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# Ocular safety of propiverine hydrochloride in elderly patients with primary open- and narrow-angle glaucoma

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**Key words**
propiverine – overactive bladder – glaucoma – ocular safety

**Abstract.** Background: Propiverine hydrochloride (P4) is an antimuscarinic drug used in overactive bladder syndrome. Methods: Two studies were performed: one in 24 patients with open-angle glaucoma (OAG) treated with topical β-blockers, one in 24 patients with narrow-angle glaucoma (NAG) treated with pilocarpine ± topical β-blockers. Patients were treated in randomized, placebo-controlled, double-blind parallel-group fashion (15 : 9 attribution to P4 vs. placebo (PL)). Treatments: Single-blind PL dose in the morning of day 1 for baseline; double-blind 15 mg P4 or matched placebo t.i.d. from the afternoon of day 1 until the morning of day 7. Results: In the morning of day 7, trough mean serum P4 concentrations were 169.4 ng/mL (CV (coefficient of variation): 0.55) and 140.7 ng/mL (CV: 0.56) in OAG and NAG; at 3:15 hours after dosing: 237.4 ng/mL (CV: 0.47) and 212.4 ng/mL P4 (CV: 0.38), respectively. P4-treatment led to a prompt (OAG) or more gradient (NAG) increase in pupil diameter (PUD), with a maximum difference from PL of 0.97 mm (95% confidence interval (CI): 0.67 – 1.27) and 0.87 mm (95% CI: 0.36 – 1.39) in OAG and NAG, respectively. However, there was no average increase in intraocular pressure (IOP) or increase in noteworthy safety-relevant individual IOP values (or changes thereof). There was no effect on visual acuity or accommodation. Conclusions: 1-week treatment with P4 appeared to be safe 1) in OAG patients treated with topical β-blockers and 2) in NAG patients treated with topical pilocarpine ± β-blockers, irrespective of whether the eyes had previously been treated with glaucoma surgery or laser therapy.

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## Introduction

Propiverine HCl (2,2-diphenyl-2-(1-propoxy)-acetic acid-(1-methyl-piperid-4-yl)-ester-hydrochloride; CAS-Registry-N° 54556-98-8) is a benzilic acid derivative with calcium-modulating and antimuscarinic properties that is beneficial and effective in the treatment of overactive bladder syndrome (OAB) and neurogenic detrusor overactivity (NDO).

Among the treatment options for OAB [1, 2, 3, 4], medications with antimuscarinic properties assume a predominant position. Five molecularly-distinct muscarinic receptor subtypes have been identified: $M_1$, $M_2$, $M_3$, $M_4$, and $M_5$, and many tissues contain mixed populations of different receptor subtypes [5]. The urinary bladder contains both $M_2$ and $M_3$ receptors, constituting ~ 80% and 20% of its total muscarinic receptors, respectively [6, 7]. In the bladder, the $M_3$ subtype is generally considered to be the main mediator site of the beneficial responses of anticholinergic medication in OAB, but there is increasing evidence that $M_2$-modulation might play an important role as well [8]. $M_3$ is present not only in the bladder but also in the salivary glands, colon, and the eyes.

Although generally considered quite efficacious, there are limitations to the use of anticholinergic drugs in OAB because of pharmacological extension effects, i.e., untoward anticholinergic effects in nonurological organ systems; these might affect the gastrointestinal tract (e.g., dyspepsia, constipation, nausea), cardiovascular system (e.g., tachycardia, palpitations), central nervous system (e.g., somnolence, dizziness, cognitive impairment), and vision (e.g., blurred vision due to impaired accommodation). This risk has led to regulatory restrictions in terms of contraindications and special warnings, cautionary statements and provisions, also with regard to

the ocular safety of these compounds and their use in patients with "glaucoma" in particular.

The studies reported here were carried-out off-label to evaluate the ocular safety (primary outcome), overall safety and tolerability, and pharmacokinetics (secondary outcome) of a steady-state, 1-week treatment with repeated oral doses of propiverine HCl in patients with open-angle (OAG) and chronic narrow-angle glaucoma (NAG) who were not affected by OAB.

## Methods

Two studies were conducted with the same methodology, one in patients with primary open-angle glaucoma (OAG, study I), and one in patients with chronic narrow-angle glaucoma (NAG, study II). The study in NAG was conducted after uneventful conclusion of the study in OAG. The protocol, subject information, and informed consent form of both studies were reviewed and approved by an independent ethics committee and the competent authorities. The studies were planned, conducted, analyzed, and reported in accordance with the principles of Good Clinical Practice, the Declaration of Helsinki and the provisions for the orderly conduct of clinical trials in the country of conduct.

### *Study subjects*

The trial participants were screened from the patient pool of the Dept. Glaucoma and Anterior Segment Surgery, Clinic of Eye Diseases, University Hospital "Alexandrovska", Medical University of Sofia, Sofia, Bulgaria.

In order to be eligible, the patients had to provide informed consent before the start of any trial-related procedure.

