European Urology

Eur Urol 2000;37:702–708

Accepted after revision: August 24, 1999

Efficacy and Cardiac Safety of Propiverine in Elderly Patients – A Double-Blind, Placebo-Controlled Clinical Study

W. Dorschner[a], J.U. Stolzenburg[a], R. Griebenow[b], M. Halaska[e], G. Schubert[c], G. Mürtz[c], M. Frank[d], F. Wieners[d]

[a]Department of Urology, University of Leipzig, [b]Medical Clinic II, University of Cologne, [c]Apogepha Arzneimittel GmbH, Dresden, and [d]Phamos Pharmacological Research, Berlin, Germany; [e]Department of Gynaecology, Prague University, Prague, Czech Republic

Key Words

Propiverine · Urge incontinence · Urge-stress incontinence · Electrocardiography

Abstract

The study investigated the efficacy and cardiac safety of propiverine in the elderly, because the induction of life-threatening ventricular arrhythmia has been reported for some drugs prescribed in the therapy of urinary incontinence. Ninety-eight patients (21 male, 77 female; 67.7 ± 6.3 years of age) suffering from urgency, urge incontinence or mixed urge-stress incontinence were included in the double-blind, multicentre, placebo-controlled, randomized study. After a 2-week placebo run-in period, the patients received propiverine (15 mg t.i.d.) or placebo (t.i.d.) for 4 weeks. Before (V1, V2) and during the treatment period (V3, V4), standard ECGs and 24-hour long-term ECGs were recorded. Propiverine caused a significant reduction of the micturition frequency (V2: 8.7 ± 4.2, V4: 6.5 ± 3.2 ml; $p \leq 0.01$), reflected in a significant increase in the average micturition volume (V2: 163.5 ± 65.9, V4: 216.3 ± 101.5 ml; $p \leq 0.01$) and a significant decrease in episodes of incontinence (–54%; $p = 0.048$). These findings were confirmed by the overall assessment at V4, in which approximately 90% of patients under propiverine either had no urge incontinence or urge symptoms, or showed improvement. Resting and ambulatory electrocardiograms indicated no significant changes. Neither the frequency-corrected Q–T interval nor other cardiac parameters were relevantly altered. The frequency of cardiac events (Lown classes IVa/b) was random, revealing no difference between placebo and propiverine. The incidence of adverse events was very low (2% dryness of the mouth under propiverine) and confirmed by the findings from the quality of life questionnaires. A favourable benefit-risk ratio without the induction of any cardiac arrhythmia in the treatment of elderly patients suffering from urgency, urge incontinence or combined urge-stress incontinence is therefore proven for propiverine.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0302–2838/00/0376–0702 $17.50/0

Accessible online at:
www.karger.com/journals/eur

Prof. Wolfgang Dorschner
Department of Urology, Leipzig University
Liebigstrasse 21
D–04104 Leipzig (Germany)
Tel. +49 341 971 9001, Fax +49 341 971 9009

Introduction

Although the problem of incontinence is not specific to any client group, the elderly are particularly susceptible due to several reasons related to the ageing process [1, 2]. Pollakiuria, nycturia, imperative urgency and incontinence are clinical symptoms of urge incontinence, indicating two types of dysfunction of the urinary bladder: detrusor hyperactivity and detrusor hypersensitivity. Loss of urine during an increase in abdominal pressure without detrusor instability is defined as stress incontinence. A combination of urge incontinence and stress incontinence frequently occurs [1].

Besides behaviour and bladder training, pharmacotherapy is the main method used for urge incontinence therapy. The effective treatment of urge incontinence and urgency should reduce the severity and frequency of symptoms, thus improving the patients' quality of life. Current standard treatment comprises anticholinergic agents and/or calcium antagonists.

Propiverine hydrochloride is a bladder spasmolytic with calcium antagonistic and anticholinergic properties. Studies of human urinary bladder muscle revealed the inhibition of acetylcholine-induced contractions and of calcium influx from the extracellular space. Compared with atropine or oxybutynin, propiverine exhibits a less potent anticholinergic effect. Its effects are enhanced by an additional calcium-antagonistic effect [3]. This advantageous pharmacological profile of propiverine comprising a dual mode of action in one molecule has also proven its efficacy and safety in clinical application [4, 5].

