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STIMULATION OF B3-RECEPTOR-INDUCED CENTRAL NEUROGENIC EDEMA AND VITiated ELECTROLYTE HOMEOSTASIS IN EXPERIMENTAL RODENT MODEL

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Abstract.
Mirabegron is one of the recently introduced treatments for overactive bladder which avoids the undue effects of antimuscarinics such as constipation, headache, and dry mouth. This study investigated chronic relatively high doses of beta3 adrenergic receptor activation effect on electrolyte hemostasis and possible consequence on the central nervous system viability. In the present study, serum sodium, potassium, chloride, and calcium ion levels using flame photometry had been measured and eosin and hematoxylin staining for cerebral vasculature in the brain striatum. Results showed that chronic administration of mirabegron has a modest decrease in sodium, chloride, and potassium levels while increasing calcium serum levels. Moreover, edema and neuronal degeneration have been observed in Wistar rats. In summary, a chronic high dose of beta 3 adrenergic agonist Mirabegron might have a deleterious effect on electrolytes in question homeostasis due to loss of selectivity to beta 3 adrenoceptor when administered in a high dose.

Key words. Sodium, potassium, chloride, calcium, mirabegron, B3-adrenoreceptor.

Introduction.
Worldwide prevalence of lower urinary tract symptoms, overactive bladder (OAB), and urinary incontinence are high, and the numbers of affected people tend to increase with time approximately 4.3 billion, especially in developing regions [1]. The incidence of urgent urinary incontinence related to OAB is approximately 10 in women and 14% in men which makes it one of the most encountered complaints worldwide [2], the latter causing great social and economic burdens on both individuals and families. In severe cases, it causes a great deal of distress and embarrassment [3,4]. Mirabegron is the first clinically used selective beta-3 adrenergic receptor agonist which is approved to treat OAB symptoms [5,6]. Overactive bladder is defined as urgency, with or without urgency urinary incontinence, with increased daytime frequency and nocturia [7]. These symptoms are indicators of urodynamically detrusor overactivity. However, it can be due to other factors causing ureterovesical dysfunction [8,9]. The distribution of functional beta-adrenoceptors (1, 2, and 3) was reported by Tyagi et. al. in the urothelium and detrusor muscle of the human bladder which revealed that selective beta3 adrenergic receptor agonist solabegron evoked a significant concentration-dependent relaxation of the isolated bladder trips. These findings suggested the selective beta3 adrenoceptor agonist as a potential novel treatment for OBD [10]. Mirabegron has unique mechanisms of action to treat OBD by stimulating the beta-3 adrenergic receptor by doing so it increases voiding intervals through increases the compliance of the urinary bladder by detrusor urinary bladder smooth muscle relaxation which in turn increases urinary bladder accommodation to larger urine volume without urination urgency [11-15]. In addition, Mirabegron has been suggested to treat several other clinical conditions like erectile dysfunction related to lower urinary tract symptoms /benign prostatic obstruction patients by clinical report however, the mechanism of action in this clinical situation was not illustrated clearly [16] Mirabegron is considered a new advance in the treatment of OAB symptoms cause the commonly used treatment was antimuscarinic agents causing troublesome adverse effects, for instance, dry mouth, confusion, constipation, headache, and glaucoma [17,18], and although other treatments for has been proposed to treat OAB symptoms like tramadol, gabapentin and botulinum toxin [19-21], however, antimuscarinic had considered being the mainstay of treatment for OAB for decades. The safety and tolerability of mirabegron draw great attention. Clinical safety was reported by Nitti V W et. al. through pooling data from three randomized, placebo-controlled, double-blind, and over 12 weeks of three different mirabegron doses (25,50, and100mg daily) which revealed that mirabegron treatment was associated with main hypertension, nasopharyngitis, and even urinary tract infection among other less incident adverse events [22,23]. As part of phase four studies, a multicenter, randomized, double-blind, placebo-controlled, parallel comparison clinical study investigated the efficacy and safety profile of mirabegron, which revealed that mirabegron reduces OAB symptoms in men after 12 weeks of treatment [24]. Also, a recent clinical study showed the efficacy of 50 mg of mirabegron in improving women suffering from OAB and urgency urinary incontinence or mixed urinary incontinence versus placebo including micturition frequency, and urinary incontinence [25]. Several studies have investigated the impact of mirabegron on different body organs and functions for instance female sexual function and the possible cognitive adverse effects and high incidence of headache and migraine [26-28]. Philip et al. have reported that elevation of potassium chloride has stimulatory effects on bladder detrusor smooth muscle. The latter finding can be one of the mechanisms of action that can control OAB [29]. Activation of beta-3 adrenergic receptor has intriguing effects on mineral homeostasis which might have a role in its effect on bladder detrusor smooth muscle. This study aims to investigate whether Mirabegron's mechanisms of action could include its effect on the homeostasis of sodium, potassium, and/or calcium.