In study I, all patients suffered from primary bilateral OAG diagnosed at least 3 months before and presented without previous surgery. Eligible patients were to have an intraocular pressure (IOP) for each eye < 22 mmHg.

In study II, the patients suffered from primary chronic narrow- or closed-angle glaucoma (NAG) diagnosed at least 3 months before. Only in 21/48 eyes had there been previous surgery or laser intervention for NAG. Eligible patients were to have an IOP for each eye < 22 mmHg. All eyes were treated with topical pilocarpine (mostly one 1% drop in each eye 3 times daily).

In both studies, patients with confounding comorbidity or comedication were excluded from enrolment.

Participating patients received fair reimbursement of the costs incurred for participating in the trial.

### *Study setting*

The treatments and the investigations thereof took place whilst the patients were hospitalized at the phase I-II study clinic of the Dept. Clinical Pharmacology & Therapeutics, UMHAT "Tsaritsa Yoanna-ISUL", Medical University of Sofia, Sofia, Bulgaria.

### *Study design*

Each study was carried-out as a prospective, randomized, placebo-controlled, double-blind parallel-group trial evaluating the ocular and systemic safety and tolerability of repeated doses of propiverine hydrochloride in patients with primary OAG (study I) and NAG (study II).

### *Trial medications and treatments*

In each study, 24 patients were enrolled and assigned at random to treatment with propiverine or placebo (15 : 9 attribution) in an investigator- and patient-blinded fashion. Computer-generated lists of random numbers were used for random allocation of individual supplies to trial participants in blocks of 4 (per study). The lists were generated by a third party not otherwise involved in the study procedures. Matched supplies of active and control medication were used. Individualized medication boxes were packed and numbered for each participant according to the randomization plan. Each participant was assigned by the investigator at random to one of the treatment numbers allocated to the site in the order of admission for hospitalization and was only treated with the materials of the corresponding medication pack. Throughout the study until formal closure of the database, the randomization codes were known only to the central site processing the medication supplies. Investigators, trial staff, outcome assessors (including

ocular and general safety assessments), quality control monitors, data entry staff, data analysts, and trial participants were blinded with regard to treatment assignment. The blind was lifted formally only after all data had been collected and verified such that the databases could be closed; any subsequent change to the data was to be trailed; no such changes after closure of the database occurred. Bioanalytical data were only released to the data center after closing of the databases.

In both studies, all patients first received a placebo dose on the morning of day 1 in single-blind fashion in order to establish and characterize an appropriate baseline. Subsequently, the patients were treated in double-blind fashion with the randomly allocated medication from the afternoon of day 1 to the morning of day 7 according to a t.i.d regimen (18 doses). Active medication consisted of repeated doses of 15 mg propiverine HCl (immediate-release formulation – Mictonorm®, APOGEPHA Arzneimittel GmbH, Dresden, Germany, batch N° 009 039) 3 times daily. Propiverine or matched placebo (batch N° 807 047) were administered at 08:00, 16:00, 24:00 o'clock ± 1 hour. On day 1, the afternoon dose was to be administered after completion of all baseline tests after a single-blind morning placebo dose. Morning doses on days 1, 2 – 7 were to be administered after an overnight fast and rest. The evening dose of day 6 was administered exactly 8:00 hours before the profiling morning dose the next day. Medications were administered with 100 mL tap water at room temperature. The subjects remained fasted up to 0:30 hour after the morning dose, when a standardized light breakfast was served; further meals were served at 4:00, 7:00, and 10:00 hours after morning dosing.

## Ocular test methods, blood pressure, and pulse rate

On days 1 and 7, ocular tests of each eye were carried out before (–0:45 hours) and at 2:50, 5:50, and 7:50 hours after the morning dose; additionally, these tests were performed on the morning of day 2 – 6 starting at 2:50 hours after dosing; the ocular tests consisted of the following (in sequence of conduct): 1) measurement of the pupil diameter (PUD-Pupilscan II® Model 12A Keeler Instruments Inc., Broomall, PA, USA), 2) correction for best vision at distance (with stepwise corrections (dioptry, sphere, cylinder)), 3) visual acuity with the best correction for vision at distance, 4) accommodation (difference between the best and the minimal dioptric corrections for near vision), and 5) the intraocular pressure (IOP by applanation tonimetry – Perkins device – in sitting position after a sitting rest of at least 5 min and after local anesthesia with Novesin® instillation). Sitting blood pressure (systolic and diastolic blood pressure (SBP/DBP)) and pulse rate (PR) were measured each time after completion of the ocular tests.

## Pharmacokinetic sampling and drug assay

Blood samples for the determination of propiverine HCl (P4) and its main metabolite (P4NO) in serum were taken prior to dosing on the morning of day 1 (pretreatment blank), day 2 and day 7 (= trough), and at ~ 3:15 hours after morning dosing ($\approx C_{max}$) on study days 2 and 6. The concentrations in serum were determined by means of a validated, sensitive, and specific HPLC (high-performance-liquid-chromatography)-assay (lower limit of quantitation: 15.6 ng/mL).

