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Can Oral Fesoterodine Be an Alternative for Intravesical Oxybutynin Instillations in Children with Neuropathic Bladder Dysfunction?

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Abstract
Purpose: A low-pressure bladder in children with neuropathic bladder dysfunction can be achieved using anticholinergic medication. Due to the significant side effects of oral oxybutynin, our patients are treated with daily intravesical oxybutynin instillations. Newer oral anticholinergic medication, such as fesoterodine, claim to have fewer side effects in a once daily formulation. Because once-daily oral intake is easier than performing twice-daily intravesical instillations, we studied the effects of switching from intravesical oxybutynin to oral fesoterodine and compared the clinical response, urodynamic parameters and side effects. ***Patients and Methods:*** Twenty children (11 girls, 9 boys, 4–17 years) with neuropathic bladder dysfunction who perform clean intermittent catheterization and use intravesical oxybutynin instillations twice daily were included in this prospective study. Voiding diaries, a behavioural checklist, urodynamic investigations, vital signs and blood samples were evaluated at baseline during treatment with intravesical oxybutynin and repeated after 40 days of oral fesoterodine. ***Results:*** Out of 20, 13 (65%) children showed an identical objective dryness (pad-test), 2 (10%) improved and 5 (25%) got worse. Seven (35%) children reported equal dryness, 7 (35%) reported improvement and 6 (30%) reported that it got worse. From a urodynamic perspective, 13 (65%) children remained identical, 3 (15%) improved and 4 (20%) got worse. Four (20%) children reported a light to moderate dry mouth, 1 (5%) a headache, 1 (5%) behavioural changes during fesoterodine administration, 1 (5%) an increased appetite, 1 (5%) nausea and 1 (5%) hot flushes. ***Conclusions:*** The urodynamics after 40 days of fesoterodine were in 16 (80%) identical or better and could be a safe alternative for oxybutynin instillations in children with neuropathic bladder dysfunction.

Introduction

Neurogenic detrusor overactivity (NDO) is seen in children with congenital neuropathic bladder disturbance like spinal dysraphism [1]. The consequence of a congenital neuropathic bladder disturbance is in about 27% a urinary sphincter underactivity with a low pressure

