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Fluoroquinolone antibacterials enhance UVA-induced skin tumors

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Abstract

Fluoroquinolone antibacterials are known to be phototoxic, both in vivo and in vitro. The action spectrum for the phototoxicity of the quinolones lies mainly in the UVA region. During studies of systemic drug phototoxicity, Johnson et al. (Dundee) induced dose-dependent phototoxicity in Swiss albino mice, and severe phototoxic reactions were followed by the development of skin tumors. The present study was designed to compare the ability of several quinolones to produce photobiologic effects following chronic, subphototoxic UVA radiation. To compare the activities of different quinolones (lomefloxacin, fleroxacin, ciprofloxacin, ofloxacin and nalidixic acid), doses that result in similar plasma and skin levels of drug were administered by gavage to slightly pigmented Skh-1 hairless mice for up to 78 weeks. 8-Methoxypsoralen (8-MOP) was used as a positive control, and unirradiated, drug-treated and irradiated and unirradiated drug-free controls were also used. No signs of phototoxicity were seen, except for minimal-to-slight erythema and swelling of the skin in animals of the lomefloxacin–UVA group. Skin tumors (1 mm in diameter or larger) were observed in all the irradiated groups and the incidence was increased in all the groups treated with the test articles. The cumulative tumor prevalence was accelerated, the median latent periods were shortened and tumor onset was significantly enhanced by 8-MOP plus UVA, lomefloxacin plus UVA and fleroxacin plus UVA, as compared with vehicle plus UVA-exposed animals. The majority of skin tumors (with the exception of lomefloxacin and 8-MOP) were benign. The majority of squamous cell carcinomas in the lomefloxacin group were of a histologic type different from those previously reported in UVA-exposed animals. Thus, all the fluoroquinolone antibiotics studied have the capability of enhancing UVA-induced phototumorigenesis, but only lomefloxacin caused the development of cystic squamous cell carcinomas in the majority of treated animals. © 1997 Elsevier Science S.A.

Keywords: Fluoroquinolone antibacterials; UVA-induced skin tumours; Phototoxicity

1. Introduction

Phototoxic skin reactions following systemic administration have been reported for numerous drug classes [1–3]. For the class of fluoroquinolone antibacterials, the potential to cause phototoxic skin reactions in humans has been reported [4–13]. The mechanisms involved in the phototoxicity of quinolones may depend on the drugs themselves [14], on the generation of toxic photo-products [15] or, as recently suggested, on the generation of active oxygen radicals [16,17]. The action spectrum for phototoxicity lies mainly in the UVA region [3].

Clinical experience concerning the phototoxic potential of quinolones has been confirmed by in vitro [3,18] and in vivo animal tests [19,20]. Preliminary studies performed by a group of investigators at the University of Dundee, using fleroxacin followed by UVA radiation, induced dose-dependent phototoxicity in the shaved, dorsal skin of Swiss albino mice. Severe phototoxic skin reactions were followed by the development of papillomas on exposed skin [20]. Studies performed at F. Hoffmann-La Roche Ltd., Basel, using various quinolones for comparative purposes, confirmed the experimental findings of skin papillomas after phototoxic exposure to fleroxacin and other quinolones. They further showed that there was great variation in the plasma levels of the various drugs when measured after single oral or intraperitoneal administration of 5.0 mg of the drug per animal [21].

The purpose of the present study was to assess the potential of fleroxacin to induce photobiologic effects in a chronic study using oral drug administration, followed by UVA irradiation, and to compare the results obtained with those for other quinolones (Fig. 1) under conditions that produce similar plasma levels.

2. Materials and methods

2.1. Test articles

- Lomefloxacin, Lot 7743.84 Batch B, synthesized at the laboratories of F. Hoffmann-La Roche Ltd., Basel. Ele-

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mentary analysis (C, H, N) corresponds to the chemical analysis of lomefloxacin.

