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Mirabegron an update – What is new?.

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ABSTRACT

Mirabegron is an orally active β_3 adrenoceptor agonist useful for the symptomatic relief of overactive bladder (OAB) .Originally it was developed to treat diabetes and then its use was focused for OAB. This drug has been shown to reduce the resting intravesical pressure and contraction frequency in anesthetized rates without affecting the amplitude of micturition contraction. It has also shown to reduce the non-micturition bladder contractions in an awake rat model with bladder outlet obstruction. Mirabegron is known to be a cytochrome P450 (CYP) 2D6 inhibitor and shown a concern for pharmacokinetic interactions. It has shown a low incidence of adverse effects as compared to antimuscarinic drugs which are the first line of treatment in OAB. Hence it has been shown to be one of the most notable alternative drugs to antimuscarinic agents in the treatment of OAB.
Key words: Mirabegron; overactive bladder, β_3 adrenoceptor agonist

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INTRODUCTION

Human β_3 adrenoceptors was cloned in 1989 and was initially identified in adipose tissue. Now it has been identified in the human heart, gall bladder, gastrointestinal tract, prostate, detrusor muscles of the urinary bladder and brain. Activation of beta-adrenoceptor (AR) causes bladder relaxation induced by sympathetic nerve activation during the storage phase. Based on mRNA expression it has been found that, at least 95% of the adrenoceptor message in human bladder comprises the β_3 adrenoceptor subtype. Studies have shown that the relaxant effects induced by adrenergic receptor stimulation in human detrusor are mediated via β_3-AR activation. Thus selective β_3 agonist can play a significant part in the treatment of overactive bladder.[1]

Overactive bladder (OAB) is characterized by symptoms of urinary urgency , with or without urgency incontinence, usually with increased daytime frequency and nocturia.[2] The prevalence of OAB increases with age .It is more common in women than men and in Asia it's prevalence is about 53.1%.[3] The treatment for this disorder includes non-pharmacological treatment and pharmacological treatment. Non pharmacological treatment includes bladder retraining, pelvic floor strengthing exercises and fluid management.[4] Current guidelines recommend oral antimuscarinics drugs as a first line of pharmacologic treatment in the management of overactive bladder. But because of its antimuscarinics adverse effects other treatment options have been tried.[5] The development of Mirabegron which is an orally active β_3 agonist approved by the FDA in June 2012 is one step towards the better treatment options for the management of overactive bladder.

Chemistry

The chemical name of Mirabegron is 2-(2-aminothiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy- 2-phenylethyl] amino}ethyl)phenyl]acetamide having an empirical formula of $C_{21}H_{24}N_4O_2S$ and a molecular weight of 396.51. The structural formula of Mirabegron is:

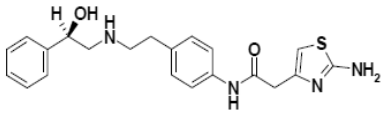

Figure 1: Structure of Mirabegron

It is a white powder which is practically insoluble in water and soluble in methanol and dimethyl sulfoxide.[6]

Mechanism of Action

Mirabegron activates the beta 3 receptors on the detrusor muscle of the bladder to facilitate filling of the bladder and storage of urine without inhibiting bladder voiding

contractions. Hence detrusor relaxation is mainly mediated by the cyclic adenosine monophosphate pathway.[7]

β_3 - AR agonists have been found to directly cause dose-dependent detrusor relaxation during the storage phase of the micturition cycle and inhibit neurogenic detrusor over activity and experimentally induced or bladder outlet obstruction (BOO)-associated OAB . It has been shown that, compared with other agents (including antimuscarinics), β_3-AR agonists increase bladder capacity with no change in micturition pressure and residual volume.[8] Which makes Mirabegron a novel treatment option for OAB.

Pharmacokinetics

Mirabegron is well tolerated orally. It is extensively distributed in the body. The bioavailability of the drug is dose dependent and is 35% with 50mg of the drug. The plasma protein binding is 71% and the terminal half life is 50 hours. The therapeutic dose of the drug used for overactive bladder is 25 mg once daily which can be increased to 50mg per day. Food does not interfere with the absorption of the drug. The metabolism can be by different processes like glucuronic conjugation, oxidation and N-dealkylation. It is said to inhibit cytochrome P450 (CYP) 2D6 and has raised concern over pharmacokinetic drug interactions. The drug is excreted in urine and feces.[9]

Adverse Effect or Toxicity Profile

The most common adverse effects encountered by the investigators were gastro-intestinal disorders, including constipation, dry mouth, dyspepsia and nausea. Researchers have also found a small increase in the mean pulse rate with the use of this drug. However it did not cause any cardiovascular adverse event. Other adverse effects like hypertension, nasopharyngitis, urinary tract infection and headache were also reported. There are also reports of serious adverse events like breast cancer, lung neoplasm and prostate cancer. In a study conducted in Japan there was a case of Steven Johnson syndrome with 100 mg of Mirabegron. No specific antidote has been developed for over dosage. In post marketing surveillance Mirabegron has been known to have caused urinary retention in patients with bladder outlet obstruction and in patients taking antimuscarinic medications.[10]

Drug Interactions

Since Mirabegron is a moderate CYP2D6 Inhibitor, the drugs metabolized by CYP2D6 like metoprolol and desipramine when co-administered with Mirabegron will have an increase plasma concentration. When the drug was combined with digoxin or warfarin the Cmax was increased by 29% and 4% respectively.[10]

Use In Specific Populations

Mirabegron belongs to category C and its use in pregnancy is only indicated when the benefit outweighs the risk. It is not known whether the drug is excreted in human milk but studies have found that this drug has been found in milk of rats. The safety and effectiveness in pediatric patients have not yet been established. No dose adjustment is required in elderly.

