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CLINICAL AND URODYNAMIC EFFECTS OF PROPIVERINE IN PATIENTS SUFFERING FROM URGENCY AND URGE INCONTINENCE

A Multicentre Dose-optimizing Study*

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Abstract. The efficacy and tolerability of propiverine hydrochloride (15, 30, 45, 60 mg/d) were evaluated in the treatment of 185 patients suffering from urgency/urge incontinence in an open, randomized, multicentre parallel-group trial lasting 21 days. The effects on bladder volume and pressure were assessed on the basis of urodynamics and micturition frequency. Subjective adverse reactions were recorded.

The bladder capacity and compliance increased and bladder pressure decreased in a dose dependent manner following therapy with 15, 30, 45 and 60 mg/d. In 70% of the patients a decrease in micturition frequency was observed after 15 mg/d, and in 80% after 30 to 60 mg/d. Subjective anticholinergic symptoms were reported by 21, 40 and 28% of the patients following therapy with 30, 45 and 60 mg/d. 15 and 30 mg were the daily doses with the most favourable ratio of efficacy in micturition frequency to tolerability.

The results suggest that propiverine is a safe and effective drug for the treatment of urgency and urge incontinence. Individual treatment with an initial dosage of 30 mg/d should be recommended.

Key words: Urodynamics, clinical trial, urgency, urge incontinence, urospasmolytics, propiverine hydrochloride.

INTRODUCTION

Propiverine hydrochloride (propiverine-HCl) is in use as an urospasmolytic agent since 1981. It is a benzylic acid derivative with musculotropic antispasmodic activity and moderate anticholinergic effects. The oral absolute bioavailability of propiverine-HCl is approximately 35% (6). It is excreted via the ductus choledochus and the kidneys, mainly in the form of metabolites.

In a number of clinical trials propiverine has been shown to be an effective therapy in various forms of bladder incontinence with a moderate incidence of adverse drug reactions (2, 4, 13, 14). The most common side effects are anticholinergic symptoms. No liver toxicity or other serious side effects were reported.

In order to optimize therapy the efficacy and tolerability of propiverine in daily doses of 15, 30, 45 and 60 mg was evaluated in the treatment of urgency and urge incontinence.

MATERIALS AND METHODS

The study was designed as an open, randomized, multicentre parallel-group trial. The treatment lasted 21 days. Propiverine hydrochloride (Mictonorm®, dragees 15 mg; APOGEPHA Arzneimittel GmbH, FRG) was administered at daily doses of 15, 30 (b.i.d.), 45 (t.i.d.) and 60 mg (q.i.d.) for therapy of patients suffering from urgency or urge incontinence.

185 patients (4 male, 181 female) from ten centres were included. The patients suffered from urge incontinence (n = 80) or urgency (n = 105) according to ICS standardization. 80% of all patients had urodynamically verified detrusor instability. Patients were excluded if they had neurogenic bladder dysfunctions, florid urinary tract infections, gastrointestinal obstructions or cardiovascular diseases. Potential pregnancy was an exclusion criterion in addition to concomitant medication which could have an affect on detrusor function.

An initial examination was performed before the patients entered the study and after a one-week run-in period treatment they were treated for 21 days with randomized daily dosages.

* CF. appendix.

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Table I. *Demographic data of 185 patients treated orally with propiverine hydrochloride for 21 days*

		Oral daily dose (mg)			
		15	30	45	60
Number		46	47	49	43
male/female		0/46	1/47	1/48	2/41
Age (yr)	mean	48	47	47	50
	range	18–79	21–71	29–66	27–77
Height (cm)	mean	165	170	165	164
	range	148–175	154–180	154–180	150–178
Body weight (kg)	mean	68	67	68	72
	range	42–95	46–99	50–84	49–96

Fluid cystometry (medium fill, 50–70 ml/min), uroflowmetry and voiding diaries were evaluated before and after the treatment. Similar urodynamic methodology was used at each centre.

At the end of the treatment period subjective scorings of efficacy and tolerability were recorded by patients and physicians in a visual analogue scale (0–100%) and an ordinal scale (1–4: "very good", "good", "satisfactory", "insufficient"). The patients were questioned about nausea, vomiting, tremor, nervousness, palpitations, dryness of mouth, headache, dizziness, confusion, blurred vision, tiredness and constipation, in a standardized pattern (0–3: "no", "mild", "moderate", "strong") , before and after therapy.

Standard serum laboratory parameters: glucose, sodium, potassium, chloride, calcium, phosphate, ALAT, ASAT, ALP, Gamma-GT, total bilirubin, urea, uric acid, triglycerides and cholesterol as well as ESR, Hb, Hk, erythrocytes, leukocytes, thrombocytes, Quick, PTT, thrombin time in blood and glucose and protein in urine were measured during the run-in and after the treatment period.

