Original Article

Effectiveness of Mirabegron in Children with Nocturnal Enuresis

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Abstract

Enuresis is a common complaint that presents in the primary care setting. It is important to rule out secondary causes of enuresis; however, most cases are considered primary. Most children that experience enuresis will not have symptoms that progress past adolescence. Medications can help to control symptoms while the child is in the process of developing out of primary enuresis. Mirabegron has promising results for nocturnal enuresis symptoms in children.

INTRODUCTION

First-line treatment of Primary monosymptomatic nocturnal enuresis (PMNE) involves education and giving information on enuresis. In such cases, the spontaneous resolution rate has been shown to be 15% (**1**).

1. Non pharmacological Treatment

1.1. Urotherapy

First-line treatment involves simple behavioral changes such as carrying the child to the toilet at night or awakening him or her for urination, along with daily motivation and exercises aimed at increasing bladder capacity. In children, non-surgical and non-pharmacological methods that correct voiding habits (**2**) must be the backbone of any treatment (**3**).

Standard urotherapy involves educating families regarding enuresis and its treatment, offering suggestions for voiding patterns and frequency, and treating constipation when present. The early diagnosis and treatment of constipation not only improves enuresis, but untreated constipation may also lead to treatment refractory enuresis (**2**)**.**

Although limiting fluid intake is routinely advised to all patients with enuresis, its efficiency has not been proven. Similarly, avoidance of drinks with a diuretic effect (such as those containing caffeine) is advised, although the effect of this has also not been investigated(**4).**

1.2 Enuresis alarm

The exact mechanism of alarm therapy is not well understood, one of the possible mechanisms has been explained by classic conditioning theory (The child is woken by the bell in order to get up and complete voiding into the toilet. A more appropriate approach is an operant type of behavioral technique in which the child learns to suppress his/her bladder emptying during sleep. It has a response rate of 60% and the long term success rate was reported as 43%)**(5).**

Alarm is Placed under the bed linens or applied to the undergarments, the alarm senses wetness and arouses the patient with an audible or vibratory alarm. Nearly two-thirds of patients become dry while using the alarm, thus making it an excellent therapeutic option. Of those who become dry on therapy, nearly half will relapse. Overlearning is the process whereby newly dry patients are given extra fluids prior to bedtime while still using the device, and has been shown to lower relapse rates. An interesting finding is that the alarm increases nocturnal bladder capacity, which may explain why children after successful treatment are often able to sleep dry without nocturia. **(6).**

2.Pharmacological Treatment

2.1. Desmopressin

Desmopressin is a synthetic analog of arginine vasopressin, which reduces urine output. It is believed that desmopressin treats nocturnal enuresis by decreasing urine volume at night. Desmopressin has been available as an intranasal spray and in tablet formulations for the treatment of primary nocturnal enuresis for many years; a convenient, sublingual oral desmopressin lyophilisate (MELT) formulation is a more recent development **(7).**

The ICCS suggest that the best candidates for this therapy are those with nocturnal urine production > 130% of expected bladder capacity for age (nocturnal polyuria). While actively taking the medication, 30 and 40% of children are estimated to be full and partial responders, respectively **(8).**

It is a well tolerated drug with some uncommon side effects such as headache and emotional disturbances, and a very rare possible side effect of water intoxication **(5).**

2.2. Imipramine and Other Tricyclic Antidepressants

Tricyclic medications affect the central nervous system by inhibiting the reuptake of serotonin and noradrenaline from synaptic alpha receptors. They show an effect on the sleep center in the brain and also have anticholinergic, antispasmodic, and local anesthetic effects (**9**).

The most frequently used tricyclic antidepressant for enuresis treatment is imipramine. Imipramine is moderately effective (50%) and has a high relapse rate. Clinical response has been shown to be in correlation with plasma levels, although it has been reported that measurement of serum levels is not of any clinical significance. Imipramine is cardiotoxic at high dosages, and cases of death resulting from cardiotoxicity have been reported. Therefore, it appears not to be suitable for first-line treatment of enuresis. Its dosage is 25 mg for children under 6 years of age (20-25 kg [44lb, 1oz to 55lb, 2oz] weight) and 50-75 mg for those over 11. It is taken orally 1 hour before sleep (**9**).

2.3. Oxybutynin and Other Anticholinergic Drugs

Anticholinergic treatment is intended to prevent involuntary detrusor contractions. Anticholinergic treatment has been demonstrated to significantly decrease or cure urge incontinence in children, and can be discontinued 6 months after a complete response has been observed. Oxybutynin is a commonly used anticholinergic agent for the treatment of small capacity bladder and detrusor over-activity in children (**3**).

Literature reports the effect of oxybutynin to be between 47-71%, with an even higher response rate when it is combined with desmopressin. A recent study found the response and relapse rates of oxybutynin, desmopressin, and imipramine after 6 weeks of use to be 71% vs 63.3% vs 61.3% and 31.8% vs 57.9% vs 63.2%, respectively (**10**).

