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ARCHIVE OF Urological Research OPEN ACCESS JOURNAL

ISSN: 2692-4706 DOI: https://dx.doi.org/10.17352/aur

Research Article

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

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Received: 14 April, 2021
Accepted: 23 April, 2021
Published: 26 April, 2021

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Keywords: Amitritpyline; Interstitial cystitis; Lower urinary tract symptoms; Mirabegron; Bladder pain syndrome

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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

Citation: Pereira-Correia JA, Nahoum LA, Aldred Pinto JE, Fernandes Muller VJ (2021) Mirabegron to manage symptoms of interstitial cystitis / bladder pain syndrome: A stone for two birds? Arch Urol Res 5(1): 020-023. DOI: https://dx.doi.org/10.17352/aur.000032

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 polaciuria.

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

Table 1: Patients' demographic data.

	Average	Range
Age	52	35–66
	Female	Male
Gender	25	0
	Caucasian	Afro-descendant
Ethnicity	13	12

Table 2: Results of the B-PIIS evaluation after the use of amitriptyline alone vs. combined with mirabegron.

Patient	B-PIIS		
	Pretreatment	Amitritptilyne	Amitriptilyne + Mirabegron
1	56	52	28
2	62	60	33
3	63	60	30
4	45	45	33
5	55	51	31
6	49	44	29
7	62	59	32
8	67	64	33
9	57	53	27
10	62	60	32
11	56	53	28
12	64	63	26
Average	58	55	30
p-value (Amitriptyline + Mirabegron vs. Amitriptyline alone) 0.033			

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Table 3: ICSI-ICPI and PUF evaluations after the use of amitriptyline alone vs. combined with mirabegron.

Patient	ICSI – ICPI			PUF		
	Pretreatment	Amitritptilyne	Amitriptilyne + Mirabegron	Pretreatment	Amitritptilyne	Amitriptilyne + Mirabegron
1	27	26	18	24	20	8
2	25	24	15	23	21	10
3	30	29	12	25	24	11
4	29	28	10	21	22	10
5	31	31	17	19	22	8
6	26	25	12	22	21	12
7	27	21	11	24	20	9
8	30	29	15	25	21	10
9	28	25	10	25	24	11
10	31	26	13	19	16	9
11	24	25	19	17	17	9
12	32	30	14	27	24	9
Average	28	27	14	22	21	10
p-value (Amitriptyline + Mirabegron vs. Amitriptyline alone)	0.038			0.048		

Table 4: Results of the OAB-V8 questionnaire before and after treatment with mirabegron for S-LUTS and urinary frequency.

	OAB-V8		OAB-V8 (Urinary Frequency)	
Patient	Pretreatment	Mirabegron	Pretreatment	Mirabegron
1	40	35	5	4
2	38	34	4	4
3	35	32	5	4
4	37	32	4	4
5	33	29	4	4
6	33	30	4	4
7	32	28	5	4
8	31	22	5	5
9	27	25	5	4
10	28	23	4	4
11	30	25	4	4
12	31	25	4	4
Average	33	28	4.4	4.1
p-value	0.048		0.99	

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.

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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 beta-3 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 noticed 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 analgesic 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

1. ICS Comittees. (2018) Interstitial Cystitis/Bladder Pain Syndrome [IC/BPS]. Link: https://bit.ly/3vd35zH

2. Lee KS,Choo MS, Seo JT, Oh SJ, Kim HG, et al. (2015) Impact of overactive bladder on quality of life and resource use: results from Korean Burden of Incontinence Study [KOBIS]. Health Qual Life Outcomes 13: 89. Link: https://bit.ly/32CQXfj

3. Coyne KS, ChrisPayne MPH, Bhattacharyya SK, Revicki DA, Thompson C, et al. (2004) The Impact of Urinary Urgency and Frequency on Health-Related Quality of Life in Overactive Bladder: Results from a National Community Survey. Value in Health 7: 455-463. Link: https://bit.ly/32GPVic

4. Vasudevan V, Moldwin R (2017) Addressing quality of life in the patient with interstitial cystitis/bladder pain syndrome. Asian J Urol 4: 50-54. Link: https://bit.ly/2RWpAuy

5. Clemens JQ, Mullins C, Ackerman AL, Bavendam T, van Bokhoven A, et al. (2019) Urologic chronic pelvic pain syndrome: insights from the MAPP Research Network. Nat Rev Urol 16: 187-200. Link: https://bit.ly/2QRxaGk

6. Kim HJ (2016) Update on the Pathology and Diagnosis of Interstitial Cystitis/ Bladder Pain Syndrome: A Review. Int Neurourol J 20: 13-17. Link: https://bit.ly/3tIOuM4

7. Engeler D, Baranowski AP, Berghmans B, Borovicka J, Cottrell AM, et al. (2019) EAU Guideline: Chronic Pelvic Pain. Link: https://bit.ly/3dGia75

8. Ferreira-Valente MA, Pais-Ribeiro J, Jensen MP (2012) Further validation of a portuguese version of the Brief Pain Inventory Interference Scale. Clinica y Salud 23: 89. Link: https://bit.ly/3tMH0HX

9. Victal ML, D'Ancona CAL, Junqueira RJ, et al. (2015) Test-retest reliability and discriminant validity for the Brazilian version of "The Interstitial Cystitis Symptom Index and Problem Index" and "Pelvic Pain and Urgency/Frequency (PUF) Patient Symptom Scale" instruments. Transl Androl Urol 4: 594-599. Link: https://bit.ly/2QoaSMg

10. Acquadro C, Kopp Z, Coyne KS, Tubaro A, Choo MS, et al. (2006) Translating overactive bladder questionnaires in 14 languages. Urology 67: 536-540. Link: https://bit.ly/3dIRra3

11. American Urological Association. (2014) AUA Guidelines on Diagnosis and Treatment of Overactive Bladder in Adults. Link: https://bit.ly/3dGa7Hs

12. Burkhard FC, Bosch JLHR, Cruz F (2020) EAU Guidelines on Urinary Incontinence in Adults.

13. de Groat WC, Griffiths D, Yoshimura N (2015) Neural control of the lower urinary tract. Compr Physiol 5: 327-396. Link: https://bit.ly/3gyOevE

14. Bahns E, Ernsberger U, Janig W, Nelke A (1986) Functional characteristics of lumbar visceral afferent fibers from the urinary bladder and urethra in the cat. Pflugers Arch 407: 510-518. Link: https://bit.ly/3dIRGBZ

15. Iggo A (1955) Tension receptors in the stomach and urinary bladder. J Physiol 128: 593-607. Link: https://bit.ly/3aB6YH0

16. Aizawa N, Homma Y, Igawa Y (2012) Effects of mirabegron, a novel β3-adrenoceptor agonist, on primary bladder afferent activity and bladder microcontractions in rats compared with the effects of oxybutynin. Eur Urol 62: 1165-1173. Link: https://bit.ly/3slYKmq

17. Aizawa N, Homma Y, Igawa Y (2015) Effects of L-arginine, mirabegron, and oxybutynin on the primary bladder afferent nerve activities synchronized with reflexic, rhythmic bladder contractions in the rat. Neurourol Urodyn 34: 368-374. Link: https://bit.ly/3ek6Bl6

18. Lena MD, Tolls V, Kelly KL, Nickel JC (2018) Mirabegron as adjuvant treatment for patients with interstitial cystitis/bladder pain syndrome. Can Urol Assoc J 12: E100- E104. Link: https://bit.ly/3xiPclC

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