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Treatment with Propiverine in Children Suffering from Nonneurogenic Overactive Bladder and Urinary Incontinence: Results of a Randomized Placebo-Controlled Phase 3 Clinical Trial

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Abstract

Background: Until now no confirmatory clinical trial in children suffering from nonneurogenic overactive bladder (OAB) and urinary incontinence could demonstrate superiority for antimuscarinics over placebo.

Objectives: The following study was conducted to prove efficacy and tolerability of propiverine compared to placebo.

Design, Setting, and Participants: A randomized, double-blind, placebo-controlled phase 3 trial with parallel-group design in children aged 5–10 yr was performed. Prior to the 8-wk medical therapy urologic baseline diagnostics, a 3-wk lifestyle advice (urotherapy) was established.

Intervention: After re-evaluation of in- and exclusion criteria and uroflowmetry, only children fulfilling the requested criteria were allocated to a body-weight-adjusted therapy (10 or 15 mg propiverine twice daily or corresponding placebo).

Measurements: Efficacy parameters derived from bladder diary and a micturition volume protocol. Decrease in voiding frequency per day was chosen as primary efficacy parameter; secondary endpoints included voided volume and incontinence episodes. A safety assessment was conducted.

Results and Limitations: Of 171 randomized children, 87 were treated with propiverine and 84 with placebo. The primary efficacy parameter showed a decrease in voiding frequency (–2.0 episodes for propiverine versus –1.2 for placebo; $p = 0.0007$). Superiority could also be demonstrated for voided volume (31.4 vs. 5.1 ml; $p < 0.0001$) and incontinence episodes (–0.5 vs. –0.2 episodes per d; $p = 0.0005$). The trial design did not allow for separate evaluation of the effect of urotherapy prior to medical treatment. Propiverine was well-tolerated in children. Altogether 23% of side-effects were reported for propiverine and 20% for placebo.

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Conclusions: This clinical trial showed superior efficacy of propiverine over placebo and good tolerability for the treatment of children suffering from OAB and urinary incontinence. An important additional factor for the success of the trial was a modified trial design with previous urotherapy.

Trial Registration: ClinicalTrials.gov Identifier: NCT00603343.

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1. Introduction

To the best of our knowledge, publications of confirmatory clinical trials in children suffering from nonneurogenic overactive bladder (OAB) and urinary incontinence demonstrating superiority of antimuscarinics over placebo are still missing. On the other hand, antimuscarinics—for example, propiverine hydrochloride (in the following referred to as propiverine)—are very well-established in these children as well as in children suffering from neurogenic detrusor overactivity [1–6]. Reflecting this fact, the International Consultation on Incontinence (ICI) recommends antimuscarinic treatment for this indication in children so far with a lower level of evidence (level 3, grade B/C) [7].

Since 1985, propiverine is labelled for treatment of children with nonneurogenic detrusor overactivity, incontinence, urgency, and/or small bladder volume from age 5 yr and neurogenic detrusor overactivity from age 1 yr in Germany, Czech Republic, and Slovakia used as tablets with 5 mg

propiverine in a recommended daily dose of 0.8 mg/kg body weight (BW).

Earlier studies [5,8,9] already demonstrated efficacy and safety of propiverine, but did not fulfill all strict criteria from the current guidelines or standards of good clinical practice (GCP).

The trial presented here was designed according to the recommendations of the German authorities and the current international treatment guidelines provided by the ICI in 2002 [10] and was performed between June 2004 and December 2006.

2. Materials and methods

The study was conducted by 38 investigators from six European countries.

