Concentrations of Gatifloxacin in Plasma and Urine and Penetration into Prostatic and Seminal Fluid, Ejaculate, and Sperm Cells after Single Oral Administrations of 400 Milligrams to Volunteers

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Received 5 January 2000/Returned for modification 31 July 2000/Accepted 12 October 2000

Gatifloxacin (GTX), a new fluoroquinolone with extended antibacterial activity, is an interesting candidate for the treatment of chronic bacterial prostatitis (CBP). Besides the antibacterial spectrum, the concentrations in the target tissues and fluids are crucial for the treatment of CBP. Thus, it was of interest to investigate its penetration into prostatic and seminal fluid. GTX concentrations in plasma, urine, ejaculate, prostatic and seminal fluid, and sperm cells were determined by a high-performance liquid chromatography method after oral intake of a single 400-mg dose in 10 male Caucasian volunteers in the fasting state. Simultaneous application of the renal contrast agent iohexol was used to estimate the maximal possible contamination of ejaculate and prostatic and seminal fluid by urine. GTX was well tolerated. The means (standard deviations) for the following parameters were as indicated: time to maximum concentration of drug in serum, 1.66 (0.91) h; maximum concentration of drug in serum, 2.90 (0.39) µg/ml; area under the concentration-time curve from 0 to 24 h, 25.65 µg · h/ml; and half life, 7.2 (0.90) h. Within 12 h about 50% of the drug was excreted unchanged into the urine. The mean renal clearance was 169 ml/min. The gatifloxacin concentrations in ejaculate, seminal fluid, and prostatic fluid were in the range of the corresponding plasma concentrations which were 1.92 (0.27) µg/ml at approximately the same time point (4 h after drug intake). The concentrations in sperm cells (0.195, 0.076, and 0.011 µg/ml) could be determined in three subjects. The good penetration into prostatic and seminal fluid, the good tolerance, and the previously reported broad antibacterial spectrum suggest that GTX may be a good alternative for the treatment of chronic bacterial prostatitis. Clinical studies should be performed to confirm this assumption.

Fluoroquinolones have already been used successfully in the treatment of chronic bacterial prostatitis (CBP) and are recommended as first-line treatment for this indication (1, 6). This recommendation is based on their antibacterial activity; on their ability to penetrate into prostatic tissue, prostatic fluid, seminal fluid, and ejaculate; and on clinical studies (6). Although in about 60% of patients with symptoms of chronic prostatitis significant prostatic inflammation can be demonstrated (4), an etiologically recognized pathogen, such as Escherichia coli, Klebsiella spp., Proteus spp., Enterococcus faecalis, or Pseudomonas aeruginosa, is only isolated in up to 10% of these patients (14). In the vast majority of patients, bacterial evaluation either fails to identify a pathogen (nonbacterial prostatitis), or identifies so-called atypical bacteria, like Mycoplasma spp., Ureaplasma spp., and Chlamydia spp. These atypical pathogens are, however, not well covered by the antibacterial activity of the classical fluoroquinolones, e.g., ciprofloxacin or ofloxacin. Thus, the treatment of CBP remains a challenging issue, and new fluoroquinolones with improved antibacterial activity also against gram-positive pathogens and Mycoplasma and Chlamydia species, as well as against anaerobes, may be considered for the treatment of CBP.

Gatifloxacin, a new fluoroquinolone antibiotic, has a broad spectrum of activity encompassing both gram-positive and gram-negative organisms, as well as anaerobes (2). It also has activity against Mycoplasma and Chlamydia spp. (5). Since the antibacterial spectrum and the concentrations in the target tissues are crucial for the treatment of CBP, it was of interest to investigate its penetration into prostatic and seminal fluid. The results of this study could serve as a basis for a clinical study protocol (dosage selection and estimate of clinical and bacteriological efficacy) to test gatifloxacin in the treatment of CBP and vesiculitis.

(This work was presented in part at the 21st International Congress of Chemotherapy, Birmingham, United Kingdom, 4 to 9 July 1999.)

MATERIALS AND METHODS

Study design. This was a single-dose, one-way, open-labeled, noncontrolled, single-center, phase 1 study. The study was approved by the institutional and local ethics committees, and written informed consent was obtained from each volunteer.

