



Case report

Respiratory dysfunction following initiation of mirabegron: A case report

Elizabeth S. Malsin^{a,*}, John M. Coleman^b, Lisa F. Wolfe^c, Anna P. Lam^a^a Northwestern University Feinberg School of Medicine, Division of Pulmonary and Critical Care Medicine, 240 East Huron Street, McGaw Pavilion, Suite M-349 Chicago, Illinois 60611, USA^b Northwestern University Feinberg School of Medicine, Division of Pulmonary and Critical Care Medicine, 676 North St. Clair, Arkes Pavilion Suite 1400 Chicago, IL 60611, USA^c Northwestern University Feinberg School of Medicine, Division of Pulmonary and Critical Care Medicine, 240 East Huron Street, McGaw Pavilion, Suite M-341, Chicago, IL 60611, USA

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ABSTRACT

Background: Mirabegron, a β 3 adrenergic receptor agonist, is FDA approved for treatment of overactive bladder. Approved in 2012 in the US, there have been no reports of any effects of mirabegron on pulmonary function.

Case presentation: We report the case of a 65 year old male with a history of Parkinson's disease, OSA, and aspiration pneumonia presenting with subacute worsening dyspnea and found to have worsening restrictive ventilatory defect with a pattern consistent with neuromuscular weakness. After recalling that initiation of mirabegron correlated with onset of his worsening symptoms, the patient decided to perform a trial period off the drug. He subsequently reported prompt improvement in his respiratory symptoms, which was confirmed objectively by pulmonary function tests. In this case, mirabegron was temporally associated with subacute worsening of the patient's pulmonary restrictive physiology, with subsequent resolution after discontinuation of the medication.

Conclusions: The mechanism of this adverse effect is unknown, but we speculate that this effect may be potentially mediated by the effect of β 3 adrenergic receptor agonism on skeletal muscle, in this case in a patient with pre-existing neuromuscular disease. Careful assessment of patients who develop shortness of breath while on mirabegron should include an assessment for restrictive lung disease secondary neuromuscular dysfunction. Additional study is needed of the effects of β 3 agonism on skeletal muscle.

1. Background

Mirabegron is a β 3-adrenergic receptor agonist prescribed for overactive bladder. While several β 3 agonists have been developed, only mirabegron is FDA approved. The most commonly reported adverse effects of mirabegron include hypertension, tachycardia, headache, dizziness, constipation, diarrhea, abdominal pain, back pain, arthralgias and sinusitis. The only pulmonary complication reported was development of a pulmonary neoplasm. We report a case of a patient who developed restrictive ventilatory defect following the initiation of mirabegron.

2. Case presentation

Our patient is a 65 year-old man with a history of Parkinson's disease, obstructive sleep apnea on CPAP, and aspiration pneumonia. His

medications include mirabegron, finasteride, pramipexole, albuterol as needed, modafinil, carbidopa-levodopa, metformin, multivitamins, and ibuprofen as needed. In July 2017, he presented with increased dyspnea on exertion. He noted worsening dyspnea for several weeks, with progression to dyspnea with activities of daily living. He denied constitutional symptoms, including changes in his physical strength, muscle spasms or worsening tremor. His vital signs were unremarkable; exam was notable for mild diaphoresis and dyspnea at rest, but a normal lung exam.

Pulmonary function tests (PFT) revealed decline in seated forced expiratory volume in 1 s (FEV1) to 3.10 L (78% predicted) from 4.13 L (92%) two years prior; decline in forced vital capacity (FVC) 3.79 L (72%) from 4.95 L (102%); FEV1/FVC ratio 82%, and total lung capacity (TLC) 7.17L (90%, from 7.99L (105%)), with a normal diffusion capacity of carbon monoxide (DLco) of 26.9 mL/mmHg/minute (93%). Also notable were supine FVC 3.43L (65%) and FEV1 2.72 L (69%).

* Corresponding author.

E-mail addresses: Elizabeth.malsin@northwestern.edu (E.S. Malsin), colemanjm@northwestern.edu (J.M. Coleman), lwolfe@northwestern.edu (L.F. Wolfe), lam4@northwestern.edu (A.P. Lam).

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Seated maximal inspiratory pressure (MIP) was 69 cm H₂O (64%) and maximal expiratory pressure (MEP) was 77 (38%). High-resolution computed tomography scan of the chest showed ground glass opacities in the right lower lobe, stable 3 mm nodule in the left lower lobe, and stable moderate air trapping. The patient was initiated on a bronchial hygiene regimen and sent for follow-up with his neurologist given concern for the patient's Parkinson's disease contributing to new onset neuromuscular respiratory disease, given the pattern of limitation on his PFT.

