**Study Number:** 92-OATA 001

**Study Title:** Electrophysiological heart effects of repeated iv. Atropine injections, repeated oral dosage of tolterodine and placebo to healthy human volunteers in a parallel group design (study B)

**Study Objectives:** The study was designed to discover potential electrophysiological heart effects of tolterodine at two different doses in healthy human volunteers. A comparison was made to treatment with placebo and treatment with atropine.

As a secondary objective a pharmacokinetic evaluation of tolterodine was performed.

**Study design:** The study was single-blind, placebo controlled and with three parallel arms. It was randomized for 36 subjects, 12 in each of the three groups. The three groups received the following sequences of drug:

Table 38.

| Group | Atropine day | Wash-out | 7 days of tablets | Follow up |
|---|---|---|---|---|
| A | 5 saline injections | 3-7 days | Placebo tablets b.i.d. | 2 days |
| B | 5 atropine injections | 3-7 days | tolterodine, 2 mg b.i.d. | 2 days |
| C | 5 atropine injections | 3-7 days | tolterodine, 4 mg b.i.d. | 2 days |

**Subjects:** The study was designed for 36 healthy volunteers, 12 in each of the three groups. The choice of sample size was based on power considerations and on results from previous studies of utilizing determination of $QT_c$-prolongation in healthy subjects.

Phenotyping for Cytochrome P-450 2D6 (Debrisoquine) and 2C19 (Mephenytoin) was performed prior to the study and the result was used in the inclusion/exclusion process. The procedure was as follows:

After emptying the bladder at bedtime, each subject took one tablet of Mephenytoin (100 mg) and 1/2 a tablet Debrisoquine (10 mg) orally. Urine was collected over night and the concentration relation (metabolic ratio, MR) between Debrisoquine and 4-OH-Debrisoquine as well as the concentration relation between the enantiomers of mephenytoin (enantiomeric ratio, S/R) were determined by

A subject with a metabolic ratio of more than 12.2 for Debrisoquine / 4-OH-Debrisoquine and/or a S/R enantiomeric ratio of mephenytoin of approximately 1 were considered as a poor metabolizer.
The analysis of urine for phenotyping as described (above) was performed at

**Dosage Forms, Dosage and Administration:**
tolterodine table. 2 mg Pharmacia AB). Batch no 3022-0-A1
Placebo (tolterodine) table. Pharmacia AB). Batch no DFP 344
Atropine sulph. inj. sol., 0.5 mg/ml Pharmacia AB), Batch no SG 090A.
Sodium chloride, sterile solution 9 mg/ml. Pharmacia AB), Batch no 3011222.
Debrisoquine tablet, 20 mg (for phenotyping). Batch no 1180.
Mephenytoin tablet, 100 mg (for phenotyping). Batch no 361 F3576.

Saline injections:
I.v. injection of 5 ml saline during 1 minute with a subsequent catheter flush with 5 ml saline. The procedure was repeated 5 times with half an hour intervals.

Atropine day:
I.v. injection of 1 ml atropine (0.5 mg/ml) in 4 ml saline during 1 minute with a subsequent catheter flush with 5 ml saline. The procedure was repeated 5 times with half an hour intervals. Five doses of atropine were a maximum and it was optional to give fewer injections at the discretion of the investigator.

tolterodine /placebo day 1- 7:
The subjects received tolterodine, 2 mg b.i.d. (one active and one placebo tablet), 4 mg b.i.d. (two active tablets) or 2 placebo tablets b.i.d. during 7 consecutive days. At day 7 the tablets were given in the morning only.

The tablets were intended to be taken in the morning (8 am) and evening (8 pm) and were to be swallowed with half a glass of water. The exact time was to be recorded on a special form by the subjects.

**Blood sampling:** Blood samples (7 ml) for determination tolterodine in serum was drawn by means of an intravenous catheter as follows:
Day 1: Prior to first dose (baseline) and 0.5, 1, 1.5, 2, 3.5, 5, 7, 9 and 12 hours thereafter.
Day 4: Prior to morning dose and 1 and 5 hours after morning dose.
Day 7: Prior to morning dose and 0.5, 1, 1.5, 2, 3.5, 5, 7, 9 and 12 hours thereafter.
Day 8: 24 hours after last dose
Day 9: 48 hours after last dose

**Analytical methodology:**

## RESULTS

### ECG-variables

Atropine treatment

During atropine/placebo treatment there were statistically significant differences between treatments for the ECG- variables HR, QT, $QT_c$, TDUR and T-wave amplitude (positive deflection, +Tampl in leads I-III, aVF, $V_1$-$V_6$ and negative deflection, -Tampl in leads aVR and $V_1$) as regards mean changes from baseline.

For the other ECG-variables investigated in this study (PDUR, PR, QRS and T-wave amplitude - positive and negative - in other leads than those mentioned above) no more than occasional statistically significant differences could be shown, although there were tendencies to a decrease in mean value for several of these variables.

The differences between placebo and atropine are fully expected. The increase in HR which is a result of the parasympathetic inhibition by atropine is logically followed by a shortening of several individual ECG parameters. The manual evaluation of T wave morphology in $V_{1-6}$ after atropine did not reveal any change in this parameter.

Tolterodine treatment

During tolterodine /placebo treatment statistically significant differences between treatments as regards mean changes from baseline could be seen only on a few isolated occasions in time.
HR was not influenced by 2 mg dosage level. With 4 mg, however, in less than half of the measurements, there was a statistically significant increase (range; 7-13 beats/min., i.e. < 20%). These increases

occurred clustered to the first hours after the morning dose, i.e. around time for $C_{max}$ This finding was fully expected due to the anticholinergic nature of the drug.
The manual evaluation of T-wave morphology in lead $V_{1-6}$ did not reveal any change in this parameter after administration of tolterodine.

No evidence of any increase in QT or $QT_c$ after administration of tolterodine were seen, neither when looking at the group mean values nor when looking at the individual extreme values.
Minimum and maximum group mean values of QT and $QT_c$ during the atropine day and during tolterodine day 1 and 7 are shown in Table 39.

**Table 39.** Minimum and maximum group mean values and (SD) of QT and QTc during the atropine day and during tolterodine day 1 and 7.

| QT (ms) | | Placebo group | tolterodine 2 mg b.i.d. | tolterodine 4 mg b.i.d. | Atropine |
|---|---|---|---|---|---|
| Baseline* | | 420 (29) | 429 (27) | 419 (17) | 410 (18) |
| Day 1 | maximum<br>minimum | | | | |
| Day 7 | maximum<br>minimum | | | | |
| **QTc (ms)** | | **Placebo group** | **tolterodine 2 mg b.i.d.** | **tolterodine 4 mg b.i.d.** | **Atropine** |
| Baseline* | | 421 (21) | 425 (19) | 415 (13) | 410 (15) |
| Day 1 | maximum<br>minimum | | | | |
| Day 7 | maximum<br>minimum | | | | |

- 2nd baseline measurement

The normal $QT_c$ is often stated to be below 440 ms. Recent literature have however shown that the normal variability of QT and $QT_c$ is substantially higher than previously anticipated. Normal ranges of $QT_c$ of up to 506 ms and of QT up to 487 have been reported. Furthermore, for individual subjects a high degree of daily variability in $QT_c$ has been shown.

For comparison, the minimum and maximum extreme values obtained during baseline measurement, during day 1 and during day 7, for the different groups in this study are presented in Table 40. Individual values of a $QT_c > 440$ were frequently seen also in our material.

**Table 40.** Minimum and maximum extreme values of QT and $QT_c$ during the atropine day and during tolterodine day 1 and 7.

| QT (ms) | | Placebo group | tolterodine 2 mg b.i.d. | tolterodine 4 mg b.i.d. | Atropine |
|---|---|---|---|---|---|
| Baseline* | maximum<br>minimum | | | | |
| Day 1 | maximum<br>minimum | | | | |
| Day 7 | maximum<br>minimum | | | | |
| **QTc (ms)** | | **Placebo group** | **tolterodine 2 mg b.i.d** | **tolterodine 4 mg b.i.d** | **Atropine** |
| Baseline* | maximum<br>minimum | | | | |
| Day 1 | maximum<br>minimum | | | | |
| Day 7 | maximum<br>minimum | | | | |

* 2nd baseline measurement

**Blood pressure**

Atropine treatment

During atropine/placebo treatment there were statistically significant differences between treatments for diastolic blood pressure but not for systolic blood pressure as regards mean changes from baseline. Here, baseline was defined as the mean of the two replicate BP measurements recorded immediately before the first iv. injection. These significant differences were present between 1 hour 15 min (after 3rd dose) and 2 hours 15 min. (after the 5th dose). For diastolic blood pressure there was an estimated average difference between atropine treated subjects and placebo treated subjects of about +10% (of baseline). An increase in diastolic blood pressure was expected, but its magnitude (6.1 - 8.9 mm Hg as a range) was somewhat higher than anticipated.

Tolterodine treatment

During tolterodine/placebo treatment there were no statistically significant differences between treatments; neither for diastolic nor for systolic blood pressure as regards mean changes from baseline other than on a few isolated occasions in time.

The baseline was defined as the mean of the two replicate measurements recorded immediately before the first tablet intake on day 1 of tolterodine/placebo treatment.

**Serious adverse events:** No serious adverse events occurred during the trial.

**Pharmacokinetics:** Mean pharmacokinetic parameters of tolterodine and the 5-Hydroxymetabolite (5-HM) are presented in Table 41, below.

