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THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SOLIFENACIN SUCCINATE IN PATIENTS WITH MILD, MODERATE, AND SEVERE RENAL DISEASE

Aims of Study

Overactive bladder (OAB) is characterized by symptoms of urinary frequency and urgency, with or without incontinence, in the absence of local pathology that would account for these symptoms. OAB affects 50 to 100 million individuals worldwide and has a significant negative impact on quality of life. Solifenacin succinate (Vesicare®; YM905) is a new, bladder-selective, muscarinic receptor antagonist with significant potential to ameliorate OAB symptoms. The prevalence of OAB increases with age, as does the prevalence of renal insufficiency. Solifenacin is primarily cleared through hepatic metabolism, but urinary excretion does play a minor role in clearance from the body. Given that solifenacin will likely be used in patients with impaired renal function, we designed a study to evaluate the safety, tolerability, and pharmacokinetics of solifenacin in the setting of mild, moderate, and severe renal disease.

Methods

This study was a multisite, open label study of 24 subjects (6 patients with mild, 6 with moderate, and 6 with severe renal disease, as well as 6 weight- and age-matched healthy volunteers). The study population (predominantly white and African-American) included 16 males and 8 females, ranging in age from 41 to 80 years. Subjects received a single oral dose of 10 mg solifenacin, followed by serial assessments over a 336-hour period. Serial physical examinations, electrocardiograms (ECGs), analysis of solifenacin blood levels, and general well-being assessments were performed. An analysis of variance (ANOVA) was carried out to assess the effect of renal impairment; the 90% confidence intervals (CI) were examined for the ratio of the test group mean relative to the reference group mean (equivalent to Schuirmann's two 1-sided tests) at the 0.05 level of significance. In addition, linear regression analyses were performed to study the relationship between various pharmacokinetic (PK) parameters and creatinine clearance.

Results

No serious adverse events occurred during the study, and all subjects completed the study. The majority of adverse events were mild, with only 3 distinct events determined to be related to the study drug (muscle cramps, dry mouth, and pitting edema). Minor fluctuations occurred in laboratory findings that were consistent with the disease state or preexisting illness of some subjects. There were no clinically relevant or treatment-related changes in vital signs, ECG, or physical examinations. The PK results for solifenacin indicate a higher exposure for renally impaired patients in general (Table). Terminal phase half-life ($t_{1/2}$) appeared to increase for renally impaired patients relative to healthy subjects. Overall, the statistical comparison results indicate a significant effect of renal impairment on the PK of total solifenacin (90% CI, for the most part, fell outside the established ranges for the PK parameters evaluated). Linear regression analysis examining the relationship between creatinine clearance and PK parameters showed no statistically significant relationship for C_{max}, but other parameters, including $AUC_{0\text{-}inf}$, did display significance.

Table. Pharmacokinetic parameters

Renal status		**C_{max} (ng/mL)**	**t_{max*} (h)**	**$AUC_{0\text{-}inf}$ (ng.h/mL)**	**$t_{1/2}$ (h)**
Healthy	**Mean**	15.7	6.00	1190	68.2
	SD	*3.38*	*5, 8*	*402.8*	*27.22*
Mild impairment	**Mean**	17.5	5.50	1784	89.1
	SD	*3.29*	*3, 8*	*791.9*	*34.53*
Moderate impairment	**Mean**	15.2	5.00	1559	90.6
	SD	*4.41*	*3, 6*	*554.7*	*27.26*
Severe impairment	**Mean**	20.6	3.50	2530	111
	SD	*10.51*	*2, 8*	*669.8*	*38.3*

*Median (min, max) shown for t_{max}

Conclusions

The results of this study provide evidence for a higher exposure of total solifenacin in patients with renal impairment, compared to healthy controls. However, no significant safety or tolerance concerns were revealed in this study.