

新キノロン系抗菌薬 gatifloxacin の臨床第 I 相試験, I. 単回経口投与

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健常成人男子を対象として、新キノロン系抗菌薬 gatifloxacin (GFLX) の臨床第 I 相試験を行い、単回経口投与時の安全性および体内動態について検討した。試験ではまず、本薬の空腹時投与を 20mg から開始し、50, 100, 200, 400 および 600mg と増量した。また、食事または probenecid の併用による影響について、同一の被験者において GFLX 200mg の単回経口投与で検討した。

被験者延べ 40 例によるいずれの投与量における自覚および他覚症状、血圧、脈拍数、体温、心電図、血液学的検査、血液生化学検査および尿検査において、GFLX の投与と関連のある異常所見は認められなかった。また、400 および 600mg の投与における聴力検査、眼科的検査、平衡機能検査および尿中薬物結晶検査においても、GFLX の投与と関連のある異常所見は認められなかった。

GFLX 100, 200, 400 および 600mg の空腹時単回経口投与では、最高血清中濃度到達時間 (T_{max}) は 1.41~2.28 時間、最高血清中濃度 (C_{max}) はそれぞれ 0.873, 1.71, 3.35, 5.41 $\mu\text{g}/\text{mL}$ 、無限時間までの血清中濃度-時間曲線下面積 (AUC_{0- ∞}) はそれぞれ 7.00, 14.5, 32.4, 53.5 $\mu\text{g}\cdot\text{h}/\text{mL}$ で投与量に比例して増加した。消失相における血中半減期 (T_{1/2 β}) は、投与量によらず 6.93~8.41 時間であった。尿中には投与 72 時間後までに 81.6~87.9% が未変化体として排泄され、400mg 投与後 72 時間までの糞中排泄率は 5.7% であった。また、血清たん白結合率は薬物の濃度によらずほぼ一定であり、その平均値は約 20% であった。唾液中濃度は血清中濃度の約 80% であった。食後投与では空腹時投与に比べ、AUC_{0- ∞} が 12.7 $\mu\text{g}\cdot\text{h}/\text{mL}$ とわずかに低下したが、C_{max} は 1.65 $\mu\text{g}/\text{mL}$ 、T_{max} は 1.86 時間、T_{1/2 β} は 6.52 時間であり、食事の影響はなかった。Probenecid 1.5g (500mg \times 3) の同時投与では、AUC_{0- ∞} が 20.6 $\mu\text{g}\cdot\text{h}/\text{mL}$ へ、T_{1/2 β} が 10.2 時間へと、GFLX の単独投与時に比べそれぞれ増加または延長し、見かけの全身クリアランスは 235 から 164 mL/min へ、腎クリアランスは 197 から 122 mL/min へ、排泄比 (固有腎クリアランス/クレアチニン・クリアランス) は 2.28 から 1.35 へとそれぞれ低下した。これらのことから、本薬の腎排泄には尿細管分泌が関与することが示唆された。

以上、GFLX の投薬に起因すると考えられる重篤な副作用は認められず、体内動態および各種細菌に対する抗菌力を考えると、本薬は各種感染症に対する効果が期待された。

Key words : gatifloxacin, AM-1155, 臨床第 I 相試験, 安全性, 体内動態

Gatifloxacin (GFLX, AM-1155) は杏林製薬株式会社で開発された新キノロン系抗菌薬である。本薬は化学構造上、キノリン骨格6位にフッ素, 7位に3-methyl-1-piperazinyl基, 8位にmethoxy基を有し, グラム陽性および陰性菌, 嫌気性菌, クラミジア属, マイコプラズマなどに対して, 強力な抗菌活性と広範な抗菌スペクトルを有する¹⁾。

GFLXは各種毒性試験および一般薬理試験結果から, 高い安全性を有することが推定された²⁾。そこで, 今回, 健康成人男子を対象に本薬の安全性および体内動態について検討することを目的に, 臨床第I相試験を実施したので, その成績を報告する。

I. 試験方法

1. 被験者

本試験に参加した被験者の背景をTable 1に示す。被験者は, 試験の目的, 内容, 薬剤の性質などについて十分な説明を受けた上で, 自由意志により書面にて参加に同意した成人男子志願者延べ40例であった。これら被験者は, 試験に先立ち, 理学的検査, 血液学的検査, 血液生化学検査, 尿検査, 免疫学的検査, 心電図, 聴力検査, 眼科的検査および問診をうけて, 対象として適格であることが, 治験担当医師により確認された。被験者の年齢は21~38歳, 体重は51.3~83.2kg, 身長は163.6~188.0cmであった。試験は医療法人社団新風会丸山病院にて治験審査委員会の承認を得て, 平成3年7月~同年10月の期間に実施した。

2. 被験薬剤

被験薬剤として, GFLXを無水物として20または50mgを含有するカプセル剤(それぞれLot No. S170010, S170020), あるいは100mgを含有する錠剤(Lot No. S170030およびS190050)を使用した。これらは杏林製薬(株)から提供された。また, 併用薬としてprobenecid 250mgを含有するベネシッド錠(科研製薬株式会社)を用いた。

3. 試験スケジュールおよび検査項目

試験はGFLX 20mgの空腹時投与から開始し, 安全性に問題がないことを確認し50mgへと増量した(第1期)。さらに安全性を確認しつつ, 100, 200, 400, 600mgへと増量した。また, 200mgの空腹時投与から2週間の休薬期間においてGFLXの吸収に及ぼす食事の影響を調べるため, 同一被験者に対して食後30分で200mgの単回投与を行った。食事の内容は, パン, 牛乳, マーガリン, チーズ, ゆで卵, オレンジジュースであった。さらに, 約2ヵ月の休薬期間において, 腎排泄機序を検討するために, GFLX 200mg経口投与の1時間前, 12および24時間後にそれぞれprobenecid 500mgを併用した(以上, 第2期)。被験者数は, 第1期で各2例, 第2期

では各6例とした。いずれの試験においても, 薬剤は約150mLの水とともに投与された。被験者は薬剤投与前日から, 第1期では投与後48時間まで, 第2期では投与後72時間まで医師の管理下に置かれた。試験スケジュールをFig. 1に, 試験項目をTable 2にそれぞれ示す。投与前, ならびに投与後の所定時間において, 血圧, 脈拍数, 体温, 心電図, 血液学的検査, 血液生化学検査, 尿検査などの各種検査を実施し, 自覚および他覚症状を随時記録した。また, 400および600mgの投与では聴力検査, 眼科的検査, 平衡機能検査を実施すると共に, 尿および尿沈渣中の薬物による結晶の有無を光学顕微鏡で調べた。

4. 生体試料の採取

薬物濃度測定のための試料は, Fig. 1のスケジュールに従って採取した。第1期の試験において, 20mgでは血液を投与前ならびに投与後0.5, 1, 2, 3, 4, 8時間に, 50mgでは投与前ならびに投与後0.25, 0.5, 1, 2, 3, 4, 8, 12, 22.5時間に, 尿を投与前ならびに投与後0~24, 24~48時間でそれぞれ採取した。第2期の試験においては, 血液を投与前ならびに投与後0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48時間に, 尿を投与前ならびに投与後0~2, 2~4, 4~6, 6~8, 8~12, 12~24, 24~48, 48~72時間でそれぞれ採取した。血液からは常法により血清を分離した。また, 200および400mgの空腹時投与では, 血液と同時に唾液の採取も行った。400mgの空腹時投与では24時間毎の糞便を投与後72時間まで採取した。さらに, 血清たん白結合を測定するため200mgの空腹時投与後1, 3, 6および12時間, ならびにprobenecid併用時, GFLXの投与後3時間に, 血液をそれぞれ採取し, 常法により血清を得た。

5. 薬物濃度の測定

血清, 尿, 糞および唾液中GFLX濃度は, 杏林製薬株式会社中央研究所にて高速液体クロマトグラフ(HPLC)法³⁾により測定した。糞便は0.1M塩酸により抽出した後, 0.1M水酸化ナトリウムで中和し, これを試料とした。また, 400mgの空腹時投与における尿を, β -glucuronidase (*Escherichia coli*由来, ペーリンガー・マンハイム・山之内)により加水分解(50,000FU/mL, pH 7.0, 37°C, 2時間)後, その薬物濃度を測定し, 未処理の試料中濃度(非抱合体濃度)との差から, グルクロン酸抱合体濃度を算出した。さらに, 200mgの空腹時投与における血清および尿について, *Bacillus subtilis* ATCC 6633を検定菌とした薄層カップ法(bioassay法)により薬物濃度を測定し, HPLC法による測定値との相関を検討した。

HPLC法による検出限界は, 血清および唾液で0.01 μ g/mL, 尿および糞でそれぞれ0.1 μ g/mL, 0.4 μ g/g, bioassay法による検出限界は血清で0.025 μ g/mL, 尿

Table 1. Background of subjects

| 1) Step 1 | | | | |
|--------------------------|---------------|-----------|-------------|------------------|
| Dose (mg) | Volunteer no. | Age (yrs) | Height (cm) | Body weight (kg) |
| 20 | A 1 | 28 | 169.8 | 61.7 |
| | A 2 | 28 | 167.9 | 59.8 |
| | Mean | 28.0 | 168.9 | 60.8 |
| 50 | B 1 | 32 | 169.0 | 53.5 |
| | B 2 | 26 | 166.2 | 66.4 |
| | Mean | 29.0 | 167.6 | 60.0 |
| 2) Step 2 | | | | |
| Dose (mg) | Volunteer no. | Age (yrs) | Height (cm) | Body weight (kg) |
| 100 (Fasting) | C 1 | 38 | 167.2 | 51.3 |
| | C 2 | 22 | 169.7 | 61.1 |
| | C 3 | 28 | 163.6 | 53.0 |
| | C 4 | 30 | 170.0 | 60.5 |
| | C 5 | 27 | 174.2 | 80.0 |
| | C 6 | 21 | 173.9 | 77.3 |
| | Mean | 27.7 | 169.8 | 63.9 |
| | S.D. | 6.2 | 4.0 | 12.1 |
| 200 (Fasting) | D 1 | 28 | 173.8 | 66.2 |
| | D 2 | 22 | 166.0 | 67.9 |
| | D 3 | 26 | 176.2 | 56.6 |
| | D 4 | 38 | 172.3 | 66.5 |
| | D 5 | 27 | 170.8 | 60.9 |
| | D 6 | 24 | 170.4 | 53.2 |
| | Mean | 27.5 | 171.6 | 61.9 |
| | S.D. | 5.6 | 3.5 | 6.0 |
| 400 (Fasting) | E 1 | 27 | 172.5 | 72.3 |
| | E 2 | 38 | 165.0 | 58.7 |
| | E 3 | 34 | 169.4 | 61.3 |
| | E 4 | 26 | 188.0 | 69.4 |
| | E 5 | 33 | 170.6 | 69.9 |
| | E 6 | 25 | 176.6 | 83.2 |
| | Mean | 30.5 | 173.7 | 69.1 |
| | S.D. | 5.2 | 8.0 | 8.7 |
| 600 (Fasting) | F 1 | 33 | 168.9 | 58.4 |
| | F 2 | 27 | 168.5 | 64.8 |
| | F 3 | 26 | 176.1 | 78.3 |
| | F 4 | 29 | 169.9 | 62.6 |
| | F 5 | 31 | 179.0 | 74.4 |
| | F 6 | 32 | 170.6 | 63.1 |
| | Mean | 29.7 | 172.2 | 66.9 |
| | S.D. | 2.8 | 4.3 | 7.7 |
| 200 (Non-fasting) | G 1 | 28 | — | 66.4 |
| | G 2 | 22 | — | 68.6 |
| | G 3 | 26 | — | 57.3 |
| | G 4 | 38 | — | 66.6 |
| | G 5 | 27 | — | 63.0 |
| | G 6 | 25 | — | 53.9 |
| | Mean | 27.7 | — | 62.6 |
| | S.D. | 5.5 | — | 5.8 |
| 200 (With probenecid) | H 1 | 28 | — | 66.5 |
| | H 2 | 22 | — | 68.9 |
| | H 3 | 26 | — | 58.7 |
| | H 4 | 38 | — | 66.4 |
| | H 5 | 27 | — | 59.5 |
| | H 6 | 25 | — | 54.7 |
| | Mean | 27.7 | — | 62.5 |
| | S.D. | 5.5 | — | 5.6 |

— : Not measured (same as volunteers D1~D6)

1) 20 and 50 mg (Step 1)

| Item | Before dosing | Time after administration (h) | | | | | | | | | |
|---------------------------------|---------------|-------------------------------|---|---|---|----------------|----|----------------|-----------------|---------|---|
| | | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 24 | 48 | |
| Drug administration | | ↑ | | | | | | | | | |
| Food intake | | | | △ | | | △ | | △ | △ | △ |
| Blood sampling | ○ | ↑↑↑ ^{1a} | ↑ | ↑ | ↑ | ↑ | | ↑ ¹ | ↑ ^{1b} | | |
| Urine sampling | ○ | ←—————→ | | | | | | | | ←—————→ | |
| Laboratory test | ○ | | | | | | | | ○ | | |
| Clinical examination | | | | | | | | | | | |
| Objective symptoms ² | ○ | | | | | | | | ○ | | |
| BP, PR, BT ³ | ○ | ○○○ | ○ | ○ | ○ | ○ ¹ | ○ | ○ ¹ | ○ | | |
| ECG | ○ | | ○ | | | | | | ○ | | |

Subjective symptoms, if any, were to be reported to the doctor in charge at any time.

1: Only for 50 mg single-dose study

2: Auscultation, percussion, inspection, and palpation

3: BP: blood pressure; PR: pulse rate; BT: body temperature

a: 0.25 h

b: 22.5 h

2) 100, 200, 400, and 600 mg (Step 2)

| Item | Before dosing | Time after administration (h) | | | | | | | | | |
|-------------------------------------|---------------|-------------------------------|------------------|----------------|---|----------------|----------------|----------------|-----------------|---------|----|
| | | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 24 | 48 | 72 |
| Drug administration | | ↑ ¹ | ↑ ² | | | | | ↑ ¹ | ↑ ¹ | | |
| Food intake | | △ ² | | △ | | | △ | | △ | △ | △ |
| Blood sampling | ○ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ |
| Urine sampling | ○ | ←—————→ | | | | | | | | ←—————→ | |
| Crystals in urine ³ | ○ | | | | | | | | | | |
| Feces sampling ³ | ○ | ←—————→ | | | | | | | | ←—————→ | |
| Protein binding | ○ | ○ ⁵ | ○ ^{1,5} | ○ ⁵ | | | ○ ⁵ | | | | |
| Saliva sampling ⁶ | ○ | ○○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | |
| Laboratory test | ○ | | | | | | | ○ | | | |
| Clinical examination | | | | | | | | | | | |
| Objective symptoms ⁷ | ○ | | | | | | | | ○ | | |
| BP, PR, BT ⁸ | ○ | ○○○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | | |
| ECG | ○ | | ○ | | | | | | ○ | | |
| Audiometry ⁹ | ○ | | | | ○ | | | | ○ ¹⁰ | | |
| Ophthalmological test ³ | ○ | | | | | ○ ⁹ | | | | | |
| Balance test ³ | ○ | | ○ | | | | | | | | |
| Creatinine clearance ^{1,5} | ○ | ←—————→ | | | | | | | | | |

Subjective symptoms, if any, were to be reported to the doctor in charge at any time.

1: Only for probenecid interaction study in fasting volunteers

2: Only for 200 mg single-dose study in non-fasting volunteers

3: Only for 400 and 600 mg single-dose studies in fasting volunteers

4: Only for 400 mg single-dose study in fasting volunteers

5: Only for 200 mg single-dose study in fasting volunteers

6: Only for 200 and 400 mg single-dose studies in fasting volunteers

7: Auscultation, percussion, inspection, and palpation

8: BP: blood pressure; PR: pulse rate; BT: body temperature

9: Eldoptometry and photostress test

10: Funduscopy

Fig. 1. Schedule for single-dose study of gatifloxacin

Table 2. Laboratory test items

| | |
|---------------------------------------|--|
| 1. Physical examination | Auscultation, percussion, inspection, palpation, blood pressure, pulse rate, body temperature |
| 2. Hematology | RBC, Hemoglobin (Hb), WBC, Hematocrit (Ht), platelet, WBC differential count |
| 3. Blood biochemistry | GOT, GPT, Al-P, LDH, LAP, γ -GTP, ChE, total protein, A/G ratio, BUN, creatinine, uric acid, Na, K, Cl, Ca, P, glucose, total cholesterol (Chol-T), triglyceride, total bilirubin |
| 4. Urinalysis | pH, protein, glucose, urobilinogen, occult blood, urinary sediment |
| 5. ECG | 12 leads at rest |
| 6. Crystal in urine ¹ | Observation with microscope |
| 7. Audiometry ¹ | Audiography |
| 8. Ophthalmological test ¹ | Eidoptometry, funduscopy, photostress test |
| 9. Balance test ¹ | Stabilography |
| 10. Pharmacokinetics | Concentration in serum, saliva ² , urine and feces ³ , protein binding ⁴ |
| 11. Renal function ¹ | Creatinine clearance |

1: Conducted at doses of 400 and 600 mg.

2: Conducted at doses of 200 and 400 mg.

3: Conducted at dose of 400 mg.

4: Conducted at dose of 200 mg with and without probenecid.

で0.25 $\mu\text{g}/\text{mL}$ であった。血清および尿中クレアチニン濃度は、オートマチックアナライザー（日立7150形）により測定した。

6. 血清たん白結合率の測定

血清1 mLを遠心型たん白結合試験器MPS-1（アミコン）に供し、遠心限外ろ過（4℃）により限外ろ液を得た。限外ろ液中薬物濃度をHPLC法⁶⁾により測定し、原血清および限外ろ液中薬物濃度をそれぞれ総濃度、遊離型濃度として、結合率を求めた。

7. 薬物速度論的解析

第2期の試験において、血清中GFLX濃度の推移を2-compartment open modelに当てはめて解析した。計算には非線形最小二乗法プログラム“PAG-CP[®]”（株）インターデック）を使用した。当てはめ計算の結果に基づき血清中における最高濃度（Cmax）、Cmax到達時間（Tmax）、0から無限時間までの血清中濃度—時間曲線下面積（AUC_{0-∞}）、消失相における血中半減期（ $T_{1/2\beta}$ ）、消失相における見かけの分布容積（ V_{β}/F ）、定常状態における見かけの分布容積（ V_{ss}/F ）、見かけの全身クリアランス（ CL_r/F ）をそれぞれ算出した。また、投与後72時間までの尿中排泄量をAUC_{0-∞}で除することにより腎クリアランス（ CL_R ）を算出した。さらに、200mgの空腹時投与、ならびにprobenecidの併用投与において、薬剤投与後3時間の血清中非結合型薬物濃度を同時刻の血清中総薬物濃度で除することにより、血清中非結合型薬物濃度分率（fu）を求めた。ついで、GFLXの CL_R をfu

で除することにより固有腎クリアランス（ $CL_{R, \text{int}}$ ）を、血清および尿中クレアチニン濃度および尿流量からクレアチニン・クリアランス（Ccr）を求め、 $CL_{R, \text{int}}$ をCcrで除することにより排泄比を算出した。

一方、GFLX 200および400mgの空腹時投与後の唾液中薬物濃度について、モデルによらない方法により解析し、実測値からCmaxおよびTmaxを求めた。また、消失相における唾液中濃度を一次速度式に近似し、最小二乗法により消失速度定数（kel）を求めた後、 $T_{1/2}$ を算出した [$T_{1/2} = 0.693/\text{kel}$]。さらに、台形法により投与後48時間までの唾液中濃度—時間曲線下面積（AUC₀₋₄₈）を求め、これに48時間における唾液中濃度（ C_{48} ）をkelで除した値を加えることによりAUC_{0-∞}を算出した [$AUC_{0-∞} = AUC_{0-48} + C_{48}/\text{kel}$]。

8. 統計学的解析

結果は、平均値および標準偏差として示した。GFLX 200mg投与時の血清および尿に関するHPLC法とbioassay法による測定値、200および400mg投与時の唾液中濃度と血清中濃度の測定値について、それぞれ線形回帰分析により相関を解析した。また、GFLX 100~600mgの範囲におけるCmaxおよびAUC_{0-∞}の投与量比例性を、線形回帰分析により解析した。さらに、食事またはprobenecid併用によるGFLXの薬物速度論的パラメータ値への影響について、対応のあるt検定により評価した。P = 0.05を有意水準とした。

Table 3-1. Vital signs

1) 20 mg single-dose study in fasting volunteers

| Item | Volunteer no. | Time after administration (h) | | | | | | | | |
|---------------------------------------|---------------|-------------------------------|----------------|--------|--------|--------|--------|--------|--------|--------|
| | | -1 | 0 ^a | 0.5 | 1 | 2 | 3 | 4 | 8 | 22.5 |
| Blood pressure ^b (mmHg) | A1 | 110/63 | 103/59 | 101/59 | 103/58 | 104/63 | 106/62 | 105/57 | 110/59 | 115/67 |
| | A2 | 109/58 | 109/64 | 102/57 | 109/60 | 111/66 | 112/65 | 108/63 | 113/63 | 115/62 |
| Pulse rate ^b (/min) | A1 | 66 | 66 | 66 | 66 | 63 | 62 | 62 | 73 | 71 |
| | A2 | 61 | 66 | 57 | 59 | 60 | 60 | 61 | 66 | 62 |
| Body temperature (°C) | A1 | 36.0 | 35.6 | 36.3 | 36.5 | 36.5 | 35.6 | 36.1 | 36.1 | 36.2 |
| | A2 | 36.5 | 36.3 | 36.4 | 35.7 | 36.5 | 36.3 | 36.4 | 36.5 | 36.1 |

2) 50 mg single-dose study in fasting volunteers

| Item | Volunteer no. | Time after administration (h) | | | | | | | | | | |
|---------------------------------------|---------------|-------------------------------|----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | -1 | 0 ^a | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 22.5 |
| Blood pressure ^b (mmHg) | B1 | 105/53 | 102/56 | 99/56 | 98/57 | 98/56 | 105/60 | 102/58 | 98/53 | 108/53 | 106/55 | 106/56 |
| | B2 | 109/63 | 108/58 | 104/60 | 102/55 | 106/58 | 110/62 | 110/59 | 118/62 | 109/59 | 108/60 | 108/60 |
| Pulse rate ^b (/min) | B1 | 44 | 45 | 42 | 42 | 42 | 41 | 41 | 49 | 54 | 56 | 45 |
| | B2 | 60 | 57 | 57 | 57 | 59 | 55 | 54 | 68 | 64 | 69 | 57 |
| Body temperature (°C) | B1 | 35.8 | 35.8 | 35.8 | 35.8 | 35.9 | 35.7 | 35.8 | 36.4 | 36.7 | 36.5 | 35.9 |
| | B2 | 36.5 | 35.7 | 36.3 | 36.2 | 36.2 | 35.6 | 35.4 | 36.4 | 36.4 | 36.3 | 35.8 |

