolic/diastolic blood pressure changes were less than 5mmHg in all cases.

Final sigmoid model describing pulse change over time:

$$Y_{ij} = \left[P\max_i \bullet time_{ij} / (PT_{50i} + time_{ij})\right] + \varepsilon_{ij}$$

$$P\max_i = \Theta_{P\max}^{plac} \bullet (1 - TRT_i) + \Theta_{P\max}^{RBX} \bullet TRT_i + \eta_{P\max i}$$

$$PT_{50i} = \Theta_{PT50}^{} \bullet \left(1 + \Theta_{PT50}^{conm} \bullet CONJ_i\right) + \eta_{PT50i}$$

Where:

Y_{ij} = change in pulse from baseline/screening visit (beats/minute) for the i^{th} patient at the j^{th} time;

$Pmax_i$ = the maximum change in pulse from baseline (beats/minute) for the i^{th} patient;

PT_{50i} = the time required to obtain half of the maximum pulse change (days) for the i^{th} patient; and

ε_{ij} = a random variable describing the difference between the predicted pulse change and the actual pulse change for the i^{th} patient at the j^{th} time.

TRT_i = treatment indicator variable in the i^{th} patient with a value of 1 for patients receiving treatment with reboxetine and 0 for patients receiving placebo;

Θ_{Pmax}^{plac} = the typical value of the maximum change in pulse from baseline for patients receiving placebo;

Θ_{Pmax}^{RBX} = the typical value of the maximum change in pulse from baseline for patients receiving treatment with reboxetine, regardless of dose;

$\eta_{Pmax\,i}$ = the persistent difference between the true value of Pmax in the i^{th} patient and the typical value; the η_i are independent, identically distributed statistical errors with a mean of 0 and a variance of ω^2;

$CONJ_i$ = dichotomous indicator variable in the i^{th} patient with a value of 1 for the concomitant use of benzodiazepines which undergo conjugation or glucuronidation and 0 otherwise;

Θ_{PT50} = the typical value of the time required to obtain half of the maximum pulse change for patients not receiving concomitant benzodiazepines which undergo conjugation or glucuronidation;

Θ_{PT50}^{conj} = the mean proportional increase or decrease in PT_{50} associated with the use of benzodiazepines which undergo conjugation or glucuronidation; and

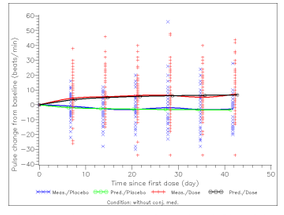
η_{PT50j} = the persistent difference between the true value of PT_{50} in the j^{th} patient and the typical value; the η_i are independent, identically distributed statistical errors with a mean of 0 and a variance of ω^2.

Table 5: Parameter Estimates for the Final Model Describing Pulse Change Time Course

Parameter	Population Mean		Magnitude of Inter-individual Variability (SD)	
	Final Estimate	%SEM	Final Estimate	%SEM
Pmax placebo (beats/minute)	-4.14	93.2	12.69	19.9
Pmax RBX (beats/minute)	8.03	24.8		
PT_{50} (days)	8.76	31.3	18.87	111.2
Conj. Benzo. Effect on PT_{50}	-0.584	32.4		
Residual Variability (SD)	6.93	9.0	NA	NA

NA = Not Applicable Conj Benzo = benzodiazepines undergoing conjugation

Figure 2: Effect of Treatment with Reboxetine on Pulse Change Simulated with the Final Model



- Model-predicted pulse rate change = increase of approximately 8 beats/minute by study day 7 for any RBX dose (1, 2, or 4mg b.i.d.).
- Concomitant antianxiety medications which undergo conjugation accelerate the maximum expected pulse change due to RBX by 58%.

REFERENCES

1. NONMEM® Users Guides, 5th ed. (1995); Beal SL, Sheiner LB (Eds.) NONMEM® Project Group, University of California at San Francisco, San Francisco.
2. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron 1976*; 16:31-41.
3. SAS® Institute Inc. The LOGISTIC procedure. In:SAS/STAT User's Guide, Volume 2, 4th edition.

CONCLUSIONS

- The pharmacokinetics of both R,R(-) and S,S(+) RBX can be adequately described using a one-compartment model with first-order absorption and elimination.
- The population estimates for apparent oral clearance and volume of distribution of the R,R(-) enantiomer were substantially lower than that of the S,S(+) enantiomer, but both exhibited similar elimination half-lives.
- Covariate analysis indicated that clearance of only the R,R(-) enantiomer was influenced by weight and gender, but not to any clinically significant degree.
- A statistically significant positive relationship exists between the risk of the occurrence of combined adverse events and RBX dose.
- RBX treatment results in an approximate increase in pulse rate of 8 beats/minute, with no significant influence from dose, demographics, or concomitant medications.