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A Review in Efficacy and Safety of Mirabegron in Treating Overactive Bladder

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ABSTRACT

Mirabegron is a new drug established to treat overactive bladder syndrome. It can be used in combination or alone. The drug has been studied well; using an appreciable number of Phase II and Phase III trials showing good outcomes. OAB is defined as urinary urgency, usually with urinary frequency and nocturia, with or without urgency urinary incontinence, in the absence of any other pathology.[1] OAB occurs in both men and women and it has a significant impact on the quality of life. The use of anticholinergic medication has been the mainstay of managing overactive bladder when conservative measures are not enough. Many patients stop anticholinergic medication because of the side effects and more recently the concerns about the effect of an anticholinergic burden and the development of dementia have been studied. Activation of β3 adrenoceptors has been shown to relax the detrusor muscle and subsequently lead to the development of the first β3 adrenoceptor agonist. Side effects including constipation, hypertension and tachycardia are similar to anticholinergic medication. There is remarkably less dry mouth incidence in mirabegron group. Mirabegron can to be used safely in combination with solifenacin and tamsulosin.

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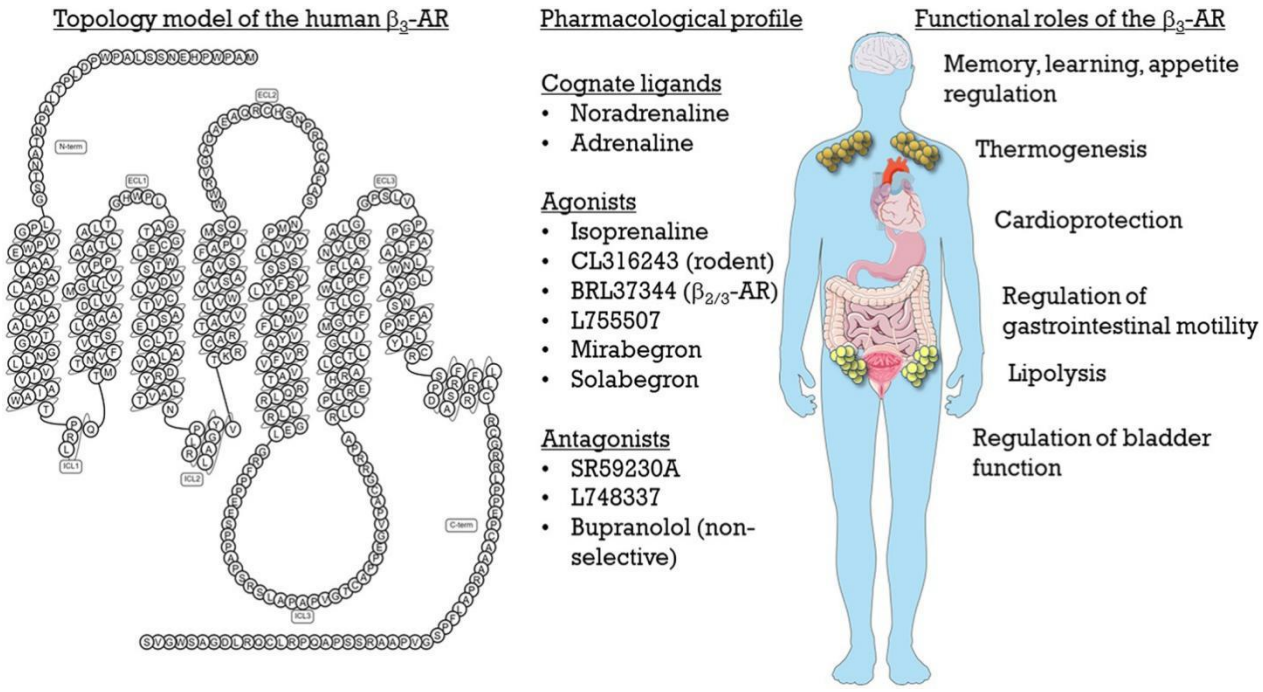
INTRODUCTION

Overactive bladder (OAB) is a common and bothersome symptom complex, which significantly affects patients' quality of life. Approximately 400 million people worldwide suffer with symptoms of urgency and frequency (dry OAB) and a proportion will have associated urgency incontinence (wet OAB). The prevalence of OAB increases with age with approximately 30–40% of the population over 75 being affected. The International Continence Society defines the OAB syndrome as urinary urgency, usually with frequency and nocturia with or without urgency urinary incontinence. For the management of overactive bladder syndrome (OAB) in over 30 years, mirabegron is the first of a new class of drugs licensed. It is a human β3-adrenoceptor agonist developed by AstellasPharma Inc. for the treatment of OAB[4]. Mirabegron has been using increasingly as an alternative to antimuscarinics in the last few years for treating patients with OAB. It was licensed for the treatment of OAB and has been approved for use in Japan in 2011, USA and Canada in 2012, and Europe in 2013.