- Fleroxacin (Lot 903037), synthesized at the laboratories of Kyorin Pharmaceuticals Ltd., Tokyo (purity, 99.8%).
- Ciprofloxacin, Lot PHC-I-3, extracted from CIPROXIN® at the laboratories of F. Hoffmann-La Roche Ltd., Basel (purity, about 100%).
- Ofloxacin, Lot TTH-I-147/G, extracted from GYR-AMID® at the laboratories of F. Hoffmann-La Roche Ltd., Basel (purity, about 99.67%).
- Nalidixic acid, Lot 40593/2, purchased from Janssen Chemica (purity, 99.9%).
- 8-Methoxypsoralen (8-MOP), Lot 19C-0218, i.e. the positive control, was purchased from SIGMA.

The chemical structures of the quinolone test articles are given in Fig. 1.

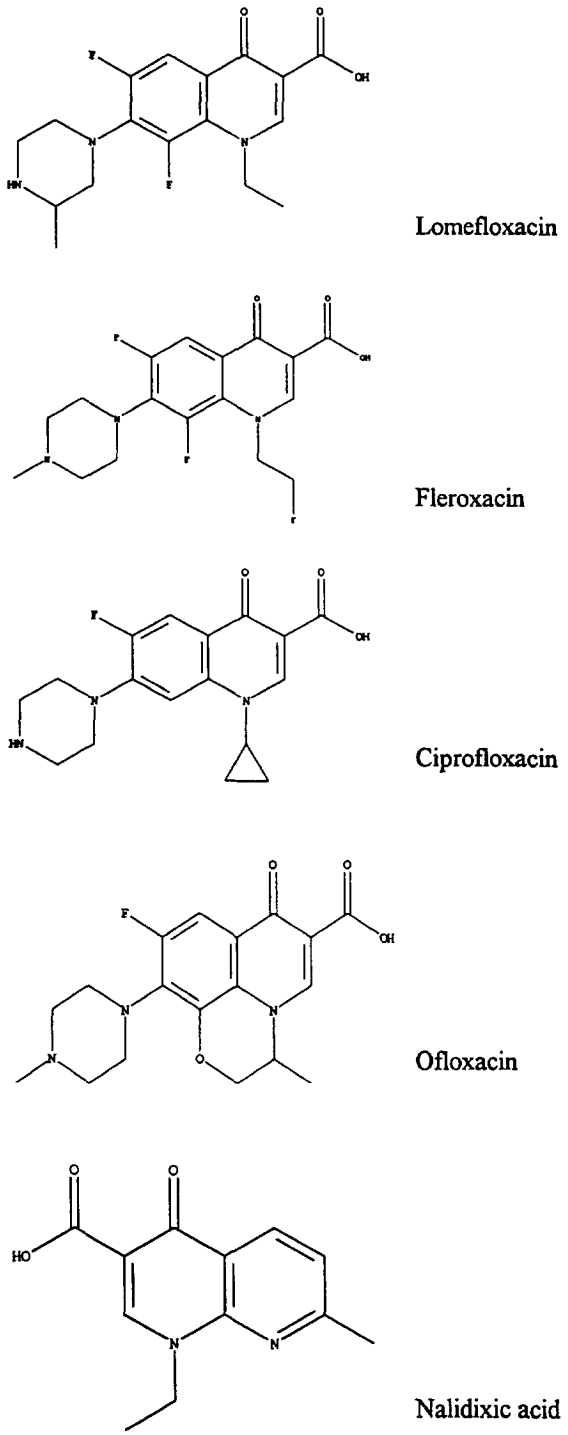

Fig. 1. Structure of quinolone compounds discussed in this paper: (a) lomefloxacin; (b) fleroxacin; (c) ciprofloxacin; (d) ofloxacin; (e) nalidixic acid.

