Myrbetriq™ (Mirabegron) to Reduce Pain and Discomfort Following Ureteral Stent Placement

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Background

Ureteral stents are used extensively in urologic patients suffering from stones, ureteral obstruction secondary to strictures and malignancy, as well as post-operatively in various urologic procedures that involve the ureters and/or kidneys. These stents are a frequent source of pain and discomfort to urologic patients.

Typically ureteral stents may cause a wide spectrum of lower urinary tract symptoms (LUTS). These include urinary frequency, urgency, dysuria, incomplete emptying, flank pain and suprapubic pain[1]. Patient discomfort may lead to increased need for narcotic or other pain medications and increase length of hospital stay. This may also result in greater patient anxiety and a reduced quality of life. A major source of discomfort in these scenarios is thought to result from a spastic response of the bladder and/or ureter in response to the indwelling foreign object.

It has been shown that stimulation of β(3)-adrenoceptors (β-AR) causes relaxation of mammalian ureteral smooth muscle[2]. β(3)-AR are expressed in human ureter smooth muscle at the mRNA level[3,4]. β(3)-AR agonists can relax ureter smooth muscle, which results in reduction of both the frequency and force of contraction in the acutely obstructed ureter[5].

Myrbetriq™ has been approved for the treatment of overactive bladder symptoms such as urinary frequency, urgency and urgency urinary incontinence. These symptoms are similar to the symptoms that patients usually suffer from with ureteral stent placement and are a source of extreme agony and discomfort to patients. Utilizing the proven therapeutic effect of Myrbetriq™ on the detrusor smooth muscle and the possible reduction of ureter smooth muscle tone could be clinically and practically relevant in patients with ureteral pain associated with stent placement.

We hypothesize that Myrbetriq™, as a β(3)-AR agonist[6], could harbor a great therapeutic potential for controlling storage bladder symptoms (LUTS) and ureteral pain associated with ureteral stent placement.

Study Objective and Endpoints

The objective of this pilot study is to assess whether Myrbetriq™ will improve post-operative ureteral pain and discomfort, reduce bladder storage symptoms and increase quality of life following ureteral stenting. This study will be conducted as an exploratory pilot investigation. In doing so, we will confirm the potential effect size for reduction in associated pain following stenting within this study population. Results from this pilot study will also be used to assess feasibility for the design and conduct of a larger, prospective study in this population.

Primary Endpoints:

- Improvement from baseline in the Incontinence Symptom Severity Index (ISSI) in the Myrbetriq™ group at the 1 week follow-up and 2 week follow-up compared to placebo group.
- Improvement from baseline in the number micturition per 24 hours and the number of incontinence episodes in the Myrbetriq™ group at the 1 week follow-up and 2 week follow-up compared to placebo group.

Exploratory Endpoints:

- Improvement in pain and discomfort perception using a 10 point Visual Analog Scale for pain assessment (VAS) at the 1 and 2 week follow-up.
- Improvement from baseline on the Patient Global Impression of Severity (PGI-S) at the 2 week follow-up.

- Reduction in pain medicine intake at the 2 week follow-up.

Study Methods

This study is a prospective, randomized, double-blind, placebo-controlled 2 week clinical trial to evaluate the efficacy of Myrbetriq™ to reduce ureteral stent related pain and bladder symptoms in subjects undergoing a urologic procedure involving ureteral stenting. The study will be conducted at Southern Illinois University (SIU) School of Medicine, Department of Urology and its affiliated hospitals in Springfield, IL.