Study subjects. Ten male Caucasian volunteers, 18 to 33 years old (mean age, 23 years) with a body weight ranging from 63 to 97 kg (mean, 77 kg) and a body height ranging from 172 to 190 cm (mean, 180 cm) were included. The subjects were considered healthy according to history, physical examination, electrocardiogram, and standard laboratory tests, including hepatitis virus and human immunodeficiency virus screen. Prior to administration of the study drug, and 24 h after dosing, routine hematology, urine, biochemistry, and electrocardiogram analyses were repeated. Vital signs (blood pressure, pulse rate, and oral
temperature) were assessed, and each subject underwent a full physical examination.

The subjects had no known or suspected intolerance or hypersensitivity to quinolones or related drugs and no evidence or history of psychiatric illness, suicide risk, epilepsy, or alcohol or drug abuse. Before drug intake, screening for benzodiazepine, opiates, amphetamine, and cannabis was performed by a rapid enzyme immune assay (Boehringer, Mannheim, Germany) in the Laboratory Schubach, Passau, Germany. Blood and breath alcohol tests were negative for all subjects before drug intake.

The subjects did not use any medication in the 2 weeks prior to the study, any enzyme-inducing or -inhibiting drug during 2 months prior to the study, or any experimental drug during 3 months prior to the study. Subjects were not likely to require any medication during the study period, except one subject who used a local antiviral cream (aciclovir [Zovirax] 1 day prior to study for the treatment of herpes labialis. Six of the subjects reported current tobacco use, while four reported that they had never used tobacco. Five subjects reported regular use of alcohol, while five reported that they did not regularly consume alcohol (i.e., consumed fewer than 3 to 7 pints of beer per week).

**Study procedure.** No recreational drugs or alcohol consumption were allowed during the course of the study, 24 h before drug administration to 48 h postdose. Subjects were not allowed to consume antacids or other drugs containing zinc, magnesium, or calcium within 6 h of gatifloxacin ingestion. All subjects complied with this.

After an overnight fast, baseline urine and blood samples were taken. Subsequently, the subjects received one tablet of 400 mg of gatifloxacin (product no. CG5501; batch no. 0112097; expiration date July 2000) provided by Grünenthal GmbH, Stolberg, Germany. The tablet was taken by the oral route under medical supervision with 200 ml of mineral water, including mouth check to assure swallowing. At the time of oral study drug administration, subjects also received 5 ml of a single intravenous dose of the renal contrast medium iohexol (Omnipaque-300; Schering, Berlin, Germany), corresponding to 2.325 g of iohexol (1.5 g of iodine). Standard breakfast and lunch were served 3 and 5 h after drug administration, respectively. Supper was ad libitum.

Blood samples were taken immediately prior to and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 h after drug administration into heparinized tubes. Prostatic fluid was obtained by prostatic massage within 5 days prior to (baseline) and 4 h after study drug administration. Subsequently, at each occasion of prostatic fluid collection ejaculate was obtained by masturbation. Ejaculate samples were divided: one aliquot was taken without further treatment for the measurement of gatifloxacin concentration in ejaculate and the other aliquot was used to measure the concentration of gatifloxacin in seminal fluid and sperm cells following the separation of seminal fluid from the sperm cells as follows. The ejaculate (50 ml) was poured on a silicone layer (100 µl) and centrifuged using a Microfuge (Beckman, Munich, Germany) at 10,000 rpm for approximately 1 min. The lower aqueous layer was 20% perchloric acid. Subsequent high-performance liquid chromatography (HPLC) analysis was performed on the perchloric acid layer as described for ejaculate.

After prostatic fluid and ejaculate were obtained, the subjects were allowed to empty their bladders for the first time after drug administration, and the urine (0- to 4-h period) was collected. In addition, to the 4-h sample, urine samples of the 4- to 8-h and 8- to 12-h periods were also collected from all subjects.

**Safety.** All subjects who received a dose of gatifloxacin were included in the evaluation of safety, which included review of treatment-emergent, clinical adverse events (AEs) and laboratory AEs.

