Mirabegron for Overactive Bladder:

A Novel, First-in-Class β3- Agonist Therapy

Mohammed Imran,[1] Abul Kalam Najmi,[2] Shams Tabrez[3]

[1]Department of Pharmacology, Hamdard Institute of Medical Sciences and Research and Associated Hakeem Abdul Hameed Centenary Hospital, Jamia Hamdard, New Delhi -110062, India
[2]Department of Pharmacology, Faculty of Pharmacy, Jamia Hamdard, New Delhi -110062, India
[3]Department of Physiology, Hamdard Institute of Medical Sciences and Research and Associated Hakeem Abdul Hameed Centenary Hospital, Jamia Hamdard, New Delhi -110062, India

Corresponding Author:

Mohammed Imran, MD
Assistant Professor, Department of Pharmacology, Hamdard Institute of Medical Sciences and Research and Associated Hakeem Abdul Hameed Centenary Hospital, Jamia Hamdard, New Delhi-110062, India.

Tel: +91 954 007 5851
E mail: drimran@aol.in

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Purpose: To discuss the pharmacotherapeutic aspects of Mirabegron which is a first-in-class novel β3 receptor agonist drug recently approved by the food and drug administration (FDA) for the treatment of overactive bladder (OAB).

Materials and Methods: We conducted a computerized search of the MEDLINE/PUBMED databases with the word Mirabegron, β3 receptor agonist and overactive bladder.

Results: Effect of Mirabegron on β3 adrenergic receptor purportedly releases nitric oxide (NO) by an increase in intracellular Ca^{2+} through accumulation of cyclic adenosine monophosphate (cAMP). Along with NO which relaxes the detrusor muscle, it also releases an urothelial-derived inhibiting factor (UDIF) that inhibits contractions. It increases the bladder capacity by causing bladder relaxation during the storage phase.

Conclusion: Mirabegron appears to be a promising treatment in OAB patients by shifting its management from reducing detrusor over-activity to inducing relaxation. Also it lacks the troublesome side effects associated with the standard antimuscarinic management.

Keywords: mirabegron; β3 receptor agonist; urinary bladder; overactive; drug therapy

INTRODUCTION

Overactive bladder (OAB) includes constellation of symptoms such as urinary urgency, urge urinary incontinence, nocturia and frequency. Urgency is the hallmark of OAB. Patients may describe it as a sudden compelling desire to urinate that is difficult to defer. While urinary frequency is defined as voiding more than eight times in a 24-hour period, Nocturia is defined as the need to wake up one or more times per night for urination.[1]

Urinary bladder physiology

Normal bladder stores urine when the sympathetic nervous system (SNS) relaxes the detrusor muscle and closes the sphincters at the bladder outlet. It also inhibits the parasympathetic nervous system (PNS). When it attains a volume of around 200-400 ml, signal moves from the peripheral nervous system including autonomic, somatic and sensory afferent innervations to the central nervous system resulting in a sensation of urge. Normal urination begins after the release of acetylcholine (Ach) from the PNS and thereby contraction of the detrusor muscle. At the same time SNS opens the internal sphincter and somatic nervous system opens the external sphincter. Multiple outgoing and incoming neural pathways and neurotransmitters are involved in urine storage and voiding processes.[2,3]

Pathophysiology of OAB

OAB has multifactorial etio-pathogenesis. Causes of the detrusor muscle overactivity may be neurogenic, myogenic, or idiopathic in origin. Any of these may result in a constellation of urinary symptoms associated with OAB. Increased contraction in overactive bladders is due to hypersensitivity to cholinergic agonists through muscarinic (M2 or M3) receptors. Acetylcholine released from PNS causes activation of M3 receptors which is responsible for bladder contraction. It causes rise in cytosolic calcium (Ca^{2+}) from intracellular sarcoplasmic reticulum stores through activation of G-protein coupled receptor (GPCR) mediated phospholipase C breakdown. Generation of Inositol triphosphate (IP3) triggers Ca^{2+} release. M2 receptor activation conversely causes a fall in cyclic adenosine monophosphate (cAMP) preventing relaxation.[4]

Antimuscarinic drug management

Antimuscarinic drugs antagonize the effects of acetylcholine on muscarinic receptors. They reduce the contractions of the detrusor smooth muscle of the bladder and thus reduce the intensity of urge symptoms. Because of the associated troublesome anticholinergic side effects, newer antimuscarinics have been discovered to selectively target M3 receptors to reduce the side effects and increase the efficacy. But they still have limitations of producing adverse events.[5] Therefore, now, there would be a shift in management from reducing over activity to producing relaxation of the urinary bladder.

Mirabegron – a novel β3 agonist

The FDA, recently in June 2012, has approved a drug called Mirabegron in USA which had earlier been approved in Japan in 2011. The present review was conducted to have a rationale, pharmacotherapeutic and comprehensive information of this new class of drug for the management of OAB.

