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Clinical experiences with tolterodine

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Abstract

Tolterodine is the first muscarinic receptor antagonist that has been specifically developed for the treatment of overactive bladder. The objectives in the discovery program were to design a potent muscarinic receptor antagonist that is equipotent to oxybutynin in the bladder, but less potent in salivary glands, with the aim of improving tolerability (less dry mouth) in patients with overactive bladder. Tolterodine is non-selective with respect to the muscarinic M_1–M_5 receptor subtypes, but has a greater effect on the bladder than on salivary glands *in vivo*, in both animals and humans. Clinical results show that the efficacy and safety of tolterodine in overactive bladder is equal to that of oxybutynin, but that tolterodine is significantly better tolerated by the patients.

Keywords: Urinary bladder; Urge incontinence; Dry mouth; Selectivity; Human

Introduction

Overactive bladder is a chronic and debilitating urological condition (characterised by the symptoms of frequency and urgency, with or without urge incontinence) which has a profound effect on the quality of life and activities of daily living for the patients [1]. Muscarinic receptor antagonists are routinely used in the treatment of overactive bladder and the efficacy and safety of oxybutynin (e.g. Ditropan®) in this condition have been well documented [2,3]. However, at least 50% of patients treated with oxybutynin experience dry mouth [2], which often results in discontinuation of treatment [2–4]. Tolterodine is the first muscarinic receptor antagonist that has been specifically developed for the treatment of overactive bladder.

Pharmacological data from functional *in vitro* and radioligand binding studies show that tolterodine is equipotent to oxybutynin in the urinary bladder, whereas the affinity of tolterodine is 8-fold lower than that of oxybutynin in salivary glands [5,6]. Tolterodine shows a selectivity for the bladder over salivary glands in the anaesthetised cat, while oxybutynin and

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other M_3-selective antagonists show the opposite selectivity in this model [5,6]. The selectivity of tolterodine *in vivo* is not due to muscarinic receptor subtype selectivity, since tolterodine is non-selective with respect to the M_1–M_5 receptor subtypes [5,6]. This tissue-selectivity can probably also not be attributed to secondary actions in smooth muscles, because screening of >50 receptors and other targets, showed that tolterodine exhibits significant affinity only at muscarinic receptors [Nilvebrant, unpublished data].

Bladder function is complex, and several muscarinic receptor subtypes may be involved. Data on tolterodine and oxybutynin (M_3/M_1 selective) and other antagonists, indicate that both M_3 and M_2 receptors may be important for bladder contraction *in vivo* [5,6]. This is supported by results from other studies on bladder contraction *in vitro* and *in vivo* [7]. It has further been found that prejunctional excitatory M_1 receptors might be important in bladder function [8]. The pharmacological profile of tolterodine has been reported and reviewed elsewhere [5,6 and refs. therein]. This paper will concentrate on the clinical experience with tolterodine. The documentation of tolterodine in patients represents the largest clinical development program that has been undertaken for any drug in the treatment of overactive bladder [9].

Early clinical studies with tolterodine

Clinical phase I studies in healthy volunteers

The first phase I study with tolterodine (0.2–12.8mg) showed that the effect on the bladder was more marked and long-lasting than the effect on salivation. After 12.8mg, volunteers reported micturition difficulties up to 16h post-dose [10]. The effects of tolterodine (6.4mg) on the bladder were objectively measured by cystometry in another study. The pharmacological effect on the bladder was immediate and sustained (>5h post-dose), while the effect on salivation was apparent only around the peak serum concentration (1–2h post-dose) [11]. This indicated that the effect on the bladder might be dose-limiting. A twice daily (bid) dosage regimen was therefore selected for the phase II dose-finding studies in patients [6,12].

