A Multicenter, Double-Blind, Randomized, Placebo Controlled Trial of a Neurokinin-1 Receptor Antagonist for Overactive Bladder

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Abbreviations and Acronyms

AE = adverse experience
ER = extended release
LS = least squares
NK-1R = neurokinin-1 receptor
OAB = overactive bladder
SP = substance P
TKs = tachykinins

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For other articles on a related topic see pages 762, 769 and 783.

Purpose: Neurokinin-1 receptor dependent mechanisms may regulate urinary frequency and urgency. We conducted this study to assess the efficacy and tolerability of the neurokinin-1 receptor antagonist serlopitant vs placebo or tolterodine in patients with overactive bladder.

Materials and Methods: This randomized, double-blind, 69-center trial enrolled adults with overactive bladder (8 or more average daily micturitions and 1 or more daily urge incontinence episodes). After a 1-week placebo run-in the patients were randomized to 8 weeks of daily 0.25, 1 or 4 mg serlopitant, 4 mg tolterodine extended release or placebo. Patients kept 7-day voiding diaries. The primary end point was change from baseline in micturitions per day. Secondary end points included urgency, total incontinence, urge incontinence episodes and incidence of dry mouth.

Results: Of 557 patients randomized 476 completed the trial and had valid efficacy data for analysis. Mean change from baseline in daily micturitions was significantly greater for 0.25 (–1.1) and 4 mg (–1.1) serlopitant, and for tolterodine (–1.5) than for placebo (–0.5), but not for 1 mg serlopitant (–0.8). No serlopitant dose response was demonstrated. Tolterodine was numerically superior to all doses of serlopitant in mean micturitions per day and secondary end points. The incidence of dry mouth on serlopitant (3.3%) was comparable to placebo (4.6%) and lower than tolterodine (8.8%). Serlopitant was generally well tolerated.

Conclusions: Serlopitant (0.25 and 4 mg) significantly decreased the primary end point of daily micturitions but not the secondary end points compared with placebo. Serlopitant was generally well tolerated. Thus, NK-1 receptor antagonists may have a role in the treatment of overactive bladder but this compound does not offer advantages in efficacy compared to tolterodine.

Key Words: receptors, neurokinin-1; tolterodine; muscarinic antagonists; urinary bladder, overactive

Overactive bladder (defined by the International Continence Society as urgency with or without urge incontinence, usually with frequency and nocturia)[1] is prevalent in Europe[2] and the United States,[3] and has a negative impact on patient quality of life such as difficulty performing activities of daily living, depression and stress.[4] Epidemiological surveys reveal that approximately 17% of adults older than 40 years have OAB.[2,3,5] The incidence increases with age to more than 30% for those older than 75

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years.[2,5] Although the prevalence of OAB is about equal in men and women, OAB with urinary incontinence is more prevalent in women (55%) than in men (16%).[3]

The mainstays of pharmacological treatment of OAB are antimuscarinic agents, such as oxybutynin and tolterodine, that block the parasympathetic acetylcholine receptors in the bladder and reduce the intensity of the detrusor muscle contraction.[6] Antimuscarinic agents show modest efficacy in OAB by decreasing the number of daily micturition and urge incontinent episodes. However, they are also associated with characteristic anticholinergic side effects such as dry mouth, dry eyes and constipation, which may limit their use in practice.[7,8] Poor long-term patient compliance with antimuscarinics is likely attributed to the modest efficacy and anticholinergic side effects.

