Mirabegron to manage symptoms of interstitial cystitis / bladder pain syndrome: A stone for two birds?

João Antonio Pereira-Correia¹,2*, Luiza Amaral Nahoum², João Ernesto Aldred Pinto¹ and Valter José Fernandes Muller¹

¹Department of Urology, Servidores do Estado Federal Hospital, Brazil
²Faculty of Medicine, Estácio de Sá University, Brazil

Abstract

Background: Interstitial Cystitis / Bladder Pain Syndrome (IC/BPS) patients often experience lowered quality of life due to pain, urinary urgency, and increases in urinary frequency. Like many chronic pain disorders, IC/BPS is poorly understood and treatment unsatisfactory.

Materials and methods: We prospectively monitored the effects on pain and urinary complaints, of mirabegron associated with amitriptyline, for randomly selected women with IC/BPS.

Results: Twenty-five women were randomly selected to treat pain symptoms of IC/BPS and 12 followed up until the end of the study. All patients showed improvement on all questionnaires referring to pain IC/BPS symptoms and urinary storage symptoms. There was no statistically significant improvement in urinary frequency.

Conclusions: We suggest that mirabegron can work controlling urinary urgency and pain of IC/BPS patients.

Introduction

According to the latest update from the International Continence Society (ICS), Interstitial Cystitis / Bladder Pain Syndrome (IC/BPS) is defined as: “persistent or recurrent chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as an urgent need to void or urinary frequency. Diagnosed in the absence of any identifiable pathology which could explain these symptoms” [1].

IC/BPS patients often experience lowered quality of life due to pain, urinary urgency, and increases in urinary frequency [2,3]. However, it is clinically difficult to address the pain component in particular because it overlaps with comorbid conditions such as depression, poor sleep, and inability to work [4]. According to the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, like many chronic pain disorders, IC/BPS is poorly understood and treatment unsatisfactory [5]. Therefore, in the present study we present evidence for the use of mirabegron to manage the symptoms of IC/BPS.

Materials and methods

From July 2018 to December 2019, we prospectively monitored the effects of mirabegron in the adjuvant treatment...
of women with IC/BPS. The demographic profile of the sample is shown in Table 1.

All experimental protocols were approved by the local ethics and research committee. Patients were recruited by computerized random selection from a chronic pelvic pain outpatient clinic if they had experienced IC/BPS symptoms (as defined by the ICS) for at least 6 months, in the absence of any identifiable pathology which could explain these symptoms. Patients with urological diseases were excluded (urinary tract infection, neurogenic lower urinary tract dysfunction, urethral diverticula, bladder or urethral cancer, urinary stones, stress urinary incontinence, mixed urinary incontinence), as were those with pelvic gynecological diseases (uterine, vaginal or cervical cancers, endometriosis and vaginitis). Chronic users of any type of drug were also excluded.

Inclusion criteria were based upon histopathological study of the bladder internal wall [6] for the presence of mast cell infiltration and inflammation without associated hydrodistension. Inclusion criteria also included the presence of storage lower urinary tract symptoms (S–LUTS) represented by urinary urgency and polacuria.

All patients underwent treatment using amitriptyline 75mg daily, following the recommendations of the current version of the guideline of the European Association of Urology [7], for at least 6 months. The initial amitriptyline dosage was 25 mg/day, with weekly increments of 25mg until reaching the dose of 75mg/day. No other treatment for IC/BPS was adopted in this period.

After this period, for patients who did not show improvement in pain complaints with the use of amitriptyline, we chose to prolong the use of this antidepressant for another 6 months, but now with the addition of mirabegron 50 mg/day to control S–LUTS.

For pain assessment, the portuguese version of the Brief Pain Inventory Interference Scale (B–PIIS) [8] was used on the first day of prescription of amitriptyline, after 6 months of amitriptyline treatment, and after 6 months of mirabegron plus amitriptyline. At the same time the brazilian portuguese validated instruments: Interstitial Cystitis Symptom Index and Problem Index (ICSI–ICPI) [9] and Pelvic Pain and Urgency / Frequency Patient Symptom Scale (PUF) [9] were also applied. For analysis of the S–LUTS, the portuguese version of the overactive bladder questionnaire (OAB–V8) was used [10].

All statistical analyses were performed using GraphPad Prism™ software, version 7 (La Jolla, CA, USA), applying the Kolmogorov–Smirnov test for normality analysis. For data with a Gaussian distribution, a comparative inter-group evaluation Student’s t-test was used. However, for data with a non–Gaussian distribution, the Kruskal–Wallis test was used, adopting the standard significance value of p < 0.05.

Results

Twenty-five women were randomly selected to treat pain symptoms of IC/BPS using amitriptyline 75mg/ day. Fifteen of these patients did not respond to the medication and therefore proceeded to phase two of the present study, receiving 50mg/day mirabegron.

Of the 15 patients who used amitriptyline combined to mirabegron, 3 abandoned treatment due to intolerable side effects (dry mouth). They were withdrawn from the study and other types of therapeutic options were offered.