Metabolism- extensive and poor metabolisers

Tolterodine is extensively metabolised in the liver, mainly via cytochrome P450 2D6 (CYP 2D6) to the 5-hydroxymethyl derivative (5-HM, labcode DD 01)[6]. The pharmacological profile of this metabolite is almost identical to that of tolterodine and 5-HM contributes to the therapeutic effect [6]. Some individuals (about 7% of Caucasians) lack the CYP 2D6 enzyme (poor metabolisers) and can not form 5-HM, but get higher serum levels of tolterodine [12]. A concentration-effect relationship has been demonstrated between the sum of unbound serum concentrations (tolterodine+5-HM) and clinical effects on the bladder (phase II data) [12]. Clinically effective serum concentrations are comparable to the K_i/K_B-values determined for tolterodine and 5-HM at bladder muscarinic receptors. It was concluded that 5-HM is responsible for the clinical effect in extensive metabolisers, whereas the clinical effect in poor metabolisers is due to tolterodine. The efficacy, safety and tolerability were similar in poor and extensive metabolisers. The same dose of tolterodine can therefore be used, irrespective of metabolic phenotype [6,12].

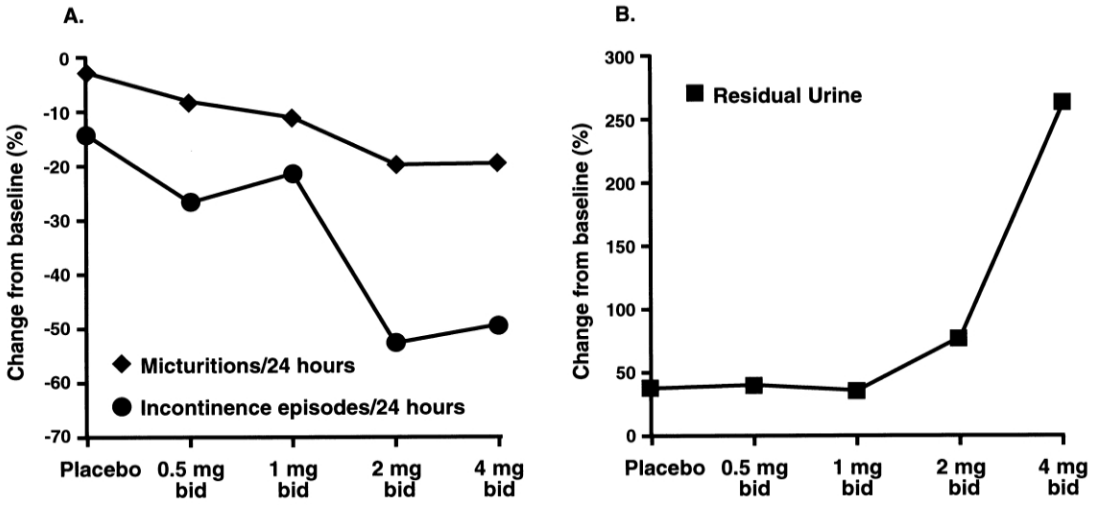

Fig. 1. Efficacy results in phase II. Panel A shows the dose-dependent decrease in number of micturitions and incontinence episodes/24h after 2 weeks of treatment with tolterodine. Panel B shows the increase in residual urine after 2 weeks of tolterodine treatment.

Clinical phase II studies in patients with detrusor instability or detrusor hyperreflexia

Tolterodine 0.5, 1, 2 and 4mg bid and placebo (2 weeks) were compared in 4 phase II studies (319 patients). A pooled analysis of urodynamic variables indicated that tolterodine 4mg was the most effective dose [12]. A dose-dependent effect was also seen on number of micturitions/24h and number of incontinence episodes/24h, but 4mg tolterodine did not have a greater effect than 2mg on these symptoms (Fig.1). This was attributed to the dramatic increase in residual volumes in the 4mg group (Fig.1). Apparently, tolterodine 4mg interfered with the normal bladder function, resulting in incomplete emptying and decreased functional bladder capacity. There were 4 cases of urinary retention in the 4mg group [12]. Tolterodine 1 and 2mg bid were therefore selected for evaluation in the phase III program.