3) 100 mg single-dose study in fasting volunteers

| Item | Volunteer no. | Time after administration (h) | | | | | | | | | |
|---------------------------------------|---------------|-------------------------------|----------------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | -1 | 0 ^a | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 22.5 |
| Blood pressure ^b (mmHg) | C1 | 113/59 | 112/59 | 99/51 | 101/52 | 96/50 | 107/54 | 111/55 | 108/54 | 112/58 | 107/55 |
| | C2 | 131/72 | 124/70 | 122/69 | 122/65 | 121/67 | 131/70 | 127/68 | 128/69 | 133/72 | 119/66 |
| | C3 | 122/66 | 129/70 | 122/68 | 116/65 | 119/69 | 117/64 | 126/68 | 126/65 | 125/62 | 115/61 |
| | C4 | 107/58 | 99/56 | 101/58 | 104/56 | 100/55 | 106/58 | 115/59 | 105/56 | 106/54 | 101/51 |
| | C5 | 103/58 | 105/58 | 107/62 | 110/61 | 100/56 | 100/57 | 102/55 | 110/57 | 115/61 | 98/53 |
| | C6 | 139/70 | 114/61 | 116/65 | 113/62 | 131/71 | 128/64 | 123/60 | 121/64 | 131/64 | 118/62 |
| Pulse rate ^b (/min) | C1 | 62 | 62 | 59 | 59 | 57 | 60 | 71 | 64 | 68 | 61 |
| | C2 | 90 | 76 | 73 | 75 | 74 | 70 | 81 | 77 | 82 | 80 |
| | C3 | 51 | 50 | 54 | 52 | 54 | 52 | 59 | 58 | 59 | 55 |
| | C4 | 52 | 51 | 48 | 50 | 48 | 49 | 61 | 58 | 52 | 49 |
| | C5 | 45 | 45 | 44 | 49 | 46 | 47 | 59 | 62 | 67 | 49 |
| | C6 | 59 | 54 | 54 | 55 | 55 | 63 | 70 | 63 | 62 | 58 |
| Body temperature (°C) | C1 | 35.8 | 36.1 | 36.1 | 36.5 | 36.3 | 36.7 | 36.7 | 36.3 | 36.5 | 35.8 |
| | C2 | 36.3 | 36.2 | 36.7 | 36.5 | 36.1 | 36.3 | 36.5 | 36.6 | 36.7 | 36.0 |
| | C3 | 36.0 | 36.2 | 36.2 | 36.1 | 36.2 | 36.1 | 36.3 | 36.5 | 36.7 | 36.1 |
| | C4 | 36.1 | 36.1 | 36.2 | 35.8 | 36.1 | 35.8 | 36.4 | 36.0 | 36.3 | 35.6 |
| | C5 | 35.4 | 35.5 | 35.9 | 36.0 | 36.1 | 35.6 | 36.5 | 36.4 | 36.3 | 35.4 |
| | C6 | 36.0 | 36.2 | 36.5 | 36.7 | 36.5 | 36.8 | 37.0 | 36.7 | 36.7 | 36.0 |

a: Just before dosing

b: Mean of 2 determinations

II. 成績

1. 自覚および他覚症状

本薬に起因すると考えられる異常は認められなかった。

2. 血圧, 脈拍数, 体温

試験結果を Table 3 に示す。いずれの試験においても異常な変動は認められなかった。

3. 心電図

本薬に起因すると考えられる異常所見は、いずれも認められなかった。

4. 臨床検査

試験結果を Table 4 に示す。血液学的検査, 血液生化学検査および尿検査において、本薬に起因すると考えら

Table 3-2. Vital signs

4) 200 mg single-dose study in fasting volunteers

| Item | Volunteer no. | Time after administration (h) | | | | | | | | | | |
|---------------------------------------|---------------|-------------------------------|----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | -2 | 0 ^a | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 22.5 |
| Blood pressure ^b (mmHg) | D1 | 111/65 | 108/57 | 112/65 | 108/59 | 110/60 | 109/61 | 109/60 | 112/59 | 114/57 | 113/59 | 108/59 |
| | D2 | 120/67 | 116/57 | 117/55 | 111/56 | 108/57 | 114/58 | 113/59 | 119/62 | 119/61 | 118/59 | 118/63 |
| | D3 | 112/60 | 111/60 | 106/59 | 114/58 | 109/60 | 108/61 | 112/55 | 109/55 | 120/60 | 113/62 | 108/59 |
| | D4 | 136/75 | 136/77 | 126/76 | 127/77 | 132/73 | 120/73 | 123/75 | 124/70 | 124/71 | 133/73 | 123/70 |
| | D5 | 121/61 | 119/59 | 114/56 | 113/62 | 113/60 | 115/57 | 122/61 | 117/58 | 120/60 | 126/65 | 124/62 |
| | D6 | 113/60 | 97/53 | 100/57 | 105/58 | 100/55 | 95/52 | 106/60 | 104/57 | 108/54 | 101/54 | 110/58 |
| Pulse rate ^b (/min) | D1 | 52 | 51 | 52 | 54 | 54 | 53 | 53 | 59 | 53 | 58 | 52 |
| | D2 | 53 | 51 | 51 | 49 | 53 | 50 | 51 | 70 | 71 | 72 | 48 |
| | D3 | 70 | 56 | 65 | 62 | 61 | 58 | 63 | 69 | 68 | 67 | 61 |
| | D4 | 51 | 49 | 49 | 48 | 46 | 46 | 46 | 52 | 49 | 55 | 48 |
| | D5 | 57 | 46 | 47 | 48 | 47 | 45 | 46 | 61 | 55 | 58 | 53 |
| | D6 | 64 | 55 | 54 | 54 | 56 | 55 | 54 | 62 | 61 | 61 | 67 |
| Body temperature (°C) | D1 | 36.1 | 36.0 | 36.2 | 36.4 | 36.6 | 36.2 | 36.4 | 35.2 | 35.9 | 36.2 | 36.1 |
| | D2 | 35.7 | 35.5 | 35.9 | 36.0 | 36.5 | 35.8 | 35.5 | 36.2 | 36.4 | 35.5 | 35.3 |
| | D3 | 35.9 | 35.8 | 35.6 | 35.3 | 36.5 | 36.5 | 35.8 | 36.5 | 36.7 | 36.2 | 36.0 |
| | D4 | 35.5 | 35.5 | 35.7 | 36.4 | 36.0 | 36.0 | 36.1 | 35.9 | 35.9 | 36.0 | 34.8 |
| | D5 | 36.2 | 36.0 | 36.2 | 36.3 | 36.6 | 36.1 | 36.4 | 36.6 | 36.5 | 36.6 | 36.2 |
| | D6 | 36.4 | 36.0 | 36.4 | 36.5 | 36.7 | 36.4 | 36.7 | 36.5 | 36.8 | 36.4 | 36.0 |

5) 400 mg single-dose study in fasting volunteers

| Item | Volunteer no. | Time after administration (h) | | | | | | | | | | |
|---------------------------------------|---------------|-------------------------------|----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | -1 | 0 ^a | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 22.5 |
| Blood pressure ^b (mmHg) | E1 | 136/71 | 122/69 | 136/74 | 138/77 | 137/79 | 128/74 | 130/74 | 126/70 | 121/70 | 129/70 | 122/71 |
| | E2 | 118/66 | 120/66 | 113/59 | 119/61 | 116/63 | 121/62 | 121/65 | 116/60 | 116/63 | 122/62 | 113/61 |
| | E3 | 115/69 | 114/68 | 109/60 | 111/64 | 109/66 | 111/61 | 108/66 | 116/60 | 113/61 | 110/57 | 112/63 |
| | E4 | 114/66 | 118/68 | 109/62 | 113/62 | 109/60 | 111/61 | 110/58 | 105/57 | 106/57 | 113/60 | 108/61 |
| | E5 | 114/67 | 111/63 | 114/64 | 107/61 | 114/63 | 113/58 | 112/61 | 125/70 | 111/62 | 116/60 | 111/60 |
| | E6 | 111/63 | 111/61 | 107/57 | 112/64 | 107/56 | 109/57 | 110/60 | 111/56 | 110/58 | 104/53 | 104/56 |
| Pulse rate ^b (/min) | E1 | 61 | 63 | 63 | 64 | 62 | 61 | 58 | 67 | 65 | 66 | 58 |
| | E2 | 56 | 57 | 55 | 55 | 55 | 55 | 55 | 57 | 56 | 58 | 59 |
| | E3 | 76 | 68 | 62 | 63 | 65 | 63 | 65 | 73 | 69 | 67 | 67 |
| | E4 | 47 | 53 | 50 | 50 | 50 | 50 | 50 | 60 | 53 | 56 | 45 |
| | E5 | 69 | 68 | 71 | 67 | 72 | 67 | 70 | 82 | 68 | 70 | 68 |
| | E6 | 58 | 53 | 53 | 58 | 58 | 56 | 53 | 58 | 56 | 61 | 54 |
| Body temperature (°C) | E1 | 36.1 | 36.6 | 36.9 | 36.9 | 37.0 | 36.5 | 36.4 | 36.4 | 36.7 | 36.7 | 36.4 |
| | E2 | 35.7 | 36.0 | 36.5 | 36.3 | 36.8 | 36.5 | 36.5 | 36.4 | 35.9 | 36.5 | 36.3 |
| | E3 | 36.0 | 36.4 | 36.6 | 36.5 | 36.4 | 36.2 | 36.4 | 36.2 | 36.3 | 36.5 | 36.1 |
| | E4 | 36.0 | 36.3 | 36.5 | 36.2 | 36.7 | 36.8 | 36.9 | 36.8 | 36.8 | 36.7 | 36.1 |
| | E5 | 35.2 | 36.1 | 36.6 | 36.8 | 36.6 | 36.1 | 36.5 | 36.2 | 36.0 | 36.7 | 36.5 |
| | E6 | 35.3 | 35.6 | 36.3 | 35.7 | 35.7 | 36.3 | 35.8 | 35.1 | 36.0 | 35.8 | 35.4 |

6) 600 mg single-dose study in fasting volunteers

| Item | Volunteer no. | Time after administration (h) | | | | | | | | | | |
|---------------------------------------|---------------|-------------------------------|----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | -1.5 | 0 ^a | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 22.5 |
| Blood pressure ^b (mmHg) | F1 | 120/66 | 106/56 | 110/57 | 107/56 | 109/58 | 108/56 | 100/55 | 117/63 | 106/55 | 113/58 | 116/65 |
| | F2 | 104/61 | 97/59 | 100/61 | 106/60 | 91/49 | 96/54 | 95/54 | 107/61 | 106/59 | 94/55 | 102/61 |
| | F3 | 124/75 | 126/70 | 121/72 | 127/71 | 127/71 | 118/67 | 126/68 | 127/64 | 127/68 | 122/68 | 123/70 |
| | F4 | 111/60 | 111/57 | 111/60 | 112/66 | 108/54 | 109/58 | 105/57 | 117/60 | 107/59 | 113/57 | 112/63 |
| | F5 | 117/72 | 115/67 | 118/68 | 113/66 | 117/66 | 125/71 | 121/67 | 106/57 | 110/62 | 123/68 | 118/66 |
| | F6 | 116/65 | 106/59 | 106/66 | 117/67 | 106/66 | 104/58 | 107/55 | 114/60 | 121/63 | 119/66 | 118/65 |
| Pulse rate ^b (/min) | F1 | 61 | 63 | 62 | 62 | 65 | 69 | 61 | 72 | 68 | 73 | 61 |
| | F2 | 61 | 59 | 55 | 58 | 62 | 60 | 57 | 69 | 62 | 68 | 55 |
| | F3 | 50 | 49 | 51 | 49 | 54 | 55 | 57 | 55 | 55 | 59 | 52 |
| | F4 | 61 | 62 | 67 | 65 | 65 | 61 | 63 | 73 | 62 | 70 | 63 |
| | F5 | 75 | 64 | 66 | 67 | 64 | 69 | 66 | 68 | 63 | 70 | 65 |
| | F6 | 62 | 54 | 58 | 55 | 64 | 58 | 55 | 62 | 64 | 64 | 54 |
| Body temperature (°C) | F1 | 35.4 | 35.9 | 35.9 | 36.0 | 36.1 | 36.6 | 36.5 | 36.7 | 36.6 | 36.8 | 35.8 |
| | F2 | 36.1 | 36.0 | 36.5 | 36.0 | 36.5 | 36.4 | 36.9 | 36.2 | 35.9 | 35.9 | 36.0 |
| | F3 | 35.8 | 35.9 | 36.3 | 36.3 | 36.5 | 35.9 | 36.9 | 36.7 | 36.0 | 36.7 | 36.0 |
| | F4 | 35.8 | 35.6 | 36.2 | 36.1 | 36.4 | 36.0 | 36.5 | 36.4 | 36.4 | 36.2 | 35.7 |
| | F5 | 35.0 | 35.8 | 35.8 | 35.9 | 36.0 | 36.0 | 36.6 | 35.8 | 36.0 | 35.5 | 35.5 |
| | F6 | 36.2 | 36.3 | 36.8 | 36.8 | 36.9 | 36.9 | 37.0 | 37.0 | 37.0 | 36.8 | 36.2 |

a : Just before dosing

b : Mean of 2 determinations

Table 3-3. Vital signs

7) 200 mg single-dose study in non-fasting volunteers

| Item | Volunteer no. | Time after administration (h) | | | | | | | | | | |
|------------------------------------|---------------|-------------------------------|----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | -2 | 0 ^a | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 22.5 |
| Blood pressure ^b (mmHg) | G1 | 117/64 | 112/58 | 107/56 | 109/60 | 113/61 | 108/59 | 107/60 | 120/61 | 118/60 | 107/56 | 109/60 |
| | G2 | 118/60 | 125/61 | 119/56 | 122/59 | 122/62 | 114/62 | 112/55 | 129/63 | 131/69 | 134/67 | 107/56 |
| | G3 | 116/62 | 107/61 | 113/59 | 110/55 | 103/54 | 106/58 | 101/56 | 104/49 | 116/64 | 118/61 | 112/62 |
| | G4 | 128/75 | 129/70 | 122/71 | 120/68 | 124/71 | 128/73 | 131/76 | 119/68 | 129/74 | 128/69 | 122/72 |
| | G5 | 123/63 | 117/60 | 122/61 | 123/60 | 124/59 | 121/60 | 117/59 | 124/59 | 122/62 | 124/63 | 125/65 |
| | G6 | 104/54 | 109/59 | 121/61 | 110/55 | 117/61 | 104/55 | 112/60 | 108/55 | 104/53 | 115/59 | 101/55 |
| Pulse rate ^b (/min) | G1 | 54 | 62 | 58 | 61 | 60 | 56 | 53 | 69 | 57 | 63 | 53 |
| | G2 | 55 | 62 | 58 | 57 | 58 | 54 | 55 | 76 | 71 | 76 | 53 |
| | G3 | 65 | 62 | 68 | 69 | 69 | 66 | 67 | 70 | 73 | 79 | 67 |
| | G4 | 52 | 54 | 54 | 53 | 53 | 49 | 47 | 57 | 53 | 57 | 51 |
| | G5 | 58 | 56 | 55 | 61 | 60 | 51 | 49 | 69 | 60 | 64 | 60 |
| | G6 | 58 | 67 | 65 | 64 | 58 | 57 | 59 | 68 | 63 | 66 | 59 |
| Body temperature (°C) | G1 | 36.3 | 36.2 | 36.5 | 36.9 | 36.7 | 36.5 | 36.4 | 36.1 | 36.4 | 36.7 | 36.1 |
| | G2 | 35.6 | 35.8 | 36.4 | 36.5 | 36.5 | 35.8 | 35.1 | 35.2 | 37.0 | 36.8 | 35.5 |
| | G3 | 36.0 | 36.3 | 36.6 | 36.6 | 36.6 | 36.2 | 36.3 | 36.2 | 37.0 | 36.3 | 35.9 |
| | G4 | 35.8 | 35.8 | 35.7 | 35.9 | 36.5 | 35.7 | 35.3 | 36.3 | 35.9 | 36.8 | 35.4 |
| | G5 | 35.7 | 36.4 | 36.7 | 36.7 | 36.8 | 36.0 | 36.3 | 36.7 | 36.6 | 36.5 | 36.2 |
| | G6 | 36.1 | 36.1 | 36.5 | 36.5 | 36.9 | 36.5 | 36.8 | 36.6 | 36.6 | 36.5 | 35.9 |

8) Probenecid interaction study in fasting volunteers

| Item | Volunteer no. | Time after administration (h) | | | | | | | | | |
|------------------------------------|---------------|-------------------------------|----------------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | -1.5 | 0 ^a | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 22.5 |
| Blood pressure ^b (mmHg) | H1 | 114/62 | 103/60 | 108/59 | 105/56 | 107/57 | 97/56 | 103/57 | 101/53 | 106/56 | 106/60 |
| | H2 | 116/65 | 115/62 | 116/56 | 111/57 | 105/52 | 103/49 | 105/55 | 119/58 | 126/62 | 125/66 |
| | H3 | 108/61 | 100/59 | 104/51 | 107/58 | 99/53 | 100/55 | 97/54 | 104/56 | 110/58 | 106/59 |
| | H4 | 141/80 | 125/76 | 125/75 | 124/71 | 126/73 | 125/74 | 128/76 | 121/69 | 123/69 | 127/75 |
| | H5 | 113/60 | 113/58 | 110/54 | 113/58 | 110/57 | 112/55 | 111/58 | 106/54 | 112/54 | 113/60 |
| | H6 | 102/55 | 97/57 | 107/60 | 112/61 | 106/60 | 104/59 | 105/58 | 103/55 | 100/53 | 106/63 |
| Pulse rate ^b (/min) | H1 | 56 | 56 | 58 | 56 | 57 | 55 | 58 | 62 | 66 | 54 |
| | H2 | 55 | 56 | 55 | 54 | 56 | 57 | 58 | 69 | 68 | 59 |
| | H3 | 64 | 63 | 63 | 62 | 66 | 62 | 62 | 74 | 75 | 67 |
| | H4 | 51 | 49 | 49 | 49 | 49 | 51 | 48 | 54 | 53 | 51 |
| | H5 | 49 | 50 | 44 | 47 | 52 | 46 | 45 | 68 | 56 | 52 |
| | H6 | 55 | 55 | 54 | 52 | 55 | 58 | 58 | 68 | 59 | 63 |
| Body temperature (°C) | H1 | 36.5 | 36.5 | 36.6 | 36.8 | 36.7 | 36.9 | 36.4 | 37.0 | 36.6 | 36.2 |
| | H2 | 35.2 | 36.1 | 35.9 | 35.9 | 36.4 | 36.2 | 36.4 | 36.3 | 35.9 | 35.8 |
| | H3 | 35.8 | 36.0 | 36.3 | 36.0 | 36.6 | 36.1 | 36.5 | 36.8 | 36.9 | 36.0 |
| | H4 | 35.2 | 35.4 | 36.1 | 35.8 | 35.7 | 35.8 | 36.0 | 36.6 | 35.5 | 35.7 |
| | H5 | 36.4 | 36.2 | 36.2 | 36.4 | 36.6 | 36.3 | 36.3 | 36.4 | 36.0 | 36.5 |
| | H6 | 35.9 | 35.6 | 35.7 | 36.0 | 36.2 | 36.0 | 36.7 | 36.9 | 37.2 | 35.9 |

a: Just before dosing

b: Mean of 2 determinations

れる異常変動は認められなかった。

5. 聴力検査, 眼科的検査, 平衡機能検査

400および600mg投与時に実施した検査において, 本薬に起因すると考えられる異常所見は認められなかった。

6. 尿中結晶の観察

400および600mg投与時の尿および尿沈渣について, 薬物による結晶は認められなかった。

7. HPLC法とbioassay法による測定値の相関

HPLC法とbioassay法による測定値の相関をFig. 2に示す。血清中濃度について,

$$(\text{Bioassay}) = 0.937 \cdot (\text{HPLC}) - 0.0092, \\ \text{相関係数 } 0.987 (P < 0.01)$$

尿中濃度について,

$$(\text{Bioassay}) = 0.919 \cdot (\text{HPLC}) + 0.450, \\ \text{相関係数 } 0.993 (P < 0.01)$$

とほぼ1:1の有意な相関が認められた。

8. 20または50mg投与後の体内動態(第1期)

GFLX 20または50mg投与後の血清中濃度をTable 5およびFig. 3に, 尿中濃度および累積尿中排泄率をTable 6, 7およびFig. 4にそれぞれ示す。GFLX 20

