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Reduced Phototoxicity of a Fluoroquinolone Antibacterial Agent with a Methoxy Group at the 8 Position in Mice Irradiated with Long-Wavelength UV Light

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A newly developed fluoroquinoline, Q-35 (8-OCH_3), in which a methoxy group was substituted at the 8 position of the quinoline nucleus, was very stable under irradiation with long-wave UV light (UVA). Derivatives, a fluoroquinolone with no substitution (the 8-H analog) and one in which a fluorine was substituted (the 8-F analog), were degraded in their solutions by the UVA irradiation. The phototoxic inducibility by these derivatives was further studied in a murine model. When mice were dosed orally with 800 mg of Q-35 (8-OCH_3) per kg of body weight, the maximum dose given, and exposed to the UVA light, no inflammatory lesions were observed in their ears. Ear redness was marked in mice given more than 12.5 mg of the 8-F analog or 200 mg of the 8-H analog per kg. Histopathological changes, edema, and infiltration of neutrophils were also observed microscopically in groups receiving the 8-H or 8-F analog but not in groups receiving Q-35 (8-OCH_3). Similar inflammatory reactions were observed to occur in a dose-dependent manner with other available fluoroquinolone antibacterial agents such as lomefloxacin, enoxacin, norfloxacin, ciprofloxacin and ofloxacin. These results suggest that the introduction of a methoxy group at the 8 position of the quinolone nucleus is important for the reduction of phototoxicity.

Fluoroquinolone antibacterial agents cause, although at low frequency, specific side effects such as gastrointestinal and central nervous system symptoms (5, 8), juvenile joint toxicity (17), convulsion induction under conditions of concomitant medication with nonsteroidal anti-inflammatory drugs and theophylline (21, 22), and severe phototoxicity (3, 12). In the case of phototoxicity, it has been empirically shown that marketed fluoroquinolones with halogens such as fluorine and chloride substituted at the 8 position of the quinolone nucleus have a relatively high incidence of clinical side effects.

Q-35 is a new compound with an 8-methoxyl substituent, a compound in which a methoxy group was substituted at the 8 position of the quinolone nucleus. Its antibacterial spectrum is broad, ranging from gram-positive to gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus*, *Pneumococcus* spp. (10, 14), and *Mycoplasma pneumoniae* (7).

We have previously demonstrated that solutions of fluoroquinolone derivatives with no substitutions (8-H) or with a fluorine substitution (8-F) were very unstable under irradiation with long-wave ultraviolet light (UVA) compared with Q-35, the parent compound with an 8-methoxyl substituent (15). Interestingly, the irradiated solutions of 8-F and 8-H analogs had reduced antibacterial activities and increased cytotoxicity to cultured mammalian cells. No such change was seen in the solution of Q-35 (8-OCH_3).

The present study demonstrates that oral administration of 8-H and 8-F analogs, but not Q-35 (8-OCH_3), results in inflammatory lesions in the ears of mice irradiated with UVA.

MATERIALS AND METHODS

Antibacterial agents. Three derivatives (Fig. 1) having a methoxyl substituent (Q-35) (8-OCH_3), a fluorine substituent (8-F), or no substituent (8-H) at the 8 position of the quinolone ring were synthesized at the Exploratory Research Laboratories, Chugai Pharmaceutical Co. Ciprofloxacin (CPFX) (Bayer Pharmaceuticals, Osaka, Japan), lomefloxacin (LFLX) (Hokuriku Pharmaceutical Co., Ltd., Fukui, Japan), ofloxacin (OFLX) (Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan), norfloxacin (NFLX) (Kyorin Pharmaceutical Co., Ltd., Tokyo, Japan), and enoxacin (ENX) (Dai-Nippon Pharmaceutical Co., Osaka, Japan) were also extracted and purified from marketed tablets.

UVA irradiation system. The source of UVA was a bank of 13 black-light fluorescent bulbs (FL20S · BLB; 32.5 mm by 58 cm) (Toshiba, Tokyo, Japan) arranged in parallel at 5.5-cm intervals, with a spectroscopic distribution between 300 and 400 nm and a peak at 352 nm. A pane of glass, 3-mm thick, was used as a filter to eliminate B-range UV light. Each mouse was placed alone in a separate irradiation cage

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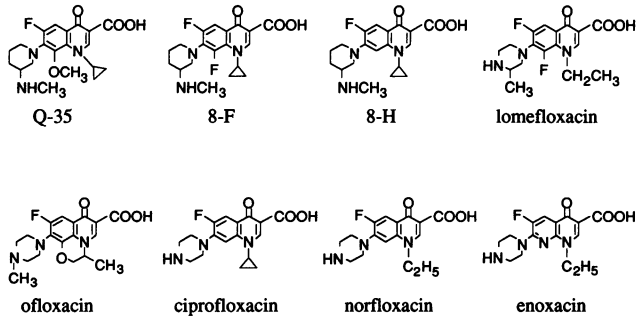

FIG. 1. Chemical structures of Q-35 and other fluoroquinolones.

