Drugs 1998 Jun; 55 (6): 813-820
0012-6667/98/0006-0813/$08.00/0



# Tolterodine

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## Contents



## Summary

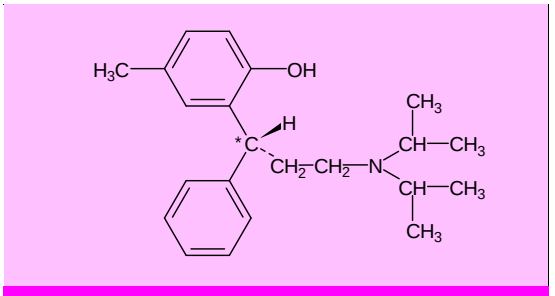
▲ Tolterodine is a competitive muscarinic receptor antagonist which has recently been launched for the treatment of overactive bladder.

▲ Tolterodine shows functional selectivity for the bladder over the salivary glands *in vivo*, which is not attributable to muscarinic receptor subtype selectivity. It is as potent as oxybutynin in inhibiting bladder contraction, but is much less potent in inhibiting salivation, suggesting that it may have less propensity to cause dry mouth in clinical use.

▲ In patients with overactive bladder, tolterodine significantly reduces the frequency of micturition and number of incontinence episodes, while increasing the average volume voided. The onset of pharmacological action of tolterodine is <1 hour and therapeutic efficacy is maintained during long term treatment.

▲ In comparative trials, tolterodine and oxybutynin are equivalent in terms of efficacy. However, tolterodine is significantly better tolerated than oxybutynin, particularly with respect to the incidence and severity of dry mouth. No clinically relevant ECG changes have been noted with tolterodine.

| Features and properties of tolterodine | |
|---|---|
| **Indications** | |
| Treatment of overactive bladder with symptoms of urinary urgency, frequency or urge incontinence | Launched |
| **Mechanism of action** | |
| Muscarinic receptor antagonist | |
| **Dosage and administration** | |
| Recommended dosage | 2mg twice daily |
| Dosage in impaired hepatic function | Maximum 1mg twice daily |
| Route of administration | Oral |
| **Pharmacokinetic profile** | |
| Peak plasma concentration | 2.5 μg/L after 2mg dose |
| Time to peak plasma concentration | 2.5h |
| Elimination | Mostly in urine (77%) |
| Elimination half-life | 2.4h |
| **Adverse events** | |
| Most frequent | Dry mouth |




**Tolterodine**

Overactive bladder is a common and distressing problem. Extrapolation of available data[1,2] suggests that it may affect more than 50 million individuals in the developed world (data on file, Pharmacia & Upjohn). However, accurate estimation of the prevalence of urinary incontinence, one symptom of overactive bladder, is limited by the reluctance of individuals to admit to this disorder and by between-study differences in assessment criteria used.

Overactive bladder occurs in both sexes and is a result of involuntary contractions of the detrusor muscle during bladder filling. The characteristic symptoms are frequency of micturition, a strong and sudden desire to micturate resulting from involuntary detrusor contractility (urgency) and, if the contraction cannot be suppressed, involuntary urine loss (urge incontinence).

Current management of overactive bladder encompasses both nonpharmacological (e.g. bladder training) and pharmacological strategies. Antimuscarinic agents are the most common drugs used, as both normal voiding processes and involuntary detrusor contractions during bladder filling are mediated mainly by muscarinic receptors.[3]

Tolterodine is a new muscarinic receptor antagonist for the treatment of patients with overactive bladder with symptoms of urinary urgency, frequency or urge incontinence.