**Analytical methods.** Plasma and urine samples for gatifloxacin analysis were measured at CEPHAC, Saint Benoît Cedex, France. Prostatic fluid, ejaculate, cell-free seminal fluid, and sperm cell samples were analyzed for gatifloxacin at IBMP, Nürnberg-Heroldsberg, Germany. Iohexol concentrations in urine, ejaculate, and seminal and prostatic fluid were also determined at IBMP.

**Assay of gatifloxacin in plasma and urine.** Gatifloxacin concentrations in plasma were assayed at CEPHAC by a validated HPLC method, with fluorometric detection. Gatifloxacin was extracted by using a liquid-liquid extraction method with 20% perchloric acid. Subsequent high-performance liquid chromatography (HPLC) analysis was performed on the perchloric acid layer as described for ejaculate.

After prostatic fluid and ejaculate were obtained, the subjects were allowed to empty their bladders for the first time after drug administration, and the urine (0- to 4-h period) was collected. In addition, to the 4-h sample, urine samples of the 4- to 8-h and 8- to 12-h periods were also collected from all subjects.

**Assay of gatifloxacin in plasma and urine.** Gatifloxacin concentrations in plasma were assayed at CEPHAC by a validated HPLC method, with fluorometric detection. Gatifloxacin was extracted by using a liquid-liquid extraction method with 20% perchloric acid. Subsequent high-performance liquid chromatography (HPLC) analysis was performed on the perchloric acid layer as described for ejaculate.

**Assay of gatifloxacin in plasma and urine.** Gatifloxacin concentrations in plasma were assayed at CEPHAC by a validated HPLC method, with fluorometric detection. Gatifloxacin was extracted by using a liquid-liquid extraction method with 20% perchloric acid. Subsequent high-performance liquid chromatography (HPLC) analysis was performed on the perchloric acid layer as described for ejaculate.
In addition, the body fluid/plasma ratios were determined using the concentration in plasma at the corresponding sampling time. Single-dose, noncompartmental pharmacokinetic parameters of gatifloxacin were calculated for each subject dosed with gatifloxacin according to standard methods by using PHAR- NCA software (Innaphase, Paris, France; version 1.3).

**Urinary contamination of prostatic fluid, ejaculate, and seminal fluid.** The theoretical (maximum) urinary contamination of prostatic fluid, ejaculate, and seminal fluid was estimated assuming that the total iohexol concentration of these fluids could have been derived from the corresponding iohexol urinary concentration according to the following formula: urinary contamination of fluid (\%) = fluid iohexol (micrograms per milliliter) × 100/urinary iohexol (micrograms per milliliter). Theoretical maximum percent urinary contaminations of ejaculate, seminal fluid, and prostatic fluid were calculated from the iohexol concentrations in urine and the corresponding fluids. The theoretical maximum percent urinary concentration of the ejaculate ranged between 0.01 and 0.04%, that of the seminal fluid ranged between 0.01 and 0.04%, and that of prostatic fluid ranged between 0.01 and 0.16%. Thus, the highest possible urinary contamination of 0.16% in prostatic fluid could have contributed up to 0.64 μg/ml to the prostatic fluid concentration of gatifloxacin (patient 6), considering the urinary gatifloxacin concentration of 399 μg/ml. The measured gatifloxacin concentration of that prostatic fluid was 1.91 μg/ml. If urinary contamination is assumed as mentioned before, the real concentration in prostatic fluid would have been 1.27 μg/ml, with a corresponding concentration in plasma of 1.75 μg/ml, resulting in a true prostatic fluid-to-plasma ratio of 0.73. If all fluid-to-plasma ratios are corrected by this means, the median (range) true fluid-to-plasma ratio of gatifloxacin can be calculated as 1.10 (0.73 to 1.61) for prostatic fluid, 0.99 (0.77 to 1.17) for seminal fluid, and 0.99 (0.83 to 1.25) for ejaculate. Concentrations in sperm cells could only be determined in three subjects and were 0.195, 0.076, and 0.011 μg/ml.

Gatifloxacin was well tolerated. A total of two treatment-emergent AEs (headaches) were reported by 2 of the 10 (20%) subjects. Both were classified to be of moderate intensity and were judged to have no relationship to study medication but rather to study conditions, e.g., no caffeine intake.

