CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-771

PHARMACOLOGY REVIEW(S)

DF

Review and Evaluation of Pharmacology/Toxicology Data

DEC 22 1997

HFD-580/Alex Jordan, PhD

NDA 20-771

Detrusitol (tolterodine)

Table of Contents

Review and Evaluation of Pharmacology/Toxicology Data

HFD-580/Alex Jordan, PhD

EFN: 001

NDA: 20-771

Serial No: Original NDA submission

Information to sponsor: Yes ( ) No (X)

Completion date:

Sponsor: Pharmacia & Upjohn Co.

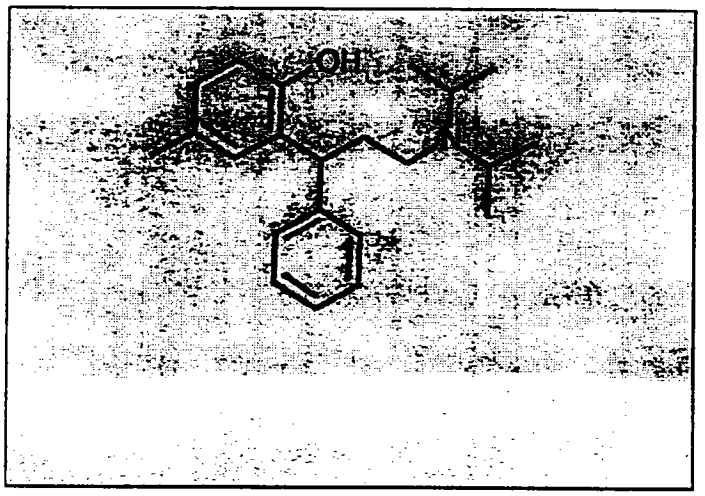
Manufacturer: same

Drug name: Tolterodine

Chemical name: (+)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine hydrogen as the L(+)-tartrate salt.

CAS number:

Structure:



Molecular weight: 475.6 as L(+)-tartrate

Relevant IND/NDA/DMF: IND

Drug class: anticholinergic

Indication: Urge incontinence, urgency, and frequency.

Clinical formulation (and components): Tablets of 0.5, 1 and 2 mg. Inactives are microcrystalline cellulose, calcium hydrogen phosphate, sodium starch glycolate, magnesium stearate and silica anhydrous.

Route of administration: oral

Proposed clinical protocol:

Studies reviewed within this submission:

Studies not reviewed within this submission:

Disclaimer - use of sponsor's material:

Introduction/drug history:

Previous clinical experience:

PHARMACOLOGY

Summary of pharmacology: Sponsor's summary:
It is generally agreed that contractions of the human urinary bladder are mediated mainly via stimulation of cholinergic muscarinic receptors and, consequently, the clinical management of detrusor instability and urinary urge incontinence has for a long time been based on the use of muscarinic receptor antagonists. The usefulness of the currently used antimuscarinic drugs is, however, limited because of their pharmacokinetic properties (e.g. the low and variable absorption from the gastrointestinal tract) or because of intolerable side effects, like dryness of the mouth (e.g. oxybutynin). Thus, there is a need for antimuscarinic drugs with more selective actions on the urinary bladder and less pronounced effects on salivary glands.

Tolterodine is a new muscarinic receptor antagonist intended for the treatment of detrusor instability and urinary urge incontinence. This compound was selected for development with the objective to achieve a separation of the antimuscarinic effects on urinary bladder and salivary glands. Pharmacological data indicate that tolterodine has a favorable tissue-selectivity in vivo, since it was more effective in inhibiting urinary bladder contractions than salivation in the anesthetized cat.

Tolterodine is a potent and competitive antagonist at muscarinic receptors in isolated urinary bladder preparations from the rat, guinea pig and man. The affinity for urinary bladder muscarinic receptors (K_B) is in the range of nM. The potent antimuscarinic action on the urinary bladder has been confirmed in vivo (IC50 19-35 ug/L), in anesthetized cat.

Tolterodine has a favorable tissue-selectivity in vivo, since it is significantly more potent in inhibiting acetylcholine-induced bladder contractions (ID50 105 nmol/kg) than electrically induced salivary secretion (ID50 268 nmol/kg) in anesthetized cat.

Tolterodine has some structural similarities to terodiline (Mictrol, Micturin) which was withdrawn from the market due to suspected associations with cardiac events, particularly; Torsades de Pointes and QTc prolongation. Clear effects on the ECG (QT, QTc, T-wave) have been observed only at mean serum levels of 500-1000 ug/l in anesthetized dog, although sporadic effects were seen at much lower serum concentrations. Blood pressure and respiratory parameters in the dog are not affected even at the high serum levels. The antimuscarinic potency constitutes a major difference between tolterodine and terodiline. In vitro, tolterodine is 40-80 times more potent that

terodiline on urinary bladder preparations from guinea pig and humans. In the anesthetized cat, tolterodine is 25 times more potent that terodiline in inhibiting cholinergically-induced bladder contractions. Tolterodine is more specific for antimuscarinic receptors than is terodiline which cross reacts with histamine and alpha-adrenergic receptors and calcium channels with a potency only 1.7-8 times less than its potency at the muscarinic receptor.

Effects on the CNS, intestinal motility, water and electrolyte excretion in the mouse have been observed at doses of tolterodine (<15 mg/kg, p.o.) which are expected to result in serum levels >80 ug/L. The degree of serum protein binding of tolterodine differs between species. The serum levels of unbound drug at which secondary effects have been observed in dog and mouse are at least 30 and 50 times, respectively, higher than the average peak serum level reached in most subjects after oral administration of 4 mg bid. in the phase I studies.

Significant effects of tolterodine on a-adrenergic receptors (IC50 2800 nM), histamine receptors (IC50 380 nM), the neuromuscular junction (IC50 > 30000 nM) and calcium channels (IC50 5200-6800 nM) in vitro have been observed only at concentrations much higher than those required for a complete inhibition of carbachol-induced contractions of isolated urinary bladder strips (IC50 14 nM).

In man, dog and mouse, tolterodine is metabolized by oxidation of the methyl group in the substituted benzene ring, yielding the 5-hydroxymethyl derivative of tolterodine (DD 01) as one major metabolite. In man, similar serum levels of this metabolite and the parent compound have been found after repeated administration of tolterodine. The 5-hydroxymethyl metabolite has been synthesized and evaluated in the same pharmacological models as tolterodine.

