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

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BACKGROUND
Enzyme 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 women, and represents a significant health concern. It is one of the inevitable consequences of the aging process, and is also frequently found in men with certain conditions such as hypertension, diabetes, hypothyroidism, cardiovascular disease, or from injuries such as spinal cord damage. Currently, first-line treatment for men with various 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 erectile function in response to sexual stimulation.

Avanafil, a potent and highly specific PDE-5 inhibitor, 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 compared to other marketed PDE-5 inhibitors, equal or superior sustained activity compared to tadalafil, and faster tmax when needed, greater specificity for the PDE5 isoenzyme, and the possibility of reduced risk of drug-drug interactions. Since the formation of free radicals is catalyzed by CYP3A4, it is possible that the pharmacokinetics (PK) of avanafil may be meaningful differences in the PK of avanafil were observed among subjects with different hepatic function.

METHODS
This was an open-label, non-randomized, 3-period, crossover, 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 dose of avanafil following an overnight fast. Serum blood samples drawn from prestudy to 24 hours postdose were quantified for plasma avanafil using a validated LC-MS/MS method. 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.

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 Cmax, AUC0-t, and AUC0-∞ were similar across the three subjects with moderate hepatic impairment and those with normal hepatic function, peak exposure, as measured by Cmax, for subjects with moderate hepatic impairment was about half that of subjects with normal hepatic function.
- The CL/F, V/F, t1/2, and tmax 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 comparison 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 Cmax and AUC0-t, were similar across subjects with mild hepatic impairment compared to subjects with normal hepatic impairment. The geometric mean AUC0-∞ values were similar between the two cohorts.
- The nonparametric statistical comparison of plasma avanafil tmax and t1/2 values between subjects with mild or moderate hepatic impairment and normal hepatic function showed that the p-value of 0.05. This suggests that the differences between the median tmax and t1/2 with mild or moderate hepatic impairment and those with normal hepatic function were not significantly different.

CONCLUSIONS
The peak and total exposure 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 AUC0-∞ values were similar between the two cohorts. Moreover, tmax and t1/2 values were not affected by hepatic impairment. Since no statistically meaningful differences were observed among subjects with different degrees of hepatic function, avanafil dose adjustments are not recommended for patients with mild or moderate hepatic impairment.