Possible Relationship between Phototoxicity and Photodegradation of Sitafloxacin, a Quinolone Antibacterial Agent, in the Auricular Skin of Albino Mice

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Received March 7, 2000; accepted May 3, 2000

We compared the phototoxic potential of the quinolone antibacterial agent sitafloxacin with those of lomefloxacin and sparflloxacin. Female BALB/c mice were given a single intravenous administration of sitafloxacin, lomefloxacin, or sparflloxacin at 10 or 40 mg/kg, followed by ultraviolet-A (UVA) irradiation for 4 h (21.6 J/cm²). At 10 mg/kg, all quinolones induced either none or minimum inflammation in the auricle. At 40 mg/kg, sitafloxacin induced mild phototoxic inflammation in the dermal skin, while lomefloxacin and sparflloxacin induced very severe inflammation. In particular, 2/5 animals of the lomefloxacin group showed partial necrosis in the dermis and epidermis. We then determined the time course change of sitafloxacin concentrations in serum and auricular tissue by high performance liquid chromatography. Sitafloxacin concentrations in the auricle were markedly decreased under UVA irradiation, whereas those in sera were not affected. Furthermore, we examined the severity of sitafloxacin-induced phototoxicity under varied duration of UVA irradiation. The severity of phototoxicity increased with increasing duration of UVA irradiation, and statistical analysis showed a close correlation between the severity and the decreased area under the drug concentration curve under UVA irradiation (ΔAUCauricle). The severity was decreased with delay in commencement of UVA irradiation, indicating the importance of commencement time of irradiation in the experimental condition of the phototoxicity study. It might be attributed to the decrease in ΔAUCauricle after administration. These results suggest that sitafloxacin possesses milder phototoxic potential than lomefloxacin or sparflloxacin and is degraded in the auricular skin under UVA irradiation, and that the severity of phototoxicity is directly proportional to the ΔAUCauricle.

Key Words: phototoxicity; quinolone; sitafloxacin; ultraviolet-A; auricle; toxicokinetics; AUC.

Quinolone antibacterial agents, including ciprofloxacin, enoxacin, norfloxacin, lomefloxacin, sparflloxacin, ofloxacin, levofloxacin, fleeroxacin, and pefloxacin, have been reported to induce photosensitivity in humans at very low incidence (Christ and Lehnert, 1990; U.S. Food and Drug Administration, 1993; Yamaguchi et al., 1994, 1995). Photosensitivity includes phototoxicity and photoallergy, and many cases of quinolone-induced photosensitivity have a phototoxic nature. The phototoxic reaction is linked to exaggerated sunburn, and the action spectrum of the toxicity is thought to be included in the wavelength range of ultraviolet-A (UVA) (Christ and Lehnert, 1990).

In general, reactive oxygen species (ROSs), generated through photodynamic Type I and Type II reactions in the simultaneous presence of a photosensitizer and exciting light, are involved in the mechanisms of drug phototoxicity (Giriotti, 1990). Intense interest has been focused on oxidative stress in the elucidation of the mechanisms of quinolone phototoxicity. It has been reported that photohemolysis, induced by nalidixic acid, is oxygen-dependent (Fernández et al., 1987, 1990), and that Y-2611, sparflloxacin, lomefloxacin, nalidixic acid, ciprofloxacin, and enoxacin induce lipid peroxidation of the human erythrocyte membrane, and of squalene under UVA irradiation (Fujita and Matsu, 1994; Wada et al., 1994). In addition, Umezawa et al. (1997) directly detected singlet oxygen and/or superoxide anion in quinolone solutions under UVA irradiation.

