First North American experience of propiverine use in children with overactive bladder

Élisabeth Lapointe, Narcisse Singbo, Élizabeth Naud, Stéphane Bolduc

Division of Urology, CHU de Québec - Université Laval Research Centre, Quebec, QC, Canada

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Abstract

Introduction: In 2017, propiverine was approved in Canada for overactive bladder (OAB) in adults and children. There is, however, scarce data on its efficacy and tolerability in the pediatric population. Our primary objective was to assess the efficacy and tolerability of propiverine as a treatment for pediatric OAB. Our secondary objective was to compare propiverine to molecules already investigated in historical cohorts.

Methods: We conducted a retrospective analysis of a prospectively maintained database and reviewed 58 patients who received propiverine since 2017. Efficacy and tolerability were assessed through voiding diaries, postvoid residuals (PVR), changes in the number of incontinence and urgency episodes (grade 1 to 3), and on reported adverse events.

Results: In total, 58 patients (37 boys) initiated treatment at a mean age of 9.5±3.2 years. Patients were on propiverine for an average of 15.9±12.4 months. Mean bladder capacity increased from 120 ml to 216 ml, and % expected bladder capacity (%EBC) increased from 37% to 59%. The average increased rate of %EBC was 0.5% per month ($p<0.001$). Of the 58 patients, eight stopped the medication completely without symptom recurrence, 21 were still on medication, and six were on dose-tapering. Due to side effects, seven interrupted their treatment. Compared to molecules used in our service, propiverine offered comparable efficacy and tolerability. Our study had limitations, including the absence of a placebo group and its retrospective design.

Conclusions: Propiverine appears to be an efficient and safe option for treating OAB in children and is approved as such.

Introduction

Overactive bladder (OAB) is a relatively common condition in the pediatric population. It can be defined as: urinary urgency usually with frequency and nocturia, with or without urge incontinence, in the absence of a urinary tract infection (UTI) or other pathology.[1] According to the most recent large-scale studies, the prevalence of OAB in children is estimated at around 15–20% and is higher in boys. It also tends to decrease with age.[2,3] Lower urinary tract symptoms (LUTS) are a real burden within our services, as they are accountable for 40% of pediatric urology consults.[4] LUTS are also known for harming the patient's quality of life (QoL). Patients can experience poor self-esteem, social isolation, and behavioral changes, negatively impacting their development.[5] Some studies even addressed the possibility that childhood urinary symptoms predict adult OAB symptoms, which underlines the importance of early treatment.[6] Conservative measures are the mainstay for the treatment of OAB and should be initially attempted in all cases.[7] Failure of these conservative measures requires other treatment options.

Antimuscarinics can be initially tried, as they are considered first-line pharmacological OAB therapy;[8] however, their use has not been as thoroughly studied in children as in the adult population, hence the present study's interest. Also, patients tend to interrupt their treatment since antimuscarinics often come with side effects, such as xerostomia, eyes and skin dryness, constipation, flushing, dizziness, insomnia, and blurred vision.[9-12] The optimal management of OAB requires a treatment that offers both efficacy and an acceptable tolerability profile.

Oxybutynin was, until recently, the only U.S Food and Drug Administration (FDA) and Health Canada-approved antimuscarinic for children. In 2017, propiverine was approved in Canada to treat OAB in adults and children.[11] Despite its use for many years in Europe and Asia,[12,13] propiverine has not been prescribed and studied much in North America. Since there is an obvious need for efficient and safe drugs for treating OAB in children, we believe it is essential to assess the efficacy and tolerability of propiverine in this specific population. We hypothesized that propiverine was as efficient and safe as other molecules currently used to treat OAB. Our primary objective was to assess the efficacy and tolerability of propiverine as a first- or second-line pharmacological treatment of OAB in children. Our secondary objective was to compare propiverine to other molecules already investigated in our historical cohorts.