**Table 41.** Mean (SD) Pharmacokinetic Parameters of tolterodine and 5-Hydroxymetabolite (n=II).

| | Tolterodine | | | | 5 - H M | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose, bid** | **Cmax, (µg/l)** | **tmax, (h)** | **AUC*, (µg - h/l)** | **t½,z, (h)** | **Cmax, (µg/l)** | **tmax, (h)** | **AUC*, (µg - h/l)** | **t½,z, (h)** |
| 2 mg, ** day 1 | 2.2 (2.1) | 2.0 (0.9) | 12.1 (15.1) | 2.4 (0.7) | 2.1 (0.6) | 2.0 (0.8) | 12.2 (4.3) | 3.2 (1.5) |
| 2 mg, ** day 7 | 2.5 (2.3) | 2.5 (1.1) | 11.8 (14.2) | 2.4 (0.9) | 2.2 (0.7) | 2.5 (1.0) | 12.1 (3.3) | 3.4 (1.7) |
| 4 mg, day 1 | 4.2 (5.2) | 2.2 (0.9) | 22.4 (33.8) | 2.5 (0.7) | 4.2 (1.4) | 2.5 (1.2) | 25.0 (9.8) | 3.3 (1.2) |
| 4 mg, day 7 | 4.6 (6.1) | 2.6 (1.0) | 23.0 (34.1) | 2.2 (0.5) | 4.4 (1.2) | 2.8 (1.3) | 25.5 (7.3) | 3.2 (0.8) |

* The AUC values are presented as $AUC_0^{\infty}$ after single-dose administration and $AUC_0^{12}$ after multiple dose administration.
** Note that subject no 29 received only atropine and is not included in this table.

No accumulation of tolterodine or its metabolite 5-HM was seen after multiple-dose administration. $C_{max}$ and AUC increased proportionally with increasing dose, suggesting linearity of pharmacokinetics. Tolterodine and 5-HM were present within the same concentration range.

**Sponsor's Conclusions:**

- Intermittent intravenous administration of atropine in doses of 0.5 mg significantly depressed T-amplitude and shortened the T-duration, QT and QTc between cumulative doses of 1 - 2.5 mg.

- Tolterodine, 2 and 4 mg b.i.d. did not prolong QT or $QT_c$.

- Tolterodine, 2 and 4 mg b.i.d. did not influence either T-wave amplitude, T-wave duration or T-wave morphology.

- Tolterodine, 2 and 4 mg b.i.d. has not created any kind of safety concern; neither regarding cardiovascular evaluation, clinical chemistry, hematology, urinalysis nor adverse events.

- No accumulation of tolterodine or its 5-hydroxymetabolite was seen after multiple dose administration.

**Study Number:** 93-OATA 004

**Study Title:** Pharmacological effects are kinetics of tolterodine in poor and extensive metabolizers of debrisoquine.

**Study Objectives:** To investigate the pharmacological effects and kinetics of tolterodine in poor and extensive metabolizers of debrisoquine.

**Study design:** This was an open, comparative, multiple dose study.

**Subjects:** 16 healthy male volunteers were enrolled

Phenotyping for Cytochrome P-450 2D6 (Debrisoquine) and 2C19 (Mephenytoin) was performed prior to the study and the result was used in the inclusion/exclusion process. The procedure was as follows:

After emptying the bladder at bedtime, each subject took one tablet of Mephenytoin (100 mg) and 1/2 a tablet Debrisoquine (10 mg) orally. Urine was collected over night and the concentration relation (metabolic ratio, MR) between Debrisoquine and 4-OH-Debrisoquine as well as the concentration relation between the enantiomers of mephenytoin (enantiomeric ratio, S/R) were determined by

A subject with a metabolic ratio of more than 12.2 for Debrisoquine / 4-OH-Debrisoquine and/or a S/R enantiomeric ratio of mephenytoin of approximately 1 were considered as a poor metabolizer.
The analysis of urine for phenotyping as described (above) was performed at

**Test Product:** Tolterodine, 2 mg tablets, batch No. 3022-O-A-1.

**Treatment Duration:** 4 mg b.i.d. for 8 days.

Results:
The pharmacokinetic parameters of tolterodine from poor and extensive metabolizers are included in Table 42.

Table 42.

| | F (%) | Cmin (µg/l) | Cmax (µg/l) | Cl (l/h) | t½ (h) |
|---|---|---|---|---|---|
| EM | 17±9.5 | 0.38±0.09 | 5.1±5.6 | 45±12 | 2.2±0.37 |
| PM | 65±26 | 15±6.0 | 38±15 | 9.5±1.8 | 9.6±1.5 |

**Sponsor's Conclusions:**

- Tolterodine L-tartrate 4 mg b.i.d. and 1.8 mg infusion has not created any kind of safety concern; neither regarding cardiovascular evaluation, clinical chemistry, hematology, urinalysis, nor adverse events.

- Tolterodine is highly and selectively metabolized by CYP2D6 to DD01.

- It seems that the higher tolterodine concentrations in the poor metabolizers compensate for the absence of the active metabolite DD01 in these subjects.

**Study Number:** CTN 93-OATA-007

**Study Title:** Tolerability and pharmacokinetic effects of tolterodine L-tartrate in elderly. A randomized double-blind study in healthy volunteers.

**Objectives:** To investigate safety and tolerability of tolterodine in elderly with special reference to cardiovascular effects. To investigate the pharmacokinetics after single- (1, 2 and 4 mg) and multiple-dose (2 mg b.i.d.) administration.

**Study Design:** Randomised double-blind parallel group design (4 groups).

**Subjects :** 8 male and 18 female healthy elderly volunteers (age 64-80 years) were enrolled in the study. Two (2) subjects, (poor metabolizers) were treated separately and received the doses unblinded.

**Test product:** Tolterodine L-tartrate tablets, 1 mg (Pharmacia AB). Batch No: B039303
*Composition*

| Active ingredient: | | | |
|---|---|---|---|
| Tolterodine L-tartrate | mg | | |
| Other ingredients: | | Tablets coated with: | |
| Cellulose microcrystalline | mg | Eudragit E 100 | mg |
| Calciumhydrogen phosphate | mg | Titaniumdioxide | mg |
| Sodium starch glycolate | mg | Talc | mg |
| Magnesium stearate | mg | Magnesium stearate | mg |
| Silica anhydrous | mg | Polyethylene glycole | mg |
| | | Vanillin | mg |

**Reference product:** Placebo (Pharmacia AB). Batch No: B019303
*Composition*

| Ingredients: | | Tablets coated with: | |
|---|---|---|---|
| Cellulose microcrystalline | mg | Eudragit E 100 | mg |
| Calciumhydrogen phosphate | mg | Titaniumdioxide | mg |
| Magnesium stearate | mg | Talc | mg |
| Silica anhydrous | mg | Magnesium stearate | mg |
| | | Polyethylene glycole | mg |
| | | Vanillin | mg |

**Duration of treatment:** 1, 2, and 4 mg single-dose administration and 2 mg b.i.d. for 5 days.

**Blood and Urine Sampling:**
Single dose administration: Venous blood samples were drawn before administration of study drug and at 15, 30, 45 minutes and at 1, 1.5, 2, 4, 6, 8, 10, 12, 24 and 25 hours after drug administration.

Multiple dose administration: Venous blood samples were drawn immediately before administration on day 4, before administration of study drug on day 5 and at the following times after administration on day 5: 15, 30, 45 minutes, 1, 1.5, 2, 4, 6, 8, 10, 12, 24 and 25 hours.

Urine: A urine sample was collected immediately before dosing on day one (single dose part). Urine was collected quantitatively in the intervals 0-12 and 12-24 hours during single dosing and on day five during multiple dosing. Each urine sample was carefully shaken and a 10 ml aliquot was prepared. The samples were frozen and stored at -20 °C until analyzed for unchanged drug and DD 01.

**Analytical Methodology:**

**Serum protein binding:**
The degree of in vivo binding to serum proteins was estimated for tolterodine and DD 01. The free concentration (Cu) and total serum concentration (Cs) were measured in the 1 hour serum sample after the last dose (day five, multiple dose session). Free fraction (fu) was to be estimated from the ratio of Cu to Cs. Free concentration, Cu, in serum was to be measured by means of equilibrium dialysis.

**RESULTS**
**Safety:** No treatment related effects on clinical laboratory safety variables were seen comparing screening to post-study assessment. No clinically significant findings were seen considering changes in QTc, or in the other measured ECG parameters .

**Pharmacokinetics:** A summary of the pharmacokinetic parameters is presented below.

**Table 43.** Mean (SD) Pharmacokinetic Parameters of Tolterodine and DD 01 after multiple dose (5 days) administration of 2 mg b.i.d. tolterodine L-tartrate

| Analyte | tmax (h) | Cmax (µg/l) | Cav (µg/l) | $t_{1/2}$ (h) | AUC0-t (µgh/l) | $CL_o$ (l/h) | fe (% of dose) |
|---|---|---|---|---|---|---|---|
| tolterodine | 0.9 (0.28) | 1.6 (0.95) | 0.52 (0.37) | 2.8 (0.69) | 6.2 (4.4) | 343 (239) | <1.0 |
| DD 01 | 1.0 (0.24) | 2.7 (0.66) | 1.0 (0.34) | 3.6 (0.67) | 12 (4) | ---- | 14 (4.8) |

**Table 44.** Mean (SD) Pharmacokinetic Parameters of Tolterodine and DD 01 after single oral administration of tolterodine L-tartrate.

| | tolterodine | | | | | | DD 01 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dose (mg) | tmax (h) | Cmax (µg/l) | Cav (µg/l) | $t_{1/2}$ (h) | AUC 0-t (µgh/l) | $CL_o$ (l/h) | tmax (h) | Cmax (µg/l) | Cav (µg/l) | $t_{1/2}$ (h) | AUC 0-t (µgh/l) |
| 1 | 0.83 | 0.78 | 0.22 | 2.4 | 2.6 | 372 | 0.88 | 1.1 | 0.47 | 3.9 | 5.7 |
| (n=6) | (0.20) | (0.46) | (0.13) | (1.2) | (1.6) | (235) | (0.14) | (0.39) | (0.16) | (1.1) | (2.0) |
| 2 | 0.72 | 1.6 | 0.36 | 1.9 | 4.4 | 353 | 0.83 | 2.5 | 0.92 | 2.9 | 11 |
| (n=6) | (0.20) | (0.55) | (0.12) | (0.68) | (1.4) | (151) | (0.38) | (0.73) | (0.31) | (0.2) | (3.7) |
| 4 | 0.63 | 3.8 | 1.2 | 2.8 | 14 | 399 | 0.71 | 5.0 | 2.1 | 3.6 | 25 |
| (n=6) | (0.14) | (3.2) | (1.0) | (0.48) | (12) | (330) | (0.19) | (2.1) | (1.0) | (0.72) | (12) |

Poor metabolizers
The poor metabolizers showed no detectable concentrations of DD 01. The half-life of tolterodine was 3-4 times longer than in extensive metabolizers, Table 45.