The aims of this study are the investigation of the possible adverse effect of continuous stimulation of beta 3 adrenoceptors on brain tissue morphology and electrolyte hemostasis.

Materials and methods.
Animals: Randomly chosen ten male Wistar rats aged between 3-4 months were used in the current study. All animals were kept under a controlled environment at a temperature 23-25°C and humidity of 50-55%. All animals had access to food and water ad libitum. All the protocols and procedures had been approved by Ninevah university [30-32].
Ten rats were divided into two groups, first group was administered 6 mg/kg of mirabegron while the second group was administered tap water orally once daily for three months.

**Biochemical analysis:** Blood samples of five rats from each group were exsanguinated by Retro orbital blood withdrawal. The serum was separated by centrifugation 1000g after lifting the blood sample at from temperature for 30-60min Electrolytes analysis of Sodium, potassium, and calcium concentrations in serum were measured by flame photometry Instrumentation Laboratory, Lexington, MA.

**Histological study:** Rat's brains were kept in paraformaldehyde 10% in phosphate saline buffer overnight for fixation then embedded in paraffin for sectioning and stained with Hematoxylin-eosin.

Statistical analysis: An unpaired t-test was performed to compare between mirabegron group and the control group, using GraphPad Instant software for tabulation. A P value of <0.05 was considered statistically significant.

**Results.**

Three months of mirabegron 6 mg/kg orally once daily significantly decreases serum sodium and chloride level (P<0.5) in comparison with the control group. Potassium levels also significantly decreased in mirabegron in comparison with the control group. While calcium level significantly elevated with mirabegron use (figure 1).

Rat's brain which was treated for three months with Mirabegron sections showed signs of necrosis and neuronal degeneration (figure 2) under the light microscope.

**Discussion.**

The current study showed that three months of treatment of rats with 6 mg/kg of mirabegron caused a decrease in both sodium and potassium levels and an increase in calcium levels.

Moreover, 6mg/kg of mirabegron for three months, caused neuronal degeneration and edema.

Idiopathic adrenoceptor is one of the adrenergic receptors activated by catecholamines. Beta adrenoceptor activation is through beta-adrenoceptor-adenylyl cyclase-protein kinase A cascade. Beta 3 adrenoceptors consist of seven membrane-spanning domains consisting of three intra and three extracellular loops plus one extracellular and one intracellular terminal [33]. Beta 3 adrenoceptor is present mainly in the bladder detrusor muscle and in adipose tissue [34].

Mirabegron has drawn a great deal of attention recently because of its unique mechanism of action by direct blocking beta 3 adrenoceptor in the detrusor muscle treating over-active bladder of both neurogenic and non-neurogenic origin. Recently, Mirabegron has been suggested to treat obesity in relatively high doses through an increase in energy expenditure without an increase in blood pressure or heart rate (avoiding cardiovascular undesirable effect) through besieging of white adipose tissue to brown adipose tissue when given in doses of 50 and 100 mg daily while 150 and 200 mg caused cardiovascular adverse effect [35,36].

Zhang and his coworker reported functional pain syndromes and brain damage associated with increased catecholamine activity as they report that continuous activation of beta 2 and beta 3 adrenoceptors for 14 days results in pain at several body regions through the release of pro-inflammatory cytokine tumor necrosis factor-alpha [37]. Consistently, another study by Kline revealed the attenuation of catechol-O-methyltransferase activity can lead to enhanced chronic pain perception in humans, and this pain perception is mediated by beta-adrenoceptors [38]. Functional pain and comorbid depression due to the Catechol-O-methyltransferase enzyme which is responsible for catecholamines metabolism polymorphism has been investigated and the results shown blocking COMT enzyme caused pain and depressive-like behavior was prominent in females who administered COMT inhibitor OR486 continuously over 14 days in addition to increase glucocorticoid receptor expression a well-know stress related receptor [39].

Mild activation of beta2 adrenoceptor can lead to an intracellular influx of potassium causing hypokalemia which in turn decreases the reactivity of detrusor muscle [40-42]. The latter might be one of the suggested mechanisms through which mirabegron can treat OAB. Calcium elevation in this study is not

**Figure 1.** Disturbances of electrolyte homeostasis (Na, K, Cl, and Ca) stimulation of B3 receptor. Data expressed as mean±SD. *p<0.05 as compared to after stimulation of B3 receptor or control group.

**Figure 2.** Representative image for Brain (a) control, (b) after 3-month stimulation of B3 receptor with Mirabegron. H and E stain, 100X and 400X.
clear and these action could increase the chance of application of mirabegron for musculoskeletal delimita including spinal injury [43].

**Conclusion.**

The current study highlights the possible central nervous system adverse effect of mirabegron when used in relatively high doses over an extended time for the first time. The latter effect might be due to the beta 2 or 1 adrenoreceptor not being excluded and whether these effects due to electrolytes disturbance could be a marker for these neurological adverse effects need more studies.

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