(4.0 by 9.5 by 6.0 cm). UVA intensity was kept at 5.6 mW/cm^2, as measured by a UV radiometer (UVR-365; Tokyo Kogaku Kikai Co., Ltd., Tokyo, Japan), by adjusting the distance from the light source with a cage stand with a height controller (Fig. 2). This UVA intensity is equivalent to that of natural sunlight at midday in summer.

Analytical method. Antimicrobial agents were dissolved in 0.1 M phosphate buffer (pH 7.0) to a final concentration of 20 μg/ml and irradiated with 25 J of UVA per cm^2 while being stirred with a magnetic bar. Nonirradiated solutions were used as a control.

The solutions were analyzed by a high-performance liquid chromatography (HPLC) system consisting of a model LC-6A pump (Shimazu, Kyoto, Japan) with a Capcel Pak C18 (Shiseido, Tokyo, Japan). The mobile phase containing 0.01 M potassium dihydrogen phosphate-acetonitrile (78:22 for Q-35, 80:20 for the 8-F analog, and 84:16 for the 8-H analog) and 0.005 M 1-pentane sulfonic acid was pumped at a flow rate of 1.0 ml/min. A Waters 911J photodiode-array detector (Millipore Corporation, Bedford, Mass.) set at 200 to 400 nm was used for analyzing UV absorption spectra.

Phototoxicity test. Groups of six female BALB/c mice, 9 to 11 weeks old and weighing 19.0 to 26.0 g, were housed in a plastic cage and maintained in an air-conditioned room (21 to 25°C; 45 to 65% humidity) under a 14-h–10-h light-dark cycle. They were freely given laboratory feed (CE-2; CLEA Japan Inc., Tokyo, Japan) and water.

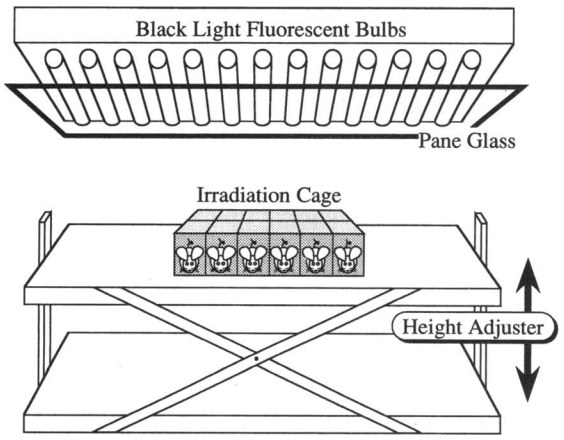

FIG. 2. UVA irradiation system. Twelve mice at once are irradiated in a partitioned cage by black-light fluorescent bulbs. UVA intensity is constantly kept at 5.6 J/cm^2 by a height adjuster.

The dose levels of fluoroquinolones were determined by preliminary tests. In consideration of a decrease in spontaneous locomotion found in mice treated orally without UVA irradiation, the highest dose of fluoroquinolone given was 800 mg/kg of body weight.

Six mice were assigned to each group. Mice were orally administered a quinolone solution of 10 ml/kg and exposed to UVA for 2 h. Control mice receiving distilled water were also irradiated. Irradiation at a dose of 5.6 mW/cm^2 was performed for 2 h consecutively, and the cumulative photoenergy was 40 J/cm^2. Ear redness as a phototoxic parameter was blindly scored at 30 min and at 24, 48, and 72 h after the completion of irradiation. The scores are as follows: 0, normal; 1, very slight erythema; 2, well-defined erythema; 3, moderate-to-severe erythema; 4, severe erythema to slight eschar formation.

Histopathology. The ears of euthanized mice were cut off 72 h after dosing and fixed in 10% formalin solution. Lesion sections were routinely processed in paraffin, sectioned at 2 to 4 μm, and stained with hematoxylin and eosin, after which microscopic examination was performed blindly.

Pharmacokinetic experiment. Mice were euthanized so that plasma could be obtained and the ears could be removed at 0.5, 1, 2, 4, and 8 h after oral administration of 200 mg of Q-35 (8-OCH_3), 8-F analog, or 8-H analog per kg.

Concentrations in the plasma were analyzed by an HPLC system as described above. The detector was a Shimazu RF530 spectrofluorimeter operating at an excitation wavelength of 295 nm for Q-35, 270 nm for the 8-F analog, and 275 nm for the 8-H analog and emission wavelengths of 500, 440, and 432 nm, respectively. The ears were added to 1.5 ml of 0.1 M phosphate-buffered saline (PBS), pH 7.2, per 100 mg of tissue and homogenized. Concentrations in the ear extracts were determined by a disk-agar diffusion method using *Klebsiella pneumoniae* IFO 3512 as the test organism and calculated from a standard curve.

