

BAY o 9867 (Ciprofloxacin) の薬動力学的研究

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西ドイツ・バイエル社で合成されたピリドン・カルボン酸系の抗菌剤 BAY o 9867 (Ciprofloxacin) について、健康成人男子志願者を対象に 1 回 300, 400 mg, 1 日 2 回, 7 日間連続使用し、血中濃度、唾液中濃度、尿中排泄を検討した。300 mg 使用群での最高血中濃度は使用後 1 ~ 2 時間にみられ、平均 $0.89 \sim 0.93 \mu\text{g/ml}$ で、唾液中濃度は使用後 2 ~ 4 時間で最高となり、その時の濃度は平均 $0.33 \sim 0.46 \mu\text{g/ml}$ であった。累積尿中回収率は平均 $29.1 \sim 36.4\%$ であった。400 mg 使用群では最高血中濃度は 300 mg 使用群と同様使用後 1 ~ 2 時間にみられ、平均 $1.50 \sim 2.05 \mu\text{g/ml}$ で、唾液中濃度は使用後 2 ~ 4 時間で最高となり、濃度は $0.46 \sim 0.82 \mu\text{g/ml}$ であった。累積尿中回収率は平均 $29.8 \sim 35.2\%$ であった。

試験期間中、自覚症状をチェックし、各種臨床検査を実施して、BAY o 9867 の安全性を検討した。300 mg 使用群で 1 例、GPT の上昇が、また、400 mg 使用群で 1 例に GOT, GPT, 他の 1 例で GOT, GPT, γ -GTP の上昇が認められたが、いずれも一過性であった。その他、自覚症状、血液一般・血液生化学・尿検査においては、BAY o 9867 使用と関連すると思われる異常所見は認められなかった。また、経時的に尿中結晶存否について検索を行ったが、結晶析出はみられなかった。

BAY o 9867 (Ciprofloxacin) は西ドイツ・バイエル社で合成されたピリドン・カルボン酸系の新しい抗菌剤で、その化学構造は Fig. 1 に示す如くである。本剤はグラム陽性菌および緑膿菌を含むグラム陰性菌に対し幅広い抗菌スペクトラムと強い抗菌活性を有する^{1,2)}。今回、我々は本剤の 1 回 300 mg および 400 mg 1 日 2 回, 7 日間連続使用による薬物動態ならびに安全性について検討した。

I. 対象および方法

1. 被験者

被験者は、Table 1 に示す 10 名で、年齢 22 ~ 25 歳、体重 $54 \sim 63.2 \text{ kg}$ 、身長 $160 \sim 175 \text{ cm}$ の健康成人男子である。被験者はいずれも理学的検査ならびに所定の臨床検査にもとづき本試験に適すると判定されたものである。試験に先立ち、被験者には薬剤の種類、薬理作用、副作用、試験の意義内容等について十分な説明をしたのち、文書にて同意を得た。

2. 試験薬剤

試験薬剤は 1 錠中 BAY o 9867 100 mg を含有する白色錠 (Lot No. 974244)、および 200 mg を含有する白色錠 (Lot No. 974228) を使用した。

3. 使用量・用法

投与量は 1 回 300 mg および 400 mg で、1 日 2 回, 7 日間連続使用した。本剤を朝・夕食の 1 時間後に水 100 ml とともに服用させた。

被験者は投与開始前夜から終了翌朝まで入院させた。食事ならびに飲水は Fig. 2 に示すスケジュールに従い一定の時刻に全員同一のものを摂取させた。

4. 検査スケジュール

本試験のスケジュールを Fig. 2 に示した。検査項目は Table 2 に示す如くである。自覚症状については問診によるほか、各被験者自身が所定の用紙に記入した。また、尿中結晶の有無については経時的に採取した尿を対象に顕微鏡下 (尿沈渣) で観察した。

Fig. 1 Chemical structure of BAY o 9867

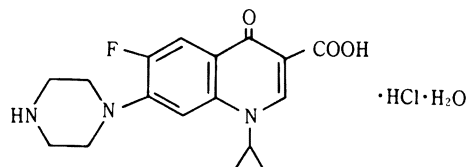
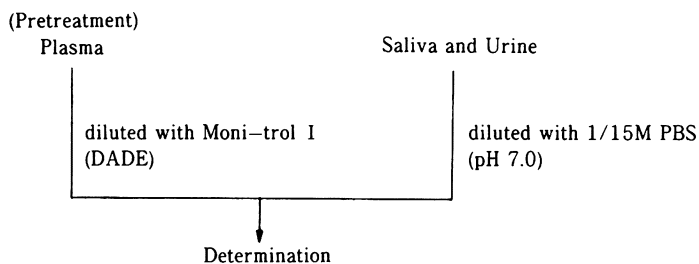


Table 2 Examination items

| |
|--|
| 1. Signs and symptoms |
| 2. Blood pressure, Pulse rate, Body temperature, ECG |
| 3. Laboratory tests |
| 1) Hematology : RBC, WBC, WBC Differential, Hb, Ht, Platelets, Prothrombin time |
| 2) Biochemistry : GOT, GPT, γ -GTP, Al-P, LDH, T-bilirubin, ChE, A/G, T-protein, BUN, Creatinine, Na ⁺ , K ⁺ , Cl ⁻ , Ca ⁺⁺ , T-cholesterol, TG, BS |
| 3) Urinalysis : pH, Protein, Sugar, Urobilinogen, Sediments |
| 4. Plasma concentration, Urine concentration (Urinary excretion) |
| 5. Saliva concentration |

Fig. 3 Bioassay method of BAY o 9867 concentrations in body fluids



(Determination : Agar well method)

Test organism : *E. coli* Kp

Medium : Heart Infusion Agar (Difco) 40 g/L

Medium amount : 10 ml seed layer/90 mm Petri dish

Inoculum size : 1% of overnight culture (Heart Infusion Broth, 37°C)

Diluent for standard solution : Plasma ; Moni-trol I (DADE)

Saliva and urine; 1/15M PBS (pH 7.0)

Well size : 8 mm

Incubation : 37°C, 18 hr

Detection limit : 0.02 µg/ml

5. 濃度測定

血液、唾液、尿中濃度測定用検体の採取スケジュールはFig. 2の通りである。検体は、採取後速やかに凍結し、測定時まで -20°C 以下で保存した。

薬物濃度の測定はAgar well法¹⁾により行った。測定法の概略をFig. 3に示す。

II. 試験成績

1. 血中濃度

BAY o 9867 1回300 mgまたは400 mgを1日2回、7日間計14回連続使用後の血中濃度の推移をTable 3, 4, Fig. 4に示す。300 mg使用群の血中濃度は初回投与後1~2時間で最高(平均 $0.89\ \mu\text{g/ml}$)に達し、その後の使用でも同様の推移(平均 $0.89\sim 0.93\ \mu\text{g/ml}$)を示

し、最高濃度の上積みは認められなかった。毎回使用前の濃度は、初日2回目投与前で平均 $0.19\ \mu\text{g/ml}$ であり、以後は平均 $0.19\sim 0.20\ \mu\text{g/ml}$ の値で推移し、連続使用による経日的な底上げは認められなかった。400 mg使用群の血中濃度は初回使用後2時間で最高(平均 $1.50\ \mu\text{g/ml}$)に達し、以後使用3, 5, 7日目の測定で最高血中濃度はいずれも第1回目使用后1~2時間でみられ、平均 $1.50\sim 2.05\ \mu\text{g/ml}$ の値を示し、連続使用による最高血中濃度の上積みはみられなかった。毎回使用前の濃度は初日、2回目使用前で平均 $0.27\ \mu\text{g/ml}$ であり、以後は平均 $0.27\sim 0.38\ \mu\text{g/ml}$ で推移し連続使用による底上げは認められなかった。

これらの測定値にもとづき Two compartment open

Table 3 Plasma concentrations of BAY o 9867 after multiple oral administration to male healthy volunteers
300mg \times 2/day \times 7 days

| Day | Volun- teer No. | Time after administration (hr) | | | | | | | | | | AUC 0~24hr (μ g \cdot hr/ml) |
|---------|--------------------|--------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|---|
| | | 0 | 1 | 2 | 4 | 6 | 10 | 12 | 13 | 15 | 24hr | |
| 1st day | 1 | — | 0.69 | 0.83 | 0.72 | 0.40 | 0.20 | 1.09 | 0.86 | 0.54 | 0.14 | 11.70 |
| | 2 | — | 1.28 | 1.25 | 0.51 | 0.33 | 0.14 | 0.70 | 0.93 | 0.70 | 0.15 | 12.56 |
| | 3 | — | 0.22 | 0.72 | 0.87 | 0.46 | 0.19 | 0.31 | 0.56 | 0.73 | 0.21 | 11.26 |
| | 4 | — | 0.67 | 0.84 | 0.55 | 0.35 | 0.19 | 0.36 | 0.49 | 0.37 | 0.28 | 9.22 |
| | 5 | — | 0.93 | 0.83 | 0.55 | 0.36 | 0.24 | 0.16 | 0.28 | 0.78 | 0.29 | 11.33 |
| | Mean \pm S.E. | — | 0.76 0.17 | 0.89 0.09 | 0.64 0.07 | 0.38 0.02 | 0.19 0.02 | 0.52 0.17 | 0.62 0.12 | 0.62 0.08 | 0.21 0.03 | 11.21 0.55 |
| 3rd day | 1 | 0.19 | 0.36 | 0.97 | 0.81 | 0.23 | 0.17 | 0.37 | 0.63 | 0.65 | | |
| | 2 | 0.14 | 0.46 | 1.00 | 0.76 | 0.17 | 0.13 | 0.39 | 0.59 | 0.69 | | |
| | 3 | 0.13 | 1.07 | 0.85 | 0.50 | 0.13 | 0.16 | 0.91 | 0.94 | 0.46 | | |
| | 4 | 0.23 | 1.10 | 0.83 | 0.44 | 0.16 | 0.27 | 0.13 | 0.21 | 0.27 | | |
| | 5 | 0.28 | 0.30 | 0.79 | 0.74 | 0.27 | 0.19 | 0.21 | 0.24 | 0.58 | | |
| | Mean \pm S.E. | 0.19 0.03 | 0.66 0.18 | 0.89 0.04 | 0.65 0.07 | 0.23 0.03 | 0.17 0.03 | 0.40 0.14 | 0.52 0.14 | 0.53 0.08 | | |
| 5th day | 1 | 0.21 | 0.60 | 0.69 | 1.06 | 0.18 | 0.19 | 0.25 | 0.46 | 0.70 | | |
| | 2 | 0.15 | 0.46 | 0.83 | 0.82 | 0.19 | 0.15 | 0.23 | 0.38 | 0.68 | | |
| | 3 | 0.19 | 1.57 | 1.07 | 0.50 | 0.15 | 0.24 | 0.15 | 0.27 | 0.56 | | |
| | 4 | 0.17 | 0.94 | 0.78 | 0.85 | 0.24 | 0.23 | 0.93 | 0.83 | 0.63 | | |
| | 5 | 0.23 | 1.06 | 1.05 | 0.64 | 0.23 | 0.20 | 1.00 | 1.08 | 0.82 | | |
| | Mean \pm S.E. | 0.19 0.01 | 0.93 0.19 | 0.88 0.08 | 0.77 0.10 | 0.20 0.02 | 0.51 0.19 | 0.60 0.15 | 0.60 0.04 | 0.68 0.04 | | |
| 7th day | 1 | 0.20 | 1.02 | 0.89 | 0.72 | 0.45 | 0.22 | 0.32 | 0.32 | 0.96 | 0.22 | 13.14 |
| | 2 | 0.20 | 1.09 | 0.94 | 0.65 | 0.36 | 0.17 | 1.40 | 0.83 | 0.48 | 0.14 | 12.11 |
| | 3 | 0.16 | 0.70 | 0.86 | 0.61 | 0.40 | 0.17 | 1.35 | 0.98 | 0.55 | 0.14 | 12.15 |
| | 4 | 0.16 | 1.26 | 0.71 | 0.39 | 0.36 | 0.14 | 0.72 | 0.88 | 0.71 | 0.21 | 11.94 |
| | 5 | 0.30 | 0.41 | 1.19 | 0.74 | 0.51 | 0.26 | 0.65 | 0.75 | 0.69 | 0.29 | 13.34 |
| | Mean \pm S.E. | 0.20 0.03 | 0.90 0.15 | 0.92 0.08 | 0.62 0.06 | 0.42 0.03 | 0.19 0.02 | 0.89 0.21 | 0.75 0.11 | 0.68 0.08 | 0.20 0.03 | 12.54 0.29 |