However, a calcium-antagonistic mode of action might be associated with the multiple occurrence of ventricular tachycardia (in particular 'torsade de pointes' tachycardia), which has been reported under treatment with terodiline [6–9]. These cardiac arrhythmias were probably caused by the concentration-related prolongation of the frequency-corrected Q–T (Q–Tc) interval [10]. However, this phenomenon has not been reported for anticholinergic drugs, such as oxybutynin [11].

Consequently, considering the calcium-antagonistic mode of action of propiverine, a study was initiated with two major aims: (1) to enhance the well-documented general risk profile of propiverine by focusing on cardiac safety; furthermore, the deliberately chosen elderly patient population is prone to cardiac arrhythmia due to its multimorbidity (coronary heart disease, myocardial failure) and multimedication; (2) to confirm the efficacy of propiverine in bladder instability especially in elderly patients, who represent the majority suffering from urgency and urge incontinence; in order to restrict invasive diagnostic approaches in elderly frail patients, non-invasive procedures have to be applied instead of urodynamics [12, 13].

Table 1. Demographic and baseline data

	Placebo (n = 49)	Propiverine (n = 49)
Sex		
Male	12	9
Female	37	40
Mean age, years	66.5±6.0	68.4±6.5
Urgency[1]	19	21
Urge-stress incontinence	30	28
Concomitant diseases	18	16
Arterial hypertension	11	8
Coronary heart disease	6	6
Myocardial failure	1	2
Concomitant medication	21	23
Calcium antagonists	2	7
Other drugs with cardiac effects	19	16

[1] 30 of the 40 patients with urgency additionally suffered from urinary incontinence.

Patients and Methods

The study was conducted in a prospective, double-blind, randomized, placebo-controlled, parallel-group, multicentre design. It was performed in accordance with the Declaration of Helsinki and approved by an Ethical Committee. The patient's written informed consent was obtained.

A total of 107 patients were enrolled in the study; 9 were excluded from the efficacy analysis due to non-compliance (no 24-hour long-term ECG; n = 3), premature withdrawal (n = 2) and infringement of urological exclusion criteria (n = 4). The demographic and baseline characteristics of the 98 evaluable patients are depicted in table 1. There were no statistically significant differences between the two groups. Cardiac events of Lown classes ≥I occurred in about 50% of the study population and in 24% higher gradings in Lown classification [14], thus reflecting a cardiac-risk population.

Diagnostic procedures comprised the patient's history, clinical investigation and Gaudenz's incontinence questionnaire, and allowed classification into urgency, urge incontinence and mixed urge-stress incontinence. Besides these clinical diagnoses, one inclusion criterion was an age of 60 years. Other inclusion parameters derived from micturition diaries were frequency >7 episodes/24 h, urinary incontinence >0 episodes/24h, and micturition volume <300 ml/micturition (uroflow).

The following exclusion criteria had to be taken into consideration: acute urinary tract infection, mechanical or functional bladder-emptying disorders, residual urine of more than 20% of the voided volume by ultrasound, micturition volume of more than 300 ml in uroflow, renal insufficiency, concomitant medication interfering with

Table 2. Flow chart

	Run-in period		Treatment period	
	V1 (day –14)	V2 (day 0)	V3 (day 7)	V4 (day 28)
Clinical examination	+			
Patient's history	+			
Standard ECG	+	+	+	+
Long-term ECG	+	+	+	+
Laboratory	+	+		+
Micturition diaries		+	+	+
Psychometry		+	+	+
Uroflowmetry	+	+	+	+
Ultrasound of the bladder	+	+	+	+
Incontinence questionnaire	+	+		+

the drug studied (neurotropic/musculotropic spasmolytics, centrally acting muscle relaxants, psychopharmacological agents or drugs for the treatment of Parkinson's disease, anti-arrhythmics) and clinically relevant variations in the laboratory parameters prior to the study. For ethical reasons, patients suffering from serious, life-threatening cardiovascular diseases had to be excluded: myocardial infarction within the previous 3 months, unstable coronary heart disease, implanted cardiac pacemaker, decompensated myocardial insufficiency, tachycardia or bradycardia at rest, second- or third-degree atrioventricular block, complete bundle branch interventricular heart block, chronic atrial fibrillation and ventricular extrasystoles Lown IVb in the prestudy ECG monitoring.