Pretreated children had to undergo a 4-wk wash-out phase before attending to the trial. The four clinical trial visits are demonstrated in the flowchart (Table 1). At visit 1 a check of in- and exclusion criteria (Table 2), urologic baseline diagnostics and uroflowmetry was performed. Enrolled children and their parents received detailed lifestyle advice (urotherapy) according to the International Children's Continence Society (ICCS)

Table 1 – Flowchart

	Visit 1 (day – 21)	Visit 2 (day 0)	Visit 3 (day 28)	Visit 4 (day 56)
Handout of bladder diary	X		X	
Handout of children's diary	X			
Handout of micturition volume protocol		X	X	
Return of bladder diary		X		X
Return of children's diary		X		
Return of micturition volume protocol			X	X
Uroflowmetry	X			
Sonography/postvoid residual urine	X	X	X	X
Demographic data and patient's history	X			
Inquiry about incontinence episodes	X	X		X
Urinalysis	X	X	X	X
Physical examination	X	X		X
Blood pressure/heart rate	X	X	X	X
ECG	X*	X*		X
Check of concomitant medication	X	X	X	X
Check of inclusion/exclusion criteria	X	X		
Lifestyle advice (urotherapy)	X			
Randomization		X		
Handout of trial medication		X	X	
Query of side effects		X	X	X
Evaluation of efficacy (investigator, patient, parents)				X
Evaluation of tolerability (investigator, patient, parents)				X

* ECG could be performed either at visit 1 or at visit 2.

Table 2 – Inclusion and main exclusion criteria

Inclusion criteria	Male and female children 5–10 yr of age 17–45 kg body weight Micturition frequency ≥ 8 per d Incontinence episodes ≥ 1 within 7 d
Main exclusion criteria	Bladder capacity > age expected capacity [(age + 1) \times 30] in ml Postvoid residual urine >10 ml Treatment of overactive bladder symptoms within the last 28 d Urinary tract infection at the time of study inclusion Monosymptomatic enuresis Dysfunctional voiding Constipation Forbidden concomitant medication Clinically relevant diseases of the kidneys, liver, gastrointestinal tract, cardiovascular system Congenital anomalies of the genitourinary tract or nervous system Psychological or neurological disorders with impact on bladder function Preexisting medical contraindications for antimuscarinics Known hypersensitivity to propiverine hydrochloride

with explanation of normal body and lower urinary tract (LUT) function, voiding position, timed voiding, drinking habits, quality of beverages, and prevention of constipation for the 3-wk run-in period. A specially designed children's diary with small paintings and space for symbols after each voiding was handed out to improve the compliance of children and to keep them busy with their own voiding behaviour.

In between visit 1 and visit 2 uroflowmetry was centrally approved regarding maximum voided volume and exclusion of other underlying diseases; for example, dysfunctional voiding and mechanical obstruction (a statistical evaluation of these parameters was not intended). At visit 2 all in- and exclusion criteria had been rechecked and uroflow was performed again if necessary. An informed consent was obtained from parents and children. Only patients without other underlying LUT symptoms and who still fulfilled the requested criteria received study medication for a period of 8 wk (57.5 ± 5.6 d).

Randomization was performed within fixed blocks (ratio 1:1) by an independent unit, assigning the random numbers in increasing order per centre. Depending on body weight children were treated twice daily with propiverine (coated tablets 5 mg) or corresponding placebo:

- BW 17.0 to 27.9 kg: 20 mg propiverine/d (dosing schedule 2-0-2)
- BW 28.0 to 45.0 kg: 30 mg propiverine/d (dosing schedule 3-0-3).

Due to the lack of an adequate statistical database for estimating required sample size in children, an interim analysis with adaptive design [11] was planned following the recruitment of 60 patients. Thereafter propiverine was already superior to placebo ($p = 0.0043 < 0.0102$) but the national regulatory authority recommended a continuation of the trial. Sample size for an additional second part of trial was estimated with 104 patients. For confirmatory analysis of the primary efficacy variable one-sided tests were carried out at a significance level of $\alpha = 0.025$ and $\beta = 0.2$.

Efficacy parameters were assessed by questioning about voiding behaviour and incontinence episodes over the last 7 d

and with a 3-d bladder diary (fluid intake, voided volume, voiding frequency, incontinence episodes) on the weekend before visit 2 and visit 4. Families were reminded to conduct both bladder diaries under comparable drinking habits.