Clinical phase III studies

The phase III program for tolterodine comprised 8 double blind, randomised studies in 15 countries and involved 2080 patients. Four of the 8 studies were 4 weeks in treatment duration and compared tolterodine 1 and 2mg bid versus placebo. The other 4 studies were 12 week treatment duration studies. Two of these compared tolterodine (2mg bid) to oxybutynin (5mg tid —i.e., three times daily) and placebo, one study compared tolterodine (2mg bid) to oxybutynin (5mg tid) and one study compared tolterodine (1 and 2 mg bid) to placebo. Micturition diaries were used for measurement of efficacy in all studies, with numbers of micturition/24h as the primary end-point. Efficacy was measured also by urodynamics in one of the studies comparing tolterodine 1 and 2mg to placebo during 4 weeks [13]. Several reports of individual phase III studies have been published and reviewed [3,9,14 and refs. therein].

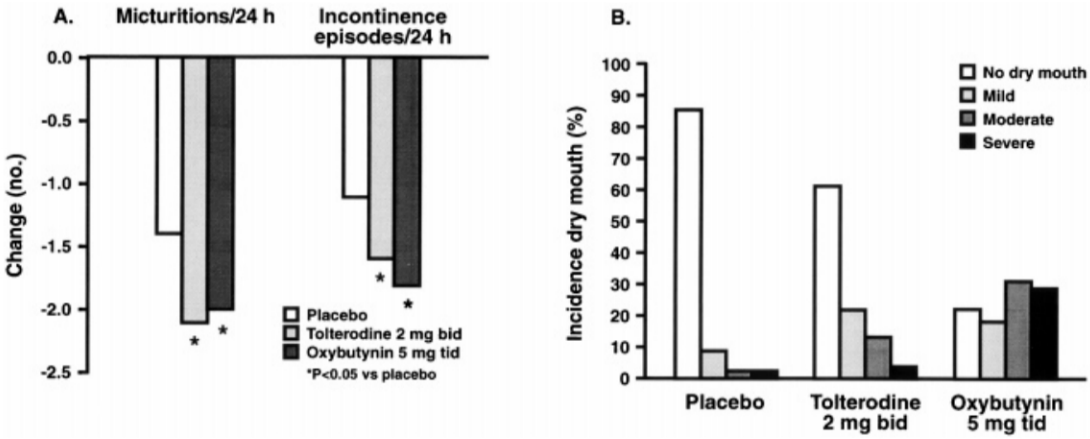

Fig. 2. Efficacy and tolerability of tolterodine 2mg bid, oxybutynin 5mg tid and placebo, after 12 weeks of treatment (phase III results). Panel A shows the decrease in the number of incontinence episodes and micturitions/24h. Panel B shows the incidence of dry mouth (none, mild, moderate, or severe) for the different treatment regimens used in phase III.

Efficacy

Tolterodine 1 and 2mg bid were both superior to placebo in efficacy, although the difference between tolterodine 1 and 2mg was not always clear-cut, as measured by micturition diary variables [9,14]. However, the study with urodynamic evaluation showed a dose-effect relationship and that only the effect of tolterodine 2mg (not 1mg) was significant [13]. The greater effect of tolterodine 2mg over 1mg was further manifested in the subjective assessment of patients perception of improvement of their bladder condition [3,9].

In each of the comparative 12 week studies, tolterodine 2mg bid was shown to be equivalent to oxybutynin 5mg tid with regards to efficacy on micturition and number of incontinence episodes. A pooled analysis of data showed that both tolterodine and oxybutynin are significantly more effective than placebo (Fig 2), although a statistical significance was not achieved for all efficacy variables in each individual study [9,14]. As compared to base-line values, the number of micturitions/24h decreased by 20% for both tolterodine and oxybutynin. The number of incontinence episodes/24h decreased by 40–60% and the mean volume voided per micturition increased by 18–28%. Patients overall subjective perception of improvement of their bladder condition was also similar for tolterodine and oxybutynin [3,9]. Interestingly, the compliance was higher in the tolterodine than in the oxybutynin group [9].