The study comprised four visits (V1: day –14, V2: day 0, V3: day 7, V4: day 28). Following a 2-week placebo run-in phase, patients were randomized to propiverine (15 mg three times a day; registered as Mictonorm® and Detrunorm®; manufactured by Apogepha Arzneimittel GmbH, Dresden, Germany) or placebo (three times a day) for a 4 week treatment period.

For efficacy assessment the pretreatment values (V2) were compared with the posttreatment values (V4) and comprised the following target variables (table 2): (1) micturition diary: micturition frequency, micturition volume, incontinence episodes; (2) uroflow: average and peak flow and urine volume; each measurement was carried out twice during each visit; volumes <100 ml were excluded from evaluation; (3) ultrasound: residual urine; (4) urge score documented in Gaudenz's incontinence questionnaire; (5) patient's and physician's assessment of the improvement of clinical symptoms by a 4-point scale (symptom-free, improved, unchanged, worsened).

Safety assessment comprised the following parameters as stated in the flow chart (table 2): (1) ECG at rest (12-channel ECG): intervals I–III, aVR, aVL, aVF, V1–V6 (850 mm/s); (2) 24-hour ambulatory ECG according to standard methods (by Holter Recorder 2488; Ela Medical, Munich, Germany): heart rate, P–Q interval, QRS interval, Q–T interval, Q–Tc interval according to Bazett's formula; the 24-hour long-term ECG was evaluated by both a computer-assisted evaluation system (Elatec, Ela Medical) and manual evaluation; the ventricular extrasystoles were classified according to the Lown classification; furthermore, the minimum and maximum heart rates were recorded and supraventricular disturbances of heart rhythm were qualitatively assessed; (3) laboratory parameters according to standard chemical laboratory methods: serum concentration of sodium, potassium, calcium, magnesium, chloride, SGOT, SGPT, γ-GT, AP, LDH, creatinine, urea and uric acid; (4) adverse events: by directly interviewing the patient; (5) quality of life: by psychometric questionnaires (Giessen Complaint Survey and the Basle Subjective Well-Being Survey).

For statistical analysis, the paired t test or the Wilcoxon rank sum test was applied. Statistical significance was considered at a level of $p<0.05$ on a two-tailed basis.

Table 3. Micturition diary and uroflow before (V2) and after treatment (V4)

	Placebo		Propiverine	
Micturition diary				
Micturition volume, ml				
V2	187.0		163.5	
V4	178.0		216.3	
Difference	–8.4	–1.6%	+55.3[2]	+32%
Micturition frequency, episodes				
V2	7.1		8.7	
V4	6.5		6.5	
Difference	–0.6	–8.4%	–2.1[2]	–22.0%
Incontinence, episodes				
V2	0.4		0.9	
V4	0.2		0.3	
Difference	–0.1	–36.6%	–0.6[1]	–54.5%
Uroflow				
Micturition volume, ml				
V2	207.1		185.9	
V4	226.2		233.0	
Difference	+19.1	+9.2%	+47.0[2]	+25.3%

Difference: V4 – V2; [1] $p \leq 0.05$, [2] $p \leq 0.01$.

Results

Efficacy

Micturition Diary. Propiverine resulted in a significant decrease in micturition frequency by 2.1 ± 3.1 episodes (V2: 8.7 ± 4.2, V4: 6.5 ± 3.2; –22%; $p<0.01$; table 3). By contrast, no statistically significant changes were observed with placebo (V2: 7.1 ± 3.0, V4: 6.5 ± 3.5 episodes). The increase in the mean micturition volume under propiverine of 55.3 ml (V2: 163.5 ± 65.9, V4: 216.3 ± 101.5 ml) was also statistically significant (+32%; $p \leq 0.01$; table 3). Patient-documented episodes of incontinence occurred very rarely. A reduction by –0.6 episodes/day (V2: 0.9, V4: 0.3 episodes/day; –55%) in the propiverine group attained significance in comparison with the reduction by 0.1 episodes/day in the placebo group (V2: 0.4, V4: 0.2 episodes/day; –37%; table 3).

