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TOPIC PAPER

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Efficacy, tolerability and safety profile of propiverine in the treatment of the overactive bladder (non-neurogenic and neurogenic)

Abstract Propiverine hydrochloride (propiverine) is a compound that has neurotropic and musculotropic effects on the urinary bladder smooth muscle. Controlled clinical trials have shown its effectiveness in treating detrusor hyperreflexia and in treating patients with symptoms of an overactive bladder; this is true not only for adults but in children and the elderly as well. European and Japanese studies have also documented that propiverine is well tolerated. It is better tolerated than oxybutynin (particularly in regard to frequency and severity of dryness of the mouth). In several Japanese studies authors demonstrated that propiverine is well tolerated on a long-term basis. Voigt reported an adverse event incidence rate of 13% in a follow-up investigation during 10 years of treatment. A post-marketing drug surveillance consisting of 4390 patients provided additional data concerning efficacy and safety of propiverine. It is one of the few drugs recommended for the treatment of detrusor overactivity by the Committee on Pharmacological Treatment during the First International Consultation on Incontinence.

Key words Propiverine · Overactive bladder · Efficacy · Tolerability · Safety

According to the results of the recent European Overactive Bladder Survey, 17% of the 16 776 people interviewed were affected by symptoms attributable to an overactive bladder [42]: 14% reported frequency, 9% urgency and 6% urge incontinence. The treatment for these overactive bladder (OAB) symptoms is based on training programs (bladder drill) and pharmacotherapy.

Propiverine hydrochloride (referred to in the following as propiverine) is one of the few drugs recommended for treating detrusor overactivity by the Committee on Pharmacological Treatment, chaired by K.E. Andersson, during the First International Consultation on Incontinence [5].

European [20] and Japanese [17] reviews published so far have focused on treating symptoms of the OAB in the elderly [66] and on treating detrusor hyperreflexia [33].

However, this review deals comprehensively with the following aspects of propiverine: (1) pharmacology and pharmacokinetics, (2) efficacy, (3) tolerability, (4) safety, (5) post-marketing drug surveillance (PMS) and (6) summary and future perspectives.

The most important clinical studies cited are graded according to the levels of evidence as proposed by the Canadian Task Force on the Periodic Health Examination [8], implemented by the American College of Obstetricians and Gynecologists and recently adopted by the National Health Service Reasearch Development Centre.

Due to the fact that propiverine was launched in Japan in 1993 and is the most frequently prescribed anticholinergic drug there, studies conducted in Japan have been included in this review.

Pharmacology and pharmacokinetics

Propiverine hydrochloride, a benzilic acid derivative, is a compound that has neurotropic and musculotropic effects on the urinary bladder smooth muscle.

After being administered orally, propiverine is rapidly and almost completely absorbed [18]. The absolute bioavailability of 15 mg propiverine, when administered orally, amounts to 40%. Propiverine's bioavailability does not depend on food intake. It undergoes an extensive first-pass effect, whereby it is rapidly metabolised

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in humans and animals. The main site for metabolic degradation of propiverine is the liver. Three major metabolites could be detected quantitatively in human serum and propiverine N-oxide is the main metabolite [18, 76].

The plasma protein binding of propiverine amounts to approximately 90%, whereas the major metabolites are bound to about 60% to plasma proteins [41]. Repeated oral dosages within the therapeutic range (e.g. 20 mg b.i.d. [15]) led to a steady state mean trough level of about 60 ng/ml in healthy volunteers after 4–5 days.

Recent results revealed a mean terminal elimination half-life of about 15 h [12]. A remission of clinical effect can be expected within 4–5 days following withdrawal of the drug. Despite the low-renal clearance below 1 ml/min for propiverine and its main metabolite propiverine N-oxide [21], drug accumulation does not occur after long-term treatment.

Several radioligand binding studies demonstrated propiverine's affinity for muscarinic receptors. But it had a significantly lower affinity for the cardiac M_2 receptors than routine reference drugs [44]. Studies with urinary bladder strips of various species showed how propiverine has an inhibiting effect on acetylcholine-induced contraction (anticholinergic/neurotropic effect) [55]. Furthermore, a dosage-dependent effect on KCl-induced contraction (spasmolytic/musculotropic effect) was observed [29]. Propiverine was as effective as a combination of atropine and nifedipine in blocking the electrical stimulation of rabbit urinary bladder strips (Fig. 1 [28]). This finding indicates that atropine-resistant, but nifedipine-sensitive, smooth muscle contractions are inhibited. However, higher concentrations were required [28].

Propiverine was also observed to interact directly with calmodulin and thereby caused the activity of actomyosin ATPase to be inhibited, which also resulted in the smooth muscle of the urinary bladder relaxing [35].

The effect of propiverine on the urinary bladder was investigated in various animal species. In the dog, propiverine increased maximum bladder volume and showed inhibitory effects on electrically-induced periodic contractions of the detrusor [27]. In the rat, maximum bladder volume also increased significantly 49].

Recently, in a validated animal model that used the Göttingen mini-pig, the influence of propiverine on the detrusor smooth muscle during the stimulation of bladder contractions by sacral anterior root stimulation (SARS) and on electrically-induced salivation, on blood pressure and heart rate were evaluated and compared to those of tolterodine [57]. Propiverine reduced the maximum bladder pressure during SARS as efficiently as tolterodine (Fig. 2). The effects on salivation will be reported in the section on tolerability.

In summary, pharmacodynamic investigations showed anticholinergic and additional effects on calcium influx and calcium homeostasis in urinary bladder preparations, thus proving the dual mode of action of propiverine in relaxing detrusor smooth muscle.