The area under the concentration-time curve (AUC) of Q-35 derivatives was calculated from pharmacokinetic parameters, the mean values (n = 4) of the concentrations in plasma or ears between 0 and 8 h after oral administration according to the trapezoidal rule.

Statistical analysis. We used the Wilcoxon rank-sum test to compare the scores of murine ear redness as a parameter of phototoxicity. For the maximum concentration of drug in serum (C_{max}) values for the pharmacokinetic experiment, the significance of difference among Q-35 and its derivatives was analyzed by Student's t test.

RESULTS

Changes in HPLC chromatograms and UV absorption spectra in solutions irradiated with UVA. No changes after UVA irradiation at 25 J/cm^2 were observed in the HPLC chromatogram of Q-35 (8-OCH_3) solution (Fig. 3). In contrast, the irradiated solutions of the 8-H and 8-F analogs were remarkably decreased compared with the peak height of the unchanged compound, with simultaneous generation of some unknown peaks with UV absorption spectra different from those of the control.

Phototoxicity of fluoroquinolones with 8-position substitutions. When mice were orally administered 50 mg of the 8-F analog or 200 mg of the 8-H analog per kg, marked redness at the ears was observed from 30 min to 72 h after the completion of the UVA irradiation ($P < 0.01$; Table 1). The phototoxic development of 8-F was observed to occur weakly, even at a dose of 12.5 mg/kg, without significance.

