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An Overview on Mixed Action Drugs for the Treatment of Overactive Bladder and Detrusor Overactivity

Key Words

Overactive bladder • Detrusor overactivity • Propiverine • Oxybutynin • Flavoxate

Abstract

Objectives: To provide an overview on the efficacy, tolerability, safety and health-related quality of life (HRQoL) of drugs with a mixed action used in the treatment of overactive bladder (OAB). **Evidence Acquisition:** MEDLINE database and abstract books of the major conferences were searched for relevant publications from 1966 to 2011 and using the key words ‘overactive bladder’, ‘detrusor overactivity’, ‘oxybutynin’, ‘propiverine’, and ‘flavoxate’. Two independent reviewers considered publications for inclusion and extracted relevant data, without performing a meta-analysis. **Evidence Synthesis:** Old and conflicting data do not support the use of flavoxate, while both propiverine and oxybutynin were found to be more effective than placebo in the treatment of OAB. Propiverine was at least as effective as oxybutynin but with a better tolerability profile even in the pediatric setting. Overall, no serious adverse event for any product was statistically significant compared to placebo. Improvements were seen in HRQoL with treatment by the oxybutynin transder-

mal delivery system and propiverine extended release. **Conclusions:** While there is no evidence to suggest the use of flavoxate in the treatment of OAB, both oxybutynin and propiverine appear efficacious and safe. Propiverine shows a better tolerability profile than oxybutynin. Both drugs improve HRQoL of patients affected by OAB. Profiles of each drug and dosage differ and should be considered in making treatment choices.

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Introduction

Overactive bladder (OAB) syndrome is defined by the International Continence Society (ICS) as ‘urgency, with or without urge incontinence, usually with frequency and nocturia’ [1]. Various studies have reported a prevalence of up to 17% for the symptoms of the OAB complex [2–4] with approximately 34 million affected patients in the USA [5] and an incidence that increases with age affecting approximately 30–40% of those >75 years [3, 6].

OAB results in a significant deterioration in health-related quality of life (HRQoL) [7–9]; the affected patients experience significant reductions in mental health, health

perceptions and bodily pain scales when compared with community controls [9]. There are additional consequences of the higher incidence of OAB in the elderly, since urinary urgency, nocturia and incontinence have been shown to be associated with an increased incidence of falls and fractures in this group. Healthcare costs related to OAB will inevitably increase with the increasing life expectancy of the population [10].

A great number of drugs, with different potential pharmacologic targets, both within the efferent mechanisms controlling detrusor muscle function and its afferent innervation, have been evaluated in the treatment of OAB. Antimuscarinic agents are currently the first-line pharmacotherapy for OAB. Parallel to these agents, some drugs used to block detrusor overactivity (DO) have been shown to have more than one mechanism of action. They all have a more or less pronounced antimuscarinic effect and, in addition, an often poorly defined 'direct' action on bladder muscle. The main drugs with a mixed action used in the treatment of OAB are: oxybutynin chloride, propiverine hydrochloride, and flavoxate hydrochloride [11].

The primary aim of this study was to perform an overview on the efficacy of drugs with a mixed action used in the treatment of OAB. Secondary aims were an overview on their tolerability, safety and HRQoL.

Materials and Methods

We performed a MEDLINE search for peer-reviewed studies published from 1966 from 2011. The key words 'overactive bladder', 'detrusor overactivity', 'oxybutynin', 'propiverine', and 'flavoxate' were used. Two individuals (A.D.A. and M.A.C.) independently screened the titles and abstracts of each citation. The reference lists of the eligible articles were reviewed and the 'related citations' PubMed feature was utilized. Publications in languages other than English were not considered; however, abstracts in English as parts of non-English full manuscripts were also assessed. Abstract books from several major conferences were also reviewed. No meta-analysis was performed. Efficacy was measured by continent days, mean voided volume, urgency episodes, and micturition frequency. Tolerability and safety were measured by means of adverse event and withdrawal rates. HRQoL was measured by various instruments.