Efficacy

According to Abrams and Wein [2] "the overactive bladder is a medical condition referring to the symptoms of frequency and urgency, with or without urge incontinence. Roughly half of the people with these symptoms also suffer from urge incontinence, when appearing in the absence of local pathological or metabolic factors that would account for these symptoms". In contrast to this terminology, which is based on clinical symptoms only, according to the International Continence Society (ICS [1] detrusor overactivity can only be defined by urodynamics. The following terminology is applied: "detrusor instability" is used for detrusor overactivity without evident neurological reason and "detrusor

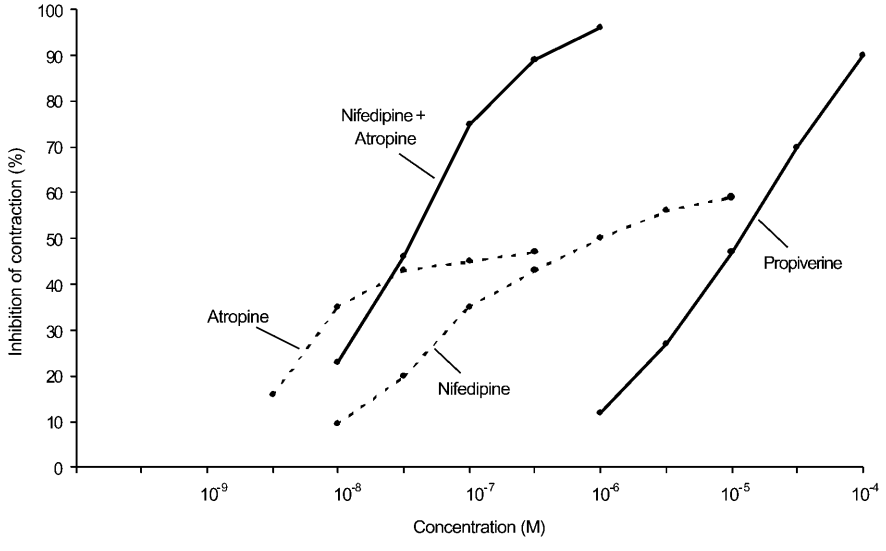

Fig. 1 Inhibition of detrusor contraction (%) by atropine, nifedipine, atropine and nifedipine compared to propiverine according to Kaneko and Nakano (From [28])

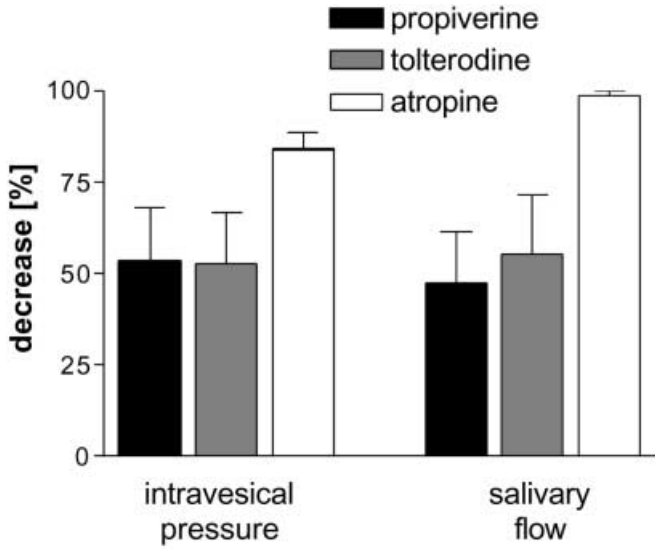

Fig. 2 Relative inhibitory effects (mean ± SEM) of propiverine and tolterodine on intravesical pressure and salivary flow derived from a standardized model of in-vivo investigations according to Scheepe et al. (From [57]). Atropine was used as internal standard

hyperreflexia'' is used for detrusor overactivity due to an overt neurological reason. From the clinical point of view, detrusor hyperreflexia is an entity of its own. Studies focussing on detrusor hyperreflexia are therefore presented separately.

Evaluating anticholinergic effects are still under discussion. Some favour improving symptoms and quality of life as outcome measures [36], others favour at least, additional urodynamic data [1]. However, in this regard one has to differentiate between patient groups. For those suffering from detrusor hyperreflexia, pharmacotherapy's goal is not only to control incontinence, but also to achieve an intravesical low-pressure situation, which is only measurable by urodynamics. On the other hand, the primary purpose for those suffering from OAB is to attain continence, which can be evaluated by micturition charts.

Efficacy in detrusor hyperreflexia

Detrusor hyperreflexia is mainly due to suprasacral spinal or suprapontine cerebral lesions. In suprasacral spinal lesions detrusor hyperreflexia is mostly combined with detrusor-sphincter-dyssynergia. These patients consequently suffer from reflex incontinence as well as from unbalanced voiding. The objective of treating this particular group of patients is therefore to achieve continence and balanced voiding. The therapy of choice is pharmacological detrusor relaxation to eliminate reflex incontinence, which is very often combined with intermittent catheterization to achieve balanced bladder emptying. A suitable drug for detrusor hyperreflexia should increase functional bladder capacity and decrease detrusor contractility.