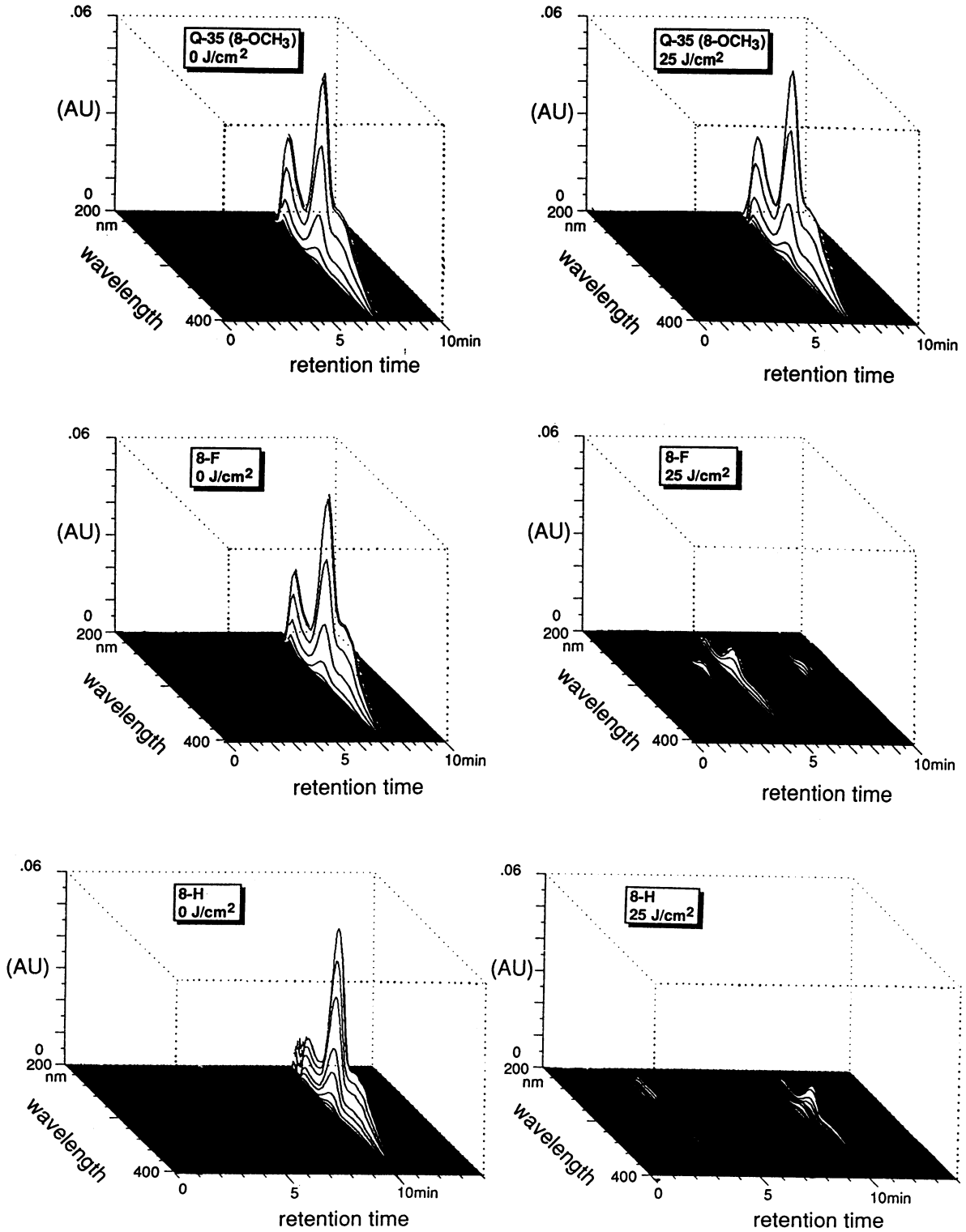

FIG. 3. Changes in HPLC chromatograms and UV absorption spectra in the irradiated solutions of fluoroquinolones with substitutions at the 8 position. The solutions, dissolved at 20 μg/ml in 0.1 M PBS, were irradiated with 25 J/cm^2. UV absorption spectra were analyzed by a photodiode-array detector set at 200 to 400 nm.

TABLE 1. Induction of inflammatory reaction in the ears of mice receiving Q-35 (8-OCH_3) or its derivatives

Quinolone	Dose (mg/kg)	No. of mice irradiated	Result at time after irradiation[a]:				No. of mice with inflammation
			30 min	24 h	48 h	72 h	
None (control)	0	6	0	0	0	0	0
Q-35	200	6	0	0	0	0	0
	800	6	0	0	0	0	0
8-F	3.125	6	0	0	0	0	0
	12.5	6	3 (0.5)	3 (0.5)	0	0	3
	50	6	6 (2.0)[b]	6 (2.7)[b]	6 (3.0)[b]	6 (2.7)[b]	6
8-H	50	6	0	0	0	0	0
	200	6	6 (1.5)[b]	6 (1.7)[b]	6 (1.7)[b]	4 (1.2)	6
	800	6	6 (3.0)[b]	6 (3.0)[b]	6 (3.0)[b]	6 (3.0)[b]	6

[a] Number of animals with ear redness. Numbers in parentheses represent the mean score of ear redness as follows: 0, normal; 1, very slight erythema; 2, well-defined erythema; 3, moderate-to-severe erythema; 4, severe erythema to slight eschar formation.
[b] $P < 0.01$.

The inflammatory changes increased in a dose-dependent manner. Mice receiving 800 mg of Q-35 (8-OCH_3) per kg or distilled water had no changes. These visual observations were confirmed by histopathological examination (Table 2). Ear preparations from mice given 50 mg of the 8-F analog per kg had prominent edema and slight infiltration of inflammatory cells, especially neutrophils, in the subcutaneous tissue and the corium (Fig. 4). A similar observation was noted for mice given 800 mg of the 8-H analog per kg (data not shown). No histopathological changes were found in mice given 800 mg of Q-35 (8-OCH_3) per kg.

Absorbability and distribution into the murine ears of fluoroquinolones with 8-position substitution. Concentrations in the plasma and the ear tissues after oral administration of 200 mg of Q-35 or its derivatives per kg were determined. All derivatives were well absorbed and distributed into the dermal tissues (half-life = 0.5 h), as shown in Fig. 5 and 6. The pharmacokinetic parameters are given in Tables 3 and 4.

In the plasma, the C_{max} and the AUCs from 0 to 8 h (AUC_{0-8}s) of Q-35 (8-OCH_3) and the 8-F and 8-H analogs were 7.45 ± 1.99, 16.58 ± 2.88, and 2.25 ± 0.70 μg/ml and 20.66, 38.26, and 5.66 μg · h/ml, respectively. The C_{max} of Q-35 was significantly higher than that of the 8-H analog ($P < 0.01$) and lower than that of 8-F ($P < 0.01$).

For the concentrations in dermal tissues, the C_{max}s and AUC_{0-8}s of Q-35 and the 8-F and 8-H analogs were 7.64 ± 1.87, 13.26 ± 3.21, and 4.66 ± 2.91 μg/g and 30.39, 39.70, and 14.93 μg · h/g, respectively. The C_{max} of the 8-F analog was significantly higher than those of the 8-H analog ($P < 0.01$) and Q-35 ($P < 0.05$). There were no significant differences between the C_{max}s for Q-35 and the 8-H analog. These data for the dermal tissue agreed well with those for the above-mentioned plasma parameters.