Methods

We conducted a retrospective analysis of a prospectively maintained database. We reviewed 58 patients aged 4–19 years old with refractory urinary incontinence due to non-neurogenic OAB. Our research ethics committee approved the study. All patients underwent urotherapy before trying any pharmacological treatment. Resolution of constipation, good hydration habits, voiding schedule, and optimal voiding position were taken care of before introducing any antimuscarinic medication.[14] It is not in our routine to perform full urodynamics studies before initiating pharmacological treatment. Therefore, no patient in this study underwent urodynamics.

Propiverine was intended as a first or second molecule when OAB symptoms persisted. Patients were recruited based on the analysis of their medical records. Subjects were eligible for the study if they were prescribed a weight-adjusted dose of propiverine (10–45 mg) between September 2017 and September 2021, diagnosed with OAB by a pediatric urologist, and attended at least one followup visit after their first prescription. From patient records, we extracted age at baseline, gender, previous OAB treatments, past medical history (attention deficit and hyperactivity disorder [ADHD], recurrent UTIs, and others), other medications, particularities on physical exam, initially prescribed propiverine dose, and new voiding comorbidities, such as constipation, UTIs, and an increased postvoid residual (PVR, abnormal >20 ml). The initial dose prescribed was 0.8 mg/kg (maximal dose 1.1 mg/kg) for children with a body mass inferior to 35 kg and was separated into two doses using 5 mg tablets. For children with a body mass higher than 35 kg, we prescribed 30 or 45 mg of propiverine using a once-a-day tablet.[15] We increased medication dosage throughout followup visits until the resolution of symptoms or the appearance of bothersome side effects. We documented all changes in dosage in our analysis.

To address our primary outcome, we collected information on efficacy and tolerability for the initial visit and each subsequent followup visit available in the patient record.

Firstly, the efficacy was assessed by including questions on significant OAB symptoms during the routine medical surveys. Therefore, the analysis included the documentation of urgency (graded from 0–3), urinary incontinence (UI), and nocturnal enuresis. Also, to ensure an objective quantification of the efficacy outcome, three-day voiding diaries were included in the analysis when available in patients' records (usually at every clinic visit). Voiding diaries allow us to get information about the mean voided volume and maximal voided volume. To overcome any age-dependent changes in bladder capacity and to allow measuring propiverine efficacy on this matter accurately, we used the percent expected bladder capacity (%EBC) by dividing the mean voided volume (excluding first-morning void) on voiding diaries by the expected bladder capacity (EBC) for age [(age+1) x 30].[1] Change in %EBC reports more accurately on the molecule's efficacy since a variation in capacity can occur strictly because of children's growth. Therefore, changes in voided volumes over months under propiverine allowed us to assess the evolution of the mean voided volume. It also allowed us to define improvement under propiverine as a progressive increment of the %EBC, combined with an improvement of OAB symptoms.

Secondly, we assessed the tolerability by documenting patient-reported side effects, such as constipation, xerostomia, and other central nervous system side effects. Each treatment interruption due to treatment-related adverse events (TRAE) was considered in the tolerability assessment. To evaluate the molecule's tolerability, we also considered increased PVR and frequency of UTI episodes as adverse events. Compliance was also assessed by questioning families: >80% was deemed to be good compliance to medication.

We hypothesized that patients would improve by reducing their number of incontinence and urgency episodes and increase their mean voided volume using propiverine. Therefore, categorical variables were reported as counts and percentages, and descriptive statistics (mean and standard deviation or medians and quartiles) were reported for continuous variables. Paired tests were used to assess the evolution of mean voided volume and %EBC scores at different time points of followup, and linear regression models with the generalized estimating equation method were used to estimate the average monthly variation. Patients were censored when data was lacking.

Results

The study included 58 patients (21 girls, 37 boys). Table 1 provides further information on patient characteristics. The mean age at initiation of propiverine was 9.5±3.2 years (range 4–19). The initial propiverine dose was based on the patient's

Table 1. Patient characteristics

Gender, n		ADHD	ADHD medication	Naive to treatment[1]	Age at initiation of propiverine, yr, mean (SD)	Treatment duration, months, mean (SD)
M	F					
37	21	12	9	25	9.5 (3.2)	15.9 (12.4)

[1]Propiverine was used first-line; the remaining 33 patients attempted at least one antimuscarinic prior to propiverine use. ADHD: attention deficit hyperactivity disorder; F: female; M: male; SD: standard deviation

weight and increased until the incontinence was resolved, or side effects occurred. The mean duration of treatment with propiverine was 15.9±12.4 months (range 0–44).