2.2. Test animals

Female Skh-1 mice (Grl:Skh-1hr BR, slightly pigmented), bred at Charles River Wiga Germany, Sulzfeld, were used. During an acclimatization period of at least 10 days, the mice, aged 5–7 weeks and weighing between 15 and 30 g, were selected on the basis of normal appearance and the absence of disqualifying skin lesions. They were distributed by stratified randomization to 20 experimental groups, each consisting of 24 animals (Table 1), and were individually identified by ear tag, colored tail marking and cage number.

2.3. Animal husbandry

The mice were housed in groups of six in Macrolon® Type III cages with a minimum floor area of 810 cm^2 and minimum height of 15 cm. Four cages constituted a group. For UVA exposure, the mice were transferred to stainless steel wire-mesh cages with 24 individual radiation compartments per cage. Each compartment had a floor area of approximately 50 cm^2 and a height of approximately 12 cm.

The animals were checked daily for morbidity and mortality. Moribund animals were killed and, if indicated (i.e. when skin tumors at least 1 mm in diameter were found), skin specimens were taken for histopathological examination. The term 'tumor' as used in this study refers to the morphologic observation of a localized excrescence distinguishable from the surrounding skin by elevation, circumscribed borders and (usually) by a change in color and/or surface texture.

The animals were housed in air-conditioned rooms with 15–20 air changes per hour and a temperature of 22($\pm$2) °C, relative humidity of 55($\pm$10%) and a dark–light cycle of 12 h, using fluorescent F40T12G0 'gold' lamps.

A pelleted standard rodent diet (KLIBA No. 343, Klingentalmühle AG, Kaiseraugst, Switzerland) was available ad libitum. Water was provided from a local drinking water source and was available ad libitum in the housing and in the irradiation cages. Analyses for bacteriologic and possible chemical contamination were performed monthly.

2.4. UV radiation source

A bank of eight Philips type TL-K 40W 10R tubes (main spectral output, 350–400 nm; peak, 370 nm) was used [22]. The mice were irradiated in special irradiation cages, as

Table 1
Test articles, groups, doses of drug and/or UVA

Test article	Group[a]	Number of animals	Concentration (mg ml^{-1})	Dose (mg kg^{-1})	UVA (J cm^{-2})
Controls	C	24	Vehicle	—	25
	D	24	Vehicle	—	—
	E	24	—	—	—
Lomefloxacin	A	24	0.5	25	25
	B1	24	0.5	25	—
	B2	24	0.5	25	—
Fleroxacin	A	24	0.2	10	25
	B1	24	0.2	10	—
	B2	24	0.2	10	—
Ciprofloxacin	A	24	5.0	250	25
	B1	24	5.0	250	—
	B2	24	5.0	250	—
Ofloxacin	A	24	0.6	30	25
	B1	24	0.6	30	—
	B2	24	0.6	30	—
Nalidixic acid	A	24	0.1	5	25
	B1	24	0.1	5	—
	B2	24	0.1	5	—
8-MOP	A	24	0.2	10	(3.5)/2
	B1	24	0.2	10	—

[a]A, treated and irradiated; B1, treated only (unirradiated); B2, treated only (unirradiated; for toxicokinetics); C, vehicle control, irradiated; D, vehicle control, unirradiated; E, untreated control, unirradiated.

detailed above. The distance between the light source and the backs of the animals was adjusted in such a manner that the resulting radiation energy was approximately 2.0 mW cm^{-2} at the skin surface, as measured using an RM-2D digital radiometer with a spectral sensitivity that closely matched the spectral output of the source. The radiation intensity of the tubes was checked every 2 months.

2.5. Drug and radiation doses

For the purpose of this study, oral doses of the compounds were chosen that were expected to give plasma levels 2–4 h after gavage similar to that achieved by 0.2 mg of fleroxacin per animal per day. The doses were selected on the basis of the results of preliminary phototoxicity-range-finding studies, taking toxicokinetic data into consideration (data on file at Hoffmann-La Roche, Ltd). The test compounds were administered by gavage using a standard vehicle that contained sodium carboxymethyl cellulose. The oral drug doses used per animal were as follows: lomefloxacin, 0.5 mg; fleroxacin, 0.2 mg; ciprofloxacin, 5.0 mg; ofloxacin, 0.6 mg; nalidixic acid, 0.1 mg; 8-MOP, 0.2 mg [23].