The beta-adrenoceptors are distributed in adipose tissue, heart, vascular systems and the bladder. Studies in the pathophysiology of OAB have demonstrated three subtypes of beta-adrenoceptors in the detrusor muscle and urothelium. The β3 subtype was identified in 1989 and is the predominate adrenoceptor in the bladder and direct stimulation is responsible for mediating detrusor relaxation in humans and can increase bladder capacity. At a molecular level, the β3 adrenoceptor activation leads to opening of big conductance calcium activated potassium channels or activation of adenylyl cyclase with subsequent formation of cyclic adenosine monophosphate. The development of a β3 adrenoceptor agonist to cause detrusor relaxation is a further weapon in the armamentarium of both primary care physicians and specialist urologists, geriatricians and urogynaecologists. Two types of contraction have been observed in the human detrusor muscle: voiding and spontaneous involuntary contractions (IDCs) during bladder filling[1].



OAB often coexists in men with voiding symptoms secondary to benign prostatic obstruction. There are only two papers investigating this combination. The first study was an open-label randomized two-arm, two-sequence study to investigate the safety profiles of dual therapy with both medications, in particular assessment of cardiovascular side effects [van Gelderenvan *et al*. 2014][9]. There were no clinically relevant cardiovascular side effects noted. The second study investigated the combination of mirabegron with tamsulosin in male patients with mixed OAB and voiding lower urinary tract symptoms [Ichihara *et al*. 2015]. This was a randomized multicentre Japanese study of 96 men, which showed a significant improvement in urgency, urgency incontinence and nocturia with combination therapy as compared with monotherapy. These two studies show the safety of using mirabegron as add-on therapy in combination with tamsulosin in male patients with benign prostatic obstruction.

Use of mirabegron in the treatment of heart failure

The β_1-adrenoceptor is the predominant β-adrenoceptor subtype in the heart that regulates cardiac function (both the force and rate of myocardial contraction and relaxation). However, in heart failure, there is sustained activation of $\beta_{1/2}$-adrenoceptors due to increased catecholamine release from the sympathetic nerves and adrenal glands. This has adverse effects on cardiac function, leading to desensitization and internalization of $\beta_{1/2}$-adrenoceptors, loss of contractile function, cardiac remodelling, calcium overload and cardiomyocyte loss. As such, β-adrenoceptor blockers (such

as carvedilol, bisoprolol and metoprolol) are used to treat heart failure, as they can slow the heart rate, allowing the left ventricle to fill up more completely[2].

Off-target effects of mirabegron

While mirabegron has been defined as a β_3-adrenoceptor agonist, off-target effects at other receptors and transporters have been reported. In the Australian Public Assessment Report for mirabegron to the Therapeutic Goods Administration (Department of Health Therapeutic Goods Administration: Australian Public Assessment Report for Mirabegron, 2014), mirabegron was reported to bind weakly (K_i 1–11 μM) to α_1-adrenoceptors, noradrenaline transporters, dopamine transporters, muscarinic M_2 receptors and the sodium channel site 2[5].

PHARMACOLOGICAL ACTION OF MIRABEGRON IN OVERACTIVE BLADDER

Mirabegron is a potent and selective beta 3 adrenergic receptor agonist. Once beta 3 receptors are activated, the detrusor smooth muscle relaxes to allow for larger bladder capacity.

The beta adrenoceptor are distributed in adipose tissue, heart, vascular system and the bladder. 3 types of beta-adrenoreceptors in the detrusor muscle and urothelium. The predominate adrenoceptor in the bladder and direct stimulation is responsible for mediating detrusor relaxation in humans and can increase the capacity of bladder. At molecular level the beta 3 adrenoceptor activation leads to the opening of big conductance of calcium activated potassium channels or activation of adenyl cyclase adenosine monophosphate[8]. Two types of contraction have been observed in human detrusor muscle: voiding and spontaneous involuntary contractions (IDCs) during bladder filling. Beta2 adrenoceptor agonist have a pronounced effect on spontaneous contractile activity in the detrusor muscle In vitro therefore reducing the bladder tone and afferent input which is related to the storage symptoms of the OAB syndrome.

In addition, it has been demonstrated that BETA3-AR Agonist can directly inhibit afferent nerve firing in spinal cord transacted rats. These drugs have many fewer if any, cardiovascular side effects compared with beta 1and 2 AR agonist. Pilot studies already reported beneficial effects with terbutaline and clenbuterol.

PHARMACOKINETICS

Mirabegron is rapidly absorbed after oral administration. The time to maximum plasma concentration (Tmax) is approximately 3-4 hours and the plasma half life is 40- 50 hours.

About 70% of the compound is bound to plasma proteins, like albumin and α1-acid glycoprotein. Volume of distribution is approximately 1670 L.Its oral bioavailability ranges from 24% to 53%, which differs according to dose and gender. The absolute bioavailability increases from 29% to 35% at a dose of 25mg and 50 mg respectively. Bioavailability reduced when given with food; with low fat food affects the absorption than high fat food.

The Cmax and AUC of mirabegron are not determined by the age of the patient. The Cmax and AUC are approximately 40%–50% higher in females compared to males. Gender differences in Cmax and AUC are mainly the because of differences in body weight and bioavailability[7].

