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Randomized, controlled pilot trial of solifenacin succinate for overactive bladder in Parkinson's disease

Theresa A. Zesiewicz [a, *], Marian Evatt [b], Camille P. Vaughan [c], Israt Jahan [a], Carlos Singer [d], Raul Ordorica [e], Jason L. Salemi [f], Jessica D. Shaw [a], Kelly L. Sullivan [g], Non-Motor Working Group of the Parkinson Study Group (PSG)

[a] Department of Neurology, University of South Florida, Tampa, FL, USA
[b] Department of Neurology, Atlanta VA Medical Center and Emory University, Atlanta, GA, USA
[c] Department of Medicine, Atlanta VA Medical Center and Emory University, Atlanta, GA, USA
[d] Department of Neurology, University of Miami, Miami, FL, USA
[e] Department of Urology, University of South Florida, Tampa, FL, USA
[f] Department of Family and Community Medicine, Baylor College of Medicine, Houston, TX, USA
[g] Department of Epidemiology, Jiann-Ping Hsu College of Public Health, Georgia Southern University, Statesboro, GA, USA

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ABSTRACT

Objective: To evaluate the efficacy of solifenacin succinate in Parkinson's disease (PD) patients suffering from overactive bladder (OAB).
Background: Urinary dysfunction is a commonly encountered non-motor feature in PD that significantly impacts patient quality of life.
Design/methods: This was a double-blind, randomized, placebo-controlled, 3-site study with an open label extension phase to determine the efficacy of solifenacin succinate in idiopathic PD patients with OAB. Patients were randomized to receive solifenacin succinate 5–10 mg daily or placebo for 12 weeks followed by an 8-week open label extension. The primary outcome measure was the change in the mean number of micturitions per 24 h period. Secondary outcome measures included the change in the mean number of urinary incontinence episodes and the mean number of nocturia episodes.
Results: Twenty-three patients were randomized in the study. There was no significant improvement in the primary outcome measure in the double-blind phase, but there was an improvement in the number of micturitions per 24 h period in the solifenacin succinate group compared to placebo at a mean dose of 6 mg/day ($p = 0.01$). In the open label phase, the mean number of urinary incontinence episodes per 24 h period decreased ($p = 0.03$), as did the number of nocturia episodes per 24 h period ($p = 0.01$). Adverse events included constipation and xerostomia, which resolved after treatment was discontinued.
Conclusions: In this pilot trial, solifenacin succinate treatment led to an improvement in urinary incontinence, despite persistence in other OAB symptoms.

1. Introduction

Parkinson's disease (PD) is a degenerative disorder caused by a progressive loss of dopaminergic neurons in the substantia nigra, and is characterized by both motor and non-motor symptoms, including urinary dysfunction. Urinary incontinence, frequency, and overactive bladder (OAB) symptoms contribute to decreased quality of life for patients with PD [1,2]. Urinary dysfunction occurs more commonly in patients with PD than healthy control populations and affects approximately 30–40% of PD patients based on validated questionnaires [3–5]. Despite the high prevalence of urinary symptoms in the PD population, there are no published double-blind, randomized, placebo controlled clinical trials that have evaluated treatments for OAB in this population. The identification of effective treatments for OAB is an unmet need in PD patients.

While the etiology of urinary dysfunction in PD is complex, the deposition of alpha-synuclein in brain structures may contribute to

* Corresponding author. University of South Florida, Department of Neurology, 12901 Bruce B. Downs Blvd, MDC Box 55, Tampa, Florida 33612, USA. Tel.: +1 813 974 5909.
E-mail address: tzesiewi@health.usf.edu (T.A. Zesiewicz).

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impaired cortical integration of sensory input from the bladder. The loss of appropriate basal ganglia output reduces inhibition of the micturition reflex, causing detrusor muscle hyperactivity [6]. Acetylcholine binding of the M3and M2 muscarinic receptor subtypes found in the bladder also leads to detrusor contraction [7].