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in the bladder, in 10% detrusor areflexia with sphincter overactivity and in 63% NDO and sphincter overactivity, also called detrusor sphincter dyssynergia (DSD) [2]. In the long term, secondary pathological-anatomical changes can occur with consequent vesico-ureteral reflux, hydronephrosis, an increased risk of urinary tract infections, renal damage and renal insufficiency [3]. Fifty-eight per cent of untreated patients develop renal damage after 3 years [3]. The primary treatment goal in this patient group is to keep the intravesical detrusor pressure low from birth in order to preserve kidney function [3]. This can be achieved by frequent emptying of the bladder by clean intermittent catheterization (CIC) in combination with anticholinergic medication [3]. The secondary treatment goal is to achieve socially acceptable continence at an appropriate age [4]. Anticholinergic medication lowers the frequency of involuntary bladder contractions, can lower the intravesical pressure, prevents the development of a hypertrophic bladder and augments the bladder capacity [3]. However, anticholinergics cause side effects due to concomitant suppression of the muscarinic receptors in the rest of the body [5]. The oldest and most well-known anticholinergic used to suppress detrusor overactivity is oxybutynin, a mild muscarinic-3 receptor selective antagonist [3]. It is registered for the use in children and adults with neuropathic and non-neuropathic bladder disturbances [3, 6]. Franco et al. [6] conducted a multicentre open-label trial with 3 oral oxybutynin formulations (tablet, syrup, extended release formulation). Although this trial was not designed to compare efficacy or side effects, they reported no significant differences in efficacy or side effects between them [6]. In 1998, Buyse et al. [7] showed a reduced first pass metabolism of intravesical use of oxybutynin, which results in less formation of N-desethyl-oxybutynin (N-DEO), which is responsible for the side effects, and therefore intravesical application is claimed to give less side effects compared to oral administration. A recent randomized controlled trial in an adult population with NDO showed equal efficacy of intravesical oxybutynin administration to oral administration [8]. Thus, oral application of oxybutynin can be replaced by intravesical administration in the paediatric neuropathic bladder patient group who perform daily CIC. Although a twice-daily intravesical oxybutynin administration is an efficient treatment in children with neuropathic bladder dysfunction, it is a rather complex procedure compared to taking one tablet a day. Ready-to-use solutions are lacking, so usually patients and their caregivers have to prepare a solution for intravesical administration themselves, which is time consuming and could therefore lead to less compliance in intravesical administration [9]. More recently developed anticholinergics, such as solifenacin, tolterodine and fesoterodine, pretend to have a similar high affinity for muscarinic receptors in the detrusor and bladder mucosa as oxybutynin, but with a less number of side effects, despite oral application [10]. Tolterodine and the newer prodrug fesoterodine have the same active metabolite: 5-hydroxymethyltolterodine (5-HMT) [11]. The study of Maruyama et al. [12] shows that 5-HMT, compared with the active metabolite of oxybutynin, may bind more selectively to muscarinic receptors in the human bladder than in the parotid gland, by consequence they cause less dryness of the mouth. Fesoterodine is rapidly and completely hydrolyzed by non-specific esterases into 5-HMT. These esterases are genetically identical in the whole population. The pharmacokinetics of fesoterodine seems more stable than tolterodine as tolterodine is metabolized to 5-HMT by CYP450 2D6, which subject genetic polymorphism with poor and extensive metabolizers in the population [13]. In addition, tolterodine acts by tolterodine itself and 5-HMT, fesoterodine acts only by 5-HMT. 5-HMT is more hydrophilic than tolterodine and consequently, fesoterodine penetrates the blood-brain-barrier less easily, compared with tolterodine, reducing the chances of neurological side effects [14, 15].

Tolterodine and fesoterodine are registered for use only in the adult population but are used off-label in paediatric population as well. Fesoterodine is available in a slow release tablet formula and needs to be taken only once daily. Our aim was to assess the efficacy, safety and tolerability of oral fesoterodine once daily in our population of children with neuropathic bladder dysfunction who perform CIC and compare this with intravesical oxybutynin given twice daily, assuming to find a comparable or even a more favourable side effects profile.

Patients and Methods

Between March and June 2013, an academic, monocentric, open-label, pilot study with 1 study-arm was conducted. The design of the study is shown in Figure 1.

The Clinical Trial Center of UZ Leuven, the Medical Ethics Committee and the Federal Agency for Medicines and Health Products approved this study. The unique numbers of this trial are: S54913 and EUDRA-CT 2012-005295-33. Children with NDO and sphincter overactivity (DSD) proved by a urodynamic study (UDS) performing daily CIC taking intravesical oxybutynin hydrochloride (0.3–0.6 mg/kg/24 h divided over 2–3 instillations a day) were included. The children needed to be older than 4 years