The in vitro and in vivo pharmacological profiles of DD 01 are virtually identical to those of tolterodine. The high antimuscarinic potency was the most prominent feature of both compounds. In view of the antimuscarinic potency of DD 01 and pharmacokinetic data, it can be concluded that the 5-hydroxymethyl metabolite contributes significantly to the therapeutic effect of tolterodine. Available data on the general pharmacology of DD 01 indicate that the safety margin for the 5-hydroxymethyl metabolite is at least as high as for the parent compound. Similar serum concentrations of tolterodine and the 5-hydroxymethyl metabolite have been observed in most subjects following repeated administration of tolterodine (2 and 4 mg bid., respectively).

SAFETY PHARMACOLOGY

Sponsor's summary

Central nervous system

The gross behavioral effects of tolterodine have been investigated using the Irwin dose-range test in the mouse. Tolterodine was orally administered for 7 days. No effects were observed at a dosage of 1.5 mg/kg. Mild to moderate behavioral and pharmacological dose-related changes (increased locomotor activity, increased touch response, vocalization and mydriasis) were observed at > 15 mg/kg.

In another study in the mouse, tolterodine was given as single oral doses. This study included tests of analgesic action (Haeffner's method), synergism or antagonism of hexobarbital induced anesthesia (sleeping time), pentetrazol-induced and electric shock-induced convulsion, respectively. Except for increased spontaneous locomotor activity after the highest dose (150 mg/kg), no significant effects of tolterodine were observed.

The effect of tolterodine (0.3 - 30.0 mg/kg, s.c.) on total activity, locomotion and rearing has been studied in the rat (non-GLP study). Tolterodine did not affect the total activity or locomotion at doses < 10 mg/kg (total serum levels < 70 ug/ml), while a significant increase in motor activity was observed at > 10 mg/kg. Oxybutynin produced a significant increase in motor activity already at the lowest dose, 0.3 mg/kg.

The no observed effect level was 1.5 mg/kg in the Irwin test and 75 mg/kg in the second study. Thus, oral administration of tolterodine seemed to have little or no effect on the central nervous system in the mouse and the effects observed were those expected of antimuscarinic compounds.

Cardiovascular and respiratory systems

Heart rate, blood pressure and ECG have been monitored by means of telemetry in conscious dogs orally treated with tolterodine. Effects of tolterodine on the cardiovascular and respiratory systems have also been evaluated in the anesthetized dog and cat.

Heart rate

Heart rate remained unaffected in conscious dogs treated with tolterodine 0.2 mg/kg/day p.o., for 10 days, while an almost two-fold increase occurred after 1 mg/kg. This effect was observed both on day 1 and day 9. In dogs treated with 4.5 mg/kg, an increased heart rate was recorded only on day 1. This was interpreted as a possible development of tolerance during treatment with high doses of tolterodine.

In anesthetized dogs, heart rate remained unaffected by tolterodine (i.v. inf.) up to a dose of 1.6 mg/kg. However, when tolterodine was given as i.v. bolus doses, heart rate increased at low doses ($\leq$ 0.3 mg/kg), but decreased at high doses ($\geq$1.0 mg/kg) in two out of three animals In the anesthetized cat, a small (4-10%) reduction in heart rate was observed at $\geq$0.3 mg/kg.

The expected antimuscarinic effect on heart rate is an increase. This was observed in the conscious dog after treatment with 1 mg/kg (tolterodine: 103 ug/l, DD 01: 25 ug/l). In anesthetized dogs, increased heart rate was observed after bolus doses of tolterodine (90-250 ug/l).

Blood pressure

In conscious dogs, tolterodine 0.2 mg/kg/day (p.o.) produced no effects on blood pressure. Systolic pressure remained unaffected at all dose-levels, while diastolic pressure increased after 1 mg/kg (10-30%) and 4.5 mg/kg (35-40%).

In anesthetized dogs, tolterodine (i.v. inf.) had no effect on blood pressure. The highest accumulated dose was 1.6 mg/kg. Similarly, i.v. bolus doses of tolterodine had little or no effect, up to 1 mg/kg

In the anesthetized cat, tolterodine had in general no effect on blood pressure per se. The threshold dose for inhibition of the decrease in blood pressure induced by acetylcholine (0.5 ug/kg, i.v.) was 0.1 mg/kg, while the response to noradrenaline (0.25 ug/kg) was unaffected.

Thus, in conscious dogs, the diastolic blood pressure was slightly increased at 1 mg/kg (tolterodine 103 ug/l, DD 01: 25 ug/l). In the anesthetized dog and cat, blood pressure was not affected by tolterodine up to mean serum levels of > 1000 ug/l.

Blood flow
Tolterodine had little or no effect on mesenteric arterial blood flow in the anesthetized cat, but an increase was observed at 1 mg/kg.

ECG-parameters
In conscious dogs, potential effects on the ECG pattern were studied using telemetry technique. Repeated oral treatment with tolterodine 0.2, 1 and 4.5 mg/kg did not induce any arrhythmia's or other abnormalities in the ECG pattern, except for a slight (10-20%) prolongation of the QT-interval after 9 days of treatment with 4.5 mg/kg

In the anesthetized dog, no signs of arrhythmia's were noted during continuous i.v. inf. of tolterodine. The PQ- and QRS-intervals remained unaffected up to the highest accumulated dose (1.6 mg/kg), while the NOEL for effects on QT-interval, QTc, and the T-wave was 0.04 mg/kg. Marked effects on these parameters were only observed at ≥ 0.4 mg/kg. Increased amplitude and duration of the T-wave was also observed after high (≥1.0 mg/kg) i.v. bolus doses.

In the anesthetized cat, EGG parameters were not affected by tolterodine 0.03 mg/kg (i.v. inf.). A decreased T-wave amplitude was observed at ≥0.1 mg/kg.

Thus, changes in EGG pattern were recorded only after high doses of tolterodine. In conscious dogs, a slight prolongation of the QT-interval was found after 9 days of treatment with 4.5 mg/kg (tolterodine: > 600 ug/l, DD 01: 100 ug/l). In the anesthetized dog, marked effects were noted only at mean serum levels of > 500 ug/l.