Flavoxate Hydrochloride

The main mechanism of flavoxate's effect on smooth muscle has not been established. A moderate calcium antagonistic activity, the ability to inhibit phosphodiesterases and the local anesthetic properties are some of the

proposed mechanisms of action of the drug, while no antimuscarinic effect was found [12]. However, the drug inhibits the contraction induced by muscarinic receptor stimulation and by electrical field stimulation in strips of human bladder with comparable efficacy to oxybutynin [13]. In animal studies, it has been demonstrated that when flavoxate was administered intracerebroventricularly or intrathecally, it abolished isovolumetric rhythmic bladder contractions in anesthetized rats [14]. Caine et al. [15] demonstrated that flavoxate inhibited potassium-induced contractions on the human detrusor, prostatic adenoma, prostatic capsule, and bladder neck, with a slightly greater activity in the prostatic and bladder neck tissues.

Daily Dosage

With respect to uninhibited detrusor contractions, a daily dosage of 1,200 mg of flavoxate for the treatment of DO was significantly superior to 600 mg/day while tolerability was excellent for both regimens [16].

Comparative Studies

Comparative studies of the early 1970s demonstrated improvement rates of 83% in patients with DO treated with flavoxate 200 mg t.i.d. [17]. Milani et al. [18] showed no difference in efficacy between flavoxate 1,200 mg/day and oxybutynin 15 mg daily in 41 women with idiopathic motor or sensory urgency, with flavoxate showing fewer and milder side effects.

Wehnert and Sage [19] performed a crossing-over study on 46 patients suffering from urgency/urge incontinence and treated with propiverine 45 mg/day and flavoxate 300 mg/day for 4 weeks versus placebo. Both groups showed a significant reduction of micturition frequency and an increase of the compliance, whereas the placebo was ineffective. A markedly growth of the maximal bladder capacity was obtained only by propiverine. Both agents keep likewise to an improvement of the symptoms or urgency/urge incontinence.

Fehrmann-Zumpe et al. [20] studied the efficacy of flavoxate in an observational study by collecting data on a total of 1,800 patients given flavoxate over 2 weeks for urge incontinence. A subgroup of 618 patients without urinary tract infections or benign prostatic hyperplasia were treated with flavoxate only showing a reduction of dysuria (37%), nocturia (53%), and both daytime (61%) and nighttime urge (69%). Bladder volume at first urge sensation increased by 36%. In 89.2% of all patients the residual urine volume was stable or decreased. Both groups showed better results with flavoxate q.i.d. (800 mg) compared to t.i.d. (600 mg).

Gu et al. [21] studied flavoxate on 361 patients with urgency/incontinence through an unblinded, uncontrolled clinical trial. Patients were given 200 mg t.i.d., orally, for 2 weeks, although 33 patients received a daily dosage of 1,200 mg. 228/336 evaluated patients (67%) were completely cured of urgency/incontinence symptoms, 66/336 (20%) were improved and 42/336 (13%) patients were unchanged. Flavoxate was also effective in 77.4% of patients refractory to previous anticholinergic treatment. Treatment did not increase the end-residual volume and adverse events (AEs) occurred only in 4 (1.3%) patients, 2 (0.6%) of which discontinued the therapy. The 1,200-mg dose produced a complete cure in 82% of patients and improvement in the remaining 18%, with no side effects.

Contrarily to the aforementioned studies, several investigators comparing the effects of flavoxate with those of placebo have not been able to show any beneficial effect of the drug at dosages up to 400 mg t.i.d. [22–24]. Briggs et al. [22] studied the effect of flavoxate on only 6 elderly patients with uninhibited detrusor contractions associated with urinary incontinence and consequently the outcomes of their study have to be interpreted with caution. However, Chapple et al. [23] reported in 1990 on a double-blind, placebo-controlled, crossover trial of flavoxate in idiopathic detrusor instability, while Dahm et al. [24] provided a randomized, double-blind, parallel-group, placebo-controlled and multicenter investigation with adequate statistical power on the efficacy of flavoxate 400 mg t.i.d. for the treatment of OAB. The conclusion (with high level of evidence) of both these studies was that flavoxate cannot be recommended for clinical use.