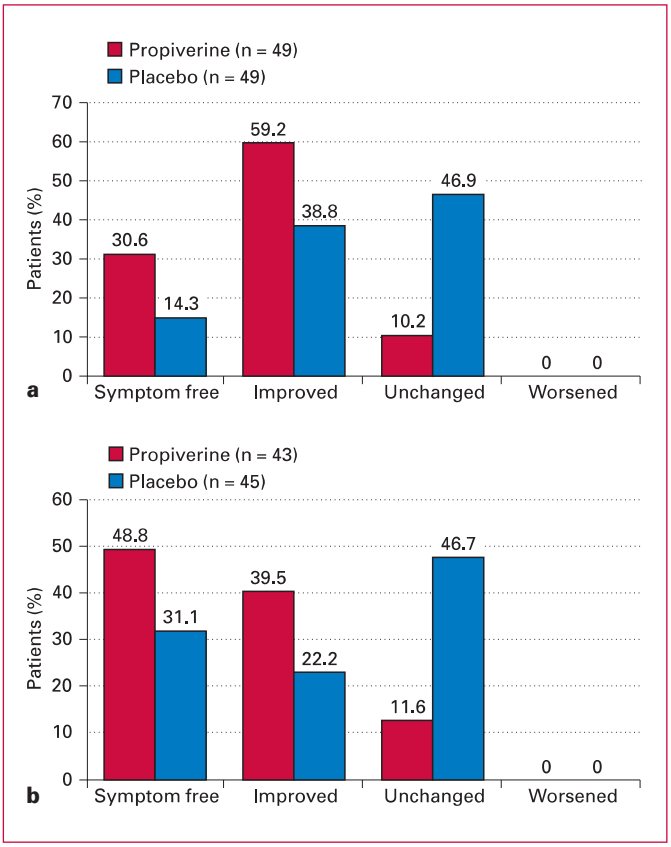

Fig. 1. Subjective assessment by patients of efficacy of treatment on symptoms of urgency (**a**; n = 98) and incontinence (**b**; n = 88).

.

Uroflow. A statistically significant increase in micturition volume by 47.0±80.0 ml (+25%) was observed with propiverine (V2: 185.9±56.5, V4: 233.0±76.9 ml; $p < 0.01$). The minor increase under placebo by 19.1±101 ml (V2: 207.1±62.6, V4: 226.2±100.1 ml; +9%) was not statistically significant ($p = 0.23$; table 3). Neither the peak flow nor the average flow were significantly altered by propiverine treatment.

Ultrasound. Ultrasound revealed no clinically relevant residual urine. No significant changes in the mean residual urine were measured under propiverine (V2: 6.6±9.0, V 4: 7.2±12.4 ml) or placebo either (V2: 6.6±9.5, V4: 5.9 ±8.0 ml).

Gaudenz Questionnaire. A marked, statistically significant decrease in the urge score after 4 weeks of propiverine treatment was documented (V2: 10.4±6.9, V4: 3.7±4.8; $p \leq 0.0001$). The reduction under placebo was considerably lower (V2: 6.5±5.4, V4: 5.0±5.0 urge points; $p = 0.0197$). Statistical significance was attained between the groups ($p = 0.02$).

Assessment of the Improvement of Clinical Symptoms. In the patient's assessment; improvement of urgency under propiverine was significant compared to placebo ($p = 0.0015$; symptom-free: 30.6 vs. 14.3%; improved: 59.2 vs. 38.8%; unchanged: 10.2 vs. 46.9%). Improvement of incontinence yielded comparable, significant alterations ($p = 0.003$; symptom-free: 48.8 vs. 31.1%, improved: 39.5 vs. 22.2%, insufficient: 11.6 vs. 46.7%; fig. 1).

In the physician's assessment; improvement of urgency was significant under propiverine in comparison with placebo ($p = 0.0001$; symptom-free: 30.6 vs. 10.2%, improved: 57.1 vs. 38.8%, unchanged: 12.2 vs. 51.0%). Comparable, significant changes resulted for the improvement of incontinence ($p = 0.003$; symptom-free: 41.9 vs. 28.9% , improved: 46.6 vs. 20.0% , unchanged: 11.6 vs. 51.1%).

Closely corresponding assessments of these clinical symptoms resulted from both patient and physician.