Table 4-1. Clinical laboratory tests

1) 20 and 50 mg single-dose study in fasting volunteers

| Item | Normal range | Volunteer no. | | | | | | | |
|--|--------------|---------------|-------|-------|-------|-------|-------|-------|-------|
| | | A1 | | A2 | | B1 | | B2 | |
| | | B | A | B | A | B | A | B | A |
| Hematology | | | | | | | | | |
| RBC ($\times 10^4/\text{mm}^3$) | 354 - 574 | 516 | 494 | 476 | 477 | 443 | 430 | 548 | 529 |
| Hb (g/dL) | 12.0 - 18.0 | 15.2 | 14.7 | 15.3 | 15.4 | 13.7 | 13.5 | 15.7 | 15.4 |
| WBC ($/\text{mm}^3$) | 3500 - 8300 | 5200 | 6000 | 7800 | 6000 | 7200 | 8300 | 8400 | 7400 |
| Ht (%) | 38.0 - 51.0 | 45.0 | 43.2 | 46.6 | 46.8 | 41.0 | 40.0 | 47.4 | 45.5 |
| Platelet ($\times 10^4/\text{mm}^3$) | 12.0 - 40.0 | 24.3 | 23.3 | 26.6 | 25.3 | 26.1 | 26.1 | 22.6 | 22.7 |
| Differential WBC | | | | | | | | | |
| Eosinophils (%) | 0 - 10 | 6 | 9 | 1 | 1 | 4 | 5 | 3 | 3 |
| Basophils (%) | 0 - 5 | 1 | 0 | 0 | 0 | 2 | 1 | 0 | 0 |
| Neutrophils stabs. (%) | 0 - 19 | 10 | 8 | 8 | 6 | 2 | 7 | 6 | 6 |
| Neutrophils segs. (%) | 28 - 68 | 32 | 37 | 65 | 62 | 43 | 51 | 51 | 55 |
| Lymphocytes (%) | 17 - 57 | 39 | 40 | 22 | 25 | 47 | 33 | 34 | 33 |
| Monocytes (%) | 0 - 10 | 12 | 6 | 4 | 6 | 2 | 3 | 6 | 3 |
| Blood biochemistry | | | | | | | | | |
| GOT (K.U.) | 5 - 40 | 14 | 14 | 15 | 14 | 13 | 12 | 14 | 11 |
| GPT (K.U.) | 4 - 35 | 13 | 13 | 10 | 10 | 11 | 11 | 20 | 17 |
| Al-P (K.A.U.) | 2.5 - 11.5 | 6.5 | 6.5 | 3.9 | 4.2 | 5.5 | 5.8 | 5.1 | 5.2 |
| LDH (W.U.) | 170 - 450 | 216 | 198 | 288 | 260 | 209 | 203 | 184 | 203 |
| LAP (G.R.U.) | 110 - 172 | 136 | 138 | 187 | 186 | 165 | 160 | 155 | 140 |
| γ -GTP (IU/L) | 0 - 50 | 16 | 15 | 25 | 25 | 32 | 30 | 12 | 11 |
| ChE (Δ pH) | 0.6 - 1.3 | 0.89 | 0.85 | 0.71 | 0.70 | 0.76 | 0.75 | 1.07 | 1.07 |
| Total protein (g/dL) | 6.0 - 8.0 | 7.3 | 6.9 | 6.8 | 6.5 | 6.3 | 6.4 | 7.1 | 6.8 |
| A/G ratio | 1.0 - 2.5 | 1.4 | 1.4 | 1.7 | 1.8 | 1.7 | 1.7 | 1.8 | 1.8 |
| BUN (mg/dL) | 8.0 - 20.0 | 13.9 | 13.7 | 12.1 | 13.1 | 20.7 | 18.7 | 12.5 | 12.0 |
| Creatinine (mg/dL) | 0.6 - 1.3 | 1.1 | 1.2 | 1.1 | 1.0 | 1.2 | 1.1 | 1.2 | 1.1 |
| Uric acid (mg/dL) | 2.9 - 6.5 | 7.7 | 7.1 | 5.2 | 4.7 | 5.6 | 5.6 | 5.0 | 5.3 |
| Electrolyte | | | | | | | | | |
| Na (mEq/L) | 134 - 145 | 140 | 140 | 140 | 141 | 141 | 141 | 143 | 140 |
| K (mEq/L) | 3.4 - 5.0 | 4.1 | 4.1 | 4.4 | 4.6 | 4.0 | 4.2 | 4.3 | 4.5 |
| Cl (mEq/L) | 98 - 110 | 105 | 105 | 104 | 105 | 107 | 107 | 107 | 105 |
| Ca (mEq/L) | 4.0 - 5.0 | 4.6 | 4.4 | 4.7 | 4.7 | 4.5 | 4.5 | 4.5 | 4.5 |
| P (mg/dL) | 2.0 - 4.5 | 3.2 | 3.4 | 4.0 | 4.6 | 3.9 | 4.3 | 3.6 | 3.9 |
| Glucose (mg/dL) | 70 - 110 | 86 | 92 | 85 | 92 | 92 | 95 | 103 | 103 |
| Chol-T (mg/dL) | 120 - 230 | 174 | 175 | 183 | 179 | 117 | 121 | 149 | 142 |
| Triglyceride (mg/dL) | 40 - 170 | 84 | 86 | 97 | 85 | 37 | 34 | 98 | 167 |
| Total bilirubin (mg/dL) | 0.3 - 1.2 | 0.7 | 0.6 | 1.7 | 1.1 | 0.8 | 0.8 | 0.8 | 0.7 |
| Urinalysis | | | | | | | | | |
| pH | 4.8 - 7.5 | 5.4 | 5.4 | 5.4 | 5.2 | 5.6 | 5.4 | 5.4 | 5.4 |
| Protein | - | - | - | - | - | - | - | - | - |
| Glucose | - | - | - | - | - | - | - | - | - |
| Urobilinogen | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm |
| Occult blood | - | - | - | - | - | - | - | - | - |
| Sediment RBC(/F) | 1 - 2 | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment WBC(/F) | 1 - 2 | n.s. | n.s. | 8-10 | 8-10 | n.s. | n.s. | n.s. | n.s. |
| Sediment epithelium(/F) | 1 - 3 | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment oxalate crystals | - | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment casts | - | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |

B: Before dosing. A: 24 h after dosing.

n.s.: Nothing specially

および50mgの投与後、平均血清中濃度はそれぞれ1および3時間で最高に達し、その濃度は0.21, 0.34 $\mu\text{g}/\text{mL}$ であった。投与後48時間までの累積尿中排泄率の平均値は、それぞれ72.9, 87.9%であった。

9. 100, 200, 400または600mg投与後の体内動態(第2期)

GFLX 100, 200, 400または600mg投与後の血清中

濃度をTable 8およびFig. 5に、薬物速度論的パラメータをTable 9に示す。血清中濃度は、投与後1.41~2.28時間でピークに達し、GFLX 100, 200, 400および600mg投与時のCmaxはそれぞれ0.873, 1.71, 3.35および5.41 $\mu\text{g}/\text{mL}$ 、AUC_{0-∞}はそれぞれ7.00, 14.5, 32.4および53.5 $\mu\text{g} \cdot \text{h}/\text{mL}$ であった。Cmax, AUC_{0-∞}と投与量にはそれぞれ良好な相関が見られ、これらのパラメー

Table 4-2. Clinical laboratory tests

2) 100 mg single-dose study in fasting volunteers

| Item | Volunteer no. | | | | | | | | | | | |
|--|---------------|------|------|------|------|------|------|------|------|------|------|------|
| | C1 | | C2 | | C3 | | C4 | | C5 | | C6 | |
| | B | A | B | A | B | A | B | A | B | A | B | A |
| Hematology | | | | | | | | | | | | |
| RBC ($\times 10^4/\text{mm}^3$) | 472 | 448 | 506 | 511 | 448 | 435 | 530 | 509 | 497 | 522 | 537 | 554 |
| Hb (g/dL) | 13.8 | 13.1 | 15.2 | 15.0 | 14.4 | 14.0 | 15.4 | 14.7 | 16.3 | 17.1 | 16.2 | 16.5 |
| WBC (/mm ³) | 7500 | 6800 | 4700 | 4500 | 3700 | 3500 | 6600 | 6400 | 7300 | 8100 | 5500 | 5000 |
| Ht (%) | 41.6 | 39.6 | 44.6 | 45.0 | 42.5 | 41.5 | 46.6 | 44.7 | 46.6 | 48.9 | 47.1 | 48.1 |
| Platelet ($\times 10^4/\text{mm}^3$) | 23.8 | 25.2 | 24.1 | 26.2 | 18.9 | 18.3 | 23.0 | 19.2 | 17.3 | 15.7 | 19.2 | 21.7 |
| Differential WBC | | | | | | | | | | | | |
| Eosinophils (%) | 3 | 4 | 4 | 1 | 1 | 1 | 3 | 8 | 3 | 3 | 3 | 3 |
| Basophils (%) | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 |
| Neutrophils stabs. (%) | 8 | 7 | 3 | 4 | 2 | 6 | 8 | 6 | 4 | 4 | 6 | 6 |
| Neutrophils segs. (%) | 54 | 62 | 49 | 59 | 42 | 35 | 47 | 50 | 58 | 64 | 44 | 50 |
| Lymphocytes (%) | 28 | 23 | 40 | 31 | 50 | 50 | 35 | 32 | 30 | 23 | 37 | 35 |
| Monocytes (%) | 7 | 4 | 3 | 4 | 5 | 8 | 6 | 4 | 5 | 5 | 10 | 5 |
| Blood biochemistry | | | | | | | | | | | | |
| GOT (K.U.) | 13 | 11 | 19 | 17 | 15 | 13 | 13 | 12 | 14 | 16 | 18 | 17 |
| GPT (K.U.) | 10 | 9 | 23 | 21 | 10 | 7 | 13 | 12 | 11 | 11 | 13 | 13 |
| Al-P (K.A.U.) | 12.7 | 11.7 | 8.8 | 8.9 | 5.0 | 4.9 | 6.1 | 6.0 | 5.9 | 6.6 | 6.0 | 5.9 |
| LDH (W.U.) | 226 | 204 | 202 | 205 | 330 | 289 | 227 | 203 | 228 | 227 | 288 | 260 |
| LAP (G.R.U.) | 146 | 135 | 130 | 142 | 134 | 124 | 122 | 123 | 139 | 160 | 169 | 172 |
| γ -GTP (IU/L) | 15 | 13 | 25 | 21 | 15 | 13 | 18 | 17 | 31 | 33 | 16 | 13 |
| ChE (Δ pH) | 0.72 | 0.68 | 0.84 | 0.84 | 0.78 | 0.75 | 1.04 | 0.98 | 0.93 | 0.97 | 0.99 | 1.00 |
| Total protein (g/dL) | 6.7 | 6.3 | 7.1 | 7.1 | 6.5 | 6.1 | 7.1 | 7.0 | 6.7 | 7.0 | 7.4 | 7.3 |
| A/G ratio | 1.6 | 1.6 | 1.6 | 1.5 | 1.9 | 2.0 | 1.7 | 1.5 | 1.5 | 1.6 | 1.6 | 1.5 |
| BUN (mg/dL) | 15.6 | 12.3 | 12.7 | 13.9 | 12.8 | 10.9 | 16.5 | 17.0 | 13.9 | 13.5 | 15.4 | 18.0 |
| Creatinine (mg/dL) | 1.0 | 1.0 | 1.0 | 1.1 | 1.1 | 1.1 | 1.1 | 1.1 | 0.9 | 1.0 | 1.1 | 1.1 |
| Uric acid (mg/dL) | 5.8 | 5.7 | 5.5 | 6.0 | 5.8 | 5.2 | 5.0 | 6.0 | 5.3 | 5.1 | 5.0 | 5.9 |
| Electrolyte | | | | | | | | | | | | |
| Na (mEq/L) | 142 | 142 | 141 | 140 | 140 | 140 | 142 | 141 | 140 | 140 | 140 | 138 |
| K (mEq/L) | 4.1 | 4.1 | 3.8 | 4.2 | 4.0 | 4.4 | 4.0 | 4.5 | 4.2 | 5.2 | 3.9 | 3.9 |
| Cl (mEq/L) | 109 | 105 | 107 | 104 | 105 | 105 | 108 | 106 | 107 | 107 | 104 | 103 |
| Ca (mEq/L) | 4.4 | 4.4 | 4.6 | 4.8 | 4.4 | 4.5 | 4.6 | 4.7 | 4.3 | 4.5 | 4.5 | 4.8 |
| P (mg/dL) | 3.1 | 2.8 | 3.6 | 3.5 | 3.5 | 3.7 | 3.8 | 3.8 | 3.0 | 3.4 | 3.4 | 3.3 |
| Glucose (mg/dL) | 96 | 101 | 98 | 97 | 92 | 95 | 91 | 97 | 103 | 100 | 89 | 89 |
| Chol-T (mg/dL) | 192 | 184 | 221 | 217 | 189 | 178 | 166 | 148 | 190 | 197 | 132 | 137 |
| Triglyceride (mg/dL) | 122 | 84 | 111 | 74 | 81 | 71 | 80 | 66 | 124 | 91 | 107 | 64 |
| Total bilirubin(mg/dL) | 0.7 | 0.6 | 1.2 | 1.2 | 1.1 | 0.8 | 1.0 | 0.8 | 1.1 | 1.1 | 0.9 | 0.8 |
| Urinalysis | | | | | | | | | | | | |
| pH | 5.8 | 5.8 | 5.6 | 5.6 | 5.6 | 5.6 | 5.2 | 5.2 | 5.8 | 5.6 | 6.0 | 5.8 |
| Protein | — | — | — | — | — | — | — | — | — | — | — | — |
| Glucose | — | — | — | — | — | — | — | — | — | — | — | — |
| Urobilinogen | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± |
| Occult blood | — | — | — | — | — | — | — | — | — | — | — | — |
| Sediment RBC(/F) | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment WBC(/F) | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment epithelium(/F) | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment oxalate crystals | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment casts | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |

B: Before dosing. A: 24 h after dosing.
n.s.: Nothing specially

タは投与量に比例して増加した (Fig. 6)。 $T_{1/2\beta}$ は 6.93~8.41 時間, $V\beta/F$ は 1.98~2.31L/kg と, いずれも投与量によらずほぼ一定であった。

GFLX 200 または 400mg 投与後の唾液中濃度を Table 10 および Fig. 7 に, 薬物速度論的パラメータを Table 11 にそれぞれ示す。唾液中濃度は, それぞれ投与後 2.0, 2.5 時間でピークに達し, C_{max} は 1.55, 3.05 $\mu\text{g}/\text{mL}$,

$AUC_{0-\infty}$ は 11.2, 25.3 $\mu\text{g} \cdot \text{h}/\text{mL}$, $T_{1/2}$ は 9.28, 7.06 時間であった。次に, 唾液中濃度と血清中濃度の相関を Fig. 8 に示す。唾液中濃度は血清中濃度に有意に相関し, その直線の傾きは 0.810 であった。

$$(\text{唾液中濃度}) = 0.810 \cdot (\text{血清中濃度}) - 0.0668,$$

$$\text{相関係数 } 0.857 (P < 0.01)$$

投与後 72 時間までの尿中濃度および累積尿中排泄率を

Table 4-3. Clinical laboratory tests

3) 200 mg single-dose study in fasting volunteers

| Item | Volunteer no. | | | | | | | | | | | | | |
|--|---------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|----------------|-------|-------|--|
| | D1 | | D2 | | D3 | | D4 | | D5 | | | D6 | | |
| | B | A | B | A | B | A | B | A | B | A | A ¹ | B | A | |
| Hematology | | | | | | | | | | | | | | |
| RBC ($\times 10^4/\text{mm}^3$) | 490 | 498 | 569 | 554 | 500 | 512 | 485 | 499 | 507 | 500 | | 480 | 491 | |
| Hb (g/dL) | 15.4 | 15.7 | 16.3 | 16.0 | 15.3 | 15.7 | 15.1 | 15.4 | 15.9 | 15.9 | | 14.3 | 14.8 | |
| WBC ($/\text{mm}^3$) | 5200 | 4900 | 10200 | 9500 | 6000 | 5900 | 4900 | 5300 | 4600 | 4300 | 4100 | 4500 | 3900 | |
| Ht (%) | 45.5 | 45.9 | 48.5 | 47.2 | 45.1 | 45.9 | 44.2 | 45.3 | 46.7 | 45.9 | | 41.5 | 42.3 | |
| Platelet ($\times 10^4/\text{mm}^3$) | 18.3 | 17.8 | 25.2 | 27.1 | 27.4 | 26.6 | 17.8 | 17.3 | 22.8 | 21.9 | | 25.0 | 27.3 | |
| Differential WBC | | | | | | | | | | | | | | |
| Eosinophils (%) | 2 | 3 | 2 | 2 | 4 | 10 | 1 | 4 | 9 | 16 | 8 | 9 | 10 | |
| Basophils (%) | 2 | 0 | 0 | 0 | 2 | 0 | 0 | 3 | 0 | 0 | 1 | 0 | 3 | |
| Neutrophils stabs. (%) | 3 | 5 | 7 | 5 | 10 | 8 | 7 | 3 | 10 | 8 | 7 | 6 | 5 | |
| Neutrophils segs. (%) | 38 | 49 | 51 | 61 | 56 | 55 | 42 | 56 | 34 | 33 | 39 | 42 | 41 | |
| Lymphocytes (%) | 52 | 39 | 34 | 30 | 25 | 21 | 46 | 31 | 39 | 39 | 40 | 41 | 39 | |
| Monocytes (%) | 3 | 4 | 6 | 2 | 3 | 6 | 4 | 3 | 8 | 4 | 5 | 2 | 2 | |
| Blood biochemistry | | | | | | | | | | | | | | |
| GOT (K.U.) | 14 | 14 | 11 | 11 | 12 | 12 | 18 | 14 | 14 | 13 | | 11 | 11 | |
| GPT (K.U.) | 11 | 10 | 12 | 11 | 9 | 8 | 13 | 11 | 15 | 12 | | 8 | 7 | |
| Al-P (K.A.U.) | 4.2 | 4.0 | 5.8 | 5.8 | 7.2 | 7.1 | 4.2 | 4.4 | 6.8 | 6.6 | | 6.9 | 7.1 | |
| LDH (W.U.) | 191 | 190 | 201 | 210 | 191 | 201 | 294 | 271 | 251 | 243 | | 241 | 241 | |
| LAP (G.R.U.) | 133 | 126 | 131 | 131 | 159 | 159 | 130 | 126 | 180 | 174 | | 162 | 166 | |
| γ -GTP (IU/L) | 14 | 14 | 13 | 12 | 10 | 9 | 26 | 22 | 21 | 21 | | 5 | 6 | |
| ChE (Δ pH) | 0.73 | 0.74 | 0.92 | 0.82 | 0.79 | 0.79 | 0.93 | 0.90 | 0.91 | 0.89 | | 0.73 | 0.76 | |
| Total protein (g/dL) | 6.6 | 6.6 | 6.9 | 6.8 | 6.7 | 6.5 | 6.6 | 6.3 | 7.1 | 6.9 | | 6.7 | 6.7 | |
| A/G ratio | 1.8 | 1.9 | 1.8 | 1.8 | 1.9 | 2.0 | 1.6 | 1.7 | 1.8 | 1.9 | | 1.9 | 1.9 | |
| BUN (mg/dL) | 13.1 | 15.3 | 11.1 | 12.9 | 9.5 | 10.6 | 14.4 | 13.8 | 14.7 | 15.3 | | 16.5 | 14.6 | |
| Creatinine (mg/dL) | 1.1 | 1.1 | 1.0 | 0.9 | 0.9 | 0.9 | 1.2 | 1.2 | 1.2 | 1.1 | | 1.1 | 1.1 | |
| Uric acid (mg/dL) | 5.3 | 5.6 | 5.3 | 5.7 | 2.8 | 3.1 | 5.0 | 4.9 | 5.7 | 5.7 | | 4.9 | 5.0 | |
| Electrolyte | | | | | | | | | | | | | | |
| Na (mEq/L) | 141 | 139 | 140 | 140 | 142 | 139 | 143 | 141 | 141 | 140 | | 142 | 141 | |
| K (mEq/L) | 4.3 | 4.0 | 4.6 | 4.5 | 4.7 | 4.4 | 4.2 | 4.4 | 4.5 | 4.2 | | 4.0 | 4.2 | |
| Cl (mEq/L) | 105 | 104 | 104 | 104 | 106 | 104 | 107 | 106 | 105 | 105 | | 107 | 106 | |
| Ca (mEq/L) | 4.8 | 4.6 | 4.9 | 4.9 | 4.8 | 4.7 | 4.7 | 4.5 | 4.9 | 4.9 | | 4.5 | 4.5 | |
| P (mg/dL) | 4.0 | 4.0 | 3.5 | 3.4 | 3.1 | 3.4 | 2.3 | 2.8 | 3.2 | 3.4 | | 3.6 | 3.5 | |
| Glucose (mg/dL) | 91 | 86 | 91 | 88 | 88 | 96 | 96 | 95 | 92 | 92 | | 92 | 96 | |
| Chol-T (mg/dL) | 129 | 128 | 176 | 167 | 112 | 110 | 218 | 214 | 166 | 167 | | 141 | 145 | |
| Triglyceride (mg/dL) | 70 | 47 | 194 | 144 | 63 | 50 | 124 | 130 | 142 | 102 | | 63 | 64 | |
| Total bilirubin(mg/dL) | 1.8 | 1.7 | 0.8 | 0.7 | 0.8 | 0.8 | 1.0 | 0.7 | 0.8 | 0.7 | | 1.1 | 1.1 | |
| Urinalysis | | | | | | | | | | | | | | |
| pH | 5.8 | 5.8 | 5.8 | 5.2 | 6.0 | 6.0 | 5.8 | 5.6 | 5.8 | 5.8 | | 6.4 | 5.8 | |
| Protein | — | — | — | — | — | — | — | — | — | — | | — | — | |
| Glucose | — | — | — | — | — | — | — | — | — | — | | — | — | |
| Urobilinogen | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm | | \pm | \pm | |
| Occult blood | — | — | — | — | — | — | — | — | — | — | | — | — | |
| Sediment RBC(/F) | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | n.s. | n.s. | |
| Sediment WBC(/F) | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | n.s. | n.s. | |
| Sediment epithelium(/F) | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | n.s. | n.s. | |
| Sediment oxalate crystals | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | n.s. | n.s. | |
| Sediment casts | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | | n.s. | n.s. | |

B: Before dosing. A: 24 h after dosing. A¹: 48 h after dosing.

n.s.: Nothing specially

Table 12, 13およびFig. 9に示す。尿中濃度は、GFLX 100, 200, 400および600mg投与後2~4または4~6時間でピークに達し、8~12時間後にはその値の1/5~1/2となった。また、尿中濃度は投与量に比例して上昇し、ピーク濃度はそれぞれ221, 240, 675および953 $\mu\text{g}/\text{mL}$ であった。投与後72時間までの累積尿中排泄率は、それぞれ81.6, 83.4, 83.2および87.9%であった。

400mg投与後の尿中に、グルクロン酸抱合体は認められなかった。400mg投与後72時間までの糞中濃度および累積糞中排泄率をTable 14, 15およびFig. 10に示す。400mg投与における累積糞中排泄率は、5.7%であった。

GFLX 200mgの空腹時単独投与時における、GFLXの血清たん白結合率をFig.11に示す。血清たん白結合率は0.29~2.00 $\mu\text{g}/\text{mL}$ の範囲で血清中濃度によらずほぼ