In end stage renal disease and hepatic impairment no studies have been conducted hence Mirabegron is not recommended in these patients. But in case of severe renal impairment the daily dose should not exceed 25mg, no dose adjustment is required in mild or moderate renal impairment.[10]

Precautions and Contraindications

Mirabegron can increase the blood pressure. In two studies conducted on healthy volunteers it was associated with increase in supine blood pressure. So periodic blood pressure monitoring is required in prehypertensive and hypertensive patients. There are no contraindications for the use of Mirabegron.[10]

Summary on the Clinical Trials

A clinical trial conducted by Chapple et al on patients with overactive bladder (OAB) reported their phase IIA results. The study showed a significant improvement in mean number of micturitions per hour with 100 mg and 150 mg of Mirabegron compared to placebo. No severe adverse effects were observed in this study except a small mean increase in pulse rate.[11] Following this there was a phase IIB trial conducted in Europe which was a dose-ranging study with Mirabegron in the does 25mg, 100mg, 150 mg and 200 mg in patients with OAB .In this study there was a decrease in the mean number of micturitions per 24 hours dose-dependently and it was statistically significant with 50 mg of Mirabegron compared to placebo. The mean volume of voided urine per micturition also increased dose dependently and was statistically significant with 50 mg of Mirabegron compared to placebo. The incidences of adverse effects were common to all groups. The commonest adverse effects being constipation, dry mouth, dyspepsia and nausea and a small but significant increase in mean pulse rate as in the previous study.[12]

A multicentric Phase III trial conducted in USA and Canada where the safety and efficacy of 50 & 100 mg of Mirabegron was compared with placebo in OAB . This study showed statistically significant improvement in the mean volume voided / micturition when compared to placebo. The most common adverse effects encountered in all the treatment groups was hypertension, urinary tract infection, headache and nasopharyngitis.[13] Another phase III multicentric trial was conducted in Australia and Europe on patients with OAB. In this trial Mirabegron was compared with placebo and tolterodine. The researchers found a statistically significant improvement of the key symptoms of OAB from baseline in patients with

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Mirabegron compared with placebo. Here the commonly reported adverse effects were hypertension, dry mouth and headache in all the treatment groups.[14]

Table 1: Various clinical trials of Mirabegron

	Author	Design	No of patients	dose	Indications	Outcome
1.	Chapple et al	Randomized placebo controlled Phase IIA trial	314	4 groups: Mirabegron 100mg Mirabegron 150mg Tolterodine 4mg , Placebo for 4 weeks	OAB	Change in mean volume voided was dose-dependently increased
2.	Chapple et al	Randomized Phase II b trial	928	5 groups: Mirabegron 25mg Mirabegron 100mg Mirabegron 150mg Mirabegron 200mg Placebo for 12 weeks	OAB	The mean volume voided per micturition was greater for 150 mg than placebo Improvement in the number of incontinence and micturitions per 24 hour compared to placebo
3.	Nitti V et al	Multicentric ,randomized, double blind	1328	3 groups: Mirabegron 50mg Mirabegron 100mg Placebo for 12 weeks	OAB	Improvement in the number of incontinence and micturitions per 24 hour compared to placebo
4.	Khullar V et al	Multicentric ,randomized, double blind	1978	4 groups: Mirabegron 50mg Mirabegron 100mg Tolterodine 4mg , placebo for 4 weeks	OAB	

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Table 2: Comparison between Mirabegron and antimuscarinic drugs

	Mirabegron	Antimuscarinic drugs
Mechanism	Stimulates β_3 receptors at the detrusor musclesof thebladder	Blocks the muscarinic receptors on the detrusor muscle and also structures outside the bladder
Pharmacokinetics	Inhibits cytochrome P450 2D6	No effect on cytochrome P450
Actions	Improves the storage capacity of the bladder without inhibiting bladder voiding	Inhibit bladder voiding causing urinary retention
	Reduces Frequency of rhythmic bladder contractions [8]	Decreases the amplitude of bladder contractions [8]
	Incidence is low	Incidence is high
Adverse effects	Nil	
Contraindications		Glaucoma, BPH

CONCLUSION

Mirabegron has a distinct mechanism of action and safety profile. Therefore it may provide a good therapeutic alternative for the treatment of OAB in patients who are intolerant or have an suboptimal response to anti- muscarinic agents. Mirabegron can be used to treat OAB especially in patients with benign prostatic hyperplasia, without increasing post void residuals which is an advantage over antimuscarinic drugs. However more post marketing surveillance reports are required to come to a definite conclusion regarding the advantages of Mirabegron over antimuscarinic drugs.

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