# Pharmacokinetics of Single-Dose Reboxetine in Volunteers with Renal Insufficiency

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Reboxetine is a new selective norepinephrine reuptake inhibitor (selective NRI) for the short- and long-term treatment of depression that is effective and well tolerated at a dose of 8 to 10 mg/day. This study assessed the pharmacokinetics of reboxetine in volunteers with renal impairment. A single 4 mg dose of reboxetine was administered to a total of 18 volunteers with mild (n = 6), moderate (n = 6), or severe (n = 6) renal impairment (creatinine clearance: 56-64, 26-51, and 9-19 ml/min, respectively), and reboxetine concentrations were measured in plasma by HPLC. Mean $AUC_\infty$ increased by 43% (mild vs. severe; p < 0.01) as renal function declined, while renal clearance and total urinary excretion of unchanged reboxetine decreased by 67% and 62%, respectively (mild vs. severe; p < 0.01 for both parameters). $t_{max}$ and $t_{1/2}$ were not significantly different between groups. In comparison with historical data from young healthy volunteers, $AUC_\infty$ and $t_{1/2}$ are at least doubled in volunteers with renal impairment, while $CL_r$ is halved. This pharmacokinetic study has shown that increasing renal dysfunction leads to increasing systemic exposure to reboxetine, particularly in severe renal insufficiency, although reboxetine was well tolerated by all volunteers. Thus, a reduction of the starting dose of reboxetine to 2 mg twice daily would be prudent in patients with renal dysfunction.

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R eboxetine is a new selective norepinephrine reuptake inhibitor (selective NRI), which has been shown in placebo- and comparator-controlled clinical trials to be both effective and well tolerated at a dose of 8 to 10 mg/day in patients with depression.[1,2]

Studies in healthy volunteers given single oral doses of reboxetine 4 mg have shown that absorption of the drug is unaffected by food and that its plasma pharmacokinetics are approximately linear.[3,4] Reboxetine has an elimination half-life of approximately 13 hours. Elimination mainly occurs via extensive hepatic metabolism,[5] principally by the CYP3A4 isoenzyme.[6] As a reflection of this, little unchanged drug (9%) is excreted in the urine. Indeed, renal clearance (0.18 l/h) is only about one-tenth of plasma clearance (1.74 l/h).[3] In normal subjects, reboxetine is 97% bound to plasma proteins.[3] Repeated administration did not result in significant accumulation: at steady state after repeated administration of reboxetine 2 mg twice daily, the accumulation factor was approximately 2.[7]

While reboxetine is a racemic mixture of the R,R(-) and S,S(+) enantiomers, the bioavailability of each enantiomer is similar,[8] and the two enantiomers have similar affinities for CYP3A4.[6] These data suggest that factors affecting the metabolism of one enantiomer will affect the other to a similar degree and indicate that it is appropriate to measure concentrations of reboxetine in plasma using a non-enantiomer-specific assay, as in the present study.

The purpose of this study was to compare the pharmacokinetics of reboxetine following administration of a single 4 mg oral dose of the drug to volunteers with varying degrees of renal impairment, as part of the clinical development of reboxetine.

## SUBJECTS AND METHODS

### Study Population and Design

Eighteen volunteers of either gender who had renal insufficiency but who were otherwise healthy gave their informed consent and were divided into three groups of equal size ($n = 6$) on the basis of target renal creatinine clearance ($CL_{Cr}$) normalized to 1.73 m$^2$—Group I, $CL_{Cr}$ 60 to 80 ml/min; Group II, $CL_{Cr}$ 30 to 50 ml/min; and Group III, $CL_{Cr}$ 10 to 20 ml/min—as outlined in Food and Drug Administration (FDA) guidelines.[9] Creatinine clearance was estimated from serum creatinine concentrations using the Cockcroft-Gault formula.[10] All subjects were given a single oral dose of reboxetine 4 mg, in tablet form, with 100 ml water after an overnight (8-10 h) fast. No food or liquid other than water was permitted until a standard meal was served, 4 hours after reboxetine administration. Reboxetine was supplied by Farmitalia Carlo Erba (now Pharmacia & Upjohn), Milan, Italy. The study was conducted at the Centre Hospitalier General de Dreux, France, and the Centre Hospitalier d'Annecy, France, after approval by the local ethics committees and in accordance with the principles of the Declaration of Helsinki (1964) and subsequent amendments.