Electrophysiological studies
Tolterodine (10uM) did not affect the upstroke, the amplitude or the duration of the action potential in papillary muscles from the right ventricle of guinea pig heart and it had no significant effects on K+-currents in isolated cardiac myocytes. A small, but significant (4-6%) prolongation of the action potential duration was seen at concentrations of uM.

Tolterodine reduces the inward Ca++-current in myocytes with an IC50 of 5.4 uM. This agrees well with the calcium antagonist potency determined in pharmacological studies (5.2 and 6.8 uM) on cardiac tissue from guinea pig.

Tolterodine is a weak and relatively non-selective calcium antagonist, since it also blocks sodium channels. In experiments with isolated Perkinje fibers from dogs, terodiline decreased the action potential amplitude and the maximal rate of depolarization (upstroke) of the action potential. The threshold concentration for significant effects was 1-2 uM and at 10 uM the rate of depolarization was depressed by 55%.

In papillary muscles from guinea pig myocardium, terodiline had no significant effects on the action potential configuration (amplitude and duration) but, at 10 uM, it depressed the maximal

rate of depolarization. This indicates the terodiline blocks the fast inward Na+-current in cardiac myocytes. The sponsor states that drugs associated with Torsades de Pointes have in general been shown to interact with the repolarization phase of the action potential during which the outward current is carried by K+ ions. This is important since tolterodine has no significant effect on K+-currents in isolated guinea pig myocytes.

Humans given 2 mg bid have a Cmax of about 6.5 ug/l (tolterodine + DD 01) which is equivalent to about 19 nM (from sponsors table vol 14, pg. 5/3/13). Tolterodine had a small but significant effect on the duration of the action potential of papillary muscles from guinea pigs at 100 nM. Effects on sodium and calcium channels occurred in the concentration range of uM or greater. The concentration differences between the cardiac effects and the serum levels in humans seen to provide an adequate margin of safety.

Respiration
Respiratory parameters in the anesthetized dog were not affected by tolterodine (i.v. inf.), up to the highest dose 1.6 mg/kg. A reduction in tidal volume and an increased respiration rate were observed after 3 mg/kg (i.v. bolus). In the anesthetized cat, respiratory rate and tidal volume remained unaffected by tolterodine < 0.1 mg/kg. A minor decrease (9%) in tidal volumes was noted at 0.3 mg/kg and a pronounced effect (41%) after 1 mg/kg.

Telemetry study in the conscious mouse
This study is described separately, since it was not a true pharmacological study. Unexpected moralities occurred at tolterodine 30 and 40 mg/kg/day in the 13 and 26 week toxicity studies in the mouse. Since the cause of death was not obvious, it was decided to undertake a screening for cardiovascular effects at toxic dosages, using telemetry technique.

Mice were treated with high dosages of tolterodine (20, 40 and 80 mg/kg/day p.o.) or vehicle, during 14 days. Heart rate, EGG and body temperature were registered daily, up to 4 h after dose. No mortality's occurred during this period of treatment and the study was therefore continued for another 7 day's. In conjunction with this, the dosage in the original low dose-group (20 mg/kg) was increased to 160 mg/kg/day.

A dose-dependent decrease in body temperature and a concomitant decrease in heart rate were observed during treatment with tolterodine is dosages up to 80 mg/kg for 21 days or 160 mg/kg for 7 days. However, there were no signs of arrhythmia's and ocular inspection of EGG patterns revealed no abnormalities. One mouse in the 160 mg/kg group died during the third week, but this was not considered to be related to tolterodine treatment.

Gastrointestinal tract

Effects of tolterodine on intestinal motility in the mouse have been investigated in two studies, using charcoal propulsion tests. In the first study, intestinal motility in male mice was not affected by tolterodine (1.5 mg/kg p.o.), while a dose-related decrease in motility was seen after >15 mg/kg. A complete inhibition of the charcoal propulsion was seen in 80% of the animals at 150 mg/kg.

An increased mortality rate in male mice occurred in the carcinogenicity studies and the cause of death was related to a marked bowel distention. A second study on intestinal transit was therefore carried out in young (6 weeks) and old (1 year) animals of both sexes, to investigate possible sex and age related differences in the sensitivity to tolterodine. The dosages of tolterodine (5, 15 and 45 mg/kg po) were selected to cover the dose-range used in the carcinogenicity studies.

A severe reduction of intestinal transit was noted only at the highest dose (45 mg/kg) and this effect was always greater in males than in females. In both young and old males, the no effect dose was 15 mg/kg. The females seemed to be more sensitive, with a no effect dose of 5 mg/kg in young females. In older females, an effect was recorded already at 5 mg/kg, but this was considered a threshold dose.

The decreased intestinal motility seen after high doses of tolterodine is related to its primary antimuscarinic action. The no observed effect level appears to be higher than the 1.5 mg/kg determined in the first study. The higher sensitivity of males at the highest dose may explain the increased mortality among males during the carcinogenicity studies.

Renal function

The effect of tolterodine on renal function has been investigated in female mice. The animals were given an oral load of physiological saline and tolterodine in oral doses of 1.5, 15 and 150 mg/kg and 1.5, 5, 10, 15, 50 and 150 mg/kg, respectively.

In the first study, no effect on urinary parameters was observed at 1.5 mg/kg. A significant increase in diuresis, micturition volume and urinary excretion of sodium and chloride, together with decreased urinary specific gravity was observed after 15 mg/kg. The excretion of potassium was not affected. Small volumes of residual urine were noted in 60% of the mice. The effect on diuresis was not dose-related because, at 150 mg/kg, the only finding was that all animals developed residual urine.

In the second study, the same pattern was found, but at higher doses. Thus, at 50 mg/kg micturition volume and diuresis were increased. However, there were no changes in excretion of sodium, potassium and chloride ions. Some animals showed small amounts of residual urine. At 150 mg/kg, there were no effects on the urinary parameters, except for the presence of small volumes of residual urine.

Thus, tolterodine was found to increase diuresis in mice, but the results in the two studies were not consistent, since the no observed effect level was 1.5 and 15 mg/kg, respectively. The reasons for this discrepancy are not clear, but the effects occurred at high doses and they were not dose-related.