Safety and tolerability

Tolterodine 2mg bid was equal to both placebo and oxybutynin 5mg tid, with respect to general safety and there were no cardiovascular safety concerns in the studies of tolterodine [3,9,14]. Except for dry mouth, tolterodine did not differ from placebo in the incidence of classical antimuscarinic side-effects, while oxybutynin had a higher incidence of side-effects related to the gastro-intestinal tract [9,14]. Dry mouth was the most commonly reported ad-

verse event for all groups: placebo (16%), tolterodine (40%) and oxybutynin (78%). However, it was classified as moderate to severe by 60% of patients on oxybutynin, as compared to only 17% for tolterodine and 6% for placebo (Fig 2). Withdrawals from the studies because of side-effects were significantly less frequent in tolterodine (8%) and placebo (5%) patients, than in the oxybutynin group (20%). Similarly, 32% of patients treated with oxybutynin required a dose-reduction, as compared to only 9% in the tolterodine and 4% in the placebo group [9]. Tolterodine was thus significantly better tolerated than oxybutynin in these studies.

Long-term results

The efficacy and tolerability of tolterodine have been confirmed in long-term open-label studies of 9–12 months duration. Thus, for example, 512 of 815 (63%) patients completed treatment for 12 months with maintained efficacy and only 3% of patients withdrew because of dry mouth [3,14]. Similar results were reported for 854 patients offered to enter a 9-month treatment period [3]. The use of antimuscarinic agents in overactive bladder (primarily oxybutynin) has previously been disappointing because the compliance among patients has been low [2] and in more than 80% of the patients resulted in discontinuation of treatment within 6 months, due to side-effects, primarily dry mouth [4].

General comments and considerations regarding clinical trials in overactive bladder

Overactive bladder is a difficult condition for clinical trials because objective urodynamic findings do not always correlate well with the subjective symptoms of the patient. Urodynamics was therefore used for evaluation of efficacy in only one of the phase III studies, while micturition diaries were used in all studies to measure the meaningful patient variables. Frequency of micturition/24h was the primary end-point, whereas numbers of incontinence episodes/24h and mean volume voided per micturition were secondary end-points. This is important, with respect to the outcome of the individual phase III studies because, although all patients had symptoms of an overactive bladder, all of them were not incontinent. Therefore, the individual phase III studies on tolterodine were not powered to measure statistically significant decreases in incontinence episodes [9].

This is illustrated by a later, large study comparing tolterodine 2mg bid (n=514) to placebo (n=508) for 12 weeks, in which the number of incontinence episodes was used as primary end-point. Thus, tolterodine 2mg bid significantly decreased the number of incontinence episodes (46%) and the number of micturitions (15%), while the mean volume voided increased by 21% [15]. Overall, these results were very similar to those of the phase III studies and showed statistically significant changes as compared both to base-line values and placebo, for all efficacy variables. Interestingly, this study also attempted to measure the effect on urgency, a symptom that probably is more bothersome and relevant to the patient, than frequent micturitions *per se*. The results showed a decreased sensation of urgency in 40% of tolterodine patients *vs.* 26% on placebo and this was accompanied by a 36% decrease in the number of pads used in the tolterodine group *vs.* a 13% decrease in the placebo group [15].

Similarly, the placebo effect was fairly high in all tolterodine studies and this was not unexpected, because the frequent use of micturition diaries to measure subjective effects intro-

duced an element of bladder training into these studies. Bladder training is indeed important in the management of patients with overactive bladder and it is certainly effective in the short term, although it also affects the placebo response in clinical trials of drugs [9,15].

Another important point is the dose of oxybutynin used in the comparative phase III studies (5mg tid). This is the recommended dose, but it is well known that many patients cannot tolerate this dose of oxybutynin. In clinical practise it is therefore common to use a lower dose or dose-titration [3,14]. However, in order not to underestimate the efficacy of oxybutynin, the recommended dose was used, but with a possibility to reduce the dose in case of intolerable side-effects. A comparative study using tolterodine 2mg bid, but a lower dose of oxybutynin (2.5mg, increasing to 5mg bid, with a possibility to revert to the lower dose) in patients °50 years was therefore done[14]. The results confirmed that the two drugs are equally effective, whereas tolterodine still has a superior tolerability profile-even in comparison to a lower than recommended dose of 5mg tid for oxybutynin [3,14].

