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Treatment of Lower Urinary Tract Symptoms in Children With Constipation Using Tegaserod Therapy

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ABSTRACT

INTRODUCTION: Tegaserod, a selective 5-HT4 agonist, is a promotility agent used for the treatment of adults with irritable bowel syndrome with constipation and chronic idiopathic constipation. In children, constipation is commonly associated with lower urinary tract symptoms (LUTS). The purpose of the present retrospective investigation was to assess the effectiveness of tegaserod to treat children with refractory LUTS and either persistent constipation or persistent abdominal pain following resolution of constipation.

METHODS: A chart review was conducted for all patients who had not responded to a bowel program (high fiber diet, increased fluid intake, stool softeners, senna laxatives) and were treated with tegaserod over a 2-year period. Inclusion criteria included LUTS and persistent constipation or persistent abdominal pain even though constipation appeared to be adequately controlled. Tegaserod dosing started at 2 mg twice daily and increased to a maximum of 6 mg twice daily until the patient had regular bowel movements and experienced no abdominal pain. The dose was reduced if patients exhibited signs of diarrhea or cramping. Senna laxative use was discontinued for all patients following tegaserod initiation. Treatment response was determined by presence of symptoms and measurement of postvoid residual (PVR) urine at baseline and final evaluation.

RESULTS: A total of 19 patients (11 girls, 8 boys) with a mean age of 9.3 years (range, 3-15 years) received tegaserod treatment. At baseline, 16 patients had an elevated PVR (mean = 91.2 mL) and 11 patients had a history of recurrent urinary tract infections. Tegaserod was well tolerated by all patients with no discontinuations; 2 patients had a dose reduction from 6 mg to 2 mg twice daily. All patients had resolution of abdominal pain. Urinary incontinence improved in all but 4 patients and there was complete resolution of urinary urgency, urinary frequency, and urinary tract infections. The average PVR volume of 14.2 mL after treatment was significantly reduced when compared with pretreatment levels (P = .0005).

CONCLUSION: The effects of tegaserod may be due to more than changes in stool volume in the colon, because there was a reduction in LUTS and improved emptying of the bladder.

Abbreviations and Acronyms

CIC = chronic idiopathic constipation
IBS-C = irritable bowel syndrome with chronic constipation
LUTS = lower urinary tract symptoms
OAB = overactive bladder
PVR = postvoid residual
UTI = urinary tract infection

KEYWORDS: Lower urinary tract symptoms; Constipation; Children; Tegaserod; Serotonin or 5-HT

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INTRODUCTION

Pediatric overactive bladder (OAB) syndrome is characterized by urinary frequency, urgency, and urge incontinence [1]. This syndrome has been routinely managed with the use of anticholinergics, timed voiding, and a bowel program. Several studies and surveys have shown substantial overlap of lower urinary tract symptoms (LUTS) and constipation in pediatric patients with OAB. Loening-Baucke [2] in 1997 showed that there was a marked improvement in LUTS in children being treated for constipation in their clinic. Of 234 constipated children, 29% had daytime urinary incontinence, 34% had nighttime incontinence, and 11% had urinary tract infections (UTIs). After one year, constipation was relieved in 52% of the patients. All patients who had their constipation completely corrected ceased having UTIs; 80% of the patients had their daytime urinary incontinence corrected, and 63% of the patients had their nighttime incontinence corrected. The present authors have seen similar findings in their patients over the years, in that patients who had persistent bowel issues continued to have problems with incontinence and recurrent UTIs and those with resolution of the bowel issues had relief from the other problems.