The side effects of oxybutynin include dry mouth, headache, nausea, vomiting, tachycardia, and blurred vision. In children who cannot tolerate oxybutynin, Tolterodine may be used, as it has a better side effect profile and is more bladder-selective when compared to oxybutynin (**11**).

2.4. Other Drugs Used in the Treatment of Nocturnal Enuresis

Although many drugs and their combinations have been investigated for use in nocturnal enuresis, only a few have been found to be effective. Despite having demonstrated better effects when compared to a placebo, indomethacin, diclofenac, diazepam, and atomoxetine are rarely used due to their side effects and lack of high-quality data (**3)**.

2.5. Combined Therapy

A recent study compared the efficacy of combination therapy with desmopressin and an anticholinergic to desmopressin monotherapy for the first line treatment of children with primary monosymptomatic nocturnal enuresis (PMNE). The efficacy was evaluated by International Children's Continence Society criteria at 1 and 3 months after treatment initiation. The combination therapy group showed a higher rate of complete response than the monotherapy group (20.4% vs. 6.1% at 1 month of treatment; 46.9% vs. 22.4% at 3 months of treatment). In terms of success (response and complete response), there was a significant difference between the two groups after 3 months of treatment. The study concluded that combination therapy with desmopressin plus an anticholinergic is quicker and more effective than desmopressin monotherapy in reducing PMNE **(12).**

Beta-3-Receptor Agonists

These agents elicit a direct inhibition of afferent nerve firing independent of the relaxing effects on bladder smooth muscle **(13)**.

MIRABEGRON

There are 3 types of β-adrenoceptors (β1, β2, β3) in bladder detrusor muscle as well as urothelial lining, β3 being most predominant of them. β3 receptors excitation causes detrusor smooth muscle relaxation. Mirabegron which is β3 receptor agonist, has been extensively used as well as studied for treatment of OAB. Mirabegron has been found to be safe, effective, well-tolerated. As far as incidence of dry mouth is concerned, it had similar results to placebo in almost all trials **(14)**.

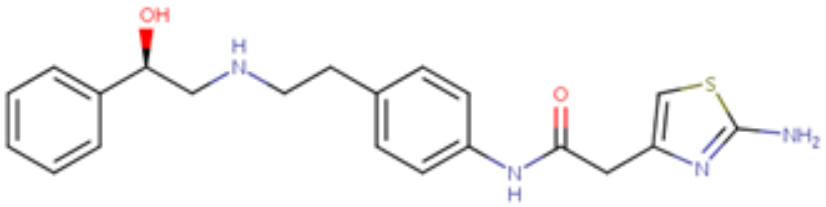

Figure (1): Mirabegron.

The good efficacy and tolerability profile of mirabegron has reported, and may suggest its inclusion as an initial management in algorithm protocol for newly diagnosed OAB in children. Longer term evaluation is still needed to assess its persistent safety, efficacy, discontinuation rate, and tachyphylaxis **(15)**

Mirabegron approved for the treatment of overactive bladder and neurogenic detrusor overactivity in adult. However, their use in children (≥ 3 years) has only recently been approved for patients with neurogenic detrusor overactivity (**16).**

PHARMACOLOGY OF MIRABEGRON

The beta-adrenoceptors are distributed in adipose tissue, heart, vascular systems and the bladder 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. Two types of contraction have been observed in the human detrusor muscle: voiding and spontaneous involuntary contractions (IDCs) during bladder filling. Preclinical and clinical studies showed β3 adrenoceptor agonists have no significant negative effect on the voiding contraction therefore limiting the risk of urinary retention**(17)**.

β3 adrenoceptor agonists have shown 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 **(18)**.

In June 2012, the FDA approved the first beta-3-receptor agonist, mirabegron, for symptoms of urge urinary incontinence, urgency, and urinary frequency associated with OAB. Beta-3-receptor agonists act directly to inhibit afferent nerve firing independent of the relaxing effects on the bladder smooth muscle. In one trial, mirabegron was shown to be safe and efficacious over a one-year period **(13)**.

In another multicenter, randomized, double-blind, parallel-group placebo- and tolterodine-controlled phase 3 trial, mirabegron significantly improved the number of incontinence episodes and the number of micturitions per 24 hours compared with placebo and was well tolerated **(19)**.

SIDE EFFECTS

Mirabegron does not have the same adverse effects as anticholinergic agents and, thus, may be more tolerable in some individuals who experience side effects with anticholinergics. Mirabegron 50 mg caused dry mouth with an incidence similar to placebo and significantly lower than antimuscarinics. However, patients who use mirabegron could suffer from side effects such as raised blood pressure, tachycardia, urinary tract infections, constipation, headache, back pain, and dizziness. Less common side effects include palpitations, atrial fibrillation, urticarial, and joint pain and swelling **(20)**.

Mirabegron is contraindicated in patients with severe uncontrolled hypertension, and advice about regular monitoring is being introduced because of cases of severe hypertension. It stated that mirabegron is contraindicated in patients with severe uncontrolled hypertension. It also recommended that blood pressure should be checked before starting treatment and monitored regularly during treatment, especially in patients with hypertension **(21)**.

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