Mean values and standard deviations of quantitative variables, and absolute as well as relative frequency of qualitative variables before and after treatment were used for the descriptive statistics. Changes from pre- to post-treatment were tested by a sign test (3). The relation of VAS values to changes and to relative dosages per body weight were evaluated by simple linear regression. The significance level in all tests was set to 5% ($p < 0.05$). All data processing and calculations were performed by using the statistical standard program package STATGRAPHICS®.

RESULTS

Patients

The treatment groups were comparable in terms of mean age, body height and weight (Table 1).

Six patients (3%) were withdrawn from the trial after 7, 12 or 14 days due to following adverse reactions (dose group): swollen eyelids (15 mg), gastralgia (30 mg), sweat outburst (45 mg) and flush, gastralgia, circulatory disturbances (60 mg).

Urological data

At run-in cystometry (Table 2) the average bladder capacity at first urge varied from 139 to 148 ml in the four groups, and at strong (unbearable) urge from 256 to 279 ml. The mean level of bladder pressure at strong urge was between 22.8 and 26.3 cmH_2O, and the mean compliance between 24.2 and 26.8 ml/cmH_2O. Before treatment the mean number of micturitions, recorded by voiding diaries, varied between 11 and 13 per 24 h, the average volume of micturitions were between 130 and 144 ml.

Assessment of cystometric variables after treatment over 21 days (Table 2) demonstrates that the capacity at first and at strong urge increased significantly compared to baseline in each dosage group. Mean changes of first urge volume were closely related to the daily dosage (Fig. 1).

At strong urge the intravesical pressure decreased on average by 1.8, 2.4 and 2.1 cmH_2O after 30, 45 and 60 mg/d respectively. No decrease was observed after 15 mg/d. The volume-pressure ratio increased significantly in groups 15–60 mg/d. Bladder compliance was elevated in all dose groups with statistical significance in the 30, 45 and 60 mg/d groups.

The micturition volume, as assessed by uroflowmetry, increased in all groups. This was

Table II. *Cystometric and uroflowmetric observation and voiding diaries before and after oral therapy with propiverine hydrochloride for 21 days (mean, SD, n) * $p < 0.05$ significant change from pre-treatment values, sign test (3)*

		Oral daily dose (mg)										
		15			30			45			60		
Method Parameter	day	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD	n
Cystometric observation													
Capacity at first urge (ml)	0	139	63	46	148	88	47	141	82	49	142	65	42
	21	166*	86	45	186*	83	46	192*	85	48	189*	102	39
Capacity at strong urge (ml)	0	256	91	46	279	109	47	279	106	49	273	107	43
	21	296*	113	45	340*	122	46	342*	134	48	322*	130	39
Pressure at strong urge (cmH_2O)	0	25.3	18.5	45	22.8	15.8	47	24.2	13.9	47	26.3	22.0	43
	21	25.9	20.1	44	21.0	13.2	46	21.8*	15.3	46	24.2	18.3	39
Volume/Pressure at strong urge (ml/cmH_2O)	0	15.4	12.0	45	20.9	23.2	47	15.9	11.1	47	20.8	21.0	43
	21	19.2*	14.8	44	22.0*	13.0	46	24.1*	17.7	46	22.1*	17.4	39
Compliance ($\Delta V/\Delta p$) (ml/cmH_2O)	0	25.3	15.2	29	26.8	26.2	31	26.1	28.2	35	24.2	25.1	30
	21	30.8	18.4	32	35.0*	33.0	32	32.7*	25.6	34	32.0*	24.7	25
Uroflowmetric observation													
Maximal urinary flow rate (ml/s)	0	20.8	9.7	45	20.0	10.0	45	20.4	8.9	48	19.7	9.3	42
	21	20.3	8.5	45	19.6	8.6	46	20.0	7.3	48	19.6	8.2	39
Micturition volume (ml)	0	228	145	45	223	127	45	207	122	48	220	149	42
	21	261	156	45	240	133	46	229	125	48	237*	123	29
Voiding diaries													
Micturition frequency (per 24 h)	0	12.9	6.2	37	11.9	5.0	40	11.0	4.5	44	11.3	4.6	43
	21	9.5*	4.7	45	7.3*	2.4	45	7.5*	2.8	48	8.7*	3.8	39
Micturition volume (mean) (ml)	0	130	60	37	133	74	40	144	74	44	144	98	37
	21	174*	84	45	199*	98	45	201*	65	48	177*	91	39