Summary of effects observed after oral administration

The lowest oral doses used in studies on general pharmacology in the dog (0.2 mg/kg) and mouse (1.5 mg/kg) result in serum concentrations of tolterodine that are fairly similar to those found in most human subjects treated with tolterodine 2 mg bid (tolterodine 3.6 ug/l and DD 01 2.9

ug/l). No pharmacological effects were found in the mouse and dog at these doses. However, in the mouse, the no observed effect level was in several studies considerably higher than 1.5 mg/kg. This may indicate that the true NOEL is closer to 15 than to 1.5 mg/kg.

Most of the effects recorded at higher doses (mouse >15 mg/kg, dog >1 mg/kg) were, as expected, of an antimuscarinic nature. Thus, increased motor activity, mydriasis, decreased intestinal motility, development of residual urine and increased heart rate can all be attributed to the primary action of tolterodine and DD 01 at muscarinic receptors.

The mechanisms behind the effects on urinary parameters observed in the mouse at dosages between 15 and 50 mg/kg (e.g. increased diuresis and decreased urinary specific gravity) and the prolongation of the QT- interval in the dog (4.5 mg/kg) are not known. However, similar effects have been recorded in toxicity studies in the mouse and dog.

Prolongation of the QT-interval in the dog was recorded at 4.5 mg/kg in the 26 week toxicity study, but the values were within the normal range. The no observed toxic effect dose in the mouse is 10 mg/kg and 4.5 mg/kg was the top-dose used in the long term toxicity studies in the dog. Thus, considering the high dosages at which tolterodine in the general pharmacological studies was found to affect urinary parameters in the mouse (15-50 mg/kg) and the QT-interval in the dog (4.5 mg/kg), these findings are probably of little pharmacological significance.

General pharmacological effects of tolterodine

Systemic Effect	Species	Sex	No Observed Effect			Effect		
			Dose mg/kg p.o.	Serum levels ug/l Tolterodine T/U	DD 01 T/U	Dose mg/kg p.o.	Serum levels ug/l Tolterodine T/U	DD 01 T/U
Cardiovascular								
Heart rate and diastolic blood pressure	Dog	M,F	0.2	3.8/0.08	1.1/0.3	1	103/2.2	25/8
ECG (QT-interval)	Dog	M, F	1	103/2.2	25/8	4.5	>600/13	100/32
Central nervous system	Mouse	M	1.5	2.1/0.3	2.4/1.7	15	>83/13	>63/45
	Mouse	M	75	n.d.	n.d.	150	n.d.	n.d.
Gastrointestinal								
	Mouse	M	1.5	2.1/0.3	2.4/1.7	15	>83/13	>63/45
	Mouse	F	5	n.d.	n.d.	15	>83/13	>63/45
	Mouse	M	15	>83/13	>63/45	45	n.d.	n.d.
Renal function								
	Mouse	F	1.5	2.1/0.3	2.4/1.7	15	>83/13	>63/45
	Mouse	F	15	>83/13	>63/45	50	n.d.	n.d.

Serum levels are Cmax

T = Total concentration, U = Unbound concentration. n.d. = not determined. Serum levels in the mouse were not determined in conjunction with the pharmacological studies. Data on the lowest dose used, 1.5 mg/kg, were obtained in pharmacokinetic studies. For the 15 mg/kg dose, data determined for the no observed toxic effect dose (10 mg/kg) are quoted.

Serum concentrations in the mouse were not measured after oral administration of tolterodine 15 mg/kg. However, based on data for the no toxic effect dose (10 mg/kg) in the mouse, 15 mg/kg can be expected to result in serum concentrations that are >83 ug/l (unbound 13 ug/l) for tolterodine and >63 ug/l (unbound 45 ug/l) for DD 01. The serum protein binding differs between species and this must be taken into account when comparisons to human serum levels are made.

The unbound concentrations of tolterodine and DD 01 at which effects were observed on the central nervous system, gastrointestinal tract and renal function in the mouse are approximately 100 and 40 times, respectively, higher than the unbound concentration expected to be achieved in most patients after tolterodine 2 mg bid (tolterodine: 0.13 ug/l, DD 01: 1.04 ug/l). Almost the same ratios (100 and 30 times) are found for the unbound concentrations of tolterodine and DD 01 at which a prolongation of the QT-interval in the dog was recorded, while the effect on heart rate occurred at concentrations that are about 17 (tolterodine) and 8 (DD 01) times higher than those expected in humans.
However, it should be noted that poor metabolizers of tolterodine will get higher concentrations of tolterodine, but no measurable levels of DD 01. Similarly, the serum levels of tolterodine and DD 01 may be affected by drug interactions. This has been studied in humans, since it cannot be adequately addressed in animal studies.

Studies on DD 01

Some studies have been performed on the general pharmacology of DD 01 in the dog and mouse. However, it must be emphasized that the data obtained after oral administration of DD 01 are of a limited value. Serum levels were not measured and the metabolic fate of DD 01 after oral administration has not been investigated.

Potential effects of DD 01 on the central nervous system were investigated using the Irwin dose-range test in the mouse. No abnormalities were observed at 1.5 mg/kg, while mild behavioral and pharmacological dose-related changes (e.g. increased locomotor activity)
were observed after >15 mg/kg. In another study, a significant increase in spontaneous locomotor activity was found only after 75 and 150 mg/kg. Intestinal motility and renal function in the mouse were not affected by DD 01 in doses < 15 mg/kg (p.o.), while higher doses resulted in the same effects as seen with tolterodine-i.e. decreased intestinal transit and increased diuresis.

Effects of DD 01 on the cardiovascular and respiratory systems were evaluated in the anesthetized dog (i.v. inf.). No signs of arrhythmia's were noted during infusion of DD 01. Heart rate decreased slightly during infusion of 1.5-4.5 mg/kg, but the mean value did not differ significantly from that recorded in saline treated control animals.

The NOEL was considered to be 0.29 mg/kg (126 ug/l, unbound concentration 40 ug/l) with respect to EGG-parameters. This concentration is >35 times higher than the unbound concentration of DD 01 expected to be reached in most patients on treatment with tolterodine 2 mg bid. Blood pressure and respiratory parameters remained unaffected by DD 01 up to the highest accumulated dose (4.5 mg/kg).

Thus, although direct comparisons cannot be made, the general pharmacological profile of DD 01 seems to be similar to that of tolterodine.