**Table 45.** Pharmacokinetic parameters of tolterodine in Poor Metabolizers (P-450 2D6).

| Subject No. | Dose (mg) | tmax (h) | Cmax (µg/l) | Cavg (µg/l) | $t_{1/2}$ (h) | AUC* (µgh/l) | $Cl_o$ (l/h) | $f_e$ (% of dose) |
|---|---|---|---|---|---|---|---|---|
| | 2 | 0.75 | 7.4 | 8.9 | 11 | 108 | 13 | n.a. |
| | 2 | 1.5 | 12 | 18 | 15 | 214 | 6.4 | n.a. |
| | 2 bid | 2.0 | 25 | 18 | 16 | 215 | 6.4 | 8.4 |

The single-dose pharmacokinetics suggests dose proportionality. The steady-state maximum concentrations of tolterodine and DD 01 were 1.6 and 2.7 µg/l, respectively and the respective, half-lives were 2.8 and 3.6 hours. No accumulation of tolterodine or DD 01 was seen after b.i.d. multiple dose administration with the exception of the poor metabolizer. This subject had a two-fold accumulation, which is in accordance with the longer half-life (16 hours).

Steady-state serum concentration-time profiles of tolterodine and DD 01 after multiple doses of tolterodine (2 mg b.i.d.) are depicted in Figures 6 and 7.

Figure 6. Serum Concentration versus Time Profile of Tolterodine

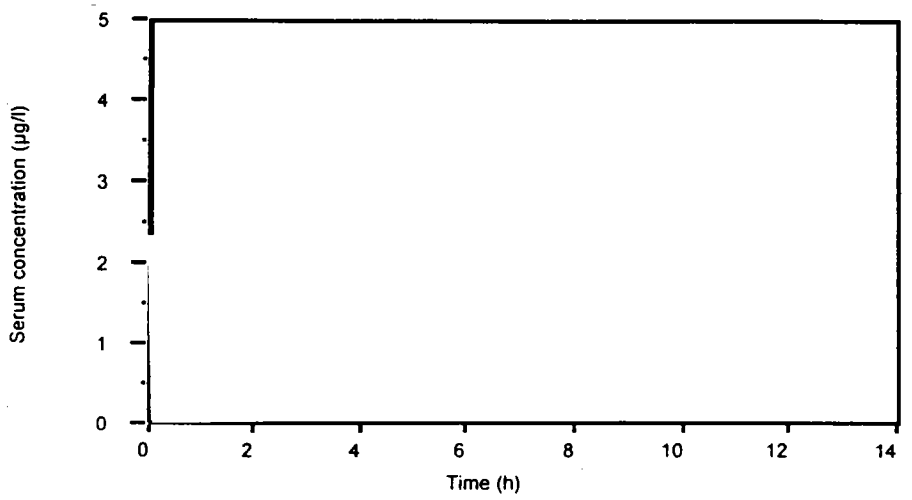
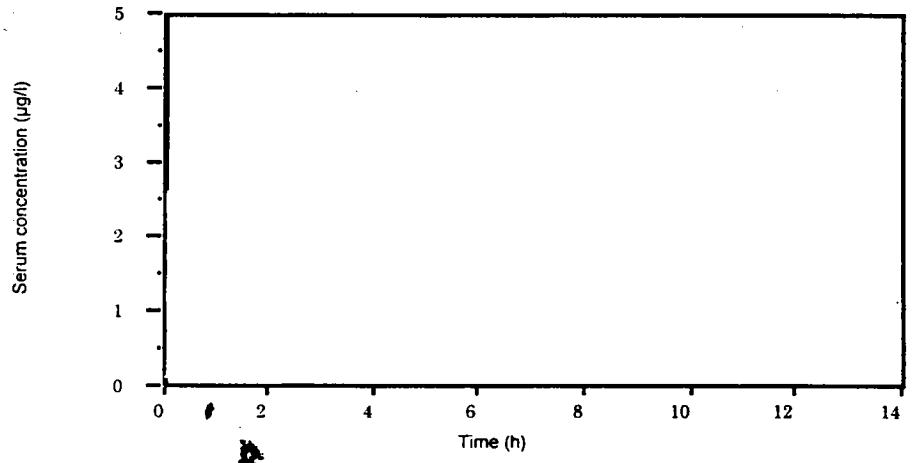



Figure 7. Serum Concentration versus Time Profile of DD01.




**Sponsor's Conclusions:**

- From the present study with elderly subjects it can be concluded that tolterodine 1, 2 and 4 mg given as single doses and 2 mg b.i.d did not create any kind of safety concerns; neither regarding cardiovascular effects (ECG, heart rate and blood pressure), clinical chemistry, hematology, urinalysis nor adverse events.

- The single-dose pharmacokinetics suggests dose proportionality with respect to $C_{max}$ and AUC.

- No accumulation of tolterodine or DD 01 was seen after multiple dose with exception for the poor metabolizer. This subject had a two-fold accumulation, which is in accordance with the longer half-life in this subject.

- $C_{avg}$ , $C_{max}$ and AUC of tolterodine and DD 01 increased proportionally with increasing dose and time. There were no consistent dose-dependent changes in half-life of tolterodine or DD 01 or oral clearance of tolterodine.

- The serum concentration levels of DD 01 was about the same or a little higher than those of tolterodine. No accumulation of either tolterodine or DD 01 was seen after multiple-dose administration.

**Study Number:** CTN: 94-OATA-013

**Study Title:** Safety and tolerability of tolterodine after multiple-dose administration to elderly subjects: A randomized, double-blind, placebo-controlled study

**Objectives:** The primary objective was to assess the safety and tolerability of multiple doses of tolterodine in elderly subjects at least 70 years of age. A secondary objective was to determine the serum concentrations of both tolterodine and DD 01, and a final objective was to assess the feasibility of administration of micturation charts in this age group.

**Study Design:** This was a multi-center, randomized, double-blind, parallel, three groups, placebo controlled study.

**Subjects:** Thirty three elderly subjects 70 years of age or older; at least 50% >75 years were enrolled in the study. The subjects were randomized, 7 to the placebo and 26 to the active treatment (14 - 1 mg and 12 - 2 mg) groups. Four subjects (12%) were phenotype for CYP2D6 as poor metabolizers according to the dextro-methorphan assay.

**Test product:** Tolterodine L-tartrate tablets (0.5 and 1 mg) batch No. BB121027 and B039303, respectively

**Duration & Dosage:** The subjects received either placebo, or tolterodine 1 or 2 mg b.i.d. for 28 consecutive days.

**Assay Methodology:**

**Blood Sampling:** Venous blood samples (5 mL Vacutainer® tube, no additives) for assessment of serum drug / metabolite levels were collected pre- and post-morning dose at 0, 0.5, 1, 2, 4, 6 and 8 hr on Days 1 and 28. On Day 7, four blood samples were obtained at 0, 0.5, 1 and 2 hours post-morning dose.

**Results**

***Kinetics after a Single Dose (Day 1)***

Absorption of tolterodine was rapid with the $T_{max}$ attained following both doses between 0.5 to 2 hours. For the 1 and the 2 mg doses respectively, the single dose estimates (mean ± SD) of tolterodine were: $C_{max}$ 2.8 (±2.8) and 2.8 (±2.1) ng/mL, $AUC_{0-\infty}$ 7.09 (±4.75) and 8.76 (±6.09) ng.hr/mL, the terminal half-life ($t_{1/2},\lambda_z$) 2.06 (±0.68) and 2.16 (±0.44) hr. Body weight normalized estimates of $CL_o$ were 2.18 (±1.43) and 3.02 (±1.64) L/hr/kg, and for $V_d,\lambda_z$ were 6.2 (±4.30) and 9.0 (±4.7) L/kg following the 1 and 2 mg doses, respectively.

Except for $C_{max}$, no statistically significant differences between the 1 and 2 mg doses were seen in the dose-normalized tolterodine estimates: $AUC_{0-\infty}$ ($p = 0.218$), $CL_o$ ($p = 0.660$) or $V_d$ ($p = 0.761$) following single doses. Both $T_{max}$ and $t_{1/2},\lambda_z$ were independent of the dose.

For DD 01, the estimates of $T_{max}$ and $C_{max}$ (mean ± SD) were 0.9 (±0.4), 0.8 (±0.3) hr and 2.0 (±1.4) and 3.5 (±1.6) ng/mL following the 1 and 2 mg tolterodine doses, respectively. The $AUC_{0-\infty}$ (mean ± SD) for those respective doses were 10.7 (±7.41) and 16 (±8.05) ng.hr/mL. Terminal $t_{1/2},\lambda_z$ for DD 01 was about 3.57 (±1.41) and 2.89 (±0.37) hr following the 1 and 2 mg tolterodine doses, respectively. Except for $t_{1/2},\lambda_z$, no statistically significant differences between the 1 and 2 mg single doses were seen in the dose-normalized DD 01 parameters $C_{max}$ ($p = 0.155$) or $AUC_{0-\infty}$ ($p = 0.094$). Overall, the DD 01 elimination profile was similar to tolterodine.