MATERIALS AND METHODS

We searched the MEDLINE/PUBMED databases of the National Library of Medicine for the comprehensive information on the newly introduced mirabegron therapy for OAB. The terms used for the search included mirabegron, β3 receptor agonist, overactive bladder and the combinations of these terminologies. All the relevant information obtained from other than PubMed/Medline search was also incorporated.

RESULTS

Mirabegron

It is first-in-class selective β3 adrenergic receptor agonist. It is indicated for treatment of OAB in 25 mg extended release once daily starting dose and may be progressed

to once daily 50 mg recommended dose.[6] Activation of β3-adrenoceptors (β3-ARs) by mirabegron increases bladder capacity by causing bladder relaxation as induced by sympathetic nerve activation especially during the storage phase of the fill-void cycle.[7]

Mechanism of Action

It has been demonstrated in rat experiments that activation of β3-AR by isoproterenol in urothelial cells can release nitric oxide (NO) by increasing the intracellular Ca^{2+} through cAMP accumulation. Activation of β3-AR not only causes relaxation by releases NO but also inhibits detrusor muscle contraction by releasing an urothelial derived inhibiting factor (UDIF). This implies that β3-AR agonists helps bladder storing capacity through direct inhibition of the detrusor as well as inhibition of the bladder afferent neurotransduction.[8,9]

Pharmacokinetics

The starting dosage of Mirabegron is 25 mg once daily with or without food. It reaches a bioavailability of 29% at a dose of 25 mg which further increases to 35% at a dose of 50 mg. It is extensively distributed in the body with a volume of distribution (aVd) of approximately 1670 L. It is moderately bound to the plasma protein (71%) with equal affinity to the albumin and alpha-1-acid glycoproteins. It attains a 2 fold higher concentration in red blood cells than in plasma.[10] There is a difference between linearity of intravenous and oral pharmacokinetics parameters. The drug concentration after i.v. dosing shows the linearity in the range of 7.5 – 50 mg, however there is increased bioavailability through oral route as the dose increases from 29% for 25 mg to 45% at 150 mg.[11]

Multiple enzymatic pathways are involved in mirabegron metabolism involving dealkylation, oxidation, and glucuronidation and amide hydrolyis. Although CYP3A4 and CYP2D6 isoenzymes metabolise this drug their role is limited in overall elimination. Other than these isoenzymes, its metabolism may also involve butyrylcholinesterase, uridine diphospho-glucuronosyltransferases and alcohol dehydrogenase. Two major pharmacologically inactive metabolites were detected in human plasma and these represent 16% and 11% of the total exposure. Approximately 25% of it is excreted unchanged in the urine and there is no excretion in the feces with a terminal half-life of approximately 50 hours. Renal clearance is mainly dose dependent due to tubular secretion and glomerular filtration and it (CLR) is approximately 13 L/h.[7] There is no apparent age difference in the pharmacokinetics parameters but women show approx. 40% higher Cmax (Maximum Concentration reached) and AUC (Area Under the Curve) than men and approx. 20% higher even after the weight correction.[12]

It is effective within 8 weeks in doses of 25 mg and 4 weeks in doses of 50 mg respectively after its administration as once a dose. Therefore dose may be increased to 50 mg once daily after assessing individual patient efficacy and tolerability. It has been advised in prescribing information to take it with water, swallowed whole and should not be chewed, divided, or crushed. It has been cautioned not to exceed beyond 25mg once daily in patients with severe renal impairment and patients with moderate hepatic impairment (Child-Pugh Class B). It is not recommended for use in patients with end stage renal disease (ESRD), or in patients with severe hepatic impairment (Child-Pugh Class C). It is supplied in two different strengths of 25 mg as well as 50 mg extended-release tablets.[13]

It has been approved with certain precautions and warnings that should be exercised while prescribing. Periodic monitoring of blood pressure is recommended as it can increase blood pressure especially in hypertensive patients. Although it is not recommended for use in severe uncontrolled hypertensive patients but randomized placebo-controlled studies (data submitted for its approval) show dose dependent increase in supine blood pressure in healthy volunteers. Approximately mean maximum systolic/diastolic blood pressure increase was 3.5/1.5 mmHg over the placebo in healthy volunteers as compared to the 0.5 – 1 mmHg increase over placebo in OAB patients. There is also a risk of

urinary retention in patients with bladder outlet obstruction and in patients taking anticholinergic drugs for OAB.[7]

Interactions

It is a moderate inhibitor of CYP2D6. It can increase metoprolol and desipramine concentration. Appropriate monitoring is recommended and dose adjustment may be necessary for narrow therapeutic index CYP2D6 substrates such as thioridazine, flecainide, propafenone and digoxin. Despite these limitations in prescribing information, however, there is no contraindication associated with this drug.[14] It has also shown to interact with warfarin by increasing the Cmax by approximately 4% and AUC by 9% after the multiple doses of 100mg, however there is no effect following a single dose administration of 25 mg on the warfarin pharmacodynamics endpoints such as International Normalized Ratio (INR) and prothrombin time. A cautious use is advised along with the warfarin intake.[7]