We have demonstrated that oral administration of quinolones plus UVA irradiation induces auricular skin inflammation, including dermal edema and neutrophil infiltration, in BALB/c mice (Shimoda et al., 1993). This reaction was inhibited by antioxidants in the early stage and by cyclooxygenase inhibitors in both the early and later stages (Shimoda et al., 1996). Further, we demonstrated that the simultaneous presence of quinolone with UVA irradiation stimulated BALB/c 3T3 mouse fibroblast cells to release prostaglandin (PG) E₂ in vitro (Shimoda et al., 1997), which was inhibited by cyclooxygenase inhibitors, antioxidants, inhibitors of protein kinase C, and tyrosine kinase (Shimoda and Kato, 1998). Based on these results, we have proposed a hypothesis for the following sequence of events: ROSs are generated from quinolone under UVA irradiation; ROSs trigger the activation of protein kinase...
C and tyrosine kinase in dermal fibroblasts; protein kinase C and tyrosine kinase activate cyclooxygenase, resulting in synthesis of cyclooxygenase products such as PGs; and cyclooxygenase products released from fibroblasts induce skin inflammation (Shimoda, 1998).

Quinolone phototoxicity is thought to be induced by interaction between quinolone and UVA light. Therefore, skin concentration of quinolone during UVA exposure could be crucial for inducing phototoxicity. To the best of our knowledge, however, there is no report dealing with toxicokinetics of quinolones under UVA irradiation.

Sitafloxacin, (-)-7-[(7S)-7-amino-5-azaspiro[2.4]heptan-5-yl]-8-chloro-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid sesquihydrate is a fluoroquinolone under development, with a broad spectrum and high in vitro activity against various aerobic and anaerobic gram-positive and gram-negative organisms (Sato et al., 1992).

We conducted the present study to compare the phototoxic potential of sitafloxacin with those of lomefloxacin and sparfloxacin in BALB/c mice and to examine the relationship between toxicokinetics and phototoxicity of sitafloxacin under UVA irradiation.

**MATERIALS AND METHODS**

**Test substances.** Sitafloxacin, lomefloxacin, and sparfloxacin were synthesized at Daiichi Pharmaceutical Co., Ltd (Tokyo, Japan). Sitafloxacin was dissolved in 1 N HCl-added physiological saline (pH 1.8) and adjusted to pH 4.5 with 0.1 N NaOH aqueous solution. Lomefloxacin and sparfloxacin were dissolved in 0.02 N NaOH in physiological saline. These compounds were formulated to obtain a constant dosage volume of 10 ml/min and sterilized by a Millipore filter (Millex GV 0.22 μm, Bedford, MA). Dose levels and concentration in the serum and auricle are expressed in terms of free base or anhydrate. Although these quinolones have been developed as peroral formulations for clinical use, we administered them intravenously to mice in order to minimize the deviations of data.

**Animals.** Female BALB/c mice, aged 5 weeks, were purchased from Charles River Japan, Inc. They were housed in an air-conditioned room (temperature, 23 ± 2°C; humidity, 55 ± 15%; light/dark cycle, 12:12 h) for acclimation to the environment until used. Commercial laboratory chow (F-2, Funabashi Farms, Funabashi, Japan) and chlorinated tap water were available ad libitum. For the experiments, 6-week-old mice, apparently in normal health, were used. The animals were cared for in accordance with the in-house guidelines for the care and use of laboratory animals.

**Phototoxic potential of sitafloxacin, lomefloxacin, and sparfloxacin (Experiment 1).** Based on the result of a preliminary study, we selected the dose levels of 10 and 40 mg/kg for comparing the phototoxic potential among sitafloxacin, lomefloxacin, and sparfloxacin. Mice were intravenously administered sitafloxacin, lomefloxacin, or sparfloxacin via the tail vein, at the rate of 1 ml/min, using a 27-gauge needle and a disposable syringe. Immediately after administration, mice were placed individually in partitioned chambers covered with a 3-mm pane of glass to eliminate wavelengths below 320 nm and were irradiated with UVA at 1.5 mW/cm² for 4 h (21.6 J/cm²) (Wagai et al., 1989). Black light tubes (FL20SBLB, Toshiba, Japan), which radiate wavelengths from 300 to 400 nm (peak at 360 nm), were used as the source of UVA, and the intensity of UVA was measured at 365 nm by a UVX digital radiometer (UVP Inc., San Gabriel, CA). For the control group, mice were administered the vehicle and irradiated with UVA for 4 h. The day of drug administration was designated as day 1.