## Safety assessment and provisions

The studies were conducted under close medical surveillance. The patients were hospitalized in a clinical pharmacology study clinic from the evening of day 0 until the morning of day 9. A qualified ophthalmologist reviewed each patient in the morning and was on call during the entire study. The subjects were to report any untoward change in their condition spontaneously; additionally, they were regularly asked about their wellbeing. The following ocular findings were to be reported as noteworthy: 1) any IOP value ≥ 22 mmHg, 2) any IOP increases > 3 mmHg (relative to the value at the corresponding time on day 1), and 3) any need for an increase of the ocular antiglaucoma baseline medication. Clinical laboratory safety tests (hematology, clinical chemistry, urinalysis) were carried-out at the screening visit and the end-of-trial safety follow-up visit.

Table 1. Main demographic features of the subjects with open-angle glaucoma (OAG – study I) and chronic narrow-angle glaucoma (NAG – study II); data are presented as mean ± SD or number (%).

| Study | OAG: study I | | NAG: study II | |
|---|---|---|---|---|
| Treatment: | Propiverine (P4) | Placebo (PL) | Propiverine (P4) | Placebo (PL) |
| Sex (N, (%)) | 15 (100%) | 9 (100%) | 15 (100%) | 9 (100%) |
| Male | 4 (26.7%) | 3 (33.3%) | 0 (0 %) | 2 (22.2%) |
| Female | 11 (73.3 %) | 6 (66.7%) | 15 (100 %) | 7 (77.8%) |
| Age (year) | 64.13 ± 10.3 | 64.3 ± 11.9 | 64.7 ± 8.8 | 56.3 ± 15.2 |
| Body height (BH, cm) | 164.6 ± 8.0 | 167.9 ± 5.5 | 163.0 ± 7.8 | 163.1 ± 9.5 |
| Body weight (BW, kg) | 76.1 ± 11.5 | 76.1 ± 7.9 | 70.1 ± 10.9 | 69.4 ± 14.3 |
| Broca-index | 1.19 ± 0.17 | 1.13 ± 0.13 | 1.11 ± 0.12 | 1.09 ± 0.12 |

Table 2. Main baseline features of the eye investigations upon recruitment of the subjects with open-angle glaucoma (OAG – study I) and chronic narrow angle glaucoma (NAG – study II); data are presented as mean ± SD or median (range).

| Study: | OAG: study I | | NAG: study II | |
|---|---|---|---|---|
| Treatment: | Propiverine (P4) | Placebo (PL) | Propiverine (P4) | Placebo (PL) |
| Pupil diameter – OD | 4.33 ± 0.81 | 4.22 ± 0.67 | 3.53 ± 1.20 | 3.19 ± 1.31 |
| Pupil diameter – OS | 4.61 ± 1.02 | 4.31 ± 0.62 | 3.39 ± 1.25 | 3.99 ± 2.04 |
| IOP (mmHg) – OD | 18.97 ± 2.52 | 18.50 ± 2.73 | 17.43 ± 3.27 | 16.33 ± 2.54 |
| IOP (mmHg) – OS | 18.00 ± 2.37 | 18.06 ± 2.08 | 17.90 ± 3.09 | 16.22 ± 2.45 |
| Visual acuity – OD | 0.90 (0.20 – 1.00) | 1.00 (1.00 – 1.00) | 0.60 (0.20 – 1.00) | 1.00 (0.40 – 1.00) |
| Visual acuity – OS | 1.00 (0.09 – 1.00) | 1.00 (0.50 – 1.00) | 0.80 (0.30 – 1.00) | 0.40 (0.10 – 1.00) |
| Gonioscopy – OD | 3 (3 – 4) | | 2 (1 – 2) | |
| Gonioscopy – OS | 3 (3 – 4) | | 2 (1 – 2) | |
| cup:disc-ratio – OD | 0.4 (0.2 – 0.9) | | 0.4 (0.2 – 0.6) | |
| cup:disc-ratio – OS | 0.4 (0.2 – 0.8) | | 0.4 (0.2 – 0.6) | |

OD = right eye; OS = left eye.

## *Statistical analysis*

At each time point of evaluation, PUD and IOP were measured twice. The mean of these values was used for the further calculations. For each time point of evaluation under trial medication (day 2 to day 7), the IOP and PUD were time-matched, i.e., expressed as change from the value at the corresponding time on baseline day 1. For each time point of evaluation, estimates were calculated by ANOVA for the mean treatment differences (propiverine minus placebo) of the time-matched IOP and PUD of both eyes (18 observation units for placebo (PL), 30 units for active medication (P4)).

## *Further information*

Further information on the trials, including the trial protocols, can be obtained on request to the corresponding author.