Safety

Standard ECG. No significant differences resulted in the parameters heart rate, P–Q interval, QRS interval, Q–T interval or Q–Tc interval during the run-in phase, under medication or between the two groups during the four visits of the study.

24-Hour Long-Term ECG. There was no significant change in the basic values within either the propiverine or the placebo group. The minimum heart rate increased insignificantly in the propiverine group (V2: 56.9±8.6 beats/min, V4: 58.6±8.2 beats/min) and decreased insignificantly in the placebo group (V2: 54.8±6.8 beats/min, V4: 53.0±6.4 beats/min). However, the minimum heart rate under propiverine rose significantly in comparison with placebo ($p < 0.001$). For the maximum heart rate, no significant differences were observed between the two groups (propiverine V2: 119.9±18.3, V4: 121.6±14.8 beats/min; placebo V2: 117.6±18.3, V4: 119.6±12.9 beats/min).

During all four visits, about 50% of the patients could be classified in the Lown classes I–IVa/b. About 24% of the patients showed ventricular extrasystoles of the Lown classes II–IVa/b under both propiverine and placebo on the occasion of at least one of the four visits. Five patients in the propiverine and 5 patients in the placebo group showed ventricular extrasystoles of Lown classes IVa/b during the run-in period (V1 or V2). Six patients in the propiverine and 5 patients in the placebo group showed ventricular extrasystoles of the Lown IVa/b category in the treatment phase only (V3: propiverine 5, placebo 2; V4: propiverine 3, placebo 4). One patient in each group documented ventricular extrasystoles in the pre- and posttreatment phase as well (table 4a, b). Neither a sustained ventricular tachycardia, paroxys-

mal supraventricular tachycardia, intermittent atrial fibrillation nor a torsade de pointes tachycardia were observed in any of the patients.

The distribution of all cardiac events – newly manifesting or disappearing Lown events – was similarly random in both groups during the study.

Laboratory Parameters. Statistically significant changes in the laboratory parameters or the electrolyte concentrations emerged neither within nor in the comparison between the two treatment groups.

Adverse Events. Adverse events were observed in 2 patients of the propiverine group. However, only 1 case of dryness of the mouth could be directly attributed to drug therapy. The other case – an irritation of the pancreas – was considered to be causally unrelated to the medication. In the placebo group, 8 patients complained of adverse events, all of which were classified as unrelated to the medication.

Quality of Life. Results from the Giessen Complaint Survey revealed that the incidence rate of anticholinergic side-effects did not significantly differ between the groups. However, the incidence of cardiac complaints was significantly lower in the propiverine group than in the placebo group ($p < 0.02$) at the end of treatment (V4).

The individual psychometric questions from the Basle Subjective Well-Being Survey showed that propiverine significantly improved scores on the following scales: tired-fresh, taciturn-talkative and retiring-gregarious ($p \leq 0.05$). Vitality and social extraversion scores improved markedly (although not statistically significantly) with propiverine but remained unchanged with placebo.

Table 4a. Frequency of ventricular extrasystoles in the Lown classes IVa/b at the four study visits.

	Placebo group	Propiverine group
Placebo run-in period	4	5
Placebo run-in and treatment period	1	*1*
Treatment period	5	*6*

Placebo run-in period, placebo group (V1 and V2); placebo run-in period, propiverine group (V1 and V2); treatment period, placebo group (V3 and V4); in italics: *treatment period, propiverine group (V3 and V4).*

Discussion

The patients examined in this study suffering from urgency, urge incontinence or mixed urge-stress incontinence represent the typical characteristics of a geriatric population. Cardiovascular diseases such as coronary heart disease, arterial hypertension and myocardial failure are ac-

Table 4b. Distribution of the Lown classes in patients suffering from at least one IVa/b extrasystole during the course of the study