Solifenacin succinate, a drug approved by the United States (US) Food and Drug Administration (FDA) to treat OAB symptoms, acts by competitively inhibiting the action of acetylcholine. Because solifenacin succinate has been studied previously in older adult populations as a muscarinic receptor antagonist with greater selectivity for bladder muscarinic receptors [8], we hypothesized it would be well tolerated in PD patients with OAB symptoms.

2. Methods

This was a double-blind, randomized, placebo-controlled study that evaluated the efficacy of solifenacin succinate in idiopathic PD patients with OAB, defined as at least 8 voids per 24 h period and at least daily urinary urgency. The study was conducted at 3 centers in the US, each of which obtained institutional research board approval, and was registered on clinicaltrials.gov as NCT01018264. Eligibility criteria required participants to be aged 40–80 years, have a stable dose of anti-parkinsonian medication 4 weeks prior to study entry, score 1.0 to 3.0 on the Modified Hoehn and Yahr scale, have evidence of prostate specific antigen less than or equal to 4 (males only) within the last 12 months, and have a bladder scan at screening documenting post void residual of 200 ml or less. Inclusion criteria included patients with PD as determined by the UK Parkinson's Disease Society Brain Bank Criteria for the diagnosis of Parkinson's Disease [9]. Participants were not eligible if any of the following were present: history of prostate cancer or transurethral resection of the prostate (TURP) (males only), severe renal disease, blood urea nitrogen (BUN) 50% greater than normal (normal BUN levels should be within a range of 5–20 mg/dL with creatinine between 0.7 and 1.4 mg/dL), major hepatic impairment (cirrhosis, viral hepatitis, nonalcoholic steatohepatitis, Wilson's disease, or hemochromotosis), history of bladder outflow obstruction or gastrointestinal obstructive disorders, history of narrow angle glaucoma, history of pelvic radiation, active urinary tract infection, or history of chronic severe constipation. Additional exclusion criteria included: current treatment with ketaconazole, CYP3A4 inhibitors, certain contraindicated antiarrhythmics (flecainide, digoxin), antipsychotics, tricyclic anti-depressants, psychotropics, anticholinergics/antispasmodics, arylalkylamines, anti-androgens, antihypertensives. Participants who were currently taking selective serotonin-norepinephrine reuptake inhibitors, estrogens or acetylcholinesterase inhibitors were required to have a stable dose for 90 days prior to enrollment. All participants were on optimal treatment for their PD symptoms and PD medications were at stable doses prior to enrollment.

Using a computer generated randomization schedule, participants were randomized to receive solifenacin succinate or placebo for 12 weeks followed by an 8-week open-label extension (Fig. 1) in a 1:1 ratio without blocking or stratification. An unblinded team member who was not involved in patient enrollment or assessments labeled medication kits with study ID numbers according to the randomization schedule. Kits were dispensed to participants in sequential order and were identical in appearance other than ID number. Sealed emergency unblinding envelopes were available at each site in case required by adverse events, but all blinded team members and participants remained blinded until the open label phase. Participants were enrolled from March 2010–March 2013.

The primary outcome in the double-blind phase was the change in mean number of micturitions per 24 h period as recorded on a 3-day bladder diary. Secondary outcome measures included the change in the mean number of urinary incontinence episodes, the mean number of nocturia episodes, urinary urgency as measured by the Patient Perception of Intensity of Urgency Scale (PPIUS) [10], the mean change in Patient Perception of Bladder Condition (PBC/PPBC) [11], PD quality of life (PDQOL) [12], incontinence quality of life (IQOL) [13], and clinical global impression (CGI). In order to calculate nocturia episodes, participants recorded in a bladder diary the time they went to bed for the night, the time they awoke for the day, and the times during each void. Nocturia episodes were defined as voids occurring after bedtime and before awake time. The Unified Parkinson's Disease Rating Scale (UPDRS) [14] was also performed at each visit.