# Results

## *Subjects*

The studies were carried out from May to June 2001 (study I) and February – July 2002 (study II). In each study, 24 Caucasian patients with primary OAG (study I) or NAG (study II) were enrolled. 60 patients were screened for enrolment: 32 in study I (OAG) and 28 in study II (NAG); 48 were confirmed to be eligible, 12 subjects were excluded for the following reasons: patient's decision for personal reasons (n: 4), withdrawing consent (n: 2), being affected by possibly confounding comorbidity (n: 5), taking prohibited comedication (n: 1) or having unsuitable veins (n: All 1). All eligible subjects were randomly assigned to double-blind parallel-group treatment with propiverine or placebo (15 : 9 attribution). No subject was discontinued prematurely. All completed the study for both periods and treatments.

Table 3. *Number of subjects with open-angle glaucoma* (OAG – study I) and chronic narrow-angle glaucoma (NAG – study II) per category of concomitant eye medication and per category of previous glaucoma intervention (OD = right eye, OS = left eye).

| Study: | OAG: study I | | NAG: study II | | | |
|---|---|---|---|---|---|---|
| Treatment: | Propiverine (P4) | Placebo (PL) | Propiverine (P4) | | Placebo (PL) | |
| Concomitant eye medication | | | | | | |
| Ocular pilocarpine | None | None | All | | All | |
| Ocular β-blockers | All | All | 14/15 | | 8/9 | |
| Brinzolamid | 2/15 | None | None | | None | |
| Latanoprost | 1/15 | 1/9 | None | | None | |
| Previous interventions | | | OD | OS | OD | OS |
| No intervention | All | | 8 | 10 | 5 | 4 |
| Laser irodotomy | None | | 3 | 3 | 1 | 1 |
| Surgical trabeculectomy | None | | 4 | 2 | 2 | 4 |
| Laser + surgery | None | | 0 | 0 | 1 | 0 |

The demographic characteristics of the trial populations are detailed in Table 1. The disease features of the two study populations and their distribution across the treatment groups are detailed in Table 2. There were no noteworthy findings on funduscopy in any of the subjects. In study II, most subjects had gonioscopy-score 2 (narrow angle); score 1 (very narrow angle) was recorded for 4 eyes. Concomitant medication that was permitted to be continued throughout the study is summarized in Table 3. In study I (OAG), all patients were treated with topical β-blockers; 2 patients also took brinzolamide and 2 further patients took latanoprost. In study II (NAG), all eyes were treated with 1 drop of 1% pilocarpine at least 3 times daily; all but 2 patients also received topical β-blockers, mostly timolol 0.5% 1 drop in each eye twice daily; none of the NAG-patients took brinzolamide or latanoprost. All medications had been used at the same regimen since at least 1 month before the start of the study, and the regimen was kept unchanged throughout the study.

None of the OAG patients had a previous glaucoma intervention (laser or surgery); 27/48 eyes of the patients with NAG had no previous eye intervention (Table 3).

## *Serum concentrations of propiverine and its main metabolite*

The first dose of the trial medication was administered in the evening of day 1. The serum concentrations of P4 and P4NO before and at 3:00 hours after morning dosing on day 2 (3rd dose) and day 7 (last dose) are summarized in Figure 1A (OAG) and Figure 1B (NAG). There was relatively large between-subject variability. Levels of exposure are comparable with those expected under therapeutic conditions in this population of mainly elderly patients.

## *Effects on pupil diameter (PUD) and intraocular pressure (IOP)*

The time courses of the mean (± s.e.m.) time-matched PUD and IOP-data during the course of the study are shown in Figure 2 (OAG) and Figure 3 (NAG). The estimated treatment differences between P4 and PL are detailed in Table 4.

In the patients with OAG (study I), there was a distinct and consistent increase in pupil diameter under active medication; the effect was statistically significant and largest on the morning of day 6 (estimated difference for P4-PL: 0.99 mm, 95% confidence interval (CI): 0.69 – 1.29); in contrast, there was no rise in mean IOP, and the differences of the mean time-matched values between P4 and PL remained small except on the morning of day 4, when the IOP values for the patients treated with PL were unexpectedly very low (Figure 2) (Table 4).

In the patients with NAG (study II), there was a relatively slow rise in mean PUD, less consistently than in the patients with OAG and with far more baseline scatter (also re-