As primary efficacy parameter the change in voiding frequency between baseline and end of treatment was chosen. Therefore patients were classified as responder to therapy if voiding frequency decreased by at least 1.5 voidings. Secondary efficacy variables included voided volume, incontinence episodes per day as well as within 7d and weekly maximum voided volume. For the last parameter, parents were introduced to a micturition volume protocol recording the amount of urine of one single voiding per week when the child was having strong desire. This protocol is suitable to monitor variances in bladder capacity over time. A subjective evaluation of benefit from therapy and final tolerability was assessed at visit 4 by children, parents, and investigators.

Safety assessment included continuous recording of character, intensity, and frequency of all adverse events. Vital signs (blood pressure, pulse rate, urinalysis, and electrocardiogram) were analysed. Although propiverine has a proven cardiac safety in adults, additional information in children should be obtained. In agreement with ethics committees, electrocardiogram (ECG) was performed facultative because not all investigators were able to perform a high-quality ECG at the study site.

All randomized patients receiving one or more doses of trial medication were included into the intent-to-treat population (ITT). Demographic data and baseline characteristics were analysed for safety, ITT, and per protocol (PP) population, stratified by gender. Sensitivity analyses of the efficacy variables were planned and conducted stratified by gender and dose group according to body weight using the ITT population. The age-dependent analyses have been included afterwards. For subjective evaluation of efficacy and tolerability by parents, patients, and investigator, Cochran-Mantel-Haenszel tests were used. Efficacy parameters have been presented with mean and standard deviation. For all ANCOVA models, two-sided 95% confidence intervals (CI) were calculated for the treatment difference "propiverine–placebo."

Terminology within this publication was adapted to the current report from the Standardization Committee of the ICCS from 2006 [12].

3. Results

3.1. Demographics

Of 303 enrolled children (194 male, 109 female) at the first visit 171 children (107 male, 64 female; safety population) were finally randomized and medically treated (Fig. 1). The remaining 132 children (43.6%) were excluded after the run-in period of urotherapy because of diagnostic findings such as inappropriate uroflowmetry, maximum voided volume showing expected bladder capacity according to age, voiding frequency below 8 micturitions per day, missing incontinence episodes within 7 d, postvoid residual urine (PVR) > 10 ml, and other issues such as withdrawal of informed consent or compliance problems.

The ITT population consisted of 164 patients (104 male, 60 female). Seven children had been withdrawn after randomization because of side-effects (two propiverine, one placebo), insufficient efficacy or absence for further evaluation (both placebo) and other reasons (one propiverine, one placebo).

Mean age of the children was 7.0 yr; the mean body mass index (BMI) was 16.31 kg/m². The propiverine and placebo group were comparable regarding demographic and clinical characteristics (Table 3).

3.2. Efficacy

Overall 171 children (safety population) were randomized and treated body-weight adjusted either with propiverine ($n = 87$) or with placebo ($n = 84$). Table 3 summarizes the demographic data for the