Adverse effects

The data from four clinical trial studies mentioned in prescribing information released by FDA were used to evaluate the safety and efficacy of Mirabegron in OAB patients.[7] The studies 1, 2 and 3 were done for a period of 12 weeks as double–blind, placebo controlled in 2736 patients including 432 patients on 25 mg, 1375 on 50 mg and 929 on 100 mg strength once daily. Study 4 was done to evaluate safety over a period of 1 year as randomized, fixed dose, double blind, active–controlled in 1632 patients including 812 patients on 50 mg and 820 patients on 100 mg strength. Out of the 1632 patients in study 4 only 564 patients completed the study for full one year. The most frequent (0.2%) adverse events in three (Study 1, 2 and 3) 12 weeks studies that led to the discontinuation of the drugs in clinical studies were nausea, headache, hypertension, diarrhea, constipation, dizziness and tachycardia. The serious adverse events associated with these studies were atrial fibrillation (0.2%) and prostate cancer (0.1%) found in more than one patient and at a rate greater than placebo. While study 4 was discontinued by the participants due to adverse events such as constipation (0.9%), headache (0.6%), dizziness (0.5%), hypertension (0.5%), dry eye (0.4%), nausea (0.4%), blurred vision (0.4%) and urinary tract infection (0.4%) which were reported in more than 2 patients and at a rate greater than active control, the serious adverse events in this study included cerebrovascular accidents (0.4%) and osteoarthritis (0.2%). In addition, a few cases of malignancies like breast cancer, lung neoplasm and prostate cancer were reported in more than two patients taking 100 mg dose of Mirabegron. The rate of neoplasm in patients taking Mirabegron 50 mg, Mirabegron 100 mg and active control once daily were 0.1%, 1.5% and 0.5% respectively in study 4.[7]

In general, there are some adverse reactions reported which demand caution in use of this therapy. The most common adverse reactions (i.e., in greater than 2% of patients) were hypertension, nasopharyngitis, urinary tract infection and headache. Other adverse events exceeding placebo rate and reported by 1% or more patients are hypertension, nasopharyngitis, urinary tract infection, headache, constipation, upper respiratory tract, infection, arthralgia, diarrhea, tachycardia, abdominal pain and fatigue. Those side effects developing in less than 1% of patients include palpitations, increased blood pressure, glaucoma, dyspepsia, gastritis, abdominal distension, sinusitis, rhinitis, increased GGT, increased AST, increased ALT, increased LDH, nephrolithiasis, bladder pain, vulvovaginal pruritus, vaginal infection, urticaria, leukocytoclastic vasculitis, rash, pruritus, purpura, lip edema [7]

The approval of Mirabegron was based on three placebo-controlled phase 3 studies in which 12 weeks treatment from 25 mg and 50 mg dose resulted in statistically significant improvement in co-primary efficacy endpoints. That is the change from baseline to the end of the treatment after 12 weeks in respect of mean number of incontinence episodes per 24 hours and mean number of micturition per 24 hours based on a 3 day micturition diary. Mirabegron in 25 mg strength reduced incontinence episodes by 1.36 from a baseline of 2.65 with a significant difference of 0.40 versus

placebo in 12 weeks (*P*-value=0.005). The micturition episodes reduced by 1.65 from a baseline of 11.68 with a significant difference of 0.47 versus placebo (*P* = .007). While 50 mg strength reduced the incontinence episodes by 1.38 from a baseline of 2.51 with a significant difference of 0.42 (*P* = .001). The micturition episodes reduced by 1.60 from a baseline of 11.66 with a difference of 0.42 versus placebo (*P*= .015).[7]

Although antimuscarinic drugs are the standard treatment in OAB management but their adverse effects and declining efficacy leads to long term compliance issues. Mirabegron is a new class of drug acting through dual mechanism of inhibiting afferents and causing relaxation of detrusor muscle. One of the animal studies compared the effects of Oxybutynin with the Mirabegron on single unit afferents activities of Aδ-fibers and C-fibers in response to the bladder filling. It was found to be superior in inhibiting the afferents and suppressing the micro contractions of urinary bladder.[15]

Limitations

The safety and efficacy studies have not been conducted in pediatrics patients and use for pregnant ladies are only advised after individualizing the risk benefit assessment. However it is excreted in the human milk and therefore not recommended in nursing females while no dose adjustment is required for geriatric patients.[10]

CONCLUSION

This class of drugs have the great potential in shifting the management of the OAB through a different mechanism of action which has never tried earlier. Although Mirabegron has lower side effects as compared to the earlier drugs used in the management of OAB but it has yet to be standardized in respect of the gender pharmacokinetics variations and a few specified populations. The drug is to be used on an individual basis till long term studies prove the safety of the drug for long term intake.

CONFLICT OF INTEREST

None declared.

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