### Study Procedures

All volunteers were closely monitored throughout the study. Vital signs and adverse events were recorded, and routine laboratory investigations were conducted on blood and urine samples. Blood samples (~10 ml) were taken before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 32, 48, 56, and 72 hours after reboxetine administration. Samples were collected into heparinized tubes, centrifuged and the plasma aliquoted in duplicate, and stored at −18°C. Urine was collected before and over periods of 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 hours after drug administration. Volume and pH were measured, and a 50 ml portion was stored at −18°C.

Reboxetine concentrations in plasma and urine samples were analyzed by non-enantiomer-specific reverse-phase HPLC with UV detection at 210 nm, as described previously.[3] Briefly, after addition of pH 9.1 0.05 M Tris buffer to 1 ml plasma, samples were extracted with diethyl ether and then reextracted from the organic phase with 5 mM $H_3PO_4$. The resulting aqueous solution was then washed with *n*-hexane prior to analysis by reverse-phase HPLC. Reboxetine, used as the standard, was provided by Farmitalia Carlo Erba, Milan, Italy. The internal standard was phenme-

trazine hydrochloride. Linearity and reproducibility were verified up to 200 ng/ml. The interday precision was calculated as the coefficient of variation (CV) of quality control samples and ranged from 7.1% to 12.1% in plasma and from 5.0% to 6.7% in urine at concentrations from 20 ng/ml to 150 ng/ml. The interday accuracy, expressed as the mean ratio of found to added amount of reboxetine, ranged from 95.0% to 102.0% in plasma and from 96.0% to 100.0% in urine. The limit of quantification was 10 ng/ml in plasma (CV = 9.5%). There was no interference from reboxetine metabolites.

The extent of binding of reboxetine to plasma proteins was determined in vitro by equilibrium dialysis of radiolabeled [$^{14}$C]-reboxetine with pretreatment plasma samples using a Dianorm Equilibrium Dialyzer, equipped with membranes having a molecular cutoff of 10,000. Briefly, 200 μl pH 7.4 buffer was spiked with [$^{14}$C]-reboxetine (Farmitalia Carlo Erba, Milan, Italy) at a nominal concentration of 100 ng/ml and dialyzed for 2 hours at 37°C against a predose plasma sample from each subject. Radioactivity was measured in each compartment dialyzed by using a Beckman liquid scintillation counter.

### Data Analysis

The following pharmacokinetic parameters were determined by noncompartmental analysis[11] using Siphar software (Simed, Créteil, France). Maximum plasma concentration ($C_{max}$) and time to $C_{max}$ ($t_{max}$) were taken from the observed data points. The area under the plasma drug concentration-time curve was calculated by the trapezoidal method from first to last measurable reboxetine concentration and extrapolated to infinity ($AUC_\infty$) using the ratio of the last measured concentration to the terminal slope. Terminal elimination half-life ($t_{1/2}$) was estimated from linear regression of the natural logarithm of the terminal slope as a function of time. The total amount of reboxetine excreted in urine (Ae) and the amount of reboxetine excreted in the urine, as a percentage of the total dose given ($Ae_{cum}$), were determined. Renal clearance ($CL_r$) was calculated from total urinary excretion divided by $AUC_\infty$, and oral clearance ($CL_{PO}$) was derived from the dose divided by $AUC_\infty$.

All values are reported as mean and standard deviation. One-way analysis of variance (ANOVA) was used to assess intergroup variations in $C_{max}$, $AUC_\infty$, $Ae_{cum}$, and $CL_r$. Analysis of $t_{max}$ was performed using the Kruskal-Wallis test. The level of significance was set at $p < 0.05$.