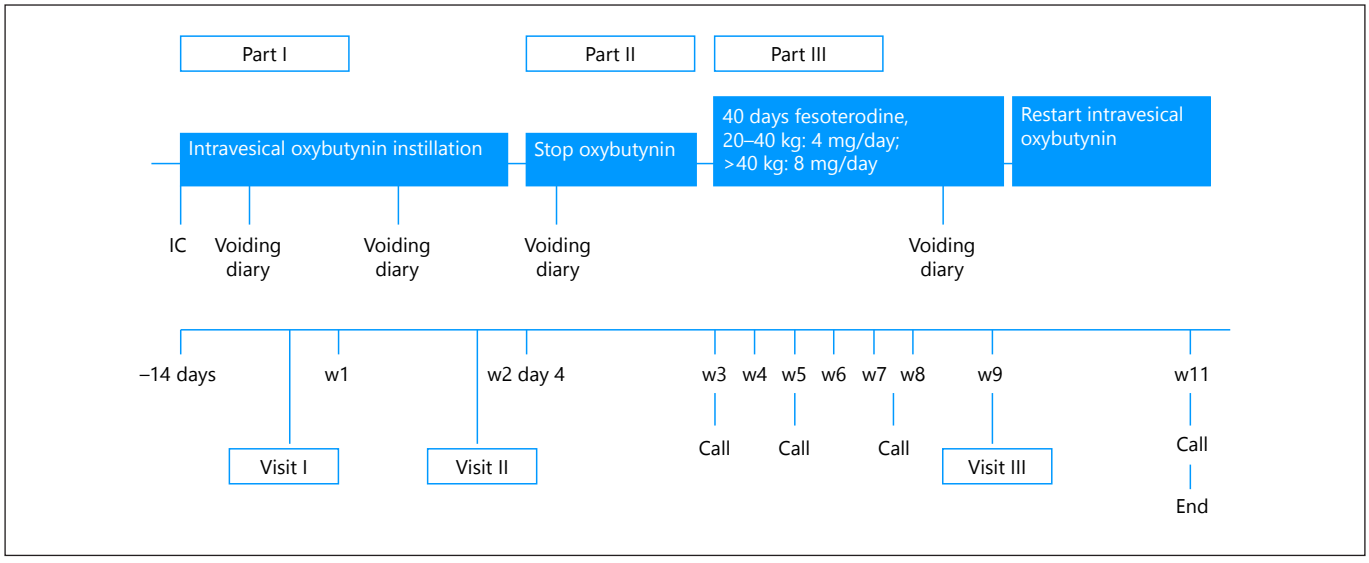

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Fig. 1. Design and chronology of the study. Visit I: vital signs, clinical examination, blood samples, urine sample. Visit II: urine sample, urodynamics, vision tests, behavioral checklist. Visit III: urine sample, urodynamics, vision tests, behavioral checklist, vital signs, clinical examination, blood samples. IC, informed consent; Call, phone call; w, week.

of age because they had to be able to swallow an entire tablet, so that the prolonged release formula could work. Based on previous studies with tolterodine, which has the same active metabolite as fesoterodine, and the results of the pharmacokinetic behaviour of fesoterodine in a study with paediatric subjects, we calculated that a maximal dose of fesoterodine of 0.2 mg/kg/24 h would be safe [16–18]. The child's body weight had to be at least 20 kg because fesoterodine is available in 4 and 8 mg slow release tablets. The exclusion criteria were as follows: soya or peanut allergy (fesoterodine, Toviaz® contains soya); galactose-intolerance, lactase-deficiency, glucose-galactose malabsorption (Toviaz® contains lactose); every medical condition that disturbs the absorption of fesoterodine (gastrectomy, gastro-intestinal hypomotility, myasthenia gravis, gastro-intestinal obstruction, severe colitis ulcerosa, toxic megacolon); a surgical urological procedure that interferes with the study results (urinary sphincterotomy, artificial urinary sphincter, bladder augmentation); a comorbidity that interferes with the study results (bladder stones, angle closure glaucoma, severe liver disorders); clinical relevant abnormal hematologic, hepatological, renal or cardiologic status, combination with systemic CYP3A4-inducers or potent CYP3A4-inhibitors, antispasmodic, parasympathomimetic or cholinergic medication, intravesical botulin toxin injections 9 months prior to the study; electrostimulation of the bladder in the 30 days prior to the study; combination with diuretics, alpha-blockers, tricyclic antidepressants or some neuroleptics, intake of other experimental medication 4 weeks or 5 half-lives prior to the study; pregnancy; relatives of the research team. If the child was taking oral anticholinergic medication in addition to the intravesical oxybutynine instillations, this medication was stopped before the onset of the study. All children structurally empty their bowels 1–2 times a week by colon rinsing, as part of the multidisciplinary treatment of this patient group. A clinically significant urinary infection (symptomatic pyuria and bacteriuria) was treated with nitrofurantoin or according to the urine culture and antibiogram and if needed an increased CIC frequency. Written informed consent was obtained from at least one of the parents and from the children themselves if they were older than 12 years old. The study duration was 12 weeks and Figure 1 represents the study procedure. In those 12 weeks, 7 patient contacts were done, either in the form of clinic visits or telephone interviews. During the first 2 patient contacts, the current urinary tract status was collected while on intravesical oxybutynin treatment by filling out 2 voiding diaries and urodynamics. In the second part of the study, intravesical oxybutynin instillations were stopped for 4 days as a washout of the medication. During this washout, the child and parents were asked to fill a third voiding diary. The third part of the study consisted of 40 days of oral fesoterodine administration, a slow release tablet every morning, instead of intravesical oxybutynin, and the CIC was continued. Children with a body weight 20–40 kg took 4 mg per day, children with a body weight of more than 40 kg a day took 8 mg per day. They had to contain their normal life style but had to avoid grapefruit because this fruit interferes with the metabolism of fesoterodine.