Drug Interactions

Interaction of tolterodine with other drugs could theoretically occur at three different sites-at receptors, at binding proteins in serum, or at enzymes involved in the metabolism of tolterodine.

Tolterodine is a potent muscarinic receptor antagonist and it appears to have little or no affinity at other potential cellular targets. Pharmacological interactions of tolterodine with drugs having other mechanisms of action seem therefore unlikely. However, concomitant administration of tolterodine and drugs which activate or block muscarinic receptors may obviously affect the primary action of tolterodine.

The binding of tolterodine to serum proteins is not extremely high (about 96% in humans) and it is constant over a wide concentration range. Clinically significant interactions due to displacement of tolterodine from the binding protein are therefore not expected to occur.

Tolterodine is almost exclusively eliminated by metabolism. Potential interactions with other drugs are therefore likely to be of metabolic origin. Tolterodine is primarily metabolized by the isoenzyme cytochrome P450 2D6, which is polymorphically distributed, resulting in poor and extensive metabolizers. Since the cytochrome P450 2D6 isoenzyme is not present in animal species, interaction studies with tolterodine have been focused on human in vivo studies.

Summary of Safety Pharmacology:

- Tolterodine is a potent and competitive muscarinic receptor antagonist. It binds with high affinity and specificity to muscarinic receptors, as compared with other potential cellular targets.

- Tolterodine is significantly more potent in inhibiting acetylcholine-induced urinary bladder contractions than electrically-induced salivation in vivo, in the anesthetized cat. The bladder selectivity demonstrated in vivo cannot be attributed to selectivity for a single muscarinic receptor, since tolterodine is non-selective with respect to the human m1-m5 receptors.

- The 5-hydroxymethyl metabolite, DD 01, exhibits a similar antimuscarinic profile as tolterodine, both in vitro and in vivo. In view of the antimuscarinic potency of DD 01 and pharmacokinetic data from both humans and animals, it can be concluded that this metabolite contributes significantly to the therapeutic effect.

- Secondary actions of tolterodine in the conscious dog and mouse have only been recorded after oral administration of high doses, resulting in high serum levels of both tolterodine and DD 01.

- In the conscious dog, an increased heart rate was recorded at unbound serum concentrations of tolterodine and DD 01 that were 17 and 7 times, respectively, higher than those expected to be reached in most patients treated with tolterodine 2 mg bid. The corresponding ratios for effects on the EGG (QT-prolongation) were 100 for tolterodine and 40 for DD 01. Almost the same ratios (>100 and >30) were found for the unbound concentrations at which effects on the central nervous system, gastrointestinal tract and renal function were recorded in the mouse.

- Poor metabolizers of tolterodine will get higher concentrations of tolterodine, but no measurable levels of DD 01. Similarly, the serum levels of tolterodine and DD 01 may be affected by drug interactions. This issue cannot be adequately addressed in animal studies and has therefore been studied in humans.

- Most of the secondary effects are of an antimuscarinic nature. Thus, increased heart rate, increased locomotor activity, mydriasis, decreased intestinal motility and development of residual urine can all be attributed to blockade of muscarinic receptors.

PHARMACOKINETICS/TOXICOKINETICS

Summary of PK/TK:
Pharmacokinetics of tolterodine has been studied in rat, mouse and dog.

Differences between species were seen in systemic exposure. At similar oral doses, the serum concentrations of tolterodine in the dog were more than 50 and 30 times higher compared to rat and mouse respectively. The serum concentration in man was, after adjustment to the much higher dose given in the animals, in the same range as seen in the dog. With increasing dose, there was an non-proportional increase in Cmax and AUC in mouse and dog. The differences seen between species in the exposure of tolterodine was reduced when a comparison was based on unbound concentration in serum.

The binding to serum proteins varied between the species. The unbound fraction was in dog and cat less than 1% but in rodents between 7.9-20.1%. In man the unbound fraction was 2.1%. Orosomucoid was found to be a major binding protein.

Tolterodine was extensively metabolized. The metabolic pathway in dog and mouse was similar to that in man. The main metabolic pathway was

In rat another metabolic pathway involving hydroxylation of the unsubstituted aromatic ring was found.

The 5-hydroxymethyl metabolite (DD 01) has been shown to be pharmacologically active. In dog and mouse the serum concentration of the metabolite ranged from the same to four times lower the concentration of the parent molecule; in man the metabolite ranged from about equal concentrations to not measurable concentrations. The protein binding of the metabolite was however much lower than that of tolterodine, resulting in a higher unbound concentration in serum of the metabolite compared with tolterodine (4-10 fold) in dog and mouse.

The excretion of radioactive material in urine was, after an oral dose of radioactively labeled tolterodine (4 mg/kg bw) 9% in the rat, 50% in the dog, and in man 75% of a dose of 5 mg. Most of the radioactivity represented metabolites, mainly the carboxylated metabolite, while the parent molecule was present only in low amounts. After an iv dose in the rat, the main part of the radioactivity was found in feces (75%) indicating a high biliary excretion in this species.

In conclusion, mouse and in particular dog, exhibit similarities to man regarding pharmacokinetic profile and metabolite pattern.

Systemic exposure: At the no-observed-adverse effect doses in general toxicology studies

	Mouse	Dog	Man
Dose	10 mg/kg	0.5 mg/kg	2 mg bid
tolterodine	fu=16%	fu=2.1%	fu=3.7%
Cmax	83	65	3.6
Cmax u	13	1.4	0.13
AUC	238	166	17
AUC u	38	3.5	0.63
DD01	fu=72%	fu=32%	fu=36%
Cmax	63	12	2.9
Cmax u	45	3.8	1.0
AUC	166	52	14
AUC u	119	17	5.0

Concentrations in ug/l, fu = unbound fraction in serum, u = unbound concentration, n.d. = undetectable. AUC is estimated for a dose interval of 24 hrs in animals and 12 hrs in man. To compare exposures between humans and animals, the human AUC should be doubled.

Systemic exposure: At the highest doses in the carcinogenicity studies.

	Mouse	Rat		Man
Dose	30 mg/kg	20 mg/kg (F)	30 mg/kg (M)	2 mg bid
tolterodine	fu=16%	fu=22%		fu=3.7%
Cmax	18	14	23	3.6
Cmax u	2.9	3.1	5.1	0.13
AUC	355	291	462	17
AUC u	57	64	102	0.63
DD01	fu=72%	fu=63%		fu=36%
Cmax	10	n.d.	n.d.	2.9
Cmax u	7.2			1.0
AUC	198			14
AUC u	143			5.0

concentrations in ug/l; u=unbound concentration; fu=fraction unbound; n.d.=not detectable; AUC in animals over 24 hrs, man over 12 hrs.

