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THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SOLIFENACIN SUCCINATE IN PATIENTS WITH HEPATIC IMPAIRMENT

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. Solifenacin is primarily metabolized by cytochrome P450 isoenzyme 3A4 (CYP3A4) in the liver; drugs so metabolized may have altered pharmacokinetics in patients with hepatic insufficiency. As it is likely that some patients with OAB will have concomitant liver disease, we studied the safety, tolerability, and pharmacokinetics of solifenacin succinate in patients with liver function impairment.

Methods

This study was a single-center, open-label, parallel study of 8 patients with moderate hepatic impairment (7 to 9 on the Child-Pugh classification) and 8 gender-, age-, and weight-matched healthy volunteers. All patients (3 females, 5 males; aged 22 to 66 years) and healthy volunteers (3 females, 5 males; aged 25 to 68 years) were Caucasians. Each enrolled subject received a single dose of 10 mg solifenacin on day 1, and serial plasma concentrations were measured. Solifenacin levels in blood were sampled in patients with hepatic impairment at multiple time points from 0 to 168 hours and from 312 to 336 hours. Healthy subjects were sampled from 0 to 168 hours. Safety assessments, including vital signs, adverse events, 12-lead electrocardiograms (ECG), and safety laboratory tests were performed. Healthy subjects and impaired patients were examined at 1 week poststudy. The primary pharmacokinetic parameters were solifenacin $AUC_{0\text{-}inf}$ and C_{max} for solifenacin. The log-transformed $AUC_{0\text{-}inf}$ and C_{max} values of solifenacin were subjected to analysis of variance.

Results

In patients with moderate hepatic impairment, an increase in solifenacin $AUC_{0\text{-}inf}$ by 60% was observed compared to healthy subjects, with a confidence interval (CI) of 1.05 to 2.43 (Table). The mean C_{max} showed no significant difference between healthy and impaired individuals (point estimate 0.99; CI: 0.70 to 1.40). Mean $t_{1/2}$ was twice as high in patients than in healthy individuals. There were no serious adverse events. Analysis of vital signs, ECG, and safety laboratory parameters revealed no safety issues.

	Solifenacin			
	t_{max} (h)	**C_{max} (ng/mL)**	**$AUC_{0\text{-}inf}$ (ng.h/mL)**	**$t_{1/2}$ (h)**
Healthy subjects	5.96	11.0	749	49.9
Hepatic impairment	4.77	10.3	1042	106

Conclusions

Moderate hepatic impairment influenced the pharmacokinetics of 10 mg of orally administered solifenacin succinate; however, this dose was well tolerated in patients with this degree of hepatic impairment. Although the observed differences were not considerable, it is advisable to treat patients with hepatic impairment with caution. Therefore, it is recommended that patients with moderate hepatic impairment receive not more than 5 mg solifenacin succinate once daily.