The animals were observed for skin appearance, and auricular thickness was measured using a dial thickness gauge (Peacock G-5, Otsuki MFG, Japan) at time 0 (before administration) and 4 h (immediately after the end of UVA irradiation) following administration on day 1, then once daily thereafter. On day 8, the mice were sacrificed by bleeding under ether anesthesia. The auricles were removed, fixed in 10% buffered formalin, embedded in paraffin wax, sectioned, stained with hematoxylin and eosin, and examined histologically. Differences in auricular thickness between the control and quinolone-treated groups were statistically analyzed using Dunnett's test.

**Toxicokinetics of sitafloxacin under UVA irradiation in the serum and auricle (Experiment 2).** Thirty mice were intravenously administered 10 or 40 mg/kg sitafloxacin once and immediately irradiated with UVA at 1.5 mW/cm². At 15 min, 30 min, 1 h, 2 h, and 4 h after administration, three mice each were anesthetized with ether and blood was drawn via the inferior vena cava. After clotting, the blood samples were centrifuged to obtain sera. The left auricle was removed and longitudinally cut into 2 pieces. For non-UVA control, mice were administered 10 or 40 mg/kg sitafloxacin and housed under the normal ambient conditions of an experimental room, in which UVA intensity was detected at less than 0.01 mW/cm², until blood and auricle sampling.

Each serum sample (25 μl) was mixed with 1 ml of 50 mM KH₂PO₄ (pH 2) and 50 or 10 μl of 20% DX-9484 (0.2 μg/ml) as an internal standard (IS). A piece of the halved auricle was placed in 1 ml of 1 N NaOH containing 50 μl IS and treated at 100°C for 1 h. These samples were subjected to solid phase extraction, in preparation for a high performance liquid chromatography (HPLC) procedure. Following passage through a Bond Elut C8 LRC column (Uniflex, Tokyo, Japan) activated with MeOH, H₂O, and 50 mM KH₂PO₄, the samples were washed with 50 mM KH₂PO₄ and tetrahydrofuran (THF)/H₂O (20/80, v/v), and then eluted with THF/0.15% H₃PO₄ (50/50, v/v). The concentration of sitafloxacin in the eluate was measured with an HPLC system consisting of a constant flow pump (LC-10AD, Shimadzu Co., Tokyo, Japan), an automatic injector (AS-8010, Tosoh Co., Tokyo, Japan), an Inertsil ODS-2 column (UniFlex, Tokyo, Japan) activated with MeOH, H₂O, and 50 mM KH₂PO₄, and an integrator (C-R4A, Shimadzu Co., Kyoto, Japan). A THF/50 mM KH₂PO₄/1 M CH₃COONH₄ (19/81/1, v/v/v) mixture was used as the mobile phase at the flow rate of 1 ml/min. The column temperature was kept at 30°C.

**Severity of sitafloxacin-induced phototoxicity under various periods of UVA irradiation (Experiment 3).** Table 1 shows the group composition for this experiment. Mice were intravenously administered sitafloxacin at 40 mg/kg once, and were irradiated with UVA starting immediately to 15 min after administration (0–15 min), 15–30 min, 0–30 min, 0–1 h, 1–2 h, 30 min–2 h, 15 min–2 h, 0–2 h, 1–4 h, 30 min–4 h, or 0–4 h. For non-UVA control, mice were housed under the normal ambient conditions of an experimental room after intravenous administration of 40 mg/kg sitafloxacin. For vehicle control, mice were administered 1 N HCl-added physiological saline (pH 4.5) in the same way, and were irradiated with UVA for 4 h.

All animals were observed for skin appearance before administration and immediately after the end of irradiation on day 1, and once daily thereafter. On day 8, the mice were sacrificed by bleeding under ether anesthesia, and the auricles were examined histologically. In this experiment, auricular thickness was not measured, because histological examination had been found to be more sensitive in detecting the phototoxic inflammation in Experiment 1.

Each animal was scored for phototoxic reactions in accordance with the following criteria: 0, no change; 0.5, only auricular erythema noted; 1, slight neutrophil infiltration and/or focal minimum edema histologically evident in the dermis; or 2, diffuse edema with neutrophil infiltration histologically evident in the dermis. The mean phototoxic score was calculated for each group.