— : less than detection limit (0.02 μ g/ml)

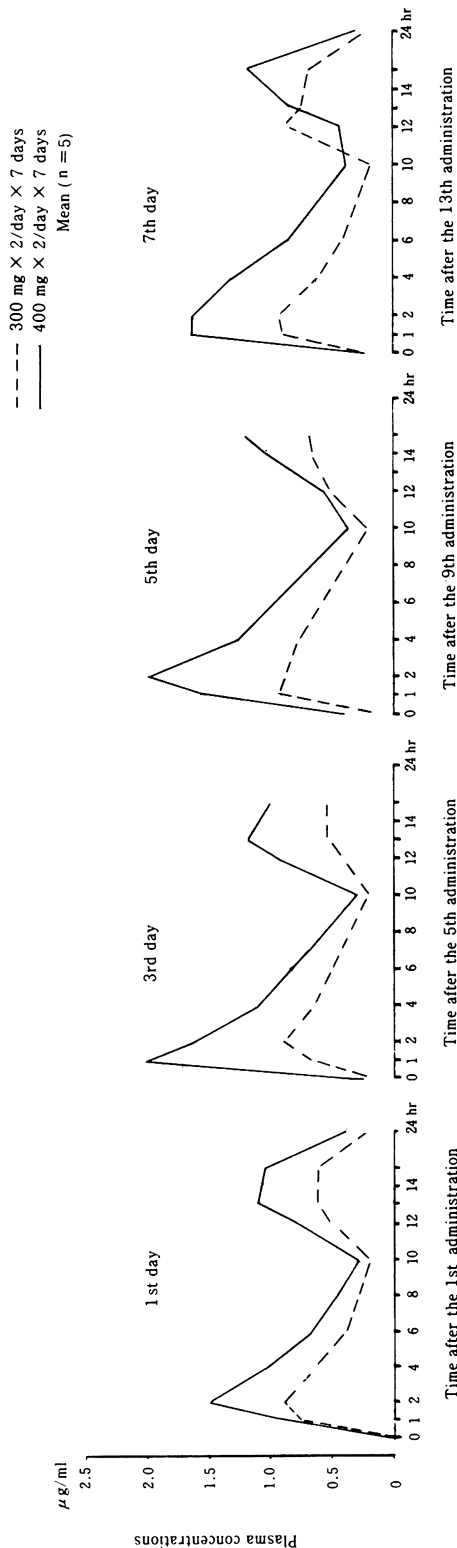
Table 4 Plasma concentrations of BAY o 9867 after multiple oral administration to male healthy volunteers

400mg × 2/day × 7days

| Day | Volunteer No. | Time after administration (hr) | | | | | | | | | | AUC 0~24hr ($\mu\text{g}\cdot\text{hr}/\text{ml}$) |
|---------|---------------|--------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--|
| | | 0 | 1 | 2 | 4 | 6 | 10 | 12 | 13 | 15 | 24hr | |
| 1st day | 6 | — | 1.52 | 1.95 | 1.42 | 1.03 | 0.37 | 1.09 | 1.17 | 1.14 | 0.54 | 23.58 |
| | 7 | — | 1.59 | 2.02 | 0.95 | 0.56 | 0.23 | 0.20 | 0.34 | 0.88 | 0.53 | 16.93 |
| | 8 | — | 0.03 | 1.26 | 1.03 | 0.57 | 0.24 | 0.21 | 0.30 | 1.22 | 0.37 | 15.55 |
| | 9 | — | 0.18 | 0.68 | 1.02 | 0.72 | 0.34 | 0.59 | 1.77 | 1.27 | 0.33 | 18.43 |
| | 10 | — | 1.40 | 1.60 | 0.68 | 0.43 | 0.19 | 1.75 | 1.90 | 0.76 | 0.20 | 17.58 |
| | Mean ±S.E. | — | 0.94 0.34 | 1.50 0.25 | 1.02 0.12 | 0.66 0.10 | 0.27 0.03 | 0.77 0.29 | 1.10 0.34 | 1.05 0.10 | 0.39 0.06 | 18.41 1.37 |
| 3rd day | 6 | 0.36 | 1.31 | 1.91 | 1.75 | 0.49 | 0.49 | 1.71 | 1.41 | 1.09 | 0.90 | |
| | 7 | 0.25 | 2.38 | 1.86 | 1.06 | 0.26 | 0.26 | 0.41 | 1.02 | 0.90 | 0.92 | |
| | 8 | 0.33 | 2.40 | 1.55 | 0.84 | 0.24 | 0.24 | 0.37 | 0.50 | 0.92 | 1.27 | |
| | 9 | 0.28 | 0.81 | 1.46 | 1.23 | 0.32 | 0.32 | 0.44 | 1.52 | 1.45 | 0.76 | |
| | 10 | 0.12 | 3.37 | 1.51 | 0.72 | 0.15 | 0.15 | 1.77 | 1.45 | 0.76 | 0.99 | |
| | Mean ±S.E. | 0.27 0.04 | 2.05 0.45 | 1.66 0.09 | 1.12 0.18 | 0.29 0.06 | 0.94 0.33 | 1.18 0.19 | 1.10 0.42 | 1.14 2.10 | 0.99 0.09 | |
| 5th day | 6 | 0.34 | 1.36 | 1.99 | 1.75 | 0.50 | 0.50 | 0.87 | 1.10 | 1.14 | 0.61 | |
| | 7 | 0.33 | 0.90 | 2.04 | 1.34 | 0.32 | 0.32 | 0.38 | 0.42 | 2.10 | 1.11 | |
| | 8 | 0.37 | 0.98 | 2.14 | 1.01 | 0.32 | 0.32 | 0.32 | 0.34 | 0.61 | 1.05 | |
| | 9 | 0.65 | 1.28 | 2.24 | 1.58 | 0.46 | 0.46 | 0.55 | 1.06 | 1.11 | 0.24 | |
| | 10 | 0.21 | 3.06 | 1.61 | 0.61 | 0.17 | 0.17 | 0.67 | 1.19 | 1.05 | 0.53 | 30.68 |
| | Mean ±S.E. | 0.38 0.07 | 1.52 0.40 | 2.00 0.11 | 1.26 0.20 | 0.35 0.06 | 0.56 0.10 | 0.86 0.18 | 0.82 0.18 | 1.20 0.24 | 1.75 0.24 | 30.68 2.86 |
| 7th day | 6 | 0.62 | 1.31 | 1.77 | 2.24 | 1.51 | 0.71 | 0.86 | 1.31 | 1.75 | 0.29 | 19.68 |
| | 7 | 0.26 | 1.76 | 1.90 | 1.07 | 0.59 | 0.26 | 0.19 | 0.20 | 1.52 | 0.29 | 18.30 |
| | 8 | 0.23 | 0.46 | 1.18 | 1.30 | 0.93 | 0.42 | 0.47 | 0.75 | 1.13 | 0.28 | 21.06 |
| | 9 | 0.28 | 2.42 | 1.73 | 1.32 | 0.93 | 0.41 | 0.33 | 1.09 | 0.99 | 0.37 | 13.13 |
| | 10 | 0.09 | 2.26 | 1.55 | 0.69 | 0.35 | 0.07 | 0.28 | 0.90 | 0.58 | 0.20 | 20.57 |
| | Mean ±S.E. | 0.30 0.09 | 1.64 0.35 | 1.63 0.12 | 1.32 0.26 | 0.86 0.20 | 0.37 0.11 | 0.43 0.12 | 0.85 0.19 | 1.19 0.20 | 0.33 0.06 | 20.57 2.86 |

— : less than detection limit (0.02 $\mu\text{g}/\text{ml}$)

Fig. 4 Plasma concentrations of BAY o 9867 after multiple oral administration to male healthy volunteers



modelにより算出した Pharmacokinetic parameters を Table 5 に示す。300 mg 使用群での C max. は平均 $0.95 \sim 1.09 \mu\text{g/ml}$, T max. は平均 $1.4 \sim 2.0 \text{ hr.}$, $\text{AUC}_{0-10 \text{ hr.}}$ は平均 $4.91 \sim 6.04 \mu\text{g} \cdot \text{hr/ml}$, 使用 1, 7 日目での生物学的半減期 T $_{1/2}$ は, それぞれ 3.53 および 3.57 hr. であった。400 mg 使用群での C max. は平均 $1.57 \sim 2.30 \mu\text{g/ml}$, T max. は平均 $1.4 \sim 2.4 \text{ hr.}$, $\text{AUC}_{0-10 \text{ hr.}}$ は平均 $7.77 \sim 10.81 \mu\text{g} \cdot \text{hr/ml}$, 使用 1, 7 日目での生物学的半減期 T $_{1/2}$ は, それぞれ 3.17 および 3.15 hr. であった。

2. 唾液中濃度

BAY o 9867 300 mg または 400 mg を 1 日 2 回, 7 日間連続使用後の唾液中濃度の推移を Table 6, 7, Fig. 5 に示す。BAY o 9867 使用後の唾液中最高濃度は, いずれの使用量においても使用 2 または 4 時間後の測定時に認められ, 300 mg 使用群で平均 $0.33 \sim 0.46 \mu\text{g/ml}$, 400 mg 使用群で平均 $0.46 \sim 0.82 \mu\text{g/ml}$ であり, 血中濃度と同様投与量に依存した濃度上昇が認められた。

3. 尿中排泄

BAY o 9867 300 mg または 400 mg を 1 日 2 回, 7 日間連続投与後の尿中排泄量ならびに累積尿中排泄率を Table 8, 9, Fig. 6 に示す。300 mg 使用群では初回投与後 24 時間で平均 29.1% の排泄率で以後若干増加するもののほぼ一定した排泄率を示し, 平均 $32.6 \sim 36.4\%$ の累積尿中排泄率であった。400 mg 使用群では, 初回投与後 24 時間で 29.8% 排泄され, 2 日目以降は平均 $31.8 \sim 35.7\%$ の累積尿中排泄率を示した。

4. 安全性

1) 自覚症状ならびに臨床検査値

BAY o 9867 300 mg または 400 mg のいずれの用量群においても自覚的異常を訴えるものはなく, また服薬中の血圧, 脈拍数, 体温, 心電図などに異常所見は認められなかった。Fig. 2 に従って検査された臨床検査の結果を Table 10, 11 に示す。

300 mg 使用群で 1 例に GOT の軽度上昇がみられた。400 mg 使用群では 1 例に GOT, GPT, 他の 1 例で GOT, GPT, γ -GTP の軽度上昇がみられたが, これらはいずれも一過性で, その後の追跡調査では正常域に復していた。