**Table I**  Demographic Characteristics of Volunteers with Renal Insufficiency

| | Group I (Mild Renal Impairment) | Group II (Moderate Renal Impairment) | Group III (Severe Renal Impairment) |
|---|---|---|---|
| Gender: M/F | 5/1 | 2/4 | 4/2 |
| Age (years) | | | |
| Mean ($\pm$ SD) | 54 $\pm$ 10 | 45 $\pm$ 8 | 55 $\pm$ 9 |
| Range | 41-63 | 35-55 | 46-65 |
| Weight (kg) | | | |
| Mean ($\pm$ SD) | 74 $\pm$ 13 | 66 $\pm$ 6 | 70 $\pm$ 16 |
| Range | 52-88 | 56-75 | 42-86 |
| Creatinine clearance (ml/min) | | | |
| Mean ($\pm$ SD) | 60 $\pm$ 3 | 37 $\pm$ 10 | 13 $\pm$ 4 |
| Range | 56-64 | 26-51 | 9-19 |

**Table II**  Mean Values of Pharmacokinetic Parameters

| Parameter | Group I (Mild Renal Impairment) | Group II (Moderate Renal Impairment) | Group III (Severe Renal Impairment) | Healthy Volunteers[a] |
|---|---|---|---|---|
| $C_{max}$ (ng/ml) | 151 $\pm$ 22 | 176 $\pm$ 26 | 203 $\pm$ 54 | 111 $\pm$ 28 |
| $t_{max}$ (h) | 1.83 $\pm$ 1.69 | 1.08 $\pm$ 0.97 | 1.58 $\pm$ 0.86 | 2.4 $\pm$ 1.8 |
| $AUC_{\infty}$ (ng$\cdot$h/ml) | 4140 $\pm$ 652 | 4462 $\pm$ 1507 | 5923 $\pm$ 1066 | 2106 $\pm$ 881 |
| $t_{1/2}$ (h) | 24.0 $\pm$ 5.6 | 23.0 $\pm$ 7.5 | 25.9 $\pm$ 6.9 | 12.5 $\pm$ 2.9 |
| $CL_{PO}$ (l/h) | 0.99 $\pm$ 0.15 | 0.97 $\pm$ 0.28 | 0.70 $\pm$ 0.14 | 2.21 $\pm$ 0.87 |
| $CL_r$ (l/h) | 0.09 $\pm$ 0.05 | 0.07 $\pm$ 0.03 | 0.03 $\pm$ 0.02 | 0.19 $\pm$ 0.07 |
| $Ae_{cum}$ (% of dose) | 9.15 $\pm$ 4.71 | 7.37 $\pm$ 2.83 | 3.44 $\pm$ 1.66 | 8.3 $\pm$ 2.0 |
| % unbound in plasma | 5.25 $\pm$ 0.68[b] | 4.78 $\pm$ 1.08[b] | 4.85 $\pm$ 0.37[b] | 2.93 $\pm$ 0.05[c] |

Values shown are mean $\pm$ SD.
a. Edwards et al.[3]
b. 100 ng/ml.
c. 200 ng/ml.

## RESULTS

Individual creatinine clearance values, after normalization to 1.73 $m^2$, fell into three nonoverlapping groups, each comprising six volunteers: Group I (mild renal impairment), 56 to 64 ml/min; Group II (moderate renal impairment), 26 to 51 ml/min; and Group III (severe renal impairment), 9 to 19 ml/min. These ranges differed slightly from the target ranges due to inherent day-to-day variability in creatinine clearance. Demographic details of volunteers are shown in Table I; mean age and weight were not significantly different between groups (age: $p = 0.143$; weight: $p = 0.508$).