In poor metabolizers (n = 4), tolterodine $C_{max}$ ranged from ng/mL and was attained in ~1 hr. Consistent with the magnitude of the dextromethorphan phenotype estimate, the corresponding $AUC_{0-\infty}$ ranged from ng.hr/mL and the $CL_o$ from L/hr/kg. Although the kinetic parameters obtained from PMs were not compared statistically to those obtained from EMs, it is apparent that relatively higher values of $C_{max}$, $AUC_{0-\infty}$ and $t_{1/2},\lambda_z$ for tolterodine were observed.

*Kinetics after Repeat Dosing (Day 28): Steady-State*

Given the short half-life of tolterodine, its steady state was easily achieved by Day 28. The steady-state estimates (mean ± SD) of $C_{max}$ were 2.4 (±1.6) and 4.1 (±3.8) ng/mL, and were attained within 1 hr ($T_{max}$) post-1 and 2 mg doses (b.i.d regimen), respectively. For these two doses, the estimates of $AUC_{0-12}$ were 8.59 (± 4.87) and 13.5 (±9.38) ng.hr/mL. The $t_{1/2},\lambda_z$ was about 2 hr for both dose levels, hence independent of dose. Weight normalized oral clearance ($CL_o$) at steady-state was 1.94 (±1.69) and 2.61 (±2.42) L/hr/kg, while estimates of $V_d,\lambda_z$ were 5.69 (±5.41) and 7.5 (±5.9) L/kg following twice daily regimen of 1 and 2 mg doses, respectively, for 28 days.

No statistically significant differences were apparent between the 1 and 2 mg dose levels in the dose-normalized estimates for tolterodine $C_{max}$ ($p = 0.647$), $AUC_{0-12}$ ($p = 0.909$), $CL_o$ ($p = 0.298$) or $V_d$ ($p = 0.796$). $T_{max}$ ($p = 0.867$) and $t_{1/2},\lambda_z$ ($p = 0.713$) were unaltered. Lack of dose effect on kinetic parameters suggested dose-independent kinetics for the two dose levels.

At steady state, the peak metabolite concentrations following both doses were similar to the $C_{max}$ of the parent drug. The estimates (mean ± SD) of $C_{max}$ were 2.5 (±1.5) and 3.9 (±2.2) ng/mL, which were attained at about 1 hr ($T_{max}$) following the 1 and 2 mg tolterodine doses, respectively. The corresponding estimates of $AUC_{0-12}$ were 10.60 (± 4.74) and 18.30 (±9.07) ng.hr/mL, and the $t_{1/2},\lambda_z$ were 3.74 (±0.77) and 3.67 (±1.20) hr, respectively.

No statistically significant differences between the 1 and 2 mg doses were seen in the dose-normalized kinetic estimate for DD 01 $C_{max}$ ($p = 0.389$) and $AUC_{0-\infty}$ ($p = 0.902$). No dose related changes were apparent in $T_{max}$ ($p = 0.91$) or $t_{1/2},\lambda_z$ ($p = 0.187$) on Day 28. Metabolite kinetics at steady-state supported the assessment based on the parent drug of a lack of dose effect on kinetics.

In the poor metabolizers (n = 3), tolterodine $C_{max}$ ranged from ng/mL, attained in ~1 hr. Consistent with the magnitude of the dextromethorphan phenotype estimate, the corresponding $AUC_{0-12}$ (area over a dosing interval) ranged from ng.hr/mL and the $CL_o$ from L/hr/kg. Due to bioanalytical limitations, tolterodine kinetics could not be estimated for one PM (#102).

***Single versus Multiple Dose Pharmacokinetics***

Multiple oral dosing (steady-state) with 1 mg resulted in no significant changes (signed rank test) in tolterodine $T_{max}$ ($p = 0.25$), $C_{max}$ ($p = 0.867$), $AUC_{0-12}$ ($p = 0.432$), $t_{1/2},\lambda_z$ ($p = 0.695$), $CL_o$ ($p = 0.509$) or $V_d$ ($p = 0.769$) compared to the estimates following the first dose on Day 1. Similarly, no significant changes in pharmacokinetic parameters, attesting to a lack of accumulation, could be detected following the 2 mg twice daily regimen compared with the first dose kinetics. The steady-state/single dose ratios (R; accumulation factor) for $C_{max}$ and AUC, estimating drug accumulation, were 1.05 and 1.25, respectively, following the 1 mg dose, while for the 2 mg dose these were 1.45 and 1.46. Although an increase of 46% in the mean $C_{max}$ for tolterodine was observed when Day 28 data for the 2 mg are compared to the

single dose; given the variability in EMs (due to phenotype status), this change was not statistically different ($p = 0.211$). The power was < 94% based on $C_{max}$ estimate. Obviously, two subjects with relatively high $C_{max}$ could account for increase in the mean $C_{max}$ (see 95% CI). However, the steady-state (Day 28) mean $AUC_{0-12}$ for tolterodine following the 2 mg dose was significantly ($p = 0.027$) higher compared to the $AUC_{0-\infty}$ estimate following the first dose (Day 1).

No significant changes were apparent in DD 01 kinetics following 1 and 2 mg doses of tolterodine that suggested drug accumulation. Interestingly, the DD 01 $t_{1/2},\lambda_z$ estimate increased significantly ($p = 0.019$) at steady-state (Day 28) following the 2 mg dose.

The ratio estimates for DD 01 $C_{max}$ and AUC were 1.27, 1.15 (1 mg) and 1.12, 1.16 (2 mg), respectively, and did not suggest any accumulation. Overall, both the parent drug and the metabolite data failed to exhibit and support accumulation following 1 or 2 mg tolterodine b.i.d. regimen.

***Dose-proportionality Assessment***

The following analysis was performed in order to provide indications regarding dose proportionality or deviations from that and may serve as supportive data to a formal dose proportionality study. Figure 3 shows AUC vs. tolterodine dose regression (forced through zero) plots. Although limited in nature to address the dose-proportionality, these data are suggestive of proportionality based on single doses ($r^2 = 0.183$, slope = 4.95 [95% CI: 3.31-6.59]) and linear kinetics based on steady-state ($r^2 = 0.198$, slope = 7.10 [95% CI: 4.92-9.28]). The low coefficients of determination are reflective of the intersubject variability inherent in the magnitude of the extensive metabolizer phenotype. Given the degrees of freedom, the correlation coefficients for both regressions are statistically significant. The overlap (estimation error) in the slope estimates for the single and multiple dosing states appears to be related to this variation.

**Sponsor's Conclusions:**

- Relative to the placebo, both 1 and 2 mg tolterodine doses administered on a b.i.d. regimen for 28 days were well tolerated in elderly subjects (age: ≥70 years).

- Tolterodine and DD 01 kinetics in this cohort appear to be similar to those previously reported.

- Tolterodine kinetics following the 2 mg b.i.d. regimen suggested minor accumulation.

- There were no clinically significant findings with respect to safety variables, including ECG, blood pressure, heart rate, clinical chemistry or hematology.

**Study Number:** 95-OATA-022

**Title of the study** The influence of food on the bioavailability of tolterodine. An open, single dose cross over study in healthy volunteers.

**Objective:** To study the influence of food on the bioavailability of tolterodine after a single dose administration of 2 mg.

**Study Design:** Open, single-dose, cross-over

**Subjects:** Twenty-four healthy females and males.

**Study product:** Tolterodine L-tartrate tablet, 2 mg Batch No. A 049404.

**Statistical methods:** Descriptive statistics, including means and standard deviations were calculated for the pharmacokinetic parameters. $AUC_{-}$, and $C_{max}$ were evaluated with analysis of variance (ANOVA) and 90% confidence interval

**Results**

Table 47. Pharmacokinetic parameters (mean ± SD; median with range for $t_{max}$) for tolterodine and DD 01 after oral administration of tolterodine with and without food.

| Parameter | Tolterodine | | DD 01 | |
|---|---|---|---|---|
| | Food | Fasting | Food | Fasting |
| $C_{max}$ (µg/l) | 2.7 ± 1.8 | 1.9 ± 1.4 | 2.1 ± 0.65 | 2.3 ± 0.89 |
| $AUC_{\infty}$ (µg·h/l) | 11.6 ± 11.7 | 8.63 ± 10.0 | 11.0 ± 2.76 | 10.2 ± 3.10 |
| $t_{max}$ (h) | 1.0 (0.5 - 3.0) | 1.0 (0.5 - 4.0) | 1.0 (0.5 - 3.0) | 1.0 (0.5 - 2.0) |
| $t_{½z}$ (h) | 2.3 ± 0.54 | 2.3 ± 0.73 | 3.2 ± 0.99 | 3.2 ± 0.96 |
| $CL_o$ (l/h) | 209 ± 148 | 376 ± 382 | | |

Table 48. $AUC_{\infty}$ and $C_{max}$ ratios, i.e. relative bioavailability (geometric mean with 90 % CI) for tolterodine and DD 01. Treatment with food compared to fasting.

| | $AUC_{\infty}$ ratio | $C_{max}$ ratio |
|---|---|---|
| Tolterodine | 1.53 (1.35 - 1.72) | 1.49 (1.30 -1.71) |
| DD 01 | 1.09 (1.04 - 1.15) | 0.96 (0.87 - 1.06) |

**Sponsor's Conclusions:**

- Bioequivalence could not be concluded for tolterodine when given with and without food. A 53% increase in serum levels ($AUC_{\infty}$) was seen when the drug was given with food. However, more importantly, bioequivalence was shown for the active metabolite DD 01 with respect to both $AUC_{\infty}$ and $C_{max}$, when treatment with food was compared to fasting administration.

- Approximately 75 % of the systemically available tolterodine is metabolized to DD 01 by CYP2D6 in extensive metabolizers. This implies that other routes of elimination have a minor contribution to the systemic clearance. In the present study all subjects were extensive metabolizers. The effect of food on the pharmacokinetics of tolterodine in poor metabolizers can thus not be evaluated. However, assuming that the effect seen in extensive metabolizers is due to limited capacity of CYP2D6 (which is not present in poor metabolizers) no food effect is expected in the poor metabolizers.