Subjects will be enrolled per the inclusion/exclusion criteria. Subjects will be screened and consented prior to their stent placement procedure for stone disease. Patients will be formally enrolled and randomized post-operatively based on no severe complications intra-operatively, such as extensive extravasation, hematoma could confound the pain and compromise the results. All subjects will complete at baseline and all follow-up visits: 1) the Incontinence Symptoms Severity Index (ISSI), 2) American Urologic Association symptom score (AUASS) 3) the Visual Analog Scale (VAS) to represent change in acute pain 4) the Patient Global Impression of Severity (PGI-S) quality of life scale 5) a voiding diary for 1 to 3 days preceding day, 7, and stent removal visits, and then 14 days after the stent removal (if done by day 28) to obtain base line diary and 6) a narcotic log starting after surgery through 14 days after stent removal (if done by day 28). The ISSI will be used to assess any change in voiding symptoms. This scale has been validated to efficiently capture and quantify urological symptoms[7]. The voiding diary is used to capture the number of micturition per day, urgency and associated incontinence. The VAS has been validated to measure changes in acute pain that are clinically significant[8]. The PGI-S has been proven to efficiently summarize a patient's perception to change in severity in regards to lower urinary tract symptoms (LUTS)[9]. Subjects will undergo a blood draw prior to stent placement (complete blood count (CBC), comprehensive metabolic panel (CMP) and urine analysis (sugar, protein, WBC/RBC, bacteria)) to verify eligibility. These laboratories will not be repeated if they were performed routinely as a part of preoperative work up. 100 subjects will be equally randomized into 1 of 2 study groups, active treatment with Myrbetriq™ or administration of a placebo. A daily 50 mg dose of Myrbetriq™ will be administered in the treatment group for up to 4 weeks initiated on the day of stent placement. A 50mg dose was chosen as the initial dose due to the acute nature of the symptoms which do not require long term therapy. It has been shown that Myrbetriq™ 50 mg taken orally once daily has superior efficacy in treatment of LUTS when compared to placebo by week 4 (the duration of this study) and this effect was maintained. A 50mg dose was proven to be safe and effective to patients in Phase III trials [10,11]. Both study groups will receive similar prescriptions of narcotics in dose and number. Patients will be given a log to record use of narcotics. If a different form of narcotics is prescribed due to side effects or allergic reaction, a narcotic analgesia converter calculator will be used to adjust for the doses, for analysis purposes. Post-operative symptoms and pain medicine intake will be assessed at days 1, 7 via telephone interview, and with a clinic visit the day of stent removal (or day 14 if stent removal postponed) and via phone 14 days after the stent is removed. If patient is to have stent removed on day 28, or later, the patient will receive a day 21 telephone call to obtain post-operative pain and pain medicine intake, as well as questionnaires. They will remain on study drug until day 28. Use of prescription, over-the-counter and supplemental medications for pain control will be captured using self-report and direct observation/recording of medication labels by the study team. These interviews will be conducted by study staff who will be blinded to the subject's treatment. Subjects will complete

the ISSI, the AUASS, voiding diary, VAS, narcotic log, and PGI-S during these follow ups. The day 14 assessments will be collected prior to their stent removal procedure.

Study Subjects

Patients will be identified and recruited through the SIU urology clinics and St. John's Hospital during a 24 month enrollment period. Participation in this study will be completely voluntary. Male and female subjects presenting with planned stent placement for ureteral obstruction or post-ureteroscopy procedures for stone, except for those undergoing uteropelvic junction obstruction, will be evaluated for participation. Should the patient decline to participate, their choice will not change their prescribed course of standard urologic treatment. After review and approval by the local Institutional Review Board, the study will enroll 100 patients that meet the inclusion criteria below and agree to participate. Annually, the study investigators perform approximately 350 stenting procedures (based on 2 previous years of clinical data).

Inclusion Criteria

1. Age ≥ 18.
2. Subject scheduled to undergo a ureteral stent placement for ureteral obstruction or post-ureteroscopy procedure.
3. Otherwise healthy subjects who are able and willing to participate in the study.
4. None of the planned interventions are documented in the labeled contraindications, warnings and precautions of the study drug.

Exclusion Criteria

1. Does NOT give consent.
2. Subject is using prohibited medications which cannot be stopped safely at the screening visit. Subject is excluded if using restricted medications not meeting protocol-specified criteria:
    (i) Phytotherapy for BPH or a 5-alpha reductase inhibitor within 3 months, with persistent urinary symptoms and AUASS more than 7.
    (ii) Taken an oral alpha agonist, anticholinergic or cholinergic medication within 5 days of the first screening visit with the following exception(s): a singular dose given in ER or on the hospital floor prior to procedure, topical anticholinergic eye drops used for glaucoma or inhaled anti-cholinergic used for COPD.
    (iii) Taken tricyclic antidepressants within 2 weeks of the first screening visit.
    (iv) Taken an estrogen, androgen, or any drug producing androgen suppression, or anabolic steroids within 3 months with the following exceptions: any topical creams for local treatment.
3. Post void residual volume > 350 mL.
4. Female subject is breastfeeding, pregnant, intends to become pregnant during the study, or of childbearing potential is sexually active and not practicing a highly reliable method of birth control.
5. Subject has known neurogenic bladder.
6. Subject with uncontrolled chronic pain problems or on chronic pain medications.
7. Subject has significant stress incontinence or mixed stress/urgency incontinence where stress is the predominant factor as determined by the investigator (for female subjects confirmed by a cough provocation test).
8. Subject has an indwelling catheter or practices intermittent self-catheterization.