2) 尿中結晶

経時的に採取した尿について, 尿沈渣を顕微鏡下で観察し, 尿中結晶の有無を検索したが, いずれの検体にも BAY o 9867 の結晶は認められなかった。

Ⅲ. 考 察

ピリドン・カルボン酸系の新しい経口抗菌剤 BAY o 9867 の薬物動態ならびに安全性について健康成人男子

Table 5 Pharmacokinetic parameters (C_{max}, T_{max}, T_{1/2} and AUC_{0-10hr}) in male healthy volunteers after the first daily dose

| Volunteer No. | Dose | 1st day | | | 3rd day | | | 5th day | | | 7th day | | | | | |
|---------------|--|--------------------------|-----------------------|-----------------------|----------------------------------|--------------------------|-----------------------|----------------------------------|--------------------------|-----------------------|----------------------------------|--------------------------|-----------------------|----------------------------------|-------|------|
| | | C _{max} (μg/ml) | T _{max} (hr) | T _{1/2} (hr) | AUC _{0-10hr} (μg·hr/ml) | C _{max} (μg/ml) | T _{max} (hr) | AUC _{0-10hr} (μg·hr/ml) | C _{max} (μg/ml) | T _{max} (hr) | AUC _{0-10hr} (μg·hr/ml) | C _{max} (μg/ml) | T _{max} (hr) | AUC _{0-10hr} (μg·hr/ml) | | |
| 1 | 300mg × 2/day × 7 days Non-fasting | 0.83 | 2 | 3.34 | 4.98 | 0.97 | 2 | 5.84 | 1.06 | 4 | 6.52 | 1.02 | 1 | 3.84 | 5.69 | |
| 2 | | 1.28 | 1 | 2.65 | 5.45 | 1.00 | 2 | 5.58 | 0.83 | 2 | 5.63 | 1.09 | 1 | 3.18 | 5.32 | |
| 3 | | 0.87 | 4 | 3.14 | 4.80 | 1.07 | 1 | 4.80 | 1.57 | 1 | 1 | 5.72 | 0.86 | 2 | 3.25 | 4.83 |
| 4 | | 0.84 | 2 | 3.99 | 4.46 | 1.10 | 1 | 4.70 | 0.94 | 1 | 1 | 6.32 | 1.26 | 1 | 3.60 | 4.55 |
| 5 | | 0.93 | 1 | 4.51 | 4.84 | 0.79 | 2 | 5.40 | 1.06 | 1 | 1 | 6.00 | 1.19 | 2 | 4.00 | 5.88 |
| Mean | | 0.95 | 2.0 | 3.53 | 4.91 | 0.99 | 1.6 | 5.26 | 1.09 | 1.8 | 6.04 | 1.08 | 1.4 | 3.57 | 5.25 | |
| ± S.E. | | 0.08 | 0.5 | 0.33 | 0.16 | 0.05 | 0.2 | 0.22 | 0.13 | 0.6 | 0.17 | 0.07 | 0.2 | 0.16 | 0.25 | |
| 6 | 400mg × 2/day × 7 days Non-fasting | 1.95 | 2 | 3.03 | 11.12 | 1.91 | 2 | 12.83 | 1.99 | 2 | 13.02 | 2.24 | 4 | 3.67 | 14.71 | |
| 7 | | 2.02 | 2 | 2.96 | 8.66 | 2.38 | 1 | 10.32 | 2.04 | 2 | 10.45 | 1.90 | 2 | 3.00 | 9.17 | |
| 8 | | 1.26 | 2 | 2.90 | 6.17 | 2.40 | 1 | 8.97 | 2.14 | 2 | 9.38 | 1.30 | 4 | 3.49 | 8.58 | |
| 9 | | 1.02 | 4 | 3.70 | 6.08 | 1.46 | 2 | 9.02 | 2.24 | 2 | 12.67 | 2.42 | 1 | 3.80 | 11.41 | |
| 10 | | 1.60 | 2 | 3.28 | 6.83 | 3.37 | 1 | 9.03 | 3.06 | 1 | 8.53 | 2.26 | 1 | 1.80 | 7.20 | |
| Mean | | 1.57 | 2.4 | 3.17 | 7.77 | 2.30 | 1.4 | 10.03 | 2.29 | 1.8 | 10.81 | 2.02 | 2.4 | 3.15 | 10.21 | |
| ± S.E. | | 0.19 | 0.4 | 0.15 | 0.96 | 0.32 | 0.2 | 0.74 | 0.20 | 0.2 | 0.89 | 0.20 | 0.7 | 0.36 | 1.31 | |

Table 6 Salivary concentrations of BAY o 9867 after multiple oral administration to male healthy volunteers
300mg X 2/day X 7days

| Day | Volunteer No. | Time after administration (hr) | | | | | | | | | | |
|---------|---------------|--------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|------|
| | | 0 | 1 | 2 | 4 | 6 | 10 | 12 | 13 | 15 | 24 | |
| 1st day | 1 | — | 0.06 | 0.27 | 0.42 | 0.12 | 0.05 | 0.55 | 0.67 | 0.19 | 0.05 | 0.05 |
| | 2 | — | 0.27 | 0.80 | 0.36 | 0.10 | 0.03 | 0.18 | 0.29 | 0.26 | 0.05 | 0.05 |
| | 3 | — | — | 0.25 | 0.53 | 0.19 | 0.06 | 0.09 | 0.17 | 0.31 | 0.24 | 0.06 |
| | 4 | — | 0.13 | 0.55 | 0.21 | 0.07 | — | 0.12 | 0.13 | 0.10 | 0.06 | 0.05 |
| | 5 | — | 0.45 | 0.28 | 0.13 | 0.06 | — | — | 0.03 | 0.20 | 0.05 | 0.05 |
| | Mean ± S.E. | — | 0.18 0.08 | 0.43 0.11 | 0.33 0.07 | 0.11 0.02 | 0.03 0.01 | 0.19 0.10 | 0.26 0.11 | 0.21 0.04 | 0.09 0.04 | 0.04 |
| 3rd day | 1 | 0.10 | 0.10 | 0.27 | 0.50 | — | 0.06 | 0.09 | 0.19 | 0.21 | — | — |
| | 2 | 0.08 | 0.08 | 0.30 | 0.40 | — | 0.03 | 0.06 | 0.15 | 0.25 | — | — |
| | 3 | 0.06 | 0.44 | 0.80 | 0.42 | — | 0.04 | 0.32 | 0.49 | 0.17 | — | — |
| | 4 | 0.02 | 0.60 | 0.54 | 0.18 | — | — | — | — | 0.04 | — | — |
| | 5 | 0.05 | 0.05 | 0.13 | 0.26 | — | 0.03 | — | 0.03 | 0.12 | 0.12 | — |
| | Mean ± S.E. | 0.06 0.01 | 0.25 0.11 | 0.41 0.12 | 0.35 0.06 | — | 0.03 0.01 | 0.09 0.06 | 0.17 0.09 | 0.16 0.04 | — | — |
| 5th day | 1 | 0.09 | 0.09 | 0.21 | 0.40 | — | 0.06 | 0.05 | 0.12 | 0.23 | — | — |
| | 2 | 0.05 | 0.05 | 0.19 | 0.51 | — | 0.04 | 0.03 | 0.06 | 0.14 | — | — |
| | 3 | 0.12 | 0.42 | 0.69 | 0.28 | — | 0.03 | 0.04 | 0.05 | 0.20 | — | — |
| | 4 | 0.03 | 0.32 | 0.31 | 0.32 | — | 0.03 | 0.36 | 0.50 | 0.18 | — | — |
| | 5 | — | 0.14 | 0.21 | 0.13 | — | — | 0.24 | 0.24 | 0.10 | — | — |
| | Mean ± S.E. | 0.06 0.02 | 0.20 0.07 | 0.32 0.09 | 0.33 0.06 | — | 0.03 0.01 | 0.14 0.07 | 0.19 0.08 | 0.17 0.02 | — | — |
| 7th day | 1 | 0.11 | 0.22 | 0.53 | 0.40 | 0.18 | 0.04 | 0.07 | 0.09 | 0.35 | 0.08 | — |
| | 2 | 0.12 | 0.23 | 0.50 | 0.38 | 0.10 | 0.04 | 0.40 | 0.51 | 0.18 | 0.05 | — |
| | 3 | 0.18 | 0.15 | 0.53 | 0.45 | 0.12 | 0.05 | 0.46 | 0.64 | 0.22 | 0.12 | — |
| | 4 | 0.04 | 0.58 | 0.53 | 0.17 | 0.05 | — | 0.21 | 0.43 | 0.27 | 0.05 | — |
| | 5 | 0.06 | 0.04 | 0.19 | 0.19 | 0.09 | — | 0.05 | 0.09 | 0.12 | 0.11 | — |
| | Mean ± S.E. | 0.10 0.02 | 0.24 0.09 | 0.46 0.07 | 0.32 0.06 | 0.11 0.02 | 0.03 0.01 | 0.24 0.08 | 0.35 0.11 | 0.23 0.04 | 0.08 0.01 | — |

— : less than detection limit (0.02 µg/ml)

Table 7 Salivary concentrations of BAY o 9867 after multiple oral administration to male healthy volunteers
400mg × 2/day × 7days

| Day | Volunteer No. | Time after administration (hr) | | | | | | | | | | | |
|---------|---------------|--------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|--|--|
| | | 0 | 1 | 2 | 4 | 6 | 10 | 12 | 13 | 15 | 24 | | |
| 1st day | 6 | — | 0.06 | 0.35 | 0.47 | 0.08 | 0.03 | 0.11 | 0.40 | 0.48 | 0.13 | | |
| | 7 | — | 0.21 | 0.52 | 0.27 | 0.11 | 0.03 | 0.03 | 0.04 | 0.20 | 0.27 | | |
| | 8 | — | — | 0.13 | 0.59 | 0.07 | — | 0.03 | 0.03 | 0.23 | 0.10 | | |
| | 9 | — | 0.13 | 0.24 | 0.77 | 0.20 | 0.24 | 0.11 | 0.58 | 0.37 | 0.17 | | |
| | 10 | — | 0.64 | 0.73 | 0.50 | 0.07 | — | 0.20 | 0.45 | 0.18 | 0.02 | | |
| | Mean ± S.E. | — | 0.21 ± 0.11 | 0.39 ± 0.11 | 0.52 ± 0.08 | 0.11 ± 0.02 | 0.06 ± 0.05 | 0.10 ± 0.03 | 0.30 ± 0.11 | 0.29 ± 0.06 | 0.14 ± 0.04 | | |
| 3rd day | 6 | 0.13 | 0.19 | 0.40 | 0.51 | 0.07 | 0.07 | 0.30 | 0.67 | 0.28 | | | |
| | 7 | 0.17 | 0.44 | 0.95 | 0.41 | 0.05 | 0.05 | 0.11 | 0.28 | 0.33 | | | |
| | 8 | 0.60 | 1.11 | 0.76 | 0.15 | — | — | 0.04 | 0.04 | 0.13 | | | |
| | 9 | 0.17 | 0.52 | 1.13 | 0.66 | 0.04 | 0.04 | 0.05 | 0.68 | 0.39 | | | |
| | 10 | 0.03 | 0.38 | 0.86 | 0.42 | 0.02 | 0.02 | 0.11 | 0.49 | 0.26 | | | |
| | Mean ± S.E. | 0.22 ± 0.10 | 0.53 ± 0.16 | 0.82 ± 0.12 | 0.43 ± 0.08 | 0.04 ± 0.01 | 0.04 ± 0.01 | 0.12 ± 0.05 | 0.43 ± 0.12 | 0.28 ± 0.04 | | | |
| 5th day | 6 | 0.12 | 0.18 | 0.32 | 0.45 | 0.05 | 0.05 | 0.09 | 0.25 | 0.23 | | | |
| | 7 | 0.18 | 0.11 | 0.42 | 0.53 | 0.05 | 0.05 | 0.08 | 0.15 | 0.45 | | | |
| | 8 | 0.03 | 0.07 | 0.60 | 0.32 | 0.02 | 0.02 | 0.04 | 0.04 | 0.11 | | | |
| | 9 | 0.41 | 0.64 | 0.91 | 0.88 | 0.06 | 0.06 | 0.06 | 0.24 | 0.39 | | | |
| | 10 | 0.05 | 0.45 | 0.91 | 0.41 | 0.02 | 0.02 | 0.06 | 0.19 | 0.36 | | | |
| | Mean ± S.E. | 0.16 ± 0.07 | 0.29 ± 0.11 | 0.63 ± 0.12 | 0.52 ± 0.10 | 0.04 ± 0.01 | 0.04 ± 0.01 | 0.07 ± 0.01 | 0.17 ± 0.04 | 0.31 ± 0.06 | | | |
| 7th day | 6 | 0.19 | 0.12 | 0.31 | 0.60 | 0.19 | 0.04 | 0.13 | 0.30 | 0.30 | 0.10 | | |
| | 7 | 0.20 | 0.39 | 0.52 | 0.55 | 0.15 | 0.06 | 0.04 | 0.02 | 0.38 | 0.23 | | |
| | 8 | 0.05 | 0.12 | 0.12 | 0.27 | 0.12 | 0.03 | 0.03 | 0.07 | 0.24 | 0.05 | | |
| | 9 | 0.18 | 1.08 | 0.58 | 0.58 | 0.18 | 0.19 | 0.02 | 0.36 | 0.23 | 0.28 | | |
| | 10 | 0.05 | 0.57 | 0.77 | 0.26 | 0.07 | — | — | 0.07 | 0.19 | 0.07 | | |
| | Mean ± S.E. | 0.13 ± 0.03 | 0.46 ± 0.18 | 0.46 ± 0.11 | 0.45 ± 0.08 | 0.14 ± 0.02 | 0.06 ± 0.03 | 0.04 ± 0.02 | 0.16 ± 0.07 | 0.27 ± 0.03 | 0.15 ± 0.05 | | |