Baseline data were compared using t-tests for continuous measures and Fisher exact or Freeman–Halton tests for categorical measures. Changes in primary and secondary outcome measures from baseline to endpoint were calculated and compared between treatment groups. For participants who withdrew prior to the double-blind endpoint, but completed a follow-up visit, endpoint values were determined using the last observation carried forward (LOCF) method. For continuous outcomes (mean number of micturitions, urinary incontinence episodes, and nocturia episodes, PDQOL, IQOL, and UPDRS), analysis of covariance (ANCOVA) was used to compare changes from baseline to endpoint during the double-blind phase, adjusting for the baseline value. Similarly for ordinal outcomes (PBC/PPBC, PPIUS, Hoehn & Yahr stage, and CGI measures), ordinal logistic regression was used with the ordinal change as the dependent variable, treatment group as the primary independent variable, and adjusting for the baseline value.

During the open-label phase of the study, changes from pre-treatment to post-treatment were assessed using the Wilcoxon signed-rank test (continuous outcomes) or the sign test (ordinal outcomes) for paired data. During both the double-blind and open-label analyses, effect sizes were calculated using the standardized mean difference (Cohen's *d*-statistic). In the open-label phase (a one group pre-post design) the effect size was calculated as the mean difference between pre- and post-treatment divided by the sample standard deviation of the difference [15]. The double-blind phase mirrored an independent two-group pre-post design; therefore, the effect size was first calculated for each treatment group. The overall effect size was computed as the difference in-group effect sizes between the solifenacin succinate and placebo groups [16]. All analyses were performed using SAS 9.3 (SAS Institute, Inc. Cary, N.C.). A SAS macro created by the University of South Florida was used to implement design-specific calculation of effect size [17].

The study was approved by Independent Ethics Committee/Institutional Review Boards and performed in accordance with the International Conference for Good Clinical Practice, the national regulations and ethical principles of the Declaration of Helsinki. All patients provided written informed consent.

3. Results

The final randomized sample consisted of 23 patients (10 solifenacin, 13 placebo) whose baseline characteristics are shown in Table 1. There were no statistically significant differences between the two groups on any baseline characteristic. Two participants failed to return bladder diaries at both follow up visits during the open-label phase. Although they were therefore excluded from the analysis of open-label diary data, they were still included in analyses of other outcomes during the open-label phase. While UI was not a criteria for inclusion, 65% (15/23) of participants reported an average of at least 1 daily episode of UI at baseline.

In the double-blind phase, the primary outcome measure (mean number of micturitions per 24 h period) did not significantly improve with the use of solifenacin succinate. However, the average number of urinary incontinence episodes per 24 h period decreased significantly in the solifenacin group (1.48 ± 2.56 to 0.30 ± 0.31) compared to placebo (1.78 ± 1.27 to 1.61 ± 1.40, $p = 0.01$). Most participants (6/9, 67%) in the active treatment group received 5 mg of solifenacin succinate throughout the double-blind portion of the study. Other measures of urinary function, including number of micturitions per 24 h period and number of nocturia episodes per 24 h period, also decreased in both groups; however, the differences in the baseline-to-endpoint changes between the groups were not statistically-significant (Table 2).

Participants who received solifenacin succinate demonstrated more of a trend toward improvement on the PPBC, a measure of perceived bother from urinary symptoms, as well as for motor function as assessed by the UPDRS. There were no significant changes in the PPIUS or measures of quality of life (PD QOL, IQOL).

In the open label phase of the study significant improvements were observed from baseline to endpoint in the mean daily number of urinary incontinence episodes (baseline $= 1.33 \pm 1.54$ to 0.52 ± 1.01; $p = 0.03$), the number of nocturia episodes (from 2.67 ± 1.08 to 1.64 ± 1.09; $p = 0.01$), the patient's perception of their bladder condition ($p = 0.01$), and the motor component of the UPDRS ($p = 0.04$) (Table 3). By the end of the open-label phase, 56% (9/16) of participants took 10 mg solifenacin succinate daily. There was no significant change in the PD-QOL or I-QOL during the open-label portion.

Solifenacin succinate was generally well tolerated. Treatment associated adverse events during the double-blind period included constipation ($n = 1/9$ participants on active treatment, 0/12 on placebo), xerostomia ($n = 2/9$ participants on active treatment, 0/12 on placebo), and urinary retention ($n = 1/9$ participants on active treatment, 0/12 on placebo), which all resolved upon treatment discontinuation.