Effect of Hepatic 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 PDE5 isoenzyme, and the possibility of reduced risk of nitrate interaction. Since the formation of the main metabolites of avanafil is catalyzed by CYP3A4, it is possible that the pharmacokinetics (PK) of avanafil may be modified by impaired liver function, partly due to reduction in the effective liver blood flow and partly due to a reduced hepato-cellular function.

OBJECTIVE

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

METHODS

- This was an open-label, non-randomized, 3-parallel-cohort, matched-control study.
- Data from 24 subjects, assigned according to hepatic function (N = 8 per cohort) were included in the analysis.
- There were 3 cohorts in this study:
  - Cohort 1: Normal hepatic function
  - Cohort 2: Mild hepatic impairment (Child-Pugh Class [Score] = A [5 – 6])
  - Cohort 3: Moderate hepatic impairment (Child-Pugh Class [Score] = B [7 – 9])
- 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 measureable 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

RESULTS

- The geometric mean plasma avanafil concentrations in subjects with normal hepatic function (Cohort 1), mild hepatic impairment (Cohort 2), and moderate hepatic impairment (Cohort 3) are presented in Figure 1.
- While plasma avanafil concentrations in subjects with normal hepatic function (Cohort 1) and mild hepatic impairment (Cohort 2) were similar, they were lower in subjects with moderate hepatic impairment (Cohort 3).
- The summaries of plasma avanafil PK parameters following the administration of a single 200 mg dose of avanafil in subjects with normal hepatic function, mild hepatic impairment, and moderate hepatic 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 hepatic impairment and normal hepatic function.
- While total exposure to avanafil, as measured by $AUC_{0-\infty}$, was comparable between subjects with moderate hepatic impairment and those with normal hepatic function, peak exposure, as measured by C_{max}, for subjects with moderate hepatic impairment was about half of that of subjects with normal hepatic function.
- The CL/F, V/F, $t_{1/2}$, and t_{max} values of avanafil were either similar or comparable among the subjects with normal hepatic function and subjects with mild or moderate hepatic impairment.
- The statistical comparisons of plasma avanafil PK parameters between subjects with mild hepatic impairment or moderate hepatic impairment versus normal hepatic function are summarized in Table 2.
- Based on geometric mean ratios, peak and total exposure to avanafil, as measured by C_{max} and AUC_{0-t}, were similar between subjects with mild hepatic impairment and normal hepatic function (the differences ranged from 0.10 to about 5%).
- Based on geometric mean ratios, peak and total exposure to avanafil, as measured by C_{max} and AUC_{0-t}, were 19 to 57% lower in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. The geometric mean $AUC_{0-\infty}$ values were similar between the two cohorts.
- The nonparametric statistical comparisons of plasma avanafil t_{max} and $t_{1/2}$ between subjects with mild or moderate hepatic impairment and normal hepatic function showed that the p-values were > 0.05. This suggests that the differences between the median t_{max} and $t_{1/2}$ values in subjects with mild or moderate hepatic impairment versus normal hepatic function were not significantly different.

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

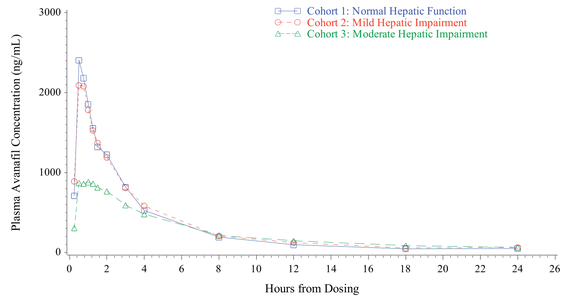

Table 1 Arithmetic and Geometric Mean Plasma Pharmacokinetic Parameters for Avanafil Following a Single 200 mg Dose of Avanafil

	Normal Hepatic Function (Cohort 1)		Mild Hepatic Impairment (Cohort 2)		Moderate Hepatic 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]	2610 ± 796 (8)	2480	2540 ± 886 (8)	2390	1270 ± 739 (8)	1060
AUC_{0-t} (ng*hr/mL)[a]	7960 ± 2160 (8)	7730	8520 ± 2920 (8)	8120	7310 ± 4210 (8)	6250
$AUC_{0-\infty}$ (ng*hr/mL)[a]	9260 ± 2210 (6)	9060	9610 ± 3660 (6)	9050	10300 ± 4490 (5)	9290
t_{max} (hr)[b]	0.50 (0.50, 1.0) (8)	.	0.50 (0.50, 2.1) (8)	.	1.1 (0.50, 3.0) (8)	.
$t_{1/2}$ (hr)[a]	7.5 ± 2.8 (6)	.	6.9 ± 1.8 (6)	.	6.1 ± 1.9 (5)	.
K_{el} (1/hr)[a]	0.103 ± 0.0337 (6)	.	0.108 ± 0.0333 (6)	.	0.124 ± 0.0412 (5)	.
CL/F (L/hr)[a]	22.5 ± 4.84 (6)	.	23.4 ± 8.61 (6)	.	24.5 ± 15.6 (5)	.
V/F (L)[a]	240 ± 93.5 (6)	.	227 ± 94.6 (6)	.	218 ± 173 (5)	.

Cohort 1: Normal hepatic function, reference
Cohort 2: Mild hepatic impairment (Child-Pugh Class [Score] A [5 – 6]), test
Cohort 3: Moderate hepatic impairment (Child-Pugh Class [Score] B [7 – 9]), 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 calcualted
SD = standard deviation

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

	Geometric LS Means (N)			Cohort 2 vs. Cohort 1		Cohort 3 vs. Cohort 1	
Pharmacokinetic Parameter	**Cohort 1**	**Cohort 2**	**Cohort 3**	**% Mean Ratio**	**90% CI[a]**	**% Mean Ratio**	**90% CI[a]**
C_{max} (ng/mL)	2480 (8)	2390 (8)	1060 (8)	96.05	62.61, 147.34	42.68	27.82, 65.47
AUC_{0-t} (ng*hr/mL)	7730 (8)	8120 (8)	6250 (8)	105.15	72.96, 151.55	80.92	56.14, 116.62
$AUC_{0-\infty}$ (ng*hr/mL)	9060 (6)	9050 (6)	9290 (5)	99.90	67.08, 148.78	102.53	67.52, 155.69
	Treatment Median (N)			**p-value**	**95% CI**	**p-value**	**95% CI**
t_{max} (hr)	0.50 (8)	0.50 (8)	1.1(8)	0.5227	0.00, 1.25	0.0636	0.00, 1.52
$t_{1/2}$ (hr)	6.4 (6)	6.9 (6)	7.1 (5)	1.0000	-4.32, 2.50	0.6481	-5.99, 2.43

Cohort 1: Normal hepatic function, reference
Cohort 2: Mild hepatic impairment (Child-Pugh Class [Score] A [5 – 6]), test
Cohort 3: Moderate hepatic impairment (Child-Pugh Class [Score] B [7 – 9]), 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.

CONCLUSIONS

The peak and total exposures to plasma avanafil were similar between the subjects with mild hepatic impairment and those with normal hepatic function. The peak and total exposure were lower in subjects with moderate hepatic impairment compared to subjects with normal hepatic function; however, the geometric mean $AUC_{0-\infty}$ values were similar between the two cohorts. Moreover, t_{max} and $t_{1/2}$ values were not affected by hepatic impairment. Since no statistically meaningful differences in the PK of avanafil were observed among subjects with different degrees of hepatic function, avanafil dose adjustments are not recommended for patients with mild or moderate hepatic impairment.