There are numerous reasons why bowel programs have been cited as being successful in the management of OAB in children. Mechanical pressure on the bladder by the stool in the bowel has been touted as one mechanism leading to OAB. More recent data indicating that there is an inhibitory reflex associated with rectal distention seems more plausible and explains why there could be associated external sphincter dyssynergia along with diminished ability to void completely in children with constipation [3]. There is new evidence from work by Jia et al [4] showing that the parasympathetic nucleus is intimately involved in the chronic constipation seen in patients with imperforate anus. This same parasympathetic nucleus is also critical to processing sensory signals from the bladder. It is possible that signal mixing or overload can occur in this site, thereby explaining the association of bowel and bladder in dysfunctional elimination. In addition, chronic periumbilical pain is a common finding in children with chronic constipation, dysfunctional elimination syndrome, and irritable bowel syndrome. Profiling and mechanistic studies have indicated that the gastrointestinal tract is the largest repository of serotonin (5-HT) within the body, and patients with irritable bowel syndrome with chronic constipation have low levels of 5-HT in the gut [5].

Tegaserod is a 5-HT4 agonist that causes increased motility of the gut [6-8]. It is used to treat irritable bowel syndrome with chronic constipation (IBS-C) and chronic abdominal pain in adult patients. Correction of the constipation and emptying of the colon leads to reduction of strong peristaltic waves and may prevent strong sudden bladder contractions that lead to urge incontinence [2,3,6-8].

The purpose of the present retrospective investigation was to assess the effectiveness of tegaserod to treat children with refractory LUTS and either persistent constipation or persistent abdominal pain following resolution of constipation.

METHODS

A retrospective chart review was conducted to identify and assess all patients with LUTS, constipation, or persistent abdominal pain that had been treated with tegaserod between April 2005 and April 2007. For the purpose of this study, LUTS was defined as 1 or more of the following symptoms: dysuria, frequency, urgency, elevated postvoid residual (PVR) urine volume, or urinary incontinence.

Prior to tegaserod treatment, all patients were on a bowel program that consisted of a high fiber diet, increased fluid intake, stool softeners (polyethylene glycol 3350 and/or mineral oil), and senna laxatives in the form of various products. Candidates for tegaserod did not respond to the standard treatment. They met the following inclusion criteria: (1) patients with persistent constipation (< 3 bowel movements per week for ≥ 6 months), (2) patients with large, painful bowel movements, (3) patients that continued to experience abdominal pain even though their constipation appeared to be adequately controlled.

All parents were informed that tegaserod was being used in an off-label method and that the medication was not approved by the Food and Drug Administration (FDA) for use in children. Dosing was started at 2 mg twice daily (the lowest recommended adult dose) and increased to 6 mg twice daily (the maximum recommended adult dose). The dose was increased to the point where the patient had regular bowel movements and experienced no abdominal pain. If patients exhibited signs of diarrhea or cramping while on the medication, the dose was reduced to the next lower level. The highest dose was used in patients who had little or no response to the lower doses. Patients who had been on the medication for more than 2 months were given respites off the medication. If symptoms recurred, the medication was restarted. Senna laxative use was discontinued for all patients following tegaserod initiation. All patients were encouraged to continue their high-fiber diet and increased fluid intake.

The investigators recorded any side effects to the tegaserod treatment. The patient's response to treatment was determined

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by the presence of urinary urgency, frequency, or incontinence, abdominal pain, or UTI. PVR urine volume was also recorded at the baseline and final evaluations.

Statistical analysis was performed using Excel (Microsoft Corp, Washington, USA). Paired t tests were used to compare PVR urine volume at baseline and the end of treatment.

RESULTS

There were 19 patients included in the record review. Their baseline demographic characteristics are included in Table 1. There were 11 girls and 8 boys, with an average age of 9.3 years (SD = 3.3; range, 3.9-15.7 years). The primary diagnosis was urinary incontinence in 12 patients, urinary frequency in 3 patients, urgency in 2 patients, and dysuria in 1 patient. The most common comorbid condition was recurrent UTI, present in 11 out of the 19 patients; 10 patients had an underlying diagnosed neuropsychiatric disorder. Elevated PVR urine volume was present in 16 out of 19 patients. The median residual volume in these patients with elevated residuals before treatment was 91.2 mL and the median volume was 63.5 mL. Previous treatments for the urinary disorders included biofeedback training for 11 patients. In addition to laxatives, concomitant pharmacologic therapy included alpha blockers for 16 patients and anticholinergic therapy for 7 patients.

