

MIRABEGRON IN TREATMENT OF NEUROLOGICAL OVERACTIVE BLADDER IN MULTIPLE SCLEROSIS PATIENTS

Hypothesis / aims of study

Overactive bladder (OAB) is a disorder of the filling phase of the bladder, characterized by symptoms of urgency, urinary frequency and nocturia, with or without urgency incontinence in the absence of any other underlying pathology. Current pharmacotherapy for OAB consists primarily of antimuscarinics which can produce side effects such as dry mouth, constipation, and blurred vision. And also with insufficient response, can produce low compliance with antimuscarinic therapy.

Also patients with neurological OAB the antimuscarinic therapy had the same effects Mirabegron is a selective β_3 -adrenoceptor agonist; the β_3 subtype has been identified in bladder smooth muscle tissue (detrusor muscle). In the human bladder, the β_3 -adrenoceptor subtype was identified to promote detrusor relaxation and urine storage. These observations suggest that drugs acting at β_3 -adrenoceptors may have therapeutic potential that was confirmed in clinical trials in patients with OAB. (Khullar V. 2013)

In this study we evaluate the potential of mirabegron, a selective β_3 -adrenoceptor agonist, for treatment of neurological overactive bladder (OAB) symptoms in patients with Multiple Sclerosis (MS)

Study design, materials and methods

A, multi-centre Open Study to Evaluate the Efficacy and Safety of Mirabegron in Neurogenic OAB Subjects affected by multiple sclerosis (MS).

The patients (n = 38) were enrolled into 2-week run-in period followed by 10 weeks a treatment period, when received mirabegron 50 mg daily.

We evaluated 38 Patients (12 Man and 26 woman ≥ 18 years of age) that were enrolled in the study. All patients had diagnosis of SM > of 3 years and a previous treatment with antimuscarinics with low efficacy.

All patients had symptoms of OAB (urinary frequency and urgency with or without urgency incontinence); a frequency of micturition on average ≥ 8 times/24 hr; and ≥ 3 episodes of urgency (grade 3 or 4), with or without incontinence, during the 3-day micturition diary period.

Major exclusion criteria included clinically significant outflow obstruction; significant post-void residual (PVR) volume (>200 ml); incontinence where stress was the predominant factor; intermittent self-catheterization; ; diabetic neuropathy; symptomatic previous or current malignant disease of the pelvic organs; contraindications for anticholinergics such as uncontrolled narrow angle glaucoma, other recognized pathologies affecting the urinary or colorectal systems; non-drug treatment including electro-stimulation therapy.

Primary endpoint was change from baseline to end-of-treatment in mean number of micturition episodes per 24 hr. Secondary endpoints included changes in mean volume voided per micturition; mean number of urinary incontinence, urgency urinary incontinence, and urgency episodes per 24 hr; severity of urgency; . Safety parameters included adverse events, and post-void residual volume.

The patients performed 3 visits : visit 1 screening and run in, visit 2 baseline and start of treatment and visit 3 at the end of treatment after 8 weeks.

At visit 1, patients received a micturition diary which was to be completed during the 3-day period preceding visit 2 and 3. For each micturition or incontinence episode, patients were asked to rate the degree of associated urgency on a 5-point categorical scale (0, no urgency; 1, mild urgency; 2, moderate urgency; 3, severe urgency; and 4, urgency incontinence).

Patients' perception of intensity of urgency scale (PPIUS) was evaluated once per visit, starting at visit 2, by completing the statement "my bladder condition ..." with one of the following: "does not cause me any problems," "causes me some very minor problems," "causes me some minor problems," "causes me some moderate problems," causes me severe problems," or "causes me many severe problems.

Patients' assessment of treatment benefit was also evaluated once per visit, starting at visit 2, with the question "has the treatment been of any benefit to you?" and three possible responses of "no," "yes, a little," or "yes, very much.

Adverse events were assessed and blood pressure and pulse rate were measured at each study visit. PVR was assessed by ultrasonography or bladder scan at visits 1, 2, and 3.

EDSS (expanded disability status scale) medium 3

Results

Mirabegron 50 mg daily resulted in a statistically significant improvement in mean change from baseline to end-of-treatment in the primary endpoint of micturition frequency (3.1 micturitions/24 hr). Mirabegron had a statistically significant effect versus baseline for secondary endpoints, statistically significant reductions from baseline to end-of-treatment in urgency episodes (2.3) and a statistically significant increase in mean volume voided per micturition (50 ml).

Mirabegron also resulted significant improvements in incontinence episodes (2.0 episodes/24 hr).

The percentage of patients classified as "responders" at end-of-treatment defined as improvement of at least one category for patients' assessment of treatment benefit was 68 %.

Patients with no results was 10 (20%); 12 % partial results.

No change in EDSS

There were no serious adverse events during the therapy; the drug demonstrated good safety and tolerability, only 1 patient suspended therapy for nausea,

Interpretation of results

The effectiveness of the treatment is demonstrated by the disappearance of urgency or reductions of micturition frequency.

This new drug is well tolerated and we haven't serious events

The majority of patients revealed a preference for this therapy and has expressed the desire to continue therapy with mirabegron

Concluding message

Mirabegron was efficacious and well tolerated in neurological patients with OAB symptoms and heralds the first of a new class of oral pharmacological therapy for OAB for more than 30 years. Without the disadvantage of a high prevalence and sometimes intolerable side effects of the conventional antimuscarinic therapy.

A large placebo-study is necessary in neurological patients for more definitive conclusions

References

1. • Khullar V, Amarengo G, Angulo JC et al (2013) Efficacy and tolerability of mirabegron, a Beta 3- Adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian Phase 3 Trial. Eur. Urol. 63: 283-95
2. • Yamaguchi O, Chapple CR. Beta3-adrenoceptors in urinary bladder. NeuroUrol Urodyn 2007; 26:752–6.
3. • Tyagi P, Tyagi V. Mirabegron, a β 3-adrenoceptor agonist for the potential treatment of urinary frequency, urinary incontinence or urgency associated with overactive bladder. IDrugs 2010; 13:713–22.

Disclosures

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