Placebo group				Propiverine group			
V1 (day –14)	V2 (day 0)	V3 (day 7)	V4 (day 28)	V1 (day –14)	V2 (day 0)	V3 (day 7)	V4 (day 28)
I	IVa (C)	0	0	IVa (C)	IIIb	*IIIb*	*II*
0	IVb (T)	0	0	IIIb	IVb (C, T)	*I*	*II*
0	IVa (C)	0	0	I	IVb (S)	*I*	*0*
IVa (C)	IVa (C)	I	I	IVa (C)	I	*0*	*1*
				I	IVa (C)	*I*	*0*
0	IVb (S)	0	IVa (3C)	IVa (4C)	IIIa	*IVa (3C)*	*IIIa*
I	I	IIIb	IVa (C)	I	I	*IIIb*	*IVa (C)*
0	0	0	IVa (C)	I	I	*I*	*IVb (T)*
I	IIIa	IVa (C)	IIIa	I	I	*IVa (C)*	*0*
IIIa	I	I	IVa (2C)	I	0	*IVb (T, S)*	*0*
I	0	IVb (S)	0	0	0	*IVb (T)*	*I*
				0	I	*IVb (C, T)*	*IVb (T)*

0, I, II, IIIa/IIIb, IVa/IVb = Lown classes; C = single couplet; T = single triplet; S = single ventricular salvo, each within 24 h/treatment period.

Placebo run-in period, placebo group (V1 and V2); placebo run-in period, propiverine group (V1 and V2); treatment period, placebo group (V3 and V4); in italics: *treatment period, propiverine group (V3 and V4).*

companied by urinary incontinence, both organ systems being affected at elevated incidence rates.

To determine the efficacy of propiverine, only non-invasive techniques were applied; the 24-hour ambulatory ECG monitoring meant that further strain on these elderly patients was avoided [15]. Some reports suggest that non-invasive techniques have an important role in the diagnosis and monitoring of incontinence in elderly patients as they are less traumatic for frail patients [16, 17]. With increased knowledge about the aetiology of incontinence in the elderly, fewer patients have to be referred for invasive urodynamic investigations, since most patients can be only diagnosed by non-invasive techniques and clinical evaluation [13, 16, 18, 19]. In these cases with no previous urodynamic assessment, therapeutic interventions over a limited period are recommended.

Numerous previous studies have demonstrated the efficacy of propiverine in the treatment of urgency and urge incontinence [20–24]. Comparable improvements have been documented by applying invasive cystometric and non-invasive parameters of micturition diaries. In the studies described by Mazur et al. [21, 22] and Voigt et al. [23], micturition diaries have been used additionally to urodynamics. A significant improvement in cystometric and micturition parameters has also been reported. The invasive cystometric parameters of maximum bladder capacity and compliance were significantly increased and bladder pressure was significantly decreased, while the clinical symptom of micturition frequency was significantly decreased by propiverine. Moreover, the subjective statements of efficacy correlate with improvements in cystometric parameters. Therefore, uncomfortable and complicated urodynamic assessments for the patient can be avoided.

The results of the current study achieved by non-invasive assessment methods correspond with those from previous studies, including urodynamics. It is important to consider that improvements in clinical symptoms such as micturition frequency and the frequency of involuntary voiding are the main target from the patient's point of view. In contrast to placebo, propiverine resulted in a significant decrease in frequency combined with a significant increase in the average micturition volume, as well as a marked reduction in the number of incontinence episodes. These findings were confirmed by the overall assessment at the end of treatment in which approximately 90% of patients treated with propiverine were either symptom free or showed improvement concerning urgency and incontinence symptoms. However, the corresponding result for the placebo group was only 50%. The marked, statistically significant decrease in the urge score after 4 weeks of propiverine treatment compared to the considerably lower reduction in the placebo group corresponds well to the micturition diaries.

In agreement with previous studies [20–24], propiverine was very well tolerated in the elderly patient population. The incidence of adverse events was very low, reflecting the well-known experience that effective treatment correlates with minor complaints of undesirable effects [21]. Furthermore, the rate of adverse events depends on the method of evaluation [25]: as expected, clinical studies prompting adverse events by direct questioning produce higher incidence rates [5]. Referring to adverse events reported spontaneously by patients generally produces much lower rates [23], as shown by the present study. The results of the quality of life questionnaires reflect the lack of any significant anticholinergic effects and cardiovascular events as well as the conspicuous efficacy in this study.