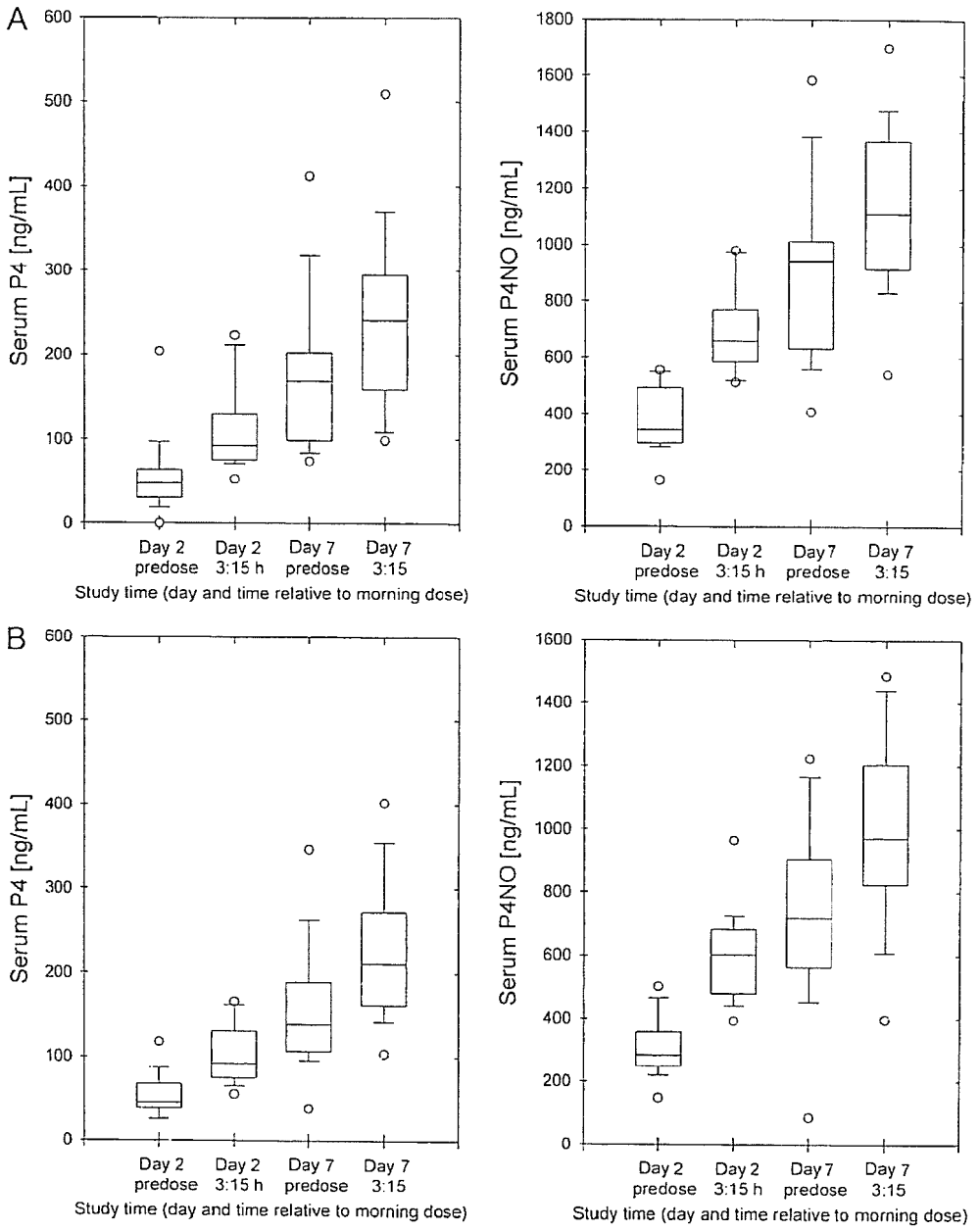


Figure 1. Box-plot of the serum concentrations of propiverine (P4) (left) and its active metabolite P4NO (right) in patients treated with propiverine in study I (OAG, N: 15 – Figure 1A) and study II (ACG, N: 15 – Figure 1B) before and 3:00 h after morning dosing on day 2 (3rd dose) and day 7 (last dose).

flecting the heterogeneity of the population); effects at 2:50 hours after morning dosing of P4 or PL were blunted by the continued use of pilocarpine in the morning, and the effect of P4 was most pronounced either before (day 7/time –0:45: estimated P4-PL difference: 0.83 mm, 95% CI: 0.24 – 1.41) or well after the morning dose of pilocarpine, i.e., at 7:50 hours after morning dosing (P4-PL: 0.87 mm, 95% CI: 0.36 – 1.39). In contrast, the time-matched IOP remained low throughout the P4-medication phase, at a level even lower than seen with PL-treatment.

## *Individual noteworthy findings on IOP*

In both studies, there were very few, mostly isolated, IOP-values exceeding 21 mmHg; in all cases this occurred in subjects with high baseline IOP-values (21 mmHg). In study II (NAG), no values exceeded 22 mmHg. In study I, noteworthy on-treatment values were in the range of 22-22.5 mmHg; 1 value of 23.5 mmHg was recorded in the morning of control day 1 (after placebo administration). There also were very