The subphototoxic dose of UVA radiation was chosen on the basis of results from preliminary dose-range-finding studies (data on file). For animals treated with quinolone antibacterials, the UVA dose was approximately 25 J cm^{-2}. For animals treated with 8-MOP, the UVA dose was 3.5 J cm^{-2} in the first week of treatment and was reduced to 2.0 J cm^{-2} from the second week of treatment, as cutaneous phototoxic symptoms developed. The total UVA radiation dose over 2 weeks was 125 J cm^{-2} to the dorsal skin for the quinolone-treated animals and 10 J cm^{-2} for the animals treated with 8-MOP (Table 1).

2.6. Experimental procedure

The test materials were administered by gavage five times every 2 weeks, according to a repetitive 2-week dosing sequence: first week—Monday, Wednesday, Friday; second week—Tuesday, Thursday. Approximately 1.5 h after oral administration, i.e. when the plasma levels had stabilized, animals of groups A (compound treated) and C (vehicle control) were exposed to UVA radiation (Table 1).

2.7. Duration of the study

A treatment regimen over 52 weeks was chosen to study the chronic phototoxic effects of orally administered quinolones on Skh-1 mice. For the groups that received fleroxacin, lomefloxacin or 8-MOP, the surviving mice were killed on completion of the 52 weeks of treatment. Because skin tumors were still minimal in mice treated with ciprofloxacin, ofloxacin or nalidixic acid at the end of 52 weeks, the experimental period for these quinolone groups and the vehicle control group was extended to 78 weeks.

2.8. Clinical observations

Once every 2 weeks, the animals were subjected to a detailed clinical examination to monitor clinical signs and the presence or progression of skin tumors and other skin lesions. The size, type, condition and localization of tumors

Table 2
Mean test compound concentrations in plasma and skin (± SD)

Test article	Plasma concentrations ($\mu g\ ml^{-1}$)		Skin concentrations ($\mu g\ g^{-1}$)	
	Week 3	Week 41	Week 3	Week 41
Lomefloxacin	0.78 ± 0.11	0.59 ± 0.22	1.34 ± 0.23	0.97 ± 0.42
Fleroxacin	0.66 ± 0.10	0.45 ± 0.03	1.05 ± 0.22	0.67 ± 0.07
Ciprofloxacin	0.94 ± 0.29	0.32 ± 0.10	1.69 ± 0.55	0.95 ± 0.42
Ofloxacin	0.69 ± 0.12	0.38 ± 0.06	1.20 ± 0.06	0.58 ± 0.09
Nalidixic acid	0.22 ± 0.04	0.48 ± 0.36	< 0.10	0.12 ± 0.10

were documented. At the end of 52 weeks, all mice bearing tumors at least 1 mm in diameter were killed to obtain skin specimens for histopathological examination. The surviving animals in the groups treated with ciprofloxacin, ofloxacin and nalidixic acid and irradiated, as well as those in the vehicle control groups C (irradiated) and E (not irradiated) were divided into two groups, one of which was treated through to the end of the 78 weeks study period, while treatment was discontinued for the other group and the animals were observed through to week 78. For ethical reasons, moribund animals and those with a high incidence of large skin tumors were killed and skin specimens taken for histopathological examination.

2.9. Toxicokinetic parameters

Plasma and skin concentration levels of the test articles were determined on day 1 as well as in weeks 3, 7, 31, 41 and 51 of the study. At each time-point, four mice from the corresponding toxicokinetic group (group B_2) were killed for blood and skin collection. The drug levels were determined using a high performance liquid chromatography (HPLC) method with either fluorescence or UV detection [24].