## 1. Pharmacodynamic Profile

### Receptor Binding Studies

- Tolterodine is a competitive, pure muscarinic receptor antagonist.[4] It is not specific for any muscarinic receptor subtype, as shown by binding studies using human muscarinic receptor subtypes (m1 to m5) expressed in Chinese hamster ovary cells.[4,5]

- Tolterodine shows similar binding affinity to oxybutynin (a muscarinic receptor antagonist showing selectivity for $M_3$ over $M_2$ receptors) in human and guinea-pig urinary bladder ($K_i$ 3.3 *vs* 4.5 and 2.7 *vs* 4.0 nmol/L, respectively).[4-6] However, tolterodine has 8-fold lower affinity than oxybutynin for muscarinic receptors in guinea-pig parotid gland ($K_i$ 4.8 *vs* 0.62 nmol/L),[4] which contains a homogeneous population of the $M_3$ muscarinic receptor subtype.

- In guinea-pig parotid gland, competitive radioligand binding studies show that tolterodine produces a concentration-inhibition curve for (–) $^3$H-quinuclidinyl benzilate binding to the right of that with oxybutynin. In contrast, the concentration-inhibition curves for the 2 drugs in the bladder are similar.[4]

- *In vitro* studies with the 5-hydroxymethyl metabolite of tolterodine (DD 01) demonstrate that the metabolite possesses a receptor binding profile almost identical to that of the parent compound.[7]

### Effects on Bladder Contractility and Salivary Gland Function

#### *Animal and* In Vitro *Studies*

- Tolterodine completely blocks electrically induced contractions of both stable and overactive human bladder *in vitro*, with a potency similar to that of oxybutynin [$IC_{50}$ (concentration producing half-maximal inhibition) 2.5 *vs* 3.2 nmol/L].[8]

- *In vitro*, both tolterodine and DD 01 are as potent as oxybutynin in inhibiting carbachol-induced contractions of guinea-pig bladder.[4-7]

- Tolterodine is more potent in bladder smooth muscle than in salivary glands *in vivo*. It has a

greater inhibitory effect on acetylcholine-induced bladder contractions than on electrically induced salivation in the anaesthetised cat (fig. 1). This cannot be attributed to muscarinic receptor subtype selectivity. Conversely, oxybutynin, which shows selectivity for $M_3$/m3 over $M_2$/m2 receptors *in vitro*, has greater selectivity for stimulated salivation than for bladder contraction in this model.[4]

- DD 01 has an *in vitro* and *in vivo* pharmacological profile almost identical to that of tolterodine.[7]

#### *Human Studies*

- Phase I studies have shown that single oral doses of tolterodine have an inhibitory effect on human bladder function. This effect occurs within 1 hour of oral administration.[9,10] In a single-dose study in healthy volunteers, the frequency of micturition difficulties with tolterodine was dose-dependent, occurring in 1 of 8 subjects who took 6.4mg and 6 of 8 who took 12.8mg.[9] This inhibitory effect on bladder function persisted for up to 16 hours after administration of tolterodine 12.8mg, at which dose stimulated salivation was also decreased.[9]

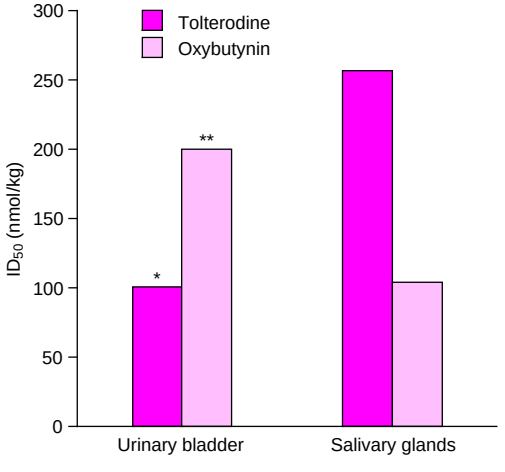



**Fig. 1.** Bladder selectivity of tolterodine. Intravenous doses of tolterodine and oxybutynin required to inhibit acetylcholine-induced bladder contraction and electrically stimulated salivation by 50% ($ID_{50}$) in the anaesthetised cat; *p < 0.05; **p < 0.01 *vs* effect on salivation.[4]

