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The risk and severity of developing symptomatic palpitations when prescribed mirabegron for overactive bladder

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ABSTRACT

Objectives: Mirabegron is a new selective β_3-adrenoreceptor agonist licensed for the treatment of overactive bladder (OAB). In clinical trials, mirabegron is well-tolerated with a low side-effect profile. There is little data available on the risks in a non-selected population. The presence of β-adrenoreceptors in cardiac and vascular tissue leads to the possibility of the development of adverse cardiovascular events. We conducted a consecutive cohort study to assess the risk of developing palpitations, the severity of the condition and to investigate any underlying risk factors that predispose patients with OAB to develop palpitations whilst taking mirabegron.

Study design: A consecutive cohort of patients with OAB was studied between February 2013 and June 2014. Patients were prescribed mirabegron 50 mg daily and outcomes assessed at 6 weeks. Patients with known cardiac arrhythmias were excluded. In patients who developed palpitations, a detailed account of their symptoms and medical history were documented and a 12-lead electrocardiogram (ECG) was performed to assess heart rate, QT interval and the presence of any persisting arrhythmia was conducted.

Results: A total of 279 patients were started on mirabegron. Eight patients (2.9%) reported palpitations whilst taking the drug. Two patients with a history of palpitations with no history of prolonged QT interval or arrhythmia on ECG developed worsening palpitations. The QTc was prolonged in two patients at 0.458 and 0.441 s (QTc <420). Three patients developed chest pain or tightness. The palpitations resolved once therapy was stopped and did not result in serious adverse events such as hospitalisation.

Conclusions: Palpitations in an unselected population have a similar incidence to that demonstrated in previous drug trials. Palpitations may be associated with a worsening of cardiovascular dysfunction.

Introduction

Mirabegron is a selective β_3-adrenoreceptor agonist approved for the treatment of overactive bladder (OAB) [1,2]. It is the first of this new class of drug to be introduced into clinical practice [3]. Mirabegron facilitates detrusor relaxation during the storage phase of the fill-void cycle via the activation of β_3 receptors [2,3]. This results in a significant reduction in the mean number of micturitions and incontinence episodes in a 24 h period [4–8]. National Institute for Health and Care Excellence (NICE) guidance has recommended the use of mirabegron for the treatment of OAB when antimuscarinic drugs are ineffective, contraindicated or have unacceptable side-effects [9].

β_3-Adrenoreceptors are predominantly found in the bladder and urothelium [2,3]. The presence of β-adrenoreceptors (β_1 and β_2) in cardiac and vascular tissue leads to the possibility of negative cardiovascular effects if there is cross reactivity. In clinical trials, mirabegron seems safe and well tolerated with a low incidence of adverse events [7,8]. However, phase III trials of mirabegron have demonstrated a small increase in pulse rate and an increase in QTc interval on electrocardiograms. Regardless, the overall adverse cardiovascular risk has been considered to be low [10]. Patients in clinical trials are selected and significant morbidity or cardiac risk factors may make patients less likely to be included in studies or may be exclusion criteria [11]. Trials of mirabegron excluded patients with a prolonged QT interval or patients taking drugs known to prolong the QT interval. There is no such screening in clinical practice where QT intervals are not routinely assessed. This could result in an increased risk of adverse cardiac events when mirabegron is used in non-selected population. Adverse cardiac events are a major worry for any drug therapy

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Table 1
Side-effects from mirabegron.

Side-effects	Number of patients 28(%)	Mirabegron discontinued due to side-effects
Palpitations	8 (2.7)	7
Heartburn	4 (1.4)	4
Urinary tract infection	4 (1.4)	4
Abdominal pain	3 (1.0)	3
Migraines	2 (0.7)	2
Dry mouth	2 (0.7)	2
Unwell	1 (0.3)	1
Lethargy	1 (0.3)	1
Vomiting	1 (0.3)	1
Rash	1 (0.3)	1
Itching	1 (0.3)	1
Difficulty voiding	1 (0.3)	0

for OAB and have previously led to the withdrawal of drugs used for OAB (terodilene).

The aim of this study was to assess the risk of developing palpitations, the severity of the condition and to investigate any underlying risk factors that predispose patients with OAB to develop palpitations whilst taking mirabegron.