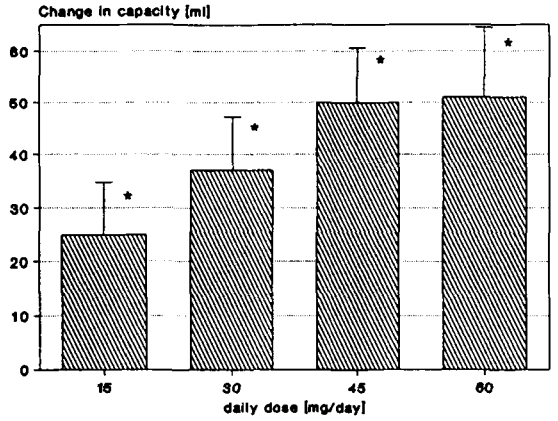

Fig. 1. Change in bladder capacity at first urge after treatment with propiverine hydrochloride over 21 days compared to pre-treatment values (mean, SEM). * $p < 0.05$, sign test (3).

statistically significant only after the highest daily dose. The mean change of maximal urinary flow rate decreased between 0.1 and 0.5 ml/s. A significant decrease in the mean micturition frequency by 2.6 to 4.6 per day was associated with a significant increase in the average micturition volume.

Subjective assessment of efficacy and tolerability

The subjective efficacy was lower after treatment with 15 mg/d as compared to 30, 45 or 60 mg/d (Table 3). The individual values of the visual analogue scale (VAS) exhibited a significant correlation with the increase in bladder volume at strong urge ($p = 0.01$, $r = 0.19$).

The tolerability was better after treatment with 15, 30 or 45 mg/d compared to 60 mg/d (Table 3). The individual values of the visual analogue scale showed a significant inverse correlation with the body-weight normalized dose ($p < 0.05$, $r = -0.16$).

Subjective adverse reactions

A summary of all patients with an increase in subjective symptoms to level 2 ("moderate") or more is given in Table 4. Reported adverse reactions were mainly mild and of an anticholinergic nature. After treatment (15, 30, 45 and 60 mg/day) blurred vision was the most common side effect reported by about 8, 16, 30 and 26% of the patients respectively. Another frequent side effect was dryness of mouth in 6, 22 and 27% respectively and tiredness (8 to 15%).

Relation of desirable and undesirable subjective effects

The number of patients with a decrease in mic-

Table III. *Subjective assessment of efficacy and tolerability of treatment with propiverine hydrochloride for 21 days (mean, SD, n)*

Parameter reported from	Scale	Oral daily dose (mg) 15 mean	SD	n	30 mean	SD	n	45 mean	SD	n	60 mean	SD	n
Efficacy													
Patients	VAS (%)	53.4	27.1	44	76.8	18.2	44	70.4	25.9	48	63.3	28.4	39
	Ordinal (1–4)	2.79	0.91	39	1.88	0.71	40	2.10	0.88	41	2.39	0.96	38
Physicians	Ordinal (1–4)	3.82	1.11	39	1.83	0.70	40	2.00	0.86	41	2.24	0.87	38
Tolerability													
Patients	VAS (%)	69.7	25.6	45	70.3	22.2	45	68.6	27.2	46	57.8	29.0	38
	Ordinal (1–4)	2.15	0.95	39	2.05	0.84	40	2.27	1.06	41	2.63	1.04	38
Physicians	Ordinal (1–4)	1.95	0.81	39	2.00	0.74	40	2.17	0.99	41	2.58	1.04	38

VAS: 0–100%; Ordinal scale: 1 = "very good", 2 = "good", 3 = "satisfactory", 4 = "insufficient"

Table IV. *Reported adverse reactions with level "2" (moderate) or more of a symptom score list (12 symptoms, 4 score levels) after oral therapy with propiverine hydrochloride for 21 days (n: number of patients with reaction)*

	Oral daily dose (mg) 15		30		45		60	
Symptoms	n	(%)	n	(%)	n	(%)	n	(%)
Any reaction	11	(24)	21	(45)	27	(53)	24	(56)
Blurred vision	4	(8)	8	(16)	15	(30)	10	(26)
Dryness of mouth	3	(6)	11	(22)	11	(22)	11	(27)
Tiredness	5	(10)	4	(8)	6	(12)	6	(15)
Dizziness	1	(2)	2	(4)	3	(6)	3	(7)
Constipation	2	(4)	3	(6)			3	(7)
Nervousness			4	(8)	1	(2)	2	(5)
Nausea	1	(2)	2	(4)	1	(2)	2	(5)
Tremor					1	(2)	3	(7)
Vomiting							3	(7)
Headache			3	(6)				
Palpitations			1	(2)	2	(4)		
Confusion							2	(5)

turition frequency as a desirable subjective effect of propiverine was evaluated, and it was related to the undesirable subjective adverse reactions (the increase by two levels in one or more symptoms), see Fig. 2.