— : less than detection limit (0.02 µg/ml)

Fig. 5 Salivary concentrations of BAY o 9867 after multiple oral administration to male healthy volunteers

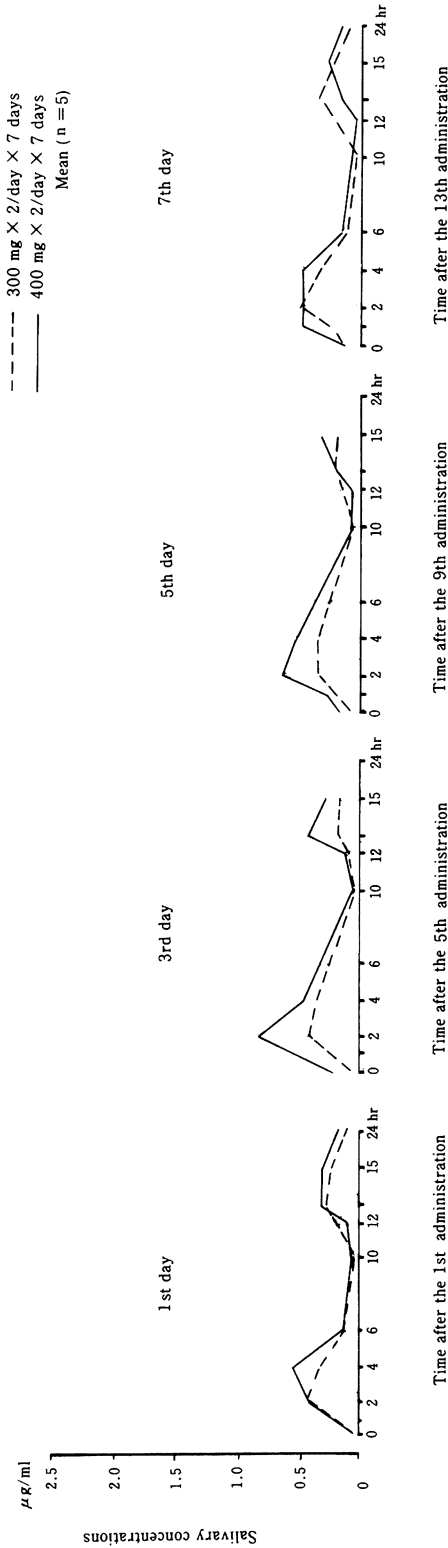


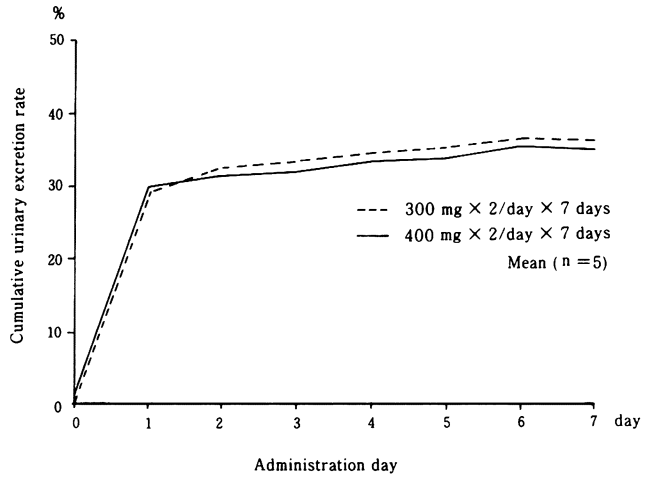
Table 8 Urinary excretion of BAY o 9867 after multiple oral administration to male healthy volunteers 300mg x 2/day x 7days

| Volunteer No. | Urinary daily excretion (mg) | | | | | | | Cumulative urinary excretion rate (%) | | | | | | |
|---------------|------------------------------|-------|-------|-------|-------|-------|-------|---------------------------------------|------|------|------|------|------|------|
| | Administration day | | | | | | | Administration day | | | | | | |
| | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th |
| 1 | 221.5 | 248.1 | 247.8 | 205.1 | 268.6 | 270.8 | 230.1 | 36.9 | 39.1 | 39.9 | 38.4 | 39.7 | 40.6 | 40.3 |
| 2 | 205.3 | 180.0 | 212.3 | 190.4 | 193.8 | 298.6 | 214.5 | 34.2 | 32.1 | 33.2 | 32.8 | 32.7 | 35.6 | 35.6 |
| 3 | 176.1 | 183.3 | 161.8 | 214.1 | 214.0 | 307.9 | 184.6 | 29.4 | 29.9 | 29.0 | 30.6 | 31.6 | 34.9 | 34.3 |
| 4 | 146.7 | 236.4 | 231.9 | 277.4 | 235.6 | 182.5 | 213.3 | 24.4 | 31.9 | 34.2 | 37.2 | 37.6 | 36.4 | 36.3 |
| 5 | 122.9 | 238.0 | 200.7 | 249.7 | 237.0 | 248.0 | 184.9 | 20.5 | 30.1 | 31.2 | 33.8 | 34.9 | 36.0 | 35.3 |
| Mean | 174.5 | 217.2 | 210.9 | 227.3 | 229.8 | 261.6 | 205.5 | 29.1 | 32.6 | 33.5 | 34.6 | 35.3 | 36.7 | 36.4 |
| ± S.E. | 18.2 | 14.6 | 14.7 | 15.9 | 12.5 | 22.4 | 9.0 | 3.0 | 1.7 | 1.8 | 1.4 | 1.5 | 1.0 | 1.0 |

Table 9 Urinary excretion of BAY o 9867 after multiple oral administration to male healthy volunteers

| Volunteer No. | 400mg×2/day×7days | | | | | | | | | | | | | |
|---------------|------------------------------|-------|-------|-------|-------|---------------------------------------|-------|------|------|------|------|------|------|------|
| | Urinary daily excretion (mg) | | | | | Cumulative urinary excretion rate (%) | | | | | | | | |
| | Administration day | | | | | Administration day | | | | | | | | |
| | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th |
| 6 | 251.2 | 291.7 | 253.4 | 295.3 | 268.1 | 343.1 | 227.0 | 31.4 | 33.9 | 33.2 | 34.1 | 34.0 | 35.5 | 34.5 |
| 7 | 143.1 | 212.9 | 216.4 | 231.8 | 282.3 | 311.6 | 240.1 | 17.9 | 22.3 | 23.9 | 25.1 | 27.2 | 29.1 | 29.3 |
| 8 | 297.5 | 302.1 | 279.4 | 363.9 | 299.8 | 353.2 | 294.5 | 37.2 | 37.5 | 36.6 | 38.8 | 38.6 | 39.5 | 39.1 |
| 9 | 288.7 | 333.7 | 348.1 | 357.6 | 344.3 | 332.8 | 331.5 | 36.1 | 38.9 | 40.4 | 41.5 | 41.8 | 41.8 | 41.7 |
| 10 | 212.8 | 211.6 | 210.5 | 278.5 | 234.9 | 405.7 | 193.1 | 26.6 | 26.5 | 26.5 | 28.5 | 28.7 | 32.4 | 31.2 |
| Mean | 238.7 | 270.4 | 261.6 | 305.4 | 285.9 | 349.3 | 257.2 | 29.8 | 31.8 | 32.1 | 33.6 | 34.1 | 35.7 | 35.2 |
| ± S.E. | 28.2 | 24.7 | 25.0 | 24.9 | 18.1 | 15.7 | 24.7 | 3.5 | 3.2 | 3.1 | 3.1 | 2.8 | 2.3 | 2.3 |

Fig. 6 Urinary excretion of BAY o 9867 after multiple oral administration to male healthy volunteers



志願者を対象にして検討した。

BAY o 9867 300 mg あるいは 400 mg 1 日 2 回, 7 日間連続使用での血中濃度の推移は連日, ほぼ一定した経過を示し, 最高血中濃度は投与後 1~2 時間でみられ, 連続投与による血中濃度の上昇はみられなかった。また, 毎回投与前の濃度についても上昇は認められていない。これらのことから, 本剤は連続投与でも蓄積傾向はないものと考えられた。BAY o 9867 の唾液濃度は血中濃度とよく相関した推移を示し, 唾液濃度は血中濃度の約 1/2~1/3 であり良好な移行を示した。

BAY o 9867 連続投与での尿中排泄率は 300 mg 投与群で平均 29.1~36.4%, 400 mg 投与群では平均 29.8~35.7% で, 連続使用においてもほぼ一定した尿中排泄率を示した。

本試験実施中本剤の安全性について詳細に検討したが, 同種抗菌剤の副作用症状は主として消化器症状が主であり, その他発疹などの過敏症状, めまい, ふらつきなどの中枢神経系の副作用症状が報告されているが³⁾, 今回の試験においてこのような所見は全くみられなかった。臨床検査所見では, 300 mg 投与群で 1 例に GPT の上昇, 400 mg 投与群の 1 例に GOT, GPT, 他の 1 例に GOT, GPT, γ -GTP の上昇が認められたが, これらはいずれも軽度で, 一過性のものであった。本剤に関する臨床試験成績のまとめでは, その約 1.2% にトランスアミナーゼの上昇が報告されており⁴⁻⁶⁾, この頻度は他の抗菌剤に比し特に高いものではなく, 今回比較的多くみられたトランスアミナーゼの上昇については軽度であり一過性