**Analysis of relationship between phototoxicity and toxicokinetics of sitafloxacin.** The area under the curve of auricular sitafloxacin concentration under UVA irradiation (AUCauricle•UVA) and that under the normal ambient
condition (AUCaure – UVA) were calculated by the trapezoid method. The correlation between the phototoxic score and the differences between AUCaure and AUCaure – UVA (\(\Delta\)AUCaure) for the various periods of UVA irradiation in Experiment 3 was statistically analyzed using a cumulative \(x^2\) test, and Kendall’s rank coefficient of correlation (\(r_k\)) between them was also calculated.

**RESULTS**

Phototoxicity of Sitafloxacin, Lomefloxacin, and Sparfloxacin

There were no changes in the vehicle control, sitafloxacin at 10-mg/kg, or lomefloxacin 10-mg/kg groups. Sitafloxacin at 40 mg/kg induced mild phototoxic change in the auricle. Auricular erythema was seen at all time points, and increased auricular thickness at 4 h and on days 3, 6, and 7 (Fig. 1a). Histologically, mild edema and neutrophil infiltration were seen in the dermis. Lomefloxacin, at 40 mg/kg, induced very severe changes. Auricular erythema was seen at all time points, and auricular thickness gradually increased up to approximately 4 times greater than that in the control groups by day 8 (Fig. 1b). Very severe edema and neutrophil infiltration were also seen in the dermis of these mice, with partial necrosis in the dermis and epidermis of 2/5 mice. Sparfloxacin induced phototoxic changes both at 10 and 40 mg/kg. At 10 mg/kg, auricular erythema was seen from day 2 to day 7, and increased auricular thickness on day 4. At 40 mg/kg, very severe thickening and dermal inflammation were seen in the auricle, which were similar to those observed in the lomefloxacin 40-mg/kg group (Fig. 1c).

Toxicokinetics of Sitafloxacin with or without UVA Irradiation

In serum, there was little difference in sitafloxacin concentration between the UVA and non-UVA groups (Fig. 2a). Serum concentrations at 15 min were 2.7 and 2.4 \(\mu\)g/ml at 10 mg/kg, and 9.7 and 11.2 \(\mu\)g/ml at 40 mg/kg under UVA and non-UVA irradiation, respectively. They decreased with a half-life (T\(_{1/2}\)) of 0.6 and 0.7 h, respectively, over 4 h after administration.

In contrast, sitafloxacin concentration was markedly decreased in the auricle under UVA irradiation (Fig. 2b). Auricular concentrations at 15 min were 4.6 and 1.7 \(\mu\)g/g at 10 mg/kg, and 21.7 and 7.9 \(\mu\)g/g at 40 mg/kg in the UVA and non-UVA groups, respectively. They decreased with T\(_{1/2}\) of 0.6 to 1.8 h over 4 h after administration.

Severity of Sitafloxacin-Induced Phototoxicity with Various UVA-Irradiation Periods

Table 2 shows the phototoxic score of each group. There was no change in the vehicle control, non-UVA control, 0–15 min, 15–30 min, 1–2 h, and 30 min–2 h groups. In the 0–30 min and 1–4 h groups, 2/5 and 3/5 mice showed erythema and mild neutrophil infiltration with or without focal edema in the dermis, respectively. In the 0–2 h and 30 min–4 h groups, 4/5 and 1/5 mice showed only erythema, but 1/5 and 4/5 mice showed focal edema with mild neutrophil infiltration in the dermis, respectively. In the 0–1 h and 0–2 h groups, focal edema with mild neutrophil infiltration was seen in the dermis of 3/5 and 1/5 mice, respectively, and overt diffuse edema with
mild neutrophil infiltration in the dermis of 2/5 and 4/5 mice, respectively. In the 0 – 4 h group, all mice showed overt diffuse edema with mild neutrophil infiltration in the dermis.

Figure 3 shows the relationship between phototoxic score and duration of UVA irradiation. The score was increased with increasing duration of UVA irradiation, but markedly decreased with delay in commencement of UVA irradiation.