22% of all patients treated with 15 mg/d reported neither desirable nor undesirable effect. This percentage was 12 to 13% after 30–60 mg/d. 70% of all patients reported a decrease in micturition frequency after 15 mg/d, 9% of this group reported subjective adverse reactions. In the dosage groups 30, 45 and 60 mg/d approximately 80% of the patients reported a decrease in micturition frequency and 21, 40 and 28% anticholinergic symptoms. 8% of the patients treated with 15 mg and 15% of those treated with 60 mg/d had adverse reactions without any improvement of micturition frequency.

Laboratory parameters

No significant or dose dependent changes during treatment were found in the laboratory parameters. There was no increase of the number of pathological values (7) after treatment compared to pre-treatment values.

DISCUSSION

The run-in evaluation of urodynamic and micturition variables demonstrated an increased micturition frequency and a decreased bladder

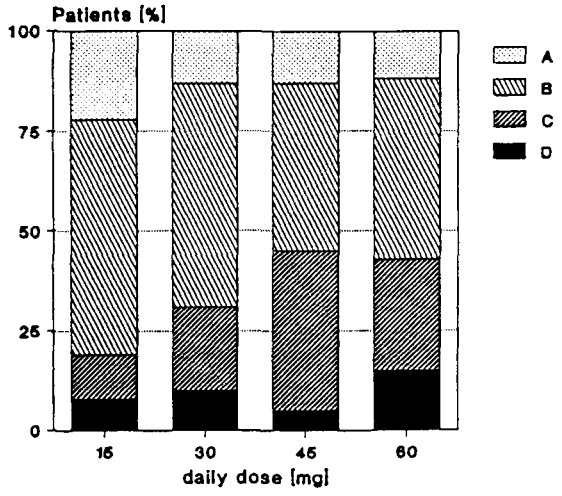

Fig. 2. Patients with decreased micturition frequency and/or increased subjective adverse reactions after treatment with propiverine hydrochloride over 21 days. A: no decreased frequency and no increased subj. symptoms; B: decreased frequency and no increased subj. symptoms; C: decreased frequency and increased subj. symptoms; D: no decreased frequency and increased subj. symptoms.

volume at first urge in a large number of patients. Pollakisuria and imperative urgency are considered to be clinical signs of urgency and urge incontinence (5).

During the 21 day treatment period there was a significant improvement in cystometric and micturition parameters. The results in this open study were in agreement with those from other trials and of similar magnitude to results obtained after treatment with other urospasmolytics in usual dosages (8, 11, 14). The effects on bladder volume at first and strong urge were dose dependent. The changes of maximal urinary flow rate were negligible. The number of micturitions were reduced significantly in all treatment groups. The reduction in this study was comparable but slightly higher than in similar studies with emepronium and oxybutynin chloride in the usual dosages for the treatment of bladder instability and motor urge incontinence (11, 12).

Propiverine was generally well tolerated. However, adverse reaction caused withdrawals in 6 patients. The subjective adverse reactions seen during the study were due to the anticholinergic properties of propiverine. The most common side effects reported were accommodation disturbances, described as blurred vision, dryness of mouth and tiredness. The profile of side effects was similar to those obtained after treatment with other anticholinergic agents (1). No palpitations were reported in the present trial.

The extensive series of laboratory investigations were performed to determine whether or not the values could be influenced by propiverine in doses up to 60 mg/d. There were no significant dose dependent changes in the laboratory values during the treatment period.

A decrease in micturition frequency was found in 70% of the patients after 15 mg/d, and in about 80% after 30 mg/d and did not further decrease with 45 and 60 mg/d. The incidence of undesirable reactions increased in proportion to the increase in daily dose. The incidence and severity of subjective symptoms after propiverine dosages 15, 30 or 45 mg/d seem to be lower than after oxybutynin or terodiline in usual dosages (9, 10, 11, 14).

15 and 30 mg seem to be the daily doses with the best ratio of desirable to undesirable effects. For individual urospasmolytic therapy an initial dose of 30 mg/d could be recommended. A dose reduction to 15 mg/d should be considered in patients with adverse reactions. If no therapeutic response is observed a dose increase to 45 mg/d should be considered. A daily dose of 60 mg could only be recommended in particular cases, after the potential benefits and risks have been carefully evaluated.

The results demonstrate a good efficacy and tolerability of propiverine in the treatment of patients suffering from urgency and urge incontinence. Taking these results and those of other authors (13, 14) into account, propiverine seems to be an attractive alternative in the urospasmolytic treatment.

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Appendix

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