Reboxetine was well tolerated by all volunteers in the study. Only 2 subjects reported adverse events: mild nausea (of doubtful relationship to treatment) and skin rash (possibly related to treatment), and there were no changes in vital signs or routine laboratory parameters that could be ascribed to the administration of reboxetine.

### Plasma Pharmacokinetics

Mean values of pharmacokinetic parameters are presented in Table II. $AUC_{\infty}$ increased significantly ($p < 0.05$) as renal function declined. Mean $AUC_{\infty}$ ranged from 4140 $\pm$ 652 ng$\cdot$h/ml in Group I, 4462 $\pm$ 1507 ng$\cdot$h/ml in Group II, and 5923 $\pm$ 1066 ng$\cdot$h/ml in Group III. Individual group comparisons showed significant differences between Groups I and III ($p < 0.05$) and between Groups II and III ($p < 0.05$). $C_{max}$ in-
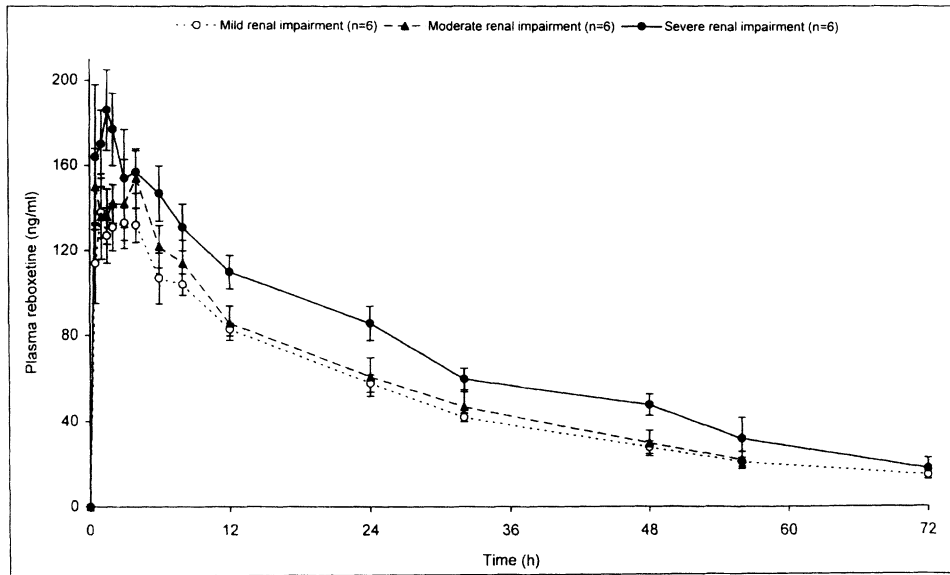
Figure 1. Mean plasma concentrations of reboxetine after oral administration of a single 4 mg dose to volunteers with renal impairment.

creased slightly with increasing renal insufficiency, from 151 ng/ml (Group I) to 203 ng/ml (Group III). Although the increases in $C_{max}$ between groups were not statistically significant, $C_{max}$ was significantly correlated with creatinine clearance when all subjects were considered individually ($p < 0.05$). $t_{max}$ and $t_{1/2}$ were not significantly affected by changes in creatinine clearance (Group I: $t_{1/2} = 24.0$ h; Group III: $t_{1/2} = 25.9$ h). Results of the plasma protein-binding determina-

tion are listed in Table II: free fractions (%) did not differ significantly among groups.