In the 12 week phase III studies, where efficacy was measured by micturition diaries, it was noticed that it took about 5–8 weeks of treatment before the effect of both tolterodine and oxybutynin reached a maximum [9]. This may seem surprising, since a direct effect on the bladder is objectively demonstrable after a single dose of tolterodine [11]. However, micturition diaries do not reflect the direct pharmacological effect on the bladder and it takes time before the patients learn to trust their medication and change their habits (e.g. scheduled voiding and fluid intake) [9,15]. Thus, it is important to note that the mean volume voided per micturition actually increases already before any change can be noted in the number of micturitions or incontinence episodes and that this reflects the pharmacological effect (increased bladder capacity) [12].

Tolterodine in elderly

The prevalence of overactive bladder increases with age and it is therefore important to demonstrate safety in this population, particularly since it is well known that e.g. oxybutynin may have a negative impact on cognitive function [16]. It has been shown that neither the efficacy, nor the safety of tolterodine seems to differ between patients aged <65 and those >65 years of age [14]. Tolterodine is >30 times less lipophilic than oxybutynin and 5-HM is another 12 times less lipophilic than tolterodine—i.e.,>350 times less lipophilic than oxybutynin. Thus, given the fact that the unbound serum concentration of 5-HM is 10 times greater than that of tolterodine, treatment with tolterodine would be expected to have a lower risk of a potential negative impact on cognitive function, than treatment with oxybutynin [17]. This is supported by tissue-distribution data in the mouse (after oral treatment with ^{14}C-tolterodine) which clearly show that the distribution of tolterodine and its metabolites into the central nervous system is very low [17] and by a recent study using quantitative EEG for measurements of potential effects of tolterodine, oxybutynin and placebo on the central nervous system. In this study, oxybutynin was shown to have significant effects on the EEG pattern, while tolterodine did not show any effects [18].

Tolterodine in children

Tolterodine is not yet licensed for use in children, but one open-label 3 month study in 22 children has been published [19]. This study included 12 children who had previously not re-

ceived drug treatment and 10 who were switched from oral or intravesical oxybutynin to treatment with tolterodine. The tolterodine dose used was 0.1 mg/kg/day (0.5–4mg/day). The results showed that tolterodine is equally effective, but better tolerated, as compared to oxybutynin in children with detrusor hyperreflexia [19]. Only one patient experienced a moderate, transient side-effect during tolterodine treatment. The dose used was higher than that recommended in adults (2mg bid—i.e., 0.06–0.07mg/kg/day). Moreover, pharmacokinetics in children is not the same as in adults and other studies indicate that children get a higher exposure. Thus, 1mg bid might be the optimal dose for children [data on file, Pharmacia]. Therefore, tolterodine should not be used in children until more documentation is available.

Tolterodine— once daily formulation

A new once daily (qd) formulation of tolterodine 4mg has recently been developed and studied *vs.* placebo in a clinical study of 12 weeks duration [20]. Tolterodine qd was significantly superior to placebo with respect to the number of incontinence episodes and other micturition diary variables. For example, incontinence episodes decreased by 71% and number of micturitions by 17%, while the volume voided per micturition increased by 24%—i.e., the results with tolterodine 4mg qd are comparable to those reported for tolterodine 2mg bid. More patients on placebo (6.5%) withdrew from treatment due to adverse events, than in the tolterodine qd group (5.3%). Dry mouth was reported by 23% in the tolterodine qd group and by 8% in the placebo group [20]. Thus, the tolerability of tolterodine may have been somewhat improved in this qd formulation, although a qd dosing might not be optimal for all patients with an overactive bladder.

Conclusion

The clinical results with tolterodine *vs.* oxybutynin confirm the preclinical studies—in which tolterodine showed a selectivity for the urinary bladder over salivary glands *in vivo*, whereas oxybutynin exhibited the reversed selectivity profile. Thus, tolterodine is equipotent to oxybutynin, with respect to the efficacy on overactive bladder symptoms in patients, but tolterodine shows a significantly better tolerability with respect to dry mouth and compliance.

