

10 years of treatment with propiverine Successful long-term therapy of urinary incontinence and symptoms of urgency

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The clinical symptoms of bladder instability like frequent passing water during the day and night and urgency with or without involuntary loss of urine can normally be treated successfully by conservative measures. The pharmacological moderation of the hyperactive detrusor together with measures of behavior therapy is the instrument of choice. According to congruent opinions in literature best results are achieved with drugs that act anticholinergically and spasmolytically. At present especially oxybutynin, propiverine, tolterodine und trospium chloride are recommended and utilised. Though these drugs show comparable efficacy, gradual differences in the incidence rate and severity code of adverse events can be found. Indeed for none of these drugs documentations extending over several years are published so far.

In 29 female patients suffering from urinary incontinence and symptoms of urgency the course of a treatment with propiverine was documented during a period of up to 10 years (between 1985 and 1996).

The verification of efficacy of propiverine on the clinical symptoms (frequency of micturition, nycturia) was carried out by a micturition diary.

Urodynamically the parameters of cystometry (bladder capacity at first urge, maximum bladder capacity, pressure at maximum capacity, compliance) and of urethrocytometry (functional length of urethra, pressure at maximum of curve, transmission factor) were collected.

Furthermore the authors used uroflowmetry (maximum urinary flow, time of micturition) as well as the perineal sonography (angle of inclination, pubourethral angle and rear vesicourethral angle) for the assessment of the efficacy.

They compared the results before therapy with propiverine with the results after 3 months and 10 years of treatment and contrasted them.

Long-term results: more than 95 percent have a benefit

During the actual questioning after 10 years the patients declared that they had discontinued the pharmacological therapy in case of decreasing symptoms but that they had taken propiverine with the same success in case of reappearance.

In total a nearly continuous intake of average 30 mg of propiverine daily over a period of 10 years resulted.

The main urodynamic parameters are summarised in table 1.

Table 1: Long-term therapy up to 10 years with propiverine - urodynamic parameters (mean values)

	before therapy	after 3 months	after 10 years
Cystometry			
max. capacity [ml]	268	336	345
cap. at first urge [ml]	136	201	210
compliance [ml/cmH ₂ O]	13.0	22,0	23.3
pressure at max. cap. [cmH ₂ O]	21.4	15.3	15.3
Uroflowmetry			
max. urinary flow [ml/s]	20.1	21.1	20.9
mean urinary flow [ml/s]	14.7	15.7	14.2
Urethrocystometry			
max. urethral pressure [cmH ₂ O]	29.6	34.6	35.7
funct. length of urethra [mm]	17.8	19.8	20.8
transmission factor [%]	68.0	68.0	71.6

After 10 years the mean maximum bladder capacity increased significantly during therapy with propiverine by 77 ml (28.7 %) in comparison with the baseline value. The mean bladder capacity at first urge increased by 54.4 % (Fig. 1).

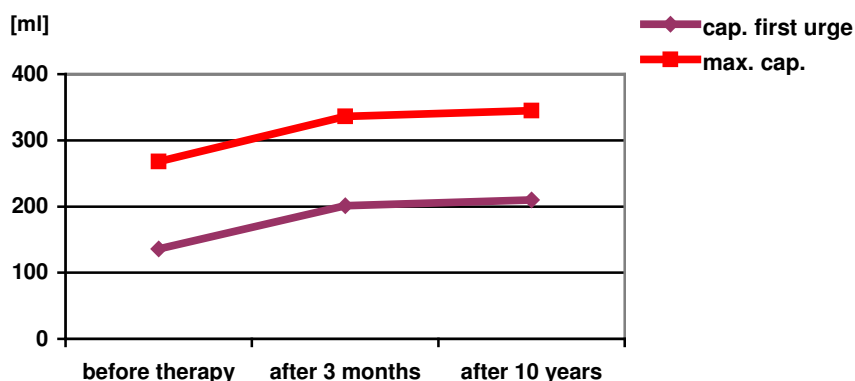


Fig. 1: Mean cystometric bladder capacity at first and at maximum urge during therapy with propiverine

The compliance maintained significantly increased by 87.3 % compared to the baseline value before therapy. The mean pressure at maximum capacity decreased by 29.0 % in spite of the only slightly increased baseline values (table 1).