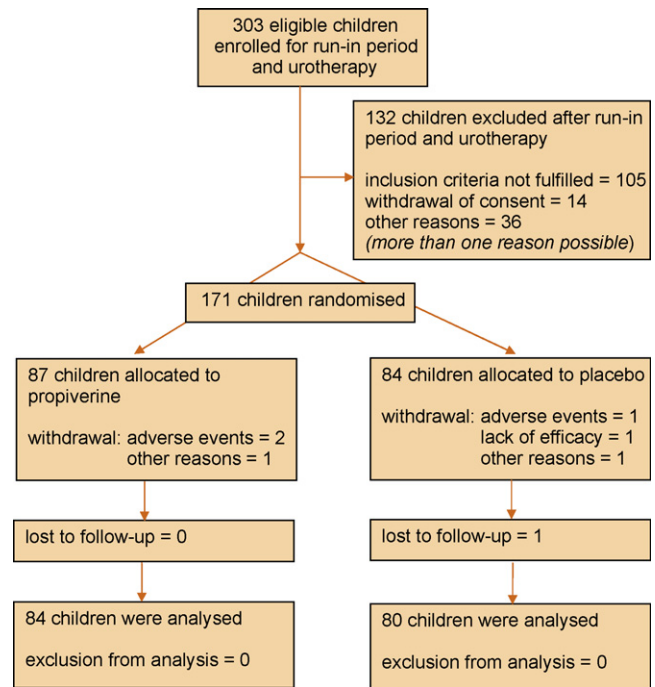


Fig. 1 – Flow diagram of the clinical trial.

ITT population. All determined efficacy parameters from the bladder diary are listed in Table 4 for the ITT population (164 children). Significant superiority of propiverine over placebo after 8 wk of medical treatment was achieved in the overall population. Separate evaluation of study endpoints for gender demonstrated significant benefit from propiverine for all but one efficacy parameters ($p = 0.0608$ for incontinence episodes per day in females). Separate analysis of the two body-weight-adjusted dose groups could not show significance for voiding frequency in children receiving doses higher than 0.9 mg/kg BW (Table 4).

Table 3 – Baseline demographic and clinical data (ITT population)*

Characteristics	Propiverine ($n = 84$)		Placebo ($n = 80$)		p -value**
Distribution of gender					
Male	$n = 49$	(58.3%)	$n = 55$	(68.8%)	0.353
Female	$n = 35$	(41.7%)	$n = 25$	(31.3%)	
Age [yr]	7.0	(1.6)	7.0	(1.4)	1.0
Height [cm]	127.1	(10.2)	127.0	(11.4)	0.953
Weight [kg]	26.8	(6.7)	26.2	(5.4)	0.530
BMI [kg/m ²]	16.4	(2.4)	16.1	(1.8)	0.368
Voiding frequency per day	8.9	(2.2)	9.1	(2.5)	0.587
Voided volume [ml]	102.9	(36.3)	100.3	(33.8)	0.636
Incontinence episodes per day	0.8	(0.8)	1.1	(1.0)	0.035
Incontinence episodes within last 7 days	5.4	(8.3)	5.4	(5.9)	1.0
Enuretic episodes within last 7 nights	3.1	(3.4)	3.3	(3.0)	0.988

* If not otherwise stated mean (standard deviation) was provided.

** Significance is given if $p < 0.05$.

Table 4 – Results for change of efficacy parameters between baseline and end of treatment for the overall population and stratified with respect to gender and dose (ITT population)*

Results	Propiverine (n = 84)		Placebo (n = 80)		p-value
Voiding frequency per day	-2.0	(2.3)	-1.2	(2.2)	0.0007**
Male	-2.2	(2.5)	-1.1	(1.9)	0.0146
Female	-1.7	(1.8)	-1.4	(2.8)	0.0384
<0.9 mg/kg BW†	-2.1	(2.2)	-0.9	(1.9)	0.0008
>0.9 mg/kg BW‡	-1.9	(2.4)	-1.4	(2.4)	0.1674
Voided volume [ml]	31.4	(29.3)	5.1	(25.1)	<0.0001
Male	32.5	(30.3)	4.8	(21.8)	<0.0001
Female	29.8	(28.3)	5.6	(31.4)	0.0014
<0.9 mg/kg BW†	28.4	(30.8)	5.1	(19.6)	0.0001
>0.9 mg/kg BW‡	33.9	(28.2)	5.0	(28.2)	<0.0001
Incontinence episodes per day	-0.5	(0.7)	-0.2	(0.9)	0.0005
Male	-0.5	(0.7)	-0.3	(1.1)	0.0038
Female	-0.4	(0.6)	-0.2	(0.7)	0.0608
<0.9 mg/kg BW†	-0.5	(0.8)	-0.2	(0.7)	0.0442
>0.9 mg/kg BW‡	-0.4	(0.6)	-0.3	(1.2)	0.0046

* If not otherwise stated mean (standard deviation) was provided.

