Summary Tolterodine is a new competitive muscarinic receptor antagonist developed for the treatment of the unstable bladder. A total of 242 patients were enrolled in a multicenter, multinational, randomized, double-blind, placebo-controlled study conducted over a period of 4 weeks in patients with detrusor overactivity and symptoms of frequency, urgency, and urge incontinence. The objective of the study was to compare the efficacy and safety of tolterodine given at 1 or 2 mg b.i.d. versus placebo. At week 4 a statistically significant increase in the volume at first contraction (p = 0.030) and maximal cystometric capacity (p = 0.034) was only in the tolterodine 2 mg b.i.d. group. Tolterodine was safe and generally well tolerated. The incidence of dry mouth, as the most commonly reported adverse event, was only 9% and of mild to moderate intensity.

The symptoms of an unstable bladder are frequency, urge incontinence, and urgency. As detrusor contractions are mediated by cholinergic muscarinic receptor stimulation, antimuscarinic drugs have been used for the treatment of unstable bladders [1]. Oxybutynin is the most commonly used of these substances. Its effectiveness has been documented in controlled clinical studies [8]. However, the clinical usefulness of oxybutynin is limited by systemic side effects, particularly dry mouth [6, 7], which may be of sufficient severity to result in poor compliance or even discontinuation of treatment [1, 3].

Tolterodine is a new potent and competitive muscarinic receptor antagonist developed for the treatment of the unstable bladder. This compound was selected for development with the objective of achieving a separation of the antimuscarinic effects on the urinary bladder and the salivary glands. Data from preclinical pharmacology studies indicate that tolterodine and a major pharmacologically active metabolite (the 5-hydroxymethyl metabolite DD 01), exhibit a favorable tissue selectivity in vivo. Thus, both tolterodine and DD 01 are significantly more potent in inhibiting urinary bladder contraction than in inhibiting salivation in the anesthetized cat. Oxybutynin shows the opposite selectivity profile in this model [5].

The objective of the study was to compare the efficacy of tolterodine given at 1 or 2 mg b.i.d. versus placebo (test for difference) and evaluate the safety after 4 weeks of treatment in patients with detrusor overactivity and symptoms of frequency and either urge incontinence, urgency, or both with regard to the urodynamic variables maximal cystometric capacity, volume of first contraction, and maximal height of wave.

Patients and methods

Study design

This was a multicenter, multinational, randomized, double-blind, placebo-controlled study carried out in patients with detrusor overactivity and symptoms of frequency, urge incontinence, and urgency.
overactivity and symptoms of frequency and either urge incontinence, urgency, or both. Patients were initially entered into a 2-week washout/run-in period (1 week of washout followed by 1 week of run-in). Eligible patients were then randomized to undergo treatment with tolterodine 1 or 2 mg b.i.d. or placebo for 4 weeks. Patients who had not received any therapy affecting the bladder (pharmacological treatment, electrostimulation, or bladder training) in the 7 days prior to study entry could be randomized after a run-in period of only 1 week. Patients were seen at entry (visit 1, -1 or -2 weeks), at baseline (visit 2, day 1), and at week 2 (visit 3) and week 4 (visit 4).

Schedule of investigational events

The schedule of investigational events is given in Table 1.

Study population

A total of 242 patients were enrolled in this international multicenter trial. Table 2 summarizes the patients' recruitment by country and treatment groups. The demographic and baseline characteristics are shown in Table 3.

Table 1 Schedule of investigational events

<table>
<thead>
<tr>
<th>Visit (days)</th>
<th>Recording/assessment</th>
<th>Run-in/washout</th>
<th>Treatment</th>
<th>Follow-up post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 (-14 to -7)</td>
<td>-</td>
<td>Run-in</td>
<td>Treatment</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Visit 2 (1)</td>
<td>-</td>
<td>Treatment</td>
<td>Follow-up</td>
<td>post-treatment</td>
</tr>
<tr>
<td>Visit 3 (13-17)</td>
<td>-</td>
<td>Treatment</td>
<td>Follow-up</td>
<td>post-treatment</td>
</tr>
<tr>
<td>Visit 4 (27-31)</td>
<td>-</td>
<td>Treatment</td>
<td>Follow-up</td>
<td>post-treatment</td>
</tr>
<tr>
<td>Visit &gt;40</td>
<td>-</td>
<td>Treatment</td>
<td>Follow-up</td>
<td>post-treatment</td>
</tr>
</tbody>
</table>

Inclusion criteria

Men or women aged at least 18 years and presenting with detrusor overactivity, defined as the existence of any phasic detrusor contraction with an amplitude of ≥10 cmH₂O or the existence of one strong detrusor contraction that caused the end of the infusion, were eligible for the study. Patients were required to show evidence of frequency (≥8 micturitions/24 h) in combination with urge incontinence (≥1 incontinence episode/24 h), urinary urgency, or both.

Exclusion criteria

Patients with significant stress incontinence or with hepatic disease, defined as twice the upper limit of the reference range for liver-function tests, or renal disease, defined as twice the upper limit of the reference range for creatinine, were excluded from the study. Other exclusion criteria were any condition contraindicating anticholinergic therapy, recurrent urinary tract infections (UTIs), interstitial cystitis, uninvestigated hematuria, or clinically significant voiding difficulty with risk of urinary retention. In addition, patients on any anticholinergic treatment, patients using an indwelling catheter, or patients who had electrostimulation therapy or bladder training (last 14 days prior to the inclusion visit) were ineligible for the study.