There was a 3-year follow-up period available on all patients. They all tolerated tegaserod well and none had to discontinue the medication due to side effects. Two patients did not tolerate the 6 mg dose due to cramping and diarrhea; their doses had to be reduced to 2 mg twice daily. Constipation was managed successfully for all patients.

Patient responses to tegaserod treatment for the outcome measure of PVR urine volume can be found in Figure 1 and Table 2. After tegaserod treatment, the average PVR was significantly reduced when compared with pretreatment levels (P = .0005). The PVR for the patients with elevated residuals came down to 14.2 mL and the median was 10 mL.

Abdominal pain was eliminated in all patients. All patients with UTIs prior to tegaserod treatment reported cessation of the infections following treatment. All patients with urgency and frequency prior to treatment had cessation of their symptoms. Urinary incontinence improved in all but 4 of 14 patients. Of the 4 patients with unresolved urinary incontinence, 3 patients were recognized as having neuropsychiatric disorders that were not being treated with appropriate neuropsychiatric medications at the time. Once these patients were treated with the appropriate neuropsychiatric medications, the incontinence episodes ceased. These patients were not taking tegaserod when they started the neuropsychiatric medications.

Table 1. Baseline Demographics for Patients in the Study (N = 19). doi: 10.3834/uij.1944-5784.2010.06.17t1

Characteristic	n	%N
Reason for initial consultation		
Incontinence	11	58
Frequency	3	15.6
Urgency	2	10.5
Hesitancy	1	5.3
Dysuria	1	5.3
UTI	1	5.3
Comorbid conditions		
Recurrent UTI	11	58
Neuropsychiatric disorder[a]		
Anxiety	4	21.1
ADD/ADHD	4	21.1
Depression	3	15.8
Other	1	5.3
Biofeedback		
Some training	11	58
No training	8	42
Concomitant medications		
OAB antimuscarinics	7	36.8
Antidepressants		
Tricyclics	3	15.7
SSRIs/SNRIs	2	10.5
Medications for ADD	4	21.0
Laxatives		
Senna stimulant	15	78.9
Osmotic	16	84.2

[a]Three patients were diagnosed with at least 2 neuropsychiatric disorders.
Abbreviations: ADD/ADHD, attention deficit (hyperactivity) disorder; OAB, overactive bladder; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; UTI, urinary tract infection.

In March 2007, tegaserod was taken off the market by the manufacturer for a potential safety signal that suggested increased cardiovascular ischemic events in elderly patients. Therefore, it became no longer available for this observational clinical study. In all 19 cases, the patients regressed over the course of several weeks and redeveloped their baseline symptoms of constipation or abdominal pain. The PVR urine values increased in all patients who had elevated residuals previously (mean [SD] = 75.1 mL [61]) once they were off the therapy for 3 months. When compared with the PVR values while on the medication, this was a significant increase (P = .0001).

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Figure 1. Postvoid Residual (PVR) Urine Volume (mL) for Individual Patients Before, During, and 3 Months After Withdrawal of Treatment With Tegaserod.
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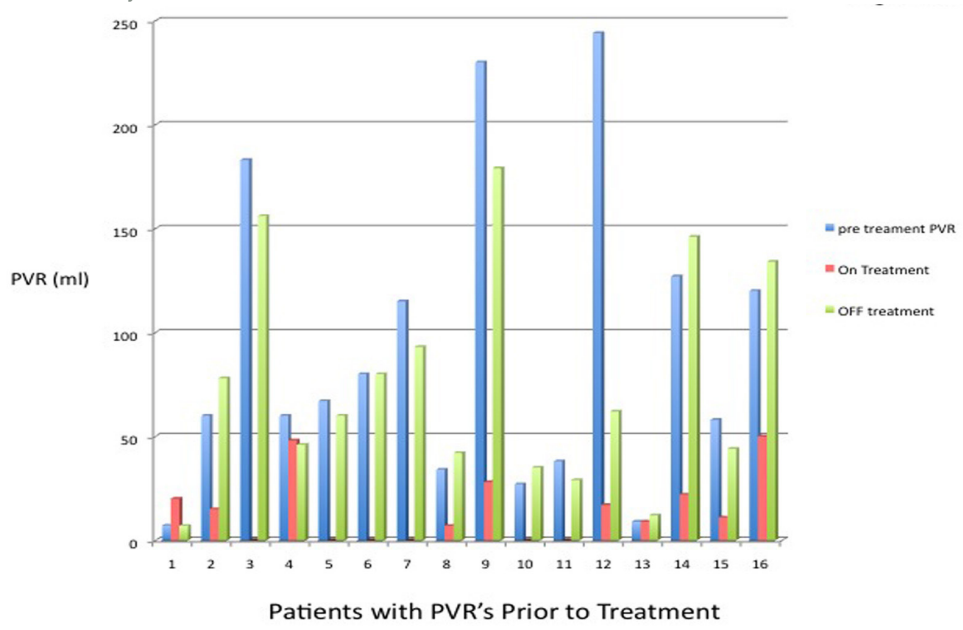