- Objective cystometric studies in 12 healthy volunteers showed that at up to 5 hours after a single oral tolterodine dose of 6.4mg, volume at first sensation and normal desire to void was increased, while detrusor pressure decreased, in comparison with baseline. Residual urinary volume was also markedly increased, indicating that this dose was excessive for clinical use.[10]

- Inhibitory effects of tolterodine on stimulated salivation in these 2 studies were apparent only around the time of peak serum drug concentrations[9,10]

## 2. Pharmacokinetic Profile

### Absorption and Distribution

- The pharmacokinetic profile of tolterodine is linear over the dose range 1 to 4mg,[11] and does not appear to be affected by age or gender.[12,13]

- Peak serum tolterodine concentrations ($C_{max}$) of 2.5 μg/L were achieved 2.5 hours after oral administration of a 2mg dose. The area under the serum concentration-time curve was 11.8 μg/L · h. Corresponding values for DD 01 were quite similar (2.2 μg/L and 12.1 μg/L · h).[14]

- The bioavailability of tolterodine is quite variable, ranging from 10 to 70% in healthy volunteers.[15] However, as tolterodine is converted to the active metabolite DD 01, this is not a relevant parameter.

- Tolterodine and DD 01 show considerable differences in their binding to plasma proteins, with 3.7% of tolterodine versus 36% of DD 01 existing as free drug.[16]

### Metabolism and Excretion

- Tolterodine undergoes extensive first-pass metabolism. Two hepatic metabolic pathways have been identified: oxidation and *N*-dealkylation,[17] mediated by the cytochrome P450 isoforms 2D6 (CYP 2D6) and 3A4 (CYP 3A4), respectively. CYP 2D6 metabolises tolterodine to DD 01.[5,15,17] Other metabolites are not considered to contribute to the pharmacological effects of tolterodine.

• Approximately 7% of Caucasians lack the CYP 2D6 enzyme (poor metabolisers) and metabolise tolterodine via CYP 3A4-mediated *N*-dealkylation. Poor metabolisers are therefore characterised by higher serum concentrations of tolterodine compared with extensive metabolisers, with no detectable concentrations of DD 01. In these individuals, the clearance of tolterodine is 9 L/h, resulting in an elimination half-life of approximately 10 hours; corresponding values for extensive metabolisers are 44 L/h and 2 to 3 hours (DD 01 has an elimination half-life of 3 to 4 hours in these individuals).[15] The therapeutic effect in poor metabolisers is therefore attributed to unbound tolterodine. In contrast, it is the sum of the unbound serum concentrations of tolterodine and DD 01 that correlates with the therapeutic effect in extensive metabolisers.[18] Since exposure to unbound active moiety (i.e. tolterodine in poor metabolisers; tolterodine + DD 01 in extensive metabolisers) is similar in all individuals, the dosage of tolterodine does not require adjustment on the basis of CYP 2D6 phenotype.

• Tolterodine is eliminated predominantly by metabolism, with unchanged drug and metabolites being excreted mainly by the renal route (77% of an administered dose). Following oral administration of radiolabelled tolterodine, most of the renally excreted radioactivity (80%) comprised 5-carboxylic acid metabolites, while approximately 5% of the administered dose was parent tolterodine (1%) and DD 01 (4.4%).[9]

### Effects of Disease on Pharmacokinetics

• In individuals with liver cirrhosis, serum drug concentrations and the elimination half-life of tolterodine are increased in comparison with those in healthy volunteers.[19] However, no serious adverse events were reported. Exposure to pharmacologically active moiety (i.e. unbound tolterodine and DD 01) is about 2-fold greater in those with liver cirrhosis compared with healthy volunteers.[18] Thus, dosage reduction is required in patients with hepatic impairment.

• The effect of renal impairment on the pharmacokinetics of tolterodine is yet to be evaluated. Because of possible accumulation of metabolites, tolterodine should be used with caution in patients with severe renal impairment until such data are available.