** The primary parameter was evaluated confirmatory with one-sided p-value; all other parameters were evaluated exploratory with the two-sided p-value. Significance is given if $p < 0.05$.

† Dose <0.9 mg/kg body weight (n = 38 propiverine, n = 32 placebo).

‡ Dose >0.9 mg/kg body weight (n = 46 propiverine, n = 48 placebo).

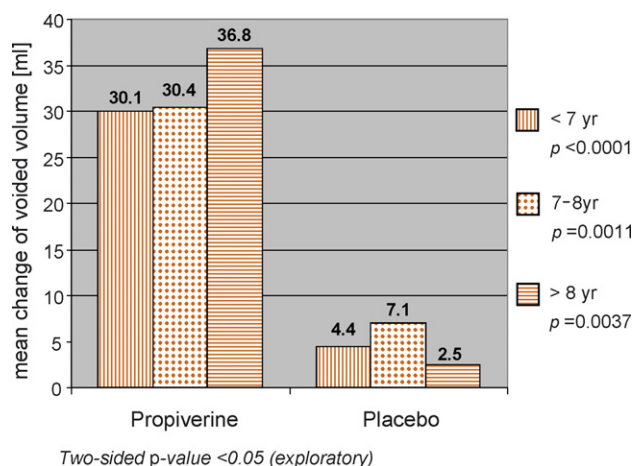


Fig. 2 – Mean changes of voided volume per single voiding from baseline to end of treatment (EoT) according to three different age groups.

The primary efficacy parameter—voiding frequency per day—was reduced about 20% from baseline (–2.0 episodes) with propiverine compared to 11% (–1.2 episodes) with placebo ($p = 0.0007$). A decrease of at least 1.5 voidings per day (defined as “response to therapy” per protocol) was achieved in 64.3% ($n = 54$) of patients with propiverine and 40.0% ($n = 32$) with placebo ($p = 0.0018$). Incontinence episodes per day were decreased by –0.5 episodes with propiverine compared to placebo with –0.2 episodes ($p = 0.0005$). The mean voided volume significantly increased at 31.4 ml on average for propiverine compared to only 5.1 ml for placebo

($p = 0.0001$). Separating these results into age groups of <7, 7–8 and >8 years, the group that benefits best were children older than 8 yr compared to baseline whereas no benefit of the placebo group in all age groups was found (Fig. 2).

Based on case history, incontinence episodes within 7 d were decreased by –2.8 episodes with propiverine versus –1.2 episodes in the placebo group ($p = 0.0002$). Enuretic episodes decreased by –0.72 episodes with propiverine compared to –0.41 episodes with placebo ($p = 0.2123$).

Efficacy could also be shown in the micturition volume protocol performed once weekly starting after 1 wk of treatment. The median of voided volume increased 36 ml in children treated with

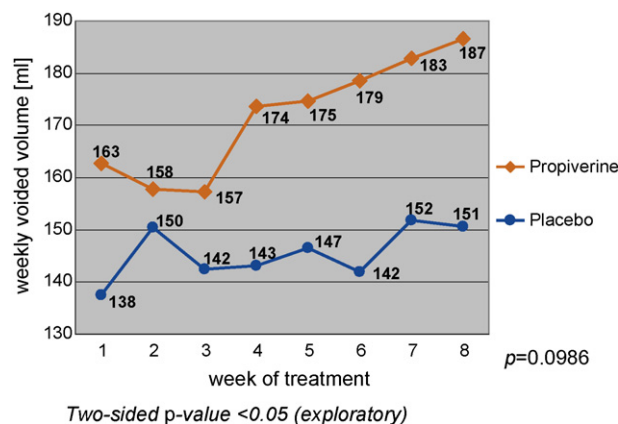


Fig. 3 – Results from the weekly micturition volume protocol with change of volume of a single voiding from week 1 to week 8 of treatment period.