Data on symptoms and voided volume evolution are presented for patients who attended a followup visit an average of four months after treatment initiation. Among all patients included in the analysis, complete dryness, which corresponds to a 100% improvement, was documented in 31 patients (53%). A partial gain (>50% to <99%) was documented in 11 patients (19%). For the remaining 16 (28%) patients, the improvement regarding continence was suboptimal (<50%) when data were collected. Of those patients, eight discontinued medication because of lack of efficacy, two stopped because of inadequate insurance coverage (initial year), and six did not specify the reason for the treatment interruption and were lost to followup.

Regarding compliance to medication, for those who took the medication for more than three months, the compliance was excellent (>90%) for every patient but two, who were only partially improved. The lack of efficacy led them to go back to the previous antimuscarinic treatment.

Other OAB symptoms, such as nocturia and urgency, were also improved by the treatment. After 10–14 months of treatment with propiverine, more than 50% of patients were not reporting any urgency or nocturia. We also observed a correlation between improvement of OAB symptoms, %EBC, and mean voided volumes. Patients presenting fewer OAB symptoms throughout the treatment period also improved their mean voided volume. The average growth would mean an increase in mean voided volume of approximately 30 ml over 12 months (Visit [V]1 to V3 in our study). Between V1 and V3, we observed a 53 ml difference between both mean bladder capacities. Therefore, a 23 ml gain was added to the child's average growth and could be attributable to propiverine (Table 2).

The EBC was also adjusted to the child's age at each visit and allowed correction for their growth. Therefore, the %EBC is the best way to attest to the evolution of the mean voided volume under propiverine treatment. We noted a significant improvement in %EBC for our patients. At V1, the mean %EBC was 37% and increased to 59% at V6. Since the study's retrospective design comes with a variation of the time between followup visits for each patient, we calculated the variation rate based on the real-time visit. The mean variation rate of %EBC was estimated at 0.5% per month ($p<0.01$) and was statistically significant. In other words, patients under propiverine for approximately a year can expect a 6% gain of their mean voided volume. The augmentation in %EBC among our patients is illustrated in Figure 1. This gain adds to the augmentation of mean voided volume related to average child growth.

Regarding the tolerability outcome, 36 (62%) patients did not report any side effects or TRAE; however, a subgroup of patients experienced TRAE. Fifteen (25.9%) patients described mild side effects: constipation (5), transient abdominal colic (2), xerostomia (2), behavioral changes (2), headache (2), drowsiness (1), and insomnia (1); five of these 15 patients discontinued their treatment because of those side effects. One patient stopped the medication because of a potential allergic reaction, but this was also noted for the other anticholinergic molecules he attempted. Two patients had an increased PVR during followup visits, and one had to stop the medication due to this TRAE. Table 3 provides more information on side effects and treatment discontinuations. Four patients (all female patients) presented six episodes of UTI. No patient interrupted the medication because of this adverse event.

To this day, 21 patients are still on propiverine; six are on dose-tapering because they are dry and have significantly improved their condition. Eight patients completely stopped propiverine following a significant improvement of their symptoms and mean voided volume. Patients with complete resolution were under propiverine for a mean duration of 17.5±9.5 months.

Our secondary objective was to compare the present study on propiverine with our team's studies over the past years (Table 4). Even if the studies' designs slightly differ, patient profiles, age at baseline, and outcomes concerning the molecules' efficacy and tolerability were comparable. Furthermore, without head-to-head studies, we observed that propiverine offers an efficacy and tolerability profile similar to other molecules already tested, such as solifenacin, mirabegron, fesoterodine, and oxybutynin extended-release.

Discussion

We present the first North American experience on propiverine use in children with OAB.