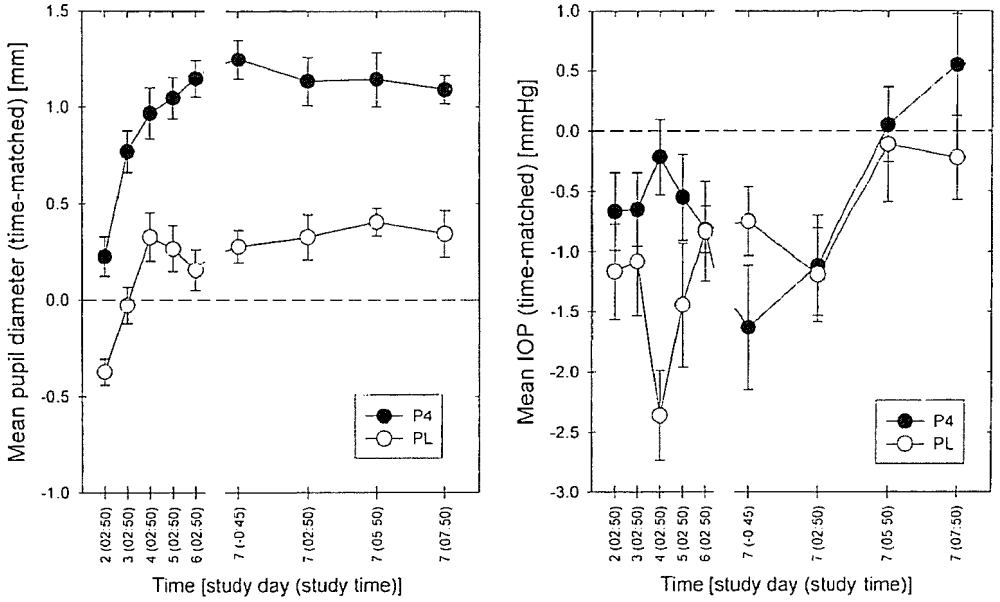


Figure 2. Time course of the arithmetic mean (± s.e.m) pupil diameter (PUD – left) and intraocular pressure (IOP – right) for the patients with primary open-angle glaucoma (study I) treated with propiverine (P4 – 15 patients, 30 eyes) and placebo (PL – 9 patients, 18 eyes) from day 2 to 7; the data are expressed as difference from the values at the corresponding times on baseline day 1 (time-matched).

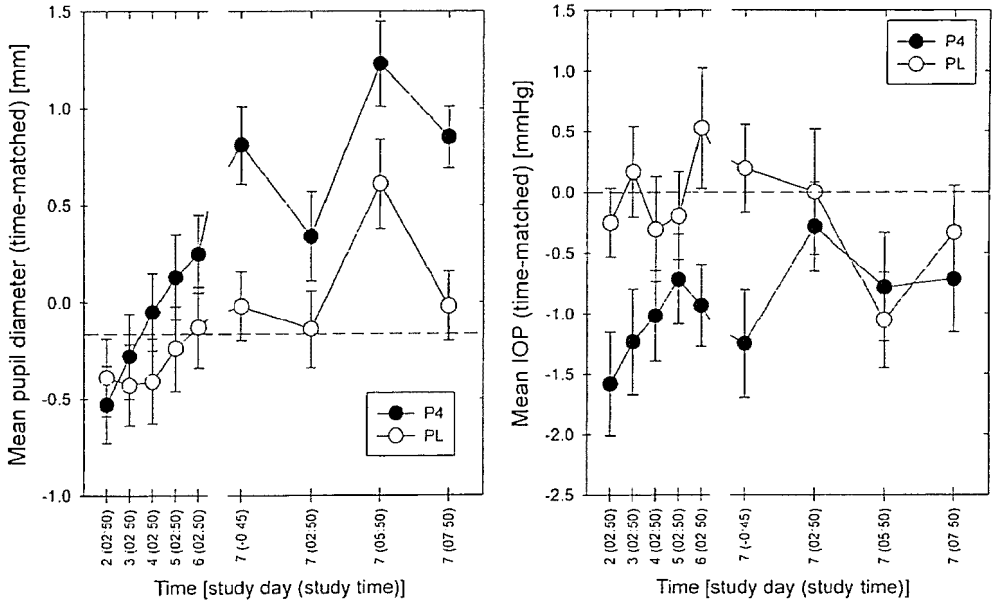


Figure 3. Time course of the arithmetic mean (± s.e.m) pupil diameter (PUD – left) and intraocular pressure (IOP – right) for the patients with primary chronic narrow angle glaucoma (study II) treated with propiverine (P4 – 15 patients, 30 eyes) and placebo (PL – 9 patients, 18 eyes) from day 2 to 7; the data are expressed as difference from the values at the corresponding times on baseline day 1 (time-matched).

few increases in IOP by more than 3 mmHg, generally in patients with low IOP-readings at baseline; in none of these cases such increases led to noteworthy high IOP-levels.

These findings were considered to reflect random IOP-fluctuations, there was no sign that such events were more frequent under treatment with propiverine. None of these events required intervention.

## *Effects on further eye criteria*

There was no evidence or sign of any average or relevant individual regression of visual acuity in the patients treated with propiverine. Furthermore, there was no indication of average or relevant individual changes in best and minimum correction for vision at near (accommodation) or treatment-related differences thereof.