Materials and methods

A consecutive cohort of patients was studied between February 2013 (when the drug became available in the UK) and June 2014. As a cohort study no apriori power calculation was performed. Patients with OAB were recruited from our urogynaecology clinic and were prescribed mirabegron 50 mg daily for 6 weeks. The evaluation was approved by the R&D department at Medway Hospital. The study group comprised of female patients greater than 18 years of age experiencing OAB symptoms. Medication was prescribed as per NICE guidelines. Mirabegron was also prescribed for women with stress predominant mixed incontinence where OAB symptoms were troublesome. Patient with known cardiac arrhythmias were excluded. Prior to the initiation of treatment, patients were warned of the small chance of developing palpitations. They were advised to stop therapy if they experienced this side effect.

Patients are routinely reviewed after taking therapy for 6 weeks to identify efficacy and to modify their treatment plan. All patients were directly questioned regarding the development of palpitations as well as completing outcome questionnaires. For patients reporting palpitations, a detailed account of their symptoms and medical history were documented to identify any predisposing risk factors. In this group, a 12-lead electrocardiogram (ECG) was performed to assess heart rate, QT interval and the presence of any persisting arrhythmia. All adverse events were registered with the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK.

Results

A total of 279 patients were started on mirabegron of whom 28 (10%) patients developed side-effects from the drug as detailed in Table 1. The entire cohort had an average age of 55.1 years and BMI of 29.7. They used a mean of 1.6 anticholinergics (range 1 to 5). Eight (2.9%) of these patients reported palpitations whilst taking the drug. The average age of the patients was 64.4 years. They had used a mean of 1.1 previous anticholinergics (range 1 to 3). The patients were white Caucasian with an average BMI of 31. Past medical history included hypertension (4), raised cholesterol levels (3) and non-insulin dependent diabetes (1). Two patients had a history of palpitations and 1 patient had well-controlled angina. Patients had no previous myocardial infarction, atrial fibrillation or cardiac surgery. With regards to the patients with a history of palpitations, one had a diagnosis of ectopic ventricular beats with a normal QT interval and mild associated left ventricular hypertrophy. The other had no demonstrable arrhythmia on 12-lead ECG, with a normal QT interval and normal echocardiogram. She was prescribed mirabegron only after the advice of a consultant cardiologist. Two patients were taking long-term β-blockers (Bisoprolol, Atenolol), for hypertension (pulse rates 56 and 54 beats per minute). A detailed drug history has been documented in Table 2. No herbal medications were used concurrently with mirabegron.

All 8 patients described palpitations that occurred at rest and began between 45 min and 10 days of starting mirabegron. The palpitations took up to 3 weeks to resolve once the drug was stopped. The symptoms had resolved in all patients prior to their return hospital visit. Due to the severity of the symptoms, a drug re-challenge was not performed and they recovered completely from their symptoms after stopping the drug. One patient with angina had worsening symptoms that required an increased usage of her Glyceryl Trinitrate (GTN) spray from monthly use to twice a week. One other patient developed chest pain associated with her palpitations while another developed chest tightness. The details of symptoms are documented in Table 3.

In seven patients, the symptoms resolved completely once mirabegron was stopped. In this group, patients took mirabegron for an average of 11 days before discontinuation. The patient with ventricular ectopics felt that her palpitations were marginally worse with mirabegron but opted to continue with the drug as she felt the palpitations were tolerable and her urinary symptoms had improved dramatically.

Electrocardiograms performed on seven patients demonstrated normal sinus rhythm with no persisting tachycardia. One patient declined the electrocardiogram. The heart rate ranged between 54 and 84 beats per minute. The QTc was prolonged in two patients at 0.458 and 0.441 s and was within a normal range for remaining five (QTc <420). Both patients were not on any other concomitant medication that is known to prolong the QTc interval (Table 3).

Table 2
Drug history and QTc values.

Patient	Age	Drug history	QTc interval
1	87	Oxycodone hydrochloride, celecoxib, omeprazole, quinine sulphate, enalapril, temazepam	Normal
2	63	Nil	Normal
3	61	Amitriptyline*, bisoprolol, doxazosin, felodipine, indapamide*, losartan, simvastatin	Normal
4	67	Metformin, trandolapril, atorvastatin, Bendroflumethiazide, aspirin	Prolonged
5	50	Nil	Declined
6	77	Lisinopril	Prolonged
7	50	Nil	Normal
8	60	Glyceryl trinitrate, alendronic acid, warfarin, atenolol, isosobide mononitrate, simvastatin, omeprazole, sulfasalazine	Normal

* Drugs that prolong QTc interval.