However, all studies agree the flavoxate treatment of DO is well tolerated, it causes no additional problems due to residual urine and it is not associated to risks of ventricular arrhythmia and sudden death in older patients.

No randomized controlled trials (RCTs) seem to have been performed with flavoxate during the last decade. The conclusions from the *Cochrane Review* stated that there is no evidence to suggest the use of flavoxate in the treatment of OAB [25]. According to the ICS, the efficacy of flavoxate compared to other therapeutic alternatives is not well documented (level of evidence 2, grade of recommendation D) [11].

Oxybutynin Chloride

Oxybutynin has several pharmacological effects in vitro, some of which seem difficult to relate to its effectiveness in the treatment of DO. This drug is a tertiary amine,

which undergoes an extensive first-pass metabolism. It has an active metabolite, N-desethyloxybutynin, and the effect of oral oxybutynin is to a large extent exerted by this metabolite. Oxybutynin has both an antimuscarinic and a direct muscle relaxant effect, and, in addition, local anesthetic actions but at concentrations far above those used clinically. Most probably, oral oxybutynin exerts its effects on the OAB by an antimuscarinic action – through a competitive antagonism of the M1, M2, and M3 subtypes of the muscarinic acetylcholine receptor [11].

More recently it has been found that oxybutynin as well as propiverine were able to suppress ATP-induced bladder overactivity other than through antimuscarinic mechanisms [26]. Intravesical oxybutynin can block the bladder-cooling reflex and increase without blocking current perception threshold sensation in the bladder in most patients with incomplete neurogenic lesion and DO [27]. Oxybutynin's local influence on C-fiber-related activity may explain part of the clinical effect of intravesical oxybutynin in neurogenic patients.

There are several available formulations of oxybutynin (immediate-release – IR; extended-release – ER; transdermal delivery – TSD; rectal administration; intravesical administration) that were overviewed by McCrery and Appell [28].

Efficacy

In 2008, two systematic reviews evaluated the efficacy and safety of different doses, formulations, routes of administration and different active principle of the currently available antimuscarinic drugs used in the treatment of OAB [29, 30]. Comparing IR and ER oxybutynin formulations [31–37], the efficacy outcomes were not suitable for meta-analysis [29, 30]. Two RCTs compared the oral and transdermal routes of administration of oxybutynin [38, 39]. Specifically, Davila et al. [38] compared the efficacy and safety of oxybutynin IR at different doses administered orally or transdermally, while Dmochowski et al. [39] evaluated transdermal oxybutynin 3.9 mg once daily and tolterodine ER 4 mg once daily. Meta-analysis of efficacy showed similar reduction in the number of incontinence episodes per 24 h (weighted mean difference 0.05; 95% CI –0.58 to 0.67; $p = 0.88$) [29].

Comparative Studies

Twelve RCTs compared efficacy and safety of oxybutynin and tolterodine [40–51]. Micturitions per 24 h, volume voided per micturition, UUI episodes, and incontinence episodes per 24 h were overlapping for the IR formulations of oxybutynin 5 mg two or three times daily

versus tolterodine 2 mg twice daily [30]. Overall, oxybutynin IR 15 mg/day was favored over tolterodine IR 4 mg/day (13.3; 95% CI 4.3–22.3; $p < 0.01$) [30].

Halaska et al. [52] compared efficacy and safety of oxybutynin IR 5 mg twice daily and trospium IR 20 mg twice daily, continuing both treatments for 52 weeks. This study showed similar efficacy for the two drugs in terms of both bladder diary variables such as mean change in micturitions and in the number of urgency episodes per 24 h, and in terms of urodynamic parameters, such as change in maximum cystometric capacity and change in volume at first contraction [52].

Zinner et al. [53] evaluated the efficacy of oxybutynin IR and darifenacin in a four-way crossover study. Darifenacin 15 mg once daily was comparable to oxybutynin in terms of the improvement in OAB symptoms, with both drugs similarly reducing the number of incontinence episodes per week and the number of micturitions and urgency episodes per day after a 2-week treatment [53].