Table 4-4. Clinical laboratory tests

4) 400 mg single-dose study in fasting volunteers

| Item | Volunteer no. | | | | | | | | | | | | |
|--|---------------|------|------|------|----------------|------|------|------|------|------|------|------|------|
| | E1 | | E2 | | | E3 | | E4 | | E5 | | E6 | |
| | B | A | B | A | A ¹ | B | A | B | A | B | A | B | A |
| Hematology | | | | | | | | | | | | | |
| RBC ($\times 10^4/\text{mm}^3$) | 485 | 469 | 458 | 466 | | 542 | 531 | 502 | 509 | 447 | 433 | 497 | 488 |
| Hb (g/dL) | 14.6 | 14.2 | 14.0 | 14.3 | | 15.8 | 15.6 | 15.7 | 15.7 | 13.9 | 13.5 | 14.7 | 14.5 |
| WBC (/mm ³) | 6700 | 6400 | 4800 | 3500 | | 6800 | 6600 | 3700 | 3500 | 4300 | 4600 | 5200 | 4500 |
| Ht (%) | 44.0 | 42.6 | 41.5 | 42.1 | | 47.1 | 46.3 | 46.1 | 46.6 | 41.3 | 40.4 | 42.1 | 41.7 |
| Platelet ($\times 10^4/\text{mm}^3$) | 31.4 | 30.9 | 25.5 | 25.9 | | 23.4 | 22.9 | 12.1 | 12.0 | 22.7 | 21.7 | 19.5 | 19.1 |
| Differential WBC | | | | | | | | | | | | | |
| Eosinophils (%) | 4 | 4 | 2 | 3 | | 1 | 6 | 8 | 6 | 1 | 0 | 5 | 4 |
| Basophils (%) | 1 | 0 | 2 | 0 | | 1 | 2 | 0 | 1 | 1 | 1 | 0 | 2 |
| Neutrophils stabs. (%) | 4 | 4 | 8 | 4 | | 9 | 11 | 3 | 3 | 6 | 4 | 6 | 7 |
| Neutrophils segs. (%) | 45 | 56 | 60 | 61 | | 47 | 49 | 40 | 43 | 51 | 54 | 48 | 45 |
| Lymphocytes (%) | 38 | 34 | 22 | 30 | | 34 | 26 | 41 | 43 | 32 | 38 | 37 | 37 |
| Monocytes (%) | 8 | 2 | 6 | 2 | | 8 | 6 | 8 | 4 | 9 | 3 | 4 | 5 |
| Blood biochemistry | | | | | | | | | | | | | |
| GOT (K.U.) | 10 | 11 | 13 | 15 | | 15 | 13 | 10 | 11 | 16 | 16 | 10 | 10 |
| GPT (K.U.) | 10 | 7 | 15 | 14 | | 22 | 18 | 9 | 7 | 21 | 19 | 10 | 8 |
| Al-P (K.A.U.) | 7.0 | 6.8 | 5.6 | 5.5 | | 5.5 | 5.1 | 5.3 | 4.9 | 4.7 | 4.8 | 6.2 | 5.8 |
| LDH (W.U.) | 292 | 269 | 312 | 267 | | 231 | 170 | 197 | 178 | 253 | 220 | 288 | 243 |
| LAP (G.R.U.) | 159 | 141 | 145 | 142 | | 141 | 140 | 155 | 141 | 141 | 140 | 117 | 109 |
| γ -GTP (IU/L) | 8 | 8 | 19 | 20 | | 24 | 24 | 22 | 23 | 26 | 25 | 10 | 9 |
| ChE (Δ pH) | 0.79 | 0.76 | 0.85 | 0.88 | | 0.82 | 0.85 | 0.73 | 0.75 | 0.98 | 0.95 | 1.01 | 1.01 |
| Total protein (g/dL) | 7.3 | 7.3 | 6.7 | 6.9 | | 7.1 | 7.2 | 6.9 | 6.9 | 7.1 | 6.9 | 7.1 | 7.1 |
| A/G ratio | 1.6 | 1.7 | 1.5 | 1.6 | | 1.5 | 1.5 | 1.6 | 1.6 | 1.7 | 1.8 | 1.7 | 1.7 |
| BUN (mg/dL) | 14.8 | 14.5 | 12.7 | 14.4 | | 11.2 | 11.0 | 12.3 | 11.3 | 15.7 | 16.3 | 15.7 | 15.1 |
| Creatinine (mg/dL) | 1.1 | 1.1 | 1.2 | 1.1 | | 1.1 | 1.1 | 1.1 | 1.0 | 0.8 | 0.9 | 1.1 | 1.1 |
| Uric acid (mg/dL) | 5.6 | 5.5 | 6.2 | 5.8 | | 5.2 | 5.0 | 5.8 | 6.0 | 5.2 | 4.7 | 8.6 | 8.1 |
| Electrolyte | | | | | | | | | | | | | |
| Na (mEq/L) | 141 | 142 | 141 | 141 | | 140 | 140 | 141 | 140 | 140 | 140 | 142 | 142 |
| K (mEq/L) | 4.6 | 4.5 | 4.2 | 4.0 | | 4.2 | 4.4 | 4.3 | 4.6 | 4.2 | 4.3 | 3.8 | 4.0 |
| Cl (mEq/L) | 105 | 106 | 105 | 106 | | 104 | 104 | 105 | 104 | 104 | 105 | 106 | 106 |
| Ca (mEq/L) | 4.8 | 4.8 | 4.5 | 4.4 | | 4.6 | 4.7 | 4.5 | 4.4 | 4.6 | 4.4 | 4.7 | 4.6 |
| P (mg/dL) | 4.0 | 3.6 | 3.7 | 3.6 | | 2.9 | 2.8 | 4.0 | 3.6 | 3.5 | 3.1 | 3.8 | 3.6 |
| Glucose (mg/dL) | 93 | 103 | 96 | 99 | | 96 | 96 | 95 | 95 | 96 | 98 | 109 | 110 |
| Chol-T (mg/dL) | 193 | 190 | 188 | 197 | | 177 | 181 | 125 | 125 | 158 | 154 | 139 | 133 |
| Triglyceride (mg/dL) | 54 | 45 | 100 | 82 | | 81 | 68 | 60 | 44 | 44 | 39 | 74 | 57 |
| Total bilirubin(mg/dL) | 1.2 | 1.1 | 0.7 | 0.6 | | 0.8 | 0.8 | 1.7 | 1.7 | 1.0 | 0.7 | 1.0 | 0.8 |
| Urinalysis | | | | | | | | | | | | | |
| pH | 5.8 | 5.0 | 5.8 | 5.2 | 5.0 | 6.2 | 5.2 | 5.6 | 5.4 | 5.4 | 5.2 | 5.4 | 5.4 |
| Protein | — | — | — | — | — | — | — | — | — | — | — | — | — |
| Glucose | — | — | — | — | — | — | — | — | — | — | — | — | — |
| Urobilinogen | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± |
| Occult blood | — | — | — | — | — | — | — | — | — | — | — | — | — |
| Sediment RBC(/F) | n.s. | n.s. | n.s. | 1-3 | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment WBC(/F) | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment epithelium(/F) | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment oxalate crystals | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment casts | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |

B: Before dosing. A: 24 h after dosing. A¹: 48 h after dosing.
n.s.: Nothing specially

一定で、その平均値は20%であった。

10. 体内動態に及ぼす食事の影響

GFLX 200mgの食後投与時における血清中濃度をTable 8およびFig. 12に、薬物速度論的パラメータをTable 9にそれぞれ示す。血清中濃度は、投与後1.86時間にピークに達し、C_{max}は1.65 $\mu\text{g}/\text{mL}$ 、T_{1/2 β} は6.52時間と、食事による影響は認められなかった。しかし、AUC_{0- ∞} は

12.7 $\mu\text{g} \cdot \text{h}/\text{mL}$ と、空腹時投与と比べて有意に減少した(P<0.01)。尿中濃度および累積尿中排泄率をTable 12, 13およびFig. 13にそれぞれ示す。投与後72時間までのGFLXの累積尿中排泄率は86.5%と、空腹投与時と比較して有意な差は認められなかった。

11. 体内動態に及ぼすprobenecidの影響

Probenecid合計1.5gの併用時におけるGFLX 200mg

Table 4-5. Clinical laboratory tests

5) 600 mg single-dose study in fasting volunteers

| Item | Volunteer no. | | | | | | | | | | | |
|--|---------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| | F1 | | F2 | | F3 | | F4 | | F5 | | F6 | |
| | B | A | B | A | B | A | B | A | B | A | B | A |
| Hematology | | | | | | | | | | | | |
| RBC ($\times 10^4/\text{mm}^3$) | 472 | 483 | 485 | 477 | 484 | 479 | 501 | 499 | 529 | 531 | 484 | 483 |
| Hb (g/dL) | 14.8 | 15.1 | 15.4 | 15.1 | 14.9 | 14.6 | 15.8 | 15.8 | 15.0 | 14.9 | 14.6 | 14.5 |
| WBC ($/\text{mm}^3$) | 6500 | 6000 | 4900 | 4700 | 5400 | 5500 | 6700 | 6400 | 4900 | 5100 | 4500 | 4600 |
| Ht (%) | 44.1 | 45.2 | 44.2 | 43.5 | 43.6 | 43.3 | 45.4 | 45.4 | 43.8 | 44.0 | 43.0 | 43.2 |
| Platelet ($\times 10^4/\text{mm}^3$) | 26.6 | 27.6 | 17.2 | 17.7 | 19.8 | 20.6 | 25.8 | 24.9 | 23.4 | 24.8 | 19.7 | 19.1 |
| Differential WBC | | | | | | | | | | | | |
| Eosinophils (%) | 1 | 2 | 11 | 8 | 4 | 2 | 4 | 1 | 5 | 5 | 1 | 1 |
| Basophils (%) | 1 | 2 | 0 | 0 | 3 | 1 | 1 | 3 | 4 | 4 | 0 | 2 |
| Neutrophils stabs. (%) | 7 | 5 | 5 | 2 | 7 | 5 | 2 | 4 | 8 | 6 | 2 | 2 |
| Neutrophils segs. (%) | 46 | 46 | 42 | 46 | 44 | 50 | 30 | 51 | 33 | 48 | 38 | 38 |
| Lymphocytes (%) | 40 | 41 | 35 | 39 | 36 | 35 | 54 | 39 | 46 | 31 | 54 | 52 |
| Monocytes (%) | 5 | 4 | 7 | 5 | 6 | 7 | 9 | 2 | 4 | 6 | 5 | 5 |
| Blood biochemistry | | | | | | | | | | | | |
| GOT (K.U.) | 19 | 16 | 16 | 17 | 16 | 15 | 22 | 18 | 15 | 14 | 19 | 17 |
| GPT (K.U.) | 22 | 21 | 20 | 20 | 22 | 20 | 20 | 19 | 21 | 20 | 24 | 24 |
| Al-P (K.A.U.) | 6.9 | 7.5 | 5.2 | 5.0 | 7.3 | 7.3 | 6.0 | 6.2 | 5.3 | 5.3 | 4.8 | 4.9 |
| LDH (W.U.) | 260 | 246 | 226 | 212 | 265 | 243 | 293 | 260 | 247 | 224 | 237 | 211 |
| LAP (G.R.U.) | 171 | 186 | 121 | 122 | 131 | 135 | 154 | 154 | 147 | 147 | 137 | 139 |
| γ -GTP (IU/L) | 25 | 27 | 14 | 13 | 13 | 14 | 13 | 13 | 21 | 21 | 49 | 49 |
| ChE (Δ pH) | 0.84 | 0.91 | 1.05 | 1.05 | 0.90 | 0.93 | 0.69 | 0.72 | 1.02 | 1.02 | 0.77 | 0.76 |
| Total protein (g/dL) | 6.6 | 6.8 | 6.8 | 6.4 | 7.3 | 7.1 | 6.7 | 6.7 | 7.2 | 7.0 | 6.6 | 6.8 |
| A/G ratio | 1.8 | 1.7 | 2.0 | 1.9 | 1.9 | 2.0 | 1.6 | 1.7 | 1.6 | 1.6 | 1.9 | 1.8 |
| BUN (mg/dL) | 12.5 | 13.7 | 22.2 | 21.7 | 17.0 | 17.1 | 14.7 | 13.2 | 13.9 | 12.4 | 16.2 | 18.8 |
| Creatinine (mg/dL) | 1.2 | 1.2 | 1.1 | 1.2 | 1.1 | 1.2 | 1.1 | 1.1 | 1.2 | 1.2 | 1.1 | 1.2 |
| Uric acid (mg/dL) | 5.8 | 5.1 | 5.7 | 5.5 | 6.1 | 5.7 | 6.0 | 5.4 | 6.2 | 6.0 | 5.8 | 5.2 |
| Electrolyte | | | | | | | | | | | | |
| Na (mEq/L) | 142 | 141 | 143 | 142 | 142 | 141 | 142 | 140 | 141 | 140 | 141 | 140 |
| K (mEq/L) | 3.9 | 4.1 | 4.2 | 4.4 | 4.3 | 4.0 | 4.6 | 4.2 | 4.7 | 4.3 | 4.1 | 4.2 |
| Cl (mEq/L) | 107 | 106 | 109 | 108 | 107 | 106 | 108 | 106 | 105 | 105 | 107 | 106 |
| Ca (mEq/L) | 4.0 | 4.3 | 4.2 | 4.3 | 4.3 | 4.5 | 4.2 | 4.3 | 4.2 | 4.2 | 4.1 | 4.3 |
| P (mg/dL) | 3.9 | 3.7 | 3.2 | 2.9 | 3.2 | 3.3 | 3.8 | 3.8 | 2.6 | 2.6 | 3.3 | 3.6 |
| Glucose (mg/dL) | 88 | 92 | 91 | 88 | 97 | 93 | 89 | 90 | 93 | 95 | 106 | 101 |
| Chol-T (mg/dL) | 194 | 197 | 161 | 151 | 180 | 181 | 184 | 185 | 194 | 192 | 222 | 219 |
| Triglyceride (mg/dL) | 131 | 129 | 193 | 101 | 78 | 47 | 77 | 59 | 106 | 89 | 92 | 66 |
| Total bilirubin(mg/dL) | 0.9 | 0.6 | 0.8 | 0.7 | 0.8 | 0.6 | 0.8 | 0.7 | 1.0 | 0.9 | 1.3 | 1.1 |
| Urinalysis | | | | | | | | | | | | |
| pH | 5.6 | 5.4 | 5.6 | 5.4 | 5.8 | 5.2 | 5.8 | 5.4 | 5.4 | 5.2 | 5.8 | 5.4 |
| Protein | - | - | - | - | - | - | - | - | - | - | - | - |
| Glucose | - | - | - | - | - | - | - | - | - | - | - | - |
| Urobilinogen | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm |
| Occult blood | - | - | - | - | - | - | - | - | - | - | - | - |
| Sediment RBC(/F) | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment WBC(/F) | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment epithelium(/F) | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment oxalate crystals | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment casts | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |

B: Before dosing. A: 24 h after dosing.

n.s.: Nothing specially

投与後の血清中濃度を Table 8 および Fig. 14 に、薬物速度論的パラメータを Table 9 および 16 にそれぞれ示す。Probenecid 併用時における血清中濃度は、GFLX 投与後 1.86 時間でピークに達し、Cmax は 1.79 $\mu\text{g}/\text{mL}$ であった。AUC_{0- ∞} は 20.6 $\mu\text{g} \cdot \text{h}/\text{mL}$ 、T_{1/2 β} は 10.2 時間であり、それぞれ単独投与時に比べて有意に増加又は延長した (それぞれ P < 0.01, 0.05)。一方、併用により、

CL_T/F は 235 から 164 mL/min、CL_R は 197 から 122 mL/min、fu は 0.815 から 0.757、CL_{R, int} は 242 から 161 mL/min、排泄比は 2.28 から 1.35 へと、それぞれ単独投与時に比べて有意に減少した (P < 0.01)。尿中濃度および累積尿中排泄率を Table 12, 13 および Fig. 15 にそれぞれ示す。投与後 72 時間までの累積尿中排泄率は 74.9% と、単独投与時に比べて有意に減少した (P < 0.05)。

Table 4-6. Clinical laboratory tests

6) 200 mg single-dose study in non-fasting volunteers

| Item | Volunteer no. | | | | | | | | | | | |
|--|---------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| | G1 | | G2 | | G3 | | G4 | | G5 | | G6 | |
| | B | A | B | A | B | A | B | A | B | A | B | A |
| Hematology | | | | | | | | | | | | |
| RBC ($\times 10^4/\text{mm}^3$) | 520 | 494 | 540 | 525 | 535 | 519 | 506 | 488 | 499 | 494 | 501 | 493 |
| Hb (g/dL) | 16.4 | 15.4 | 15.4 | 15.2 | 16.3 | 16.0 | 15.8 | 15.3 | 15.6 | 15.7 | 15.0 | 14.9 |
| WBC ($/\text{mm}^3$) | 5100 | 5400 | 9600 | 10500 | 4900 | 5800 | 5500 | 5400 | 5100 | 5300 | 5100 | 5100 |
| Ht (%) | 48.1 | 45.6 | 46.0 | 45.3 | 48.0 | 46.7 | 45.9 | 44.3 | 45.8 | 45.4 | 43.3 | 42.5 |
| Platelet ($\times 10^4/\text{mm}^3$) | 18.6 | 19.1 | 24.4 | 25.8 | 30.1 | 29.2 | 18.5 | 17.2 | 19.0 | 19.2 | 27.5 | 27.5 |
| Differential WBC | | | | | | | | | | | | |
| Eosinophils (%) | 2 | 2 | 2 | 1 | 3 | 8 | 3 | 2 | 18 | 10 | 16 | 11 |
| Basophils (%) | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 1 | 1 | 3 | 2 |
| Neutrophils stabs. (%) | 6 | 6 | 4 | 5 | 10 | 8 | 8 | 8 | 10 | 8 | 5 | 3 |
| Neutrophils segs. (%) | 49 | 44 | 52 | 53 | 49 | 50 | 48 | 45 | 39 | 42 | 40 | 39 |
| Lymphocytes (%) | 39 | 44 | 37 | 35 | 31 | 31 | 37 | 40 | 28 | 35 | 31 | 40 |
| Monocytes (%) | 3 | 4 | 5 | 5 | 7 | 2 | 4 | 3 | 4 | 4 | 5 | 5 |
| Blood biochemistry | | | | | | | | | | | | |
| GOT (K.U.) | 16 | 13 | 14 | 13 | 13 | 12 | 18 | 14 | 23 | 21 | 14 | 12 |
| GPT (K.U.) | 10 | 11 | 13 | 14 | 11 | 11 | 18 | 16 | 29 | 29 | 9 | 10 |
| Al-P (K.A.U.) | 4.4 | 4.0 | 5.5 | 5.6 | 7.8 | 7.4 | 4.3 | 4.2 | 6.8 | 6.8 | 7.6 | 7.6 |
| LDH (W.U.) | 203 | 184 | 217 | 218 | 198 | 197 | 313 | 268 | 296 | 263 | 261 | 227 |
| LAP (G.R.U.) | 144 | 125 | 146 | 151 | 170 | 174 | 143 | 142 | 199 | 189 | 163 | 162 |
| γ -GTP (IU/L) | 17 | 16 | 15 | 16 | 11 | 12 | 39 | 39 | 29 | 30 | 6 | 7 |
| ChE (Δ pH) | 0.80 | 0.74 | 1.15 | 1.10 | 0.84 | 0.82 | 1.00 | 0.96 | 0.99 | 0.99 | 0.81 | 0.79 |
| Total protein (g/dL) | 7.1 | 6.5 | 6.8 | 6.6 | 7.1 | 6.7 | 7.0 | 6.5 | 7.0 | 6.9 | 6.8 | 6.5 |
| A/G ratio | 1.7 | 1.8 | 1.7 | 1.8 | 1.8 | 1.8 | 1.7 | 1.7 | 1.9 | 1.9 | 1.8 | 1.8 |
| BUN (mg/dL) | 12.9 | 13.7 | 9.8 | 9.4 | 8.2 | 11.5 | 13.8 | 13.2 | 15.3 | 12.3 | 12.4 | 12.5 |
| Creatinine (mg/dL) | 1.1 | 1.1 | 0.9 | 0.9 | 0.9 | 0.8 | 1.2 | 1.2 | 1.1 | 1.0 | 1.0 | 1.0 |
| Uric acid (mg/dL) | 5.8 | 5.6 | 6.1 | 5.7 | 3.0 | 3.2 | 6.4 | 5.7 | 6.0 | 5.5 | 4.8 | 4.9 |
| Electrolyte | | | | | | | | | | | | |
| Na (mEq/L) | 139 | 139 | 140 | 140 | 139 | 139 | 140 | 140 | 139 | 140 | 140 | 140 |
| K (mEq/L) | 4.5 | 4.3 | 4.3 | 4.6 | 4.4 | 4.6 | 4.4 | 4.1 | 4.5 | 4.5 | 4.1 | 4.1 |
| Cl (mEq/L) | 103 | 103 | 105 | 105 | 104 | 104 | 106 | 106 | 105 | 105 | 105 | 106 |
| Ca (mEq/L) | 4.7 | 4.5 | 4.8 | 4.7 | 4.8 | 4.7 | 4.9 | 4.6 | 4.7 | 4.6 | 4.5 | 4.5 |
| P (mg/dL) | 4.7 | 4.3 | 3.8 | 3.3 | 3.4 | 3.5 | 2.7 | 2.7 | 3.2 | 3.1 | 3.5 | 3.7 |
| Glucose (mg/dL) | 94 | 93 | 90 | 94 | 92 | 97 | 94 | 95 | 93 | 92 | 104 | 100 |
| Chol-T (mg/dL) | 170 | 157 | 179 | 177 | 131 | 135 | 240 | 231 | 197 | 208 | 159 | 166 |
| Triglyceride (mg/dL) | 111 | 70 | 197 | 154 | 135 | 94 | 175 | 155 | 173 | 108 | 96 | 70 |
| Total bilirubin (mg/dL) | 2.0 | 1.2 | 0.8 | 0.6 | 0.7 | 0.6 | 1.1 | 0.8 | 0.8 | 0.6 | 0.9 | 0.8 |
| Urinalysis | | | | | | | | | | | | |
| pH | 5.8 | 5.6 | 5.6 | 5.6 | 5.8 | 5.8 | 5.4 | 5.4 | 5.8 | 5.6 | 5.8 | 5.4 |
| Protein | — | — | — | — | — | — | — | — | — | — | — | — |
| Glucose | — | — | — | — | — | — | — | — | — | — | — | — |
| Urobilinogen | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm | \pm |
| Occult blood | — | — | — | — | — | — | — | — | — | — | — | — |
| Sediment RBC(/F) | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment WBC(/F) | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment epithelium(/F) | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment oxalate crystals | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Sediment casts | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |

B: Before dosing, A: 24 h after dosing.

n.s.: Nothing specially

Ⅲ. 考 察

試験期間を通じて、自覚および他覚症状、血圧、脈拍数、体温、心電図、血液学的検査、血液生化学検査、尿検査および平衡機能検査において、また、400および600mgで実施した聴力検査、眼科的検査および平衡機能検査において、GFLXの投与と関連のある異常所見は認められなかった。一方、GFLXと同系薬のciprofloxacin⁷⁾

のように薬剤投与後の尿中排泄率が高く、かつ尿中溶解度が低い場合、尿中に薬物の結晶が析出する可能性が考えられる。そこで、我々はGFLX400mgおよび600mgによる結晶尿の可能性について検討した。このうち、GFLX 600mgを単回経口投与された被験者1例(被験者No. F2)において、1,500 $\mu\text{g}/\text{mL}$ 以上の高い尿中濃度が観察された。しかし、本試験における光学顕微鏡を用