Table 5 – Treatment related side-effects in more than 2% of treated patients in one of the treatment groups, classified by system organ class, preferred term, and treatment group (safety population)

Side-effects (SE)	Propiverine (n = 87)	Placebo (n = 84)
Any treatment-related SE	20 (23.0%)	17 (20.2%)
Infection and infestations	12 (13.8%)	13 (15.5%)
Influenza	4 (4.6%)	1 (1.2%)
Urinary tract infection	2 (2.3%)	1 (1.2%)
Gastrointestinal infection	—	2 (2.4%)
Nasopharyngitis	—	2 (2.4%)
Gastrointestinal disorders	8 (9.2%)	3 (3.6%)
Abdominal pain	3 (3.4%)	—
Dry mouth	3 (3.4%)	—
Constipation	2 (2.3%)	—
Eye disorders	4 (4.6%)	—
Accommodation disorder	2 (2.3%)	—
Nervous system disorders	2 (2.3%)	1 (1.2%)
Headache	2 (2.3%)	—

propiverine, whereas in placebo only 10 ml could be stated (Fig. 3).

Subjective final evaluation of efficacy was comparable between investigator, child, and parents. Investigators judged response rate on treatment with propiverine in 64.3% as “very good” and “good” compared to only 32.6% on placebo.

3.3. Safety and tolerability

Propiverine was well-tolerated in all treated children. Common antimuscarinic side-effects such as dry mouth, visual disturbances, and constipation were only registered in propiverine-treated children but not in the placebo group (Table 5). Compared to the applied daily dose of propiverine, only three of the above-mentioned side-effects were observed within the recommended dose of 0.8 mg/kg BW (3 out of 39 children). All other side-effects (66.7%) listed in Table 5 were found under daily treatment doses of >0.9 mg/kg BW (6 out of 48 children).

No serious adverse events were recorded during the trial. Two severe treatment-related side-effects were experienced: abdominal pain (propiverine group) and acute bronchitis (placebo group). All other adverse events were rated as mild (propiverine 35.0% and placebo 41.2%) or moderate (60.0% vs 52.9%). For safety reasons only 3 out of 171 children were discontinued from trial, although any relationship to medical treatment was not certain (propiverine: once severe abdominal pain; once diarrhoea, dyspepsia, and flatulence; placebo: gastrointestinal infection).

The mean PVR was only 3 ml, and acute urinary retention did not occur. The safety parameters urinalysis, blood pressure, and pulse rate as well

as the evaluated ECGs of 71 children did not cause any concerns in the propiverine-treated children.

Overall tolerability rated as “good” to “very good” by the investigators was identical in the propiverine and placebo group (96.6% vs. 96.4%). Assessment by patients and their parents were similar to these results.

4. Discussion

This trial should prove efficacy and tolerability of propiverine for children suffering from urinary incontinence and OAB and could demonstrate significant superiority over placebo in all analysed efficacy parameters.

One interpretation of the results is the adapted trial design, which differed in some aspects from previous studies in children; for example, urotherapy prior to medication, children’s diary, and micturition volume protocol [3,5,13]. Urotherapy improved symptoms in a number of patients, avoiding the necessity of medical treatment, and helped to identify the remaining patient target group who might benefit from antimuscarinic treatment. This strategy also minimized placebo effects in patients allocated to pharmacologic treatment. The data published by Allen [14] showed comparable results, reflecting that urotherapy significantly improved overactive bladder symptoms in 45% of children.

Because urotherapy was not in the primary focus of the trial and only one bladder diary was kept in between the first visit and randomization to treatment arms (visit 2) but not prior to start of urotherapy, a separate evaluation of the clinical effect of 3 wk of urotherapy could not be derived from the analyzed data.