2.10. Histopathology

After 52 or 78 weeks, all the animals that had developed skin tumors at least 1 mm diameter were killed and the skin tumors removed. Skin tumors from animals that died or were killed during the study were also removed. In addition, all the unirradiated vehicle control animals (group D), three mice from the irradiated vehicle control group (group C), and two animals from the unirradiated, untreated control group (group E) were killed after 52 weeks to obtain control skin for comparison. All the specimens were preserved in buffered neutral formalin, embedded in paraffin and stained with hematoxylin-eosin. Histological evaluation was carried out by two independent experts without prior knowledge of group allocation. The observed skin findings were classified according to published clinical classifications [30].

3. Results

3.1. Body weights

With the exception of the lomefloxacin-irradiated group, the mean overall body weights in all the groups were within ± 10% of the weight range of the relevant control groups. The apparent marked body weight increase in the lomefloxacin-irradiated group resulted from the development of large numbers of skin tumors in these animals.

3.2. Survival

Mortality as a result of treatment-related factors was low. A total of 19 out of the 480 experimental animals died during the period of 52 weeks. Of these, eight mice belonged to the irradiated groups treated with various quinolones or 8-MOP, and 11 animals belonged to the corresponding control groups. Between weeks 52 and 78, an additional seven animals died (one treated and six controls).

3.3. Clinical signs

No signs of phototoxicity were seen, except for minimal-to-slight erythema and swelling of the skin in animals of the lomefloxacin plus UVA group.

3.4. Toxicokinetics

The toxicokinetic monitoring of the plasma and skin concentrations showed that the plasma concentrations of lomefloxacin and ofloxacin were similar to those of fleroxacin throughout the experiment. The mean plasma and skin concentrations are given in Table 2.

The plasma concentrations of ciprofloxacin were initially higher than those of fleroxacin, while those of nalidixic acid were lower. The concentrations of ciprofloxacin tended to decrease during the course of the study, whereas those of nalidixic acid increased, and those of fleroxacin, lomefloxacin and ofloxacin remained relatively unchanged. By week 41, all the test compounds were showing comparable plasma concentrations.

The concentrations for all the test compounds were consistently higher in the skin than in the plasma, except for the

Table 3
Test articles, groups, dose of drug or UVA, latent time to tumor onset[a] and median latent period

Test article	Group	Dose		Latent time to onset (weeks)	Median latent period (weeks)
		Drug[b] (mg per animal)	UVA[c] (J cm^{-2} of skin)		
Controls	C	Vehicle	25	34	—
	D	Vehicle	—	—	—
	E	—	—	—	—
Lomefloxacin	A	0.5	25	16	22
	B1	0.5	—	—	—
Fleroxacin	A	0.2	25	28	38
	B1	0.2	—	—	—
Ciprofloxacin	A	5.0	25	50	78
	B1	5.0	—	—	—
Ofloxacin	A	0.6	25	32	66
	B1	0.6	—	—	—
Nalidixic acid	A	0.1	25	18	>78
	B1	0.1	—	—	—
8-MOP	A	0.2	(3.5)/2	4	24
	B1	0.2	—	—	—

[a]Time to appearance of first skin tumor at least 1 mm in diameter.
[b]Administered three times in the first week and twice the next week (five doses per fortnight).
[c]Administered 1.5 h after each dose of drug.

case of nalidixic acid. The changes in skin concentrations with time paralleled those in the plasma. The objective of achieving similar plasma and skin concentrations throughout the 52 weeks of the study was essentially achieved for the four fluoroquinolones. Although some consistent differences were seen in the magnitude of the effects, this is probably not sufficient to compromise the pharmacodynamic evaluation.

3.5. Skin tumors

The skin was the primary target for quinolone derivatives and 8-MOP after oral administration followed by UVA irradiation. The latent period (the week that the first tumor at least 1 mm in diameter was observed) and the median latent period (the time in weeks when 50% of the animals had at least one or more skin tumors) for each group are shown in Table 3. The first skin tumor was observed in the irradiated animals treated with 8-MOP in week 4 of the study. The number of skin-tumor-bearing animals increased with time (Fig. 2).