Table 2. Postvoid Residual Urine Volume (mL) at Baseline, Following Tegaserod Treatment, and Following Withdrawal of Tegaserod (N = 19). doi: 10.3834/uij.1944-5784.2010.06.17t2

	Baseline Measurements		PVR After Tegaserod	PVR After Withdrawal[a]
	Initial PVR	Maximum PVR		
Mean	59.4	80.0	10.3	75.1
SD	57.7	79.2	14.8	61
Patient				
1	4	7	20	7
2	0	0	0	0
3	60	60	15	78
4	0	0	0	0
5	89	183	0	156
6	50	60	48	46
7	67	67	0	60
8	50	80	0	80
9	115	115	0	93
10	34	34	7	42
11	230	230	28	179
12	27	27	0	35
13	38	38	0	29
14	51	244	17	62
15	9	9	9	12
16	127	127	22	146
17	58	58	11	44
18	120	120	50	134
19	0	0	0	0

[a]All patients were withdrawn from tegaserod for 3 months prior to obtaining this measure.
Abbreviations: PVR, postvoid residual; SD, standard deviation.

DISCUSSION

Distressing symptoms of LUTS and associated complications such as recurring UTIs continue to be a significant problem in the practice of pediatric urology. The combination of constipation and voiding symptoms has been termed *dysfunctional elimination* [9]. Successful treatment of the constipation by laxative drugs produces improvement in urinary tract symptoms in some patients [2,10]. However, clinical observations by the present authors and others have shown that LUTS may persist despite a laxative-induced return to normal bowel function [11,12]. The present retrospective report summarizes the experience of 19 children who continued to have LUTS and recurring UTIs despite aggressive laxative treatment with senna and stool-softening osmotic agents. Abnormal PVR bladder volumes were documented in 16 of the 19 children. This draws attention to persisting failure of contractile bladder function or increased outlet resistance at the bladder neck or external sphincter, despite reports by the children's parents that constipation was improved. Eleven of the 19 patients continued to experience recurring UTIs and all patients had variable abdominal pain. Clearly, laxative treatment alone did not produce the desired effect on the urinary tract abnormalities and symptoms in this group of patients.

The notion that with chronic constipation the large fecal mass retained in the rectum and sigmoid colon may exert pressure on the bladder wall or induce a more acute urethrovesical angle that is sufficient to reduce functional bladder capacity and impair emptying [13] cannot be the only causative factor involved. This conclusion is supported by evolving knowledge about the effects of various neurotransmitters on urinary bladder function that may be common to those affecting the colon. There is also a likely overlap of signaling pathways in the dorsal horn of the spinal cord for innervation of the bladder, bowel, and pelvic musculature [14-16]. The present authors did not investigate stool retention, per se. However, the fact that most of the patients in this study had laxative-induced bowel movements on a regular basis and were no longer considered constipated by the parents yet continued to have abdominal pain, poor bladder emptying, and recurring UTI's strongly suggests that mechanical pressure from retained stool and/or rectal and colonic distention was not the only source of the pathology or cause of LUTS.