The 12 patients who persisted until the end of the study showed improvement on all questionnaires referring to pain (p = 0.033) (Table 2), IC/BPS symptoms (p = 0.038 and p = 0.048) (Table 3), and urinary storage symptoms (p = 0.038) (Table 4). There was no statistically significant improvement in urinary frequency (p = 0.99) (Table 4).

After the initial 6 months of amitriptyline 75mg daily, dry mouth was observed in all 12 patients, but with no impact on quality of life that would motivate withdrawal. There were no additional side effects reported, with the insertion of daily use of mirabegron.

Discussion

The β3 agonist mirabegron is already well established as a second line therapeutic for S–LUTS resulting from OAB syndrome [11,12]. This drug was used in the present study because IC/BPS patients experienced significant S–LUTS which negatively affected quality of life.

There are differences in the etiology of S–LUTS between OAB and IC/BPS. Patients with OAB generally present an increase in urinary frequency and urinary urgency in order to prevent episodes of urinary incontinence, while patients with IC/BPS

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### Table 1: Patients’ demographic data.

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<thead>
<tr>
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</tr>
<tr>
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### Table 2: Results of the B-PIIS evaluation after the use of amitriptyline alone vs. combined with mirabegron.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pretreatment</th>
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<td>52</td>
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<tr>
<td>Average</td>
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</tbody>
</table>

p-value (Amitriptyline + Mirabegron vs. Amitriptyline alone) 0.033
present frequent and urgent urination due to the need for relief or interruption of pain complaints. In the patients discussed in the present study, due to the magnitude of their storage symptoms and lack of response to 6 months of amitriptyline, we believe that the use of mirabegron was necessary.

**Possible analgesic effect of mirabegron**

Much remains unknown about the afferent mechanisms of proprioception in the lower urinary tract. Studies have shown that there is intercommunication between afferent receptors of the urothelium and the central nervous system [13]. Based on animal studies, we know that this intercommunication is performed by low-threshold myelinated (A-delta) and unmyelinated (C-fibers) afferents that convey mechanical or noxious stimuli via the pelvic nerve to the dorsal horn of the spinal cord [14,15].

Aizawa and collaborators [16] demonstrated that mirabegron can inhibit the sensitive activity of A-delta fibers and C-fibers in rats. The same group published similar results a few years later [17]. Considering these results in the context of our findings in human patients, we can infer that this β3 agonist may decrease the pain sensation associated with IC/BPS. Additional studies will be needed to further parse these mechanisms.

**A matter of dose**

Aizawa, et al. [16,17] showed in animal studies that the inhibition of sensitive fibers is dose dependent, with higher doses producing better inhibitory responses, especially with regard to C-fibers. A 2018 study using 25mg of mirabegron/day found no significant improvements in urinary frequency or pain in 23 IC/BPS patients [18]. In our study, patients received 50mg of mirabegron/day and experienced significant reductions in pain.

**Effects on S-LUTS**

Interestingly, the effects of mirabegron on S-LUTS showed statistically significant improvements in urgency but, no statistically significant improvements in urinary frequency. Lena et al, also observed results similar to ours, using a lower dose of mirabegron for IC / BPS [18].

We believe that perhaps the inflammatory conditions associated with IC / BPS may somehow modify the action of the beta-3 agonist on the bladder. Undoubtedly, further studies are still needed to unravel this issue.

**Strengths and weaknesses**

As far as we know, our study is the first to demonstrate positive results in the control of pain in patients with IC/BPS through the use of mirabegron. Given our strict inclusion and exclusion criteria, we believe that we have assessed a sample with low heterogeneity. On the other hand, our strict criteria contributed to a small sample size and subsequent low power.
As in other chronic diseases of low prevalence, grouping patients with IC/BPS is not a simple task and we imagine that, in this context, the evaluation is valid.

Unfortunately, the study was not designed with a control group, because the analgesic action of mirabegron was actually an incidental finding. We used the β3 agonist to manage S–LUTS and found that there was an improvement in pain symptoms.

However, considering that mirabegron was not used to improve pain and that neither doctors nor patients expected this type of response, we believe that we significantly minimized the risk of being faced with a placebo effect, increasing the reliability of our findings. Our results will certainly motivate new research involving control groups.

Another criticism that can be made to our research is related to the possible confounding factor between the use of amitriptyline combined with mirabegron. As they were used together, it is difficult to say whether the good results for pain and urinary urgency management were obtained by prolonged use of the antidepressant, by the use of the β3 agonist or by a combination of both.

However, a Canadian study from 2018, evaluated patients using various types of treatments for IC/BPS, including antidepressants, for an average period of 10.5 months, and did not notice any significant improvement in pain symptoms with the addition of mirabegron 25mg/day for 6.9 months [18]. As the similarities with our research are reasonable, we can assume that the effects achieved by our group are in fact related to the possible angesic action of mirabegron in IC/BPS patients, where the double dose used made a difference.

Conclusion

We hope that further studies on the subject will bring more light to this still obscure field of medical practice but, until then, based on our findings we suggest that mirabegron at a dose of 50mg/day may work as “a stone for two birds”, controlling pain and storage symptoms of the lower urinary tract of IC/BPS patients.

References