**Relationship between Phototoxicity and Toxicokinetics of Sitafloxacin**

Figure 4 shows the relationship between the phototoxic score and $\Delta AUC_{\text{auricle}}$ over the various periods of UVA irradiation. The score was increased with increasing $\Delta AUC_{\text{auricle}}$, and close correlation was statistically demonstrated between them ($p < 0.0001, r = 0.957$).

**DISCUSSION**

We compared the phototoxic potential of the quinolone antibacterial agent sitafloxacin with those of lomefloxacin and sparfloxacin. These 3 quinolones have maximal absorption at approximately 280 and 330 nm (data not shown). Lomefloxacin and sparfloxacin are substituted with a fluorine at the 8 position of the quinolone ring and known to possess strong phototoxic potential (Domagala, 1994). At 40 mg/kg, sitafloxacin induced auricular erythema, auricular thickening, and der-
mal inflammation, but these were all mild. On the other hand, lomefloxacin and sparfloxacin showed very severe phototoxicity. With these compounds, auricular thickness increased to about 4 times that of the vehicle control group, and very severe dermal edema and neutrophil infiltration occurred. This result suggests that sitafloxacin, which is substituted with a chlorine at the 8 position, has less phototoxic potential than lomefloxacin and sparfloxacin. Moreover, sitafloxacin has been reported to have stronger antibacterial activity against various organisms than lomefloxacin and sparfloxacin (Sato et al., 1992). Therefore, the possible incidence of sitafloxacin-induced phototoxicity could clinically be much less than lomefloxacin and sparfloxacin.

We then examined the time course change of sitafloxacin concentrations in serum and auricular tissue. Sitafloxacin concentration in the auricle was markedly decreased under UVA irradiation, whereas that in serum was not affected by UVA irradiation. This result suggests that sitafloxacin is degraded in the auricular skin under UVA irradiation, but not in the blood. Photodegradation of quinolones has been reported to be associated with loss of their antibacterial activity (Ferguson et al., 1988; Leigh et al., 1991; Matsumoto et al., 1992; Phillips et al., 1990). Therefore, the antibacterial activity of sitafloxacin is speculated to be decreased in skin exposed to UVA light. In the present study, however, the serum sitafloxacin concentration was not affected by UVA, and the auricular concentrations were higher than serum concentrations, suggesting excellent penetration of this compound into the skin tissue. Therefore, skin concentration and antibacterial activity of sitafloxacin could quickly recover after termination of UVA irradiation.

Further, we examined the severity of sitafloxacin-induced phototoxicity under various periods of UVA irradiation. The increase in phototoxic score with increasing duration of UVA irradiation suggests that the severity of phototoxicity depends on auricular AUC, but not on maximum concentration (Cmax).

### Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>UVA dose (J/cm²)</th>
<th>Phototoxic score*</th>
<th>Mean phototoxic score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle control</td>
<td>21.6</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Non-UVA control</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>0–15 min</td>
<td>1.35</td>
<td>0</td>
<td>0</td>
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<tr>
<td>15–30 min</td>
<td>1.35</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0–30 min</td>
<td>2.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0–1 h</td>
<td>5.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1–2 h</td>
<td>5.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30 min–2 h</td>
<td>8.1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>15 min–2 h</td>
<td>9.45</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>0–2 h</td>
<td>10.8</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1–4 h</td>
<td>16.2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>30 min–4 h</td>
<td>18.9</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>0–4 h</td>
<td>21.6</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

* The criteria of phototoxic score are as follows: 0, no change; 0.5, only auricular erythema noted; 1, slight neutrophil infiltration and/or focal minimum edema histologically evident in the dermis; 2, diffuse edema with neutrophil infiltration histologically evident in the dermis.

**Note.** Mice were irradiated with UVA at 1.5 mW/cm².

**FIG. 3.** Relationship between phototoxic score and duration of ultraviolet-A (UVA) irradiation in BALB/c mice given a single intravenous administration of 40 mg/kg sitafloxacin and various periods of UVA irradiation at 1.5 mW/cm². Mice were irradiated with UVA from 0 to 15 min (A), 15 to 30 min (B), 0 to 30 min (C), 0 to 1 h (D), 1 to 2 h (E), 30 min to 2 h (F), 15 min to 2 h (G), 0 to 2 h (H), 1 to 4 h (I), 30 min to 4 h (J) or 0 to 4 h (K) after administration.