## Urinary Excretion

$CL_r$ and the total urinary excretion of unchanged reboxetine decreased significantly ($p < 0.05$) with increasing renal insufficiency. $CL_r$ decreased from 0.09 ± 0.05 l/h for Group I to 0.07 ± 0.03 l/h for Group II and
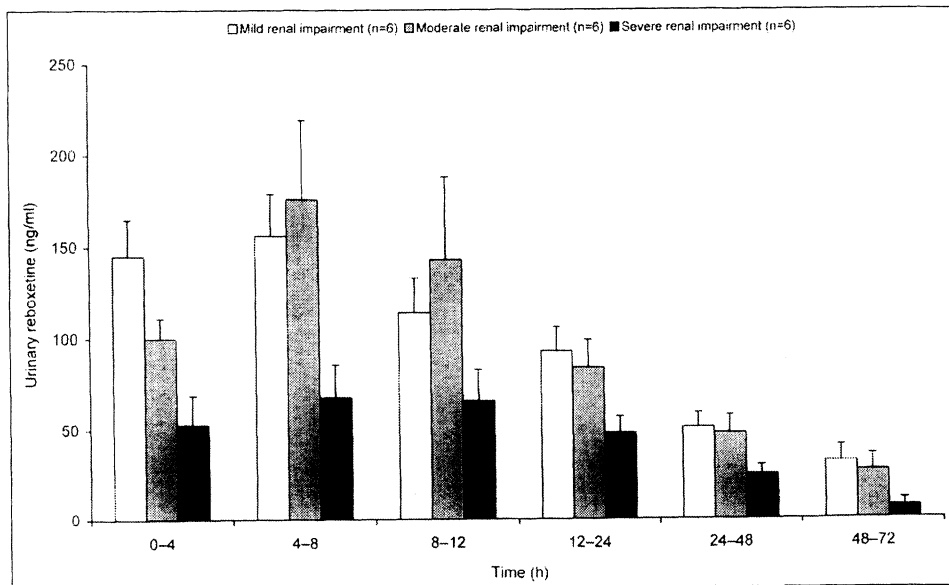


Figure 2. Mean urinary concentrations of reboxetine after oral administration of a single 4 mg dose to volunteers with renal impairment.

$0.03 \pm 0.02$ l/h for Group III. $Ae_{cum}$ decreased from $9.15\% \pm 4.71\%$ for Group I to $7.37\% \pm 2.83\%$ for Group II and $3.44\% \pm 1.66\%$ for Group III. Comparisons between groups showed a significant difference ($p < 0.01$) between Groups I and III for both parameters.

## DISCUSSION

Increasing renal dysfunction was associated with an increase in systemic exposure to reboxetine and a reduction in the renal clearance of the drug. These values are markedly different from those reported in young, healthy volunteers with normal renal function by Edwards et al[3] in an earlier study using the same assay methodology. Compared with the data from young healthy volunteers, $AUC_\infty$ and $t_{1/2}$ are doubled in the subjects with mild renal impairment (mean $CL_{Cr} = 60$ ml/min), and $CL_r$ is halved (Table II). In subjects with severe renal impairment (mean $CL_{Cr} = 13$ ml/min), the differences are correspondingly greater. The greater age of the volunteers in the present study (35-65 years vs. 21-39 years in the study by Edwards et al[3]) is unlikely to account for all the observed differences in pharmacokinetic parameters. However, despite the increased exposure, a single dose of reboxetine was still well tolerated in these volunteers with renal failure. Furthermore, it has proven to be well tolerated in studies of populations likely to have some degree of renal impairment, such as the elderly.[2]

As less than 10% of the reboxetine dose is excreted unchanged in the urine, renal dysfunction should have had minimal effects on reboxetine clearance and plasma concentrations. Drugs that are predominantly metabolized may have their clearance affected by renal dysfunction, either through effects on plasma protein binding or direct effects on metabolism.[12,13] The effect of renal dysfunction is well described,[14] but the effect of renal dysfunction on metabolism is less clear.[14,15] Due to the lack of a control group in this study and of direct comparisons of serum unbound fractions to a control group, the mechanism for the apparent effect of renal dysfunction on reboxetine pharmacokinetics cannot be determined.

