



<https://ijrps.com>

ISSN: 0975-7538

Review Article

Mirabegron - a beta-3 adrenergic agonist for overactive bladder syndrome: A review

Parasuraman S^{*1}, Muralidharan S², Jaya Raja Kumar K³

¹Unit of Pharmacology, ²Unit of Pharmaceutical Chemistry, ³Unit of Pharmaceutical Technology, Faculty of Pharmacy, Asian Institute of Medicine, Science and Technology (AIMST) University, Bedong - 08100, Kedah, Malaysia

ABSTRACT

Overactive bladder (OAB) is a urological disorder with symptoms of frequency urgency and incontinence, which substantially affects quality of life. The prevalence of OAB increased with old age Caucasians, White and Asians. The main etiological factor for OAB is lifestyle modification and stress, embarrassment, frustration, etc. OAB can be treated with anticholinergic (first-line treatment) and adrenergic agonists. Anticholinergic agents are first-line drug for the treatment of OAB; unfortunately, antimuscarinic agents are not effective in controlling OAB symptoms. In the year, 2012 US-FDA approved first β_3 adrenergic agonist (mirabegron) for the treatment of OAB. Mirabegron was developed by Astellas Pharma, Japan and introduced into the market in 2011. Recommended adult dose of mirabegron is 25 mg/day for 8 weeks. Mirabegron is a beta agonist, which can increase a blood pressure, hence it was not recommended to patients who have uncontrolled blood pressure. This review is mainly focused to discuss about mirabegron for the treatment of OAB.

Keywords: Mirabegron; overactive bladder; β_3 agonist

INTRODUCTION

Overactive bladder (OAB) affects 1 in 11 adults and 12-17% of the general population of USA (Nitti *et al.*, 2006; Ubee *et al.*, 2010). Prevalence of OAB in Asian continent is 53.1% and it is increasing with age (Ubee *et al.*, 2010). The prevalence of OAB increased with middle to old age Caucasians, Whites and Asians. OAB is a urological disorder with symptoms of frequency (urination > 8 times throughout the day), urgency (strong urge to go to the toilet to urinate with no advance warning) and urge incontinence (unable to get to the bathroom in time to urinate/ leak urine during the day without being able to control it) which substantially affects quality of life. OAB affects daily activities such as travel, physical activity, sexual function and nocturnal bladder control, which can affect sleep (Abrams *et al.*, 2000; Milsom *et al.*, 2001). Milsom *et al.*, conducted a population-based study in six European countries and they reported only 27% of people were receiving treatment for OAB (Milsom *et al.*, 2001). The most common reasons to OAB are stress, embarrassment, frustration, anxiety, annoyance, depression and it is one of the top four important health-related quality-of-life problems affecting senior citizens (others in-

clude Alzheimer's disease, loss of vision and osteoporosis) in USA (Keller, 1999). OAB can be treated with either nonpharmacological therapy (lifestyle modification, which includes dietary modification, fluid restriction and avoidance of CNS stimulants) or drug therapy. The first-line drug for treatment of OAB is an anticholinergic (antimuscarinic) agent until last decade (Sussman, 2009). In 2012, US-FDA approved β_3 adrenergic agonist (mirabegron) for the treatment of OAB. Mirabegron is commercially available in Japan and USA for the treatment of OAB. This review is mainly focused to discuss about mirabegron for the treatment of OAB.

PATHOPHYSIOLOGY OF OAB

The central and peripheral nervous system and components of lower urinary track influence the urine micturition. In most of the animal species, urinary bladder contraction mediated by cholinergic (muscarinic) stimulation. Stimulation of α_1 adrenergic receptor in detrusor muscle may inhibit the detrusor function by the adrenergic innervation through prejunctional inhibition of parasympathetic activation. However, stimulation of β adrenergic receptor has been shown predominate action (relaxation) on detrusor tissue over an adrenergic receptor.