Table 10-1 Clinical laboratory findings 300mg×2/day ×7days (Non-fasting)

| Items | | Normal range | M.Y. | | | | | | | K.S. | | | | | | | |
|-------------------------|--|---|---------|--------------|--------------|---------|--------------|--------------|--------------|----------------------------|--------------|----------------------------|--------------|--------------|---------|--------------|---------|
| | | | B | 2nd | 3rd | 5th | 7th | A | F | B | 2nd | 3rd | 5th | 7th | A | F | |
| Hematology | WBC (/mm ³) | 4000~8500 | 7700 | 7200 | 6100 | 6200 | 6600 | 7400 | 5700 | 6800 | 7600 | 7300 | 7300 | 7300 | 6900 | 8500 | |
| | RBC (×10 ⁴ /mm ³) | 400~560 | 498 | 512 | 487 | 466 | 477 | 518 | 448 | 486 | 484 | 493 | 484 | 462 | 469 | 450 | |
| | Hb (g/dl) | 14~18 | 15.8 | 16.2 | 14.5 | 14.9 | 15.1 | 15.7 | 14.2 | 16.0 | 15.5 | 15.7 | 15.4 | 15.5 | 15.3 | 15.3 | |
| | Ht (%) | 40~55 | 47.7 | 48.1 | 46.6 | 44.3 | 44.5 | 48.9 | 42.5 | 48.9 | 48.0 | 49.2 | 47.3 | 45.8 | 46.8 | 44.0 | |
| | WBC differential | Neutrophil | 2~6 | 2 | 4 | 6 | 6 | 3 | 6 | 4 | 5 | 6 | 6 | 3 | 6 | 6 | 5 |
| | | Stab. Seg. | 41~59 | 47 | 47 | 43 | 40 | 40 | 38 | 46 | 51 | 47 | 49 | 43 | 44 | 41 | 51 |
| | | Lymphocyte | 28~48 | 43 | 42 | 44 | 46 | 48 | 48 | 41 | 38 | 40 | 38 | 45 | 44 | 48 | 39 |
| | | Eosinophil | 1~3 | 3 | 3 | 3 | 2 | 4 | 3 | 3 | 3 | 2 | 3 | 2 | 1 | 1 | 1 |
| | | Basophil | 0~1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | | Monocyte | 3~7 | 5 | 4 | 4 | 5 | 5 | 5 | 6 | 3 | 5 | 4 | 6 | 5 | 4 | 4 |
| | | Platelets(×10 ⁴ /mm ³) | 12~35 | 32.7 | 27.6 | 28.6 | 26.3 | 27.8 | 30.0 | 29.7 | 26.7 | 26.6 | 27.6 | 26.9 | 28.4 | 27.1 | 33.3 |
| | | Prothrombin time(sec) | 8~12 | 10.4 | 10.8 | 9.0 | 11.3 | 11.5 | 11.2 | 11.0 | 11.1 | 10.9 | 11.2 | 11.7 | 11.6 | | |
| | Biochemistry | GOT (U) | 8~40 | 21 | 19 | 22 | 21 | 23 | 22 | 18 | 14 | 13 | 17 | 13 | 18 | 13 | 12 |
| | | GPT (U) | 5~35 | 6 | 9 | 10 | 13 | 14 | 8 | 10 | 5 | 5 | 7 | 9 | 8 | 5 | 6 |
| LDH (U) | | 170~400 | 228 | 248 | 208 | 201 | 261 | 207 | 244 | 205 | 228 | 179 | 175 | 206 | 169 | 158 | |
| Al-P (KAU) | | 2.7~10 | 4.7 | 6.3 | 5.7 | 5.4 | 5.3 | 5.7 | 4.2 | 7.0 | 8.3 | 8.0 | 7.7 | 7.2 | 7.3 | 5.4 | |
| ChE (ΔpH) | | 0.6~1.2 | 1.0 | 1.1 | 0.9 | 1.1 | 0.9 | 1.0 | 1.1 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.2 | |
| γ-GTP(U) | | <60 | 20 | 30 | 28 | 28 | 20 | 21 | 20 | 9 | 19 | 14 | 13 | 13 | 15 | 14 | |
| Total bilirubin(mg/dl) | | 0.3~1.2 | 0.7 | 0.6 | 0.6 | 0.7 | 0.6 | 0.9 | 0.4 | 0.6 | 0.4 | 0.3 | 0.4 | 0.4 | 0.7 | 0.4 | |
| Total protein(g/dl) | | 6.5~8.5 | 7.7 | 8.0 | 7.1 | 6.6 | 6.8 | 7.2 | 6.5 | 7.2 | 7.3 | 7.1 | 7.0 | 7.1 | 7.4 | 7.1 | |
| BUN (mg/dl) | | 8~20 | 12.3 | 9.8 | 14.0 | 17.6 | 17.7 | 15.0 | 22.0 | 13.9 | 11.4 | 8.1 | 14.2 | 15.6 | 19.0 | 13.5 | |
| s-Cr (mg/dl) | | 0.7~1.5 | 0.9 | 1.2 | 1.2 | 1.0 | 1.0 | 1.1 | 1.0 | 1.1 | 1.3 | 1.3 | 1.0 | 1.0 | 1.1 | 1.2 | |
| T-chol (mg/dl) | | 120~250 | 169 | 184 | 167 | 164 | 164 | 175 | 169 | 136 | 143 | 152 | 164 | 178 | 185 | 169 | |
| TG (mg/dl) | | 40~170 | 60 | 83 | 72 | 51 | 49 | 47 | 72 | 114 | 139 | 140 | 153 | 137 | 133 | 108 | |
| Na (mEq/L) | | 134~147 | 141 | 141 | 141 | 140 | 141 | 143 | 141 | 141 | 141 | 140 | 140 | 140 | 141 | 143 | |
| K (mEq/L) | | 3.5~5.5 | 4.3 | 4.1 | 3.9 | 4.0 | 3.9 | 3.9 | 3.9 | 4.3 | 4.1 | 4.3 | 4.1 | 4.1 | 4.1 | 3.8 | |
| Cl (mEq/L) | | 98~108 | 106 | 104 | 106 | 107 | 107 | 108 | 106 | 108 | 105 | 107 | 107 | 109 | 106 | 101 | |
| Ca (mEq/L) | | 4.2~5.5 | 4.9 | 5.0 | 4.3 | 4.9 | 5.0 | 4.8 | 4.5 | 4.8 | 4.4 | 4.6 | 4.7 | 4.8 | 4.8 | 4.5 | |
| A/G | | 1.1~1.7 | 1.3 | 1.3 | 1.7 | 1.5 | 1.5 | 1.5 | 1.9 | 1.3 | 1.2 | 1.3 | 1.4 | 1.4 | 1.5 | 1.5 | |
| BS (mg/dl) | | 70~120 | 94 | 109 | 96 | 93 | 91 | 89 | 97 | 95 | 100 | 99 | 94 | 91 | 93 | 102 | |
| Urinalysis | Sugar | (-)-(±) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | |
| | Protein | (-)-(±) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | |
| | Urobilinogen | (±) | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | |
| | pH | 4.7~7.5 | 5 | 7 | 5 | 5.5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5.5 | 5.5 | |
| | Sediment | RBC(/hpf) | | 1-2/3-4 | 1-2/3-4 | 2-3/3-4 | 1-2/3-4 | 1-2/3-4 | 1-2/3-4 | 1-3/3-4 | 0-1/1 | 0-1/3-4 | 0-1/3-4 | 0-1/3-4 | 0-1/3-4 | 1-2/3-4 | 1-2/3-4 |
| WBC(/hpf) | | | 1-2/3-4 | 0-1/3-4 | 2-3/3-4 | 1-2/3-4 | 2-3/3-4 | 1-2/3-4 | 1-3/1 | 1-2/1 | 2-3/3-4 | 0-1/1 | 1-2/3-4 | 1-2/3-4 | 2-3/3-4 | 2-3/3-4 | |
| Squamous/hpf epithelium | | | 2-3/3-4 | 1-2/3-4 | 1-2/3-4 | 1-2/3-4 | 1-2/3-4 | 0-1/3-4 | 1-3/1 | 1-2/1 | 2-3/3-4 | 1-2/1 | 2-3/3-4 | 0-1/3-4 | 0-1/3-4 | 1-3/1 | |
| others | | | | nubecula (+) | nubecula (+) | | nubecula (+) | nubecula (+) | nubecula (+) | nubecula (+) oxalate 1-2/1 | nubecula (+) | nubecula (+) oxalate 2-3/1 | nubecula (+) | nubecula (+) | | nubecula (+) | |

B: before, A: after, F: follow up

Table 10-2 Clinical laboratory findings

300mg×2/day ×7days (Non-fasting)

| Items | Normal range | T.O. | | | | | | | | Y.S. | | | | | | | |
|---|------------------------|----------|--------------|--------------|-------------------------------|--------------|-----------------|--------------|---------------|--------------|------------------------------|-------------------------------|-------------------------------|---------------|--------------|---------|---------|
| | | B | 2nd | 3rd | 5th | 7th | A | F | B | 2nd | 3rd | 5th | 7th | A | F | | |
| WBC (/mm ³) | 4000-8500 | 5100 | 5300 | 5200 | 5200 | 5700 | 5000 | 5000 | 4400 | 5100 | 6000 | 6100 | 6400 | 6100 | 3400 | | |
| RBC (×10 ⁴ /mm ³) | 400-560 | 464 | 484 | 475 | 475 | 463 | 464 | 459 | 481 | 493 | 482 | 479 | 497 | 509 | 451 | | |
| Hb (g/dl) | 14-18 | 16.1 | 15.5 | 15.8 | 15.7 | 16.1 | 15.6 | 15.9 | 14.8 | 15.0 | 15.1 | 15.1 | 15.7 | 15.7 | 14.3 | | |
| Ht (%) | 40-55 | 47.8 | 48.7 | 47.7 | 48.2 | 46.6 | 47.3 | 46.2 | 45.9 | 47.1 | 45.3 | 45.6 | 46.2 | 48.5 | 41.9 | | |
| Hematology WBC differential | Neutrophil | Stab. | 2-6 | 5 | 4 | 6 | 6 | 6 | 5 | 5 | 6 | 4 | 4 | 3 | 3 | 3 | |
| | | Seg. | 41-59 | 52 | 49 | 45 | 50 | 53 | 45 | 55 | 41 | 42 | 43 | 43 | 41 | 40 | 40 |
| | Lymphocyte | 28-48 | 38 | 40 | 39 | 37 | 38 | 38 | 35 | 47 | 44 | 43 | 47 | 49 | 48 | 50 | |
| | Eosinophil | 1-3 | 3 | 3 | 3 | 2 | 2 | 3 | 2 | 3 | 3 | 3 | 1 | 3 | 2 | 1 | |
| | Basophil | 0-1 | 0 | 1 | 2 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 2 | 0 | 1 | 1 | |
| | Monocyte | 3-7 | 2 | 3 | 5 | 4 | 1 | 7 | 3 | 3 | 5 | 6 | 3 | 4 | 6 | 5 | |
| Platelets(×10 ⁹ /mm ³) | 12-35 | 26.9 | 32.2 | 30.7 | 23.2 | 24.1 | 23.8 | 30.6 | 19.8 | 18.0 | 21.3 | 19.7 | 21.4 | 22.9 | 22.1 | | |
| Prothrombin time(sec) | 8-12 | 10.8 | 11.0 | 11.0 | 10.8 | 11.9 | 11.9 | 11.9 | 11.3 | 11.4 | 11.1 | 11.0 | 11.3 | 11.7 | 11.7 | | |
| Biochemistry | GOT (U) | 8-40 | 16 | 13 | 16 | 20 | 25 | 17 | 11 | 13 | 14 | 14 | 18 | 27 | 25 | 9 | |
| | GPT (U) | 5-35 | 6 | 8 | 8 | 11 | 13 | 10 | 10 | 5 | 7 | 8 | 12 | 12 | 10 | 17 | |
| | LDH (U) | 170-400 | 183 | 184 | 164 | 182 | 209 | 206 | 208 | 171 | 192 | 160 | 166 | 174 | 172 | 186 | |
| | Al-P (KAU) | 2.7-10 | 8.4 | 9.4 | 9.2 | 9.6 | 10.0 | 9.6 | 6.8 | 4.7 | 5.3 | 5.8 | 5.4 | 6.3 | 6.1 | 4.4 | |
| | ChE (ΔpH) | 0.6-1.2 | 0.8 | 0.8 | 0.7 | 0.7 | 0.8 | 1.0 | 1.0 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 1.0 | 1.0 | |
| | γ-GTP(U) | <60 | 15 | 16 | 14 | 9 | 8 | 10 | 11 | 7 | 18 | 18 | 12 | 13 | 19 | 25 | |
| | Total bilirubin(mg/dl) | 0.3-1.2 | 0.6 | 0.4 | 0.4 | 0.3 | 0.4 | 0.7 | 0.3 | 0.6 | 0.5 | 0.4 | 0.5 | 0.5 | 0.7 | 0.9 | |
| | Total protein(g/dl) | 6.5-8.5 | 7.7 | 7.6 | 7.3 | 7.4 | 7.4 | 7.6 | 7.3 | 6.6 | 6.9 | 7.1 | 7.6 | 7.3 | 7.4 | 7.1 | |
| | BUN (mg/dl) | 8-20 | 16.0 | 14.4 | 13.8 | 16.6 | 22.5 | 21.5 | 15.8 | 12.2 | 11.1 | 8.2 | 11.4 | 13.9 | 14.9 | 10.7 | |
| | s-Cr (mg/dl) | 0.7-1.5 | 1.1 | 1.3 | 1.3 | 1.1 | 1.1 | 1.1 | 1.1 | 1.0 | 1.2 | 1.2 | 1.0 | 0.9 | 1.1 | 1.1 | |
| | T-chol(mg/dl) | 120-250 | 185 | 175 | 164 | 175 | 175 | 176 | 221 | 124 | 124 | 130 | 122 | 118 | 132 | 160 | |
| | TG (mg/dl) | 40-170 | 75 | 105 | 122 | 127 | 97 | 113 | 101 | 34 | 50 | 125 | 103 | 82 | 89 | 67 | |
| | Na (mEq/L) | 134-147 | 141 | 141 | 141 | 141 | 140 | 141 | 143 | 141 | 140 | 141 | 145 | 139 | 141 | 140 | |
| | K (mEq/L) | 3.5-5.5 | 4.6 | 4.2 | 4.3 | 4.3 | 4.4 | 4.5 | 4.2 | 4.1 | 4.2 | 4.4 | 4.1 | 4.2 | 4.2 | 3.9 | |
| | Cl (mEq/L) | 98-108 | 106 | 107 | 109 | 105 | 106 | 106 | 104 | 108 | 108 | 107 | 108 | 106 | 104 | 102 | |
| | Ca (mEq/L) | 4.2-5.5 | 5.0 | 4.5 | 4.6 | 4.9 | 4.8 | 4.7 | 4.7 | 4.7 | 4.5 | 4.7 | 4.5 | 4.7 | 4.9 | 4.6 | |
| | A/G | 1.1-1.7 | 1.3 | 1.3 | 1.5 | 1.6 | 1.5 | 1.6 | 1.6 | 1.7 | 1.7 | 1.5 | 1.4 | 1.7 | 1.2 | 1.8 | |
| BS (mg/dl) | 70-120 | 96 | 109 | 102 | 90 | 93 | 89 | 95 | 100 | 111 | 106 | 98 | 97 | 95 | 95 | | |
| Urinalysis | Sugar | (-)-(±) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | |
| | Protein | (-)-(±) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | |
| | Urobilinogen | (±) | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | ± | |
| | pH | 4.7-7.5 | 5 | 5.5 | 5 | 5.5 | 5 | 5 | 5 | 5 | 6.5 | 5.5 | 6 | 5 | 5 | 7 | |
| | Sediment | RBC(hpf) | | 2-3/3-4 | 2-3/3-4 | 1-2/3-4 | 1-2/3-4 | 0-1/3-4 | 2-3/3-4 | 0-1/3-4 | 2-3/3-4 | 1-2/3-4 | 0-1/1 | 2-3/3-4 | 0-1/3-4 | 2-3/3-4 | 0-1/3-4 |
| WBC(hpf) | | | 1-2/1 | 2-3/3-4 | 1-2/3-4 | 1-2/3-4 | 1-2/3-4 | 2-3/3-4 | 0-1/3-4 | 1-2/1 | 1-2/3-4 | 2-3/3-4 | 1-2/3-4 | 1-2/3-4 | 2-3/3-4 | 0-1/3-4 | |
| Squamous(hpf) epithelium | | | 1-2/3-4 | 1-2/3-4 | 0-1/3-4 | 0-1/3-4 | 1-2/3-4 | 1-2/3-4 | 0-1/3-4 | 1-2/3-4 | 0-1/3-4 | 0-1/3-4 | 0-1/3-4 | 1-2/3-4 | 2-3/3-4 | 1-3/1 | |
| Others | | | nubecula (+) | nubecula (+) | nubecula (+) oxalate 2-3/1 | nubecula (+) | oxalate 1-2/3-4 | nubecula (+) | oxalate 1-2/1 | nubecula (+) | urate (+) oxalate 1-2/3-4 | nubecula (+) oxalate 1-2/1 | nubecula (+) oxalate 1-2/1 | oxalate 2-3/1 | nubecula (+) | | |