The calcium antagonist terodiline has been associated with cardiovascular events, including cardiac arrhythmias with prolonged Q–T intervals [7–10]. Therefore, in view of the calcium-antagonistic properties of propiverine, the thorough investigation of possible arrhythmogenic effects of propiverine was initiated under a therapeutic dosage regime. The cardiological aspects of the study outline fulfilled the criteria of the 1997 approved CPMP guideline on 'The assessment of the potential for QT interval prolongation by noncardiovascular medicinal products' [26] comprising the standard 12-lead ECG as well as 24-hour long-term ECG. The 12-lead ECG revealed no changes in the relevant parameters heart rate, P–Q interval, QRS interval, Q–T or Q–Tc interval in the standard ECG. Correspondingly, animal experiments detected no ECG effects [27]. Comparable to the standard ECGs in the 24-hour long-term ECGs, no intermittent pauses resulting from sino-atrial blocks or atrioventicular blocks, and neither intermittent interventricular branch block, paroxysmal supraventricular tachycardia nor intermittent atrial fibrillations were detected. Not a single case of sustained ventricular tachycardia, ventricular flutters or ventricular fibrillations was observed.

Even in a clinical study over a long observation period of 52 weeks, no cardiovascular risks were detected when patients were evaluated under concomitant cardiovascular therapy [21]. Because torsades de pointes only seldom occur, some authors state [28] that detection is more accurate under clinical trial conditions than under extended treatment periods or postmarketing surveillance comprising huge patient populations. In this context, a postmarketing surveillance documentation of propiverine including 1,379 patients ≥65 years of age (30.9%) evidenced neither alterations in heart rate nor serious cardiovascular adverse events despite concomitant cardiovascular treatment in

nearly 50% [29]. Moreover, pharmacovigilance of propiverine over more than 15 years (242 million tablets representing 265,000 patient-years) additionally supports the cardiac safety of propiverine under conditions of everyday practice.

To sum up, in the present study a representative group of elderly patients suffering from urgency, urge incontinence and mixed urge-stress incontinence with concomitant cardiovascular medication was examined. Clinical symptoms such as frequency, urgency and urinary incontinence improved both significantly and clinically relevantly under propiverine in comparison with placebo. Despite the proven efficacy of propiverine, no induction of ventricular arrhythmias occurred during 4 weeks of therapy. Signs of ventricular extrasystoles of the Lown classes IVa/b monitored by standard and 24-hour-ECG were randomly distributed. Therefore, a potential risk of life-threatening arrhythmias could be excluded in this study.

In conclusion, propiverine demonstrates a favourable risk-benefit ratio concerning efficacy and cardiac safety in elderly patients with urgency, urge incontinence or combined urge-stress incontinence.

Acknowledgement

The study was kindly supported by an educational grant provided by Apogepha.