The urinary bladder has two important functions *viz.* storage and emptying. Disturbance of the urinary bladder storage may results in lower urinary tract symptoms (LUTS) such as urinary urgency, frequency and urge incontinence, the components of OAB. In OAB condition person may have involuntary contractions of

* Corresponding Author

Email: parasuphd@gmail.com

Contact: +91-98438 00960; +60 138095096

Received on: 08-07-2013

Revised on: 15-09-2013

Accepted on: 17-09-2013

smooth muscle of detrusor during storage phase (Andersson and Arner, 2004).

The pathological conditions such as obstructed bladders (outline obstruction), inflammation on urinary bladder (repeated inflammatory stimuli elicit enlargement of bladder dorsal root ganglia which may reduce the activation threshold for bladder afferents), spinal cord injury (spinal cord injury may increase mechanosensitivity of C-fiber which leads to unresponsive to voluntary control by higher brain center), depression, anxiety (alterations in 5-hydroxytryptamine levels) and attention deficit disorder are contributes OAB syndrome progression (Steers, 2002). OAB and urge incontinence are more common in female gender than in male and this may be due to influence of female reproductive hormones such as estrogen and progesterone (Archer, 1999).

PHARMACOTHERAPY OF OAB

OAB can be treated with antimuscarinic agents (methantheline, emepronium, tolterodine, trospium, propantheline, oxybutynin, solifenacin, fesoterodine) (Andersson, 2004), β_3 adrenergic agonist (mirabegron) (Tyagi and Tyagi, 2010) and botulinum toxin A (Seth *et al.*, 2013; Mohee *et al.*, 2013). Stimulation of adrenergic receptor (β) facilitates urine storage through flattening and lengthening of bladder base where as stimulation of cholinergic receptor (muscarinic) facilitates urine voiding (Nitti *et al.*, 2013).

Pharmacology of β_3 adrenergic agonist

The β_3 adrenergic receptor is G-protein coupled receptor also known as ADRB3 and found in human heart, gall bladder, gastrointestinal tract, prostate, urinary bladder and in bone marrow tissues (Sawa and Harada, 2006). Stimulation of β_3 adrenergic receptor may results in various pharmacological actions such as lipolysis and thermogenesis in adipocytes and relaxation of the urinary bladder detrusor. Based on its pharmacological action many laboratories involved development of β_3 adrenergic agonist in last decade. Many of them were stopped because of its poor pharmacokinetic and pharmacodynamics effects.

In this class of drug, only mirabegron is approved for the treatment of OAB and other molecules are under investigation. Amibegron (SR58611A) is first oral active β_3 adrenergic receptor agonist, which is chemically related to the phenylaminotetralines family showed possible central nervous system effects (antidepressant and anxiolytic effect) on rodents (Stemmelin *et al.*, 2013). Amibegron development was stopped in pre-clinical stage itself. Solabegron (GW-427,353) is another β_3 adrenergic receptor agonist, which is under development. Solabegron is being developed for the treatment of OAB and irritable bowel syndrome (IBS). A phase-II clinical study of Solabegron for OAB and IBS showed significant improvement in quality of life, compared to placebo (Solabegron, 2013). The phase-III

clinical trial of the solabegron in a large number of population is in progress. The successful and first commercially available drug in this class is mirabegron, which is licensed in Japan and USA for the treatment of OAB (Gras, 2012; FDA news, 2013).

Mirabegron

Mirabegron [YM-178; 2-(2-amino-1,3-thiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide] is a potent β_3 adrenergic receptor agonist developed by Astellas Pharma, Japan and it was approved by US-FDA in July 2012 for the treatment of overactive bladder. It is a novel, once-daily, orally active, first-in-class selective β_3 adrenergic receptor agonist that used to improve the symptoms associated with OAB (Gras, 2012; Teijlingen *et al.*, 2012).

