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SAFETY AND EFFICACY OF ANTICHOLINERGIC THERAPY WITH PROPIVERINE IN CHILDREN SUFFERING FROM OVERACTIVE BLADDER

Hypothesis / aims of study

Besides the well established urotherapy with effective changing of micturition and drinking behaviour, oral anticholinergics achieved importance as effective additional therapy in children suffering from overactive bladder with urgency, frequency and urge incontinence. Previous information about pharmacokinetics of the hitherto used substances in children has been obtained mostly from studies performed with adult patients. The study described below was conducted to evaluate pharmacokinetics in children aged 5-10 years as well as to obtain dose-response information concerning efficacy, tolerability and safety of propiverine in children to determine an optimal efficacy-tolerability-relation.

Study design, materials and methods

In total 30 children (18 boys and 12 girls) aged 5-10 years (mean 7.1 years) with the symptoms of bladder overactivity and urinary incontinence were included into this open-label, dose-escalating phase II study. Groups of 10 children received either 5 mg or 10 mg or 15 mg propiverine twice daily for two weeks. The study was started with the lowest dose. For all surveyed children in this study an additional assessment of all efficacy and safety parameters was also undertaken depending on body weight adjusted dose groups.
As main inclusion criteria a frequency of more than 6 micturitions during the awake period, incontinence episodes of more than one per week during daytime and urgency at least once daily were required.

Results

All but 3 children in the lowest dose group obtained a benefit from the therapy (90.0% of all treated children). A decrease of 1.7, 2.2 and 2.3 micturitions per day (Tab.1) could be recorded for the three doses. All three groups showed a reduction of 0.3, 0.7 and 0.8 incontinence episodes during waking hours (Tab.2) from baseline as well as an increase in the median voided volume in diary of 18, 28 and 54 ml (Tab.3) from baseline.
The medication was well tolerated. Only one child in the highest dose group was withdrawn drug-related due to accommodation disorders, the most common side effect in this study. No urinary retention was observed in all three dose groups and only one child with the lowest dose showed residual urine of 47 ml at one time. No safety concerns regarding clinical chemistry, hematology or ECG were observed.
Concerning pharmacokinetic results there was a more than two-fold increase of the exposure with propiverine when increasing the administered dose from 5 to 10 mg twice daily, but a less than three-fold increase from 5 to 15 mg twice daily. No difference in exposure of propiverine existed when comparing 10 and 15 mg twice daily.

Interpretation of results

All main efficacy parameters – the number of micturitions, the incontinence episodes and the voided volume – showed dose-dependent differences from baseline with an improvement of the symptoms in children. Based on the combined pharmacokinetic, safety and efficacy data propiverine is effective and well tolerated in children aged 6-10 years.

Concluding message

The pharmacokinetic results confirm the recommendation of a body weight adjusted dose of this medication (within the dose group of 0.6 to 0.9 mg/kg/in two daily doses). The data suggest a therapeutical dose of 10 to 15 mg twice daily for these children.

Average number of micturitions per day		5 mg b.i.d n=8	10 mg b.i.d n=10	15 mg b.i.d n=9
Baseline	Mean (SD)	8.3 (1.7)	7.9 (2.5)	7.1 (1.5)
	Median (min,max)	8.2 (6.3,12.0)	7.0 (5.3,12.7)	7.0 (5.3,10.7)
Week 2	Mean (SD)	6.3 (2.3)	5.6 (2.0)	5.2 (0.8)
	Median (min,max)	5.7 (4.0,10.3)	5.0 (3.7,10.7)	5.3 (4.0,6.3)
Change from baseline	Mean (SD)	-2.0 (1.4)	-2.3 (2.4)	-1.9 (1.6)
	Median (min,max)	-1.8 (-4.3,0.3)	-2.0 (-8.3,1.0)	-1.7 (-6.0,-1.0)
	LS Mean (SEM)	-1.7 (0.6)	-2.2 (0.5)	-2.3 (0.5)

Table 1: Average number of micturitions during waking hours (based on diary)

Average number of incontinence episodes		5 mg b.i.d n=8	10 mg b.i.d n=10	15 mg b.i.d n=9
Baseline	Mean (SD)	1.4 (1.1)	0.9 (0.7)	0.8 (0.6)
	Median (min,max)	1.0 (0.3,3.7)	0.8 (0.0,2.3)	0.7 (0.0,1.7)
Week 2	Mean (SD)	0.8 (1.0)	0.3 (0.4)	0.1 (0.3)
	Median (min,max)	0.5 (0.0,2.3)	0.0 (0.0,1.3)	0.0 (0.0,1.0)
Change from baseline	Mean (SD)	-0.6 (1.1)	-0.7 (0.8)	-0.7 (0.7)
	Median (min,max)	-0.7 (-2.3,1.3)	-0.5 (-2.3,0.3)	-0.7 (-1.7,0.3)
	LS Mean (SEM)	-0.3 (0.2)	-0.7 (0.2)	-0.8 (0.2)

Table 2: Average number of incontinence episodes per day during waking hours (based on diary)

Median volume voided per micturition (mL)		5 mg b.i.d n=8	10 mg b.i.d n=10	15 mg b.i.d n=9
Baseline	Mean (SD)	112.2 (64.6)	127.8 (45.0)	125.6 (52.2)
	Median (min,max)	105.0 (30.0,200.0)	143.8 (40.0,200.0)	131.3 (50.0,187.5)
Week 2	Mean (SD)	131.4 (52.7)	150.4 (36.2)	162.3 (56.4)
	Median (min,max)	137.5 (50.0,200.0)	150.0 (105.0,215.0)	150.0 (100.0,250.0)
Change from baseline	Mean (SD)	19.2 (27.3)	26.7 (41.9)	54.4 (28.3)
	Median (min,max)	28.8 (-36.5,45.0)	6.3 (-10.0,92.5)	55.0 (0.0,87.5)
	LS Mean (SEM)	17.9 (10.5)	28.4 (12.2)	54.3 (11.2)

Table 3: Median volume voided per micturition (based on diary)

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CLINICAL TRIAL REGISTRATION: This clinical trial has not yet been registered in a public clinical trials registry.
HUMAN SUBJECTS: This study was approved by the Regional ethics committee in Göteborg Reg.no: 176-04 and followed the Declaration of Helsinki Informed consent was not obtained from the patients.