Phototoxicity of fluoroquinolones. The phototoxic potential of available fluoroquinolone antibacterial agents was subsequently evaluated (Table 5). LFLX administration resulted in an inflammatory redness at doses of 12.5 mg/kg or more ($P < 0.01$). At a dose of 50 mg/kg, this redness was marked until 72 h after completion of the irradiation. ENX induced a phototoxic reaction in the murine ears at a dose of 200 mg/kg ($P < 0.01$). The phototoxicity of NFLX, CPFX, and OFLX was relatively weak, although it was stronger than that of Q-35 (8-OCH_3). Preparations from mice treated with these drugs showed the histopathological changes described above (data not shown).

DISCUSSION

Certain fluoroquinolones are degraded by irradiation with UV light, including natural sunlight. In particular, LFLX

TABLE 2. Histopathological findings in ear sections

Quinolone	Dose (mg/kg)	No. of mice irradiated	No. of mice with:									
			Neutrophil infiltration[a]					Edema[a]				
			−	±	+	++	+++	−	±	+	++	+++
None (control)	0	6	6	0	0	0	0	6	0	0	0	0
Q-35	200	6	6	0	0	0	0	6	0	0	0	0
	800	6	6	0	0	0	0	6	0	0	0	0
8-F	3.125	6	6	0	0	0	0	6	0	0	0	0
	12.5	6	6	0	0	0	0	6	0	0	0	0
	50	6	0	1	2	3	0	0	0	0	1	5
8-H	50	6	6	0	0	0	0	6	0	0	0	0
	200	6	6	0	0	0	0	6	0	0	0	0
	800	6	0	2	4	0	0	0	1	5	0	0

[a] −, normal; ±, very slight; +, slight; ++, moderate; +++, marked.

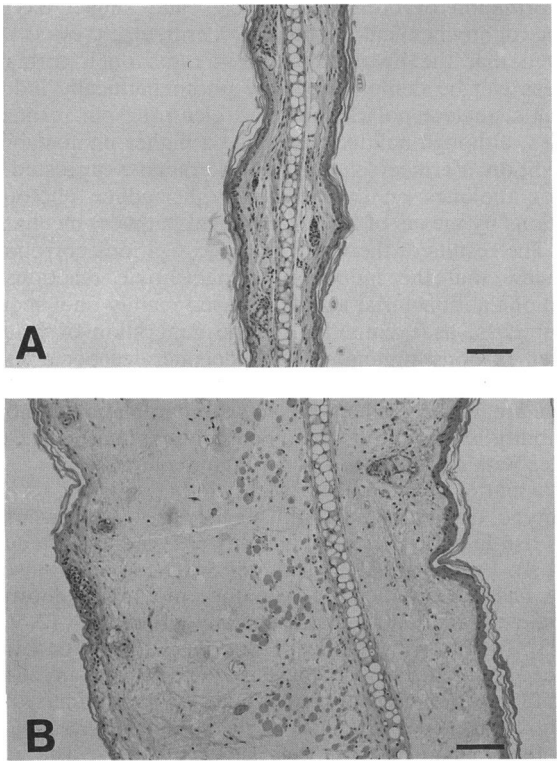

FIG. 4. Histopathological changes in murine ears. Mice were irradiated with 40 J of UVA per cm^2 for 2 h after oral administration of Q-35 (800 mg/kg) (A) or the 8-F analog (50 mg/kg) (B). The ears were removed 72 h after completion of the irradiation. Prominent edema and slight infiltration of inflammatory cells, especially neutrophils, were observed in the subcutaneous tissues and the coria of the mice treated with the 8-F analog. Bars, 100 μm.

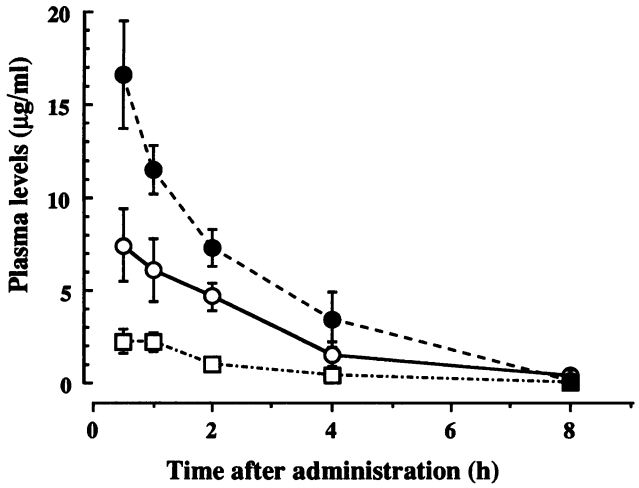

FIG. 5. Concentrations in plasma of fluoroquinolones with substitutions at the 8 position. Groups of four mice each were orally administered 200 mg of Q-35 (○), the 8-F analog (●), or the 8-H analog (□) per kg. Plasma samples were obtained 0.5, 1, 2, 4, and 8 h after administration and analyzed by the Shimazu HPLC system.