According to the ICS, oxybutynin has a well-documented efficacy in the treatment of OAB/DO (level of evidence 1, grade of recommendation A) [11].

Adverse Events

N-desethyloxybutynin is an active metabolite of oxybutynin that is thought to be responsible for many of the adverse effects associated with the use of oxybutynin [11]. N-desethyloxybutynin plasma levels may reach as many as six times that of the parent drug after administration of the IR oral formulation [11]. Alternative dosage forms have been developed in an effort to reduce blood levels of N-desethyloxybutynin and allow for a steadier concentration of oxybutynin to be achieved than is possible with the IR form. The long-acting formulations also allow once-daily administration instead of the twice-daily dosage required with the IR form. The transdermal patch, in addition to the benefits of the ER oral formulations, bypasses the first-pass hepatic effect that the oral formulations are subject to [11].

The occurrence of any AE, dry mouth, and moderate-to-severe or severe dry mouth were significantly more common with oxybutynin IR than with oxybutynin ER [29]. On the other hand, withdrawals due to AE, headache, constipation, and vision abnormality were similar for the two formulations of oxybutynin [29].

Comparing oral and transdermal formulations, dry mouth and constipation were significantly more common in those patients taking the drug orally, while localized application side effects and withdrawal due to AEs

were significantly more frequent in those patients receiving active transdermal formulations [29].

Comparing oxybutynin versus tolterodine (both IR and ER formulations), oxybutynin IR versus trospium IR as well as oxybutynin IR versus darifenacin, the occurrence of dry mouth was significantly more common for patients randomized to oxybutynin [29].

Oxybutynin IR 15 mg/day and oxybutynin IR 7.5–10 mg/day were associated with statistically significantly higher risk of withdrawal from trial due to any cause than placebo [30].

The following AEs were reported at statistically significantly higher levels in active treatments than in placebo: blurred vision (oxybutynin IR 15 and 20 mg/day); constipation (oxybutynin 15 mg/day); erythema (oxybutynin TSD 3.9 mg/day); pruritus (oxybutynin TSD 3.9 mg/day), and urinary retention (oxybutynin IR 7.5–10 mg/day) [30].

The following AEs were reported at statistically significantly higher levels in first-named active treatments than in second-named active treatments: blurred vision (propiverine IR 45 mg/day vs. oxybutynin IR 7.5–10 mg/day); nausea (oxybutynin IR 15 mg/day titrated vs. oxybutynin ER 15 mg/day titrated), and vomiting (tolterodine ER 4 mg/day vs. oxybutynin ER 7.5–10 mg/day) [30].

Propiverine

Propiverine is unique in having both anticholinergic and calcium-channel blocking effects [54, 55]. The former effects are known to suppress neurogenic detrusor contraction, while the latter have a direct spasmolytic effect on the bladder, even if the importance of the calcium-antagonistic component for the drug's clinical effects has not been established. Propiverine has no selectivity for muscarinic receptor subtypes [11].

After oral administration, propiverine is rapidly absorbed ($t_{\max}$ 2 h), but has a high first-pass metabolism, and its biological availability is about 50% [11]. The drug is then extensively biotransformed into several metabolites that could contribute to its spasmolytic action. Three propiverine metabolites (M-5, M-6 and M-14) have been shown to affect various detrusor functions, including contractile responses and L-type calcium currents, in humans, pigs and mice, albeit with different potency [56]. Propiverine could also suppress ATP-induced bladder overactivity other than through antimuscarinic mechanisms [26].

The half-life of propiverine itself is about 11–14 h [11]. An ER preparation is currently available [57].

Propiverine in a Pediatric Population with Idiopathic DO

Although OAB is thought to be highly prevalent among children as well as in adults, the evidence in the field of drug treatments has been quite limited [58], and the International Consultation on Incontinence recommends antimuscarinic treatment for this indication in children with a low level of evidence (level 3, grade C of recommendation) [59]. However, since 1985, propiverine is labeled for treatment of children with non-neurogenic DO, incontinence, urgency, and/or small bladder volume from age 5 years and neurogenic DO (NDO) from age 1 year in Germany, the Czech Republic, and Slovakia used as tablets with 5 mg propiverine in a recommended daily dose of 0.8 mg/kg body weight [60].