References

1 Gardner J, Fonda D: Urinary incontinence in the elderly. Disabil Rehabil 1994;16:140–148.
2 Rosenthal AJ, McMurty CT: Urinary incontinence in the elderly. Postgrad Med 1995;97: 109–121.
3 Wada Y, Yoshida M, Kitani K, Kikukawa A, Ichinose A, Takahashi W, Gotoh S, Inadome A, Machida J, Ueda S: Comparison of the effects of various anticholinergic drugs on human isolated urinary bladder. Arch Int Pharmacodyn Ther 1995;330:76–89.
4 Stöhrer M, Madersbacher H, Richter R, Wehnert J, Dreikorn K: Efficacy and safety of propiverine in SCI-patients suffering from detrusor hyperreflexia – A double-blind, placebo-controlled clinical trial. Spinal Cord 1999;37: 196–200.
5 Madersbacher H, Halaska M, Voigt R, Allousi S, Höfner K: A placebo controlled multicenter study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence. Br J Urol 1999;84:646–651.
6 Andrews NP, Bevan J: Torsades-de-pointes and terodiline. Lancet 1991;338:633.
7 Conolly MJ, Astridge PS, White EG, Morley CA, Campbell Cowan J: Torsades-de-pointes ventricular tachycardia and terodiline. Lancet 1991;338:344–345.
8 Davis SW, Brecker SJ, Stevenson RN: Terodiline for treating detrusor instability in elderly people. Br Med J 1991;302:1276.
9 McCloud AA, Thorogood S, Barnett S: Torsades de pointes complicating treatment with terodiline. Br Med J 1991;302:1469.
10 Thomas HL, Higham PD, Hartigan-Go K, Kamali F, Wood P, Campbell RWF, Ford GA: Concentration dependent cardiotoxicity of terodiline in patients treated for urinary incontinence. Br Heart J 1995;74:53–56.
11 Hussain RM, Hartigan-Go K, Thomas SHL, Ford GA: Effect of oxybutynin on the QTc interval in elderly patients with urinary incontinence. Br J Clin Pharmacol 1996;41:73–75.
12 Ouslander JG: Causes, assessment, and treatment of incontinence in the elderly. Urology 1990;suppl 4:25–36.
13 Resnick NM: Noninvasive diagnosis of the patient with complex incontinence. Gerontology 1990;36(suppl 2):8–18.
14 Lown B, Wolf M: Approaches to sudden death from coronary heart disease. Circulation 1971; 44:130.
15 Chutka DS, Fleming KC, Evans MP, Evans JM, Andrew KL: Urinary incontinence in the elderly population. Mayo Clin Proc 1996;71: 93–101.
16 Johnson TM, Johnson II, Busby-Whitehead J: Diagnostic assessment of geriatric urinary incontinence. Am J Med Sci 1997;314:250–256.
17 Resnick NM, Brandeis GH, Baumann MM, DuBeau CE, Yalla SV: Misdiagnosis of urinary incontinence in nursing home women: Prevalence and a proposed solution. Neurourol Urodyn 1996;15:599–618.
18 Robinson D, McClish DK, Wyman JF, Bump RC, Fantl JA: Comparison between urinary diaries completed with and without intensive patient instructions. Neurourol Urodyn 1996;15: 143–148.
19 Malone-Lee JG, Walsh B, Maugourd MF and the Tolterodine in the elderly study group: The safety and clinical efficacy of two doses of tolterodine, compared to placebo in elderly patients. ICS Abstracts 1997;188:155–156.
20 Dorschner W, Höfner K, Dietrich F, Jacob J: Die Wirkung des Anticholinergikums Mictonorm auf den unteren Harntrakt. 1. Der Einfluss auf die Harnblasenkapazität. Dtsch Gesundheitswesen 1982;37:889–893.
21 Mazur D, Wehnert J, Dorschner W, Schubert G, Herfurth G, Alken RG: Verträglichkeit und Wirksamkeit einer Langzeittherapie mit Propiverinhydrochlorid bei Drangsymptomatik und Dranginkontinenz – Eine multizentrische Studie. Kontinenz 1994;3:17–21.
22 Mazur D, Wehnert J, Dorschner W, Schubert G, Herfurth G, Alken RG: Clinical and urodynamic effects of propiverine in patients suffering from urgency and urge incontinence. Scand J Urol Nephrol 1995;29:289–294.
23 Voigt R, Wehnert J, Blau U, Halaska M, Martan A, Michels W, Voigt P: Langzeitbeobachtung bei medikamentöser Therapie der Drang-Symptomatik der Frau. Kontinenz 1993;2: 125–127.
24 Dorschner W, Jacob J, Höfner K, Dietrich F: Die Wirkung des Anticholinergikums Mictonorm auf den unteren Harntrakt. 2. Klinische Wirkungen – Untersuchungen zur Ermittlung der Indikation. Dtsch Gesundheitswesen 1982; 37:950–952.
25 Wallander MA, Dimenas E, Svardsudd K, Wiklund J: Evaluation of three methods of symptom reporting in a clinical trial of felodipine. Eur J Clin Pharmacol 1991;41:187–196.
26 The assessment of the potential for QT interval prolongation by noncardiovascular medicinal products. CPMP Guideline 1997, p 986–996.
27 Haruno A, Kanda A, Tajima K, Yoshimura Y, Miyake H: General pharmacology of propiverine hydrochloride (P–4). 1. Effects on respiratory, circulatory and other organ systems. Pharmacomimetrics 1989;37:447–456.
28 Thomas SHL: Drug-induced QT interval prolongation. Br J Clin Pharmacol 1996;42:399–404.
29 Siegert J, Schnabel F, Schubert G, Stölzner W: Efficacy and tolerance of propiverine hydrochloride – an anticholinergic with calcium channel modifying properties – in patients with and without urinary tract disorders. 11th Biennal Meet Int Soc Upper Urinary Tract, Patras, 1996.