Tachykinins are a family of neuropeptides that include substance P and are synthesized by primary afferent fibers. Of the 3 neurokinin receptors (NK-1, NK-2 and NK-3) SP has the highest in vitro binding affinity for the NK-1 receptor.[9] Immunohistochemistry studies have demonstrated that the NK-1 receptor is located centrally and peripherally, with high concentrations in the dorsal horn of the spinal cord, striatum, hippocampus, amygdala and brainstem, and peripherally in bone marrow and epithelial cells of the gut, and lung and bladder.[10,11]

The micturition reflex involves a complex interplay of afferent and efferent pathways, and capsaicin sensitive and TK containing primary afferents may have a role in this reflex in animals.[12–14] A significant increase in the density of suburothelial SP containing nerves was found in patients with idiopathic detrusor overactivity compared with controls.[15] Data from experimental animal models suggest that TKs can induce contraction of the bladder smooth muscle, and that NK-1 receptor antagonists can reduce detrusor hyperreflexia in spinal cord injury and chemical induced cystitis models.[12–14,16] Therefore, it is reasonable to postulate that TKs may be involved in pathophysiological sensory signaling associated with detrusor overactivity.[17]

Capsaicin and resiniferatoxin are neurotoxins that deplete SP and other tachykinins from primary afferents, resulting in prolonged desensitization of TK receptors.[18] Intravesical instillation of capsaicin and resiniferatoxin demonstrated efficacy in patients with OAB.[19,20] Most recently aprepitant, a potent and selective antagonist of the human NK-1 receptor, improved OAB symptoms in a phase 2 proof of concept clinical trial.[21] However, aprepitant is not ideal for chronic dosing in the OAB population due to a potential for drug-drug interactions.

Serlopitant is a highly selective and potent antagonist for the human NK-1 receptor. In vitro, serlopitant binds with high affinity to the human NK-1R with a Kd of 46 pM, displacing substance P binding with an IC_{50} of 0.061 nM. In healthy young male subjects positron emission tomography studies of the brain demonstrated central nervous system penetration and predicted greater than 90% NK-1 receptor occupancy at steady state for doses greater than 2.5 mg.[22] The current study was designed to evaluate the safety, tolerability and efficacy of a new NK-1R antagonist, serlopitant, in adult men and postmenopausal women with OAB and incontinence.

MATERIALS AND METHODS

For this randomized, double-blind, active and placebo controlled, parallel group, 8-week dose ranging study (protocol 003) patients participated from February 21, 2006 to September 24, 2007 at 69 international centers. The final data point collection date for the primary outcome measure was August 31, 2007.

Patients

Patients were recruited from clinical research sites. Inclusion criteria required patients to be 40 to 74 years old and postmenopausal if female (no menses for at least 1 year with serum follicle-stimulating hormone levels 85% or greater of the lower limit of normal). Up to 10% of patients could be male. The proportion of male patients was limited to 10% because of potential gender differences underlying the pathophysiology of urge incontinence (eg resulting from bladder outlet obstruction in men). All patients were required to have a history of urinary urgency for at least 3 months before screening, and to meet voiding diary criteria of an average of 8 or more daily micturitions and 1 or more daily urge incontinence episodes. The number of urge incontinence episodes had to exceed the number of stress incontinence episodes. Patients were ambulatory, and in good general physical and mental health.

Exclusionary medical conditions included diabetes insipidus, uncontrolled hyperglycemia or hypercalcemia, disease or surgery affecting the urinary tract, active or recurrent (more than 6 episodes per year) urinary tract infection, hematuria or prolapsed uterus. Patients receiving therapy with serotonin and/or norepinephrine reuptake inhibitors, tricyclic antidepressants and diuretics must have been on a stable dose for at least 8 weeks before study start with no intent to change regimen during the study. Anticholinergics and smooth muscle relaxants were not allowed within 3 weeks of the start of the 1-week placebo run-in period. All patients gave written informed consent and the study was approved by all institutional review boards.

Treatment and Assessment

After the 1-week single-blind placebo run-in period patients were randomized equally among treatment groups of 0.25 mg, 1 mg or 4 mg daily serlopitant, 4 mg daily tolterodine ER or placebo (using a site based permuted block randomization allocation schedule generated by the Biostatistics Department of Merck Research Laboratories). To decrease the time to steady state and maximum