B: before, A: after, F: follow up

Table 10-3 Clinical laboratory findings

300mg×2/day×7days (Non-fasting)

| Items | | Normal range | H.F. | | | | | | | | |
|---------------------------|---|--------------|--------------|---------|------------------------------------|--------------|----------------------------------|--------------|--------------|---------|----|
| | | | B | 2nd | 3rd | 5th | 7th | A | F | | |
| Hematology | WBC (/mm ³) | 4000-8500 | 6400 | 5600 | 6900 | 6800 | 7000 | 6100 | 4200 | | |
| | RBC (×10 ⁴ /mm ³) | 400-560 | 480 | 492 | 482 | 482 | 488 | 486 | 479 | | |
| | Hb (g/dl) | 14-18 | 15.4 | 15.0 | 15.3 | 15.3 | 15.4 | 14.9 | 15.2 | | |
| | Ht (%) | 40-55 | 43.9 | 45.2 | 43.9 | 44.3 | 44.1 | 44.4 | 43.5 | | |
| | WBC differential | Neutrophil | Stab. | 2-6 | 4 | 5 | 5 | 5 | 3 | 5 | 6 |
| | | | Seg. | 41-59 | 43 | 44 | 46 | 48 | 48 | 43 | 43 |
| | | Lymphocyte | 28-48 | 44 | 43 | 42 | 41 | 41 | 47 | 44 | |
| | | Eosinophil | 1-3 | 3 | 2 | 2 | 3 | 3 | 1 | 0 | |
| | | Basophil | 0-1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | |
| | | Monocyte | 3-7 | 6 | 5 | 5 | 3 | 5 | 4 | 6 | |
| | Platelets(×10 ⁴ /mm ³) | 12-35 | 17.3 | 19.1 | 18.7 | 17.8 | 18.4 | 19.9 | 22.2 | | |
| | Prothrombin time(sec) | 8-12 | 11.6 | 11.7 | 11.3 | 11.2 | 11.7 | 11.1 | | | |
| Biochemistry | GOT (U) | 8-40 | 17 | 17 | 20 | 24 | 42 | 34 | 18 | | |
| | GPT (U) | 5-35 | 6 | 7 | 8 | 12 | 20 | 10 | 12 | | |
| | LDH (U) | 170-400 | 176 | 172 | 158 | 198 | 203 | 153 | 194 | | |
| | Al-P (KAU) | 2.7-10 | 5.6 | 5.8 | 6.0 | 6.3 | 6.4 | 5.8 | 5.1 | | |
| | ChE (ΔpH) | 0.6-1.2 | 0.8 | 0.8 | 0.8 | 0.9 | 0.8 | 0.8 | 1.1 | | |
| | γ-GTP (U) | <60 | 8 | 11 | 14 | 10 | 7 | 5 | 12 | | |
| | Total bilirubin(mg/dl) | 0.3-1.2 | 0.7 | 0.5 | 0.6 | 0.6 | 0.6 | 0.9 | 1.1 | | |
| | Total protein(g/dl) | 6.5-8.5 | 7.7 | 7.3 | 7.6 | 8.1 | 7.9 | 7.4 | 7.6 | | |
| | BUN (mg/dl) | 8-20 | 8.3 | 9.0 | 11.0 | 12.0 | 16.0 | 17.6 | 11.3 | | |
| | s-Cr (mg/dl) | 0.7-1.5 | 1.0 | 1.2 | 1.1 | 0.9 | 0.9 | 1.0 | 1.2 | | |
| | T-chol (mg/dl) | 120-250 | 170 | 152 | 157 | 157 | 159 | 158 | 191 | | |
| | TG (mg/dl) | 40-170 | 68 | 111 | 131 | 209 | 82 | 82 | 46 | | |
| | Na (mEq/L) | 134-147 | 141 | 139 | 141 | 146 | 139 | 139 | 141 | | |
| | K (mEq/L) | 3.5-5.5 | 4.2 | 3.9 | 4.4 | 3.9 | 3.9 | 4.0 | 3.9 | | |
| | Cl (mEq/L) | 98-108 | 107 | 103 | 106 | 111 | 104 | 106 | 99 | | |
| | Ca (mEq/L) | 4.2-5.5 | 5.0 | 4.7 | 4.8 | 4.9 | 4.9 | 4.7 | 5.0 | | |
| A/G | 1.1-1.7 | 1.4 | 1.4 | 1.5 | 1.6 | 1.2 | 1.2 | 1.8 | | | |
| BS (mg/dl) | 70-120 | 102 | 102 | 104 | 99 | 96 | 101 | 95 | | | |
| Urinalysis | Sugar | (-)-(±) | - | - | - | - | - | - | - | | |
| | Protein | (-)-(±) | - | - | - | - | - | - | - | | |
| | Urobilinogen | (±) | ± | ± | ± | ± | ± | ± | ± | | |
| | pH | 4.7-7.5 | 5 | 6 | 5.5 | 6 | 5.5 | 5.5 | 5.5 | | |
| | Sediment | RBC(/hpf) | | 1-2/3-4 | 0-1/3-4 | 1-2/3-4 | 0-1/3-4 | 0-1/3-4 | 1-2/3-4 | 1-3/3-4 | |
| | | WBC(/hpf) | | 1-2/3-4 | 0-1/3-4 | 1-2/3-4 | 0-1/3-4 | 2-3/3-4 | 1-2/3-4 | 1-3/3-4 | |
| Squamous(/hpf) epithelium | | | 0-1/3-4 | 0-1/3-4 | 0-1/3-4 | 0-1/3-4 | 0-1/3-4 | 1-2/3-4 | 1-3/3-4 | | |
| Others | | | nubecula (+) | | nubecula (+) oxalate 1-2/3-4 | nubecula (+) | nubecula (+) oxalate 1-3/1 | nubecula (+) | nubecula (+) | | |

B: before, A: after, F: follow up

Table 11-1 Clinical laboratory findings 400mg×2/day ×7days (Non-fasting)