Mirabegron- clinical trials

Most of the clinical studies were conducted in Caucasians (94%) and females (72%) with mean age of 59 (18-95) years. In clinical studies, mirabegron showed significantly reduced incontinence episodes at 25 and 50 mg dose levels when compared to a placebo control group.

Phase-II clinical trial (BLOSSOM) of mirabegron showed mean reduction in a number of micturition episodes in 24 h and it was found to be better than placebo. In another phase-II clinical trial (DRAGON), repeated dose administration of mirabegron at 25, 50 and 100 mg showed dose-dependent reduction in a mean number of micturition episodes and increase in the mean volume voided compare to placebo control (Digesu *et al.*, 2012).

In phase-III clinical trial of mirabegron 50 and 100 mg/day showed significant increased the incontinence episodes and improved mean urine volume voided per micturition were observed (total number of participants were 1328). In the same study, authors were reported events of cardiac arrhythmia includes tachycardia and atrial fibrillation in mirabegron treatment group. In this trail, two deaths were reported (One was in a placebo treatment group due to cardiac arrest, and another one was in mirabegron 100 mg treatment group due to stage IV metastatic colon cancer) (Nitti *et al.*, 2013). The observed cardiovascular events with mirabegron clinical trials were not clinically relevant to mirabegron (Novara and Cornu, 2013).

Mirabegron European-Australian phase-III trail, authors analysed patients micturition diary and quality-of-life. In this trail, the efficacy of the mirabegron (50 and 100 mg) was compared with placebo and tolterodine (4 mg). This was a twelve-week multicenter randomized double-blind parallel group placebo and active controlled trial conducted in 1987 subjects at 189 sites of 27 countries in Europe and Australia. The mirabegron 50 and 100 mg groups showed significant reduction in a mean number of incontinence episodes per 24 h

compared with placebo, whereas tolterodine group improvements of endpoints were observed but did not have any significant changes compare to placebo. In this trail, one cardiovascular death was reported in the tolterodine group that was due to ruptured cerebral aneurysm after 10th day of last dose (Khullar *et al.*, 2013).

PHARMACOLOGY OF MIRABEGRON

Pharmacokinetics: Mirabegron is available at the doses of 25, 50 and 100 mg for 12 weeks. The recommended starting dose for mirabegron is 25 mg/day with or without food for first 8 weeks. Based on individual response the dose of mirabegron will be increased to 50 mg/day. The predicted metabolic route for mirabegron is amide hydrolysis by endogenous esterases, glucuronidation and N-dealkylation or oxidation of the secondary amine (Teijlingen *et al.*, 2012). The t_{max} and half-life of oral mirabegron is ~ 4 h and 40 h respectively (Eltink *et al.*, 2012). Mirabegron is 71% protein bind nature and bind with albumin and alpha-1 acid glycoprotein. Mirabegron is metabolized by CYP2D6 and CYP3A4 in liver and excreted through urine. About 20% of absorbed mirabegron is excreted in an unchanged form into urine (Bhide *et al.*, 2012a; Bhide *et al.*, 2012b; Takusagawa *et al.*, 2012).

Pharmacodynamics: Mirabegron significantly reducing the mean number of incontinence episodes and micturition episodes and it was safe and well tolerated. Mirabegron relaxes the urinary detrusor muscle during the storage phase of the urinary bladder fill-void cycle by activating β_3 adrenergic receptor, which increases urinary bladder capacity (Digesu *et al.*, 2012; Novara and Cornu *et al.*, 2013; Bhide *et al.*, 2012b). In animal, β_3 adrenergic agonist (mirabegron) inhibited the bladder microcontractions, A δ -fiber activity, C-fiber activity and decreases the bladder pressure and this was not observed in anticholinergic agents (Aizawa *et al.*, 2012).

Adverse events: Most common reported adverse events are hypertension, urinary tract infection, nasopharyngitis, and headache (Nitti *et al.*, 2014). Mirabegron can increase blood pressure, hence it was not recommended for patients who have uncontrolled blood pressure. It is also moderate CYP2D6 inhibitor. Therefore, dosage adjustment required for narrow therapeutic index drugs metabolized by CYP2D6.