Earlier studies [61–63] already demonstrated efficacy and safety of propiverine, but did not fulfill all strict criteria from the current guidelines or standards of good clinical practice.

Marschall-Kehrel et al. [60] offered the first confirmatory clinical trial in children suffering from non-neurogenic OAB and urinary incontinence that demonstrated superiority for propiverine over placebo. They performed a randomized, double-blind, placebo-controlled phase 3 trial with parallel-group design in children aged 5–10 years. Propiverine was assumed in a body-weight-adjusted route (10 or 15 mg twice daily or corresponding placebo) for 8 weeks. The study showed that, compared to baseline, propiverine can achieve statistically significant reductions of the number of micturations and incontinence episodes per day over placebo, with an increase in the mean voided volume per micturition. Moreover, propiverine was quite well tolerated, with the typical antimuscarinic side effects, such as dry mouth, visual disturbances, and constipation, being reported in less than 10% of the whole cohort of patients.

Batinic et al. [64] compared the efficacy and tolerability of propiverine with that of oxybutynin and placebo in children with OAB. 266 children (propiverine (n = 85) 10 mg b.i.d.; oxybutynin (n = 91) 5 mg b.i.d.; placebo n = 90) were recruited. The treatment period of 12 weeks was followed by 2 weeks of administering half of the initial dosage. The study was finalized with a medication-free post-therapy phase of 6 weeks. The number of enuretic events per week demonstrated a marked decrease for propiverine and oxybutynin. Due to marked effects of placebo, drug effects did not reach level of significance. How-

ever, the bladder capacity at maximum urge increased significantly with propiverine and oxybutynin but not with placebo. Comparable frequencies of AEs were observed for propiverine (64) and placebo (57); in contrast, twice that number (126) occurred under oxybutynin.

Alloussi et al. [65] assessed and compared the efficacy and tolerability of propiverine and oxybutynin in children with incontinence aged 4–14 years. The treatment results of 621 children with urinary incontinence, assumed to be due to idiopathic DO, were analyzed. 437/621 of these children were treated with propiverine and 184/621 with oxybutynin. Children with day- and nighttime symptoms were included, those with nighttime symptoms only were not eligible. The primary efficacy outcome, the achievement of continence, demonstrated statistically equivalent efficacy rates of propiverine (61.6%) and oxybutynin (58.7%) with propiverine showing significant superiority in the multivariate adjusted comparison. Similar results were observed for micturition frequency/day and incontinence episodes/week. To achieve efficacy, propiverine was used in dosages lower than recommended (0.54 vs. 0.8 mg/kg body weight/day) while oxybutynin had to be used in dosages higher than recommended (0.31 vs. 0.25 mg/kg body weight/day). In the propiverine-treated children an increment of dosage corresponded to improved efficacy, while in the oxybutynin-treated children higher dosages did not correspond to improved efficacy: in the highest dosage compared to lower dosage groups efficacy, rates even deteriorated. In the propiverine-treated patients AEs manifested in 3.9%, in those treated with oxybutynin AEs manifested four-fold more often (16.3%). Discontinuation rates were 1.6 and 4.4%, respectively. The study confirmed the effectiveness of propiverine and oxybutynin in children suffering from urinary incontinence due to assumed idiopathic DO with propiverine being superior in the multivariate adjusted analysis. Propiverine was again better tolerated. Adequate diagnosis, body weight adapted dosages, dose titration and treatment periods of preferably at least 4 months or longer were suggested as the key factors for treatment success.