Pharmacokinetic parameters of tolterodine

Species	fu %	t1/2 h	Vd l/kg	Vdu	CL	Clu	Urinary	Fecal	Bioavail

					l/hxkg		Excretion 14C	Excretion 14C	ability %
Mouse	16	1.0	16	100	13	81	43	51	10-20
Dog	2.1	0.8	1.5	71	1.4	67	50	34	60
Rat	22	1.8	25		10		17	81	2-20
Man	3.7	3.7	1.6	43	0.64	17	77	17	17

fu=fraction unbound
Vdu= volume of distribution (unbound concentration)
CL=clearance; Clu= clearance (unbound concentration)

Metabolism

Metabolite screening for urinary metabolites of tolterodine has been performed in mouse, rat, dog and man. The urine was analyzed by The isolated metabolites in the

Tolterodine was extensively metabolized. The metabolite pattern in dog and mouse urine was similar to that of human urine while rat urine exhibited a markedly different pattern. Tolterodine is primarily metabolized by The major metabolites that were identified in both mouse, dog and man were the

The rat appears to metabolize tolterodine along a different route

metabolites were observed.

Excretion of radioactivity in urine and feces after administration of 14C-labelled tolterodine was studied in rat and in dog. The total recovery in the studies was >95% in the rat and > 80% in the dog.

In the rat, both intravenous (0.4 mg/kg bw) and oral doses (4, 12 and 40 mg/kg bw) were given. After the iv dose, an average of 75% of the dose was found in feces indicating a high biliary excretion. After the oral doses the main part, 90%, was excreted after the first 24 hours, mainly in the feces. An average of 9-24% was found in the urine; increasing amount with increasing dose in the interval 4-40 mg/kg bw. In the dog, only oral doses (0.5 and 4.5 mg/kg) were studied. A larger amount, about 50% of the dose, was excreted in the urine. In man, 75% of a tracer dose of 14C-labelled tolterodine (total dose 5 mg) was excreted in urine and 20% in feces.

Most of the radioactivity in urine represented metabolites, mainly the metabolite in man and dog. The parent molecule was present only in low amounts.

The pharmacokinetics of tolterodine was studied in rat, mouse and dog. There were large differences in systemic exposure between the species investigated. These differences were eliminated when based on unbound fraction of tolterodine in serum, as there were large differences in protein binding between the species. The rat differed from the other species by a different metabolic pathway.

Mouse and in particular dog exhibited similarities to man regarding pharmacokinetic profile and metabolite pattern.

TOXICOLOGY

Single and repeat dose toxicology: Acute Toxicity in mice and rats after single oral administration of Tolterodine.

Study sponsor:
Study report number: 89-22
Date: 1990
Species/strain: mice and Sprague-Dawley rats
Route: Oral gavage
Number/sex/dose: 5
Doses: 150 and 300 mg/kg for mice and 150, 300 or 375 mg/kg for rats
Duration: single dose with 14 day observation period.

There were no deaths in LD mice and 60% mortality at the high dose. All deaths occurred within 24 hrs of dosing. There was no morality in the rat study. There was a reduction in food consumption and body weight loss in the first few days after treatment in both mice and rats at all dose levels.

Acute intravenous toxicity study in the mouse.

Testing facility: Pharmacia Therapeutics Uppsala
Study number: number 93059
Date: 1994
Species/strain: mice
Route: intravenous
Number/sex/dose: 5
Doses: 8, 16 and 24 mg/kg
Duration: single administration with 14 day observation period.

No reaction to treatment at 8 mg/kg. In males treated with 16 mg/kg increased motor activity, increased respiratory frequency, piloerection and ventral recumbency was observed for short periods after dosing. One male died after having convulsions. No effects in females at this dose. Both males and females treated with 24 mg/kg showed ataxia, ventral recumbency and convulsions. An 80% mortality was recorded at this dose level.

Acute intravenous toxicity study in the rat

Testing facility: Pharmacia Therapeutics Uppsala
Study number: number 93058
Date: 1994
Species/strain: Sprague-Dawley rats
Route: intravenous
Number/sex/dose: 5
Doses: 8, 16 and 24 mg/kg
Duration: single administration with 14 day observation period.

No effects of treatment with 8 mg/kg. At 16 mg/kg, only short-lived ataxia. At 24 mg/kg there were deaths (2/5 males and 1/5 females) which occurred during or immediately after dosing. The most prominent clinical findings at 24 mg/kg were reversible ataxia, ventral recumbency and convulsions.

Repeated Dose Toxicology

Toxicity to mice by repeated oral administration for 13 weeks followed by a 4-week recovery period.

Study sponsor:
Study report number: document 20817F
Date: 1993
Species/strain: CD-1(ICR)BR mice
Route: Oral gavage
Number/sex: 16, with an additional 6/sex for recovery and 24-30/sex for toxicokinetics and metabolism studies.
Doses: 4, 12 or 40 mg/kg
Duration: 13 weeks with 4 week recovery

Mortality: Significant increase in the HD gps. No consistent findings to account for the deaths. Sponsor concludes that deaths due to pharmacological (anticholinergic) effect of the drug.

Clinical signs: None

Bodyweight changes: A significant reduction in bw gain at the HD for males and females. Sponsor did not consider the reduction to be toxicologically significant and simply reflected normal variability for mice of their age and strain at these labs.

Food consumption: No treatment related effect.

Water consumption: During wks 8 and 12, the HD animals consumed more water than controls.

Hematology: No treatment related effects.

Clin chem: No toxicologically significant changes.

Urinalysis: No toxicologically significant changes.

Gross path: No treatment related effects.

Organ wts: No toxicologically significant findings.

Histopathology: Abnormal round spermatids in 6/13 HD males compared to 3/16 control males. LD and MD were similar to controls. Testicular atrophy, prominent interstitial cells and minimal reduction of spermatogenesis was seen in low incidence in treated males but not in controls. Sponsor states that these changes are occasionally seen in controls and believe the changes are unrelated to treatment.