The enhancement of UV-induced tumorigenesis is most often estimated by examining the times to the appearance of the first tumor and to 50% tumor incidence (see statistical analysis below). For lomefloxacin, the first tumor appeared after 16 weeks and 50% incidence was reached after 22 weeks. For fleroxacin, the first tumor appeared after 28 weeks and 50% incidence was reached after 38 weeks. For ofloxacin, 50% incidence was reached after 66 weeks, and it was reached

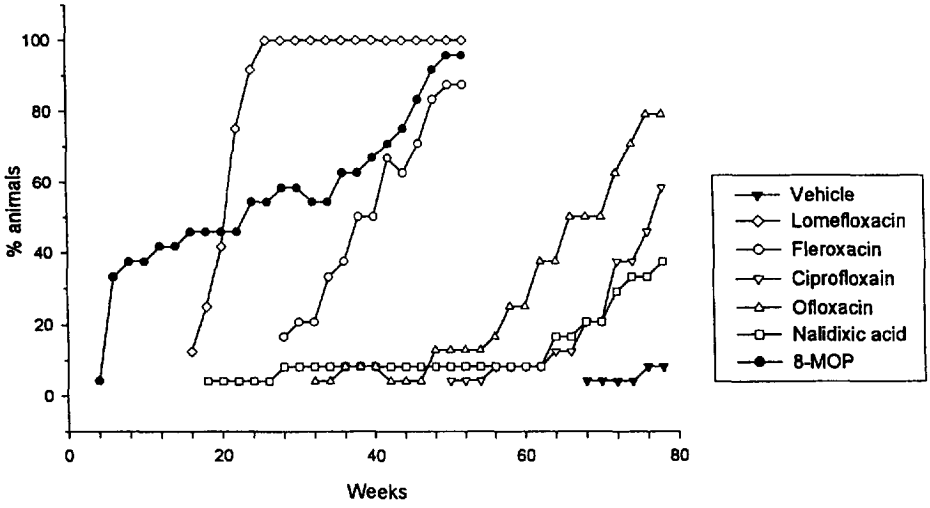

Fig. 2. Percentage of animals exhibiting skin tumors at least 1 mm in diameter plotted against time for outcomes of the chronic phototoxicity study involving five quinolones and 8-MOP in Skh-1 mice: ▼, vehicle; ◇, lomefloxacin; ○, fleroxacin; ▽, ciprofloxacin; △, ofloxacin; □, naldixic acid; ●, 8-MOP. The curve representing each study group is a cumulative distribution function.

Table 4
Number and type of skin tumor in irradiated animals

Test article	Animals with tumors	Squamous cell carcinoma	Papilloma	Kerato-Acanthoma	Solar keratosis	Other
Vehicle + UVA	4	0	3	0	0	2
Vehicle only	0	0	0	0	0	0
Untreated	1	0	0	0	0	1
Lomefloxacin	24	30	37	17	3	0
Fleroxacin	20	1	30	13	5	3
Ciprofloxacin	11	0	12	2	0	0
Ofloxacin	16	2	17	3	10	1
Nalidixic acid	9	1	11	0	1	0
8-MOP	14	12	8	6	12	2

after 78 weeks with ciprofloxacin and nalidixic acid. After 52 weeks, the incidence of skin tumors was 100% for mice dosed with lomefloxacin, 95.8% for those dosed with 8-MOP and 87.5% for mice dosed with fleroxacin, all of which were UVA irradiated.