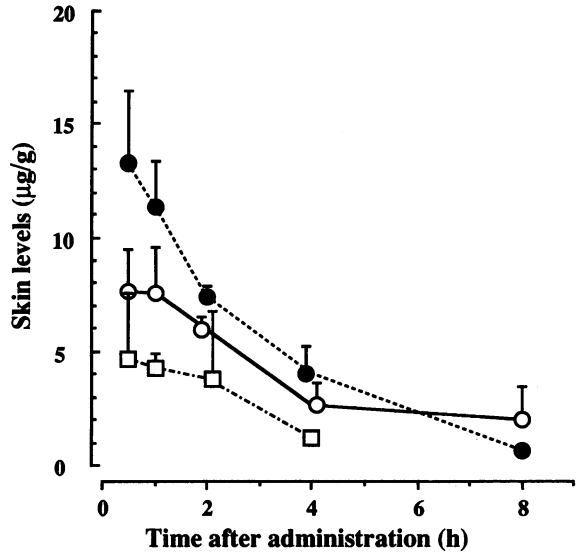

FIG. 6. Concentrations in murine ears of fluoroquinolones with substitutions at the 8 position. Groups of four mice each were orally administered 200 mg of Q-35 (○), the 8-F analog (●), or the 8-H analog (□) per kg. Ears from each mouse were homogenized and analyzed for drug concentration by a bioassay with *K. pneumoniae* IFO 3512.

and CPFX have been reported to be photodegraded by absorption of light energy (6, 13, 18). By in vitro investigation, we have previously reported that Q-35 (8-OCH_3), having a methoxyl substituent at the 8 position of the quinolone nucleus, is very stable in a solution of 20 μg/ml under UVA irradiation, although derivatives with substitutions of fluorine (8-F) or with no substitution (8-H) at the 8 position of the quinolone nucleus are degraded in the same irradiation system and produced certain unknown peaks in HPLC. Solutions of the 8-F or 8-H analog containing unknown degraded products had elevated cytotoxicity against cultured mammalian L-1210 cells, with reduced antibacterial activity. These data suggest that instability under UVA irradiation may reflect the in vivo phototoxic potential.

The present study revealed that Q-35 (8-OCH_3) induced no phototoxic reaction in the ears, even when mice received a maximum dose of 800 mg/kg followed by UVA irradiation of 40 J/cm^2. The derivative analog 8-F induced phototoxic reaction at doses of 12.5 mg/kg or more. Hematoxylin-eosin sections showed the formation of edema and infiltration of neutrophils. Another derivative analog, 8-H, also induced these reactions in the relatively high dose range of more than 200 mg/kg. The ability of the 8-F analog to induce phototox-

TABLE 3. Pharmacokinetic parameters in plasma of mice receiving 200 mg of Q-35 or its derivatives per kg orally[a]

Quinolone	T_{max}[b] (h)	C_{max}[c] (μg/ml)	AUC_{0-8}[d] (μg · h/ml)
Q-35 (8-OCH_3)	0.5	7.45 ± 1.99	20.66
8-F	0.5	16.58 ± 2.88	38.26
8-H	0.5	2.25 ± 0.70	5.66

[a] The data represent the mean values for four mice.
[b] T_{max}, time to maximum concentration of drug in serum.
[c] Mean value ± SD; $P < 0.01$.
[d] AUCs were calculated from the mean values for concentrations in plasma.

TABLE 4. Pharmacokinetic parameters in ears of mice receiving 200 mg of Q-35 or its derivatives per kg orally[a]

Quinolone	T_{max}[b] (h)	C_{max}[c] (μg/g)	AUC_{0-8}[d] (μg · h/g)
Q-35 (8-OCH_3)	0.5	7.64 ± 1.87	30.39
8-F	0.5	13.26 ± 3.21	39.70
8-H	0.5	4.66 ± 2.91	14.93

[a] The data represent the mean values for four mice.
[b] T_{max}, time to maximum concentration of drug in serum.
[c] Mean value ± SD. For the first and second values, $P < 0.05$; for the second and third values, $P < 0.01$.
[d] AUCs were calculated from the mean values for concentrations in ears.

icity was approximately 16 times stronger than that of the 8-H analog. It does not seem that reduced phototoxicity by an 8-methoxyl substituent is due to low absorbability with oral administration, since the AUC values for Q-35 (8-OCH_3) in both the plasma and the dermal tissues are relatively higher than those for the 8-H analog. Consequently, the physicochemical vulnerability to UVA appears to be closely associated with the potential to induce phototoxicity in vivo. However, it is not yet clear whether the photodegradates themselves, induced by UVA irradiation, promote the destruction of cutaneous tissues.