Propiverine in Children Affected by NDO

Madersbacher et al. [66] enrolled 255 children and adolescents with NDO at 14 study centers. In all, 127 patients given propiverine and 128 given oxybutynin were enrolled. Significant reductions in mean P(det_{max}) with respect to baseline were observed, while the mean maximum cystometric bladder capacity increased for both groups. Propiverine was better tolerated than oxybu-

tynin (fewer AEs, with lower severity grades and less premature treatment termination). Grigoleit et al. [67] retrospectively evaluated the efficacy, tolerability and safety of propiverine in children with NDO. At four specialized outpatient clinics, all children's records were scrutinized for first-line propiverine hydrochloride treatment, or second- or third-line treatment after failure of a non-selective α -blocker (phenoxybenzamine) and/or other anticholinergics (oxybutynin, trospium chloride). Altogether, 74 children and adolescents (40 boys, 34 girls; age range 11 months–19 years) were treated with propiverine (average duration 2 years and approximately 4 months; individual dose range 5–75 mg). The primary efficacy outcome parameters such as maximum cystometric capacity, maximum detrusor pressure and bladder compliance improved significantly. Phasic DO was abolished by 63%, while incontinence resolved by 54%. No safety concerns were documented. The authors concluded that propiverine is effective in NDO in children and adolescents, even in some of those cases unresponsive to other anticholinergics. The low incidence rate (<1.5%) of AEs confirms the favorable risk-benefit profile of propiverine.

Schulte-Baukloh et al. [68] also evaluated the efficacy and tolerability of propiverine in 20 children suffering from NDO. All urodynamically-assessed efficacy parameters (reflex volume (defined as volume of the first bladder spasticity), maximum detrusor pressure, maximum cystometric capacity, bladder compliance and leak point pressure) as well as the incontinence score were significantly improved. Concerning tolerability, no serious AEs occurred, although in some patients higher doses than recommended were administered. The authors concluded that propiverine is the preferable alternative to oxybutynin in the treatment of NDO in children since it is effective and well tolerated (even for higher doses).

Adult Population – Efficacy over Placebo

Several studies evaluated the efficacy and tolerability of propiverine, demonstrating a significant reduction in number of incontinence episodes and a significant increase in the average micturition volume over placebo [69]. Lee et al. [70] investigated the effects of propiverine in patients with OAB, focusing on improving urgency, the cornerstone symptom of OAB. 264 patients with OAB were randomized to receive a placebo or 20 mg propiverine once daily in a 12-week study. The daily urgency episodes reduced significantly from baseline to 12 weeks on propiverine treatment, compared with placebo (–46.0 vs. –31.3%, $p = 0.005$). Secondary endpoints, including sum

of urgency severity per 24 h, urgency severity per void, and daytime voiding frequency, were also improved significantly in the propiverine group. Overall, of those patients treated with propiverine, 38.7% rated their treatment as providing 'much benefit', compared with 15.2% of the placebo group ($p = 0.025$). AEs reported by 32 (22.5%) and 10 (12.7%) patients in the propiverine and placebo groups were all tolerable. Even if this was a short-term study using only one fixed regimen, the authors demonstrated that propiverine 20 mg once daily could be an effective treatment for patients with OAB, by improving urgency.

Jünemann et al. [57] compared the efficacy of propiverine hydrochloride IR 15 mg twice daily, propiverine hydrochloride ER 30 mg once daily and placebo in three parallel groups for the treatment of OAB. Treatment duration was 32 days. 988 patients were randomized, and 910 patients completed the protocol without major violations. The number of incontinence episodes/24 h decreased by 2.26 in the IR group ($p < 0.001$ vs. placebo), by 2.46 in the ER group ($p < 0.0001$ vs. placebo) and by 1.75 in the placebo group. The most frequent AE was dry mouth with 22.8% of the patients in the IR group, 21.7% in the ER group and 6.4% in the placebo group. The overall tolerability was rated 'very good' or 'good' by more than 80% of the investigators and patients in all three groups. The authors concluded that propiverine ER 30 mg once daily and propiverine IR 15 mg twice daily significantly reduce the number of incontinence episodes/24 h within a treatment period with both formulations being safe and well tolerated.

The clinical effectiveness of propiverine was maintained after chronic use, but symptoms were reported to recur upon discontinuation of treatment [71].

