Effect of Renal Insufficiency on the Pharmacokinetics of Avanafil, a New, Potent, Selective PDE-5 Inhibitor, in Male Subjects

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BACKGROUND

Erectile dysfunction (ED) is generally defined as a condition characterized by the inability to achieve or maintain firm erections sufficient for sexual intercourse. Although not life-threatening, ED causes considerable suffering to a large number of men and, therefore, represents a significant health concern. It is one of the inevitabilities of the aging process, and is also frequently found in men with certain conditions such as hypertension, smoking, diabetes, hyperlipidemia, cardiovascular disease, or from injuries such as spinal cord damage.

Currently, first-line treatment for men with varied causes of ED consists of oral therapy with a class of compounds known as phosphodiesterase type 5 (PDE-5) inhibitors, which have been shown to help restore penile blood flow and erections in response to sexual stimulation.

Avanafil, a potent and highly specific PDE-5 inhibitor (IC_{50} value for PDE-5 = 0.0043 – 0.0052 µM), is being evaluated for the treatment of ED. Results of clinical studies conducted to date indicate the potential of avanafil to provide rapid onset of action, improvement in erectile function comparable to other marketed PDE-5 inhibitors, rapid elimination, the potential for twice-daily dosing if needed, greater specificity for the PDE-5 isoenzyme, and the possibility of reduced risk of nitrate interaction.

Patients with ED may have some degree of renal impairment, as a consequence of age and/or co-morbid illness. Although contribution of renal clearance to the total clearance of avanafil is not significant, renal impairment may affect the hepatic metabolism and the pharmacokinetics (PK) of avanafil.

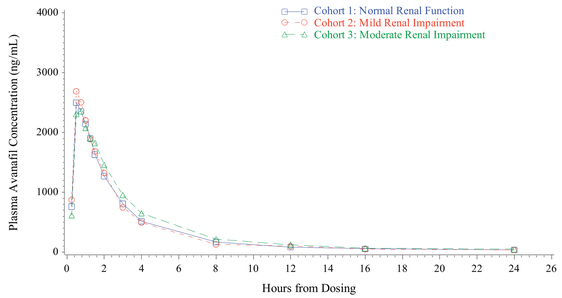
OBJECTIVE

The primary objective of this study was to compare the PK of avanafil in male subjects with mild and moderate renal impairment to those with normal renal function.

METHODS

- This was an open-label, non-randomized, 3-parallel-cohort, matched-control study.
- Data from 24 subjects, assigned according to renal function (N = 8 per cohort) were included in the analysis.
- There were 3 cohorts in this study:
  - Cohort 1: Normal renal function (CLcr ≥ 80 mL/min)
  - Cohort 2: Mild renal impairment (CLcr ≥ 50 to < 80 mL/min)
  - Cohort 3: Moderate renal impairment (CLcr ≥ 30 to < 50 mL/min)
- Subjects in each of the 3 cohorts received a single 200 mg oral dose of avanafil following an overnight fast.
- Serial blood samples drawn from predose through 24 hours postdose were quantified for plasma avanafil using a validated LC-MS/MS method.
- Noncompartmental analysis was performed on the plasma concentrations versus time profiles to derive the PK parameters of interest (maximum plasma concentration [C_{max}] , area under the curve from time 0 to the last measurable concentration [AUC_{0-t}], area under the curve from time 0 to infinity [$AUC_{0-\infty}$], time to reach C_{max} [t_{max}], apparent elimination rate constant [k_{el}], apparent elimination half-life [$t_{1/2}$], apparent total body clearance [CL/F], and apparent volume of distribution [V/F]) using WinNonlin® Professional (Version 5.0.1, Pharsight Corporation, Cary, North Carolina).
- Analysis of variance was performed on the ln-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ using the SAS® Proc Mixed procedure. Nonparametric comparisons of t_{max} and $t_{1/2}$ were conducted using the Wilcoxon Rank Sum Test (SAS® Version 9.1.3, SAS Institute, Cary, North Carolina).
- The median and 95% confidence intervals (CIs) of the differences between cohorts for t_{max} and $t_{1/2}$ values were constructed using Hodges-Lehmann estimate. Significant differences in t_{max} and $t_{1/2}$ values for the treatment comparisons were concluded if the resulting p-value was < 0.05.

Figure 1 Geometric Mean Plasma Avanafil Concentrations Versus Time in Subjects With Normal Renal Function (Cohort 1), Mild Renal Impairment (Cohort 2), or Moderate Renal Impairment (Cohort 3) - (Linear Scale)



RESULTS

- The geometric mean plasma avanafil concentrations in subjects with normal renal function (Cohort 1), mild renal impairment (Cohort 2), and moderate renal impairment (Cohort 3) are presented in Figure 1.
- Plasma avanafil concentrations were similar in subjects with normal renal function (Cohort 1), mild renal impairment (Cohort 2), and moderate renal impairment (Cohort 3).
- The summaries of plasma avanafil PK parameters following the administration of a single oral dose of 200 mg avanafil in subjects with normal renal function, mild renal impairment, and moderate renal impairment are presented in Table 1.
- Peak and total exposure to avanafil, as measured by C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, were similar between subjects with mild or moderate renal impairment and subjects with normal renal function.
- CL/F, V/F, t_{max}, and $t_{1/2}$ values of avanafil were comparable among the subjects with normal renal function and subjects with mild or moderate renal impairment.
- The statistical comparisons of plasma avanafil PK parameters between subjects with mild renal impairment or moderate renal impairment versus normal renal function are summarized in Table 2.
- Based on geometric mean ratios, peak and total exposure to avanafil between subjects with mild renal impairment and normal renal function were similar between the two cohorts (the differences ranged from approximately 4 to 12%).
- Based on geometric mean ratios, peak and total exposure to avanafil between subjects with moderate renal impairment and normal renal function were comparable between the two cohorts (the differences ranged from approximately 0.04 to 19%).
- The nonparametric statistical comparison of plasma avanafil t_{max} and $t_{1/2}$ between subjects with mild or moderate renal impairment and normal renal function showed that the p-values were > 0.05.