In a placebo-controlled, double-blind, randomised, prospective, multicentre trial [A1a Systemic review (with homogeneity) of randomised clinical trials, that reflects the highest level of evidence and, therefore, has the highest rate of recommendation.] Stöhrer et. al. [60] evaluated the efficacy and tolerability of propiverine (15 mg t.i.d.) as compared to a placebo in 113 patients suffering from detrusor hyperreflexia caused by spinal cord injuries. The treatment period of 14 days was comprised of visits at baseline (V 1) and after 14 days of treatment (V 2). The majority of patients practised intermittent catheterisation to empty their bladders. The maximum cystometric bladder capacity increased significantly in the propiverine group, on average by 104 ml (V 1: 262 ± 132 ml. V 2: 336 ± 143 ml, $P < 0.001$). Furthermore, the increase in bladder capacity at the first contraction and the decrease in maximum detrusor pressure were also statistically significant. Residual urine increased by 37 ± 71 ml in the propiverine group, significantly more than in the placebo group ($P = 0.01$), thus reflecting the therapeutically desired effect of detrusor relaxation. In agreement with these favourable urodynamic results, 63% of the patients expressed a positive improvement of their symptoms under propiverine in comparison to only 23% of those in the placebo group.

Comparable results in detrusor hyperreflexia using different propiverine dosages were reported by Mazur [38]. The results are presented in the section of this paper discussing dosage-optimising studies.

Further evidence of the effectiveness of propiverine in detrusor hyperreflexia was presented by Iwatsubo et al. [24] and Takayasu et al. [64]. Takayasu conducted a double-blind, placebo-controlled multicentric study on 70 neurogenic patients. During a treatment period of 14 days, 20 mg propiverine or a placebo was administered once daily. An increase of maximum bladder capacity, a decrease of maximum detrusor pressure and an increase of residual urine were obtained in this Japanese study as well, all of which were statistically significant compared to the placebo.

Propiverine is also effective in treating children who suffer from detrusor hyperreflexia resulting from dysraphic disorders. In a case-controlled retrospective study, Grigoleit et al. [14] reported that in 27 patients (age range 2.3–19 years) with myelomeningocele, maximum cystometric bladder capacity increased from 143.8 ± 97.3 ml to 263.0 ± 120.2 ml ($P = 0.000139$); maximum detrusor pressure decreased from 60.5 ± 44.6 cm H_2O to 33.2 ± 21.2 cm H_2O ($P = 0.0056$); and compliance increased from 7.5 ± 8.0 ml/cm H_2O to 18.3 ± 13.1 ml/cm H_2O ($P = 0.00086$). In 15/27 patients, previous anticholinergic medication (oxybutynin or trospium chloride) was not successful. However, 25/27 patients benefitted from propiverine in this series.

These studies showed that propiverine is effective in treating detrusor hyperreflexia in adults and children because it increases functional bladder capacity and decreases detrusor pressure. Thus, a low-pressure situa-

tion in the bladder is created. Continence can be achieved, mostly in combination with intermittent catheterisation.

Efficacy in patients with symptoms of the OAB

According to the definition by Abrams and Wein [2], patients included in the following studies suffered from symptoms of OAB, such as frequency, urgency and urge incontinence. However, according to the ICS definition [1] these symptoms might either be caused by detrusor overactivity (motor urge) or by detrusor hypersensitivity (sensory urge). Consecutively, the patient populations in these studies are more heterogeneous. Furthermore, Bayliss et al. [6] postulated about the existence of both a muscarinergic and a purinergic component for neurotransmission in the unstable, but not in the hyperreflexive, bladder. This might be one of the reasons as to why anticholinergics in general are more effective in treating detrusor hyperreflexia as compared to treating bladder instability.

The effectiveness of propiverine (15 mg t.i.d.) in patients with frequency, urgency and urge incontinence was investigated and compared to oxybutynin (5 mg b.i.d.) and a placebo in a randomised, double-blind, multicentre clinical trial by Madersbacher et al. [34] [A1a Systemic review (with homogeneity) of randomised clinical trials, that reflects the highest level of evidence and, therefore, has the highest rate of recommendation.] Some 366 patients (149 took propiverine, 145 oxybutynin and 72 placebo) were included. Effectiveness was assessed by micturition charts and urodynamics before (V 0) and after 4 weeks of treatment (V 4). The decrease in the frequency of micturition was more pronounced with propiverine and oxybutynin when compared to the placebo. Episodes of urgency decreased more with propiverine and oxybutynin than with the placebo. However, these results did not achieve a statistical significance.

These remarkable clinical effects are also reflected in the urodynamic results. There was a statistically significant increase in the maximum cystometric bladder capacity for propiverine (V 0: 222 ± 77 ml; V 4: 311 ± 125 ml; an increase of 89 ± 108 ml) and oxybutynin (V 0: 226 ± 75 ml; V 4: 322 ± 123 ml; an increase of 96 ± 106 ml) when compared to the placebo (V 0: 211 ± 77 ml; V 4: 263 ± 93 ml; an increase to 52 ± 92 ml). The cystometric bladder capacity to void at first desire increased under propiverine (V 0: 93 ml; V 4:160 ml) and oxybutynin (V 0: 89 ml; V 4: 160 ml), whereas only minor alterations resulted with the placebo (V 0: 93 ml; V 4: 120 ml). The global assessment of efficacy by means of voiding diaries and urodynamics proved that propiverine and oxybutynin were comparably efficient and that both were significantly superior when compared to the placebo.

Two more prospective randomised trials were performed in a crossover study design to compare the efficacy of propiverine to that of oxybutynin [74] and flavoxate [73]. Propiverine and oxybutynin were found to be at least equally effective with regard to detrusor pressure and maximum cystometric bladder capacity. Moreover, propiverine was superior to flavoxate and the placebo with respect to various clinical and urodynamic parameters. Another comparative trial conducted in Japan by Takayasu et al. [63] confirmed these results with regard to flavoxate. Flavoxate has not been recommended at the first International Consultation on Incontinence [5] because its effectiveness has not been proven by randomised clinical trials so far.