General toxicity in rats of tolterodine administered orally for two weeks.

Study sponsor:
Study number: document 89 96 616
Date: 1990
Species/strain: Sprague-Dawley rats
Route: Oral gavage
Number/sex/dose: 10
Doses: 4, 12 or 40 mg/kg
Duration: 2 weeks

Mortality: None treatment related.

Clinical signs: Salivation, occasionally red-stained, showed a dose related incidence and appeared usually within 5-15 minutes of dosing. It continued throughout the study.

Body weight: No effect.

Food consumption: No effect.

Hematology: Slight stimulation of erythropoiesis in males only. Increased platelet counts in HD males and females. Increase in WBC counts in HD males and females as well as LD females.

Clinical chemistry: No toxicologically significant changes.

Urinalysis: Reduced volume of urine and increased osmolality, density and protein concentration were seen in MD and HD males. HD females had a slightly increased volume of urine when compared to controls.

Organ wts: Small but significant increase in absolute and rel liver wts for HD males and females and MD females.

Gross pathology: No effects.

Histopathology: No toxicologically significant changes.

Toxicity to rats by repeated oral administration for 13 weeks followed by a 4-week recovery period.

Study sponsor:
Study number: 90
Date: 1991
Species/strain: CD(SD) BR rats
Route: Oral gavage
Number/sex/dose: 15
Doses: 4, 12 or 40
Duration: 13 weeks with a 4 week recovery period.

Mortality: Ten HD females died during the study. All died approximately 20 hrs after dosing. Prior to death none had displayed any obvious clinical signs of debility or intoxication. Neither macroscopic post mortem exam nor histopath exam revealed any changes that could account for the deaths.

Clinical signs: Dose related salivation together with brown staining on the muzzle and wetting of the coat.

Body weight: HD females gained less than controls. No other effects.

Food consumption: No significant effects.

Ophthalmoscopy: No effects.

Hematology: MD and HD females had a significantly lower WBC count than controls.

Clinical chem: Dose related increase in plasma cholesterol in HD rats. Some increase in plasma triglycerides also noted. Alk Phos increased in MD and HD females.

Urinalysis: HD males had more dilute urine with lower sp gravity and osmolality. Females also affected but to a lesser degree.

Gross path: No treatment related changes.

Organ weights: Increased liver wts for MD and HD females and HD males. Increased lung wts for HD rats and increased kidney wts for HD males.

Histopathology: Thyroid - Increased height of follicular epithelium and decrease colloid in HD rats.
Liver - centrilobular and/or diffuse hepatocyte enlargement in MD and HD males and females.
Lungs - Prominent, pigmented (iron positive) alveolar macrophages in MD and HD males and HD females.
Only the lung pathology was apparent after the 4 week recovery period.

General toxicity in dogs of tolterodine administered orally for two weeks.

Study sponsor:
Study number: 89 96 631
Date: 1990
Species/strain: Beagle dogs
Route: Oral capsules
Number/sex/dose: 2
Doses: 0.5, 2 or 8 mg/kg
Duration: 2 weeks

Mortality: None.

Clinical signs: Main clinical signs were those related to the anticholinergic effects of the drug; inhibition of salivation, pupil dilation and discharge from the eyes. Ataxia and drowsiness were also observed on the first day of treatment in one HD dog. Also, a low frequency of vomiting was noted among the treated dogs.

Body wts: Reduction in body wt was seen for one male and one female of the HD.

Food consumption: Reduced in HD dogs.

Ophthalmoscopic exam: No effects.

Electrocardiography: No significant effects.

Hematology: No significant effects.

Clin chem: No significant effects.

Urinalysis: Increased vol with decreased osmolality in HD dogs.

Organ wts: No effects.

Histopathology: Conjunctivitis in all HD dogs. No other treatment related effects.

Toxicity to dogs by repeated oral administration for 13 weeks.

Study sponsor:
Study number: document 91 96 112
Date: 1991
Species/strain: Beagle dogs
Route: Oral capsules
Number/sex/dose: 4
Doses: 0.5, 1.5 or 4.5
Duration 13 weeks

Mortality: None

Clinical signs: Dry mouth, pupil dilation and discharge from the eyes. All HD dogs developed conjunctivitis. Some ptosis and ataxia in 2 HD dogs on day 1 of treatment only.

Body weight: No changes.

Food/water consumption: No effects.

Ophthalmoscopy: No effects other than conjunctivitis.

EKG: No effects.

Hematology: No effects.

Clin chem: No effects.

Urinalysis: No effects.

Gross path: No effects.

Organ weights: No effects.

Histopathology: No treatment related findings.

Toxicity to Beagle dogs by repeated oral administration for 26 weeks.

Study sponsor:
Study number: 91084
Date: 1991-2
Species/strain: Beagle dogs
Route: Oral capsules
Number/sex/dose: 5
Doses: 0.5, 1.5 or 4.5 mg/kg
Duration: 26 weeks

Mortality: One LD and one MD female were sacrificed moribund with pyometra and chronic disc prolapse, respectively. Neither were treatment related.

Clinical signs: Increased pupillary response (dilation) to direct light with the MD and HD. In the high dose the effect was moderate to pronounced and persisted for 24 hrs.

Slight depression of salivation in the MD and slight to moderate in the HD. This occurred within the first 3-6 hrs after dosing particularly during the first week of treatment and sporadically after that.

There was dose-related decrease in tear flow; dry nose; increase in dry oral mucosa and corneal spots/ulcers. Corneal changes regressed with appropriate treatment. The HD dogs on the first day of dosing showed ataxia, sedation, sensitivity towards light and trembling which subsided by the following day. Thereafter only occasional ataxia and tremor were seen. In the HD, there were occasional distended abdomen and blood in the urine.

Bodyweight: No effect

Food consumption: No effect.

Hematology: No treatment related effects.

Clinical chemistry: There were sporadic changes in LFT's which were not dose and probably not treatment related.

Urinalysis: Some increase in urine volume in the MD and HD females.

Ophthalmologic exam: There was unilateral focal, superficial keratitis at 12 weeks in one control and 3 MD dogs. This was not seen in any dogs at 26 wks.

ECG: During the first hour after dosing, there was an increase in heart rate in most dogs. The lowest dose producing this effect was 1.5 mg/kg in males and 0.5 mg/kg in males. During the course of the study the dogs adapted and no treatment related effect on heart rate was noted.