**RESULTS**

The individual concentrations of gatifloxacin in plasma are shown in Fig. 1. The pharmacokinetic parameters (Table 1) showed a mean (standard deviation [SD]) $T_{\text{max}}$ of 1.66 (0.91) h, with a $C_{\text{max}}$ of 2.90 (0.39) μg/ml and a $t_{1/2}$ of 7.20 (0.90) h. The AUC$_{0-24}$ was 25.65 (2.53) μg · h/ml. A mean AUC$_{0-12}$ has been calculated (18.83 μg · h/ml) in order to estimate CI:R. The mean (SD) urinary concentration and cumulative excretion of gatifloxacin are shown in Fig. 2. Within 12 h on average 47.9% mean (SD) urinary concentration and cumulative excretion of gatifloxacin to healthy, male volunteers ($n = 10$). Within this time about 50% of the substance was excreted unchanged. Given the excreted amount of gatifloxacin (191.4 mg) and the AUC$_{0-12}$ (18.8 μg · h/ml) a mean renal clearance of 169 ml/min was calculated. The individual gatifloxacin concentrations in urine (0 to 4 h), plasma, ejaculate, seminal fluid, sperm cells, and prostatic fluid and the respective fluid/plasma ratios at 4 h after drug administration are shown in Table 2. Median (range) plasma concentration amounted to 1.92 (1.53 to 2.46) μg/ml. Median ejaculate-, seminal fluid-, and prostatic fluid-to-plasma ratios were 1.03, 1.02, and 1.29, respectively.

![FIG. 1. Composite individual profiles of gatifloxacin concentrations in plasma versus time following a single 400-mg oral dose of gatifloxacin to healthy, male volunteers (n = 10).](image1)

**TABLE 1. Pharmacokinetic parameters of gatifloxacin following a single oral dose of 400 mg administered to healthy, male volunteers (n = 10).**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>1.66</td>
<td>0.91</td>
<td>1.50</td>
<td>1.00–4.00</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (μg/ml)</td>
<td>2.90</td>
<td>0.39</td>
<td>2.93</td>
<td>2.33–3.59</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>7.20</td>
<td>0.90</td>
<td>7.10</td>
<td>5.86–8.83</td>
</tr>
<tr>
<td>AUC$_{0–24}$ (μg · h/ml)</td>
<td>25.65</td>
<td>2.53</td>
<td>25.36</td>
<td>21.32–29.90</td>
</tr>
</tbody>
</table>

![FIG. 2. Mean (SD [error bars]) urinary concentrations and cumulative renal excretion of gatifloxacin following a single 400-mg oral dose of gatifloxacin administered to healthy, male volunteers (n = 10).](image2)

Theoretical maximum percent urinary contaminations of ejaculate, seminal fluid, and prostatic fluid were calculated from the iohexol concentrations in urine and the corresponding fluids. The theoretical maximum percent urinary concentration of the ejaculate ranged between 0.01 and 0.04%, that of the seminal fluid ranged between 0.01 and 0.04%, and that of prostatic fluid ranged between 0.01 and 0.16%. Thus, the highest possible urinary contamination of 0.16% in prostatic fluid could have contributed up to 0.64 μg/ml to the prostatic fluid concentration of gatifloxacin (patient 6), considering the urinary gatifloxacin concentration of 399 μg/ml. The measured gatifloxacin concentration of that prostatic fluid was 1.91 μg/ml. If urinary contamination is assumed as mentioned before, the real concentration in prostatic fluid would have been 1.27 μg/ml, with a corresponding concentration in plasma of 1.75 μg/ml, resulting in a true prostatic fluid-to-plasma ratio of 0.73. If all fluid-to-plasma ratios are corrected by this means, the median (range) true fluid-to-plasma ratios of gatifloxacin can be calculated as 1.10 (0.73 to 1.61) for prostatic fluid, 0.99 (0.77 to 1.17) for seminal fluid, and 0.99 (0.83 to 1.25) for ejaculate. Concentrations in sperm cells could only be determined in three subjects and were 0.195, 0.076, and 0.011 μg/ml.