References

1. Lenderking WR, Nackley JF, Anderson RB, Testa MA. A review of the quality-of-life aspects of urinary incontinence. Pharmacoeconomics 1996;9:11–23.
2. Yarker YE, Goa KL, Fitton A. Oxybutynin. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability. Drugs & Ageing 1995;6(3):243–62.
3. Chapple CR. Muscarinic receptor antagonists in the treatment of overactive bladder. Urology 2000;55 (5A, Suppl):33–46.
4. Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A medium term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladder compliance. British Journal of Obstetrics and Gynaecology 1997;104:988–93.
5. Nilvebrant L, Hallén B, Larsson G. Tolterodine— a new bladder selective muscarinic receptor antagonist: Preclinical pharmacological and clinical data. Life Sciences 1997;60(13/14):1129–36.
6. Nilvebrant L. The mechanism of action of tolterodine. Reviews in Contemporary Pharmacotherapy 2000;11(1):13–27.

7. Hegde SS, Chopin A, Bonhaus D, Biaud S, Loeb M, Moy TM, Loury D, Eglen RM. Functional role of M_2 and M_3 muscarinic receptors in the urinary bladder of rats *in vitro* and *in vivo*. British Journal of Pharmacology 1997; 120:1409–18.
8. Somogyi GT, de Groat WC. Function, signal transduction mechanisms and plasticity of presynaptic muscarinic receptors in the urinary bladder. Life Sciences 1999;64 (6/7):411–19.
9. Appell RA. Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. Urology 1997;50 (6A, Suppl.):90–6.
10. Brynne N, Stahl MMS, Hallén B, Edlund PO, Palmér L, Höglund P, Gabrielsson J. Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity. International Journal of Clinical Pharmacology and Therapeutics 1997;35(7):287–95.
11. Stahl MMS, Ekström B, Sparf B, Mattiasson A, Andersson K-E. Urodynamic and other effects of tolterodine: a novel antimuscarinic drug for the treatment of detrusor overactivity. Neurourology and Urodynamics 1995;14(6):647–55.
12. Larsson G, Hallén B, Nilvebrant L. Tolterodine in the treatment of overactive bladder: analysis of the pooled phase II efficacy and safety data. Urology 1999;53(5):990–5.
13. Jonas U, Höfner K, Madersbacher H, Holmdahl TH-and the participants of the international study group. Efficacy and safety of two doses of tolterodine vs. placebo in patients with detrusor overactivity and symptoms of frequency, urge incontinence and urgency: urodynamic evaluation. World Journal of Urology 1997;15: 144–51.
14. Malone-Lee JG. The efficacy, tolerability and safety profile of tolterodine in the treatment of overactive/unstable bladder. Reviews in Contemporary Pharmacotherapy 2000;11(1):29–42.
15. Chancellor M, Freedman S, Mitcheson HD, Antoci J, Primus G, Wein A. Tolterodine, an effective and well tolerated treatment for urge incontinence and other overactive bladder symptoms. Clinical Drug Investigation 2000;19(2):83–91.
16. Katz IR, Sands LP, Bilker W, DiFilippo S, Boyce A, D'Angelo K. Identification of medications that cause cognitive impairment in older people: the case of oxybutynin. Journal of the American Geriatrics Society 1998;46(1):6–13.
17. Nilvebrant L, Påhlman I, d'Argy R. Tissue distribution of tolterodine and its metabolites: low penetration into the central nervous system. European Urology 2000;37(Suppl 2):84 (Abstract 333).
18. Dimpfel W, Todorova A, Vonderheid B. Electrophysiological evaluation of potential adverse effects of tolterodine, oxybutynin and trospium chloride on the central nervous system. Neurourology and Urodynamics 2000;19 (4):487–8 (Abstract 94).
19. Goessel C, Sauter T, Michael T, Bergé B, Staehler M, Miller K. Efficacy and tolerability of tolterodine in children with detrusor hyperreflexia. Urology 2000; 55(3):414–18.
20. Van Kerrebroeck PEVA (on behalf of the tolterodine study group). Significant decreases in perception of urgency and urge incontinence episodes with once-daily tolterodine treatment in patients with overactive bladder. Neurourology and Urodynamics 2000; 19(4):493–4 (Abstract 89).