The duration of the T wave was increased in HD males 1 hr after dosing. This effect was also seen in females and occurred about 1-5 hrs after dosing.

Organ weights: Statistically significant increased liver wt in HD males and non significant increase in HD females.

Gross path: Distended gall bladder with a large amount of bile was seen in one male and one female in the HD. Another HD female had a distended gall bladder with slightly increased amount of bile.

Histopathology: There were no histopath correlates to the enlarged livers. Aside from the two animals killed during the study, there were no toxicologically significant histopath changes.

52-week oral toxicity study in the beagle dog followed by an eight-week recovery period

Testing facility: Pharmacia & Upjohn, Helsingborg, Sweden
Study number: Study no. 95009
Date: 1996
Species/strain: Beagle
Route: Oral gelatin capsules
Number/sex/dose: 7 dogs/sex in the control and high dose and 5 dogs/sex in the low and mid doses. The extra two animals in the control and HD were assigned for an 8- week recovery period.
Doses: 0.5, 1.5 and 4.5 mg/kg/day
Duration: 52 weeks

Systemic Exposure

Dose mg/kg	Week No.	Cmax (ng/ml)				AUC (ngxh/ml)			
		Male		Female		Male		Female	
		T	DD01	T	DD01	T	DD01	T	DD01
0.5	2	72.8	12.0	50.7	9.2	161	43.1	103	27.5
	26	87.9	15.3	61.9	12.8	178	52.1	160	47.0
	52	135	15.6	46.8	12.2	393	66.6	116	35.5
1.5	2	125	41.9	105	28.2	405	169	294	107
	26	190	49.3	136	35.1	538	212	363	125
	52	249	54.3	164	38.2	565	221	380	149
4.5	2	516	137	420	100	5989	1857	2894	1149
	26	695	148	574	127	4648	1975	3217	1349
	52	771	166	401	126	4276	2117	3981	1845

Mortality: Two high dose males showed subdued behavior, urinating difficulties, dilated tensed urinary bladder, blood-stained urine, distended abdomen and pain reaction at palpation of the abdomen caused by urolithiasis and were killed. One HD female showed a chronic purulent conjunctivitis, keratitis and half-closed eyes. The signs disappeared during a 27-days (days 183-210) dose free period but returned within a few days after start of dosing despite continuous moistening of the eyes. The dog was killed for ethical reasons on day 225.

Clinical signs: Dose related decreased pupillary response to directed light was seen from the LD upward. At the MD, pronounced dilation was observed in several dogs on several occasions. At the HD, slight to total dilation was seen in most dogs on most occasions. This effect normalized during the recovery period.

There was a dose-related decrease in salivary secretion and lacrimation starting at the LD.

At the HD, conjunctivitis and occasional corneal lesions due to dry eyes were seen in several dogs, pronounced in some dogs. After 2 months, daily moistening of the eyes of HD dogs was initiated.

Body Weight: No effects were seen.

Food Consumption: Slight decrease in HD females throughout the study and during recovery.

Ophthalmoscopy: Higher frequency of keratitis and/or corneal opacities and conjunctivitis in HD animals compared to controls or the other gps. Pupillary reflex was absent in several HD dogs after 6 or 12 months of dosing.

ECG-Recordings: On day 1 and 7, treated animals of both sexes showed increased heart rate one hr after drug administration. The lowest dose giving a significant increase was 0.5 mkd. During the course of the study the dogs adapted but treatment related effects on heart rate continued sporadically until the end of the study.

A decrease in the PQ-interval was seen in both sexes primarily after treatment with the MD and HD. The QRS-interval was unchanged. In both sexes given the MD and HD, the QT-interval

decreased after the first dose (which may have been caused by the marked increase in heart rate). Both males and females showed changes in QTc during the treatment.

Hematology: No significant treatment related changes.

Clinical Chemistry: No treatment related changes.
Urinalysis: No treatment related changes.

Macroscopic Pathology: Two HD males had marked occlusive urolithiasis in the bladder and urethra along with mucosal hemorrhage and edema. Distention of the gall bladder with macroscopically normal bile was seen in some of the MD and HD male and female animals. Mucosal petechiation in the urinary bladder was seen in 1/3 and 2/5 HD males.

Organ Weights: No treatment related changes in absolute or relative organ weights were observed.

Histopathology: Two HD male dogs that were sacrificed had marked urolithiasis in the bladder and urethra which was the reason for the early sacrifice of these dogs. Mucosal and mural hemorrhage, necrosis and inflammation were seen in the urinary bladder and urethra. Both dogs had marked purulent hemorrhagic prostatitis along with inflammatory edema and congestion in the retroperitoneal soft tissues.

One HD female had corneal inflammatory cell infiltrate in both eyes and slight multifocal corneal epithelial degeneration in one eye. These changes were considered by the sponsor to be treatment related.

There was an inflammatory reaction in the urethra of both males and females which was possibly dose related. Foci of epididymal vascular and perivascular inflammation were seen in 1/5 males at the LD, 2/5 at the MD and 2/3 at the HD. Moderate chronic epididymitis was seen in another MD male.
No changes in the testis, epididymis, urinary bladder or urethra were seen in the recovery animals.

Discussion: The main adverse effects were due to tolterodine's pharmacological (antimuscarinic) effects, i.e. dry mouth, decreased tear flow and pupillary dilation. The ophthalmologic findings (keratitis, corneal opacities and conjunctivitis), seen mainly in the HD were most likely secondary to xerophthalmia induced by the antimuscarinic effects. The urolithiasis seen in two HD males was most likely secondary to increased residual urine, which predisposes to urinary infection, concrement formation and traumatic cystitis/urethritis.

Increase in heart rate was seen early in the study with some adaptation during the progress of the study but there was significant heart rate elevations in some dogs at various time points until the end of the study. Moreover, there was a general increase in heart rate (not reaching statistical significance) in almost all treated dogs at all time points throughout the study. There was no, no effect dose. Decreases in the PQ interval were probably the result of the increased heart rate.

Sub-Acute Toxicity to Mice by Dietary Administration for 13 Weeks.

Testing facility:
Study number: 9610715
Date: 10/96
Species/strain: .CD-1 (ICR) BR mice
Route: oral; mixed with diet