Efficacy

The efficacy of the treatment was assessed using clinical parameters (voiding diary, catheterization schedules and a pad test) and urodynamic parameters. During the first 2 patient contacts, the current urinary tract status was objected during intravesical oxybutynin application. At baseline, parents and children were asked to fill 2 voiding diaries. Based on the voiding diaries, the number of daily catheterizations, the catheterized urine volumes (average and [range]), the number of urine leakage incidents between catheterizations and the daily weight of urinary leakage were registered. Objective dryness was defined as no leakage between CIC and a negative pad test. The fourth voiding diary was filled in the last week of oral fesoterodine administration. A UDS was per-

formed at baseline during intravesical oxybutynin application and repeated during the third patient contact on the 40th day of oral fesoterodine application after exclusion of urinary tract infections. During the UDS, the bladder filling rate was 10 mL/min with a physiological heated solution of 37 °C. The filling was stopped when the maximum tolerated bladder volume has been reached, when leakage exceeds bladder filling, detrusor pressure increased to 40 cmH_20, or when the instilled bladder volume is more than 150% of the estimated maximal neurogenic bladder capacity (following the formula: [age in years × 24.5] + 62). The patients were in the same supine position for all UDS. Terminology of the 2016 ICCS consensus document was used for analysis of the results [2]. The ICCS does not provide terminology to define urinary continence. The *primary efficacy variable* was the maximum cystometric capacity in millilitres during UDS at intravesical oxybutynin application and at fesoterodine application. *Secondary variables* were other UDS parameters like detrusor pressure at maximum cystometric capacity in cm H_20. In case of involuntary loss of urine, the UDS parameters detrusor leak point pressure in cm H_20 as well as the filling volume of the bladder during urine loss in mLs was assessed. The voiding diary parameters that were analyzed were the average catheterized urine volume in mLs, the percentage of pads that were dry during 3 days and the average incontinence volume per day in grams.

Safety and Tolerability

Safety and tolerability of fesoterodine were compared with those of intravesical oxybutynin based on data of anamnesis during 3 clinical contacts and 4 telephone interviews, vital signs (blood pressure, heart rate, axillary temperature and body weight), clinical examination, behavioural checklists, laboratory evaluations like blood and urine samples. Telephone interviews were done after the 2nd day of oral fesoterodine administration; after 2 weeks and after 4 weeks to check for concomitant medication that could interfere with fesoterodine, we specifically asked for the development of possible side effects and subjective scaling of dryness compared with intravesical oxybutynin. At the last day of fesoterodine intake the patient was seen for the 3rd time for a clinical visit. The day thereafter, they restarted their intravesical oxybutynin treatment as it was before this study. Two weeks after stopping oral fesoterodine administration, the family was called for the last time to check for late side effects and their subjective preference of anticholinergic treatment.

Both oxybutynin and fesoterodine are associated with psychological changes [11, 19–21]. The psychological behaviour was objected by a behaviour checklist (child behaviour checklist).