Gatifloxacin was well tolerated. A total of two treatment-emergent AEs (headaches) were reported by 2 of the 10 (20%) subjects. Both were classified to be of moderate intensity and were judged to have no relationship to study medication but rather to study conditions, e.g., no caffeine intake.

**DISCUSSION**

This study of 10 healthy volunteers shows that a single oral dose of 400 mg of gatifloxacin is well tolerated and is rapidly and well absorbed with a mean (SD) $T_{\text{max}}$ of 1.66 (0.91) h, an estimated $C_{\text{max}}$ of 2.90 (0.39) μg/ml, and a mean $t_{1/2}$ of 7.20 (0.90) h. The AUC$_{0-24}$ was 25.65 (2.53) μg · h/ml. Thus, the $C_{\text{max}}$ and the $t_{1/2}$ of gatifloxacin are higher than those observed for comparable doses of enoxacin, norfloxacin, and ciprofloxacin in a similar setting (15). In this study we investigated urinary excretion only up to 12 h after oral administration, and within this time about 50% of the substance was excreted.
unchanged into urine. Earlier investigations showed that approximately 65 to 90% of gatifloxacin is excreted unchanged into the urine over 24 to 72 h (12, 17; H. Stahlberg, K. Goehler, M. Guillaume, and A. Mignot, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., p. 8–8, 1998). The concentrations in plasma and urinary excretion of gatifloxacin found in this study are somewhat lower than those found by other investigators (3, 12; Stahlberg et al., 38th ICAAC). Since the CLr was practically identical with that found by other authors (3, 12), we assume that lower absorption in our volunteers was the reason for the lower concentrations in plasma and urinary excretion.

The determination of the concentrations of antibiotics in prostatic and seminal fluid may be biased by urinary contamination (16). To estimate potential contaminations of prostatic and seminal fluid by urine, we used a model which has been published earlier (7–11). It has been proposed that by using this model it is possible to estimate the maximum possible amount of urinary contamination. In brief, the renal contrast agent iohexol, which is excreted almost exclusively via glomerular filtration by the kidneys, was administered intravenously to the subjects at the same time the study drug was given. Since the iohexol concentrations in urine are several hundred-fold greater than those in plasma or prostatic fluid, possible urinary contamination (13) the concentration of such a substance can be expected to be higher in prostatic fluid as well as in seminal fluid than that achieved with weak acids such as, e.g., β-lactam antibiotics (9, 10).

We used gatifloxacin concentrations in prostatic and seminal fluid, corrected by maximal urinary contamination, to estimate the true fluid/plasma ratios. These median (range) ratios were 1.10 (0.73 to 1.61) for prostatic fluid, 0.99 (0.77 to 1.17) for seminal fluid, and 0.99 (0.83 to 1.25) for ejaculate, respectively. Thus, gatifloxacin concentrations in ejaculate, seminal fluid, and prostatic fluid after a 400-mg oral dose are in the range of the corresponding concentrations in plasma. The median seminal fluid/plasma ratio is comparable to that of lomefloxacin (1.0 to 1.3) but is somewhat lower than that of other fluoroquinolones such as fleroxacin (1.3 to 1.7), enoxacin (2.2), ciprofloxacin (5.8 to 7.1) (6), or ofloxacin (2.6 to 4.0) (7, 8, 11). In contrast, the median prostatic fluid/plasma ratio was at least twofold higher than those reported from similar studies with norfloxacin, ciprofloxacin, lomefloxacin, enoxacin, or ofloxacin (6–8, 11), which were found to be in the range of 0.12 to 0.48.

**Conclusion.** The relatively high concentrations of gatifloxacin in prostatic and seminal fluid as compared to those of other fluoroquinolones, along with the extended antibacterial spectrum, indicate that gatifloxacin may be an appropriate therapeutic agent for CBP, which should be investigated in clinical trials. According to its pharmacokinetic properties and its good penetration into prostatic and seminal fluid, an oral dosage of 400 mg once daily appears to be suitable for investigating the efficacy of gatifloxacin in CBP.

**ACKNOWLEDGMENT**

This work was supported by Grünenthal GmbH, Aachen, Germany.

**REFERENCES**