The main objectives of treatment are to improve the mean voided volume and decrease the number of incontinence and urgency episodes. After implementing non-pharmacological methods, such as urotherapy, antimuscarinics can be

Table 2. Mean voided volumes

Period	V1 (baseline)		V3 (n=30)		V6 (n=11)	
Voided volumes	Mean volume (ml)	%EBC[1]	Mean volume (ml)	%EBC	Mean volume (ml)	%EBC
	120	37	173	49	216	59

[1]EBC was adjusted ([age(years)+1] x 30 ml) to the age of the child at each visit to compensate for the growth of the child. These data are not a variation rate of the expected bladder capacity. This is an average of the % expected bladder capacity collected at each visit, but the interval between each followup visit may vary. EBC: expected bladder capacity; V: visit.

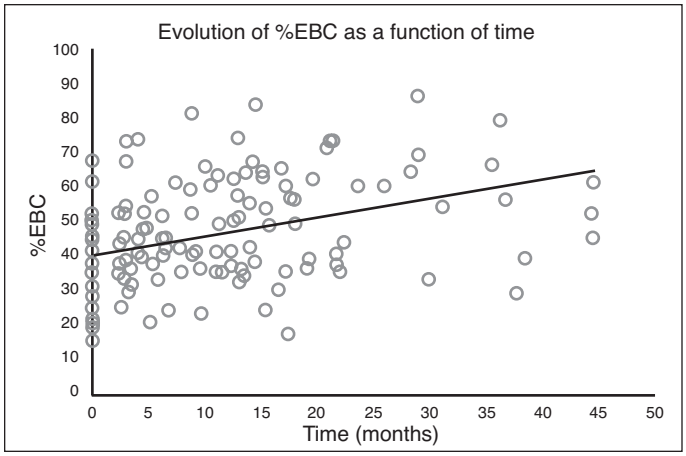

Figure 1. The augmentation in % expected bladder capacity among patient in the study cohort.

Table 3. Reported treatment-related adverse events

TRAE	Patients, n	Treatment interruptions, n
Constipation	5	0
Abdominal cramps	2	0
Xerostomia	2	0
Behavioral changes	2	2
Headache	2	1
Tiredness	1	1
Insomnia	1	1
UTIs	4	0
Allergic reaction	1	1
PVR (>20 ml)	2	1

PVR: postvoid residual; TRAE: treatment-related adverse events; UTI: urinary tract infection.

introduced. Currently, only two molecules are approved for children in Canada: oxybutynin and propiverine; however, many off-label molecules, such as solifenacin, fesoterodine, and trospium, are also used to treat children.[11-14,16]

In 2010, Alloussi and colleagues conducted a multicenter, observational cohort study to compare propiverine with oxybutynin on European children with urge incontinence due to OAB. Of the 621 children aged 5–14 years, 437 were treated with propiverine and 184 were treated with oxybutynin; 61.6% achieved continence in the propiverine group vs. 58.7% in the oxybutynin group. The treatment period before achieving continence was also longer for the oxybutynin group, and more side effects were reported than in the propiverine group.[14] The tolerability profile is an essential aspect of OAB treatment because of the high discontinuation rate associated with current treatments. Adherence to antimuscarinics in children seems higher than in adults but seems significantly lower than self-reported adherence. Poor adherence can lead to suboptimal management of symptoms.[17,18]

Considering all of this and the recent propiverine approval in Canada, we performed a retrospective analysis of a prospectively maintained database within our pediatric patients. Regarding %EBC, the gain was substantial since 80% of patients had an augmentation of their corrected bladder capacity within the first five months. Also, our eight patients who stopped propiverine after resolution of symptoms, including incontinence, took the molecule for an average of 18 months. In the most optimistic scenarios, patients can then expect a complete recovery or a medication tapering within this period. We also noted that the second followup visit (V3 at 10–14 months) was a turning point for most of our patients. Indeed, half of the patients experienced no more urgency and incontinence (day and night) approximately one year after the initiation of treatment. Mentioning that fact to patients can help them tolerate the mild adverse events sometimes experienced at the beginning of treatment and set their expectations concerning the duration of treatment. Concerning side effects, most were benign. After experimenting with constipation, xerostomia, or abdominal cramps, no patients stopped the medication. Central nervous system symptoms, such as headaches, behavioral changes, and insomnia, seemed more bothersome for our patients and led to more interruptions. Patients who were simultaneously taking ADHD medication did not experience more side effects than those who were not.