Statistical Analyses

We anticipated including 20 children as an initial pilot study in order to study the trend of efficiency, safety and tolerance rather than a formal statistical analysis. Results are given in per cent, average and range; no formal statistical testing of these results was performed. A Shapiro Wilk test was performed to identify between parametric and non-parametric distribution [22]. Given the results of the Shapiro Wilk test, we continued with the Wilcoxon matched pairs test in SPSS. We were able to note that due to the small sample size (n = 20) parametric tests are not very robust and non-parametric tests are not very powerful. Therefore, we verified our results by performing paired samples t test as well.

Table 1. Patient characteristics

	n = 20
Age, years, median (range)	13 (4–17)
Weight, kg, median (range)	31.5 (20–78)
Male, n (%)	9 (45)
Female, n (%)	11 (55)
NDO history, n (%)	
Spina bifida	15 (75)
Tethered cord	2 (10)
Caudal regression syndrome	1 (5)
Transverse myelitis	1 (5)
Traumatic spinal cord injury	1 (5)
Number of patients applying CIC, n (%)	20 (100)
Number of patients applying intravesical oxybutynin at start, n (%)	20 (100)
Concomitant medication, n (%)	12 (60)
Median study compliance, n (%)	20 (100)

CIC, clean intermittent catheterization; NDO, neurogenic detrusor overactivity.

Results

Patient Characteristics

Twenty children with a body weight of at least 20 kg were enrolled and all completed the study. Table 1 displays baseline details about the group of patients.

All children had NDO and sphincter overactivity proved by a UDS for which they performed CIC (4–6 times a day) and used intravesical oxybutynin. Out of 20 children, 12 (60%) took concomitant prophylactic antibiotics (nitrofurantoin) of whom 1 patient (5%) used erythromycin for acne, which was stopped at informed consent because it could interact with the metabolism of fesoterodine.

Efficacy

Table 2 shows the efficacy evaluations during intravesical oxybutynin and during oral fesoterodine administration in the patient group.

The primary efficacy variable, change from baseline in mean maximum cystometric capacity was 18.4 mL, which did not represent a significant increase (Wilcoxon-matched pairs test, p = 0.196). The secondary efficacy variable from UDS, change from baseline in maximum detrusor pressure was 2.4 cm H_20, which did not represent a significant increase (p = 0.563). The change from baseline in bladder filling volume during urine loss was 135.5 mL, which represented a significant increase (p = 0.038). The change from baseline in detrusor leak point

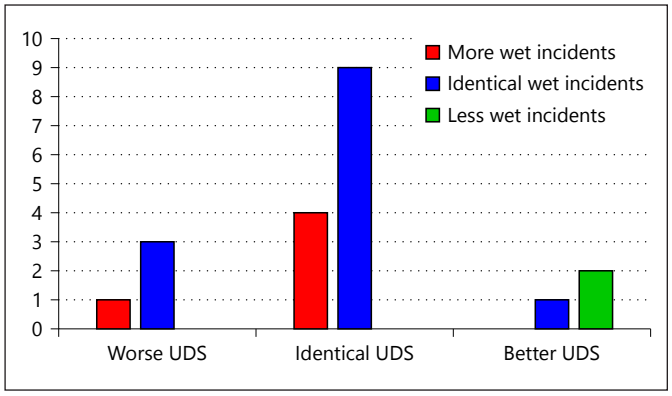

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Fig. 2. Comparison of the results of the urodynamic investigations and the voiding diaries. UDS urodynamic study.