Table 4-7. Clinical laboratory tests

7) Probenecid interaction study in fasting volunteers

| Item | Volunteer no. | | | | | | | | | | | | | | |
|---|---------------|------|----------------|----------------|------|------|------|------|------|------|------|------|------|------|----------------|
| | H1 | | | | H2 | | H3 | | H4 | | H5 | | H6 | | |
| | B | A | A ¹ | A ² | B | A | B | A | B | A | B | A | B | A | A ¹ |
| Hematology | | | | | | | | | | | | | | | |
| RBC (×10 ⁴ /mm ³) | 498 | 484 | | | 540 | 542 | 520 | 512 | 512 | 516 | 494 | 499 | 490 | 515 | |
| Hb (g/dL) | 15.7 | 15.3 | | | 15.7 | 15.8 | 16.1 | 15.9 | 15.9 | 16.4 | 15.6 | 16.0 | 14.6 | 15.7 | |
| WBC (/mm ³) | 4600 | 5000 | | | 9400 | 9900 | 5800 | 6600 | 5100 | 5400 | 3800 | 4900 | 4200 | 5400 | |
| Ht (%) | 45.8 | 44.6 | | | 45.5 | 45.8 | 46.0 | 45.3 | 45.6 | 46.1 | 45.2 | 45.6 | 41.9 | 43.5 | |
| Platelet (×10 ⁴ /mm ³) | 18.2 | 18.7 | | | 25.1 | 27.8 | 30.5 | 29.4 | 18.8 | 19.7 | 18.8 | 19.1 | 26.7 | 28.0 | |
| Differential WBC | | | | | | | | | | | | | | | |
| Eosinophils (%) | 2 | 2 | | | 4 | 2 | 7 | 4 | 3 | 5 | 12 | 10 | 12 | 4 | |
| Basophils (%) | 0 | 1 | | | 1 | 0 | 0 | 0 | 3 | 0 | 1 | 0 | 2 | 0 | |
| Neutrophils stabs. (%) | 4 | 3 | | | 9 | 5 | 12 | 9 | 6 | 10 | 3 | 9 | 2 | 8 | |
| Neutrophils segs. (%) | 40 | 45 | | | 53 | 58 | 45 | 51 | 39 | 51 | 28 | 37 | 45 | 53 | |
| Lymphocytes (%) | 48 | 44 | | | 27 | 31 | 27 | 29 | 43 | 29 | 47 | 38 | 32 | 31 | |
| Monocytes (%) | 6 | 5 | | | 6 | 4 | 9 | 7 | 6 | 5 | 9 | 6 | 7 | 4 | |
| Blood biochemistry | | | | | | | | | | | | | | | |
| GOT (K.U.) | 15 | 14 | | | 12 | 11 | 12 | 12 | 14 | 13 | 13 | 13 | 10 | 10 | |
| GPT (K.U.) | 13 | 11 | | | 11 | 10 | 8 | 8 | 12 | 11 | 14 | 13 | 8 | 6 | |
| Al-P (K.A.U.) | 4.3 | 4.0 | | | 5.8 | 5.9 | 6.6 | 6.6 | 4.6 | 4.5 | 7.1 | 6.9 | 6.8 | 7.1 | |
| LDH (W.U.) | 214 | 176 | | | 252 | 230 | 221 | 199 | 267 | 260 | 259 | 236 | 217 | 223 | |
| LAP (G.R.U.) | 138 | 130 | | | 137 | 133 | 167 | 163 | 134 | 134 | 180 | 171 | 156 | 168 | |
| γ-GTP (IU/L) | 18 | 17 | | | 14 | 14 | 13 | 12 | 32 | 32 | 19 | 17 | 7 | 7 | |
| ChE (ΔpH) | 0.83 | 0.76 | | | 1.08 | 1.16 | 0.86 | 0.87 | 0.96 | 0.96 | 0.87 | 0.90 | 0.76 | 0.81 | |
| Total protein (g/dL) | 7.2 | 6.8 | | | 7.0 | 7.2 | 6.7 | 6.8 | 6.7 | 6.8 | 7.0 | 7.1 | 6.4 | 7.0 | |
| A/G ratio | 1.6 | 1.7 | | | 1.7 | 1.7 | 1.9 | 1.8 | 1.8 | 1.7 | 1.8 | 1.8 | 1.9 | 1.8 | |
| BUN (mg/dL) | 18.0 | 17.1 | | | 13.8 | 11.3 | 13.3 | 13.6 | 16.4 | 15.4 | 13.5 | 13.1 | 14.3 | 15.4 | |
| Creatinine (mg/dL) | 1.1 | 1.1 | | | 0.9 | 1.0 | 0.9 | 0.9 | 1.1 | 1.2 | 1.0 | 1.1 | 1.0 | 1.1 | |
| Uric acid (mg/dL) | 6.0 | 3.5 | | | 6.6 | 3.5 | 3.4 | 2.9 | 5.0 | 3.5 | 5.1 | 3.4 | 5.0 | 4.0 | |
| Electrolyte | | | | | | | | | | | | | | | |
| Na (mEq/L) | 141 | 140 | | | 141 | 140 | 140 | 140 | 141 | 141 | 141 | 141 | 141 | 140 | |
| K (mEq/L) | 4.8 | 4.3 | | | 4.4 | 4.5 | 4.4 | 4.4 | 4.3 | 4.3 | 4.6 | 4.6 | 3.9 | 4.5 | |
| Cl (mEq/L) | 104 | 104 | | | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 106 | 105 | |
| Ca (mEq/L) | 4.8 | 4.6 | | | 4.8 | 4.9 | 4.7 | 4.6 | 4.8 | 4.8 | 4.8 | 4.8 | 4.4 | 4.6 | |
| P (mg/dL) | 4.7 | 4.6 | | | 3.8 | 3.1 | 3.4 | 3.1 | 2.9 | 3.3 | 3.1 | 3.5 | 4.0 | 4.0 | |
| Glucose (mg/dL) | 94 | 94 | | | 91 | 89 | 93 | 98 | 88 | 91 | 91 | 91 | 93 | 86 | |
| Chol-T (mg/dL) | 158 | 155 | | | 178 | 181 | 129 | 127 | 241 | 249 | 147 | 150 | 152 | 165 | |
| Triglyceride (mg/dL) | 84 | 71 | | | 113 | 142 | 63 | 76 | 126 | 130 | 62 | 82 | 51 | 61 | |
| Total bilirubin(mg/dL) | 1.3 | 1.9 | 1.4 | 0.9 | 0.9 | 1.2 | 0.6 | 0.9 | 1.0 | 1.2 | 0.8 | 0.8 | 1.0 | 1.7 | 1.1 |
| Urinalysis | | | | | | | | | | | | | | | |
| pH | 5.8 | 5.8 | | | 5.6 | 5.6 | 5.8 | 5.4 | 5.6 | 5.6 | 6.2 | 5.8 | 5.6 | 5.6 | |
| Protein | — | — | | | — | — | — | — | — | — | — | — | — | — | |
| Glucose | — | — | | | — | — | — | — | — | — | — | — | — | — | |
| Urobilinogen | ± | ± | | | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | |
| Occult blood | — | — | | | — | — | — | — | — | — | — | — | — | — | |
| Sediment RBC(/F) | n.s. | n.s. | | | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | |
| Sediment WBC(/F) | n.s. | n.s. | | | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | |
| Sediment epithelium(/F) | n.s. | n.s. | | | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | |
| Sediment oxalate crystals | n.s. | n.s. | | | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | |
| Sediment casts | n.s. | n.s. | | | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | |

B: Before dosing. A: 24 h after dosing. A¹: 48 h after dosing. A²: 72 h after dosing.

n.s.: Nothing specially

いた観察により、本薬由来の結晶は認められなかった。これらの事実から、本薬の健常人における安全性は高いものと考えられた。

GFLXは速やかに吸収され、投与後1~2時間にCmaxに達した。未変化体の尿中排泄率が81.6~87.9%と高いことから、本薬が消化管から良好に吸収されることが示唆された。GFLXのCmaxは、norfloxacin⁸、enoxacin⁹、

tosufloxacin¹⁰、ciprofloxacin¹¹およびsparfloxacin¹²より高く、ofloxacin¹³、lomefloxacin¹⁴、floxacin¹⁵、levofloxacin¹⁶と同等であった。AUC_{0-∞}は、floxacin¹⁵より小さく、ofloxacin¹³、lomefloxacin¹⁴、levofloxacin¹⁶と同等であった。T_{1/2 β}は、6.93~8.41時間と比較的長く、lomefloxacin¹⁴やtemafloxacin¹⁷と同等であった。つぎに、本薬の体内動態に及ぼす食事

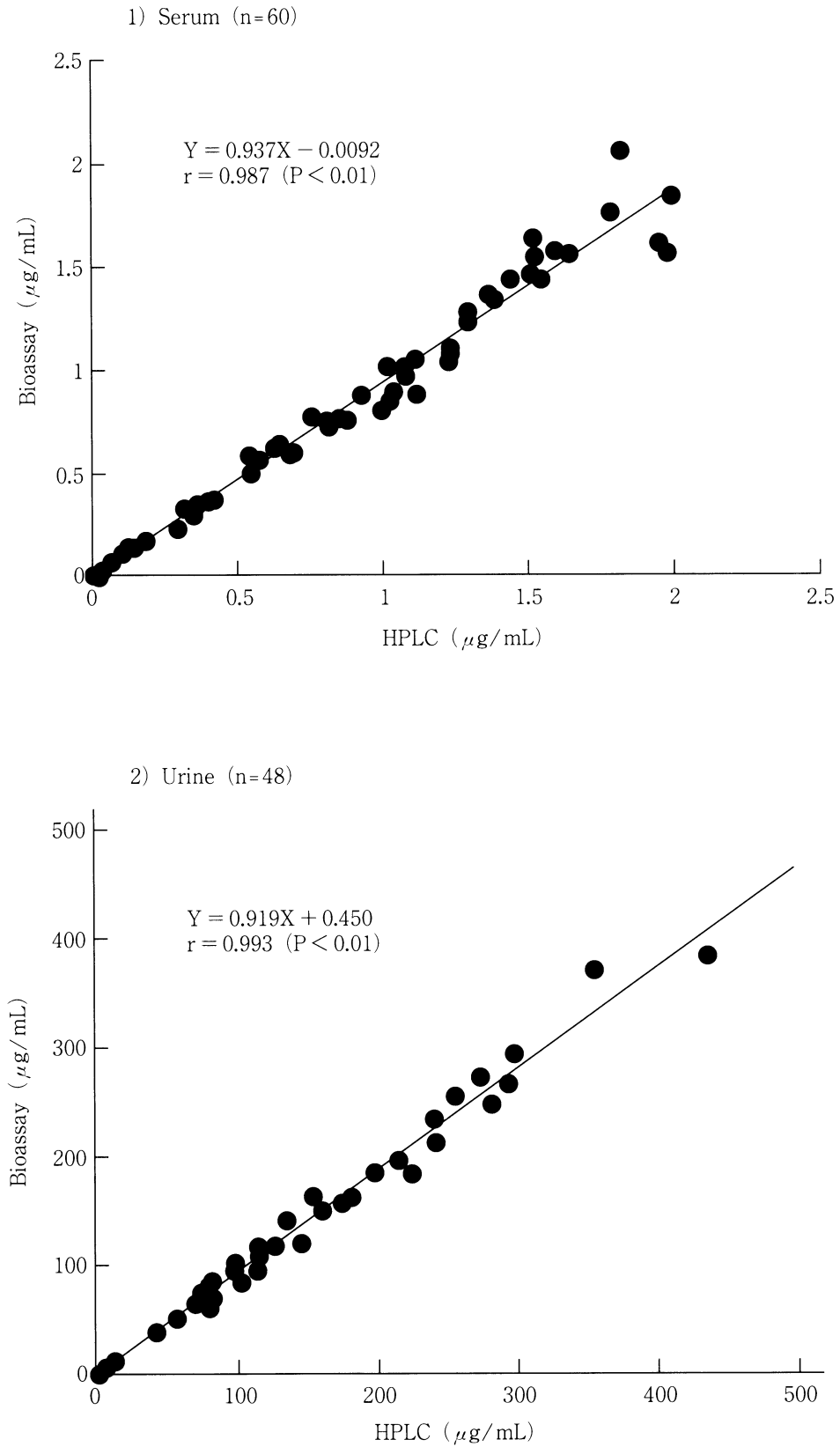


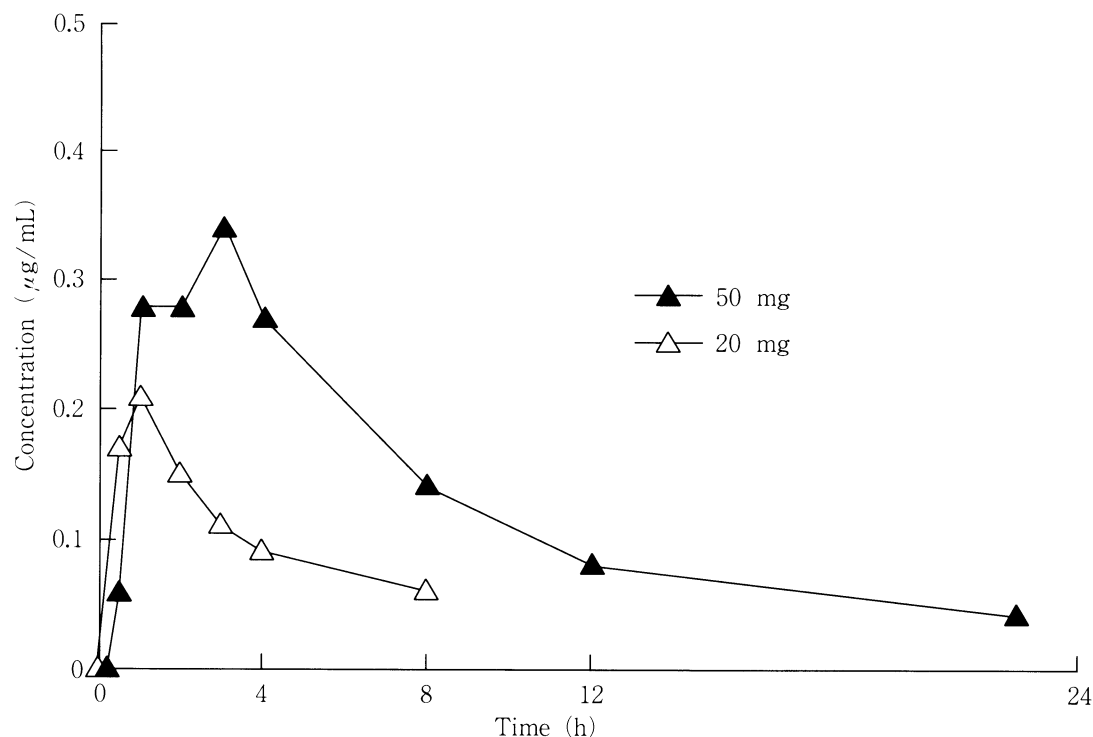
Fig. 2. Correlation between concentrations as determined by HPLC and by bioassay

Table 5. Concentrations of gatifloxacin in serum following a single oral administration of 20 or 50 mg in Step 1

| Dose (mg) | Volunteer no. | Concentration ($\mu\text{g}/\text{mL}$) | | | | | | | | | |
|-----------|---------------|---|-------|------|------|------|------|------|------|------|-------|
| | | Before dosing | 0.25h | 0.5h | 1h | 2h | 3h | 4h | 8h | 12h | 22.5h |
| 20 | A 1 | n.d. | — | 0.33 | 0.23 | 0.15 | 0.11 | 0.09 | 0.06 | — | — |
| | A 2 | n.d. | — | n.d. | 0.19 | 0.15 | 0.11 | 0.09 | 0.05 | — | — |
| | Mean | | | 0.17 | 0.21 | 0.15 | 0.11 | 0.09 | 0.06 | | |
| 50 | B 1 | n.d. | n.d. | 0.09 | 0.23 | 0.32 | 0.38 | 0.30 | 0.16 | 0.09 | 0.04 |
| | B 2 | n.d. | n.d. | 0.03 | 0.33 | 0.24 | 0.29 | 0.24 | 0.12 | 0.07 | 0.03 |
| | Mean | | | 0.06 | 0.28 | 0.28 | 0.34 | 0.27 | 0.14 | 0.08 | 0.04 |

n.d. : Not detected ($<0.01 \mu\text{g}/\text{mL}$)

— : Not tested

Fig. 3. Concentrations of gatifloxacin in serum following a single oral administration of 20 or 50 mg in fasting volunteers (means, $n=2$)

の影響を、軽食後にGFLXを単回投与し検討した。食後投与によりその $AUC_{0-\infty}$ が減少したが、 CL_r/F を除くその他の薬物速度論的パラメータに変化はみられなかった。このことから、本薬の体内動態に及ぼす食事の影響は少ないと考えられた。

本試験における尿中排泄の結果より、GFLXのF値(吸収率)は約1と考えられることから、 $V\beta/F$ は $V\beta$ に相

当し、このとき $V\beta$ は1.98~2.31 L/kgと算出される。本薬の $V\beta$ は、Sörgelら¹⁸⁾により報告されている ofloxacin, fleroxacinおよびpefloxacinにおける値より大きく、lomefloxacinおよびciprofloxacinと同等と推察される。このことは、本薬の良好な組織移行性を示唆するものと考えられる。

一般に、キノロン薬は唾液中へ良好に移行し、その唾

Table 6. Concentrations of gatifloxacin in urine following a single oral administration of 20 or 50 mg in Step 1

| Dose (mg) | Volunteer no. | Concentration ($\mu\text{g/mL}$) | | |
|-----------|---------------|------------------------------------|-------|--------|
| | | Before dosing | 0-24h | 24-48h |
| 20 | A 1 | n.d. | 15.2 | 1.0 |
| | A 2 | n.d. | 12.5 | 0.4 |
| | Mean | | 13.9 | 0.7 |
| 50 | B 1 | n.d. | 24.1 | 2.8 |
| | B 2 | n.d. | 29.6 | 1.6 |
| | Mean | | 26.9 | 2.2 |

n.d.: Not detected ($<0.1 \mu\text{g/mL}$)

Table 7. Cumulative recovery of gatifloxacin in urine following a single oral administration of 20 or 50 mg in Step 1

| Dose (mg) | Volunteer no. | Cumulative recovery (% of dose) | |
|-----------|---------------|---------------------------------|-------|
| | | 0-24h | 0-48h |
| 20 | A 1 | 64.2 | 70.2 |
| | A 2 | 73.0 | 75.5 |
| | Mean | 68.6 | 72.9 |
| 50 | B 1 | 82.9 | 88.2 |
| | B 2 | 82.9 | 87.6 |
| | Mean | 82.9 | 87.9 |

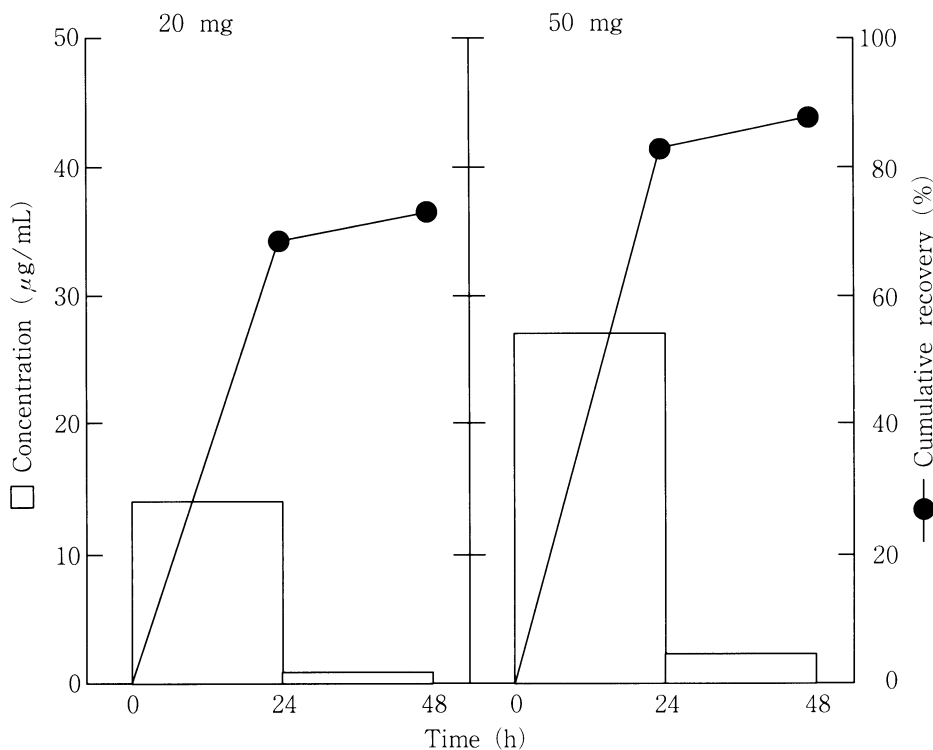


Fig. 4. Concentrations and cumulative recovery of gatifloxacin in urine following a single oral administration of 20 or 50 mg in fasting volunteers (means, $n=2$)

液中濃度は、血清中濃度に良く相関することが知られている¹⁹⁾。このうち、fleroxacin, tosufloxacin, amifloxacinの唾液中濃度は、それぞれの血清又は血漿中濃度の30~40%、またsparfloxacin, levofloxacin, temafloxacinでは70~90%であるとされる¹⁹⁾。本試験において、GFLXの唾液中濃度は血清中濃度と相関し、その濃度は血清中濃度の約80%であり (Fig. 8)、良好

な唾液中移行が示された。唾液中濃度の測定は、本薬のtherapeutic drug monitoring (TDM) としての観点からも有用であると推察された。

高い未変化体の尿中排泄の結果から、GFLXはヒトにおいてほとんど代謝されないものと考えられる。その排泄のプロフィールは、lomefloxacin¹¹⁾と同様であり、未変化体の尿中排泄率は、同系薬の中でも顕著に高いも