Although the number of patients and the study design in some of the cited studies do not fulfil present-day criteria, they support the findings of randomised clinical trials that propiverine is equieffective to oxybutynin in patients with symptoms of the overactive bladder and clearly superior to placebo.

Efficacy in patients with symptoms of OAB after transurethral resection of the prostate (TUR-P)

Symptoms of the OAB after surgical procedures in the lower urinary tract, especially after TUR-P, are frequent [58]: 52% of patients experience urgency, 32% urge incontinence and 60% involuntary detrusor contractions.

Park et al. [53] studied the effects of 4 weeks of propiverine treatment (20 mg once daily) on frequency, urgency and urge incontinence episodes, which showed an improvement in 70.8% of the patients. However, the study is not placebo-controlled, so spontaneous remissions cannot be differentiated from pharmacological effects. In a placebo-controlled study, propiverine was given for the first 10 days postoperatively; 80% of the patients showed an increased bladder capacity with 60 mg propiverine and 60% of the patients improved with 30 mg propiverine, compared to 33% of the placebo-treated patients [9].

The lack of placebo control, the limited number of patients enrolled, the fact that no distinctions were made between persistent and de novo symptoms [53] and a rather short treatment period [9] do not allow evidence-based conclusions. However, clinical experience has shown the beneficial effects of anticholinergics, including propiverine, for patients with symptoms of the OAB after TUR-P.

Propiverine in the elderly

Incontinence in the elderly is predominantly related to detrusor dysfunction. This occurs because of defective cerebral control mechanisms and degenerative changes in the detrusor morphology and consequently results in frequency, urgency and urge incontinence symptoms. Continence training programs, mostly in combination with pharmacotherapy, are the keys to success.

The efficacy of propiverine in the elderly was shown by Dorschner et al. [10]. Ninety-eight patients (67.7 ± 6.3 years of age) suffering from urgency, urge incontinence or mixed urge-stress incontinence were included in this double-blind, multicentre, placebo-controlled, randomised study (A1a Systemic review (with homogeneity) of randomised clinical trials, that reflects the highest level of evidence and, therefore, has the highest rate of recommendation.) After a 2-week placebo run-in period, propiverine (15 mg t.i.d.; $n = 49$) or a placebo (t.i.d.; $n = 49$) were administered for 4 weeks (V 0, V 4). Propiverine caused a significant reduction in micturition frequency (V 0: 8.7 ± 4.2, V 4: 6.5 ± 3.2 ml; $P = 0.01$), which was reflected in a significant increase in the average micturition volume (V 0: 163.5 ± 65.9 ml, V 4: 216.3 ± 101.5 ml; $P = 0.01$) and a significant reduction in incontinence episodes (−54%; $P = 0.048$). Therefore, propiverine was significantly superior to the placebo in the overall assessment.

Mori et al. [43] focused on 46 demented elderly inpatients (average age 80.8 years) suffering from urinary incontinence. Administering propiverine (20 mg/d) for 2 weeks improved both the cystometric bladder capacity in 46.3% and the incontinence episodes in 40% of the patients. As expected, higher improvement rates were achieved for the subgroup of patients with an overactive detrusor. Otomo et al. [52] confirmed these results in 31 demented elderly patients.

Good results with propiverine were also achieved by Welz-Barth [75] in a non-controlled clinical trial over a period of 4 weeks. Of 39 patients, 56.4% showed significant improvement with regard to frequency, urgency and urge incontinence. Urodynamics revealed a significant increase of 43.6 ± 54.4 ml (V 0: 225.4 ± 72.3 ml; V 4: 269.0 ± 82.2 ml; $P < 0.0001$) in maximum cystometric bladder capacity and by 25.9 ± 33.4 ml for the bladder capacity at first involuntary bladder contraction (V 0: 81.5 ± 41.7 ml; V 4: 107.4 ± 57.7 ml; $P < 0.0001$).

These studies, although some are not placebo-controlled, demonstrate the effectiveness of administering propiverine to the elderly. In patients with significant cognitive impairment, timed voiding and toiletting are of paramount importance to manage incontinence. Besides efficacy, tolerability is at least as important in the elderly. The favourable risk-benefit ratio of propiverine in this group of patients will be discussed in the tolerability section.

Propiverine in children

"Wetting is the Cinderella of paediatric medicine, because therapeutic options have high failure rates, definitions and terminology are bewilderingly inconsistent throughout literature and prospective controlled studies are hard to find" (van Gool et al. [68]). Evaluating the effects of anticholinergics has also been made more difficult by the fact that until recently children with monosymptomatic enuresis and those with associated frequency–urgency syndrome were, despite the different aetiologies, mixed up in clinical studies,. Nowadays, the domain of anticholinergics (e.g. propiverine) in children is the frequency-urgency syndrome due to detrusor overactivity.

Two studies were conducted in Germany [13, 59]. One of them was placebo-controlled [13] and showed the efficacy of propiverine (0.4 mg b.i.d./kg body weight, administered as Mictonetten) in 280 [59] and 74 [13] children, respectively. In another non-controlled study comprised of 105 Japanese children (6–13 years), propiverine (10 mg once daily) improved the clinical symptoms and increased the maximum functional bladder capacity (V 0: 153.2 ml, V 4: 184.7 ml) after 4 weeks of treatment (improvement rate 54.6%) [19].

