Tolterodine: an overview

Abstract Tolterodine has emerged as a new anticholinergic drug to treat detrusor instability in recent years. This substance and its major metabolite DD01 exhibit a favourable effect-to-side-effect ratio for the bladder. Several clinical studies demonstrated the drug’s efficacy in reducing the symptoms of an overactive bladder (urgency, urge incontinence and high micturition frequency) and in increasing functional bladder volume. With a clinical effectiveness comparable to oxybutynin, the side effect-profile measures up favourably to oxybutynin. Consequently, though some limitations need to be addressed, tolterodine can be regarded as the drug of first choice to treat overactive bladders in a variety of patient groups: the young (and otherwise healthy), the elderly, as well as in patients with renal and hepatic insufficiency. A new extended release formula of tolterodine has been launched that may improve patients’ compliance.

Key words Tolterodine · Overactive bladder · Urinary incontinence

Urinary incontinence is a common disorder in the Western world. The overactive bladder can be characterised by the clinical symptoms of frequency, urgency and urge incontinence. Two subforms of incontinence go along with a pathological detrusor-overactivity: motor urge incontinence, which is characterised by an “unstable bladder”, and neurogenic reflex incontinence, which is caused by a neurological disorder and is classified as “detrusor hyperreflexia”.

Detrusor contractions are mediated by cholinergic muscarinic receptor stimulation. Tolterodine is a new anticholinergic drug that was developed to treat the hyperactive/hyperreflexive bladder. The substance acts as a competitive muscarinic receptor antagonist. It has been shown that the drug has a high affinity and specificity for muscarinic receptors in vivo and it exhibits a selectivity for the bladder over salivary glands. Its active metabolite, DD01, has as nearly an identical pharmacological potential as does the non-metabolised drug. Extensive clinical studies have shown the similar effectiveness of tolterodine as compared to oxybutynin, with an improved side-effect profile.

This article on tolterodine provides an overview about the pharmacology, clinical experience, treatment results, treatment of special subgroups/safety precautions and recent advances.

Pharmacology

Tolterodine is a competitive, pure muscarinic receptor antagonist that is not specific for any of the human muscarinic receptor subtypes M1–M5 [23–25]. In human and guinea-pig urinary bladders, tolterodine shows a binding affinity that is similar to oxybutynin but tolterodine has an eightfold lower affinity for parotid gland tissue (guinea-pig) [23, 25]. This difference is most likely due to both the M3-receptor subtype affinity for oxybutynin and an M3-receptor population of the salivary glands [23]. Concentration-inhibition curves show similar results for both drugs in the bladder, but the concentration-inhibition curve of tolterodine is shifted to the right in the guinea-pig parotid gland [23]. In vitro studies with the major metabolite of tolterodine, DD01, demonstrate that the metabolite acts similarly as the parent substance itself on receptors [23, 24].

Two metabolic pathways have been identified as contributing to the pharmacological effects of tolterodine. The substance is oxidated and N-dealkylated by...
the two cytochrome P450 isoforms CYP 2D6 and/or CYP 3A4 in the liver, resulting in a high-rate first-pass metabolism [5, 25, 28]. CYP 2D6 metabolises tolterodine to DD01 directly by oxidation. At present, it is not known and not anticipated that other metabolites take part in the pharmacological effect of tolterodine. Individuals who lack the CYP 2D6 isoform of P450 cannot metabolise tolterodine to DD01 because those individuals metabolise the drug by CYP 3A4 N-dealkylation (slow metabolisation). This variation of metabolisation results in higher tolterodine serum concentrations and no detectable concentrations of DD01. Therapeutic effects of tolterodine in “slow metabolisers” are attributed to comparably high serum levels of unbound tolterodine [26]. Individuals with the CYP 2D6 isoform (fast metabolisers) do “produce” the metabolite DD01 and, as a result, the pharmacological effect of tolterodine is based on the sum of unbound tolterodine plus unbound DD01 in the serum. Both subgroups are exposed to similar amounts of pharmacologically active (unbound) substances. Therefore, the same dosage of tolterodine can be used in both CYP phenotypes and a dosage/administration adjustment is not necessary.