Table 4. Estimated differences (P4-PL) of the time-matched values of the intraocular pressure (IOP, mmHg) and the pupil diameter (PUD, mm) for both eyes in 15 patients treated with propiverine (P4 – 30 eyes) and placebo (PL – 18 eyes); the estimates are presented as the point estimates (PE) and the 95% confidence interval (CI).

| Day: | | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 7 | Day 7 |
|---|---|---|---|---|---|---|---|---|---|
| Time: | | 2:50 | 2:50 | 2:50 | 2:50 | 2:50 | -0:45 | 5:50 | 7:50 |
| OAG: study I | | | | | | | | | |
| IOP | PE | 0.50 | 0.43 | 2.14 | 0.89 | 0.02 | -0.88 | 0.16 | 0.77 |
| | CI | -0.54 to 1.54 | -0.63 to 1.49 | 1.15 to 3.14 | -0.33 to 2.12 | -0.80 to 0.83 | -2.30 to 0.53 | -0.93 to 1.25 | -0.46 to 2.01 |
| PUD | PE | 0.60 | 0.80 | 0.64 | 0.78 | 0.99 | 0.97 | 0.74 | 0.75 |
| | CI | 0.31 to 0.89 | 0.48 to 1.12 | 0.25 to 1.03 | 0.44 to 1.12 | 0.69 to 1.29 | 0.67 to 1.27 | 0.35 to 1.13 | 0.48 to 1.01 |
| NAG: study II | | | | | | | | | |
| IOP | PE | -1.33 | -1.40 | -0.71 | -0.52 | -1.46 | -1.44 | 0.27 | -0.38 |
| | CI | -2.53 to -0.13 | -2.68 to -0.12 | -1.88 to 0.45 | -1.64 to 0.60 | -2.63 to -0.29 | -2.74 to -0.15 | -1.05 to 1.60 | -1.67 to 0.91 |
| PUD | PE | -0.14 | 0.15 | 0.36 | 0.37 | 0.39 | 0.83 | 0.62 | 0.87 |
| | CI | -0.74 to 0.47 | -0.51 to 0.81 | -0.26 to 0.98 | -0.29 to 1.03 | -0.23 to 1.00 | 0.24 to 1.41 | -0.09 to 1.34 | 0.36 to 1.39 |

## *Effects on blood pressure and pulse rate*

Blood pressure and pulse rate were measured at the end of each series of eye tests. There were no differences between the treatments with regard to blood pressure and pulse rate. There was no evidence of increase in pulse rate in the patients treated with propiverine.

## *Safety and tolerability*

In study I, there were 25 adverse events (AE) in 13/24 (54.2%) subjects: 13 AEs in 7/15 (46.7%) patients treated with P4 and 12 AEs in 6/9 (66.7%) patients treated with PL. All AEs were considered as "mild". None were considered serious. AEs were mostly considered either probably or possibly treatment related. Headache and dry mouth were the most prominent findings. Headache was reported in three instances, all under treatment with P4. Dry mouth was reported by 7/9 and 5/15 of the patients treated with PL and P4, respectively. Blurred vision was reported by 1 patient from each treatment group.

In study II, there were 15 AEs in 12/24 (50%) subjects: 12 AEs in 9/15 subjects (60%) treated with P4 and 3 AE in 3/9 (33%) subjects treated with PL. The AEs were mostly considered as "mild". None were considered severe or serious. AEs were mostly considered either probably or possibly treatment related. Dry mouth was the most prominent finding, occurring in 9/15 subjects treated with P4 and in none of the patients treated with PL. Blurred vision was reported by 1 patient treated with P4.

In none of the cases was action to be taken with regard to the study medication (dose reduction or discontinuation). All of the AEs had recovered completely by the end-of-trial visit.

None of the AEs were related to the safety lab tests or changes thereof. There was no evidence or indication of clinically-relevant safety laboratory data changes during the course of the study and/or of treatment effects in this regard.

# Discussion

Antimuscarinic drugs have a well-established mydriatic effect ("belladonna" effect). Additionally, mydriatic antimuscarinic

Table 5. Number of subjects (in brackets: number of events) with noteworthy IOP events (IOP ≥ 22 mmHg and/or increase in IOP > 3 mmHg) by study (OAG = open-angle glaucoma; NAG = chronic narrow-angle glaucoma), treatment (P4 = propiverine, PL = placebo) and eye exposed (OD = right eye, OS = left eye).

| Study: | OAG: study I | | | | NAG: study II | | | |
|---|---|---|---|---|---|---|---|---|
| Treatment: | Propiverine (P4) | | Placebo (PL) | | Propiverine (P4) | | Placebo (PL) | |
| Eye: | OD | OS | OD | OS | OD | OS | OD | OS |
| Exposure | | | | | | | | |
| Number of eyes exposed | 15 | 15 | 9 | 9 | 15 | 15 | 9 | 9 |
| IOP ≥ 22 mmHg | | | | | | | | |
| Under placebo (day 1 – AM) | 2 (2) | 0 | 0 | 0 | 0 | 3 (3) | 0 | 0 |
| Under trial medication | 2 (6) | 0 | 1 (1) | 1 (3) | 1 (2) | 1 (1) | 0 | 0 |
| Exclusively under trial medication | 0 | 0 | 1 (1) | 1 (3) | 1 (2) | 0 | 0 | 0 |
| Increase in IOP > 3 mmHg | | | | | | | | |
| Under trial medication | 1 (1) | 2 (4) | 1 (1) | 0 | 1 (3) | 2 (3) | 1 (4) | 1 (2) |
| Increase in IOP > 3 mmHg and IOP ≥ 22 mmHg | | | | | | | | |
| Under trial medication | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Number of subjects (number of events). IOP = intraocular pressure.

drug effects are known to impair/relax visual accommodation (cycloplegia) resulting in blurred vision and difficulties with reading or performing close work (reduction of near vision acuity). Often, these mydriatic and cycloplegic properties are considered to constitute a particular risk for patients with "glaucoma". However, studies that are confined to investigating accommodation in young healthy subjects [8, 9] are poorly predictive of the visual safety in patients at risk, in particular those with glaucoma.