Several earlier clinical studies with propiverine (e.g. [11, 46, 69]) documenting, respectively, 24, 42 and 88 children suffering from enuresis demonstrated improvement rates of up to 80%. However, these studies are neither placebo-controlled nor did they differentiate between monosymptomatic enuresis and frequency-urgency syndrome.

In the future, placebo-controlled studies should be carried out to elucidate the value of including propiverine in the therapeutic arsenal for treating children who suffer from frequency–urgency syndrome. Prolonged follow-up periods and consideration of both spontaneous cure rates and relapse rates should be incorporated into the study plan. Areas of future research also should include children in whom vesico-ureterorenal reflux or urinary tract infections manifest in combination with frequency-urgency syndrome.

It is worth mentioning that in children who suffer from monosymptomatic enuresis, a subgroup who do not respond to desmopressin and alarms could also benefit from additional anticholinergic treatment.

Other indications

Symptoms of the OAB in combination with bladder outflow obstruction – propiverine combined with α-blockers

In about 60% of patients with bladder outflow obstruction, a concomitant detrusor overactivity causes urgency and urge incontinence. Treatment of these irritative symptoms with anticholinergics or spasmolytics may enhance the obstructive symptoms in this particular group of patients. An increase of postvoid residual urine (PVR) resulting from the detrusor relaxation limits its applicability. On the other hand, administering α-blockers alone may improve obstructive symptoms and, to a lesser extent, irritative symptoms. Therefore, the concept of combining anticholinergics with α-blockers is innovative.

The therapeutic benefit of combining propiverine with tamsulosin as compared to tamsulosin alone was evaluated by Saito et al. [56] in a randomised, multi-

centre-clinical trial for 4 weeks. Patients with benign prostatic hyperplasia (BPH) who suffer from obstructive and OAB symptoms were included. Tamsulosin (0.2 mg once daily) was administered in 59 patients and tamsulosin (0.2 mg once daily) combined with propiverine (20 mg once daily) was given to 75 patients. More favourable improvement rates of daytime frequency, urinary incontinence and urgency resulted under the combination of tamsulosin and propiverine. Statistical significance was achieved in nocturia (Table 1). Maximum flow rate increased significantly in the tamsulosin group and remained unchanged in the tamsulosin-propiverine group (Table 1). Combining propiverine and tamsulosin improved the irritative symptoms without deteriorating the obstructive symptoms. The Japanese study group concluded that, "in patients with prostatic hypertrophy accompanied by unstable bladder the combined use of propiverine and tamsulosin improves the quality of life more significantly than the administration of tamsulosin alone".

Accordingly, Nishimatsu et al. [47] demonstrated that the quality of life for 40 patients with prostatism was markedly improved when propiverine and selective α-blockers were combined.

Combining α-blockers and anticholinergics yielded promising results. However, in Saito's study infravesical obstruction was only assumed and not defined by pressure-flow studies. A further evaluation of propiverine and propiverine combined with α-blocking agents in patients with urodynamically proven urinary outflow obstruction is desirable. Propiverine is contraindicated if there is a significant degree of bladder outflow obstruction, where urinary retention may be anticipated [7]. To circumvent this difficulty for daily practice it is recommended that α-blockers be administered initially. An anticholinergic drug is added as soon as the obstructive symptoms have improved and while irritative symptoms persist.

Table 1 Propiverine in combination with tamsulosin in patients suffering from symptoms of the OAB and bladder outflow obstruction – results according to Saito et al. (From [56] and overall improvement rates (%) in subjective symptoms and voiding volume, residual urine and maximum flow at baseline (*V0*) and 4 weeks after treatment (*V4*)

	Tamsulosin	Tamsulosin + propiverine
Overall improvement		
Daytime frequency	29.6	44.7
Nocturia	22.5	44.4 (significant)
Urinary incontinence	42.9	57.1
Urgency	18.2	22.2
Voiding volume (ml)		
V0	219.6 ± 132.9	162.9 ± 88.6
V4	246.7 ± 53.1	168.2 ± 83.0
Residual urine (ml)		
V0	45.4 ± 47.2	41.4 ± 54.7
V4	35.9 ± 53.1	65.4 ± 104
Max. flow (ml/s)		
V0	11.5 ± 5.5	11.3 ± 7.2
V4	14.4 ± 6.8	11.8 ± 6.7

Propiverine for stress incontinence?

Some Japanese studies have focused on using propiverine in mixed urge-stress incontinence or stress-incontinence alone. In an open study, Ishiko et al. [23] demonstrated that the efficacy ratings for both stress incontinence and mixed urge-stress incontinence were even slightly more favourable than for urge incontinence in 102 women (who could be evaluated out of 147 recruited women) to whom an average dose of propiverine (20 mg/day) was administered for 86.3 days. Nocturnal and daytime voiding frequency, as well as nocturnal and daytime incontinence frequency were significantly decreased from the baseline values for each of these three diagnostic subgroups. No significant differences between the three subgroups in any of these parameters were demonstrated. Watanabe et al. [72] studied the effectiveness of propiverine taken (20 mg once daily) for more than 4 weeks in 82 patients with urinary incontinence, including 28 with urge incontinence, 51 with stress incontinence and three with mixed urge-stress incontinence. The mean frequency of urinary incontinence per day decreased significantly after treating both the urge incontinence (pre 7.0 ± 7.5, post 1.0 ± 2.1) and the stress incontinence (pre 3.3 ± 2.4, post 0.6 ± 1.2) subgroups. In the stress incontinence subgroup the mean weight of urine leak during the 1-h pad test decreased from 25.7 ± 41.3 g to 6.0 ± 20.7 g, but the change was not statistically significant. The rate of improvement in total subjective urinary symptoms in the urge incontinence subgroup was 95.6%, which did not differ from the corresponding value (86.4%) in the stress incontinence subgroup. The authors concluded that the treatments for these two major kinds of urinary incontinence were equally effective. Nashiro et al. [45] analysed 82 patients suffering from different types of urinary incontinence and drew similar conclusions. All these Japanese authors suggested that propiverine is useful not only for urge but also for mixed urge-stress and stress incontinence [23, 45, 72].