The pharmacodynamics of propiverine remains to be investigated. In contrast to other muscarinic receptor antagonists, propiverine exerts additional L-type Ca(2+)-channel blocking and α(1)-adrenoceptor antagonist effects; however,

Table 4. Comparison between the previous studies and the propiverine study

Studies	Patients, n	Age at baseline (years)	Mean treatement duration (months)	Voided volume difference (ml)	Achievement of continence (%)	PVR (%)	UTIs (%)	Treatment interruption due to TRAE (%)
Solifenacin (2010)	72 (30 M)	9.0	15.9	165	33	5.6	–	5.6
Solifenacin (2014)	191 (107 M)	9.0	17.4	138	18	5.2	1.6	6.3
Mirabegron (2016)	58 (44 M)	10.1	11.5	50	22	1.7	3.4	5
Fesoterodine and oxybutynin XL (2020)	62 (38 M)	8.5	4.5 (CO) 12 (ext.)	21 (CO) 26 (ext.)	68 (CO) 69 (ext.)	1.6	16.1	–
Propiverine (2021)	58 (37 M)	9.5	15.9	96	53	3.4	6.9	12

CO and ext. stand for crossover part and 12-month extension part, which were two parts of the FOXY study. M: male; PVR: increased postvoid residual (>20 ml); SE: side effects; TRAE: treatment-related adverse event; UTI: urinary tract infection; XL: extended-release.

it is not yet understood how these properties impact the clinical effects of propiverine regarding efficacy and tolerability.[17] Also, it would be interesting to know more about the receptor selectivity of the molecule since better selectivity correlated with reduced side effects.[19]

Numerous off-label options can be available for the treatment of OAB in children. As our previous studies have shown, solifenacin, oxybutynin extended-release, mirabegron, and fesoterodine all offer similar efficacy and can be great options;[20-24] however, propiverine was recently approved for children in Canada. Patients and their parents can feel more secure with taking a molecule approved for this specific population. Furthermore, propiverine offers excellent flexibility of doses. Young children are given weight-adjusted doses; older children can be given a long-acting, once-a-day formulation, maximizing compliance and decreasing the incidence of side effects. This flexibility can also ensure better side effects management and make it easier to establish a plan for tapering the medication. In our service, when dry patients reach 75% of their %EBC, we initiate a dose-reduction plan. If symptoms do not recur, we stop the medication entirely while monitoring the mean and maximal voided volumes using voiding diaries. Nevertheless, propiverine cost is higher than immediate-release oxybutynin, but equivalent to extended-release formulations. This economic factor can be considered by clinicians when a first-line therapy is needed.

Limitations

We acknowledge the limitations and bias inherent to our retrospective study.

First, we did not have a placebo group. Since antimuscarinics are known to have a high placebo response in adults, such a group could have been interesting.[25] Nonetheless, we believe the placebo effect could not exclusively explain patient progress since half of the patients tried other antimuscarinic molecules before propiverine and failed those previous treatments.

Second, the retrospective design did not allow us to use an objective scale or questionnaire to state the patients' improvement in QoL; however, we believe that improvement of symptoms is a good indicator of QoL.

Last, some of our patients simultaneously used mirabegron during part of their propiverine treatment. We noticed that patients who took longer to improve were more likely to add another molecule offering a different mechanism of action. It would be interesting to go further and conduct a controlled trial with a treatment combination of propiverine and mirabegron since dual therapy was shown as effective in previous studies.[26]

Conclusions

Propiverine appears to be an efficient and safe option for treating OAB in children, and its efficacy and tolerability seem comparable to previously studied molecules; however, dosage flexibility and recent Health Canada approval make propiverine an interesting avenue for OAB treatment in children. Further randomized controlled trials with North American children are required.

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Correspondence: Dr. Stéphane Bolduc, Division of Urology, CHU de Québec-Université Laval (CHUL), Quebec, QC, Canada; stephane.bolduc@fmed.ulaval.ca