In contrast, the present study investigated the ocular safety of a 1-week treatment regimen with propiverine hydrochloride, a well-known antimuscarinic drug to treat overactive bladder, in patients with chronic glaucoma. However, there is need for differentiation between open-angle (OAG), on the one hand, and narrow- (NAG) or closed-angle glaucoma (also termed "angle-closure glaucoma" i.e., ACG), on the other: generally, OAG is a chronic progressive condition that is not predisposed to acute exacerbations, whereas ACG, in contrast, has a high propensity of acute attacks if untreated. Although both are related to an increased IOP, OAG and ACG have a distinctly different pathophysiology, and ACG, but not OAG, is mechanistically sensitive to pupil dilatation as a potential trigger of a pupillary block.

Therefore, two studies were carried out: one in patients with chronic OAG and one in patients with ACG. In both patient groups, the investigational treatment regimen yielded therapeutically-relevant systemic levels of propiverine and its active metabolite. In both patient groups, this was associated with an increase in pupil diameter, albeit more distinctly in patients with OAG; in patients with ACG, the rise in PUD over the first days of the investigational treatment appeared to have been blunted by the baseline treatment with pilocarpine. Neither in patients with OAG nor in patients with ACG was the investigational treatment with propiverine associated with glaucoma attacks or with a need to increase baseline medication with either ocular β-blockers (OAG-patients) or pilocarpine ± β-blockers (ACG-patients). Additionally, there were no adverse effects on visual acuity or visual accommodation.

It may be argued that previous laser or surgery interventions might have reduced the risk of acute glaucoma attacks in the present trial population. However, none of the OAG patients and only 21/48 eyes of the ACG patients had a previous eye intervention. Accordingly, the risk carried by the trial population was relevant, and a further increase of this baseline risk by only including patients without any previous intervention would have been medically-ethically unreasonable. It may also be argued that baseline treatment with topical pilocarpine as practiced in all ACG, but none of the OAG patients, might have concealed ill effects caused by the investigational treatments. Withdrawal of the existing treatment with pilocarpine would have put the patients at medically-ethically unreasonable risk; in addition, although the early rise in pupil diameter was blunted in the NAG patients, there still was a quite distinct rise in pupil diameter

over the later course of the study without any ill effect, although none of the doses of pilocarpine had to be increased.

Low $M_2$ : $M_3$ muscarinic selectivity [8] and reduced pharmacokinetic peak-to-trough fluctuation have been reported to reduce the impact of antimuscarinic OAB drugs on visual accommodation [9]. Since propiverine has little $M_2$ effect and since an immediate-release formulation of propiverine HCl was used, possible differential properties of propiverine on ocular safety are more likely explained by its ancillary smooth muscle relaxing actions unrelated to its antimuscarinic effects.

In conclusion, treatment with propiverine HCl at doses of 15 mg 3 times daily appeared to be safe 1) in patients with established stable primary open-angle glaucoma treated with topical β-blockers, and 2) in patients with primary chronic narrow-angle glaucoma treated with topical pilocarpine ± β-blockers, irrespective of whether the eyes had previously been treated with glaucoma surgery or laser therapy.

The number of subjects studied was small, the treatment duration was short, and the patients were kept under close surveillance at a specialized phase I – II study clinic. Additionally, conclusions drawn from the investigations need to be seen in the perspective that the participating patients already had a well-established diagnosis of either OAG or NAG and were receiving medication accordingly. Therefore, these findings do not mitigate the need for appropriate surveillance of patients with glaucoma who are considered to be eligible for treatment of OAB with propiverine.

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## Conflicts of interest

There are no competing interests to declare. The trial reported in the present publication was sponsored by APOGEPHA Arzneimittel GmbH, Kyffhäuserstrasse 27, D-01309 Dresden, Germany. C. de Mey was responsible for the design of the trial, its coordination, the evaluation of the data, and the present publication. E. Gatchev and N. Petkova were the responsible investigators also overseeing the entire trial including the preparation and review of the present publication. C. de Mey, E. Gatchev, and N. Petkova were remunerated by the sponsor for their services provided with regard to the orderly planning, conduct, and reporting of the trial. M. Braeter was the sponsor representative who provided important contributions to the design, analysis, interpretation, and reporting of the trial. At no time did the sponsor unduly influence the data presented here or the conclusions drawn from them.

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