Comparative Studies

Propiverine versus Tolterodine

In a randomized, double-blind, multicenter trial 15 mg propiverine b.i.d. was compared to 2 mg tolterodine b.i.d. over a period of 28 days in the treatment of patients with idiopathic DO. The study demonstrated comparable efficacy (significant increase in mean maximum cystometric capacity, volume at first urge and the frequency/volume chart parameters), tolerability, and improvement in the QoL between the studied compounds [72].

Propiverine versus Oxybutynin

Abrams et al. [73] compared the effects of propiverine and oxybutynin on ambulatory urodynamic monitoring

parameters, safety, and tolerability in patients with OAB. 77 patients received two of the following treatments during two 2-week periods: propiverine 20 mg once daily, propiverine 15 mg three times daily, oxybutynin 5 mg three times daily, and placebo. A consistent order in the efficacy between active treatment groups was observed for the reduction in mean involuntary detrusor contractions (oxybutynin 15 mg $\leq$ propiverine 45 mg $\leq$ propiverine 20 mg). Differences between the oxybutynin and propiverine 20-mg groups were statistically significant for several ambulatory urodynamic monitoring endpoints. The incidence of dry mouth was significantly more pronounced in the oxybutynin group than in either propiverine group. Treatment with propiverine 45 mg resulted in the highest rates of constipation, lengthening of the visual near point, and effects on heart rate. The authors concluded that oxybutynin 15 mg was more effective than propiverine 20 mg in reducing symptomatic and asymptomatic involuntary detrusor contractions in ambulatory patients. The primary differences between the two drugs were the incidence and type of AE, which varied with the antimuscarinic receptor specificity of each agent.

Madersbacher et al. [74] assessed the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence in a randomized, double-blind placebo-controlled clinical trial. In all, 366 patients (149 on propiverine 15 mg t.i.d., 145 oxybutynin 5 mg b.i.d. and 72 placebo, ratio 2:2:1) with urgency and urge incontinence were recruited in 32 study centers. Drugs were administered for 4 weeks, using the double-dummy technique. After 4 weeks of treatment, dry mouth occurred in 53% of patients in group 1, in 67% of group 2 and in 28% of group 3, and it was less severe in group 1 than group 2. In contrast to groups 2 and 3, only patients in group 1 showed increasing tolerability during the treatment. These tolerability results were further supported by the overall tolerability assessment ('very good' or 'good' tolerability in 67% of group 1, in 59% of group 2 and in 83% of group 3). The urodynamic assessment of efficacy showed a statistically significant increase in the mean maximal cystometric bladder capacity in group 1 and in group 2 compared with group 3. The cystometric bladder capacity at first desire to void also increased in group 1 (93–160 ml) and group 2 (89–160 ml), whereas in group 3 there were only minor changes (93–120 ml). Changes in the residual urine volume within and between the treatment groups were minimal and clinically irrelevant. The overall assessment of efficacy showed significant differences between the drugs when compared with placebo.

The authors concluded that propiverine is safe, equieffective to oxybutynin, but with lower rates of AEs.

In the NDO setting, propiverine 15 mg t.i.d. or oxybutynin 5 mg t.i.d. were demonstrated equally effective in increasing bladder capacity and lowering bladder pressure with a significant trend in favor of propiverine regarding mouth dryness [75].

Propiverine versus Solifenacin

Yamaguchi et al. [76] performed a multicenter, 12-week, double-blind phase III trial randomizing men and women aged ≥ 20 years with OAB to solifenacin 5 or 10 mg, propiverine 20 mg, or placebo. Of 1,584 treated patients, both compounds demonstrated significantly greater reductions in mean voids/24 h compared to placebo with solifenacin being no worse than propiverine for this variable. There were also significantly fewer mean urgency, incontinence and urgency incontinence episodes with solifenacin and propiverine than with placebo. All active treatments versus placebo improved the volume voided and QoL. Solifenacin 10 mg reduced nocturia episodes and significantly improved urgency episodes and volume voided versus propiverine 20 mg, and solifenacin 5 mg caused less dry mouth. Solifenacin 10 mg caused more dry mouth and occurrences of constipation than propiverine 20 mg, but discontinuation rates between both treatment groups were similar. Continence was restored at endpoint in more than half of the patients on active treatment.