Within the dosage range of 1 mg–4 mg the pharmacokinetics of tolterodine are linear and do not appear to be affected by age or gender [26]. Food intake does not influence the tolterodine resorption in a relevant way [26]. The resorption is fast and peak serum concentration is reached within 1–2 h [26]. The bioavailability of tolterodine varies and ranges from 10 to 74% (in healthy volunteers) [7]. Since the substance is metabolised into the active metabolite DD01, bioavailability of tolterodine is not affected by metabolisation in a relevant way. Significant differences in plasma-protein binding were observed between tolterodine and DD01. While only 3.7% of plasma-tolterodine exist as free drug (unbound), the plasma level of free DD01 is 36% [13].

Elimination studies with radiolabelled tolterodine revealed a renal excretion of 77% and a faecal excretion of 17% [7] for the radioactivity. Less than 1% of the radiolabelled substances in the urine was unmetabolised tolterodine. 4.4% was DD01 and 80% were carboxylic acid metabolites.

**In vitro experiments and animal studies**

In vitro experiments demonstrated a complete blockade of electrically induced contractions of bladder tissue (stable and overactive human origin) when incubated with either tolterodine or oxybutynin. The concentration of half-maximal inhibition (IC50) of tolterodine was similar to the IC50 of oxybutynin [22]. Further in vitro studies with the guinea pig bladder revealed a similar potential for tolterodine and its active metabolite DD01 in inhibiting carbachol-induced tissue contractions [23–25]. Recent studies on human detrusor muscle tissue revealed that tolterodine (and trosplum chloride) were more effective in relaxing carbachol induced contractions of smooth muscle strips while oxybutynin (and flavoxate) were more effective in inhibiting contractions that were induced by electric field stimulation [31].

It was demonstrated in an experimental in vivo setting in anaesthetised cats that tolterodine has a greater inhibitory effect on bladder contractions than on the (electrically induced) secretion of the salivary glands. This effect can not be attributed to any muscarinic receptor subtype selectivity [23]. It was concluded that a higher selectivity of M3 over M2 receptors (as is the case with oxybutynin) is not necessary for an effective inhibition of bladder contraction in vivo; nevertheless, such a selectivity may have a greater impact on reducing salivation. Based on these experimental results, one may further conclude that tolterodine has a greater bladder selectivity than an inhibiting effect on the salivary glands.

Preclinical data from further animal experiments demonstrated no significant effect of tolterodine on the cardiovascular, respiratory, central-nervous, renal and gastrointestinal organ systems. Effects that were observed during administering high dosages of tolterodine can be attributed to the antimuscarinic activity of the substance (e.g. increased pulse rate, dilation of the pupil, mouth dryness, reduced gastrointestinal motility) [26]. Toxicity studies on mice revealed no organ toxicity of tolterodine [26].

Daily dosages of up to 20 mg/kg in female mice and up to 30 mg/kg in male mice had no impact on the reproductive function. However, administering daily doses of 30–40 mg/kg led to embryo-toxic and foeto-toxic events. This embryo-feto-toxicity did not occur in daily dosages of up to 20 mg/kg. The results from this experiment led to an anticipated safety range of up to 70–120-fold of the therapeutic dosage. Nevertheless, tolterodine is not recommended for pregnant or nursing women [26].

In a recently published experiment the effect of administering tolterodine orally on the diurnal micturition characteristics of male and female rats, and the drug’s influence on water intake and urine production was estimated over a period of 24 h [34]. It was shown that the female rats consumed significantly more water at baseline (weight corrected) than the male animals. After administering a single oral dose (1 mg/ml) of tolterodine, the water consumption in females decreased significantly by 42% while it did not significantly decrease in the males. The urine production in the female animals was reduced by 26% in this study, whereas it was not significantly altered in the male rats. The voiding frequency was significantly increased in male animals as compared to the baseline during the day but not during the night. The volume per void in female animals was significantly reduced after drug administration as compared to the baseline. With the small number of animals (n=19) and the short observation period it remains unclear whether the results have any relevance on the use of tolterodine in humans. So far it has not been reported