**FIG. 4.** Relationship between mean phototoxic score and ∆AUCauricle in BALB/c mice given a single intravenous administration of 40 mg/kg sitafloxacin and ultraviolet-A (UVA) irradiation at 1.5 mW/cm² for various periods. Mice were irradiated with UVA from 0 to 15 min (A), 15 to 30 min (B), 0 to 30 min (C), 0 to 1 h (D), 1 to 2 h (E), 30 min to 2 h (F), 15 min to 2 h (G), 0 to 2 h (H), 1 to 4 h (I), 30 min to 4 h (J) or 0 to 4 h (K) after administration.
Considering the results of the toxicokinetic analysis, the severity of phototoxicity is thought to depend on the AUC of the photodegraded sitafloxacin (ΔAUCauricle). Statistical analysis showing a close correlation (p < 0.0001, r² = 0.957) between the phototoxic score and ΔAUCauricle suggests that the severity of phototoxicity is directly proportional to the total amount of degraded sitafloxacin and may support our hypothesis. Our hypothesis could explain that the decrease in phototoxic score by delay in commencement of UVA irradiation is attributed to the decrease in ΔAUCauricle, resulting from rapid decrease in auricular sitafloxacin concentration after administration.

Although we examined sitafloxacin-induced phototoxicity at the constant intensity of UVA in the present study, it is readily recognizable that the severity of phototoxicity is naturally affected by UVA intensity. The period and intensity of UVA are thought to independently affect ΔAUCauricle, because the former may determine AUCauricle – UVA, while the latter may determine the degradation ratio of the test compound. In accordance with this hypothesis, indication of UVA dose would have little meaning in quinolone phototoxicity studies. Wagai and Tawara (1991a) and Marutani et al. (1995) independently evaluated the phototoxic potential of a single oral administration of ofloxac in 800 mg/kg in female BALB/c mice. The former applied UVA irradiation to mice from immediately after administration for 4 h at 1.5 mW/cm² (21.6 J/cm²), while the latter applied UVA from 30 min after administration for 2 h at 5.6 mW/cm² (40 J/cm²). Despite the UVA dose of the latter being greater than that of the former, only the former detected phototoxic inflammation in the auricular skin. Therefore, we consider that UVA intensity and AUCauricle – UVA, yet not UVA dose, are decisive factors for the severity of quinolone phototoxicity.

Marutani et al. (1993) demonstrated that Q-35, which is resistant to UV degradation, did not induce phototoxicity in BALB/c mice, while the 8-F and 8-H compounds, which are not resistant to UV degradation, induced phototoxic auricular inflammation. Their report seems to be in line with our results. However, we have demonstrated that UVA-pre-irradiated quinolones induced neither auricular inflammation in BALB/c mice in vivo nor prosta glandin production in BALB/c mouse 3T3 fibroblast cells in vitro (Shimoda et al., 1997; Wagai and Tawara, 1991b), suggesting that quinolone photoproducts are not involved in the mechanism of the phototoxicity. This contradiction could be explained as follows: ROSs are generated from quinolone during photodegradation under UVA irradiation; the ΔAUCauricle corresponds to the total amount of ROSs generated; ROSs trigger PG production in the skin tissue; the phototoxic score corresponds to the total inflammatory activity of PGs; and the photoproducts themselves have no role in the mechanism.

In conclusion, the severity of quinolone phototoxicity is thought to be directly proportional to the total amount of degraded compound, which could correspond to the total amount of ROSs generated under UVA irradiation. This hypothesis could be useful for comparison and extrapolation between experiments, in which different conditions or species are used. Further, the present study also suggests that phototoxic reactions to sitafloxacin could clinically be reduced by dosing at night or otherwise avoiding UV exposure, especially at peak concentrations.

REFERENCES