No clinically relevant changes compared to the values before therapy were found in uroflow for maximum flow or mean flow, in urethrocystometry for the parameters functional length of urethra, pressure at maximum of curve as well as transmission factor (table 1).

The urodynamic results – increase of bladder capacity at first and at maximum urge – are reflected in the effect of propiverine on the clinical symptoms.

- After 10 years the frequency of micturition during the day had decreased by 32 percent compared to the number of micturitions before therapy so that with 6.4 voidings at the average normal values existed also after 10 years.
- The frequency of micturition during the night had decreased by 43 percent compared to the baseline value (Fig. 2)

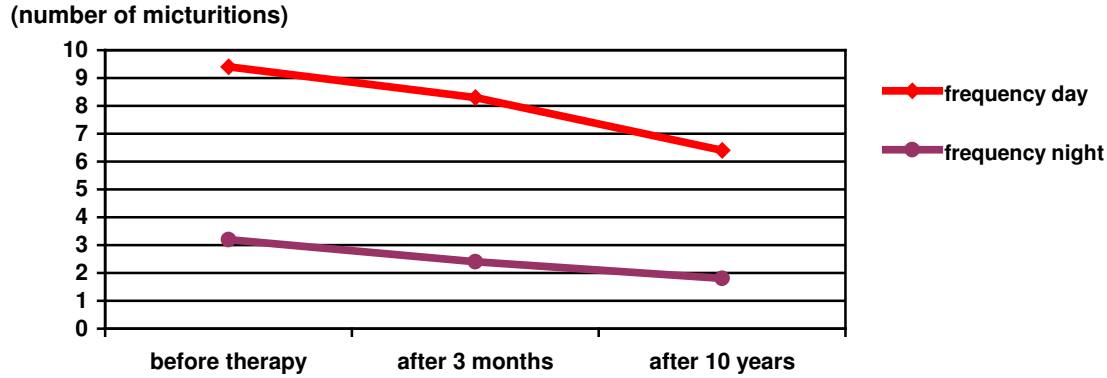


Fig. 2: Frequency of micturition at daytime and at nighttime during therapy with propiverine

- In the subjective assessment of therapy three months after beginning of medication 40.0 percent of the patients assessed propiverine to be very well effective, 21.3 percent as well effective and 25.3 percent as satisfyingly effective. In 5.3 percent the symptoms remained unchanged.

This assessment was confirmed after ten years of propiverine therapy: 34.5 percent judged the efficacy to be very good, 51.7 percent to be good and 10.4 percent to be satisfying. Overall 96.6 percent of the patients had a benefit of the therapy. That is clear due to the long time of continuing intake. Only one patient assessed the therapy to be insufficient (table 2; Fig. 3).

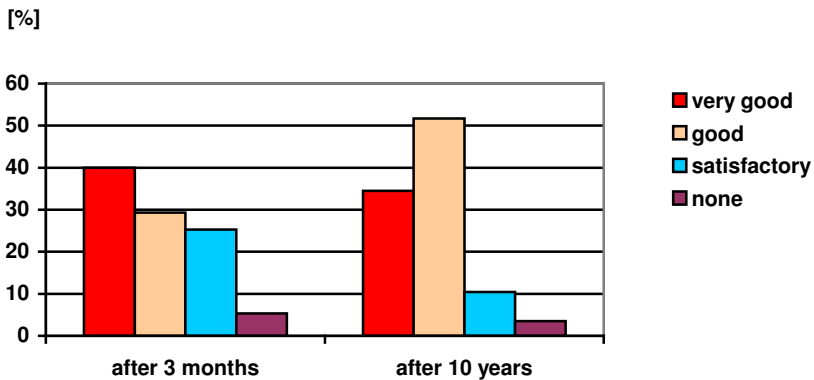


Fig. 3: Subjective assessment of the efficacy of propiverine by the patients. Also after ten years more than 80 percent of the patients assessed the efficacy to be very good or good.