### Drug Interactions

• Fluoxetine, an inhibitor of the CYP P450 2D6 isoenzyme, slows the rate of metabolism of tolterodine to DD 01 and therefore leads to increased serum drug concentrations. However, combined exposure to the sum of unbound tolterodine and DD 01 was only slightly increased when the drugs were coadministered,[20] which indicates that tolterodine dosage adjustment is not necessary in patients receiving fluoxetine or other CYP 2D6 inhibitors.

• No pharmacokinetic or pharmacodynamic interactions have been reported between tolterodine and warfarin[21] or oral contraceptives (ethinylestradiol/levonorgestrel).[22]

## 3. Therapeutic Trials

### Dose-Ranging and Placebo-Controlled Studies

• Four dose-ranging phase II studies have been performed with tolterodine.[23-26] All 319 patients included in the intent-to-treat analysis in these trials had urodynamically confirmed detrusor instability or detrusor hyperreflexia. Tolterodine was administered for 2 weeks at a dosage of 0.5, 1, 2 or 4mg twice daily to 255 patients, while the remaining patients received placebo.

• A pooled analysis of all phase II studies showed that tolterodine produced a consistent, dose-related reduction in the frequency of micturition and episodes of incontinence. Indeed, tolterodine decreased the frequency of micturition and the number of episodes of incontinence by up to 10 and 53%, respectively. There was no further reduction in the frequency of micturition when the dosage of tolterodine was increased to 4mg twice daily.[27]

• Tolterodine dose-dependently improved urodynamic variables, including significant increases ($p < 0.0001$) in bladder volume at first detrusor contraction and maximum cystometric capacity. Volume at first sensation to void and at normal and at strong desire to void were also significantly increased ($p \leq 0.0003$).[27]

• A dose-dependent increase in residual urinary volume was also apparent in all phase II studies. This was not clinically relevant at dosages ≤2mg twice daily.[27] At a dosage of 4mg twice daily, residual urinary volume increased over 4-fold compared with baseline values, and 4 patients in this treatment group developed urinary retention.[27]

• Eight double-blind, randomised, parallel-group phase III studies were performed in 15 countries (Europe, North America and Australia) in more than 2000 patients with urodynamically confirmed overactive bladder and symptoms of frequency (≥8 micturitions/24 hours), urgency and/or urge incontinence (≥1 incontinence episode/24 hours). In one study, results from 242 patients confirmed preliminary phase II cystometric findings.[28] Thus, treatment with tolterodine 2mg twice daily significantly increased ($p < 0.05$) bladder volume at first contraction and maximum cystometric capacity compared with placebo.[28]

• A global analysis showed that after 4 weeks' treatment, tolterodine 1 to 2mg twice daily was significantly more effective than placebo for reduction in frequency of micturition (–1.7 and –1.6 *vs* –0.9 per 24 hours; $p < 0.01$ and $p < 0.05$). After 12 weeks' treatment, significant improvements in all micturition variables were apparent. The number of micturitions per 24 hours was reduced by 2.3 and 2.2 versus 1.4 and the number of incontinence episodes per 24 hours by 1.7 and 1.6 versus 1.1. The volume voided per micturition increased by 27 and 35ml versus 10ml (data on file, Pharmacia & Upjohn).

• Treatment of 249 patients with tolterodine 1 or 2mg twice daily for 12 weeks resulted in significantly greater decreases in frequency of micturition and increases in the volume of urine voided per micturition compared with placebo ($n = 64$).[29] There was also a trend ($p = 0.05$) towards a greater decrease in the number of episodes of incontinence relative to placebo.[29]

• In a 4-week, placebo-controlled study, 177 elderly patients (aged ≥65 years) were treated with either tolterodine 1 or 2mg twice daily or placebo.[30] Both dosages of tolterodine significantly reduced ($p \leq 0.0005$) the frequency of micturition compared with placebo. While there was a trend towards a reduction in the number of episodes of incontinence among tolterodine recipients, this difference was significant ($p = 0.0094$) only for the 2mg dosage. Compared with placebo, volume voided per micturition also increased significantly ($p = 0.0099$) in patients treated with tolterodine 2mg twice daily.[30]

• A total of 582 of 700 (83%) and 152 of 223 (70%) patients who had participated in phase II and III studies completed 6 and 12 months' open-label treatment, respectively, with tolterodine 2mg twice daily, which could be reduced to 1mg twice daily if necessary. Tolterodine continued to be effective ($p < 0.001$ *vs* baseline) in decreasing micturition frequency and incontinence episodes, and increasing volume voided per micturition, after up to 12 months' treatment (data on file, Pharmacia & Upjohn).