In general, drug-induced phototoxic reactions are elicited by absorption of photoenergy into drugs distributed in the skin, which then provoke chemical reactions in the body. The mechanism of this reaction can be explained in a number of ways. Firstly, the photoactivated agents or photodegradates directly bind to cellular components such as DNA and proteins, and then certain organs receive cytotoxic effects. Secondarily, reactive oxygen formation, a result of transference of electrons to oxygen molecules by excited chemicals which have absorbed photoenergy, promotes nonspecific injury of the body organs. Moore et al. (16) have reported that phototoxicity induced by nalidixic acid could be due to the formation of both free radicals and singlet oxygens during photochemical reactions. Vermeersch et al. (19) showed that the involvement of a radical-pair formation process can be demonstrated by photochemically induced dynamic nuclear polarization and electron spin resonance studies, although nalidixic acid had a higher photostability. In addition, Vermeersch and coworkers have suggested that fluoroquinolones on the market might induce phototoxic reactions by means of a similar radical pathway mechanism (20). The results of these in vitro investigations corroborate the view that the induction of phototoxic reactions by quinolone antibacterial agents is based mainly on a sequential process, as exemplified by the generation of reactive oxygen in body organs. If such degenerates occur in the tissue of murine ears, they can provoke toxic reactions which are made evident by acute inflammation. Another possibility is that the degraded compounds may make conjugates with organ tissues and become allergenic.

As a matter of fact, it is well-known that nalidixic acid, the prototype of quinolone antibacterial agents, occasionally gives rise to serious photosensitivity, as an allergic reaction (1, 3, 4). Furthermore, clinical development of photosensitivity has been noticed in chemotherapy with fluoroquinolone antibacterial agents, especially with LFLX (2, 9, 11, 12, 23). In fact, some clinical cases suggest that the LFLX-induced photodermatosis occurs not only as an allergic toxicity via the immune system but also as a primary toxic reaction (9). It seems that these reactions are generally due to both mechanisms operating simultaneously. The actual mechanism of photosensitivity to fluoroquinolone remains unknown. At least, it is true that no evidence ensuring elicitation of the allergic reaction, such as generation of specific immunological effectors originating in quinolones, has yet, to our knowledge, been found. Concerning the photodermatosis evident after administration of LFLX, it appears that this could be related to the phototoxic potential of the 8-fluorine substituent, as shown in the present study.

TABLE 5. Induction of inflammatory reaction by available fluoroquinolones in UVA-irradiated mice

Quinolone	Dose (mg/kg)	No. of mice irradiated	Result at time after irradiation[a]:				No. of mice with inflammation
			30 min	24 h	48 h	72 h	
None (control)	0	6	0	0	0	0	0
LFLX	3.125	6	0	0	0	0	0
	12.5	6	6 (1.1)[b]	3 (0.5)	3 (0.5)	1 (0.2)	6
	50	6	6 (2.8)[b]	6 (2.0)[b]	6 (2.0)[b]	6 (2.0)[b]	6
ENX	12.5	6	0	0	0	0	0
	50	6	4 (0.7)	4 (0.7)	3 (0.5)	2 (0.3)	4
	200	6	6 (2.0)[b]	6 (1.8)[b]	6 (1.8)[b]	6 (1.8)[b]	6
NFLX	50	6	0	0	0	0	0
	200	6	5 (0.8)	3 (0.5)	1 (0.2)	1 (0.2)	5
	800	6	6 (1.5)[b]	6 (1.5)[b]	5 (1.0)	5 (1.0)	6
CPFX	50	6	0	0	0	0	0
	200	6	2 (0.3)	0	0	0	2
	800	6	6 (1.5)[b]	3 (0.8)	3 (0.8)	3 (0.8)	6
OFLX	50	6	0	0	0	0	0
	200	6	5 (0.8)	0	0	0	5
	800	6	6 (2.0)[b]	6 (1.7)[b]	6 (1.7)[b]	4 (0.7)	6

[a] Number of animals with ear redness. Numbers in parentheses represent the mean scores of ear redness as follows: 0, normal; 1, very slight erythema; 2, well-defined erythema; 3, moderate-to-severe erythema; 4, severe erythema to slight eschar formation.
[b] $P < 0.01$.

Additional studies are required for elucidating the reduction mechanism of the introduction of a methoxy group into the 8 position of the quinolone nucleus. It is likely that the induction mechanism of the phototoxicity by fluoroquinolones will soon be clarified in relation to the radical species they generate.