- *In vitro* data show that the free fraction of DD 01 is much higher than that of tolterodine which results in significantly higher concentrations of unbound DD 01 compared to tolterodine in extensive metabolizers. As a consequence of the equipotency of DD 01 and tolterodine it is likely that DD 01 accounts for most of the clinical effect in extensive metabolizers. The increased bioavailability of tolterodine is therefore not expected to be of any clinical relevance.

**Reviewer's Comments:**
The effect of food on the bioavailability of tolterodine in poor metabolizers (individuals genetically deficient in CYP 2D6) has not been assessed. In poor metabolizers, the primary pathway of elimination is metabolism by cytochrome P-450 3A4. A food effect may also occur in poor metabolizers and the assumption that no food effect is expected in the poor metabolizers due to lack of CYP 2D6 may not be valid.

**Study Number:** CTN 95-OATA-024

**Title of the study:** Dose proportionality of tolterodine. An open, randomized, single-dose, cross-over study in healthy volunteers.

**Objectives:** The primary objective of this study was to compare the pharmacokinetics of tolterodine and DD 01, respectively, after single oral doses of 1, 2 and 4 mg.

A secondary objective of the study was to collect serum, after the 4 mg dose, for the possible identification/quantification of metabolites of tolterodine hitherto not studied in human serum.

**Study Design:** Open, randomized, 3-period cross-over, single-dose study.

**Subjects :** Twenty-four (11 males, 13 females)

**Test product:** Tolterodine tablets 1 mg, batch no. VC 800.

**Duration of treatment:** 3 single doses with a one week wash-out between doses.

**Statistical methods:** Dose proportionality was tested by using bioequivalence criteria on dose normalized, log-transformed $AUC_\tau$ and $C_{max}$ values for both tolterodine and DD 01 after administration of a single dose of tolterodine of 1, 2 and 4 mg.

**Results:** The pharmacokinetic variables are summarized in the following table:

Table 49

| | | 1 mg | | 2 mg | | 4 mg | |
|---|---|---|---|---|---|---|---|
| Parameter[1] | | Tolterodine | DD 01 | Tolterodine | DD 01 | Tolterodine | DD 01 |
| $AUC_\tau$ | EM[2] | 3.82±3.30 | 5.71±2.08 | 7.49±8.60 | 10.7±3.85 | 15.7±18.0 | 22.4± 8.94 |
| (µg·h/l) | PM[2] | 55.7±2.83 | | 104±22.3 | | 231±23.5 | |
| $C_{max}$ (µg/l) | EM | 1.1±1.1 | 1.2±0.46 | 2.1±2.6 | 2.2±0.75 | 4.6±6.0 | 4.8±1.7 |
| | PM | 4.7±1.2 | | 9.7±2.7 | | 18.8±5.1 | |
| $t_{max}$ (hours) | EM | 1.0 (0.5-3.0) | 1.0 (0.5-3.0) | 1.0 (0.5-3.0) | 1.0 (0.5-3.0) | 1.0 (0.5-3.0) | 1.0 (0.5-4.0) |
| | PM | 1.5 (1.5-2.0) | | 1.5 (1.0-2.0) | | 1.5 (1.0-3.0) | |
| $t_{1/2z}$ ($h^{-1}$) | EM | 2.46±0.68 | 3.20±0.53 | 2.64±0.89 | 3.20±0.76 | 2.15±0.33 | 2.93±0.53 |
| | PM | 10.4±0.53 | | 9.24±0.93 | | 9.53±0.39 | |
| $CL_O$ (l/h) | EM | 304±191 | | 380 ±262 | | 408±325 | |
| | PM | 12.3±0.61 | | 13.5±2.65 | | 11.9±1.16 | |

1: mean ± SD except $t_{max}$ which is given as median (range)
2: EM = extensive metabolizers PM = poor metabolizers

The relative bioavailability (%) of the dose normalized 1 and 4 mg doses, compared to the 2 mg dose (geometric mean with 90% CI) are summarized in the following table:

Table 50.

| | $AUC_\tau$ | $C_{max}$ |
|---|---|---|
| **Tolterodine** | | |
| 1 mg | 117 (103 - 132) | 116 (99 - 137) |
| 4 mg | 102 (89 - 115) | 105 (89 - 123) |
| **DD 01** | | |
| 1 mg | 107 (99 - 115) | 107 (96 - 120) |
| 4 mg | 104 (96 - 112) | 106 (95 - 118) |

**Sponsor's Conclusions:**

- The pharmacokinetics of tolterodine, and its active metabolite DD 01, were found to be linear over the dosage range of 1 to 4 mg.

- The results indicate that the both the 1 mg and 4 mg doses are bioequivalent to the 2 mg dose after dose normalization. This means that there is a linear increase in $AUC_{\infty}$ and $C_{max}$ that is proportional to the increase in tolterodine dose. Although no formal statistical testing can be performed for the three poor metabolizers in this study, a comparison of their data for the different dose levels indicates that the pharmacokinetics of tolterodine and DD 01 are proportional to dose not only in extensive but also in poor metabolizers of debrisoquine.

- Marked increases (50-100%) in orosomucoid serum concentrations, and thus the protein binding of tolterodine were found to greatly increase tolterodine serum concentrations within individuals. This increase was also seen as a decrease in tolterodine clearance. Serum levels of DD 01 were also increased but to a lesser degree. As could be expected, the half-lives of tolterodine and DD 01 were not affected by the change in protein binding.

**Study Number:** CTN 95-OATA-026

**Title of the study:** A Phase I, open label, safety and pharmacokinetic study of tolterodine in patients with hepatic cirrhosis.

**Objectives:** The objectives were to investigate the safety and pharmacokinetics of tolterodine and DD 01 in cirrhotic patients and to determine *ex-vivo* protein binding of tolterodine and DD 01.

**Study Design:** Open label, one period, single dose.

**Subjects:** Sixteen (16) patients with hepatic cirrhosis 1) according to Child - Pugh classification (Class A or Class B liver disease) or 2) proven by liver biopsy (preferred), or liver-spleen scan ($^{99m}$Tc-sulfur colloid) compatible with cirrhosis, including moderate, diffuse, non-homogeneous uptake of the radionuclide, and spleen uptake greater than the liver on the posterior view, and a compatible medical history of cirrhosis.

**Study product:** Tolterodine L-tartrate tablet, 2 mg Batch No. A 049404.

**Duration & dosage:** Twenty four (24) hours; A single 2 mg dose

**Assay Methodology:**

**Results**
The pharmacokinetics of tolterodine in cirrhotic patients are included in Tables 51 to 55.

**Table 51. Pharmacokinetic Parameters of Tolterodine in Cirrhotic Patients by Genotype**

| Genotype | | Weight (kg) | $C_{max}$ (ng/mL) | $t_{max}$ (hr) | $AUC_{0-24}$ (ng·hr/mL) | $AUC_{0-\infty}$ (ng·hr/mL) | $Cl_o$ (L/hr/kg) | $t_{½z}$ (hr) |
|---|---|---|---|---|---|---|---|---|
| EM | Mean | 87.3 | 5.7 | 1.0 | 44.1 | 57.7 | 1.0 | 7.8 |
| | SD | 14.8 | 3.4 | 0.4 | 34.2 | 59.4 | 1.7 | 4.7 |
| | N | 14 | 14 | 14 | 14 | 14 | 14 | 14 |
| | Range | | | | | | | |
| PM | Mean | 69.9 | 8.3 | 1.8 | 109 | 161 | 0.13 | 14.6 |
| | N | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| | Range | | | | | | | |

**Table 52. Pharmacokinetic Parameters of DD 01 Post-Tolterodine in Cirrhotic Patients by Genotype**

| Genotype | | Weight (kg) | $C_{max}$ (ng/mL) | $t_{max}$ (hr) | $AUC_{0-24}$ (ng·hr/mL) | $AUC_{0-\infty}$ (ng·hr/mL) | $t_{½z}$ (hr) |
|---|---|---|---|---|---|---|---|
| EM | Mean | 87.3 | 1.4 | 1.7 | 12.2 | 14.8 | 9.8 |
| | SD | 14.6 | 0.85 | 0.9 | 6.72 | 7.32 | 7.2 |
| | N | 14 | 14 | 13 | 14 | 14 | 13 |
| | Range | | | | | | |

A between study comparison of 2 mg single dose kinetic estimates from previous studies in normal elderly and healthy volunteers (EMs), statistically significant differences ($p < 0.05$) were apparent in tolterodine $C_{max}$, $AUC_{0-\infty}$, $t_{½z}$, and $CL_o$ in cirrhotic patients. However, the tolterodine levels and half-life where lower than what is seen in healthy PMs. Such a change in kinetics was not unexpected, as hepatic metabolism to DD 01 is the primary route for tolterodine elimination in humans. Both AUC and half-life of DD 01 showed significant increases compared to estimates in EM healthy volunteers. However, DD 01 AUC was not higher in cirrhotic patients than in the elderly. Taking unbound serum concentrations into account , the total exposure in cirrhotic EMs is higher than in healthy EMs, both young and elderly. Also in cirrhotic PMs the exposure is higher than in young and elderly non-cirrhotic PMs. The exposure in cirrhotic patients appears to be about 25-50% higher than what is seen in non-cirrhotic individuals.