9. Known primary neurologic conditions such as multiple sclerosis, Parkinson's disease, diabetic neuropathy or any neurological diseases known to affect bladder function.
10. Subject has evidence of a symptomatic active urinary tract infection, chronic inflammation such as interstitial cystitis, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs, or bladder stones (which can be located in different anatomical location and can cause LUTS similar to bladder infection and pain related to their location in the bladder which could mask the treatment effect).
11. Subject who is currently under active treatment with botulinum toxin (and all other bladder paralytics) intravesically.
12. Subject has moderate to severe hepatic impairment [ALT (SGPT) or AST (SGOT) value greater than 3 times the upper limit of normal in the clinical center lab; confirmed on a second measurement].
13. Subject has severe renal impairment or End Stage Renal disease (i.e., creatinine greater than 2.0 mg/dl).
14. Subject has severe uncontrolled hypertension (defined as systolic blood pressure ≥180mmHg and /or diastolic pressure ≥ 110mmHg).
15. Subject has a clinically significant abnormal ECG in their chart or has a known history of QT prolongation or currently taking medication known to prolong the QT interval. Any patient taking Digoxin.
16. Subject has a known or suspected hypersensitivity to Mirabegron or any of the inactive ingredients.
17. Subject has a concurrent genitourinary malignancy, or active cancer (except noninvasive skin cancer) within the last 5 years prior to screening. Men with a history of prostate cancer regardless of curability are not eligible.
18. Subject has been treated with an experimental device within 30 days or received an experimental agent within the longer of 30 days or five half-lives.
19. Unable to follow protocol directions due to organic brain or psychiatric disease.
20. Intra-operative complications that require hospital admissions.
21. History of alcoholism or any other substance abuse, which, in the opinion of the investigator, would affect compliance with the protocol.

Assessment or Procedure	Baseline/ Stent Placement	Post-Op Day 1 (phone)	Post-Op Day 7 (phone)	Stent removal (Post-Op Day 14 if stent not removed) visit	Post- Op Day 21 (phone) (if stent not removed)	2 weeks after stent removal or Day 42 (phone)	Early Withdrawal
Informed Consent	X						
Verify Eligibility	X						
Review Medical & Surgical History	X						
Physical Examination (H & P)	X			BP and HR only			BP and HR only
Review Prior & Current Medications	X	X	X	X	X	X	X
Review Adverse Events		X	X	X	X	X	X
ISSI	X	X	X	X	X	X	X
VAS	X	X	X	X	X	X	X
PGI-S Quality of Life Scale	X	X	X	X	X	X	X
AUASS	X	X	X	X	X	X	X
Voiding diary			X	X		X	
Pain log		X	X	X	X	X	X
Laboratory screening tests (hematology & chemistry)	X						
Randomization	X						
Study drug administration/Accountability	X			X		X only if you have drug	X

Visit window for all visits are +/- 2 days

Study Procedures

Informed Consent

All participants will be required to provide written informed consent. The study staff will introduce the study after being informed the subject is potentially eligible. The study coordinator and/or study staff will review the informed consent document with the subject. The subject will be provided information related to the study purpose, procedures, potential risks and benefits to participation, voluntary nature of their potential participation and provide them an opportunity to ask and have answers to all questions prior to obtaining any signature. A study investigator will be available to answer any questions. Subjects will not be compensated for participation and there are no additional costs to subjects for participation in the study.