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REFERENCES

1. **Baes, H.** 1968. Photosensitivity caused by nalidixic acid. Dermatologica **136:**61–64.
2. **Baran, R., and P. Brun.** 1986. Photoonycholysis induced by the fluoroquinolones pefloxacin and ofloxacin: report on 2 cases. Dermatologica **173:**185–188.
3. **Birkett, D. A., M. Garretts, and C. J. Stevenson.** 1969. Phototoxic bullous eruptions due to nalidixic acid. Br. J. Dermatol. **81:**342–344.
4. **Boisvert, A., and G. Barbeau.** 1981. Nalidixic acid-induced photodermatitis after minimal sun exposure. Drug Intell. Clin. Pharm. **15:**126–127.
5. **Christ, W., T. Lehnert, and B. Ulbrich.** 1988. Specific toxicologic aspects of the quinolones. Rev. Infect. Dis. **10**(Suppl. 1):S141–S146.
6. **Ferguson, J., G. Philips, and J. McEwen.** 1988. Loss of antibiotic activity caused by photodegradation: in vitro studies. Br. J. Dermatol. **119:**550–551.
7. **Gohara, Y., S. Arai, A. Akashi, K. Kuwano, C.-C. Tseng, S. Matsubara, M. Matsumoto, and T. Furudera.** 1993. In vitro and in vivo activities of Q-35, a new fluoroquinolone, against *Mycoplasma pneumoniae*. Antimicrob. Agents Chemother. **37:** 1826–1830.
8. **Halkin, H.** 1988. Adverse effects of the fluoroquinolones. Rev. Infect. Dis. **10**(Suppl. 1):S258–S261.
9. **Iravani, A.** 1992. Efficacy of lomefloxacin as compared to norfloxacin in the treatment of uncomplicated urinary tract infections in adults. Am. J. Med. **92**(Suppl. 4A):75S–81S.
10. **Itoh, T., M. Otsuki, and T. Nishino.** 1992. In vitro antibacterial activity of Q-35, a new fluoroquinolone. Antimicrob. Agents Chemother. **36:**1708–1714.
11. **Jensen, T., S. S. Pedersen, and C. H. Nielsen.** 1987. The efficacy and safety of ciprofloxacin and ofloxacin in chronic *Pseudomonas aeruginosa* infection in cystic fibrosis. J. Antimicrob. Chemother. **20:**585–594.
12. **Kawabe, Y., N. Mizuno, and S. Sakakibara.** 1989. Photoallergic reactions caused by enoxacin. Photodermatol. **6:**58–60.
13. **Leigh, D. A., S. Tait, and B. Walsh.** 1991. Antibacterial activity of lomefloxacin. J. Antimicrob. Chemother. **27:**589–598.
14. **Matsubara, S., M. Matsumoto, M. Ishigai, M. Nakagami, Y. Nabuchi, F. Takahashi, and K. Tanaka.** 1991. Pharmacokinetics and pharmacology of Q-35, a new 8-methoxy quinolone, in experimental animals. Program Abstr. 31st Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1445.
15. **Matsumoto, M., K. Kojima, H. Nagano, S. Matsubara, and T. Yokota.** 1992. Photostability and biological activity of fluoroquinolones substituted at the 8 position after UV irradiation. Antimicrob. Agents Chemother. **36:**1715–1719.
16. **Moore, D. E., V. J. Hemmens, and H. Yip.** 1984. Photosensitization by drugs: nalidixic and oxolinic acids. Photochem. Photobiol. **39:**57–61.
17. **Patterson, D. R.** 1991. Quinolone toxicity: methods of assessment. Am. J. Med. **91:**6A–35S.
18. **Phillips, G., B. E. Johnson, and J. Ferguson.** 1990. The loss of antibiotic activity of ciprofloxacin by photodegradation. J. Antimicrob. Chemother. **26:**783–789.
19. **Vermeersch, G., A. Filali, and J. Marko.** 1989. Photo-CIDNP and ESR studies of a photosensitizing drug: nalidixic acid. J. Photochem. Photobiol. B **4:**85–95.
20. **Vermeersch, G., A. Filali, J. Marko, J.-P. Catteau, and A. Couture.** 1990. Evaluation photophysique du pouvoir photosensibilisant de diverses quinolones. J. Pharm. Belg. **45:**299–305.
21. **Wijnands, W. J., C. L. van Herwaarden, and T. B. Vree.** 1984. Enoxacin raises plasma theophylline concentrations. Lancet **ii:**108–109.
22. **Yamamoto, K., Y. Naitoh, Y. Inoue, K. Yoshimura, K. Morikawa, O. Nagata, S. Hashimoto, T. Yamada, and S. Kubo.** 1988. Seizure discharges induced by the combination of new quinolinecarboxylic acid antimicrobial drugs and non-steroidal anti-inflammatory drugs. Chemotherapy **36**(Suppl. 2):300–324.
23. **Yasuda, S., N. Sakakibara, Y. Sakai, and T. Tsuji.** 1992. Lomefloxacin-induced photodermatosis. Hifubyo Shinryo **14:** 1081–1084.