It is also possible that tegaserod could have had a central effect, because there is evidence in animal models that the 5-HT4 receptor agonist can act as putative antidepressant with a rapid onset of action [17,18]. It is unclear whether or not tegaserod can cross the blood brain barrier, but this central effect could explain the mood elevation that was reported by several of the patients.

The authors chose to try treatment of these resistant cases of LUTS with tegaserod, a serotonin 5-HT4 receptor partial agonist. This drug was approved at the time for treatment of IBS-C in women and chronic idiopathic constipation (CIC) in all adults. The mechanism of action of tegaserod is complex, but it involves enhancing the effects of serotonin-related signaling in the colon and possibly the spinal cord [19,20]. Serotonin, released from enterochromaffin cells in the bowel mucosa secondary to local chemical stimulation or distention of the bowel by the fecal mass, is thought to enhance neurotransmission by increasing release of the neurotransmitter acetylcholine from afferent nerve terminals in the intestine and at the level of spinal reflexes. The net effect of tegaserod is to augment acetylcholine release and thereby enhance synaptic transmission and stimulation of efferent nerves that provide effector functions controlling motility, secretion, and sensation in the gut. Studies using experimental animals and humans have demonstrated that tegaserod treatment increases bowel contractions and promotes distal movement of intestinal contents [21]. Clinically, the result is production of more frequent and softer stools. Tegaserod treatment has also been associated with a decrease in abdominal pain and bloating, which can occur in patients with IBS-C and CIC unrelated to bowel pattern [22]. The cause for improvement in pain and bloating is less well understood but, again, is considered related to an effect on serotonin in modifying afferent pain pathways.

The present study showed that when children with continuing significant LUTS and bowel dysfunction were treated with tegaserod, they responded with maintenance or resolution of their constipation and also developed clinically improved LUTS. Improvement manifested as resolution of bladder symptoms, normalization of PVR urinary volume, lack of recurring UTIs, and resolution of abdominal pain. Thus, the manifestations of LUTS and its complications were largely eliminated when their bowel treatment was changed from a standard program to tegaserod.

How is this apparently striking effect of tegaserod explained? It is plausible that prior to treatment these patients were experiencing unsuccessful colonic contractions that were triggering contractions of the bladder or leading to increased tone in the urethrovesical sphincter by shared neural pathways in the pelvis or spinal cord. These effects are similar to those described in patients with imperforate anus [23]. Further support for a link between colon and bladder sensory and contractile responses is found in experimental observations

by Pezzone and colleagues, who reported that acute colitis in rats triggers bladder hyperactivity [14-16,24]. The present authors have noted clinically that during acute worsening of colitis, patients may experience an increase in bladder voiding symptoms. When the colitis is controlled, the bladder symptoms resolve. The reason for this symptom association is unclear, but in view of the lack of inflammatory cells in the urine of these symptomatic colitis patients, some inflammation-related or induced hypersensitivity reaction operating through common neural sensory-motor pathways may be the explanation.

The present study was limited by its retrospective design. Prospective studies related to this topic are needed. An additional limitation was the lack of uroflow and electromyographic (EMG) data. Such data may have helped to identify whether or not tegaserod was acting as prokinetic agent for the bladder and thus can be a potential treatment for underactive bladder. This use is speculative but possible because the majority of the patients with elevated PVR urine volume had been taking alpha blockers, but did not respond with complete elimination of urine from their bladders.

CONCLUSION

Use of tegaserod resulted in resolution of LUTS and its complications. The authors speculate that in addition to its prokinetic effect on bowel function, tegaserod may have had a beneficial effect on mechanisms that control bladder empting and related abdominal pain in children with chronic LUTS. Accordingly, they propose that prospective, placebo-controlled clinical trials with tegaserod or other 5-HT4 agonists be conducted in patients with LUTS who do not respond to standard therapy.

Conflict of Interest: none declared.

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