| Item | Normal range | T.S. | | | | | | | K.S. | | | | | | | | | | |
|--|---|-------|----------|-------|-------|----------|----------|----------|-------|----------|-------|-------|----------|----------|----------|----------|---------|---------|----|
| | | B | 2nd | 3rd | 5th | 7th | A | F7th | B | 2nd | 3rd | 5th | 7th | A | F3rd | F7th | F14th | | |
| WBC (/mm ³) | 4000-8000 | 5000 | 5100 | 5100 | 7100 | 6500 | 5600 | 4700 | 5400 | 4800 | 4300 | 5800 | 4900 | 5000 | 6400 | 5200 | 5400 | | |
| RBC (×10 ⁴ /mm ³) | 400-530 | 430 | 410 | 431 | 454 | 448 | 428 | 423 | 495 | 484 | 513 | 507 | 492 | 487 | 490 | 522 | 525 | | |
| Hb (g/dl) | 13-17 | 14.0 | 13.2 | 13.7 | 14.0 | 14.2 | 14.0 | 14.0 | 14.5 | 14.4 | 15.1 | 14.8 | 14.4 | 14.7 | 14.7 | 15.8 | 16.1 | | |
| Ht (%) | 40-52 | 41 | 39 | 42 | 44 | 42 | 41 | 42.9 | 43 | 43 | 45 | 45 | 43 | 43 | 44 | 45.6 | 46.5 | | |
| Hematology WBC differential | Neutrophil | Stab. | 2~7 | 2 | 0 | 2 | 3 | 2 | 2 | 3 | 3 | 1 | 1 | 3 | 1 | 2 | 4 | 5 | 6 |
| | | Seg. | 45-55 | 53 | 61 | 57 | 60 | 51 | 52 | 45 | 54 | 48 | 55 | 58 | 56 | 46 | 48 | 48 | 44 |
| | Lymphocyte | 25-45 | 38 | 34 | 37 | 30 | 42 | 38 | 47 | 33 | 39 | 33 | 30 | 38 | 39 | 43 | 42 | 44 | |
| | Eosinophil | 1-5 | 2 | 1 | 0 | 2 | 3 | 2 | 2 | 2 | 5 | 3 | 1 | 4 | 4 | 2 | 2 | 2 | |
| | Basophil | 0-1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 1 | 2 | 0 | 1 | 0 | 0 | 0 | |
| | Monocyte | 2-7 | 4 | 4 | 4 | 5 | 2 | 6 | 3 | 7 | 5 | 7 | 6 | 1 | 8 | 3 | 3 | 4 | |
| | Platelets(×10 ⁴ /mm ³) | 13-35 | 24 | 22 | 24 | 27 | 25 | 22 | 25.2 | 25 | 27 | 22 | 25 | 26 | 25 | 18.4 | 24.9 | | |
| Prothrombin tim(sec) | 11-15 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | | |
| GOT (U) | 8-40 | 17 | 18 | 17 | 18 | 21 | 24 | 17 | 15 | 16 | 18 | 21 | 57 | 58 | 42 | 35 | 21 | | |
| GPT (U) | 5-35 | 9 | 9 | 11 | 10 | 10 | 18 | 12 | 14 | 15 | 13 | 17 | 48 | 59 | 47 | 43 | 23 | | |
| LDH (U) | 50-500 | 293 | 281 | 265 | 287 | 291 | 277 | 257 | 291 | 274 | 263 | 286 | 343 | 325 | 313 | 284 | 277 | | |
| Al-P (KAU) | 3-10 | 4.8 | 5.0 | 5.1 | 4.6 | 5.1 | 5.1 | 4.6 | 7.3 | 7.2 | 6.8 | 5.8 | 6.6 | 6.8 | 6.2 | 7.3 | 6.6 | | |
| ChE (ΔpH) | 0.8-1.1 | 1.3 | 1.1 | 1.1 | 1.0 | 1.1 | 1.1 | 1.2 | 1.1 | 1.2 | 1.1 | 1.1 | 1.1 | 1.1 | 1.1 | 1.2 | 1.2 | | |
| ZTT | 2-12 | 7.1 | 6.6 | 6.7 | 6.4 | 6.4 | 6.3 | 6.7 | 4.7 | 4.7 | 4.9 | 4.7 | 4.5 | 4.6 | 4.0 | 4.3 | 4.5 | | |
| γ-GTP(U) | <40 | 17 | 19 | 19 | 18 | 2 | 21 | 19 | 16 | 18 | 19 | 15 | 17 | 19 | 15 | 20 | 18 | | |
| Total bilirubin(mg/dl) | 0.2-1.0 | 0.5 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.8 | 0.9 | 0.7 | 0.5 | 0.6 | 0.5 | 0.6 | 0.9 | 0.5 | 0.8 | | |
| Total protein(g/dl) | 6.5-8.5 | 7.9 | 7.2 | 7.5 | 7.6 | 8.1 | 7.5 | 8.1 | 7.1 | 6.9 | 7.0 | 7.0 | 7.1 | 6.9 | 6.9 | 7.3 | 7.6 | | |
| BUN (mg/dl) | 8-20 | 15 | 14 | 10 | 15 | 13 | 16 | 14 | 9 | 9 | 7 | 9 | 10 | 9 | 7 | 9 | 11 | | |
| s-Cr (mg/dl) | 0.7-1.7 | 1.1 | 1.0 | 1.0 | 1.1 | 1.1 | 1.0 | 1.2 | 1.0 | 1.0 | 0.9 | 0.9 | 1.0 | 1.1 | 1.1 | 1.1 | 1.0 | | |
| T-cho(mg/dl) | 130-250 | 193 | 177 | 180 | 164 | 178 | 160 | 222 | 147 | 137 | 130 | 123 | 146 | 139 | 141 | 180 | 176 | | |
| TG (mg/dl) | 40-172 | 56 | 89 | 69 | 119 | 102 | 74 | 46 | 55 | 70 | 72 | 146 | 89 | 70 | 72 | 70 | 94 | | |
| Uric Acid | 3.0-6.5 | 4.5 | 4.3 | 3.9 | 4.6 | 4.7 | 4.6 | 5.5 | 5.0 | 5.3 | 5.0 | 5.8 | 5.8 | 5.8 | 5.7 | 4.9 | 5.3 | | |
| Na (mEq/L) | 134-147 | 139 | 139 | 138 | 140 | 138 | 139 | 138 | 141 | 143 | 140 | 145 | 140 | 140 | 142 | 140 | 142 | | |
| K (mEq/L) | 3.5-5.5 | 4.0 | 3.8 | 4.7 | 3.9 | 4.0 | 4.0 | 3.9 | 4.2 | 4.2 | 4.2 | 4.7 | 4.3 | 4.2 | 4.0 | 3.9 | 3.9 | | |
| Cl (mEq/L) | 96-107 | 102 | 101 | 102 | 102 | 98 | 99 | 102 | 103 | 104 | 101 | 101 | 98 | 100 | 104 | 103 | 103 | | |
| Ca (mEq/L) | 4.2-5.7 | 4.3 | 4.1 | 4.1 | 4.3 | 4.2 | 4.2 | 4.1 | 4.2 | 4.2 | 4.2 | 4.3 | 4.1 | 4.2 | 4.0 | 3.9 | 4.4 | | |
| A/G | 1.2-2.3 | 1.39 | 1.48 | 1.42 | 1.37 | 1.31 | 1.34 | 1.38 | 1.54 | 1.65 | 1.69 | 1.69 | 1.63 | 1.65 | 1.76 | 1.61 | 1.62 | | |
| BS (mg/dl) | 70-110 | 94 | 93 | 100 | 86 | 81 | 83 | 91 | 95 | 88 | 92 | 80 | 80 | 78 | 94 | 97 | 95 | | |
| Sugar | (-)-(±) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | | | |
| Protein | (-)-(±) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | | | |
| Urobilinogen | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | | | |
| pH | 4.7-7.5 | 6 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5.5 | | |
| Urinalysis Sediment | RBC (/hpf) | | 1-2/7-10 | | 0-1/1 | 1-2/1 | 1-2/7-10 | 0-1/1 | 1-2/1 | 0-1/1 | | 0-1/1 | 0-1/1 | 1-2/7-10 | 1-2/7-10 | 0-1/7-10 | 1-2/1 | 3-5/1 | |
| | WBC (/hpf) | | 0-1/1 | 0-1/1 | | 0-1/1 | | | 3-4/1 | 3-5/1 | 0-1/1 | | 2-3/1 | 1-2/7-10 | 0-1/1 | 0-1/7-10 | 10-12/1 | 15-20/1 | |
| | Squamous(hpf) epithelium | | | | | | 1-2/7-10 | | 3-4/1 | 1-2/7-10 | | | 1-2/7-10 | 1-2/7-10 | 0-1/7-10 | 3-5/1 | 1-3/1 | | |
| | Nubecula | | (+) | (+) | | (#) | | (+) | (+) | | | | (+) | | (+) | | (+) | | |
| | Oxalate | | (+) | (+) | (±) | (+) | | (+) | (+) | (+) | | | | | | | | 1-3/1 | |
| | Others | | | | | Mold (±) | Mold (±) | Mold (±) | | | | | | Mold (+) | | | | | |

B: before, A:after, F: follow up

Table 11-2 Clinical laboratory findings 400mg×2/day×7days (Non-fasting)