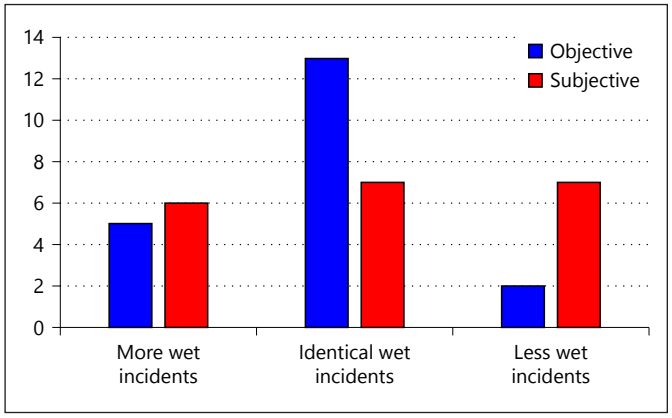

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Fig. 3. Objective and subjective continence after 40 days if oral fesoterodine is compared with intravesical oxybutynin.

pressure was 3.2 cm H_20, which did not represent a significant increase ($p = 0.674$).

The secondary efficacy variable from bladder diary, change from baseline in catheterized urine volume was –8 mL, which did not represent a significant decrease ($p = 0.247$). The change from baseline in volume urine incontinence per day was 11.9 g, which did not represent a significant increase ($p = 0.657$). The change from baseline in percentage dry pads during 3 days was –8.2%, which did not represent a significant decrease ($p = 0.215$).

During intravesical oxybutynin administration, 4 children (20%) had a detrusor pressure below 10 cm H_2O during the filling phase of the UDS. After 40 days of fesoterodine, 5 children (25%) had a detrusor pressure below 10 cm H_2O during the filling phase of the UDS. Two children had a detrusor pressure below 10 cm H_2O during both treatments.

During intravesical oxybutynin administration, 7 children (35%) did not leak during the filling phase of the UDS. After 40 days of fesoterodine treatment, 9 children (45%) did not leak during the filling phase of the UDS.

Six children (30%) had a higher detrusor leak point pressure after 40 days of fesoterodine.

From a urodynamic perspective, 13 out of 20 children (65%) remained unchanged, 3 out of 20 (15%) improved and 4 out of 20 children got worse (Fig. 2). Bladder diaries showed comparable results with 13 out of 20 patients who had identical results, 2 children improved and 5 children got worse. When we compared the subjective grade of satisfaction about their continence with the objective variables of the bladder, there was a remarkable difference between objective and subjective continence (Fig. 3). Consequently, the importance of filling in bladder diaries was again demonstrated.

We combined the results of efficacy and tolerance and looked at the treatment satisfaction and can state that 3 out of 20 children (15%) had better results with fesoterodine and 8 out of 20 children (40%) had comparable results. Nine out of 20 (45%) had less favourable results, as 4 out of these children had a UDS with less favourable results, 4 had a comparable UDS but 4 of them had less continence, 1 had a comparable UDS and comparable continence but developed behaviour changes. After this study, 5 patients continued the intravesical instillations with oxybutynin. In 1 patient, this was due to a worsening at UDS after 40 days of fesoterodine, 1 had less continence, 1 had the combination of a worse urodynamic, less continence and a headache, 1 had swallowing troubles of the oral tablets, and 1 had behaviour changes during the intake of fesoterodine. Three patients continued with the combination of oxybutynin instillations and fesoterodine because of less continence and/or worsening of the UDS with fesoterodine in monotherapy. Twelve patients continued with fesoterodine monotherapy. Seven of these patients had an identical objective continence and UDS. Three patients had an improved UDS, 2 of them also had an improved objective continence. Two patients preferred to continue fesoterodine because it was easier to use; also, the child had less urinary continence but a safe UDS.

Safety and Tolerability

There were no remarkable differences seen between the vital functions and clinical examination during both treatments. The median heart rate during intravesical oxybutynin administration was 86 bpm (range 56–116 bpm), after 40 days of fesoterodine administration this