Ayan et al [15] presented data from 72 children with nonneurogenic voiding dysfunction and urgency symptoms who were randomly allocated to three treatment groups (tolterodine or placebo together with behavioural modification and behavioural modification alone). Judging the decrease in a new, hitherto not established, dysfunctional voiding score system (DVSS) as a parameter for clinical outcome, an increase in efficacy if antimuscarinics were combined with behavioural modification was found.

Another publication supporting these experiences included holding manoeuvres to oxybutynin treatment and could show superior effects compared to antimuscarinic therapy alone [16].

In real life children might suffer from additional symptoms such as behavioural problems or other

underlying symptoms of the LUT and would probably benefit best from combination treatment, for example, propiverine with biofeedback or desmopressin [13]; however, this was out of scope of this study.

Clinical experience over two decades verified the body-weight-adjusted dose regimen of propiverine. At the same time as this trial, a dose-escalating pharmacokinetic study with body-weight-adjusted doses of 5, 10, or 15 mg propiverine twice daily in children aged 5 to 10 yr was initiated suggesting a therapeutic dose of 10 to 15 mg twice daily for this patient population [17]. The results also explain the decision as to why 48 children (55.2%) had a propiverine dose increasing the recommended 0.8 mg/kg BW per day, which has to be taken into consideration when judging the incidence of antimuscarinic side-effects.

Voiding frequency deriving from bladder diary as primary efficacy parameter seemed to be more significant in children than incontinence episodes per day, which may not occur due to coping strategies such as restricted fluid intake. According to the recommendations of ICCS [12] for bladder diary and experiences with other clinical trials in children, urgency was not included because younger children are often unable to indicate different bladder sensations, and strong desire to void is probably the only sensation they can express.

An important treatment goal in children suffering from OAB and incontinence is an observable increase of bladder volume. In several publications [18,19] a correlation between incontinence and a decreased expected bladder capacity related to age could be demonstrated in children. Only a combination of adequate fluid intake and provable increase in bladder volume leads to a reliable, effective decrease in voiding frequency and incontinence episodes.

The bladder volume in propiverine-treated children increased approximately 6-fold higher (+31 ml) than in placebo-treated children (+5 ml), which underlines older data indicating that bladder volume is an effective prognostic parameter [13]. Additionally, the home-conducted micturition volume protocol demonstrated a continuous increase of volume over time (Fig. 3).

Under propiverine, mild to moderate side-effects occurred in 95% of patients, which was comparable to placebo-treated patients (94%). The total number of side-effects in both treatment groups was comparable (propiverine 23% and placebo 20%), whereas infections of the respiratory tract were most commonly reported. The safety results support previous clinical experiences with children where dry mouth or visual disturbances occur less

frequently compared to adults when treated with propiverine [13,20,21].

5. Conclusion

For the first time a confirmatory clinical trial could demonstrate superior efficacy of an antimuscarinic (propiverine) in children suffering from OAB and urinary incontinence. The results will support the importance of propiverine for further evaluation of treatment options in these children, resulting in recommendation by ICI. The fact that urotherapy minimized placebo effects by identifying the relevant patient target group who benefits from medical treatment might be relevant for adults as well.

Author contributions: Daniela Marschall-Kehrel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Marschall-Kehrel.

Acquisition of data: Feustel.

Analysis and interpretation of data: Marschall-Kehrel; Feustel.

Drafting of the manuscript: Marschall-Kehrel; Feustel.

Critical revision of the manuscript for important intellectual content:

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Editorial Comment on: Treatment with Propiverine in Children Suffering from Nonneurogenic Overactive Bladder and Urinary Incontinence: Results of a Randomized Placebo-Controlled Phase 3 Clinical Trial

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In the adult population, overactive bladder (OAB) is a very common condition [1], with significant cost to health systems [2]. Muscarinic receptor antagonists are the first-line drug therapies, and several randomized controlled trials are available in the literature [3].