| Item | Normal range | M.K. | | | | | | | | A.N. | | | | | | | | |
|-------------------------|---|--------------------------|-------|----------|-------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|-------|
| | | B | 2nd | 3rd | 5th | 7th | A | F7th | B | 2nd | 3rd | 5th | 7th | A | F3rd | F7th | | |
| Hematology | WBC (/mm ³) | 4000-8000 | 5400 | 5000 | 4500 | 5000 | 5100 | 4500 | 4600 | 6500 | 7400 | 6600 | 6500 | 7300 | 7200 | 6800 | 9100 | |
| | RBC (×10 ⁴ /mm ³) | 400-530 | 484 | 444 | 449 | 463 | 461 | 453 | 465 | 486 | 453 | 448 | 469 | 471 | 466 | 496 | 487 | |
| | Hb (g/dl) | 13-17 | 15.7 | 14.4 | 14.2 | 15.0 | 14.8 | 15.0 | 15.1 | 15.8 | 14.6 | 14.3 | 14.9 | 14.8 | 15.1 | 15.9 | 15.9 | |
| | Ht (%) | 40-52 | 43 | 40 | 40 | 42 | 41 | 40 | 41.5 | 46 | 43 | 42 | 44 | 43 | 43 | 46.8 | 45.5 | |
| | Neutrophil | Stab. | 2-7 | 0 | 0 | 1 | 0 | 0 | 0 | 3 | 1 | 0 | 1 | 0 | 1 | 3 | 3 | |
| | | Seg. | 45-55 | 54 | 50 | 42 | 49 | 52 | 60 | 48 | 62 | 59 | 57 | 47 | 51 | 42 | 48 | 49 |
| | Lymphocyte | 25-45 | 28 | 31 | 32 | 34 | 37 | 26+1* | 41 | 31 | 36 | 35 | 41 | 40 | 48 | 41 | 40 | |
| | Eosinophil | 1-5 | 8 | 12 | 14 | 7 | 5 | 9 | 2 | 0 | 0 | 1 | 2 | 3 | 2 | 3 | 3 | |
| | Basophil | 0-1 | 2 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | |
| | Monocyte | 2-7 | 8 | 6 | 10 | 10 | 6 | 3 | 6 | 6 | 4 | 6 | 8 | 6 | 6 | 5 | 5 | |
| | Platelets(×10 ⁴ /mm ³) | 13-35 | 20 | 21 | 21 | 23 | 26 | 27 | 22.6 | 23 | 22 | 21 | 23 | 27 | 21 | 23 | 24.5 | |
| | Prothrombin time(sec) | 11-15 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | |
| | Biochemistry | GOT (U) | 8-40 | 14 | 13 | 11 | 15 | 21 | 21 | 15 | 16 | 14 | 17 | 20 | 39 | 56 | 39 | 21 |
| GPT (U) | | 5-35 | 11 | 7 | 10 | 12 | 19 | 20 | 12 | 11 | 11 | 11 | 17 | 45 | 66 | 62 | 24 | |
| LDH (U) | | 50-500 | 348 | 340 | 295 | 322 | 317 | 310 | 313 | 284 | 273 | 244 | 273 | 314 | 331 | 273 | 272 | |
| Al-P (KAU) | | 3-10 | 6.9 | 6.7 | 7.6 | 5.4 | 6.2 | 6.5 | 8.0 | 3.8 | 3.9 | 3.3 | 3.2 | 3.8 | 3.7 | 4.2 | 4.1 | |
| ChE (△pH) | | 0.8-1.1 | 1.1 | 1.0 | 0.9 | 1.0 | 0.9 | 1.2 | 1.0 | 1.4 | 1.3 | 1.2 | 1.2 | 1.3 | 0.9 | 1.5 | 1.6 | |
| ZTT | | 2-12 | 2.7 | 2.7 | 2.7 | 2.6 | 2.4 | 2.5 | 2.8 | 6.4 | 6.0 | 5.6 | 5.8 | 5.8 | 5.6 | 5.6 | 5.6 | |
| γ-GTP(U) | | <40 | 17 | 19 | 20 | 16 | 32 | 16 | 19 | 23 | 23 | 19 | 23 | 35 | 42 | 50 | 43 | |
| Total bilirubin (mg/dl) | | 0.2-1.0 | 0.9 | 0.8 | 0.5 | 0.6 | 0.6 | 0.7 | 0.6 | 0.6 | 0.5 | 0.3 | 0.4 | 0.4 | 0.4 | 0.6 | 0.4 | |
| Total protein (g/dl) | | 6.5-8.5 | 6.9 | 6.2 | 6.1 | 6.6 | 6.4 | 6.2 | 6.9 | 7.6 | 6.9 | 6.6 | 7.0 | 7.5 | 7.1 | 7.9 | 8.0 | |
| BUN (mg/dl) | | 8-20 | 14 | 10 | 8 | 9 | 9 | 9 | 8 | 11 | 8 | 7 | 8 | 8 | 8 | 11 | 9 | |
| s-Cr (mg/dl) | | 0.7-1.7 | 1.0 | 1.0 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 1.1 | 1.1 | 1.1 | 1.0 | 1.0 | 0.9 | 1.2 | 1.1 | |
| T-chol(mg/dl) | | 130-250 | 135 | 114 | 106 | 101 | 110 | 110 | 141 | 155 | 139 | 124 | 114 | 137 | 135 | 197 | 197 | |
| TG (mg/dl) | | 40-172 | 50 | 46 | 46 | 73 | 51 | 55 | 90 | 83 | 134 | 143 | 230 | 205 | 163 | 145 | 48 | |
| Uric Acid | | 3.0-6.5 | 4.3 | 3.9 | 3.7 | 4.0 | 4.0 | 4.0 | 4.3 | 5.4 | 5.5 | 4.7 | 5.5 | 5.2 | 5.5 | 6.0 | 6.1 | |
| Na (mEq/L) | | 134-147 | 142 | 141 | 140 | 144 | 140 | 140 | 142 | 139 | 141 | 139 | 141 | 139 | 140 | 140 | 139 | |
| K (mEq/L) | | 3.5-5.5 | 3.9 | 3.7 | 3.8 | 3.8 | 3.6 | 3.7 | 4.0 | 4.5 | 4.2 | 4.2 | 4.1 | 4.0 | 4.1 | 3.9 | 4.1 | |
| Cl (mEq/L) | | 96-107 | 105 | 105 | 105 | 106 | 103 | 105 | 105 | 101 | 104 | 102 | 103 | 99 | 100 | 101 | 102 | |
| Ca (mEq/L) | 4.2-5.7 | 4.2 | 3.9 | 4.0 | 4.1 | 3.9 | 4.0 | 3.8 | 4.2 | 4.0 | 3.9 | 4.2 | 4.1 | 4.1 | 4.2 | 4.0 | | |
| A/G | 1.2-2.3 | 2.00 | 1.95 | 2.05 | 2.00 | 1.91 | 1.95 | 1.76 | 1.45 | 1.65 | 1.65 | 1.59 | 1.50 | 1.54 | 1.47 | 1.50 | | |
| BS (mg/dl) | 70-110 | 94 | 93 | 96 | 88 | 82 | 77 | 91 | 90 | 83 | 85 | 79 | 76 | 71 | 91 | 96 | | |
| Urinalysis | Sugar | (-)-(±) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | | |
| | Protein | (-)-(±) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | | |
| | Urobilinogen | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | | |
| | pH | 4.7-7.5 | 5 | 6 | 6 | 6 | 5 | 6 | 5 | 6 | 6 | 5 | 5 | 6 | 5 | 5 | | |
| | Sediment | RBC (/hpf) | | 1-2/7-10 | | 1-2/7-10 | | 0-1/1 | 1-2/7-10 | 0-1/1 | 1-2/7-10 | 1-2/7-10 | | 0-1/1 | 1-2/7-10 | 1-2/7-10 | 0-1/7-10 | 0-1/1 |
| | | WBC (/hpf) | | | | 1-2/7-10 | | 1-2/7-10 | 0-1/1 | 1-2/7-10 | | 1-2/7-10 | 1-2/7-10 | | 1-2/7-10 | 1-3/1 | 1-2/1 | |
| | | Squamous(hpf) epithelium | | | 0-1/1 | 0-1/1 | | | 0-1/1 | | | | | | | 1-3/1 | 0-1/1 | |
| | | Nubecula | | | (+) | | | | (+) | | (+) | | | | | | | |
| | | Oxalate | | | | | | | (#) | (+) | | (+) | (+) | | | | (+) | |
| | Others | | | | | | Mold (±) | Mold (±) | | | | | | Mold (±) | | | | |

B: before, A: after, F: follow up *異型リンパ球

Table 11-3 Clinical laboratory findings

400mg×2/day ×7days (Non-fasting)

| Items | | Normal range | N.U. | | | | | | | |
|-------------------------|---|---------------------------|-------|----------|-------|-------|-------|----------|----------|----------|
| | | | B | 2nd | 3rd | 5th | 7th | A | F7th | |
| Hematology | WBC (/mm ³) | 4000-8000 | 5800 | 5400 | 5800 | 6000 | 5700 | 5700 | 5600 | |
| | RBC (×10 ⁴ /mm ³) | 400-530 | 481 | 490 | 496 | 497 | 480 | 479 | 445 | |
| | Hb (g/dl) | 13-17 | 14.5 | 14.5 | 15.0 | 14.8 | 14.4 | 14.6 | 14.1 | |
| | Ht (%) | 40-52 | 44 | 45 | 45 | 45 | 43 | 43 | 42.5 | |
| | Neutrophil | Stab. | 2-7 | 1 | 2 | 2 | 0 | 0 | 1 | 3 |
| | | Seg. | 45-55 | 54 | 54 | 51 | 64 | 57 | 54 | 48 |
| | Lymphocyte | 25-45 | 35 | 33 | 31 | 28 | 33 | 33 | 41 | |
| | Eosinophil | 1-5 | 5 | 6 | 8 | 5 | 6 | 8 | 3 | |
| | Basophil | 0-1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | |
| | Monocyte | 2-7 | 5 | 5 | 7 | 3 | 4 | 3 | 5 | |
| | Platelets(×10 ⁹ /mm ³) | 13-35 | 29 | 27 | 29 | 26 | 24 | 28 | 25.5 | |
| | Prothrombin time(sec) | 11-15 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | |
| | Biochemistry | GOT (U) | 8-40 | 15 | 19 | 20 | 18 | 21 | 25 | 16 |
| GPT (U) | | 5-35 | 12 | 9 | 16 | 20 | 21 | 23 | 12 | |
| LDH (U) | | 50-500 | 259 | 272 | 268 | 275 | 276 | 274 | 266 | |
| Al-P (KAU) | | 3-10 | 6.1 | 6.1 | 5.8 | 5.7 | 6.1 | 6.1 | 6.1 | |
| ChE (△pH) | | 0.8-1.1 | 1.1 | 1.2 | 1.2 | 1.1 | 1.1 | 0.9 | 1.1 | |
| ZTT | | 2-12 | 6.6 | 6.4 | 6.5 | 6.5 | 6.5 | 6.5 | 6.2 | |
| γ-GTP(U) | | <40 | 30 | 32 | 34 | 31 | 24 | 25 | 34 | |
| Total bilirubin (mg/dl) | | 0.2-1.0 | 0.6 | 0.5 | 0.3 | 0.5 | 0.4 | 0.4 | 0.4 | |
| Total protein (g/dl) | | 6.5-8.5 | 7.2 | 7.2 | 7.2 | 7.2 | 7.3 | 7.1 | 7.0 | |
| BUN (mg/dl) | | 8-20 | 9 | 10 | 8 | 11 | 9 | 9 | 11 | |
| s-Cr (mg/dl) | | 0.7-1.7 | 1.0 | 0.9 | 1.0 | 0.9 | 1.0 | 0.9 | 1.0 | |
| T-chol(mg/dl) | | 130-250 | 126 | 125 | 126 | 129 | 130 | 122 | 122 | |
| TG (mg/dl) | | 40-172 | 73 | 119 | 138 | 140 | 116 | 106 | 49 | |
| Uric Acid | | 3.0-6.5 | 5.4 | 5.1 | 4.8 | 6.0 | 5.8 | 5.5 | 5.8 | |
| Na (mEq/L) | | 134-147 | 138 | 139 | 139 | 136 | 137 | 139 | 140 | |
| K (mEq/L) | | 3.5-5.5 | 3.9 | 3.9 | 4.2 | 3.7 | 3.8 | 4.1 | 4.0 | |
| Cl (mEq/L) | | 96-107 | 100 | 101 | 102 | 103 | 100 | 101 | 106 | |
| Ca (mEq/L) | 4.2-5.7 | 4.2 | 4.1 | 4.2 | 4.4 | 4.0 | 4.3 | 3.7 | | |
| A/G | 1.2-2.3 | 1.40 | 1.40 | 1.40 | 1.48 | 1.35 | 1.45 | 1.41 | | |
| BS (mg/dl) | 70-110 | 95 | 96 | 97 | 88 | 85 | 85 | 122 | | |
| Urinalysis | Sugar | (-)-(±) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | |
| | Protein | (-)-(±) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | |
| | Urobilinogen | (±) | (±) | (±) | (±) | (±) | (±) | (±) | (±) | |
| | pH | 4.7-7.5 | 6 | 5 | 5 | 5 | 5 | 6 | 5 | |
| | Sediment | RBC(/hpf) | | 1-2/7-10 | 0-1/1 | 0-1/1 | 0-1/1 | 0-1/1 | 1-2/7-10 | 1-3/1 |
| | | WBC(/hpf) | | | | | | | | 1-3/1 |
| | | Squamous(/hpf) epithelium | | | | | | | | 0-1/1 |
| | | Nubecula | | | (+) | (+) | | | | |
| | | Oxalate | | | (+) | | (+) | (+) | (+) | (+) |
| | | Others | | | | | | Mold (±) | | Mold (±) |

B: before, A: after, F: follow up

であることを考慮すると重大な影響をおよぼすものであるとは考えられないが、増量使用に際しては留意する必要があると考えられる。その他の血液学検査、血液生化学、尿検査および理学検査などの検査成績には、問題となるような異常変動はみられなかった。CINXの大量投与時、尿中に薬物結晶の析出することが報告⁷⁾されているため本試験でも、経時的に採取した尿について、尿沈渣を顕微鏡下で観察したが、いずれの検体にも結晶の析出は認められなかった。

以上のことから、BAY o 9867は300または400 mg 1日2回7日間連続使用によっても、安定した血中濃度、尿中排泄がみられ、蓄積性もなく、安全性のある薬剤であることが示唆された。

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PHARMACOKINETICS WITH BAY o 9867 (CIPROFLOXACIN)

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Pharmacokinetic study with BAY o 9867(Ciprofloxacin), a new synthetic antimicrobial agent, was conducted in healthy male volunteers. BAY o 9867 was given 300 or 400mg b. i. d. for 7 consecutive days. Concentration of BAY o 9867 in the blood, saliva and urine were measured and the following results were obtained.

In the 300mg dose group, the peak plasma concentrations were attained 1 to 2 hours after administration and their mean values ranged from 0.89 to 0.92 $\mu\text{g/ml}$. The maximum salivary concentration was reached 2 to 4 hours after administration, and mean concentrations ranged from 0.33 to 0.46 $\mu\text{g/ml}$. The urinary recovery of BAY o 9867 was 29.1 to 36.4% within 10 hours. In the 400mg dose group, the peak plasma concentrations was reached 1 to 2 hours after administration, and their mean values ranged from 1.50 to 2.05 $\mu\text{g/ml}$. The maximum concentration of saliva was reached 2 to 4 hours after administration, and mean concentrations ranged 0.46 to 0.82 $\mu\text{g/ml}$. The urinary recovery of BAY o 9867 was 29.8 to 35.2% within 10 hours.

With regard to side effect, no subjective symptoms of adverse reaction was noted. Slight elevation of GPT was found in 1 case of 300mg dose group, and GOT, GPT and GOT, GPT, gamma GTP in 1 case of each in 400mg dose group. However, at the follow up examination, all the measurement were recovered within normal range.