Table 2. Results

		Number	Intravesical oxybutynin, mean (SD)	Fesoterodine, mean (SD)	Change from baseline	*p* value significance (2-tailed)
Primary efficacy variable	Maximum cystometric capacity, mL (UDS)	20	353.4 (117.3)	371.8 (112.1)	18.4	0.196
Secondary efficacy variables	Maximum detrusor pressure, cm H_2O (UDS)	20	28.2 (23.5)	30.6 (24.1)	2.4	0.563
	Bladder filling volume during urine loss, mL (UDS)	9	217.9 (125.6)	353.4 (126.7)	135.5	0.038
	Detrusor leak point pressure, cm H_2O (UDS)	8	18.8 (13.3)	22.0 (10.9)	3.2	0.674
	Catheterized urine volume, mL (BD)	20	147.5 (46.9)	139.5 (54.1)	–8.0	0.247
	Volume urine incontinence per day, g (BD)	12	121.0 (121.0)	132.9 (135.5)	11.9	0.657
	Dry pads during 3 days, % (BD)	20	53.3 (31.8)	45.1 (34.0)	–8.2	0.215

UDS, urodynamics; BD, bladder diary.

Table 3. Side effects

	n (%)
Light-moderate dry mouth	4 (20)
Headache	1 (5)
Behavioral changes (reversible)	1 (5)
Increased appetite	1 (5)
Nausea and hot flushes	1 (5)

was 100 bpm (range 68–117 bpm). The median temperature during intravesical oxybutynin administration was 36.85 °C (34.7–37.5 °C), and after 40 days of fesoterodine administration 36.35 °C (range 35.6–37.1 °C). No clinically significant changes were seen in laboratory variables (sodium, potassium, clearance, liver function [transaminases, bilirubin total and direct]). Fesoterodine was well tolerated. Table 3 summarizes the side effects.

The analysis of the child behaviour checklists showed in 3 children (15%) an improvement of the psychological behaviour and in 4 children a deterioration. Only in 1 child, parents subjectively recognized this deterioration in behaviour (5%). The increased appetite of 1 child was still present after stopping the fesoterodine.

Discussion

Anticholinergic therapy lowers the frequency of involuntary contractions and intravesical pressure in a neuropathic bladder, prevents the development of a hypertrophic bladder, augments the bladder capacity, postpones the first desire to void, and in this way, as stated in the literature, it protects against urinary infections [3, 23]. In combination with CIC, the kidney function is protected in children with a neuropathic bladder with DSD, and in a select group of children, urinary continence can be achieved [4]. However, anticholinergic therapy has its side effects. The inhibition of the muscarinic receptors in the salivary gland, lacrimal gland, sweat glands, ciliar body and gastro-intestinal tract can cause, respectively, dry mouth, dry eyes, anhydrosis/hyperthermia, blurred

vision and obstipation [5, 24]. M1-, M2-, M3- and M5-muscarinic receptors are present in the brain, so that lipophilic anticholinergics can pass the blood-brain-barrier and therefore could lead to learning disabilities, impaired memory and sleeping disorders [25]. The oldest and most well-known anticholinergic used to suppress detrusor overactivity is oxybutynin, a mild M3-muscarinic receptors selective antagonist [3]. It is registered for the use in children and adults with a neuropathic and non-neuropathic bladder [3, 6]. Oxybutynin has a spasmolytic, parasympathicolytic, local sedative and calcium-blocking effect on smooth muscle cells [3]. Oxybutynin is converted into the active metabolite N-DEO by the first pass metabolism of the liver. N-DEO is responsible for the side effects of oxybutynin by suppressing the muscarinic receptors in the rest of the body [26]. In 1999, an extended release oxybutynin formulation tablet was issued, so only one tablet a day could be taken, which could improve the compliance to the treatment [27].

