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STUDY DESIGN AS THE MAIN PREDICTOR FOR GOOD OUTCOME IN A RANDOMISED PLACEBO-CONTROLLED MULTICENTRE TRIAL IN CHILDREN SUFFERING FROM OVERACTIVE BLADDER AND URINARY INCONTINENCE

Hypothesis / aims of study
Several studies have been designed to investigate the positive effect of antimuscarinics in children suffering from overactive bladder and urinary incontinence. Until now significant results between antimuscarinics and placebo could only be demonstrated with oxybutinin. The most important reasons for this failure are flaws in the study design to select those children which really benefit from this therapy.
The current knowledge about diagnostics and therapy of children suffering from urinary incontinence was incorporated into the well elaborated design of the recent finalised trial.
Prior to randomisation to one of the study arms the meanwhile well established urotherapy was used in all children to brief them and the parents regarding judicious drinking and micturition behaviour and regular bowel movement to minimize possible placebo effects because of unnecessary medication in this indication. For the strategy of this study it was very important to identify the proper patient population for a directed comparison with placebo to demonstrate the convincing efficacy of this therapy in children.
The following abstract provides the design of the study and presents the most important results concerning efficacy and safety in children.

Study design, materials and methods
A randomised, double-blind, placebo-controlled parallel-group multicentre study design for this phase III trial was chosen to demonstrate the superiority of Propiverine hydrochloride compared to placebo in children suffering from overactive bladder and urinary incontinence. The study based on a 3 week run-in period to perform urotherapy intensively, followed by 8 weeks of medical treatment. Altogether 4 visits were conducted within 77 days. During the first visit amongst routine parameters an uroflow (if possible with EMG) as well as a sonography and measurement of residual urine were performed to exclude children with emptying disorders. Children and their parents received detailed life-style advices and two diaries (a diary appropriate for children to keep busy with their own micturition behaviour and a parents-child bladder-diary for completing fluid intake and micturition over three days at the end of the run-in period). Meanwhile the uroflow was sent to the Medical Advisor for central judgement of eligibility for the trial. At the second visit the investigator had to decide over randomisation for this study after evaluation of diaries and the suitability of the uroflow. Medication was handed out body-weight adjusted with to doses (10 mg in two doses or 15 mg in three doses or corresponding placebo). The parents received a micturition volume diary to measure one micturition per week during each week of treatment. The third visit was performed to control the safety aspects and to hand out a second parents-child bladder-diary to check efficacy afterwards. From 303 screened patients (193 male, 108 female, 2 without specification) at the first visit 171 patients (107 male, 64 female) were randomised and treated with medication. The remaining 132 children (43.6%) were excluded because of an inappropriate uroflow (67 patients), no fulfilling of inclusion criteria in the diary (23 patients) and different or mixed reasons (42 patients). The primary objective for evaluation of efficacy was the micturition frequency and for inclusion the frequency had to be at least 8 micturitions per day and minimum one incontinence episode within 7 days.

Results
Overall 87 children were treated with propiverine (51 boys, 36 girls) and 84 with placebo (56 boys, 28 girls). The mean age of the children was 7.0 years, the mean BMI 16.31 kg/m². Both sex groups did profit from the medical treatment.
In Table 1 the primary objective - change for micturition frequency within 24 hours – is presented. The micturition frequency was reduced on average two times more than with placebo.

Visit	Propiverine			Placebo			p value
	n	Mean	SD	n	Mean	SD	
Baseline	84	8.848	2.203	80	9.092	2.546	
EoT	84	6.869	1.902	79	7.927	2.351	
Baseline – EoT (all)	84	1.979	2.267	79	1.191	2.223	1-sided p=0.0007

Tab.1: micturition frequency within 24 hours (SD=Standard Deviation; n=number of patients)

Incontinence episodes within 7 days were reduced -2.8 times with propiverine versus -1.17 times with placebo (p=0.0002). Based on the incontinence episodes per 24 hours and correlated with the two different dose-groups (A: 17-27.9 kg BW received 10 mg b.i.d. and B: 28-45 kg BW received 15 mg b.i.d.) there was a reduction compared to placebo of -0.53 versus -0.23 episodes for group A (p=0.044) and -0.39 versus -0.29 episodes for group B (p=0.0046). The mean voided volume (based on micturition-diary) increased significantly in both dose groups +31.4 ml on average for propiverine and +5.1 ml for placebo (p=0.0001). The final evaluation of the efficacy of the treatment by investigator during the period of 8 weeks showed that 64.3 % had a very good and good response rate on propiverine compared to 32.6 % in the placebo group (Tab.2).

	Propiverine (n=84)		Placebo (n=80)		p-value
	n	(%)	n	(%)	CMH = Cochran Mantel Haenszel test
Very good	32	(38.1)	13	(16.3)	<0.0010
Good	22	(26.2)	13	(16.3)	
Moderate	16	(19.0)	19	(23.8)	
Insufficient	14	(16.7)	35	(43.8)	

Tab.2: Summary of final evaluation of efficacy by investigator

Interpretation of results

The completed study showed impressively that after performing a sufficient urotherapy and giving detailed instructions as well as a proper diagnostic much more boys remain which really need medical treatment. Obvious more girls will benefit from urotherapy and biofeedback-therapy. Following randomisation 107 boys (62.6%) and 64 girls (37.4%) fulfilled the inclusion criteria for the trial. The medication itself demonstrated homogenicity between female and male patients.

All efficacy parameters (micturition frequency, incontinence episodes per week and per day, voided volume) demonstrated a significant improvement under therapy with propiverine compared to placebo. The positive effect was seen in both of the dose groups, 10 mg and 15 mg two times daily.

Propiverine was safe and well tolerated in children suffering from overactive bladder with urinary incontinence.

Concluding message

This is the first study showing a superiority of the antimuscarinic therapy compared to placebo. All children were trained initially with the well established urotherapy and only children suffering from overactive bladder and/or urinary incontinence which did not adequate respond to a change of their micturition and drinking behaviour received a body-weight adjusted medical therapy with propiverine or corresponding placebo.

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