Table 8. Concentrations of gatifloxacin in serum following a single oral administration of 100, 200, 400, or 600 mg in Step 2

| Dose (mg) | Volunteer no. | Concentration ($\mu\text{g}/\text{mL}$) | | | | | | | | | | |
|-----------------------|---------------|---|------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| | | Before dosing | 0.5h | 1h | 2h | 3h | 4h | 6h | 8h | 12h | 24h | 48h |
| 100 (Fasting) | C 1 | n.d. | 0.31 | 0.43 | 0.97 | 0.76 | 0.62 | 0.48 | 0.38 | 0.23 | 0.07 | n.d. |
| | C 2 | n.d. | n.d. | 1.07 | 0.65 | 0.70 | 0.56 | 0.41 | 0.31 | 0.19 | 0.06 | n.d. |
| | C 3 | n.d. | 0.08 | 0.49 | 0.87 | 0.75 | 0.67 | 0.50 | 0.39 | 0.21 | 0.06 | n.d. |
| | C 4 | n.d. | 0.04 | 0.62 | 0.98 | 0.74 | 0.63 | 0.48 | 0.37 | 0.23 | 0.08 | n.d. |
| | C 5 | n.d. | 0.39 | 0.52 | 0.55 | 0.49 | 0.41 | 0.32 | 0.23 | 0.13 | 0.03 | n.d. |
| | C 6 | n.d. | 0.02 | 0.24 | 0.78 | 0.59 | 0.50 | 0.37 | 0.27 | 0.15 | 0.04 | n.d. |
| | Mean S.D. | | | 0.14 0.17 | 0.56 0.28 | 0.80 0.17 | 0.67 0.11 | 0.57 0.10 | 0.43 0.07 | 0.33 0.07 | 0.19 0.04 | 0.06 0.02 |
| 200 (Fasting) | D 1 | n.d. | 1.23 | 1.53 | 1.37 | 1.03 | 0.86 | 0.68 | 0.55 | 0.32 | 0.11 | 0.02 |
| | D 2 | n.d. | 0.93 | 2.00 | 1.79 | 1.30 | 1.08 | 0.81 | 0.63 | 0.36 | 0.10 | 0.02 |
| | D 3 | n.d. | 1.30 | 1.55 | 1.65 | 1.24 | 1.04 | 0.76 | 0.54 | 0.29 | 0.06 | n.d. |
| | D 4 | n.d. | 0.34 | 0.58 | 1.09 | 1.12 | 1.02 | 0.86 | 0.69 | 0.42 | 0.14 | 0.02 |
| | D 5 | n.d. | 1.60 | 1.83 | 1.53 | 1.24 | 1.12 | 0.82 | 0.65 | 0.40 | 0.12 | 0.02 |
| | D 6 | n.d. | 1.52 | 1.99 | 1.96 | 1.45 | 1.39 | 1.00 | 0.88 | 0.55 | 0.18 | 0.03 |
| | Mean S.D. | | | 1.15 0.46 | 1.58 0.53 | 1.57 0.31 | 1.23 0.15 | 1.09 0.17 | 0.82 0.11 | 0.66 0.12 | 0.39 0.09 | 0.12 0.04 |
| 400 (Fasting) | E 1 | n.d. | 0.02 | 0.27 | 2.15 | 3.13 | 2.53 | 1.98 | 1.55 | 1.02 | 0.28 | 0.03 |
| | E 2 | n.d. | 0.05 | 3.09 | 4.12 | 3.74 | 3.07 | 2.36 | 1.90 | 1.18 | 0.33 | 0.04 |
| | E 3 | n.d. | 1.05 | 1.83 | 3.15 | 2.84 | 2.63 | 1.78 | 1.75 | 1.09 | 0.36 | 0.04 |
| | E 4 | n.d. | 1.31 | 2.44 | 3.05 | 2.50 | 2.18 | 1.78 | 1.50 | 0.85 | 0.33 | 0.04 |
| | E 5 | n.d. | 0.46 | 1.08 | 3.85 | 3.28 | 2.49 | 1.62 | 1.25 | 0.74 | 0.19 | 0.02 |
| | E 6 | n.d. | 0.34 | 3.14 | 2.80 | 2.68 | 2.49 | 1.74 | 1.46 | 0.90 | 0.26 | 0.03 |
| | Mean S.D. | | | 0.54 0.53 | 1.98 1.14 | 3.19 0.71 | 3.03 0.45 | 2.57 0.29 | 1.88 0.26 | 1.57 0.23 | 0.96 0.16 | 0.29 0.06 |
| 600 (Fasting) | F 1 | n.d. | 0.02 | 1.44 | 3.47 | 6.52 | 4.62 | 3.43 | 2.79 | 1.73 | 0.46 | 0.06 |
| | F 2 | n.d. | 1.91 | 6.89 | 5.67 | 4.56 | 3.95 | 3.28 | 2.39 | 1.51 | 0.57 | 0.07 |
| | F 3 | n.d. | 0.21 | 2.00 | 5.86 | 4.12 | 3.61 | 2.88 | 2.43 | 1.57 | 0.46 | 0.06 |
| | F 4 | n.d. | 2.21 | 4.64 | 5.31 | 4.35 | 3.66 | 3.03 | 2.31 | 1.40 | 0.47 | 0.07 |
| | F 5 | n.d. | 0.06 | 0.46 | 1.32 | 2.83 | 3.87 | 3.36 | 2.89 | 2.08 | 0.82 | 0.13 |
| | F 6 | n.d. | 1.83 | 4.80 | 5.32 | 4.11 | 3.67 | 2.91 | 2.49 | 1.58 | 0.54 | 0.08 |
| | Mean S.D. | | | 1.04 1.04 | 3.37 2.45 | 4.49 1.77 | 4.42 1.20 | 3.90 0.38 | 3.15 0.24 | 2.55 0.23 | 1.65 0.24 | 0.55 0.14 |
| 200 (Non-fasting) | G 1 | n.d. | 0.10 | 1.30 | 1.39 | 1.13 | 0.92 | 0.68 | 0.53 | 0.32 | 0.10 | 0.01 |
| | G 2 | n.d. | n.d. | 0.09 | 0.59 | 1.66 | 1.35 | 0.84 | 0.64 | 0.35 | 0.09 | 0.01 |
| | G 3 | n.d. | 0.14 | 0.86 | 1.52 | 1.29 | 1.04 | 0.60 | 0.55 | 0.29 | 0.06 | n.d. |
| | G 4 | n.d. | 0.38 | 1.81 | 1.30 | 1.11 | 0.93 | 0.71 | 0.56 | 0.33 | 0.11 | 0.02 |
| | G 5 | n.d. | n.d. | 0.17 | 1.05 | 1.62 | 1.23 | 0.88 | 0.66 | 0.39 | 0.11 | 0.02 |
| | G 6 | n.d. | 1.52 | 1.95 | 1.89 | 1.39 | 1.15 | 0.84 | 0.69 | 0.45 | 0.14 | 0.02 |
| | Mean S.D. | | | 0.36 0.59 | 1.03 0.80 | 1.29 0.44 | 1.37 0.24 | 1.10 0.17 | 0.76 0.11 | 0.61 0.07 | 0.36 0.06 | 0.10 0.03 |
| 200 (With probenecid) | H 1 | n.d. | 1.27 | 1.77 | 1.47 | 1.31 | 1.15 | 0.91 | 0.76 | 0.48 | 0.21 | 0.03 |
| | H 2 | n.d. | 0.90 | 1.86 | 2.03 | 1.67 | 1.37 | 1.07 | 0.88 | 0.56 | 0.24 | 0.04 |
| | H 3 | n.d. | 0.19 | 0.98 | 0.92 | 1.89 | 1.38 | 1.09 | 0.93 | 0.56 | 0.20 | 0.03 |
| | H 4 | n.d. | 0.11 | 0.34 | 1.16 | 1.44 | 1.32 | 1.03 | 0.91 | 0.56 | 0.25 | 0.04 |
| | H 5 | n.d. | 0.68 | 1.80 | 1.56 | 1.60 | 1.39 | 1.12 | 0.91 | 0.59 | 0.25 | 0.05 |
| | H 6 | n.d. | 0.01 | 1.15 | 1.89 | 1.90 | 1.54 | 1.24 | 1.06 | 0.70 | 0.33 | 0.08 |
| | Mean S.D. | | | 0.53 0.50 | 1.32 0.60 | 1.51 0.42 | 1.64 0.24 | 1.36 0.13 | 1.08 0.11 | 0.91 0.10 | 0.58 0.07 | 0.25 0.05 |

n.d.: Not detected ($<0.01 \mu\text{g}/\text{mL}$)

のであった。

これまで、キノロン系抗菌薬の腎排泄機序に関し多くの報告がなされているが、同系薬はそれぞれ異なる機序で腎臓から排泄されることが知られている²⁰⁻²³。特に、尿中へ主に排泄されるキノロン薬においては、その血清中

濃度は腎排泄機序に深く関係すると考えられる。そこで、尿細管分泌過程を阻害するとされる probenecid 計 1.5g を併用し、GFLX200mg 投与後の体内動態に及ぼす probenecid の影響を検討するとともに、腎排泄機序に関する知見を得た。その結果、probenecid は本薬の $T_{1/2 \beta}$

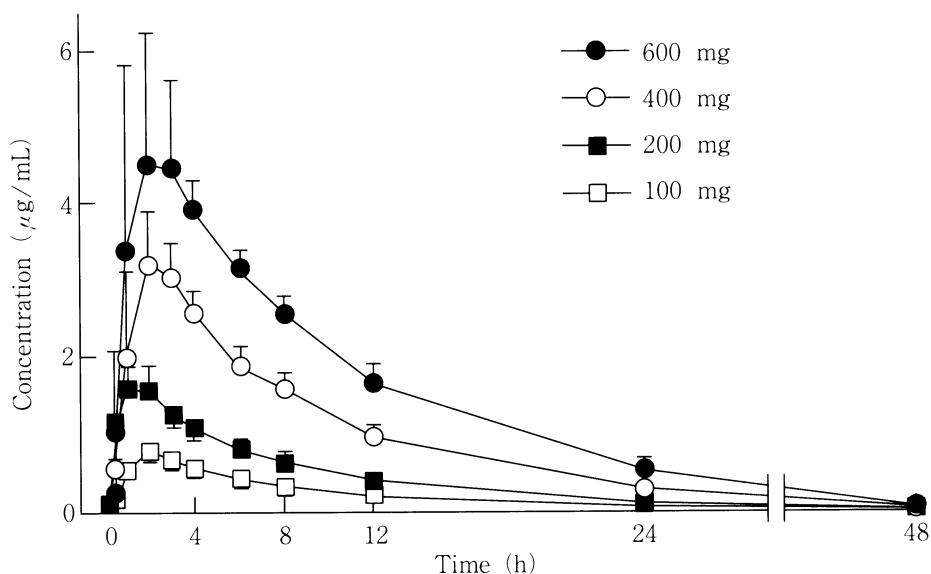


Fig. 5. Concentrations of gatifloxacin in serum following a single oral administration of 100, 200, 400, or 600 mg in fasting volunteers (Mean \pm S.D., $n=6$)

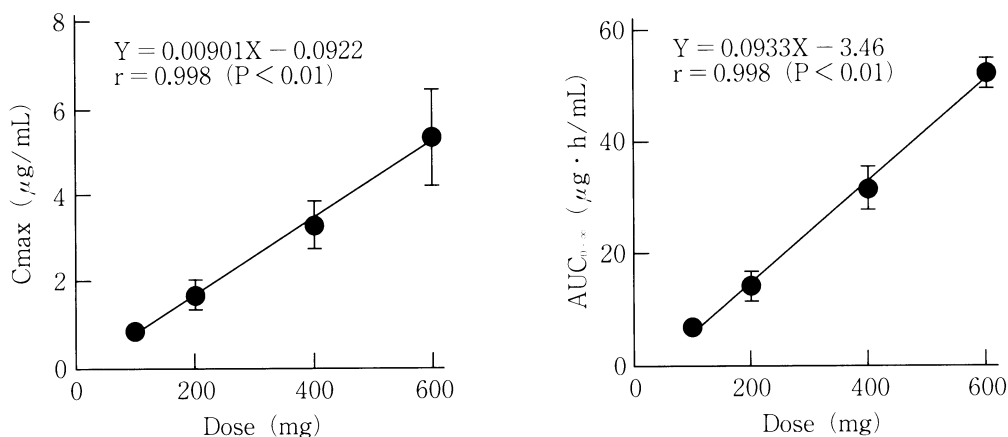


Fig. 6. Correlation between C_{max} or AUC_{0-∞} and doses (Mean \pm S.D., $n=6$)

を延長させ、AUC_{0-∞}を増加させた。また、probenecidは本薬のCL_{T/F}、CL_R、CL_{R,im}および尿中排泄率を低下させた。しかし、その他の薬物速度論的パラメータには変化はみられなかった。これらのことから、probenecidはGFLXの消化管からの吸収および分布には影響しないことが示唆された。また、GFLX単独投与時の排泄比(CL_{R,im}/C_{cr})が2.28であったのに対し、probenecidの併用でその値は1.35へと低下した。このことから、GFLXの腎排泄に尿細管分泌が関与していることが示唆された。

すなわち、GFLXの尿細管分泌過程がprobenecidにより阻害されることから、GFLXの体内動態が変化するものと考えられた。

以上、健常人において単回経口投与後、GFLXは良好に経口吸収され、そのほとんどが未変化体のまま尿中へと排泄された。また、良好な組織移行性も示唆された。薬剤に起因すると思われる副作用も認められず、本薬の抗菌力を考えると十分臨床評価に値する薬剤と思われる。

Table 9. Pharmacokinetic parameters of gatifloxacin in serum following a single oral administration of 100, 200, 400, or 600 mg in Step 2

| Dose (mg) | Volunteer no. | Pharmacokinetic parameter | | | | | | |
|-----------------------|---------------|---------------------------|----------------------|------------------------------|-----------------------|--------------------------|---------------------------|-----------------------------|
| | | C _{max} (μg/mL) | T _{max} (h) | AUC _{0-∞} (μg·h/mL) | T _{1/2β} (h) | V _d /F (L/kg) | V _{ss} /F (L/kg) | CL _T /F (mL/min) |
| 100 (Fasting) | C 1 | 1.02 | 1.63 | 7.69 | 6.01 | 2.20 | 2.05 | 217 |
| | C 2 | 1.09 | 0.812 | 7.77 | 7.30 | 2.22 | 1.81 | 215 |
| | C 3 | 0.813 | 2.33 | 7.57 | 6.34 | 2.28 | 1.97 | 220 |
| | C 4 | 0.917 | 1.97 | 8.34 | 7.60 | 2.17 | 1.83 | 200 |
| | C 5 | 0.557 | 1.56 | 4.92 | 8.03 | 2.94 | 1.97 | 339 |
| | C 6 | 0.840 | 1.49 | 5.68 | 6.27 | 2.06 | 1.75 | 293 |
| | Mean | 0.873 | 1.63 | 7.00 | 6.93 | 2.31 | 1.90 | 247 |
| | S.D. | 0.187 | 0.51 | 1.36 | 0.83 | 0.32 | 0.12 | 56 |
| 200 (Fasting) | D 1 | 1.54 | 1.08 | 12.8 | 7.43 | 2.53 | 2.22 | 260 |
| | D 2 | 2.06 | 1.22 | 14.3 | 6.17 | 1.84 | 1.61 | 233 |
| | D 3 | 1.67 | 1.30 | 12.1 | 4.87 | 2.05 | 1.85 | 275 |
| | D 4 | 1.11 | 3.02 | 13.6 | 8.13 | 2.59 | 2.08 | 245 |
| | D 5 | 1.86 | 0.820 | 14.7 | 6.47 | 2.09 | 1.93 | 227 |
| | D 6 | 2.00 | 1.02 | 19.5 | 9.55 | 2.66 | 2.09 | 171 |
| | Mean | 1.71 | 1.41 | 14.5 | 7.10 | 2.29 | 1.96 | 235 |
| | S.D. | 0.35 | 0.81 | 2.6 | 1.64 | 0.34 | 0.22 | 36 |
| 400 (Fasting) | E 1 | 2.83 | 3.14 | 31.3 | 9.76 | 2.48 | 1.92 | 213 |
| | E 2 | 4.17 | 1.86 | 38.8 | 6.37 | 1.61 | 1.50 | 172 |
| | E 3 | 3.15 | 1.96 | 35.5 | 7.73 | 2.05 | 1.87 | 188 |
| | E 4 | 2.88 | 1.76 | 31.2 | 8.25 | 2.20 | 1.94 | 214 |
| | E 5 | 3.86 | 2.01 | 27.1 | 6.22 | 1.90 | 1.57 | 246 |
| | E 6 | 3.18 | 1.16 | 30.5 | 12.1 | 2.75 | 1.54 | 219 |
| | Mean | 3.35 | 1.98 | 32.4 | 8.41 | 2.17 | 1.72 | 209 |
| | S.D. | 0.55 | 0.65 | 4.1 | 2.23 | 0.41 | 0.21 | 26 |
| 600 (Fasting) | F 1 | 5.33 | 3.19 | 54.6 | 8.90 | 2.42 | 1.75 | 183 |
| | F 2 | 6.98 | 1.12 | 53.3 | 6.13 | 1.54 | 1.44 | 188 |
| | F 3 | 5.96 | 1.50 | 50.3 | 7.82 | 1.72 | 1.51 | 199 |
| | F 4 | 5.20 | 1.57 | 51.2 | 8.66 | 2.34 | 1.91 | 195 |
| | F 5 | 3.51 | 4.75 | 57.5 | 9.51 | 1.93 | 1.64 | 174 |
| | F 6 | 5.48 | 1.56 | 54.2 | 7.63 | 1.93 | 1.75 | 185 |
| | Mean | 5.41 | 2.28 | 53.5 | 8.11 | 1.98 | 1.67 | 187 |
| | S.D. | 1.13 | 1.41 | 2.6 | 1.19 | 0.34 | 0.17 | 9 |
| 200 (Non-fasting) | G 1 | 1.48 | 1.47 | 11.7 | 6.44 | 2.40 | 2.15 | 285 |
| | G 2 | 1.69 | 2.73 | 11.1 | 5.23 | 1.98 | 1.77 | 300 |
| | G 3 | 1.53 | 1.86 | 10.8 | 4.69 | 2.19 | 2.03 | 309 |
| | G 4 | 1.86 | 0.768 | 12.9 | 7.23 | 2.42 | 2.15 | 258 |
| | G 5 | 1.39 | 3.17 | 13.4 | 8.54 | 2.93 | 1.99 | 249 |
| | G 6 | 1.97 | 1.19 | 16.4 | 6.97 | 2.28 | 1.98 | 203 |
| | Mean | 1.65 | 1.86 | 12.7** | 6.52 | 2.37 | 2.01 | 267** |
| | S.D. | 0.23 | 0.92 | 2.1 | 1.40 | 0.32 | 0.14 | 39 |
| 200 (With probenecid) | H 1 | 1.82 | 0.726 | 17.7 | 8.87 | 2.17 | 1.98 | 188 |
| | H 2 | 2.07 | 1.52 | 21.1 | 9.26 | 1.83 | 1.60 | 158 |
| | H 3 | 1.72 | 2.52 | 19.2 | 8.32 | 2.13 | 1.76 | 174 |
| | H 4 | 1.39 | 3.15 | 18.7 | 9.63 | 2.23 | 1.93 | 178 |
| | H 5 | 1.80 | 1.07 | 21.5 | 13.2 | 2.96 | 2.12 | 155 |
| | H 6 | 1.92 | 2.17 | 25.5 | 11.8 | 2.44 | 2.12 | 131 |
| | Mean | 1.79 | 1.86 | 20.6** | 10.2* | 2.29 | 1.92 | 164** |
| | S.D. | 0.23 | 0.92 | 2.8 | 1.9 | 0.38 | 0.21 | 20 |

* : Significantly different from the "200 (Fasting)" value in this table (P < 0.05)

** : Significantly different from the "200 (Fasting)" value in this table (P < 0.01)

Table 10. Concentrations of gatifloxacin in saliva following a single oral administration of 200 or 400 mg in fasting volunteers

| Dose (mg) | Volunteer no. | Concentration ($\mu\text{g/mL}$) | | | | | | | | | | |
|---------------|---------------|------------------------------------|------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| | | Before dosing | 0.5h | 1h | 2h | 3h | 4h | 6h | 8h | 12h | 24h | 48h |
| 200 (Fasting) | D 1 | n.d. | 0.06 | 1.40 | 1.50 | 0.80 | 0.71 | 0.44 | 0.37 | 0.21 | 0.07 | 0.03 |
| | D 2 | n.d. | 0.08 | 1.13 | 1.57 | 1.17 | 0.83 | 0.47 | 0.40 | 0.23 | 0.07 | 0.03 |
| | D 3 | n.d. | 0.09 | 1.77 | 1.70 | 1.32 | 0.94 | 0.47 | 0.34 | 0.16 | 0.05 | 0.02 |
| | D 4 | n.d. | 0.06 | 0.29 | 0.62 | 0.66 | 0.51 | 0.42 | 0.29 | 0.18 | 0.05 | n.d. |
| | D 5 | n.d. | 0.16 | 2.08 | 2.21 | 1.65 | 1.31 | 0.74 | 0.57 | 0.33 | 0.10 | 0.03 |
| | D 6 | n.d. | 0.15 | 0.96 | 1.56 | 1.44 | 1.12 | 0.67 | 0.54 | 0.31 | 0.11 | 0.03 |
| | Mean S.D. | | | 0.10 0.04 | 1.27 0.63 | 1.53 0.51 | 1.17 0.38 | 0.90 0.29 | 0.54 0.13 | 0.42 0.11 | 0.24 0.07 | 0.08 0.03 |
| 400 (Fasting) | E 1 | n.d. | n.d. | 0.05 | 0.94 | 1.94 | 1.93 | 1.27 | 1.04 | 0.62 | 0.12 | 0.02 |
| | E 2 | n.d. | n.d. | 0.47 | 2.77 | 3.46 | 3.17 | 1.90 | 1.38 | 0.85 | 0.20 | 0.03 |
| | E 3 | n.d. | 0.16 | 1.06 | 2.72 | 2.55 | 2.21 | 1.76 | 1.48 | 0.67 | 0.19 | 0.03 |
| | E 4 | n.d. | 0.12 | 1.52 | 2.98 | 2.95 | 2.11 | 1.21 | 1.29 | 0.60 | 0.16 | 0.03 |
| | E 5 | n.d. | 0.03 | 0.47 | 1.66 | 3.04 | 2.42 | 1.59 | 1.14 | 0.58 | 0.11 | 0.02 |
| | E 6 | n.d. | 0.02 | 1.12 | 4.16 | 3.12 | 2.66 | 1.72 | 1.49 | 0.66 | 0.15 | 0.02 |
| | Mean S.D. | | | 0.06 0.07 | 0.78 0.54 | 2.54 1.12 | 2.84 0.53 | 2.42 0.45 | 1.58 0.28 | 1.30 0.18 | 0.66 0.10 | 0.16 0.04 |