A Cochrane analysis in adults showed a better efficacy for tolterodine and a significant reduction in side effects compared to oxybutynin, for immediate as well as extended release formulation [28]. Moreover, fesoterodine instead of tolterodine might be preferred for superior efficacy [28]. A retrospective study of Youdim and Kogan [29] compared extended release and traditional oxybutynin formulations and described the extended release as equal or more efficient with fewer side effects, but physiological assessments to compare urodynamic effects for the 2 formulations were not included . Although the multicentre open label clinical trial from Franco et al. [6] was not designed to compare efficacy or adverse effects between 3 forms of oxybutynin formulations (tablets, syrup, extended release tablets) in children with detrusor hyper-reflexia, they did not observe meaningful differences between the 3 formulations. In 1998, Buyse et al. [7] showed a reduced first pass metabolism of intravesical use of oxybutynin, which results in less formation of N-DEO and therefore intravesical application is claimed to give less side effects compared to oral administration. Oral oxybutynin shows plasma levels of the active metabolite N-DEO up to sevenfold higher compared to the parent compound, whereas intravesical administration only shows a 1.2 ratio [7]. Another study showed that a local effect in the bladder wall, caused by elevated concentrations of oxybutynin, occurs after intravesical administration [30]. Also, additional studies suggested that intravesical instillation of oxybutynin could be safely and effectively administered in children [20, 21].

Although prospective comparable studies in children are lacking, Schröder et al. [8] recently published a randomized multicentre trial in adult patients with NDO showing significant superiority of intravesical 0.1% oxybutynin hydrochloride administration compared to the standard oral administration regarding the primary efficacy criterion "maximal bladder capacity" and a significantly lower incidence of anticholinergic effects. In our department, intravesical oxybutynin is administered in children with proved DSD who perform CIC experiencing too severe side effects of oral anticholinergic therapy. However, ready-to-use solutions are lacking, so often patients and their parents have to prepare a solution for intravesical administration themselves, which is time consuming and could therefore lead to less compliance in intravesical administration [9]. Moreover, due to recent problems with financial reimbursement for intravesical oxybutynin in Belgium, it is desirable to have an alternative. The aim of this study was to compare the use of intravesical oxybutynin instillations twice daily with a once daily oral slow-release fesoterodine tablet and evaluate the efficacy, safety and tolerability in our paediatric population with neuropathic bladder dysfunction who perform CIC.

This is the first study that compared oral fesoterodine with oxybutynin intravesical instillation in children from 4 years of age and at least 20 kg body weight. Malhotra et al. [16] described the pharmacokinetics and tolerability of fesoterodine in 21 children with an overactive bladder, of whom 11 were with neuropathic bladder dysfunction and 10 were with non-neuropathic bladder dysfunction. All children took 4 mg daily for 4 weeks and afterwards 8 mg daily for 4 weeks. He showed that the plasma concentration measurements of the active metabolite of fesoterodine, 5-HMT in children were analogue to those in the adult population and that fesoterodine was well tolerated. He remarked no correlation between the occurrence of side effects and a higher plasma concentration or lower body weight. The patients in our study all had an NDO and sphincter overactivity assessed with a UDS and performed CIC, so it seems to be a homogenous group. Moreover, our patients took the same dose during the whole study, based on their body weight (4 mg with a body weight between 20 and 40 kg, 8 mg with a body weight of more than 40 kg). Good tolerance was confirmed in this study, like Malhotra et al. [16] showed previously. The most serious side effect was remarkable behavioural changes in one child with severe mental retardation, which improved immediately after the discontinuation of fesoterodine. The most frequent reported side effect was dry mouth, which is common to the antimuscarinics. No patients discontinued the study because of these side effects. The results of this study have

to be interpreted with their limitations. The included population is too small for statistical analysis; moreover, in order to obtain significant results about the efficacy, more patients should be included. An additional treatment arm with oral oxybutynin with an extended release formulation could be considered to compare efficacy, safety and tolerability of oxybutynin and fesoterodine, the latter not being officially registered for children with the National Food and Drug Administration.

Conclusion

Fesoterodine could be a safe alternative for oxybutynin instillations in some children with neuropathic bladder dysfunction. However, from this study it is not predictable whether oral fesoterodine can replace intravesical oxybutynin instillations in all children with neuropathic bladder dysfunction without testing voiding diaries and UDS for evaluation of its efficacy. Additionally, patient satisfaction and side effects should be taken into consideration to provide a patient-tailored approach. A prospective randomized multicentre study with a large study population is necessary for further investigation of the efficacy of fesoterodine in children with NDO.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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