According to the ICS, propiverine has a documented beneficial effect in the treatment of OAB/DO (level of evidence 1, grade of recommendation A) [11].

Cardiovascular Safety

Several studies have demonstrated an overall favorable 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 for propiverine [69, 77].

Adverse Events

Propiverine ER 20 mg/day was found to be associated with a statistically significantly higher risk of withdrawal due to AE than placebo (RR 2.39; 95% CI 1.20–4.78; $p = 0.01$) [30].

Mild dry mouth was found to be statistically significantly more common in patients treated with propiverine than with placebo [30]. The following AEs were reported

at statistically significantly higher levels with propiverine than in placebo: blurred vision (propiverine 20, 30, and 45 mg/day) and constipation (15 mg/day; propiverine ER 20 mg/day, and IR 3 and 4.5 mg/day) [30].

Blurred vision was reported at statistically significantly higher levels with propiverine IR 45 mg/day versus oxybutynin IR 7.5–10 mg/day, while constipation was significantly higher for solifenacin 10 mg/day versus propiverine ER 20 mg/day. Nausea was significantly higher for oxybutynin IR 7.5–10 mg/day versus propiverine IR 45 mg/day [30].

Central Nervous System Side Effects of Antimuscarinic Agents

Since the muscarinic receptor mediates the excitatory and inhibitory actions of acetylcholine in the central and peripheral nervous systems, various systemic AEs may occur by the administration of antimuscarinic agents for OAB. The incidence of central nervous system (CNS) side effects by antimuscarinic agents is generally lower than that of dry mouth, but CNS side effects may be of great concern in elderly patients because of an increase of blood-brain barrier permeability with aging [78, 79]. In fact, short-term and chronic administration of oxybutynin in elderly subjects resulted in a non-degenerative mild cognitive dysfunction [80, 81].

Antimuscarinic agents are considered to exert CNS side effects by binding to brain muscarinic receptors. Oki et al. [82] have recently shown that oral administration of oxybutynin but not tolterodine and darifenacin bound significantly to muscarinic receptors in the mouse brain. However, these authors examined the effects of only single and low dose of each agent on brain muscarinic receptor binding.

Todorova et al. [83] comparatively evaluated electrophysiologic effects of antimuscarinic agents on the CNS in healthy male volunteers by using quantitative electro-

cephalography (qEEG). They found that oxybutynin significantly altered qEEG activity, whereas tolterodine and trospium induce only a slight effect on qEEG activity. Similar electrophysiological results in healthy males with oxybutynin have been shown by Pietzko et al. [84].

In addition, muscarinic receptor subtype selectivity of antimuscarinic agents may be implicated in the appearance of the CNS effect. All of five muscarinic receptor subtypes are expressed in the brain [85, 86]. The M_1 receptor was abundant in the cortex and hippocampus. In the striatum, the M_1 and M_4 receptors were distributed. In contrast, the M_2 receptor was predominantly localized in the brainstem and cerebellum. The M_3 receptor displays lower density in the brain when compared with M_1 , M_2 , and M_4 receptor expressions. The cognitive dysfunction by antimuscarinic agents may be mediated mainly by the M_1 and M_2 receptors in the CNS [87]. Oxybutynin shows selectivity for the M_1 , M_3 , and M_4 receptors, whereas tolterodine and propiverine are relatively non-selective to muscarinic receptor subtypes [88, 89]. Thus, M_1 selectivity in addition to high blood-brain barrier permeability of oxybutynin may be more apt to cause CNS side effects.

Conclusions

Both propiverine and oxybutynin are efficacious, safe, and well-tolerated treatments for OAB, which improve HRQoL. Propiverine shows a significantly better tolerability profile than oxybutynin, both for adults and children suffering from OAB. Once-a-day formulations of these agents seem to be better tolerated by patients and potentially more efficacious in improving OAB symptoms as well as in terms of patient perception of treatment impact.

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