The number of adverse events decreased during long-term therapy with propiverine during time elapsed. On direct request overall 22.7 % of side effects were documented after 3 months. After 10 years overall 15.6 % of side effects in the 29

investigated patients were found. Dry mouth was reported by three patients, tiredness and accommodation disorders were reported by one patient (table 2). Continuance in therapy indicates a low and thus tolerable degree of intensity.

Table 2: Adverse events during long-term therapy with propiverine

	before therapy	after 3 months	after 10 years
Adverse events [n]			
dry mouth	3	6	3
tiredness	1	4	1
accommodations disorders	1	6	1
dizziness	1	2	1

Determination of the residual urine after 10 years provided no clinically relevant values. There were no findings in the meantime, but in case of suspicion of existence of pathological amounts of residual urine the medication would have been discontinued. Urinary tract infections under medication were not detected in the patients.

Efficacy unchanged for ten years

In a prospective clinical trial (3) already after 14 days of therapy a good therapeutic effect of 30 and 45 mg propiverine as daily dosage was demonstrated.

Further publications report trials that demonstrated the efficacy and tolerability of 15 mg of propiverine (Mictonorm®) three times daily for time periods of 12 weeks up to 22 months in 75 women (average age 53.3 years) with urodynamically proven urge incontinence and urge symptoms (4, 5). With the documented results and the requests for 29 women the authors observed and looked over a nearly continuous therapy period with an average daily dosage of 30 mg of propiverine.

Most of the women reported that they had discontinued the medication by themselves from time to time (with the meaning of a „self-testing“).

Because the symptoms partially recurred the therapy was resumed. During the continued treatment until now the patients were like during the first treatment free from complaints, or the complaints clearly decreased. As well as the subjective feeling of the affected patients the urodynamically determined results show unchanged efficacy of the drug after ten years.

At the beginning of the documentation the average age of the patients was 53 years. For persons older than 60 years especially the increasing incidence of urge incontinence is known from epidemiologic studies (1). Though for the patients phenomena of old age with worsening of the situation of the bladder would have been increasingly expected after ten years, these were neither clinically relevant nor detectable.

In contrast the continuous intake of propiverine had obviously contributed to the maintenance of the efficiency of the urinary bladder; overall 86.2 % of the patients attested the very good or good efficacy of propiverine. The nearly continuous intake for ten years underlines on the one hand that propiverine was clearly efficacious all the time, that is that there were no effects of addiction. It underlines on the other hand also that the side effects were mild and tolerable.

As the uroflowmetry and the urethrocystometry showed the uroflow and the profile of the urethra pressure were not changed in a clinically relevant way.

These results confirm earlier published data in patients with urge, stress and combined urge/stress incontinence, who received one week each 2 x 15 mg and 3 x 15 mg of propiverine (Mictonorm®). The maximum cystometric bladder capacity as well as the compliance increased significantly, while no statistically significant effects on the parameters of the urethra (functional length of the urethra, maximum closing pressure of the urethra) were detectable (2).

No influence on stress incontinence

Due to these study results the authors concluded that propiverine does neither lead to a worsening of an existent nor to the triggering of a latent form of a stress incontinence. Thus also patients with a combined urge/stress incontinence can expect an improvement of the symptoms of the urge component without amplification of the stress incontinence by the propiverine therapy. The available results display that also the long-term intake of propiverine does not negatively influence the function of the urethra that is important for the etiology of the stress incontinence. Finally the nearly continuous intake for more than ten years reflects that with propiverine in the treatment of urge incontinence and symptoms of urgency there is no clinically relevant formation of residual urine with subsequent urinary tract infections.

So far for no drug of the group of bladder spasmolytics long-term data are available for a period of 10 years. For female patients with symptoms of urgency and urge incontinence the removal or decrease of complaints as achieved with the treatment with propiverine is a distinct improvement of the quality of life. Particularly as the incidence of side effects decreased after longer intake in most cases and the side effects were tolerated as acceptable.

Summarising it can be stated that the bladder spasmolytic treatment with propiverine is reliably effective and well tolerable also in long-term therapy.

Literature

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