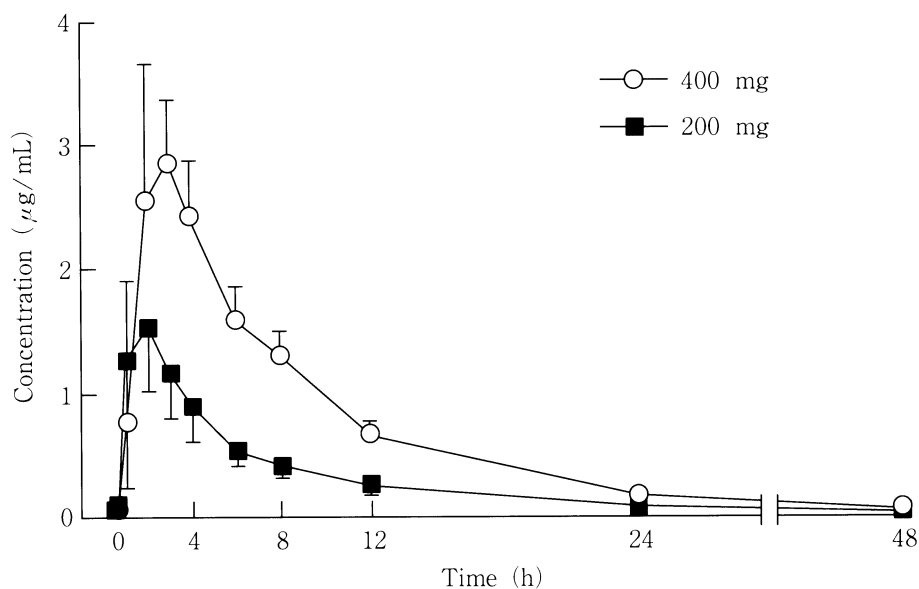
n.d.: Not detected ($< 0.01 \mu\text{g/mL}$)Fig. 7. Concentrations of gatifloxacin in saliva following a single oral administration of 200 or 400 mg in fasting volunteers (Mean \pm S.D., $n = 6$)

Table 11. Pharmacokinetic parameters of gatifloxacin in saliva following a single oral administration of 200 or 400 mg in fasting volunteers

| Dose (mg) | Volunteer no. | Pharmacokinetic parameter | | | |
|---------------|---------------|---------------------------|----------------------|------------------------------|----------------------|
| | | C _{max} (μg/mL) | T _{max} (h) | AUC _{0-∞} (μg·h/mL) | T _{1/2} (h) |
| 200 (Fasting) | D 1 | 1.50 | 2.0 | 10.1 | 10.9 |
| | D 2 | 1.57 | 2.0 | 10.8 | 10.5 |
| | D 3 | 1.77 | 1.0 | 10.4 | 9.52 |
| | D 4 | 0.66 | 3.0 | 6.37 | 6.04 |
| | D 5 | 2.21 | 2.0 | 15.8 | 9.20 |
| | D 6 | 1.56 | 2.0 | 13.6 | 9.50 |
| | Mean S.D. | 1.55 0.51 | 2.0 0.6 | 11.2 3.2 | 9.28 1.72 |
| 400 (Fasting) | E 1 | 1.94 | 3.0 | 19.0 | 7.07 |
| | E 2 | 3.46 | 3.0 | 30.3 | 7.30 |
| | E 3 | 2.72 | 2.0 | 26.8 | 7.18 |
| | E 4 | 2.98 | 2.0 | 24.9 | 7.63 |
| | E 5 | 3.04 | 3.0 | 22.3 | 6.70 |
| | E 6 | 4.16 | 2.0 | 28.4 | 6.50 |
| | Mean S.D. | 3.05 0.74 | 2.5 0.5 | 25.3 4.1 | 7.06 0.41 |

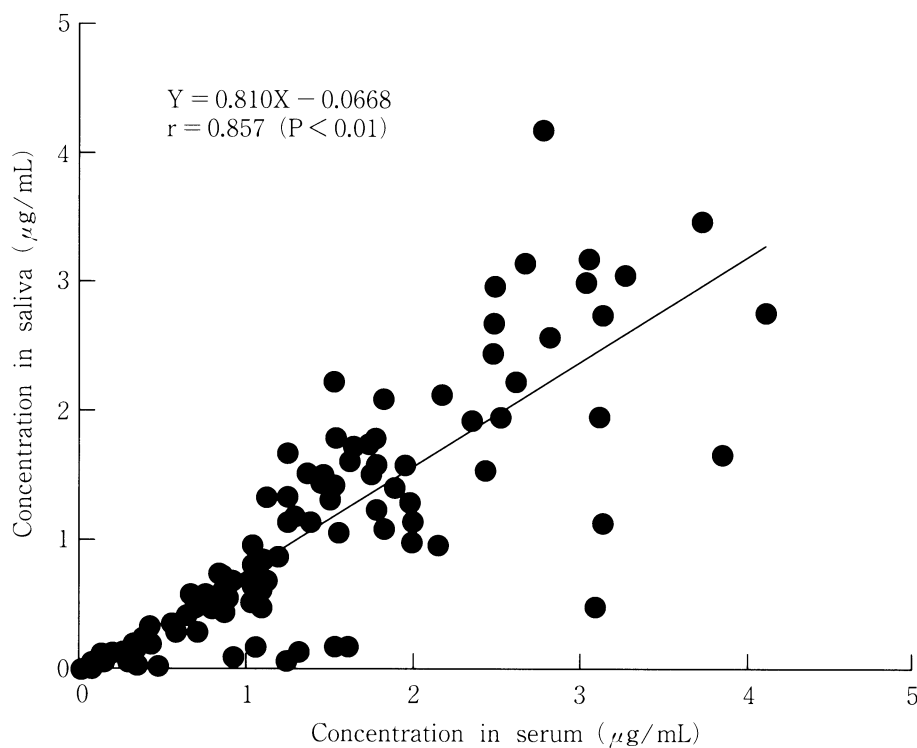


Fig. 8. Correlation between concentrations in serum and saliva (n=120)

Table 12. Concentrations of gatifloxacin in urine following a single oral administration of 100, 200, 400, or 600 mg in Step 2

| Dose (mg) | Volunteer no. | Concentration ($\mu\text{g/mL}$) | | | | | | | | | |
|-----------------------|---------------|------------------------------------|------|------|------|------|-------|--------|--------|--------|-----|
| | | Before dosing | 0-2h | 2-4h | 4-6h | 6-8h | 8-12h | 12-24h | 24-48h | 48-72h | |
| 100 (Fasting) | C 1 | n.d. | 85.7 | 100 | 148 | 171 | 47.1 | 24.4 | 3.5 | 0.6 | |
| | C 2 | n.d. | 136 | 164 | 149 | 108 | 58.1 | 38.2 | 5.9 | 1.1 | |
| | C 3 | n.d. | 244 | 358 | 275 | 167 | 83.0 | 43.1 | 9.4 | 1.6 | |
| | C 4 | n.d. | 247 | 312 | 206 | 131 | 59.4 | 17.9 | 6.4 | 1.0 | |
| | C 5 | n.d. | 148 | 128 | 121 | 83.8 | 37.9 | 23.9 | 3.3 | 0.6 | |
| | C 6 | n.d. | 63.5 | 264 | 219 | 132 | 41.1 | 30.5 | 5.3 | 1.9 | |
| | Mean | | | 154 | 221 | 186 | 132 | 54.4 | 29.7 | 5.6 | 1.1 |
| | S.D. | | | 77 | 105 | 57 | 34 | 16.5 | 9.5 | 2.2 | 0.5 |
| 200 (Fasting) | D 1 | n.d. | 257 | 296 | 275 | 135 | 127 | 78.8 | 11.6 | 1.2 | |
| | D 2 | n.d. | 116 | 161 | 154 | 81.8 | 102 | 56.8 | 12.8 | 1.2 | |
| | D 3 | n.d. | 225 | 182 | 242 | 97.9 | 74.8 | 40.8 | 6.4 | 0.8 | |
| | D 4 | n.d. | 124 | 283 | 437 | 300 | 176 | 78.1 | 10.3 | 2.2 | |
| | D 5 | n.d. | 244 | 357 | 114 | 72.5 | 113 | 81.6 | 11.1 | 2.4 | |
| | D 6 | n.d. | 69.1 | 115 | 217 | 198 | 145 | 96.8 | 12.3 | 3.1 | |
| | Mean | | | 173 | 232 | 240 | 148 | 123 | 72.2 | 10.8 | 1.8 |
| | S.D. | | | 79 | 93 | 113 | 88 | 35 | 20.0 | 2.3 | 0.9 |
| 400 (Fasting) | E 1 | n.d. | 97.5 | 586 | 682 | 545 | 398 | 261 | 42.7 | 4.4 | |
| | E 2 | n.d. | 136 | 398 | 699 | 419 | 298 | 250 | 35.6 | 3.9 | |
| | E 3 | n.d. | 107 | 344 | 735 | 529 | 345 | 182 | 28.9 | 3.5 | |
| | E 4 | n.d. | 222 | 411 | 415 | 115 | 97.9 | 102 | 25.5 | 2.6 | |
| | E 5 | n.d. | 203 | 884 | 839 | 515 | 321 | 158 | 15.5 | 1.7 | |
| | E 6 | n.d. | 550 | 773 | 677 | 328 | 322 | 242 | 30.0 | 3.7 | |
| | Mean | | | 219 | 566 | 675 | 409 | 297 | 199 | 29.7 | 3.3 |
| | S.D. | | | 170 | 222 | 141 | 166 | 103 | 63 | 9.2 | 1.0 |
| 600 (Fasting) | F 1 | n.d. | 273 | 784 | 983 | 534 | 174 | 171 | 36.6 | 4.6 | |
| | F 2 | n.d. | 869 | 1570 | 1000 | 572 | 353 | 279 | 60.3 | 5.6 | |
| | F 3 | n.d. | 308 | 782 | 363 | 455 | 379 | 341 | 56.5 | 7.7 | |
| | F 4 | n.d. | 467 | 790 | 868 | 599 | 393 | 160 | 45.7 | 5.0 | |
| | F 5 | n.d. | 179 | 904 | 1400 | 808 | 623 | 196 | 76.3 | 15.7 | |
| | F 6 | n.d. | 735 | 886 | 720 | 479 | 385 | 378 | 65.6 | 7.9 | |
| | Mean | | | 472 | 953 | 889 | 575 | 385 | 254 | 56.8 | 7.8 |
| | S.D. | | | 275 | 307 | 343 | 127 | 143 | 92 | 14.2 | 4.1 |
| 200 (Non-fasting) | G 1 | n.d. | 216 | 232 | 239 | 152 | 155 | 76.2 | 8.5 | 1.0 | |
| | G 2 | n.d. | 55.0 | 278 | 303 | 154 | 77.1 | 54.3 | 7.1 | 1.0 | |
| | G 3 | n.d. | 173 | 260 | 202 | 53.0 | 129 | 52.1 | 4.0 | 1.2 | |
| | G 4 | n.d. | 265 | 185 | 260 | 182 | 138 | 80.5 | 9.7 | 1.4 | |
| | G 5 | n.d. | 43.1 | 216 | 129 | 75.7 | 101 | 52.6 | 8.8 | 2.0 | |
| | G 6 | n.d. | 194 | 129 | 186 | 173 | 116 | 64.3 | 7.4 | 2.0 | |
| | Mean | | | 158 | 217 | 220 | 132 | 119 | 63.3 | 7.6 | 1.4 |
| | S.D. | | | 90 | 54 | 61 | 54 | 28 | 12.5 | 2.0 | 0.5 |
| 200 (With probenecid) | H 1 | n.d. | 182 | 212 | 157 | 135 | 108 | 56.0 | 16.4 | 2.9 | |
| | H 2 | n.d. | 84.0 | 129 | 113 | 67.0 | 79.7 | 38.1 | 14.3 | 5.1 | |
| | H 3 | n.d. | 86.3 | 170 | 108 | 172 | 95.4 | 36.5 | 10.7 | 3.5 | |
| | H 4 | n.d. | 21.3 | 115 | 214 | 215 | 133 | 51.0 | 14.1 | 3.8 | |
| | H 5 | n.d. | 45.4 | 136 | 106 | 41.9 | 56.3 | 40.7 | 13.3 | 5.7 | |
| | H 6 | n.d. | 48.5 | 76.8 | 138 | 124 | 73.8 | 55.6 | 19.1 | 7.6 | |
| | Mean | | | 77.9 | 140 | 139 | 126 | 91.0 | 46.3 | 14.7 | 4.8 |
| | S.D. | | | 56.7 | 47 | 42 | 64 | 27.2 | 8.9 | 2.9 | 1.7 |

n.d.: Not detected ($< 0.1 \mu\text{g/mL}$)

Table 13. Cumulative recovery of gatifloxacin in urine following a single oral administration of 100, 200, 400, or 600 mg in Step 2

| Dose (mg) | Volunteer no. | Cumulative recovery (% of dose) | | | | | | | |
|-----------------------|---------------|---------------------------------|--------|--------|--------|--------|--------|--------|-------|
| | | 0-2h | 0-4h | 0-6h | 0-8h | 0-12h | 0-24h | 0-48h | 0-72h |
| 100 (Fasting) | C 1 | 12.7 | 29.3 | 39.1 | 47.3 | 50.8 | 60.5 | 67.4 | 68.3 |
| | C 2 | 12.2 | 29.3 | 40.0 | 47.8 | 60.4 | 77.0 | 84.6 | 85.8 |
| | C 3 | 9.8 | 24.1 | 34.8 | 43.0 | 55.9 | 73.3 | 81.3 | 82.5 |
| | C 4 | 11.1 | 26.4 | 36.3 | 44.3 | 55.7 | 73.4 | 82.1 | 83.2 |
| | C 5 | 15.4 | 31.9 | 44.0 | 51.8 | 64.4 | 75.6 | 80.7 | 81.4 |
| | C 6 | 4.6 | 26.0 | 39.2 | 49.7 | 64.0 | 79.5 | 86.5 | 88.4 |
| | Mean | 11.0 | 27.8 | 38.9 | 47.3 | 58.5 | 73.2 | 80.4 | 81.6 |
| | S.D. | 3.6 | 2.8 | 3.2 | 3.3 | 5.3 | 6.7 | 6.7 | 7.0 |
| 200 (Fasting) | D 1 | 16.1 | 29.4 | 39.7 | 47.8 | 60.2 | 74.1 | 80.9 | 81.6 |
| | D 2 | 14.3 | 28.7 | 39.1 | 48.0 | 61.4 | 76.5 | 83.4 | 84.2 |
| | D 3 | 18.9 | 36.2 | 48.5 | 58.3 | 71.6 | 83.8 | 87.9 | 88.6 |
| | D 4 | 7.8 | 20.3 | 31.2 | 39.6 | 52.4 | 70.5 | 78.2 | 79.2 |
| | D 5 | 15.9 | 27.6 | 38.2 | 46.0 | 58.1 | 73.6 | 80.8 | 81.8 |
| | D 6 | 12.8 | 26.0 | 35.6 | 43.5 | 57.3 | 73.3 | 83.3 | 85.2 |
| | Mean | 14.3 | 28.0 | 38.7 | 47.2 | 60.2 | 75.3 | 82.4 | 83.4 |
| | S.D. | 3.8 | 5.2 | 5.7 | 6.3 | 6.4 | 4.6 | 3.3 | 3.3 |
| 400 (Fasting) | E 1 | 3.0 | 15.9 | 25.8 | 35.3 | 48.0 | 65.8 | 75.3 | 76.4 |
| | E 2 | 5.4 | 17.1 | 26.2 | 35.0 | 49.3 | 72.4 | 81.7 | 82.8 |
| | E 3 | 8.8 | 20.7 | 31.4 | 40.6 | 54.4 | 74.9 | 84.1 | 85.1 |
| | E 4 | 10.0 | 21.3 | 33.3 | 42.0 | 55.6 | 75.3 | 87.1 | 88.5 |
| | E 5 | 6.0 | 22.3 | 33.7 | 44.0 | 57.9 | 75.3 | 81.8 | 82.4 |
| | E 6 | 10.2 | 22.2 | 33.0 | 41.7 | 55.9 | 74.4 | 82.8 | 84.0 |
| | Mean | 7.2 | 19.9 | 30.6 | 39.8 | 53.5 | 73.0 | 82.1 | 83.2 |
| | S.D. | 2.9 | 2.7 | 3.6 | 3.7 | 4.0 | 3.7 | 3.9 | 4.0 |
| 600 (Fasting) | F 1 | 3.9 | 19.9 | 31.3 | 42.5 | 59.0 | 78.9 | 87.0 | 87.9 |
| | F 2 | 10.4 | 21.4 | 32.1 | 42.4 | 57.8 | 75.7 | 85.7 | 86.7 |
| | F 3 | 6.5 | 21.8 | 33.3 | 43.7 | 59.4 | 78.9 | 88.0 | 89.2 |
| | F 4 | 12.3 | 26.3 | 37.0 | 46.3 | 60.8 | 80.5 | 88.8 | 89.8 |
| | F 5 | 1.8 | 10.8 | 20.2 | 28.8 | 43.5 | 68.9 | 81.5 | 84.2 |
| | F 6 | 11.3 | 24.0 | 33.8 | 43.4 | 58.9 | 78.1 | 87.7 | 89.5 |
| | Mean | 7.7 | 20.7 | 31.3 | 41.2 | 56.6 | 76.8 | 86.5 | 87.9 |
| | S.D. | 4.3 | 5.3 | 5.8 | 6.2 | 6.5 | 4.2 | 2.6 | 2.1 |
| 200 (Non-fasting) | G 1 | 14.5 | 31.2 | 41.9 | 51.2 | 64.1 | 78.8 | 85.0 | 85.9 |
| | G 2 | 2.1 | 20.8 | 37.1 | 48.7 | 64.7 | 81.7 | 88.8 | 89.9 |
| | G 3 | 12.5 | 32.5 | 45.8 | 54.8 | 70.0 | 83.2 | 87.9 | 88.9 |
| | G 4 | 15.1 | 27.9 | 38.5 | 47.3 | 60.1 | 76.2 | 84.0 | 85.1 |
| | G 5 | 2.8 | 21.8 | 36.1 | 46.4 | 60.7 | 77.6 | 84.8 | 85.7 |
| | G 6 | 14.6 | 28.9 | 39.3 | 47.9 | 60.8 | 73.4 | 82.1 | 83.6 |
| | Mean | 10.3 | 27.2 | 39.8 | 49.4 | 63.4* | 78.5* | 85.4 | 86.5 |
| | S.D. | 6.1 | 4.8 | 3.6 | 3.1 | 3.8 | 3.6 | 2.5 | 2.4 |
| 200 (With probenecid) | H 1 | 9.5 | 17.7 | 24.8 | 32.5 | 39.4 | 51.9 | 61.0 | 62.8 |
| | H 2 | 8.8 | 18.1 | 25.5 | 33.5 | 46.7 | 60.2 | 73.0 | 75.8 |
| | H 3 | 7.5 | 20.3 | 25.4 | 35.3 | 50.8 | 66.5 | 76.5 | 78.2 |
| | H 4 | 4.5 | 14.0 | 21.3 | 29.9 | 44.1 | 61.4 | 71.4 | 73.5 |
| | H 5 | 9.7 | 20.6 | 29.6 | 37.9 | 50.1 | 65.5 | 77.4 | 79.9 |
| | H 6 | 7.4 | 17.6 | 25.6 | 32.8 | 47.2 | 63.1 | 75.4 | 79.0 |
| | Mean | 7.9** | 18.1** | 25.4** | 33.7** | 46.4** | 61.4** | 72.5** | 74.9* |
| | S.D. | 1.9 | 2.4 | 2.6 | 2.7 | 4.2 | 5.2 | 6.0 | 6.4 |

* : Significantly different from the "200 (Fasting)" value in this table ($P < 0.05$)** : Significantly different from the "200 (Fasting)" value in this table ($P < 0.01$)

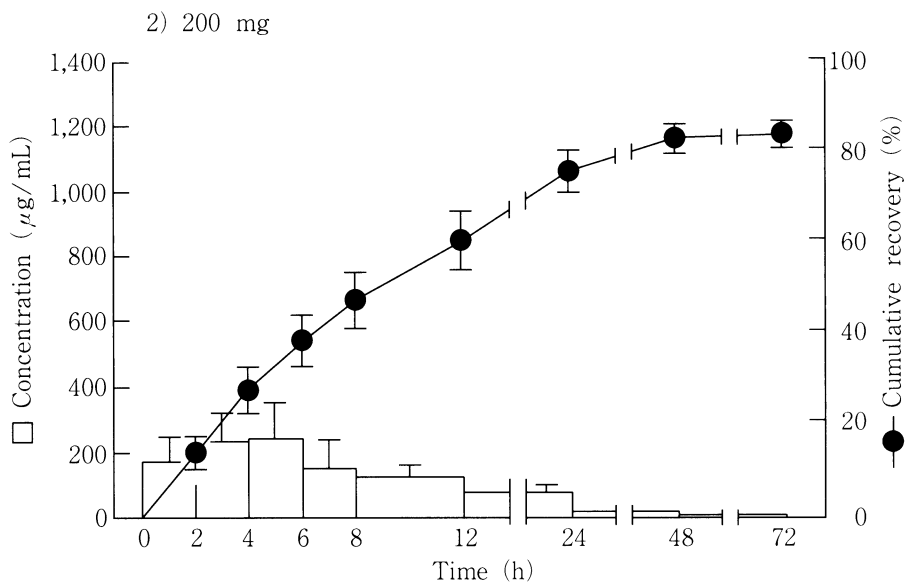
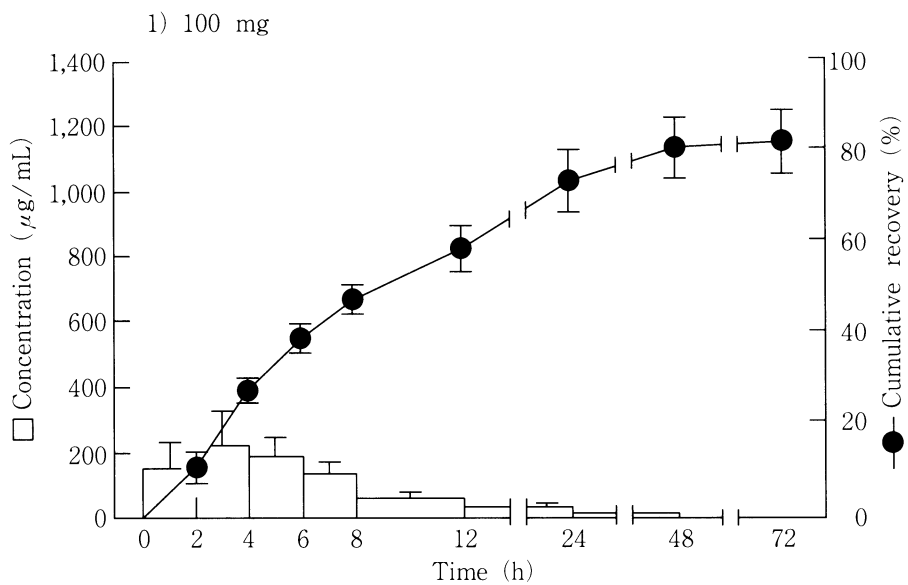


Fig. 9-1. Concentrations and cumulative recovery of gatifloxacin in urine following a single oral administration of 100, 200, 400, and 600 mg in fasting volunteers (Mean \pm S.D., n=6)