Interaction: Mirabegron is moderate CYP2D6 substrates and increase the systemic concentration of metoprolol and desipramine. Concomitant therapy with strong CYP3A4 (ketoconazole) may increase the systemic concentration of mirabegron. Mirabegron also increasing the C_{max} and AUC of digoxin and warfarin, hence monitoring concomitant therapy is essential (Mirabegron- DB08893, 2013).

CONCLUSION

Mirabegron may be alternative drug for treatment of OAB. Patients with OAB who have a poor response to antimuscarinic and intolerant of their adverse effect those can use mirabegron (β_3 adrenergic receptor agonist) for the treatment.

REFERENCES

- Abrams, P., Kelleher, C.J., Kerr, L.A., Rogers, R.G. (2000). Overactive bladder significantly affects quality of life. *American Journal of Managed Care*, vol. 6, no. 11 supplement, pp. S580-90.
- Aizawa, N., Homma, Y., Igawa, Y. (2012). Effects of mirabegron, a novel β_3 -adrenoceptor agonist, on primary bladder afferent activity and bladder microcontractions in rats compared with the effects of oxybutynin. *European Urology*, vol. 62, no. 6, pp. 1165-1173.
- Andersson, K.E. (2004). Antimuscarinics for treatment of overactive bladder. *Lancet Neurology*, vol. 3, no. 1, pp. 46-53.
- Andersson, K.E., Arner, A. (2004). Urinary bladder contraction and relaxation: physiology and pathophysiology. *Physiological Reviews*, vol. 84, no. 3, pp. 935-986.
- Archer, J.S. (1999). NAMS/Solvay resident essay award. Relationship between estrogen, serotonin, and depression. *Menopause*, vol. 6, no. 1, pp. 71-78.
- Bhide, A.A., Digesu, G.A., Fernando, R., Khullar, V. (2012a). Use of mirabegron in treating overactive bladder. *International Urogynecology Journal*, vol. 23, no. 10, pp. 1345-1348.
- Bhide, A.A., Digesu, G.A., Fernando, R., Khullar, V. (2012b). Mirabegron – a selective β_3 -adrenoceptor agonist for the treatment of overactive bladder. *Research and Reports in Urology*, vol. 4, pp. 41-45.
- Digesu, G.A., Gore, M., Khullar, V. (2012). Mirabegron use in the treatment of overactive bladder symptoms. *Future Prescriber*, vol. 13, no. 3, pp. 10-13.
- Eltink, C., Lee, J., Schaddelee, M., Zhang, W., Kerbusch, V., Meijer, J., *et al.* (2012). Single dose pharmacokinetics and absolute bioavailability of mirabegron, a β_3 -adrenoceptor agonist for treatment of overactive bladder. *International Journal of Clinical Pharmacology and Therapeutics*, vol. 50, no. 11, pp. 838-850.
- FDA approves Myrbetriq for overactive bladder in US-FDA News & Event tab. Available from <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310096.htm> [last accessed on 19/06/13].
- Gras, J. (2012). Mirabegron for the treatment of overactive bladder. *Drugs Today*, vol. 48, no. 1, pp. 25-32.