His dyspnea persisted the following month. After viewing a television commercial for mirabegron warning of possible adverse effect of shortness of breath (due to anaphylaxis), the patient correlated initiation of mirabegron for urinary urgency with the start of his symptoms, and self-discontinued his mirabegron. He returned to clinic six weeks later and reported subjective improvement of his dyspnea. His urinary urgency was noted to be at previous baseline and was deemed tolerable by the patient. He again noted no other changes to his baseline Parkinson's symptoms.

Office spirometry demonstrated increases in supine FEV1 to 4.73 mL (+13%) and maximal expiratory pressure to 102 cm (+24%). Four months later, FVC improved to 4.09L (78%) and TLC to 7.94L (108%). While the temporal relationship between the use and discontinuation of mirabegron with the patient's symptoms and change in lung function suggests respiratory muscle pathology without symptoms of simultaneous non-respiratory muscle weakness, the mechanism by which β -adrenergic receptor agonism could cause respiratory dysfunction has not been described.

3. Discussion

After caring for this patient, the authors reviewed the known physiology and pathology, as well as the literature, regarding potential mechanisms behind the development of symptomatic neuromuscular respiratory illness after the initiation of mirabegron. To our knowledge, there is no report in the literature of this potential adverse effect. However, our review did identify potential pathophysiologic mechanisms.

Three known subtypes of β -adrenergic receptors (β -AR) exist, with the β 3-adrenergic receptor (ADRB3) found in multiple tissues and constituting the predominant β -AR in the detrusor muscles of the bladder [1,2]. From RNA-Sequencing analysis and the Human Protein Atlas (dataset, highest expression levels of ADRB3 are in the ovary at 10 transcripts per million (TPM), gallbladder (2.6 TPM), and smooth muscle (1.4 TPM). Other tissues have minimal expression, including lung tissue (0.1 TPM) and skeletal muscle (0 TPM) [3,4]. However, immunostaining using the high-affinity monoclonal antibody Mab72c demonstrates β 3-receptors in skeletal muscle, adipose tissue, and myocardial tissue [5].

β 1- and β 2-adrenergic receptors, G_s-linked receptors, when activated by catecholamines mediate a rise in cyclic-AMP resulting in activation of protein kinase A [6,7]. Multiple studies have demonstrated a different mechanism for the β 3-AR, including activity via the mTOR and G_i-nitric oxide synthetase (NOS) pathways [8,9]. Studies revealing stimulation of β -AR in skeletal muscle produces anabolic effects, likely via a crucial role in protein metabolism, have spurred interest in the therapeutic potential of β -AR agonists in muscular pathologies [10–12]. Puzzo and colleagues demonstrated β 3-receptor agonism significantly increases muscle force production and myofiber area, and decreases muscle fiber stiffness [13], similar to previous reports of β 2-AR agonism, in fast-twitch fibers [14]. The novel finding that β 3-agonism decreased stiffness of muscle fibers has potential implications for diseases with high muscle stiffness, including muscle dystrophies.

The majority of patients with Parkinson's disease have muscle rigidity, which can affect any skeletal muscle. Baclofen, a gamma-aminobutyric acid (GABA)-receptor agonist, is used to treat spasticity and dystonia in Parkinson's disease. Hypotonia is the most common adverse

reaction, occurring in 2.4–34.7% of patients receiving intrathecal baclofen during trials [15]. Muscular weakness has also been reported in patients on oral baclofen for spasticity [16,17]. Baclofen impacts control of ventilation and can cause central apnea events [18], with overdose reported to cause flaccid paralysis and respiratory depression [19,20].

In our patient with Parkinson's disease, we speculate β 3-agonism of mirabegron may have had similar effects as baclofen overdose and may have acted synergistically with baclofen, resulting in decreased stiffness of respiratory muscles and worsened lung function. In light of the findings of Puzzo et al., [13] further research is needed to elucidate effects of β 3-AR agonism in muscles, and mirabegron should be closely monitored in patients with neurodegenerative and neuromuscular diseases.

Ethics approval

Not applicable.

Consent for publication

Obtained from patient (adult).

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Conflicts of interest

The authors declare that they have no competing interests.

Author contributions

ESM, JMC, AIL analyzed and interpreted patient data. ESM wrote the manuscript with JMC, AIL, LFW contributing equally to its final form. All authors read and approved the final manuscript.

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Abbreviations:

PFT	pulmonary function tests
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
FEV1/FVC	ratio of forced expiratory volume in 1 s to forced vital capacity
TLC	total lung capacity
DLco	diffusion capacity of carbon monoxide
MIP	maximal inspiratory pressure
MEP	maximal expiratory pressure
β -AR	β -adrenergic receptors
TPM	transcripts per million
GABA	gamma-aminobutyric acid

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