The clinical scenario is a little bit different for OAB in the pediatric population. Although OAB is thought to be highly prevalent among children as well, the evidence in the field of drug treatments has been quite limited [4], and the International Consultation on Incontinence recommends anti-muscarinic treatment for this indication in children with a low level of evidence (level 3, grade C of recommendation) (reference 7 in the text).

Marschall-Kehrel et al provided a good quality randomized placebo-controlled trial, evaluating the efficacy and safety of propiverine in children with OAB aged 5–10 yrs. The study showed that, compared to baseline, propiverine can achieve statistically significant reductions of the number of micturitions per day (–2.0 vs –1.2 episodes for placebo, $p = 0.0007$) and incontinence episodes per day (–0.5 vs –0.2 episodes for placebo, $p = 0.0005$), with an increase in the mean voided volume per micturition (+31.4 ml vs +5.1 ml for placebo, $p = 0.0001$) [5], results surprisingly similar to those achievable in the adults with other muscarinic-

receptor antagonists. Moreover, propiverine was quite well tolerated, with the typical antimuscarinic side-effects, such as dry mouth, visual disturbances, and constipation, being reported in less than 10% of the whole cohort of patients.

Any high-quality randomized trial that can allow treatment of patients within an evidence-based approach is clearly welcome. The authors should be commended for their efforts. Clearly, other trials evaluating the role of some of the other available muscarinic antagonists would be advisable.

Interestingly, the study suggests that lifestyle and behaviour modifications can be highly effective in children—similarly to what happens in adult patients—and they have to be considered the first-line treatment of children with OAB.

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Editorial Comment on: Treatment with Propiverine in Children Suffering from Nonneurogenic Overactive Bladder and Urinary Incontinence: Results of a Randomized Placebo-Controlled Phase 3 Clinical Trial

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Taken together, the results reported in this paper by Marschall-Kehrel and coworkers indicate that, under controlled standards of good clinical practice (GCP), propiverine showed superior efficacy over placebo and good tolerability for the treatment of children suffering from overactive bladder (OAB) and urinary incontinence [1]. Propiverine is a compound that has both anticholinergic and calcium channel blocking properties, and this dual action is claimed to be a distinctive feature of

propiverine which might, in theory, lead to improved efficacy and tolerability in the treatment of bladder hyperactivity. Recent studies in adult populations, however, showed that propiverine and oxybutynin are equally effective in increasing bladder capacity and lowering bladder pressure in patients with neurogenic detrusor overactivity, even if propiverine has better tolerability of oxybutynin for dryness of the mouth [2].

Notwithstanding the effects of placebo in reducing at least 1.5 voiding per day, 40% compared to 64.3% of the active population, could be considered not negligible, the difference with the active arm of the study (propiverine) is statistically significant. Nevertheless, this result is in line with similar studies in adults for almost all antimuscarinic drugs [3,4]. Urgency, the key symptom of OAB, was not reported in this study because Marschall-Kehrel and coworkers stated that younger children are often unable to indicate different bladder sensations, and strong desire to void is probably the only sensation they can express. This is in contrast with the study of Ayan et al (reference 15 in the text), who included urgency in the definition of voiding dysfunction, and of Rien et al, who evaluated the long-term tolerability of tolterodine extended release in children (aged 5–11 yr) with urgency urinary incontinence [5].

In conclusion, we need to realize that clinical research in the young population has repeatedly shown that children are not simply smaller versions of adults [6]. Trials tailored to children are crucial for determining the proper use of medications in the young population. Parents who give consent for their children to be enrolled in a clinical trial need to be thoroughly assured that potential hazards will be actively sought and swiftly dealt with. I think that Marschall-Kehrel's paper reaches high scientific

standards and should be read carefully by all the urologists involved in the treatment of micturition disorders in the young population. By publishing this study, *European Urology* becomes an integral part of the process of reassuring parents without forgetting that their children, it ought to go without saying, deserve no less.

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