Randomization Schema

The order of group assignment will be randomized using a simple random numbers table. Equal numbers of participants will be allocated to the two study groups: Group 1: daily Myrbetriq™ (50mg) or Group 2: placebo. The randomization procedure is concealed to the participating Urologists, residents and study coordinators. The random assignment schedule will be maintained by the pharmacist at St. John's Hospital. After the patient has provided consent to participate in the study and all inclusion/exclusion criteria have been met, the study coordinator will obtain the subject's identification (ID) number.

Data Management and Confidentiality

Study coordinators will be responsible for data collection and will ensure that forms are completed and signed. Data will be entered into an excel spreadsheet for subsequent analysis. Each subject will be assigned a study identification code (ID codes). Data collection forms and consent forms will be maintained for the duration of the study in a locked file cabinet. Electronic data will be stored on a secure server accessible via password-protected computer. Only authorized study personnel will have access to the study data. Electronic data will be maintained until all analyses have been completed. Study data will be kept for six years after study completion and then destroyed.

Statistical Analyses

Due to the exploratory nature of the efficacy endpoints within this study population, we have chosen to conduct this study as a pilot clinical trial. Descriptive summary statistics will be used primarily in the exploratory efficacy analysis. Summary statistics for these endpoints will also be provided by cohort, treatment group and visit.

Data analysis will be concluded upon the completion of the study. Subjects' age, height, weight, and other continuous baseline variables will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term. Chi-square and t-tests will be used, as appropriate, to compare percent change and mean change from baseline in the ISSI, voiding diary, narcotic log, VAS score and PGI-S at the final study visit (14 days) or at any early termination visit. A split-plot ANOVA with repeated measures will be used for each measure (ISSI, VAS and PGI-S) to compare groups (Myrbetriq™ and placebo) over time and to determine if there is an interaction between groups. Significance will be assumed when $p < 0.05$. A preliminary power analysis based on previously published data, using an estimated SD for each study group of 4.17, a sample size of 50 in each study group (Myrbetriq™ and placebo) has an 80% power to detect an ISSI difference of 25% between the two groups with a significance level (alpha) of 0.05 (two-tailed)[12].
Pertinent to each Specific Aim are the following calculations:

- Primary Endpoints: Comparison of the change from baseline in ISSI and voiding diaries between Myrbetriq™ and placebo will be made using an independent t test for continuous scoring and a chi-squared test for ordinal scoring. Inferential analyses of changes from base line in micturition episodes per 24 hours and incontinence episodes per 24 hours will be performed using a stratified rank analysis to compare to baseline and as a covariance for each treatment.
- Exploratory Endpoints: Comparison of the change from baseline of total VAS between Myrbetriq™ and placebo will be made using an independent t test for continuous scoring and a chi-squared test for ordinal scoring. Comparison of the change from baseline in PGI-S between Myrbetriq™ and placebo will be made using an independent t test for

continuous scoring and a chi-squared test for ordinal scoring. Comparison of pain medicine intake between Myrbetriq™ and placebo groups will be made using an independent t test.

Safety Considerations

Screening laboratory safety tests (hematology, chemistry), blood pressure, heart rate measurements, urinalysis, and liver function tests will be performed at the initial screening visit if they are not performed as the standard pre-operative work-up. Adverse event (AE) assessments will be reviewed by the PI and reported by study personnel as Myrbetriq™ is dispensed on a daily basis. Any reported changes in patient symptoms will be reviewed again at the end of the study. AEs will be summarized by treatment group according to the last treatment taken before the AE took place.

Data Safety Monitoring Plan

The investigators will be responsible for all study assessments and will monitor each participating subject for any adverse events. An adverse event log has been created for this study and side effects of study subjects will be collected, tabulated and reviewed. Regularly scheduled meetings of study personnel will take place (at least monthly) to review study progress and procedures. Real time management of AEs will be done per standard of care by the subjects' health care providers. Any serious AE or unanticipated problems will be reported to the Springfield Committee for Research Involving Human Subjects (SCRIHS) within 24 hours in accordance with SCRIHS policy.

Institution and Investigator Interests

SIU School of Medicine and the Principal Investigator, Ahmed El-Zawahry, MD received a grant from Astellas to support the costs of conducting this clinical trial. Astellas is the manufacturer of the drug (Mirabegron) being used in this study. Astellas is also providing the drug free of charge to subjects while participating in this study.

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