Towards the end of 52 weeks, it became evident that skin tumors were also beginning to develop in animals treated with ciprofloxacin, ofloxacin and nalidixic acid. Therefore, the study was extended, as described earlier. At the end of the 78 weeks of the study, the incidence of skin tumors was 79.2% for mice treated with ofloxacin, 58.5% for mice treated with ciprofloxacin and 37.5% for those treated with nalidixic acid, with all the mice again being UVA irradiated. There was no significant difference in the incidence of skin tumors between the subgroups that continued with or without treatment to the end of the extended study. Four animals from the vehicle treated and irradiated control group (group C) also developed skin tumors. No skin tumors or cutaneous abnormalities appeared in the unirradiated or irradiated control groups.

3.6. Histopathology

The histopathological classification used in this study is based on commonly accepted clinical classifications, as well as on those used in previous publications on quinolones [25–30]. The results of the histopathological examination of neoplasms of various types are summarized in Table 4 and can be described as follows.

- Animals exposed to 8-MOP and UVA developed a number of papillomas, solar keratoses, keratoacanthomas and squamous cell carcinomas.
- UVA alone induced a few benign lesions: papillomas and solar keratoses, similar to those described following UVA irradiation [31].
- Unirradiated animals treated with the vehicle alone or with fleroxacin, lomefloxacin, ofloxacin, ciprofloxacin or nalidixic acid developed one papilloma and a dermal sarcoma.
- Animals exposed to UVA and treated with fleroxacin, ciprofloxacin, ofloxacin or nalidixic acid developed benign skin tumors and a few malignant neoplasms, with no histologically specific differences from those previously described in the literature after UVA treatment [31].
- Animals exposed to UVA and treated with lomefloxacin exhibited a specific type of neoplastic progression. In addition to benign papillomas, a few solar keratoses and a large number of cystic squamous cell carcinomas were observed. Two squamous cell carcinomas were of the ulcerating type and the remainder were of the cystic type, with some having a papillomas component. These carcinomas are of a type not previously described following UVA irradiation [30].
- Epidermal hyperplasia and dermal fibrosis were observed in a number of animals exposed to UVA irradiation and different chemicals. These lesions were of the type usually seen with UVA irradiation [31].
- Neoplastic and non-neoplastic lesions in organs other than the skin were not systematically examined. Specific alterations related to treatment were not observed in other organs.

3.7. Statistical evaluation

For practical reasons, the data sets were limited to groups that were similarly treated throughout the study. This was achieved by using 'right-censored' data techniques [32]. Essentially, the animals withdrawn from treatment after 52 weeks were considered as withdrawn from the study, and all direct comparisons that involved groups which were terminated after 52 weeks were limited to that time period.

The existing data analysis programs for photocarcinogenicity studies are based on the following assumptions: (1) all animals are chronically exposed to carcinogenic radiation up to the time that most or all animals are affected; (2) all treatments produce the same tumor types, with only the latent period changing; (3) few tumors disappear other than by merger or trauma; (4) tumor progression can be adequately described by measurement of the maximum planar diameter and by classification into inclusive size categories.

Tumor prevalence in the vehicle control and the vehicle plus UVA groups was comparable through study week 52. Tumor prevalence was accelerated in the 8-MOP plus UVA, lomefloxacin plus UVA, and fleroxacin plus UVA groups, as

compared with vehicle plus UVA mice. Tumor prevalence in the ciprofloxacin plus UVA and nalidixic acid plus UVA groups was comparable with that for the vehicle plus UVA group through week 78. There was a slight suggestion of an enhancement of the tumor prevalence in the ofloxacin plus UVA group. Tumor onset was not significantly different in these four compounds. There was virtually no carcinogenic activity as a result of the test articles among groups not exposed to UVA.

The median (biased) latent periods were clearly shortened in the 8-MOP plus UVA, lomefloxacin plus UVA, and fleroxacin plus UVA groups, as compared with the vehicle plus UVA groups. There was a slight shortening of the biased median latent period in the ofloxacin plus UVA groups.