- Keller, S.L. (1999). Urinary incontinence: occurrence, knowledge, and attitudes among women aged 55 and older in a rural Midwestern setting. *Journal of Wound, Ostomy, and Continence Nursing*, vol. 26, no. 1, pp. 30-38.
- Khullar, V., Amarenco, G., Angulo, J.C., Cambroner, J., Høye, K., Milsom, I., *et al.* (2013). Efficacy and tolerability of mirabegron, a $\beta(3)$ -adrenoceptor agonist, in patients with overactive bladder: results from a randomized European-Australian phase 3 trial. *European Urology*, vol. 63, no. 2, pp. 283-95.
- Milsom, J., Abrams, P., Cardozo, L., Roberts, R.G., Thüroff, J., Wein, A.J. (2001). How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU International*, vol. 87, no. 9, pp. 760-766.
- Mirabegron (accession number: DB08893) Available form <http://www.drugbank.ca/drugs/DB08893> [last accessed on 18/06/13].
- Mohee, A., Khan, A., Harris, N., Eardley, I. (2013). Long-term outcome of the use of intravesical botulinum toxin for the treatment of overactive bladder (OAB). *BJU International*, vol. 111, no. 1, pp. 106-113.
- Nitti, V.W., Auerbach, S., Martin, N., Calhoun, A., Lee, M., Herschorn, S. (2013). Results of a randomized phase III trial of mirabegron in patients with overactive bladder. *Journal of Urology*, vol. 189, no. 4, pp. 1388-1395.
- Nitti, V.W., Dmochowski, R., Herschorn, S., Sand, P., Thompson, C., Nardo, C., *et al.* (2006). OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo-controlled trial. *Journal of Urology*, vol. 183, no. 6, pp. 2186-2193.
- Novara, G., Cornu, J.N. (2013). Mirabegron as a new class of oral drug for overactive bladder syndrome: many positive perspectives, some concerns. *European Urology*, vol. 63, no. 2, pp. 306-308.
- Sawa, M., Harada, H. (2006). Recent developments in the design of orally bioavailable beta3-adrenergic receptor agonists. *Current Medicinal Chemistry*, vol. 13, no. 1, pp. 25-37.
- Seth, J., Khan, M.S., Dasgupta, P., Sahai, A. (2013). Botulinum toxin-what urologic uses does the data support? *Current Urology Reports*, vol. 14, no. 4, pp. 227-234.
- Solabegron. Available form <http://www.altherx.com/> (http://www.altherx.com/development_program/about_solabegron.asp) [last accessed on 19/06/13].
- Steers, W.D. (2002). Pathophysiology of overactive bladder and urge urinary incontinence. *Reviews in Urology*, vol. 4, no. supplement 4, pp. S7-S18.
- Stemmelin, J., Cohen, C., Terranova, J.P., Lopez-Grancha, M., Pichat, P., Bergis, O., *et al.* (2008). Stimulation of the beta3-adrenoceptor as a novel treatment strategy for anxiety and depressive disorders. *Neuropsychopharmacology*, vol. 33, no. 3, pp. 574-587.
- Sussman, D.O. (2007). Overactive bladder: treatment options in primary care medicine. *Journal of the American Osteopathic Association*, vol. 107, no. 9, pp. 379-385.
- Takusagawa, S., van Lier, J.J., Suzuki, K., Nagata, M., Meijer, J., Krauwinkel, W., *et al.* (2012). Absorption, metabolism and excretion of [(14)C]mirabegron (YM178), a potent and selective $\beta(3)$ -adrenoceptor agonist, after oral administration to healthy male volunteers. *Drug Metabolism and Disposition*, vol. 40, no. 4, pp. 815-824.
- Teijlingen, R.V., Meijer, J., Takusagawa, S., Gelderen, M.V., Beld, C.V., Usui, T. (2012). Development and validation of LC-MS/MS methods for the determination of mirabegron and its metabolites in human plasma and their application to a clinical pharmacokinetic study. *Journal of Chromatography. B*, vol. 887-888, pp. 102-111.
- Tyagi, P., Tyagi, V. (2010). Mirabegron, a β_3 -adrenoceptor agonist for the potential treatment of urinary frequency, urinary incontinence or urgency associated with overactive bladder. *IDrugs*, vol. 13, no. 10, pp. 713-722.
- Ubee, S.S., Manikandan, R., Singh, G. (2010). Medical management of overactive bladder. *Indian Journal of Urology*, vol. 26, No. 2, pp. 270-278.