However, none of the three cited Japanese clinical trials were placebo-controlled. Therefore, the results are difficult to interpret, unless there is a proven effect of propiverine on the bladder outlet. The scientific rationale for stress incontinence demands urodynamically controlled studies. It could be one of the major areas for propiverine research in the future. Up to now, propiverine was targetted to treat the urge component in cases of mixed urge-stress incontinence [4, 10].

Dosage-optimising studies

The efficacy of propiverine (15, 30, 45, 60 mg/d) was evaluated in 185 patients suffering from urgency ($n = 105$) and urge incontinence ($n = 80$) in an open, randomised, multicentre parallel group trial for 21 days [40]. Of these patients, 80% suffered from detrusor instability verified by urodynamics. The effect on bladder volume and pressure was assessed by urodynamics and

micturition charts. Bladder capacity and compliance increased, and detrusor pressure decreased depending on the dosage. In 70% of the patients a decrease in micturition frequency was observed after 15 mg/day, in 80% after 30–60 mg/day. The daily doses with the most favourable efficacy-tolerability ratio were between 15 mg and 30 mg propiverine. A comparable dosage-optimizing study in patients with detrusor hyperreflexia [38] showed that micturition frequency decreased after 15 mg/day in 54% of the patients and after 30–60 mg/day in about 80%. These results are in accordance with the WHO Collaborating Centre for Drug Statistics Methodology's recommendation of 30 mg as the defined daily dosage (DDD) for propiverine.

Similar investigations were conducted in Japan on volunteers as well as on patients; a study of the dosage-effect ratio established that, by incrementally increasing the dosage by 5 mg, the optimal dosage for Japanese patients was 20 mg of propiverine administered once daily [32]. The tendency to use lower dosages of propiverine in Japan is probably attributable to two factors. The mean body weight of the Japanese population is certainly lower than of Europeans. According to Y. Igawa (personal communication) the average 60- to 69-year-old Japanese woman weighs 53.3 kg, while the average 60- to 69-year-old Japanese man weighs 61.9 kg. Moreover, in Japan, tolerability takes priority over effectiveness.

Long-term efficacy

Long-term studies conducted over 12 months in Germany on patients with detrusor hyperreflexia [37] and on those suffering from symptoms of OAB [40] evidenced a constant effectiveness (without tachyphylaxis) for treatment periods of 45, 90, 180 and 360 days. Continuing efficacy was also documented in children [13, 14].

In Japan, nine non-controlled studies focusing on long-term administration were carried out [26, 48, 50, 51, 61, 62, 65, 71, 77]. Kagawa et al. [26] evaluated the long-term effectiveness of propiverine (20 mg once daily) in 87, mostly elderly, patients (86.7% of whom were more than 60 years old) over treatment durations of up to 807 days. Yoshida et al. [77] studied the long-term efficacy of propiverine (20 mg once daily) in 116 patients with symptoms of OAB, of whom 21 were treated for more than 1 year. These long-term Japanese studies documented more than 150 patient years of propiverine treatment (Table 2). In all investigations, day- and nighttime micturition frequency and incontinence episodes decreased significantly during the surveillance period. In two long-term studies, the subjective results were confirmed urodynamically by a significant increase in maximum bladder capacity [61, 62]. All authors concluded that propiverine is effective when administered on a continuing basis.

Tolerability

Anticholinergic adverse events

The clinical studies that evaluate the efficacy of propiverine also document its tolerability. Due to the fact that propiverine, like all other drugs approved to treat OAB symptoms, is not bladder-selective, the occurrence of typical anticholinergic adverse events must be anticipated. The incidence of dryness of the mouth varied widely in several studies, depending to a great extent on the method of evaluation. For spontaneous reporting of adverse events, incidence rates of only 2% [10] are documented, whereas, as expected, higher rates of incidence were documented when patients were prompted. However, up to 30% of the placebo-treated patients reported dryness of the mouth as well [34].

Table 2 Long-term tolerability of propiverine in clinical studies conducted in Japan (From [26, 48, 50, 51, 61, 62, 65, 71, 77])

Reference	Recruited Patients (safety/efficacy evaluation)	Patients (treatment duration)		Surveillance Period (days)		Adverse events (%)	Serious adverse events
		> 6 months	> 12 months	average	maximum		
Kagawa (From [26])	87 (75/69)	26	15	168	807	22.7	none
Yoshida (From [77])	116 (89/82)	33	21	Intended 1 year		18.0	none
Ohmori (From [51])	53 (52/52)	20 (71–234 d)	Could not be evaluated	78.4	234	19.2	none
Noguchi (From [48])	147 (141/122)	81	57	241	604	15.6	none
Oeda (From [50])	34 (32/32)	11	7	intended initially 1 year		18.0	none
Tanabe (From [65])	49 (42/38) (elderly)	24	14	245	intended 1 year	16.6	none
Takaki (From [61])	120 (107/101)	12	28	Intended 1 year		25.2	none
Takaki (From [62])	32 (24 weeks)	14	1	159		21.9	none
Watanabe (From [71])	23	8	not evaluable	125	349	8.7	none

Madersbacher et al. [34] evaluated the tolerability of propiverine in comparison to oxybutynin and placebo. The incidence rates for propiverine were comparatively lower than for oxybutynin ($P = 0.022$). Furthermore, when considering severity gradings (Fig. 3) severe dryness of the mouth was statistically less frequent under propiverine (12%) as compared to oxybutynin (25%) ($P = 0.0093$), but was more frequent than with the placebo (4%).The time course of dry mouth also differed: severity increased under oxybutynin (18% after 1 week, 25% after 4 weeks), whereas it remained constant under propiverine (13% after 1 week, 12% after 4 weeks).