Mirabegron is metabolized in the liver via multiple pathways involving dealkylation, oxidation, glucuronidation and amide hydrolysis mainly by cytochrome P450 (CYP) 3A4, and CYP2D6 plays a minor role in its metabolism. The 8 mirabegron metabolites identified in human plasma do not contribute to the pharmacological activity. Appropriate monitoring and dose adjustment may be necessary while administering narrow therapeutic index drugs metabolized by CYP2D6. The elimination half life is approximately 50 hours.

Mirabegron is excreted by multiple mechanisms with no single predominating clearance pathway, and is excreted in both urine (55%) and faeces (34%). In subjects with severe renal impairment, Mirabegron AUC_{∞} and C_{max} increased 118% and 92%, respectively and with moderate hepatic impairment it is 65% and 175% respectively.

Caution should be exercised with concomitant administration of drugs that induce (e.g. rifampin) or inhibit (e.g.ketoconazole) CYP3A4 or where plasma exposure may be altered through CYP2D6 inhibition (e.g.desipramine or metoprolol) [58-60]. An evaluation of mirabegron plus tamsulosin (an α1-adrenoceptor antagonist) did not identify any clinically relevant CV effects [61] and a study of mirabegron plus solifenacin concluded that any potential interaction was not expected to be clinically relevant or require dose adjustment of either treatment.

DOSES AND DOSINGS

Dosage for overactive bladder: Adult dose (age 18 years and older)- typically starts with 25 mg taken orally once daily, If the symptoms persist then increase the dose to 50 mg orally once daily.

Special considerations:-

For people with severe kidney disease, the dose should not be more than 25 mg daily.

For people with moderate liver disease, the dose should not be more than 25 mg daily[3].

MIRABEGRON TRIALS

The safety and efficacy of mirabegron has been evaluated in multiple Phase II and Phase III clinical trials.

This includes the Phase IIa and IIb trials by Chapple et al. In 2013, they reported the results of the BLOSSOM trial.8 This was a proof-of-concept, randomized, double-blind, parallel-group, Phase IIa dose-ranging trial with mirabegron in patients with OAB. Tolterodine and placebo were used as controls. Two hundred and sixty patients were included from 31 European sites and the trial showed a statistically evident depletion in the mean micturition frequency from baseline by 17% with 100 mg and 18% with 150 mg of mirabegron, which resulted in a 9% reduction, and 11% reduction when compared with placebo and tolterodine respectively. Mirabegron has its own superior action in reducing the mean volume voided per micturition, mean number of incontinence episodes, nocturia episodes, urgency incontinence episodes, and urgency episodes per 24 hours.

This was reevaluated in the Dragon trial, which enrolled 919 patients.9 The patients were classed to five groups: placebo, and once-daily mirabegron 25, 50, 100, and 200 mg for 3 months. This showed significant dose-dependent decrease in the mean micturition frequency with 50, 100, and 200 mg of mirabegron, compared with placebo.

Nitti et al also examined the urodynamic parameters in men with lower urinary tract symptoms and bladder outflow obstruction treated with mirabegron. Two hundred male patients were included. Seventy patients were given by mirabegron 50 mg, 65 patients were given by mirabegron 100 mg, and 65 were given by placebo. Urodynamic parameters were

changed from baseline to the end of treatment in maximum urinary flow rate (Qmax) and detrusor pressure at Qmax (PdetQmax). From the study, it has been revealed that mirabegron did not adversely affect the voiding urodynamic parameters such as the bladder contractility index and the bladder voiding efficiency after 12 months of treatment, compared with placebo[6].

SIDE EFFECTS OF MIRABEGRON

Mirabegron have different adverse effects when compared to anticholinergic agents so it may be more tolerable in some individuals who experience side effects with anticholinergics. Mirabegron 50 mg causes dry mouth which is significantly lower than antimuscarinics. The occurrence of side effects such as constipation, hypertension and tachycardia were comparable to anticholinergic medication. Mirabegron has appeared to be used safely in combination with solifenacin and tamsulosin. Antimuscarinic side effects include Dry mouth, Constipation and Blurred vision. troublesome side effects include Dry mouth and Nausea and other side effects include UTI, Nasopharyngitis, Headache and Tachycardia[10].

CONCLUSION

Mirabegron is the first Beta 2 adrenoreceptor agonist licensed for use in the treatment of OAB. It is safe, effective and well tolerated new class of drug. The tolerability profile of mirabegron offers potential to improve patient adherence with treatment for OAB as dry mouth is often reason cited for stopping antimuscarinic treatment. The incidence of dry mouth with mirabegron is similar to placebo in all trials. Overall the results of Phase 3 trials are promising for mirabegron becoming a novel effective and safe drug for patient with OAB. The drug is well tolerated, with lower incidence of antimuscarinic side effects such as Constipation, dry mouth and blurred vision. Treatment with the to be marketed dose of 50 mg achieved the primary efficacy objectives although it resulted only in a reduction of 0.55 micturition per 24 hour and 0.40 incontinence episodes per 24 hour compared with placebo. Increase in BP and HR was significantly seen in phase 1 studies, pharmacokinetic interactions with other drugs and increased occurrence of new malignant event noted with 100 mg dose have raised concern.

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