### Comparisons with Oxybutynin

• Three 12-week studies have compared the clinical efficacy and tolerability of tolterodine (2mg twice daily) versus oxybutynin (5mg 3 times daily) in patients with overactive bladder,[31-33] and two of these studies included a placebo treatment arm.[31,32] In total, 807 patients were randomised: tolterodine ($n = 346$), oxybutynin ($n = 349$) and placebo ($n = 112$).

• Pooled analysis of these studies shows that, compared with placebo, both tolterodine and oxybutynin significantly ($p < 0.05$) reduced the frequency of micturition by approximately 20% compared with baseline values, while the number of episodes of incontinence was reduced by 40 to 60%

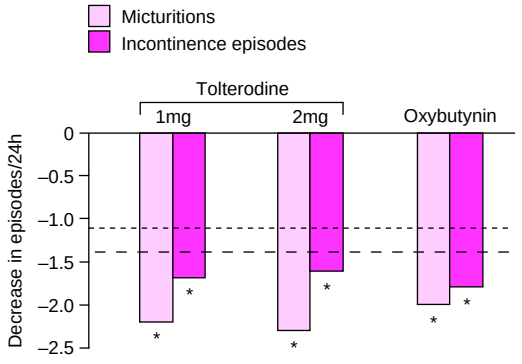



**Fig. 2.** Comparative efficacy of tolterodine. Change from baseline in number of micturitions and incontinence episodes per 24 hours after 12 weeks' treatment with either tolterodine 1 or 2mg twice daily (n = 346) or oxybutynin 5mg 3 times daily (n = 349) in patients with overactive bladder symptoms; * $p < 0.05$ *vs* placebo.[34] The dashed horizontal lines indicate the placebo effect (n = 112) on incontinence episodes (light line) and micturition episodes (dark line).

(fig. 2).[34] A similar increase in mean volume voided per micturition was also noted among tolterodine and oxybutynin recipients. For the tested efficacy parameters micturition and incontinence episodes, all comparative studies demonstrated therapeutic equivalence between tolterodine 2mg twice daily and oxybutynin 5mg 3 times daily.[31-33]

• Analysis of the effects of tolterodine on patients' perception of their bladder symptoms showed that, compared with symptoms at baseline, 41 and 52% of patients treated with tolterodine 1 and 2mg twice daily, respectively, reported an improvement in bladder symptoms after 12 weeks' treatment. Improvement in bladder symptoms was reported by 39% of placebo recipients and 50% of oxybutynin recipients. Compared with placebo, the improvement in symptoms among patients treated with tolterodine 2mg twice daily or oxybutynin was statistically significant ($p = 0.003$ and $p = 0.017$, respectively).[34]

## 4. Tolerability

• Tolterodine was well tolerated in clinical studies of up to 12 weeks' duration. In total, approximately 1600 patients received tolterodine in phase II and III studies. Adverse effects were predominantly mild to moderate in intensity and were typically antimuscarinic in nature. The most frequently reported adverse event was dry mouth. The incidence of adverse events was dose-related, with a marked increase in incidence at a dosage of 4mg twice daily.[27]

• The overall rate of discontinuation because of adverse events among patients receiving tolterodine (5%) was similar to that among placebo recipients (4%). In contrast, more than 3 times as many oxybutynin (5mg 3 times daily) recipients discontinued therapy, compared with tolterodine (2mg twice daily) recipients (20 *vs* 6%; $p = 0.001$). The most common reason for treatment discontinuation in tolterodine recipients was headache, whereas dry mouth was the most common reason in oxybutynin recipients. Indeed, 12% of oxybutynin-treated patients withdrew because of dry mouth, compared with only 1% of tolterodine 2mg recipients. 2% of tolterodine- and 1% of oxybutynin-treated patients withdrew because of headache (data on file, Pharmacia & Upjohn).