Accommodation disorders were documented between 0% [10] and 28% with propiverine [34, 60] as compared to 18% with oxybutynin [34] and 14% with the placebo [34]. However, this adverse event bothered the patients much less than dryness of the mouth.

The incidence rates for other anticholinergic adverse events are comparably lower than those cited for dryness of the mouth and accommodation disorders (Table 3). As expected, constipation is another possible adverse event: a PMS revealed incidence rates below 10% and the majority of patients considered it to be mild. Incidence rates of 9% applied to tiredness and 5% to dizziness. Further improvement in the long-term follow-up was reported (after 12 weeks, 6% for tiredness, 3% for dizziness). The total drop-out rate due to adverse events in the report of Alloussi et al. was below 5% [4].

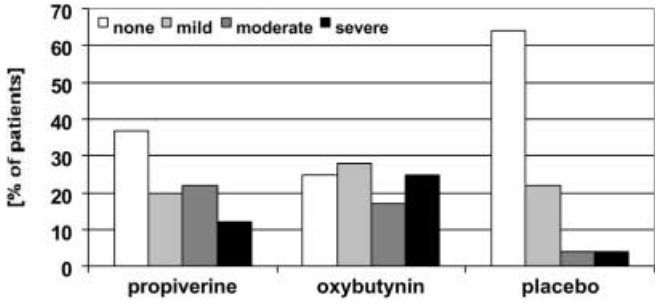

Fig. 3 Severity grading of dryness of the mouth after 4 weeks of treatment according to Madersbacher et al. (From [34])

Table 3 Incidence rates and severity of anticholinergic adverse events after 4 (*V 4*) and 12 weeks (*V 12*) of treatment with propiverine according to Alloussi et al. (From [4])

Adverse event [%]	Severity Mild	Moderate	Severe
Dryness of the mouth			
V 4	25.8	6.0	2.0
V 12	22.2	3.1	0.7
Accommodation disorders			
V 4	8.7	1.9	0.8
V 12	5.4	0.6	0.3
Constipation			
V 4	8.6	0.9	0.2
V 12	7.0	0.5	0.1
Tiredness			
V 4	8.1	0.8	0.2
V 12	5.6	0.3	0.1
Dizziness			
V 4	3.7	0.8	0.3
V 12	2.4	0.3	0.1

Differences in the underlying aetiology with regard to adverse events in gender and age can be detected: patients suffering from OAB symptoms reported adverse events more frequently than those with detrusor hyperreflexia and incidence rates were higher in females than in males. Furthermore, assessing tolerability revealed better results in patients who were successfully treated with propiverine than in non-responders. Although there is still no definite proof that the incidence rates of adverse events are age-related, children complained markedly less than adults [4, 13, 14, 59]. Hoashi [19] reported far fewer adverse events due to propiverine (1%) as compared to oxybutynin (4%) or terodiline (2.4%) in Japanese children. These tolerability results emphasise a better ability to tolerate propiverine than oxybutynin in children as well.

Propiverine was better tolerated in adults as compared to oxybutynin, according to Kondo et al. [30] based on a meta-analysis and Japanese studies [31] that cited adverse events in 6.2% of patients taking propiverine and in 24.5% of patients taking oxybutynin. Takayasu et al. [64] reported equal incidence rates for propiverine and the placebo. Different dosage schedules in Japan (20 mg once daily, BUP–4) and Europe (15 mg b.i.d. or t.i.d., Mictonorm, Detrunorm) must be taken into account.

Clinical studies comparing the tolerability of propiverine and tolterodine are still outstanding. However, animal experiments in the mini-pig under standardised conditions [57] showed no difference regarding the dryness of mouth. Propiverine decreased electrically-stimulated salivation by 61%, tolterodine by 56% (median values).

Long-term tolerability

In nine non-controlled, multicentre clinical studies, Japanese authors established that propiverine was well tolerated under long-term administration. Incidence rates of adverse events varied from 8.7% [71] up to 25.2% [61] (Table 2).

Voigt [70] reported an adverse event incidence rate of 13% in a follow-up investigation during 10 years of propiverine treatment in 29 women suffering from urgency. Improved tolerability under long-term treatment might be an advantage of using propiverine, a phenomena not documented so far for other anticholinergics.

Safety

Residual urine

Anticholinergics can induce residual urine because of a decrease in detrusor contractility that results in urinary

retention. According to the conclusions of randomised, prospective, double-blind, pivotal studies [10, 34] propiverine did not influence residual urine in patients with symptoms of OAB, whereas studies of tolterodine in unobstructed patients who also suffered from symptoms of OAB showed an increase in residual urine [25]. These clinical results are confirmed by in vivo studies of the decerebrated dog, in which propiverine did not increase residual urine in contrast to oxybutynin [67]. However, PMS with propiverine in 1476 patients [3, 4] showed a clinically relevant increase of residual urine only in a minor percentage (0.3%).