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**Table 53. Mean (± SD) Kinetic Parameters of Tolterodine in EMs Following a Single 2 mg Dose: Normal Healthy Volunteers(NHV), EM Elderly and EM Cirrhotic Patients**

| ESTIMATE | NHV (n = 21) | Elderly (n = 9) | Cirrhotic (n = 14) |
|---|---|---|---|
| Age: range (yr.) | 21-42 | > 75 | 42-68 |
| $C_{max}$ (ng/mL) | 2.11 (2.6) | 2.8 (2.1) | 5.7 (3.4) |
| $AUC_{0-\infty}$ (ng·hr/mL) | 7.49 (8.60) | 8.76 (6.09) | 57.7 (59.4) |
| $CL_o$ (L/hr/kg) | 5.65 (3.84) | 3.02 (1.64) | 1.0 (1.7) |
| $t_{½z}$ (hr) | 2.63 (0.89) | 2.16 (0.44) | 7.8 (4.7) |

**Table 54. Mean (± SD) Kinetic Parameters of DD 01 in EMs Following a Single 2 mg Tolterodine Dose: Normal Healthy Volunteers(NHV), Elderly and Cirrhotic Patients**

| | NHV (n = 21) | Elderly (n = 9) | Cirrhotic (n = 14) |
|---|---|---|---|
| Age: range (y) | 21-42 | > 75 | 42-68 |
| $C_{max}$ (ng/mL) | 2.2 (0.75) | 3.5 (1.6) | 1.4 (0.85) |
| $AUC_{0-\infty}$ (ng·hr/mL) | 10.7 (3.85) | 16.0 (8.05) | 14.8 (7.32) |
| $t_{½z}$ (hr) | 3.20 (0.76) | 2.89 (0.37) | 9.8 (7.2) |

**Table 55. Mean (± SD) Kinetic Parameters of Tolterodine in PMs Following a Single 2 mg Tolterodine Dose: Normal Healthy Volunteers (NHV), Elderly and Cirrhotic Patients**

| | NHV (n = 8) | Elderly (n = 11) | Cirrhotic (n = 2) |
|---|---|---|---|
| Age: range (yr.) | 19-47 | 60-79 | 42-68 |
| $C_{max}$ (ng/mL) | 10.0 (4.9) | n.a. | range: 6.4 - 10.2 |
| $AUC_{0-\infty}$ (ng·hr/mL) | 100 (51) | 174 (112 - 271)[1] | range: 124 - 199 |
| $CL_o$ (L/hr/kg) | | n.a. | 0.09-0.16 |
| $t_{½z}$ (hr) | 6.5 (1.6) | n.a. | range: 13.5 - 15.7 |

1: Geometric mean with 95% confidence interval
n.a.: Not available

**Protein Binding:** Due to the small sample volumes available and high protein binding, tolterodine levels were measurable in only three of the 16 patients while DD 01 levels were detected in 10 patients. No apparent time dependence was evident in DD 01 binding from serum samples collected 2 or 8 hours post-dose. Thus, individual estimates for those were averaged.

Mean percent tolterodine unbound (n=3) was 3.6±1.1% for an average orosomucoid concentration of 0.44 mg/mL. Percent DD 01 unbound (n=10) was 36±10% (18).

**Blood pressure and heart rate:** The magnitude of the change in these measures, from baseline (screening), at 2 hr post-dose and at follow-up are also provided. There were no notable or statistically significant changes in the means of any of the blood pressure or heart rate measurements, except for an increase in heart rate at follow-up compared to baseline ($p = 0.02$); this difference was only 10%.

**ECG parameters:** The magnitude of the change in these measures, from pre-dose (t=0), at 2 hr post-dose and at follow-up are also provided. There were no significant changes in any of these five parameters at 2 hr post-dose (time when tolterodine concentrations are highest). At follow-up, no significant differences were apparent for QT, QRS, and T-wave amplitude means. Though, $QT_{max}$ and QT (Lead II) were significantly lower ($p< 0.033$) at follow-up compared to pre-dose, these changes were < 4%.

**Adverse Events:** These were recorded for 2 patients. However, only one of the reports (patient no 15; rash) is related to the treatment. The other two reports (patient no. 16) were recorded one and four days before dose, respectively. The events were mild in severity, and the patients completely recovered without any intervention. No serious AE occurred during this study.

**Sponsor's Conclusions:**
The disposition of orally administered tolterodine was altered in patients with impaired liver function assessed based on Child-Pugh criteria. In extensive metabolizers, hepatic insufficiency results in increased systemic exposure to the parent drug due to diminished drug clearance, while the difference in DD 01 concentrations is negligible Cirrhotic PMs also have higher tolterodine levels compared to healthy volunteers. Taking unbound concentrations of tolterodine and DD 01 into account, the total exposure in both EM and PM cirrhotic patients was approximately 25-50% higher than what is seen in non-cirrhotic individuals.

**Study Number:** CTN 95-OATA-028

**Title of the study:** Relative bioavailability of tolterodine tablets from different production sites. An open, randomized, single-dose cross-over study in healthy volunteers.

**Objectives:** The objective of this study was to compare the bioavailability of tolterodine tablets 2 mg produced in Ascoli (Italy) compared to tolterodine tablets 2 mg produced in Malmö (Sweden), in order to show bioequivalence between the two production sites with respect to AUC and $C_{max}$.

**Study Design:** Open, randomized, 2-period cross-over, single-dose study.

**Subjects:** Twenty-four (9 male, 15 female) healthy female and male volunteers between 20 and 50 years of age were enrolled in the study.

**Test product:** Tolterodine tablets 2 mg produced in Ascoli, batch no. 6401.

**Reference product:** Tolterodine tablets 2 mg produced in Malmö, batch no. A049404.

**Duration of treatment:** 2 single doses with a one week wash-out between doses.

**Statistical methods:** Statistical methods: Bioequivalence was evaluated using back- transformed confidence intervals resulting from an ANOVA on log- transformed AUC and $C_{max}$ values for tolterodine and DD 01, respectively.

**Results**
The pharmacokinetic variables are summarized in the following table:

Table 56

| | Tolterodine | | DD 01 | |
|---|---|---|---|---|
| Parameter[1] | Ascoli | Malmö | Ascoli | Malmö |
| AUC( µg·h/l) | 6.2 ± 3.4 | 6.0 ± 3.0 | 11.0 ± 2.8 | 11.2 ± 2.8 |
| $C_{max}$ (µg/l) | 1.9 ± 1.1 | 1.9 ± 1.0 | 2.6 ± 1.0 | 2.6 ± 0.9 |
| $t_{max}$ (hours) | 1.0 (0.5 - 3.0) | 1.0 (0.5 - 1.5) | 1.0 (0.5 - 1.5) | 1.0 (0.5 - 2.0) |
| $t_{1/2z}$ ($h^{-1}$) | 2.3 ± 0.5 | 2.2 ± 0.3 | 2.8 ± 0.5 | 2.9 ± 0.5 |
| CL/F (l/h) | 287 ± 159 | 303 ± 197 | | |

1: mean ± SD except $t_{max}$ which is given as median (range)

The relative bioavailability (%; mean and 90% CI) of the Ascoli tablet compared to the Malmö tablet was:

Table 57.

| | AUC | $C_{max}$ |
|---|---|---|
| Tolterodine | 103 (94 - 114) | 103 (91 - 118) |
| DD 01 | 98 (94 - 102) | 98 (92 - 105) |

**Sponsor's Conclusions:**
Tolterodine tablets 2 mg produced in Ascoli, Italy are bioequivalent with respect to rate and extent of absorption to tolterodine tablets 2 mg produced in Malmö, Sweden.

**Study Number:** CTN 95-OATA-020

**Title of the study:** Effect of tolterodine on cytochrome P450 isoenzymes determined by three probe drugs.

**Objectives:** To investigate the *in vivo* effect of tolterodine on debrisoquine hydroxylation (CYP2D6), omeprazole hydroxylation (CYP2C19), omeprazole sulphoxidation (CYP3A4) and caffeine metabolism CYP1A2).

**Study Design:** Open label with a non-randomised cross-over group design.

**Number of subjects:** 12 healthy volunteers.

**Test product:** Tolterodine L-tartrate tablet, 2 mg (Pharmacia & Upjohn) Batch No A 049 404

**Probe drugs:** Declinax® (debrisoquine) tablet, 20 mg Batch No B 1680. Losec® (omeprazole) enteric capsules, 20 mg Batch No UK 5427. Koffein® (caffeine) tablet, 100 mg (ACO) Batch No P3A 001.

**Treatment:** 4 mg b.i.d. for 6 days.

**Results**

The mean metabolic ratios are presented in Table 58. No statistically significant difference in the metabolic ratios of the three probe drugs was obtained during co-administration of tolterodine in EMs (CYP2D6). Neither in PMs (CYP2D6) a statistically significant difference in the metabolic ratios of the three probe drugs was obtained during co-administration of tolterodine, despite the 5-10 higher tolterodine concentrations

Table 58 Mean metabolic ratios for the three probe drugs in 8 EMs and 4 PMs (CYP2D6).

| | EM / PM | | | |
|---|---|---|---|---|
| Probe drug | Enzyme | Before | During | After |
| Debrisoquine | CYP2D6 | 0.49 / - | 0.50 / - | 0.46 / - |
| Omeprazole | CYP2C19 | 2.4 / 1.6 | 2.2 / 2.6 | 2.1 / 1.6 |
| Omeprazole | CYP3A4 | 1.8 / 1.2 | 1.5 / 1.7 | 1.6 / 1.4 |
| Caffeine | CYP1A2 | 6.2 / 4.5 | 7.0 / 4.2 | 6.3 / 3.9 |

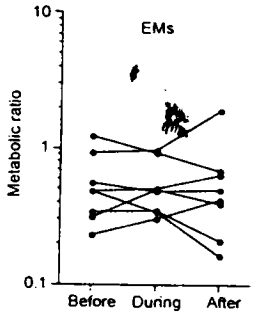


Figure 1 Metabolic ratio of debrisoquine (CYP2D6) before, during and after administration of tolterodine to EMs (CYP2D6).