Based on the analysis of onset ratios [33], tumor onset (52 weeks) was not significantly different between the vehicle control and vehicle plus UVA groups. In contrast, tumor onset was significantly enhanced ($p < 0.01$) in the 8-MOP plus UVA, lomefloxacin plus UVA, and fleroxacin plus UVA groups, as compared with the vehicle plus UVA group. At 52 weeks, tumor onset in the vehicle plus UVA group was not significantly different from that in the ciprofloxacin plus UVA, ofloxacin plus UVA or alidixic acid plus UVA group.

In summary, the cumulative tumor prevalence was accelerated, the median latent periods were shortened, and tumor onset was significantly enhanced among animals treated with 8-MOP plus UVA, lomefloxacin plus UVA and fleroxacin plus UVA compared with the vehicle plus UVA animals.

4. Discussion

The second-generation fluoroquinolone antibacterials, which are chemically related to nalidixic acid, have achieved a considerable reputation in the treatment of a broad spectrum of infectious diseases. Clinical experience has shown that adverse systemic side-effects have generally been minor, but abnormal cutaneous photosensitivity appears to be a consistent feature of the adverse reaction reports [4–13]. This is not surprising, because nalidixic acid is also a well-known phototoxic agent [12,13].

Ferguson and Johnson [3] have reviewed extensive laboratory data, showing that nalidixic acid, ciprofloxacin, norfloxacin, ofloxacin and fleroxacin are unequivocally phototoxic in vitro, with the action spectrum being mainly in the UVA region. In phototoxicity tests in vitro and in vivo (mouse), the general pattern of the phototoxic potentials of these fluorinated quinolones was less than that of nalidixic acid.

At the time of inception of this study, Johnson et al. [20] used severely phototoxic doses of fleroxacin and UVA to induce papillomas in mouse skin in a dose-dependent fashion. Because it is known that severe skin phototoxicity can lead to the formation of skin tumors [34], this chronic phototoxicity experiment was conducted with subphototoxic doses of the fluoroquinolones and nalidixic acid, except that the animals treated with lomefloxacin plus UVA exhibited some swelling and thickening of the skin.

Similar plasma and skin concentrations of all the test compounds were essentially achieved for the four fluoroquinolones throughout the 52-week oral phototoxicity study. Although some consistent differences were seen, the magnitude was not considered to be sufficient to compromise the pharmacodynamic evaluation. However, in the case of nalidixic acid, plasma concentrations comparable with those of the fluoroquinolones were only achieved near the end of the study. The skin concentrations were a factor of 5–10 lower than the plasma concentrations for nalidixic acid, whereas the skin concentrations were 2–3 times higher than the plasma concentrations for the fluoroquinolones.

As expected from the UVA doses used, the combination of vehicle alone plus UVA produced a few benign skin tumors. All the quinolone compounds tested enhanced the development of skin tumors. Except for lomefloxacin, all but four skin tumors were benign and of the type expected to be produced by chronic UVA irradiation on hairless mice [22]. In marked contrast, in the lomefloxacin group, there were 30 squamous cell carcinomas. Of these, two-thirds were of the cystic type, reaching a large size and invading deeply into the tissue underlying the skin. These squamous cell carcinomas are different from the type of hyperplastic skin lesions commonly induced by UVB, UVA or chemical skin carcinogens [30].

Photocarcinogenesis in human skin, whether as a result of UVB or the combination of a phototoxic drug and UVA, requires many years of simultaneous exposure. In PUVA therapy, continuous exposure for several years is needed to induce skin cancers in humans [35,36]—a finding that has not been duplicated in some other large studies in Europe [37,38]. In contrast, quinolone antibiotics are usually intended for short-term use only (approximately 2 weeks). Emphasis on the prevention of phototoxicity-producing exposure to sunlight or artificial UVA sources (such as sunbeds) during the brief treatment period would be expected to prevent adverse skin reactions. From the perspective of phototoxicity, fluoroquinolone antibacterial therapy should not pose any health hazard to humans under the recommended conditions of use.

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