Cardiac safety

Possible arrhythmogenic effects of propiverine (15 mg t.i.d.; $n = 49$) were thoroughly investigated in a placebo-controlled ($n = 49$), randomised clinical study, already cited under aspects of efficacy in the elderly [10]. Cardiac events of Lown classes I–IV occurred in about 50% of the study population, representing an elderly cardiac risk population (average age 67.3 years). A standard 12–lead ECG revealed no changes in heart-rate, P–Q interval, QRS interval, Q–T interval or frequency-corrected Q–T interval. In the 24-h long-term electrocardiogram (ECG), there was no detection of intermittent pauses resulting from sinoatrial or atrioventricular blocks, nor were there episodes of intermittent interventricular branch block, paroxysmal supraventricular tachycardia or intermittent atrial fibrillations. Cases of sustained ventricular tachycardia, ventricular flutter or ventricular fibrillations were not observed. These results, comprising a surveillance period of 4 weeks, are consistent with in vivo animal studies [16] and long-term clinical studies (e.g. [39]), in which no ECG effects were detected. Furthermore, a post-marketing drug surveillance [4] including 1379 patients (≥65 years of age) showed no serious cardiovascular adverse events despite concomitant cardiovascular medication in about 50% of all patients. Finally, pharmacovigilance of propiverine verified its cardiac safety under conditions of every day use.

Ophthalmologic safety – intraocular pressure and narrow-angle glaucoma

The effects of anticholinergics on intraocular pressure by relaxing the ciliary muscle are possible. A study by Pilz and Pilz [54] showed no increase of intraocular pressure with propiverine 15 mg t.i.d. in 56 patients with different kinds of glaucoma and healthy volunteers. The treatment periods were rather short (5 days). However, these results are in agreement with clinical studies [34, 48, 60, 61] and PMS [4]. Therefore, we consider that propiverine is only contraindicated in patients suffering from uncontrolled narrow-angle glaucoma.

Post-marketing drug surveillance

A PMS comprised of 4390 patients (mean age 51.2 years; 41.5% of patients 60–94 years) provided additional data concerning the effectiveness and safety of propiverine to that available from clinical studies. During the treatment period of 12 weeks encompassing three visits (V 0, V 4, V 12), daytime incontinence episodes (V 0: 3.5; V 12: 1.0), daytime frequency (V 0: 9.1; V 12: 5.8) and nocturia (V 0: 2.6; V 12: 1.0) decreased according to Alloussi et al. [4]. The PMS showed improvements that were only slightly inferior for mixed urge-stress incontinence ($n = 1413$) as compared to urge incontinence ($n = 1329$). The results were also confirmed for a subpopulation of 602 children [4].

Most of the cited European studies administered 15 mg propiverine t.i.d for daily dosages. However, PMS results revealed a move towards lower dosages (15 mg b.i.d.), especially under conditions of daily use with prolonged treatment periods [4].

Propiverine is able to meet socio-economic demands: 20% of all treated patients could completely suspend pad use, and another 20% of patients with wet pads and 20% of patients with damp pads could at least reduce pad use substantially. The percentage of patients not requiring pads more than doubled under treatment (35.8 vs 78.4%). The prescription of propiverine is a reasonable, cost-effective alternative to pads [4] and, even more importantly, increases quality of life considerably [10].

Treatment periods of almost 3 months for 4390 patients that documented 1100 patient years has so far not revealed any unknown, rare adverse events. The positive risk-benefit ratio, verified in numerous clinical trials, was also confirmed under conditions of routine clinical practice in a large patient population.

Summary and future perspectives

Propiverine is a detrusor relaxant drug with a dual mode of action comprised of neurotropic and musculotropic properties. This dual mode of action is highly effective as compared to that of oxybutynin, has a tolerability superior to that of oxybutynin and, based on in vivo animal studies, is similar to that of tolterodine.

Placebo-controlled clinical trials have evidenced the efficacy of giving propiverine to patients with detrusor hyperreflexia, in patients with symptoms of overactive bladder as well as in children with frequency-urgency syndrome. Due to the lasting effectiveness over time and the lack of tachyphylaxis, propiverine has to be considered a suitable drug for long-term therapy. Propiverine is the first medicine administered in combination with the selective α-blocker tamsulosin in a controlled clinical trial. This demonstrates that the combination of propiverine with tamsulosin yielded

statistically significant better results than tamsulosin alone in BPH patients with obstructive and irritative symptoms.

Propiverine is tolerated better than oxybutynin, particularly with respect to the incidence and severity of dryness of the mouth, as shown in comparative studies. In vivo animal studies that compare propiverine and tolterodine have demonstrated an equivalent decrease in salivation under standardised conditions, assuming that tolerability is comparable for the human as well. Furthermore, adverse events decreased during prolonged treatment, a phenomena not yet described in other anticholinergics. In the unobstructed lower urinary tract, residual urine did not increase with propiverine in contrast to oxybutynin and tolterodine, as shown in clinical studies and in vivo animal studies.

Interesting aspects for future research are the possible effects of propiverine regarding bladder outlet resistance. More experimental work should be undertaken to interpret findings that have been controversial so far. A beneficial effect of propiverine concerning residual urine is possibly mediated by a decrease in bladder outlet resistance. On the other hand, positive effects in patients suffering from genuine stress incontinence are described, suggesting an increase in bladder outlet resistance.

A preparation of liquid propiverine for intravesical instillation could further enhance its tolerability and extend its spectrum of possible applications, especially in patients who are already on intermittent catheterization.

According to the First International Consultation on Incontinence, propiverine is one of only a few acknowledged drugs that has been proven to be effective in treating symptoms of the overactive bladder and fulfils the criteria of evidence-based medicine.

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