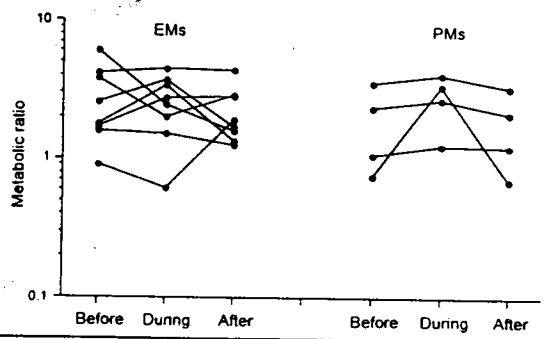


Figure 2 Metabolic ratio of omeprazole/hydroxy-omeprazole (CYP2C19) before, during and after administration of tolterodine to EMs and PMs (CYP2D6).

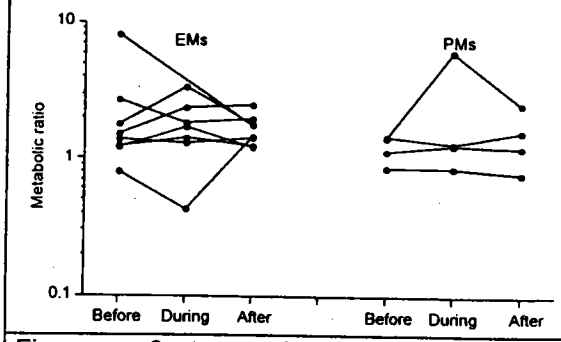


Figure 3 Metabolic ratio of omeprazole/omeprazole sulphone (CYP3A4) before, during and after administration of tolterodine to Ems and PMs (CYP2D6)

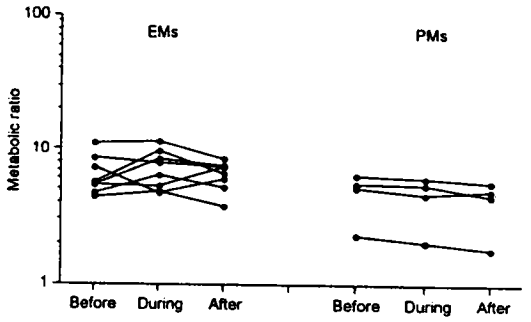


Figure 4 Metabolic ratio of caffeine/N3-demethylation (CYP1A2) before, during and after administration of tolterodine to EMs and PMs (CYP2D6).

**Sponsor's Conclusions**

- The hydroxylation of debrisoquine (CYP2D6) was not affected by tolterodine. Inhibition of CYP2D6 is not likely. Inhibitors of CYP2D6 might, however, inhibit the metabolism of tolterodine.

- The hydroxylation of omeprazole (CYP2C19) was not affected by tolterodine. Induction or inhibition of CYP2C19 is not likely.

- Omeprazole sulphoxidation (CYP3A4) was not changed by tolterodine in neither EMs nor PMs of CYP2D6 despite five to ten-fold higher concentration of tolterodine in PMs. The present data do not suggest metabolic interactions with CYP3A4 substrates.

- $N_3$-demethylation of caffeine (CYP1A2) was not affected by tolterodine. Induction or inhibition of CYP1A2 is not likely.

**Reviewer's Comment**

The affect of these probe drugs on the pharmacokinetics of tolterodine has not been assessed herein.

**Study Number:** CTN 95-OATA-030

**Title of the study:** The influence of fluoxetine on the safety and pharmacokinetics of tolterodine.

**Objectives:** The objectives of this study were to study the pharmacokinetics of tolterodine after 2 mg b.i.d. administration in psychiatric patients after co-administration of fluoxetine, 20 mg once daily and to study the safety and quantify dealkylated and carboxylated metabolites of tolterodine in serum and urine.

**Study Design:** This was an open, single sequence-group, cross-over study in psychiatric patients.

**Subjects:** 13 patients with depression or anxiety syndrome and subjective symptoms of urinary incontinence.

**Test product:** Tolterodine L-tartrate tablets 2 mg (Pharmacia & Upjohn AB) Batch no. VC 801.

**Reference product:** Fontex® capsules 20 mg (fluoxetine hydrochloride, Sweden AB) Batch no. B 2737CE.

**Duration of treatment:** Tolterodine L-tartrate, 2 mg b.i.d., Days 1-3 and Days 24-27. Fontex®, 20 mg once daily, were given on Days 4-27.

**Results**

A summary of the pharmacokinetic parameters of tolterodine and the different metabolites is given in Table 59.

Table 59. Pharmacokinetic parameters of tolterodine and its metabolites after 2 mg (b.i.d.) administration of tolterodine tartrate for 2.5 days and coadministered with fluoxetine (mean±S.D.) in EMs.

| Substance and metabolic code | | Tolterodine (Day 3) | | | | Tolterodine + Fluoxetine (Day 27 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | $t_{max}$ (h) | $C_{max}$ (µg/l) | $AUC_\tau$ (µg h/l) | $t_{1/2z}$ (h) | $t_{max}$ (h) | $C_{max}$ (µg/l) | $AUC_\tau$ (µg h/l) | $t_{1/2z}$ (h) |
| Tolterodine | Ia | 0.8±0.2 | 3.6±2.6 | 17±20 | 3.7±2.1 | 1.2±0.3 | 13±4.8 | 81±30 | 5.7±1.7 |
| DD 01 (hydroxylated tolterodine) | IIa | 0.9±0.3 | 2.9±1.3 | 14±6.4 | 4.9±3.7 | 1.1±0.3 | 1.4±0.57 | 11±4.2 | 10±3.2 |
| Dealkylated tolterodine[a] | Ib | n.a. | n.a. | n.a. | n.a. | 3.9±2.2 | 1.2±0.47 | 11±5.5 | 21±14 |
| Dealkylated hydroxylated tolterodine[b] | IIb | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| Tolterodine acid | IVa | 1.9±0.2 | 9.7±5.2 | 61±27 | 6.7±7.6 | 2.3±1.7 | 2.4±1.2 | 22±11 | 19±18 |
| Dealkylated tolterodine acid | IVb | 2.0±0.0 | 6.6±1.3 | 47±6.3 | 5.4±1.1 | 1.3±0.7 | 1.8±0.70 | 18±6.2 | 38±22 |

[a]Levels of dealkylated tolterodine <LOQ before interaction with fluoxetine. [b]Levels of dealkylated hydroxylated tolterodine <LOQ; n.a.: not applicable

A total of 16 adverse events were reported by 7 of the 13 patients during the study. The most frequent adverse event was headache, a side effect commonly reported during fluoxetine treatment.

**Sponsor's Conclusions**

- Fluoxetine significantly impaired the metabolism of tolterodine and an 4.8 fold increase of the AUC was seen in EMs.
- Only a minor change in AUC of DD 01 was seen during co-administration with fluoxetine in EMs.
- The AUC of tolterodine increased by 24% in the two PMs during fluoxetine administration.

- No indications of influence of tolterodine and fluoxetine on the clinical and laboratory safety variables were seen.

**Reviewer Comments:**

1. Fluoxetine is primarily metabolized by CYP 2D6. Therefore, in extensive metabolizers, competitive inhibition of the metabolism of tolterodine to DD01 is likely and indeed, this was observed.

2. The rate of formation of DD01 (Cmax) was significantly altered, but the extent of exposure (AUC) of DD01 was relatively unchanged in extensive metabolizers receiving fluoxetine. However, since CYP 2D6 also catalyzes the metabolism of DD01 to tolterodine acid and hence would also be inhibited by fluoxetine, this observation is not unexpected.

3. Although relatively weak, fluoxetine has been shown to have CYP 3A4 inhibitory capabilities. Therefore, the 24% increase in AUC in poor metabolizers may be due to the inhibition of the formation of dealkylated tolterodine, mediated by CYP 3A4.

**Study Number:** CTN 95-OATA-025

**Title of the study:** A phase I, randomized, double-blind, placebo-controlled, kinetic-dynamic and safety drug interaction study of tolterodine and warfarin in healthy volunteers.

**Objectives:** The objectives were;
1. to assess warfarin effects on the coagulation time when coadministered with tolterodine. This assessment was focused on the mean PT-time profiles constructed using the AUC parameter estimates for tolterodine and placebo treatments.

2. to determine warfarin kinetics for both S- and R-isomers when coadministered with tolterodine. This assessment was focused on the AUC and the $C_{max}$ of S- and R-isomers. Tolterodine/DD 01, $C_{max}$ and AUC were also estimated in the presence and absence of warfarin.

3. to assess the safety of combined therapy of tolterodine with warfarin. The safety assessments included electrocardiogram, heart rate, blood pressure, hematology, and clinical chemistry tests on blood and urine.

**Study Design:** Randomized, double-blind, placebo-controlled, two-period cross-over (employing a priming dose of warfarin 3 weeks prior to the study initiation).

**Subjects:** Twenty (20) healthy volunteers

**Test product:** Tolterodine L-tartrate tablet, 2 mg (Pharmacia & Upjohn) Batch No VC 801

**Duration & Dosage:** Tolterodine 2 mg b.i.d. for 7 days; warfarin 25 mg once on Day 4

**Assay Methodology:**

**Results**
Concomitant tolterodine produced no discernible effect on the PT response or the factor VII profile observed following a single dose of warfarin. The difference in the mean $AUC_{0-96}$ values of both treatment periods was < 4.5% for PT and < 7.5% for factor VII. The maximal responses ($E_{max}$) for the PT and factor VII were 10.82 sec, 80.1% in the placebo period and 10.96 sec, 75.1% in the tolterodine period, respectively.

Similarly, no statistically significant differences were apparent in R-and S-warfarin kinetic estimates of $C_{max}$, $T_{max}$, $AUC_{0-96}$, $AUC_{\tau}$, or $CL_0$ in the absence or presence of concomitant tolterodine. The elimination half-lives ($t_{½z}$) of R- and S-warfarin were slightly higher in the tolterodine period compared to placebo: 8% for R-warfarin and 4.9% for S-warfarin. This increase has no apparent clinical significance, as is evident from a lack of impact on coagulation time as assessed by PT and factor VII response to warfarin.