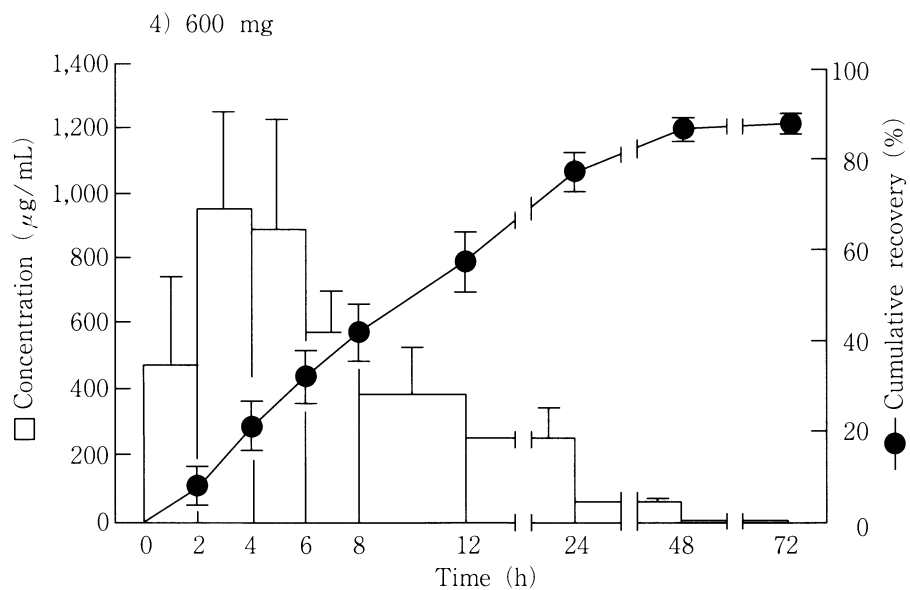
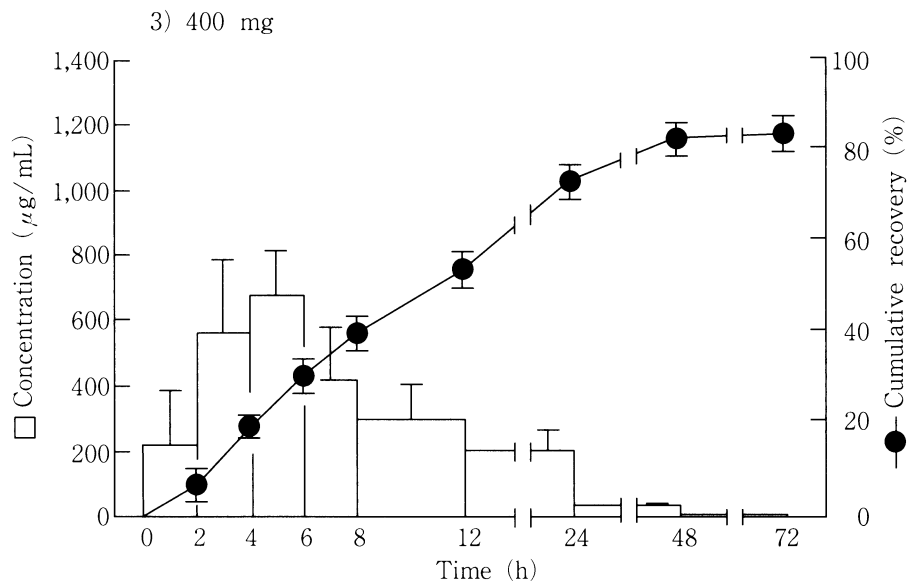


Fig. 9-2. Concentrations and cumulative recovery of gatifloxacin in urine following a single oral administration of 100, 200, 400, and 600 mg in fasting volunteers (Mean \pm S.D., n=6)

Table 14. Concentrations of gatifloxacin in feces following a single oral administration of 400 mg in fasting volunteers

| Volunteer no. | Concentration ($\mu\text{g/g}$) | | |
|---------------|-----------------------------------|--------|--------|
| | 0-24h | 24-48h | 48-72h |
| E 1 | 64.3 | 20.4 | 1.9 |
| E 2 | 113 | 65.1 | 2.6 |
| E 3 | 22.9 | 56.7 | 3.6 |
| E 4 | 65.6 | — | 55.2 |
| E 5 | 83.7 | 11.5 | n.d. |
| E 6 | — | 54.1 | 63.0 |
| Mean | 69.9 | 41.6 | 21.1 |
| S.D. | 32.8 | 23.9 | 29.6 |

— : No sample

n.d. : Not detected ($<0.4 \mu\text{g/g}$)

Table 15. Cumulative recovery of gatifloxacin in feces following a single oral administration of 400 mg in fasting volunteers

| Volunteer no. | Cumulative recovery (% of dose) | | |
|---------------|---------------------------------|-------|-------|
| | 0-24h | 0-48h | 0-72h |
| E 1 | 1.5 | 2.4 | 2.5 |
| E 2 | 4.2 | 7.3 | 7.5 |
| E 3 | 0.5 | 5.7 | 5.9 |
| E 4 | 1.8 | 1.8 | 6.3 |
| E 5 | 5.4 | 5.9 | 5.9 |
| E 6 | 0.0 | 0.9 | 6.0 |
| Mean | 2.2 | 4.0 | 5.7 |
| S.D. | 2.1 | 2.6 | 1.7 |

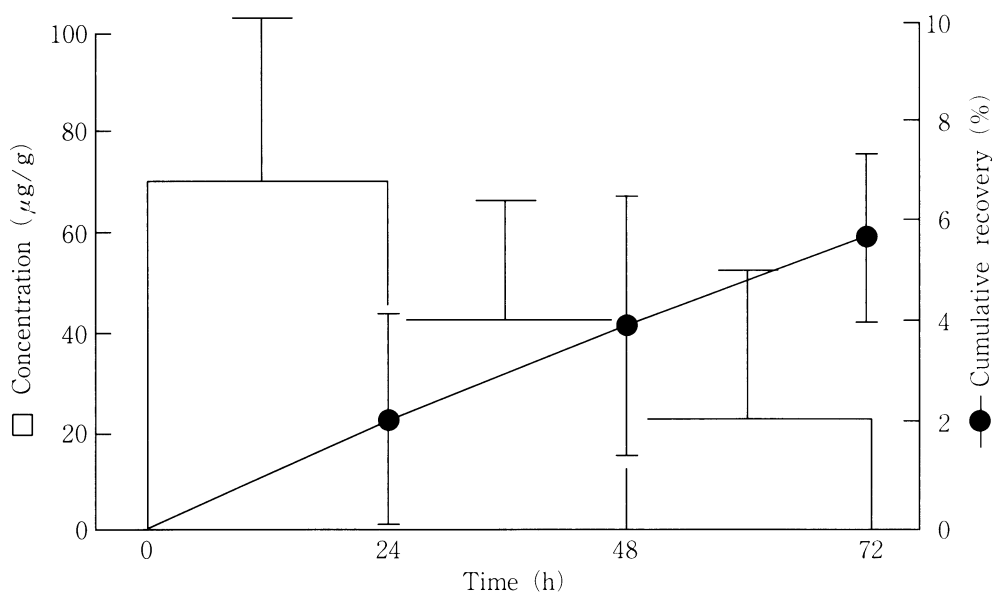


Fig. 10. Concentrations and cumulative recovery of gatifloxacin in feces following a single oral administration of 400 mg in fasting volunteers (Mean \pm S.D., $n=6$)

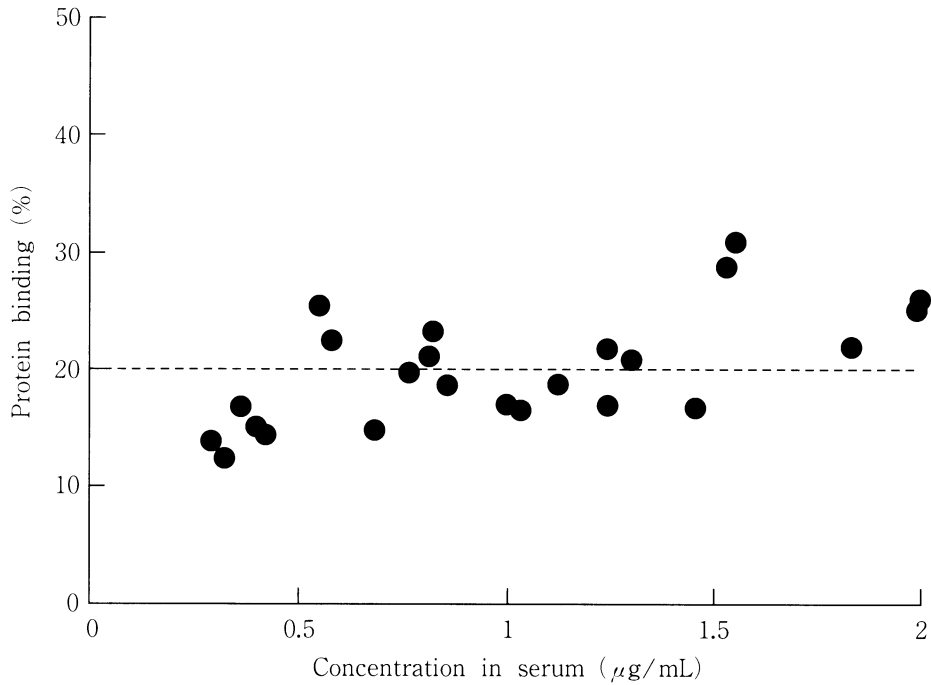


Fig. 11. Protein binding of gatifloxacin in human serum (n=24)

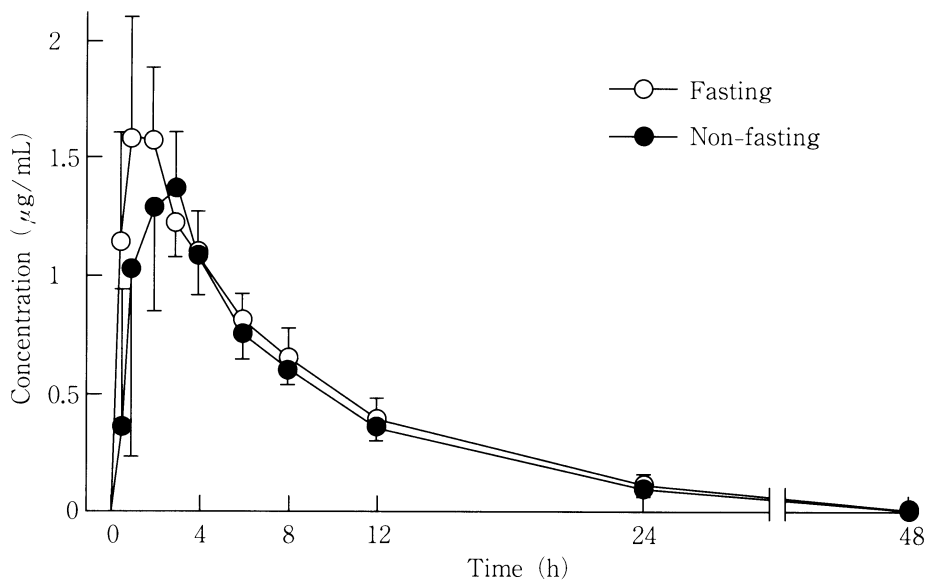


Fig. 12. Concentrations of gatifloxacin in serum following a single oral administration of 200 mg in fasting and non-fasting volunteers (Mean \pm S.D., n=6)

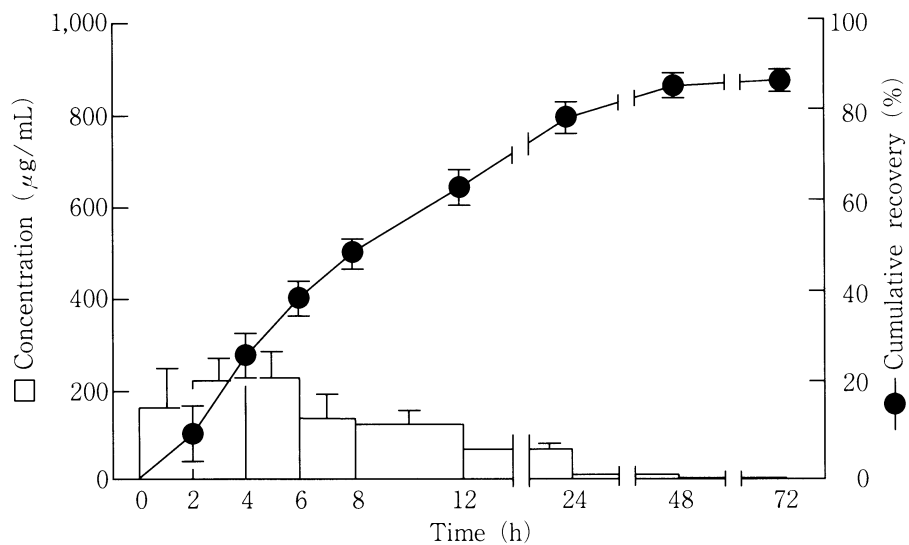


Fig. 13. Concentrations and cumulative recovery of gatifloxacin in urine following a single oral administration of 200 mg in non-fasting volunteers (Mean \pm S.D., n=6)

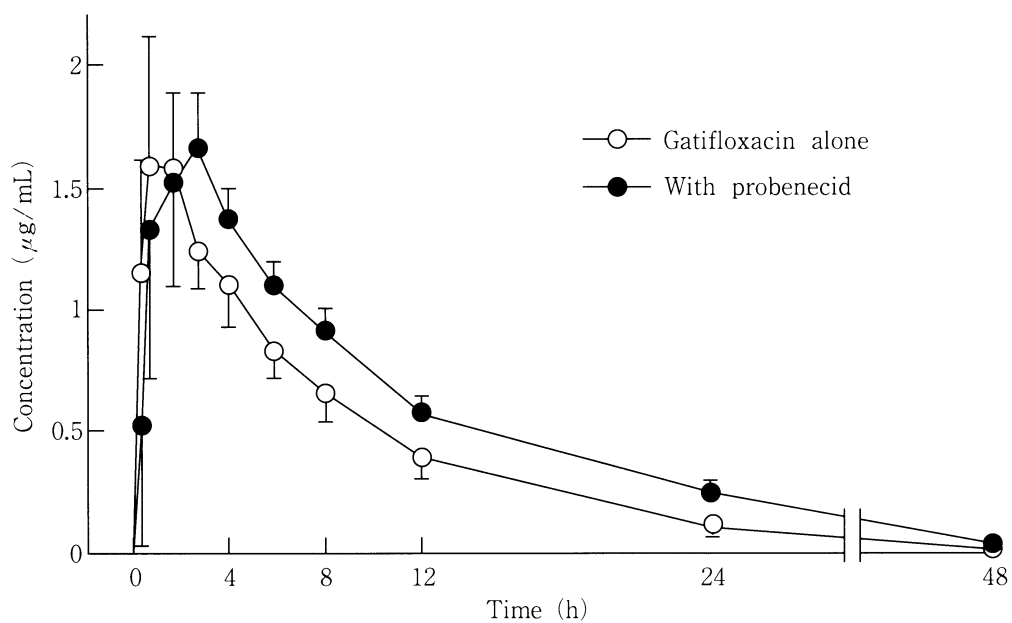


Fig. 14. Concentrations of gatifloxacin in serum following a single oral administration of 200 mg alone and with 1.5 g probenecid in fasting volunteers (Mean \pm S.D., n=6)

Table 16. Pharmacokinetic parameters of gatifloxacin following a single oral administration of 200 mg with or without 1.5 g probenecid in fasting volunteers

| Treatment | Volunteer no. | Pharmacokinetic parameter | | | | |
|--------------------|---------------|---------------------------|--------------------------|------------------|-------------------------------|-----------------|
| | | Ccr (mL/min) | CL _R (mL/min) | fu | CL _{R, int} (mL/min) | Excretion ratio |
| Without probenecid | D 1 | 111 | 213 | 0.835 | 255 | 2.30 |
| | D 2 | 111 | 196 | 0.792 | 247 | 2.23 |
| | D 3 | 110 | 244 | 0.782 | 312 | 2.84 |
| | D 4 | 106 | 194 | 0.813 | 239 | 2.25 |
| | D 5 | 99.3 | 186 | 0.831 | 224 | 2.26 |
| | D 6 | 97.8 | 146 | 0.834 | 175 | 1.79 |
| | Mean S.D. | 106 6 | 197 32 | 0.815 0.023 | 242 45 | 2.28 0.33 |
| With probenecid | H 1 | 115 | 118 | 0.779 | 151 | 1.31 |
| | H 2 | 117 | 120 | 0.743 | 162 | 1.38 |
| | H 3 | 114 | 136 | 0.746 | 182 | 1.60 |
| | H 4 | 114 | 131 | 0.785 | 167 | 1.46 |
| | H 5 | 188 | 124 | 0.763 | 163 | 0.867 |
| | H 6 | 96.3 | 103 | 0.726 | 142 | 1.47 |
| | Mean S.D. | 124 32 | 122** 12 | 0.757** 0.023 | 161** 14 | 1.35** 0.25 |

** : Significantly different from the corresponding value without probenecid (P < 0.01)

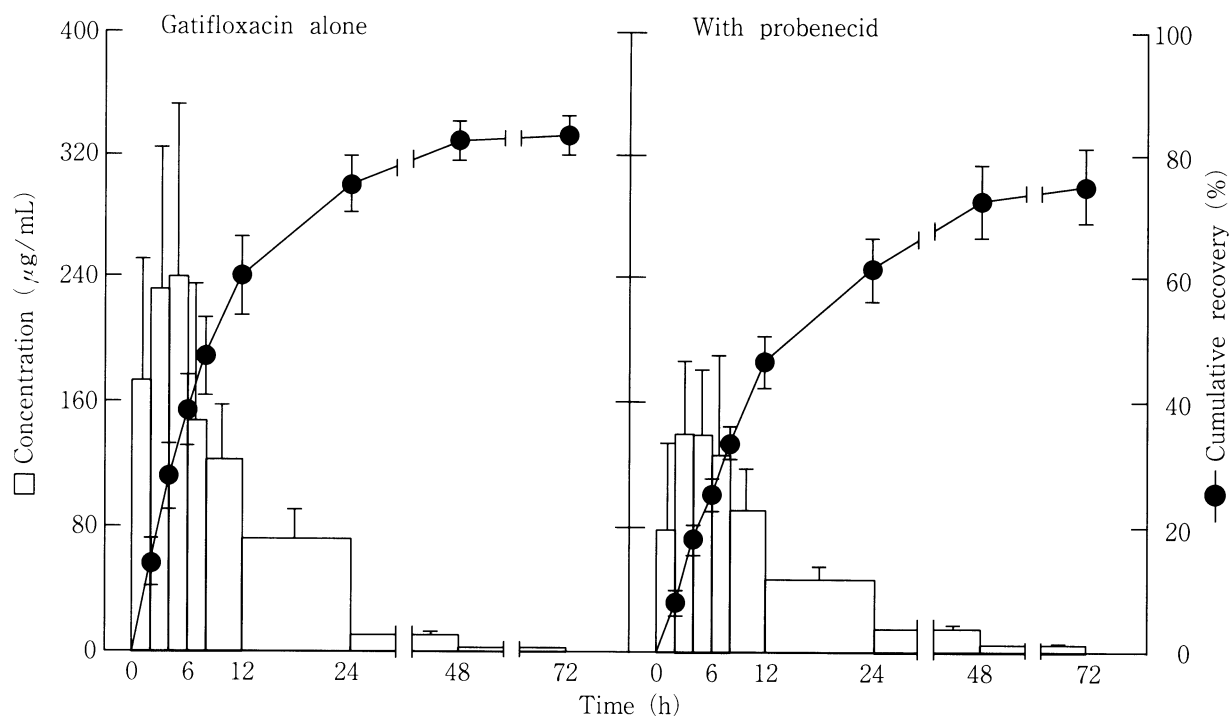


Fig. 15. Concentrations and cumulative recovery of gatifloxacin in urine following a single oral administration of 200 mg alone and with 1.5 g probenecid in fasting volunteers (Mean \pm S.D., n=6)

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Phase I study of gatifloxacin, a new quinolone I. Single-dose study

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A Phase I study of gatifloxacin (GFLX), a new quinolone, was conducted to evaluate its safety and pharmacokinetics in healthy male volunteers. Each volunteer received a single oral dose of 20, 50, 100, 200, 400, or 600 mg. At the 200 mg dose level, the effects of food intake and a concurrent dose of probenecid were also tested.

Throughout the study period, GFLX was well tolerated by all of the 40 subjects. No abnormal change was found in subjective and objective symptoms, blood pressure, pulse rate, body temperature, ECG, blood chemistry, blood biochemistry, or urinalysis. Furthermore, no crystalluria attributable to the drug and no abnormal change in audiometry, ophthalmological, or balance tests were observed at the doses of 400 and 600 mg.

Concentrations in serum reached a peak between 1.41 and 2.28 hours, and the peak concentrations (C_{max}) were 0.873, 1.71, 3.35, and 5.41 $\mu\text{g}/\text{mL}$ at doses of 100, 200, 400, and 600 mg, respectively. The respective areas under the serum concentration-time curve from time zero to infinity (AUC_{0-∞}) were 7.00, 14.5, 32.4, and 53.5 $\mu\text{g} \cdot \text{h}/\text{mL}$. Elimination half-lives ($T_{1/2\beta}$) were 6.93 to 8.41 hours, independent of dose. C_{max} and AUC_{0-∞} increased in proportion to the dose. The unchanged drug was excreted mainly in the urine, with 81.6 to 87.9% of the dose appearing within 72 hours. Fecal recovery of the unchanged drug amounted to 5.7% within 72 hours after a single oral administration of 400 mg. Serum protein binding was 20%, independent of the concentrations in serum. Concentrations in saliva were approximately 80% of those in serum.

Food intake had little effect on pharmacokinetic parameters and urinary excretion of GFLX, except the slight decrease in AUC_{0-∞} from 14.5 to 12.7 $\mu\text{g} \cdot \text{h}/\text{mL}$; C_{max}, T_{max}, and $T_{1/2\beta}$ were 1.65 $\mu\text{g}/\text{mL}$, 1.86 hours, and 6.52 hours, respectively. The concurrent administration of 1.5 g probenecid prolonged the elimination half-life to 10.2 hours, and increased AUC_{0-∞} to 20.6 $\mu\text{g} \cdot \text{h}/\text{mL}$. Furthermore, it decreased the apparent total body clearance from 235 to 164 mL/min, renal clearance from 197 to 122 mL/min, and the excretion ratio (intrinsic renal clearance of GFLX/creatinine clearance) from 2.28 to 1.35. These results suggest that tubular secretion contributed to the renal clearance of GFLX.

In conclusion, there do not appear to be any safety problems with GFLX and, taking into consideration its favorable pharmacokinetics and potent antibacterial activity, a positive clinical evaluation seems warranted.