CONCLUSIONS

Peak and total exposure to plasma avanafil was similar between the subjects with mild or moderate renal impairment and those with normal renal function. The t_{max} and $t_{1/2}$ values were not affected by renal impairment. Because no statistically meaningful differences in the PK of avanafil were observed among subjects with different degrees renal function, avanafil dose adjustments are not recommended for patients with mild or moderate renal impairment.

Table 1 Arithmetic and Geometric Mean Plasma Pharmacokinetic Parameters for Avanafil Following a Single 200 mg Dose of Avanafil

	Normal Renal Function (Cohort 1)		Mild Renal Impairment (Cohort 2)		Moderate Renal Impairment (Cohort 3)	
Pharmacokinetic Parameters	**Mean ± SD (N)**	**Geometric Mean**	**Mean ± SD (N)**	**Geometric Mean**	**Mean ± SD (N)**	**Geometric Mean**
C_{max} (ng/mL)[a]	2850 ± 1150 (8)	2650	2860 ± 859 (8)	2750	2880 ± 1110 (8)	2650
AUC_{0-t} (ng*hr/mL)[a]	8180 ± 2020 (8)	7950	7920 ± 2910 (8)	7380	9540 ± 3570 (8)	8960
$AUC_{0-\infty}$ (ng*hr/mL)[a]	8330 ± 1010 (4)	8290	7850 ± 3040 (7)	7300	10100 ± 2380 (5)	9850
t_{max} (hr)[b]	0.63 (0.50, 1.0) (8)	.	0.50 (0.50, 0.75) (8)	.	0.75 (0.50, 1.5) (8)	.
$t_{1/2}$ (hr)[a]	6.6 ± 3.7 (4)	.	5.4 ± 3.4 (7)	.	5.5 ± 1.7 (5)	.
k_{el} (1/hr)[a]	0.131 ± 0.0683 (4)	.	0.174 ± 0.112 (7)	.	0.140 ± 0.0594 (5)	.
CL/F (L/hr)[a]	24.3 ± 2.96 (4)	.	29.7 ± 13.2 (7)	.	20.8 ± 5.11 (5)	.
V/F (L)[a]	228 ± 118 (4)	.	201 ± 90.9 (7)	.	168 ± 79.3 (5)	.

Cohort 1: Normal renal function (CLcr ≥ 80 mL/min), reference
Cohort 2: Mild renal impairment (CLcr ≥ 50 to < 80 mL/min), test
Cohort 3: Moderate renal impairment (CLcr ≥ 30 to < 50 mL/min), test

[a] C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, k_{el}, CL/F, and V/F values are presented with three significant figures. $t_{1/2}$ values are presented with two significant figures.
[b] t_{max} values are presented as median (minimum, maximum) and are presented with two significant figures.
, = Value not calculated.
SD = standard deviation

Table 2 Statistical Comparisons of Plasma Avanafil Pharmacokinetic Parameters: Mild Renal Impairment (Cohort 2) and Moderate Renal Impairment (Cohort 3) Versus Normal Renal Function (Cohort 1)

Pharmacokinetic Parameter	Geometric LS Means (N)			Cohort 2 vs. Cohort 1		Cohort 3 vs. Cohort 1	
	Cohort 1	**Cohort 2**	**Cohort 3**	**% Mean Ratio**	**90% CI [a]**	**% Mean Ratio**	**90% CI[a]**
C_{max} (ng/mL)	2650 (8)	2750 (8)	2650 (8)	104.02	73.34, 147.53	99.96	70.48, 141.78
AUC_{0-t} (ng*hr/mL)	7950 (8)	7380 (8)	8960 (8)	92.79	67.93, 126.74	112.72	82.53, 153.97
$AUC_{0-\infty}$ (ng*hr/mL)	8290 (4)	7300 (7)	9850 (5)	88.09	61.43, 126.31	118.93	80.86, 174.92
	Treatment Median (N)			**p-value**	**95% CI**	**p-value**	**95% CI**
t_{max} (hr)	0.63 (8)	0.50 (8)	0.75 (8)	0.2954	-0.25 , 0.00	0.3094	0.00 , 0.25
$t_{1/2}$ (hr)	5.9 (4)	4.7 (7)	6.0 (5)	0.7768	-6.75 , 2.97	0.7133	-6.47 , 3.35

Cohort 1: Normal renal function (CLcr ≥ 80 mL/min), reference
Cohort 2: Mild renal impairment (CLcr ≥ 50 to < 80 mL/min), test
Cohort 3: Moderate renal impairment (CLcr ≥ 30 to < 50 mL/min), test

[a] The 90% CIs of the mean ratios for these comparisons were not expected to fall entirely within the 80% to 125% range, due to the small N.