No serious AEs were reported in this study. AEs were recorded for 8 subjects and the most frequent AEs were: five for headache (25%), three for coughing (15%) and two for abdominal pain (10%). These were mild to moderate in severity. No clinically significant changes were noted for vital signs (blood pressure, heart rate) or ECG parameters, within or between treatments. No clinically significant changes were apparent in select hepatic, renal, chemistry, hematology safety variables related to tolterodine, except for WBC and platelet ($p < 0.01$) at 48 hours post-warfarin dosing during treatment with tolterodine. At follow-up, however, no differences between either period were apparent. Several safety variables: bilirubin, globulin, BUN, hemoglobin, hematocrit, RBC and basophils showed significant changes ($p < 0.05$, Wilcoxon's signed rank) with both treatment arms at 48 hr post-dosing or at follow-up, relative to baseline, and could be most likely attributed to warfarin. Very small, but statistically significant differences between treatments were also seen in eosinophils ($p < 0.02$, t-test).

**Table 60. Summary of Pharmacokinetics for R-Warfarin in the Absence or Presence of Tolterodine**

| | | $C_{max}$ (ng/mL) | $t_{max}$ (hr) | $AUC_{0-24}$ (ng.hr/mL) | $AUC_{0-\infty}$ (ng.hr/mL) | $CL_o$ (mL/Hr/Kg) | $t_{½z}$ (hr) |
|---|---|---|---|---|---|---|---|
| PLAC | Mean | 1.52 | 1.65 | 57.06 | 69.10 | 4.59 | 37.27 |
| | Median | 1.51 | 1 | 56.65 | 68.31 | 4.39 | 37.26 |
| | SD | 0.23 | 1.09 | 10.67 | 14.44 | 1.23 | 6.93 |
| | N | 20 | 20 | 20 | 20 | 20 | 20 |
| | Min | | | | | | |
| | Max | | | | | | |
| | | | | | | | |
| TOLT | Mean | 1.48 | 1.95 | 57.98 | 72.49 | 4.37 | 40.28 |
| | Median | 1.47 | 2 | 59.63 | 70.67 | 4.34 | 40.39 |
| | SD | 0.21 | 1.15 | 9.82 | 17.41 | 0.98 | 8.53 |
| | N | 20 | 20 | 20 | 20 | 20 | 20 |
| | Min | | | | | | |
| | Max | | | | | | |

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**Table 61. Summary of Pharmacokinetics for S-Warfarin in the Absence or Presence of Tolterodine**

| | | $C_{max}$ (ng/mL) | $t_{max}$ (hr) | $AUC_{0-24}$ (ng.hr/mL) | $AUC_{0-\infty}$ (ng.hr/mL) | $CL_0$ (mL/Hr/Kg) | $t_{½z}$ (hr) |
|---|---|---|---|---|---|---|---|
| PLAC | Mean | 1.60 | 1.70 | 43.59 | 49.19 | 6.86 | 28.34 |
| | Median | 1.58 | 1 | 41.44 | 44.10 | 6.80 | 25.71 |
| | SD | 0.26 | 1.08 | 12.77 | 18.37 | 2.19 | 8.19 |
| | N | 20 | 20 | 20 | 20 | 20 | 20 |
| | Min | | | | | | |
| | Max | | | | | | |
| | | | | | | | |
| TOLT | Mean | 1.50 | 1.75 | 43.39 | 49.70 | 6.71 | 29.72 |
| | Median | 1.49 | 1 | 40.15 | 44.35 | 7.20 | 27.96 |
| | SD | 0.23 | 1.07 | 11.84 | 17.61 | 1.97 | 8.59 |
| | N | 20 | 20 | 20 | 20 | 20 | 20 |
| | Min | | | | | | |
| | Max | | | | | | |

**Table 62. Summary of Pharmacokinetics for Tolterodine in the Absence or Presence of Warfarin**

| | | $C_{max}$ (ng/mL) | $t_{max}$ (hr) | $AUC_{0-4}$ (ng.hr/mL) |
|---|---|---|---|---|
| Day 3 | Mean | 2.9 | 1.4 | 7.72 |
| | Median | 2.2 | 1.0 | 4.94 |
| | SD | 2.4 | 0.6 | 6.96 |
| | N | 20 | 20 | 20 |
| | Min | | | |
| | Max | | | |
| | | | | |
| Day 4 | Mean | 2.3 | 1.3 | 6.90 |
| | Median | 1.3 | 1.0 | 3.45 |
| | SD | 2.1 | 0.6 | 6.82 |
| | N | 19 | 19 | 19 |
| | Min | | | |
| | Max | | | |

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**Table 63. Summary of Pharmacokinetics for DD01 in the Absence or Presence of Warfarin**

| | | $C_{max}$ (ng/mL) | $t_{max}$ (hr) | $AUC_{0-4}$ (ng.hr/mL) |
|---|---|---|---|---|
| Day 3 | Mean | 2.4 | 1.5 | 6.72 |
| | Median | 2.4 | 1.0 | 6.33 |
| | SD | 1.1 | 0.6 | 2.78 |
| | N | 20 | 20 | 20 |
| | Min | | | |
| | Max | | | |
| | | | | |
| Day 4 | Mean | 2.0 | 1.2 | 6.25 |
| | Median | 1.9 | 1.0 | 6.14 |
| | SD | 0.78 | 0.5 | 2.43 |
| | N | 20 | 20 | 20 |
| | Min | | | |
| | Max | | | |

**Table 64. Summary of Pharmacodynamics of Warfarin in the Presence or Absence of tolterodine**

| Variable | | Treatment | | | |
|---|---|---|---|---|---|
| | | Warfarin + Placebo | | Warfarin + Tolterodine | |
| | | Mean (SD) | Range | Mean (SD) | Range |
| PT | $AUC_{0-96}$ (sec.hr) | 485.5 (295.8) | 161.4-1067 | 507.3 (366.9) | 123.8-1359 |
| | $E_{max}$ (sec) | 10.82 (5.72) | 4-22.5 | 10.96 (6.06) | 2.6-24.3 |
| | $t_{max}$ (hr) | 31.1 (8.57) | 16-54 | 35.5 (9.92) | 24-54 |
| | | | | | |
| Factor VII | $AUC_{0-96}$ (%.hr) | 4434 (1241) | 2682-6548 | 4105 (1357) | 2226-6763 |
| | $E_{max}$ (%) | 80.1 (13) | 61-115 | 75.1 (12.8) | 46-99 |
| | $t_{max}$ (hr) | 27.8 (4.2) | 16-36 | 29.2 (5.7) | 24-48 |

**Sponsor's Conclusions:**

Concomitant administration of tolterodine and warfarin to healthy volunteers did not result in any clinically significant changes in warfarin dynamics (e.g., PT and factor VII responses) or in kinetics of R- and S-isomers. Further, a single warfarin dose did not affect steady-state kinetics of tolterodine or its hydroxylated metabolite DD 01. Therefore, combined tolterodine and warfarin dosing is deemed safe and well tolerated.

**Study Number:** CTN 95-OATA-027

**Title of the study:** Influence of tolterodine on the pharmacokinetics of Neovletta®, an oral contraceptive. An open, randomized, multiple-dose cross-over study in healthy volunteers.

**Objectives:** The objectives of this study were to investigate if tolterodine, 2 mg b.i.d. for 14 days, affects the pharmacokinetics (AUC, $C_{max}$, $C_{min}$) of ethinyl estradiol and levonorgestrel in women using this oral combination contraceptive and to determination of serum levels of progesterone and estradiol at selected time points to assess the possible risk of ovulation.

**Study Design:** Open, randomized, 2-period cross-over, multiple-dose study.

**Subjects :** Twenty-four healthy female volunteers between 20 and 40 years of age were studied.

**Test product:** Tolterodine tablets 2 mg, batch no. VC 801. Neovletta tablets, batch no. 44006

**Duration of treatment:** Neovletta for 21 days in each of two periods; Tolterodine for 14 days during one of the Neovletta periods.

**Results**

The result of the pharmacokinetic analysis is presented in the following table (mean ± SD with the exception of $t_{max}$ which is given as median(range).):

Table 65

| Pharmacokinetic variable: | | $AUC_\tau$ (ng·h/l) | $C_{max}$ (ng/l) | $C_{min}$ (ng/l) | $t_{max}$ (h) |
|---|---|---|---|---|---|
| Ethinyl estradiol | Without tolterodine | 864 ± 284 | 99.7± 29.0 | 14.0 ± 8.2 | 1 (0.5 - 3) |
| | With tolterodine | 808 ± 270 | 90.0 ± 29.2 | 13.8 ± 6.6 | 1.5 (1 - 12) |
| Levonorgestrel | Without tolterodine | 79.4 ± 30.5 | 6.77 ± 2.09 | 2.02 ± 0.84 | 1 (1 - 24) |
| | With tolterodine | 70.4 ± 20.3 | 5.80 ± 1.25 | 1.79 ± 0.57 | 1.5 (1 - 12) |

The relative bioavailability (%) of the OC during the tolterodine treatment period, compared to the tolterodine-free treatment period is presented in the following table (geometric mean with 90% CI):

Table 66.

| | $AUC_\tau$ | $C_{max}$ | $C_{min}$ |
|---|---|---|---|
| Ethinyl estradiol | 93.5 (85.4 - 102.3) | 90.1 (82.5 - 98.4) | 104.9 (79.6 - 138.2) |
| Levonorgestrel | 90.3 (84.6 - 96.4) | 86.9 (80.7 - 93.6) | 90.5 (84.7 - 96.6) |

**Sponsor's Conclusion:**

No pharmacokinetic or pharmacodynamic interaction was found between tolterodine and an oral contraceptive containing ethinyl estradiol and levonorgestrel.