• Comparison of data from phase III trials in which patients received 12 weeks' treatment with either tolterodine 2mg twice daily (n = 474) or oxybutynin 5mg 3 times daily (n = 349) showed that dry mouth occurred in 40 *vs* 78% of patients.[34] Dry mouth was also less severe in tolterodine recipients than in oxybutynin-treated patients (fig. 3). 29% of oxybutynin recipients rated dry mouth as severe compared with only 4% of tolterodine recipients.

• Other adverse events reported in ≤11% of tolterodine-treated patients included headache, fatigue, dizziness, abdominal pain, constipation and dyspepsia. The incidence of these adverse events was similar to that reported by placebo recipients.[29,31-33]

• In the 3 phase III studies that included an oxybutynin treatment arm,[31-33] this drug was associated with a significantly higher ($p = 0.001$) proportion of patients requiring dosage reduction as a

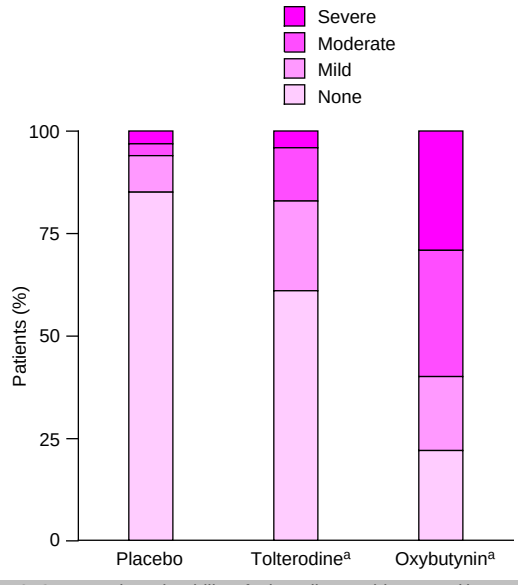



**Fig. 3.** Comparative tolerability of tolterodine. Incidence and intensity of dry mouth in patients receiving placebo (n = 176), tolterodine (2mg twice daily; n = 474) or oxybutynin (5mg 3 times daily; n = 349) for 12 weeks in comparative studies.[29,31-33]
a Including patients who required dosage reduction.

result of adverse events than tolterodine (31 *vs* 9%). Although dosage reduction permitted many oxybutynin recipients to remain on treatment, these patients continued to report a higher overall frequency of adverse events than those on tolterodine 2mg twice daily (66 *vs* 50%).

- In phase I studies, single oral doses of tolterodine of up to 6.4mg had no clinically significant effect on either blood pressure or heart rate.[9,10] Multiple doses of tolterodine (2 or 4mg twice daily) had no clinically relevant cardiovascular effects in healthy volunteers or elderly patients.[35] There were no adverse effects on the ECG during phase II studies, with the exception of a slight increase in heart rate in a few patients.[27]

- In healthy volunteers, tolterodine dosages of up to 4mg twice daily did not alter the QT or $QT_c$ intervals (corrected for heart rate using Bazett's formula) or other ECG parameters.[35] Concomitant treatment with thiazide diuretics in 12 patients did not produce any significant ECG changes.[36]

- No clinically relevant effects of tolterodine on standard laboratory parameters have been documented in clinical trials.[37]

- A study of 177 elderly patients (aged ≥65 years) showed that there were no additional tolerability concerns with tolterodine in this population.[30]

## 5. Tolterodine: Current Status

Tolterodine is a new muscarinic receptor antagonist which has recently been launched for treatment of patients with overactive bladder with symptoms of urinary urgency, frequency or urge incontinence.

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