The pharmacokinetics of some other antidepressants is also altered in renal insufficiency. Selective serotonin reuptake inhibitors (SSRIs) are not excreted by the kidneys to a great extent, although in renal dysfunction, plasma concentrations of paroxetine are increased,[16] and a lower dose is recommended. Caution is also advised for other SSRIs in patients with renal insufficiency.[17]

The dose of reboxetine for the treatment of otherwise healthy patients with depression is typically 8 to 10 mg/day.[1,2] The present pharmacokinetic study has shown that increasing renal dysfunction leads to increasing exposure to reboxetine, although reboxetine remains well tolerated. In the light of the doubling of AUC and the halving of renal clearance, a reduction of the starting dose of reboxetine to 4 mg/day, in divided doses (2 mg twice daily), would appear to be appropriate in patients with renal insufficiency.

In conclusion, we have shown that increasing renal impairment leads to a greater exposure to reboxetine; thus, a reduction of the starting dose to 2 mg twice daily would be prudent in renal dysfunction.

## REFERENCES

1. Montgomery SA: Reboxetine: additional benefits to the depressed patient. *J Psychopharmacol* 1997;11(4, Suppl.):S9-S15.

2. Mucci M: Reboxetine: a review of antidepressant tolerability. *J Psychopharmacol* 1997;11(4, Suppl.):S33-S37.

3. Edwards DMF, Pellizzoni C, Breuel HP, Berardi A, Castelli MG, Frigerio E, et al: Pharmacokinetics of reboxetine in healthy volunteers: single oral doses, linearity and plasma protein binding. *Biopharm Drug Dispos* 1995;16:443-460.

4. Pellizzoni C, Strolin Benedetti M, Poggesi I, Frigerio E, Toon S, Langley SJ: Pharmacokinetics of reboxetine in healthy volunteers: relative bioavailability and food effect. *Pharmacol Res* 1995; 31(Suppl.):41.

5. Dostert P, Strolin Benedetti M, Poggesi I: Review of the pharmacokinetics and metabolism of reboxetine, a selective noradrenaline reuptake inhibitor. *Eur Neuropsychopharmacol* 1997;7(Suppl. 1): S23-S35.

6. Wienkers LC, Allievi C, Hauer MJ, Wynalda MA: Cytochrome P-450-mediated metabolism of the individual enantiomers of the antidepressant agent reboxetine in human liver microsomes. *Drug Metab Dispos* 1999;27:1334-1340.

7. Pellizzoni C, Poggesi I, Jørgensen NP, Edwards DMF, Paus E, Strolin Benedetti M: Pharmacokinetics of reboxetine in healthy volunteers: single against repeated oral doses and lack of enzymatic alterations. *Biopharm Drug Dispos* 1996;17:623-633.

8. Fleishaker JC, Mucci M, Pellizzoni C, Poggesi I: Absolute bioavailability of reboxetine enantiomers and effect of gender on reboxetine enantiomers. *Biopharm Drug Dispos* 1999;20:53-57.

9. U.S. Department of Health and Human Services: *Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling.* Rockville, MD: Food and Drug Administration, Center for Drug Evaluation and Research, 1998.

10. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.

11. Gibaldi M, Perrier D: *Pharmacokinetics*, 2nd ed. New York: Marcel Dekker, 1982.

12. Al-Habet S, Ibrahim S, Baweja R, Venitz J: Effect of renal disease on the disposition of highly metabolized oral drugs (abstract). *PharmSci* 1998;1(Suppl.):S-465.

13. Yuan R, Venitz J: Disposition of a highly metabolized drug in renally impaired patients (abstract). *PharmSci* 1998;1(Suppl.): S-467.

**14.** Lam YWF, Banerji S, Hatfield C, Talbert RL: Principles of drug administration in renal insufficiency. *Clin Pharmacokinet* 1997;32:30-57.

**15.** Touchette MA, Slaughter RL: The effect of renal failure on hepatic drug clearance. *Ann Pharmacotherapy* 1991;25:1214-1223.

**16.** van Harten J: Clinical pharmacokinetics of selective serotonin reuptake inhibitors. *Clin Pharmacokinet* 1993;24:203-220.

**17.** Leonard BE: SSRI differentiation: pharmacology and pharmacokinetics. *Hum Psychopharmacol* 1995;10:S149-S158.