

Phototoxicity in quinolones: comparison of ciprofloxacin and grepafloxacin

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Skin photosensitizing reactions have been reported during treatment with fluoroquinolone antibiotics. The incidence and severity of such reactions, however, appear to differ between agents. The photosensitizing effect of grepafloxacin 400 and 600 mg once daily was compared with that of ciprofloxacin 500 mg bd and placebo in a double-blind trial involving 32 healthy subjects. Skin photosensitivity, expressed as the minimal erythema dose (MED), was measured before treatment and towards the end of the 7 day treatment period. Grepafloxacin showed a mild photosensitizing effect comparable to that of ciprofloxacin, with significant reductions in MED at 335 ± 30 and 365 ± 30 nm. However, few subjects showed MEDs outside the normal range, and MEDs consistently returned to baseline values within 1 week of stopping treatment. No significant differences between the effects of grepafloxacin and ciprofloxacin could be observed. It is concluded that grepafloxacin has a weak, UVA-dependent and rapidly reversible photosensitizing effect.

Introduction

Drug-induced photosensitivity of the skin is attracting increasing attention. Photosensitivity has been reported with a variety of drugs in recent years, and is now recognized as a significant clinical problem by clinicians, regulatory authorities and the pharmaceutical industry.^{1,2} Indeed, it has been recommended that all new drugs should be screened for photosensitizing effects before they are subjected to clinical trials, in order to reduce potential distress to patients.¹

Quinolone antibiotics have been shown to be effective and well tolerated in the treatment of a broad spectrum of bacterial infections. However, the prototype of this group, nalidixic acid, is known to cause skin photosensitivity in humans,^{3,4} and hence it might be expected that other members of this class would also have the same effect. Indeed, photosensitizing reactions have been reported during treatment with a number of fluoroquinolones, including ciprofloxacin,⁵ ofloxacin,⁶ norfloxacin,⁷ enoxacin,⁸ lomefloxacin⁹ and sparfloxacin.¹⁰ The photosensitivity associated with these latter agents, however, appears to differ from that associated with nalidixic acid.¹¹ Nalidixic acid has been reported to produce pseudo-porphyrin reactions, with skin fragility and blistering at exposed sites in the presence of normal porphyrin values.

By contrast, the most common cause of photosensitization with the newer fluoroquinolones is phototoxicity: an immediate or delayed inflammatory reaction resulting from cellular damage,¹¹ with skin lesions manifesting themselves as reddening and, when severe, with blistering and subsequent peeling. These lesions are sometimes described as an exaggerated sunburn reaction, but this description may be an oversimplification, as photosensitizing drugs can often be distinguished from each other by the morphology and time-course of the skin lesions.² This reaction can occur in any individual with sufficient cutaneous concentration of photosensitizer and enough exposure to radiation of the appropriate wavelength. Less commonly, photosensitization may present as photo-onycholysis, with separation of the nail plate from the nail bed.¹²

Fluoroquinolones differ in their capacity to cause photosensitization reactions. Early reports with ciprofloxacin, ofloxacin, norfloxacin and enoxacin suggested that the incidence of such reactions was low (less than 2.4%), and that most reactions were mild.¹¹ More recently, however, higher incidences (up to 10–15%) have been reported with lomefloxacin⁹ and feroxacin,¹³ and there is also evidence that the severity of photosensitization reactions may be greater with these agents.¹⁴

Grepafloxacin (\pm -1-cyclopropyl-6-fluoro-1,4-dihydro-5-methyl-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolone

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carboxylic acid) is a new fluoroquinolone currently undergoing clinical development. This paper describes a clinical trial designed to evaluate the photosensitizing potential of grepafloxacin in healthy subjects. Since ciprofloxacin has previously been shown to have a low phototoxic potential,¹¹ it was used in this study as a comparison against which grepafloxacin phototoxicity could be measured.

Subjects and methods

Subjects

A total of 32 healthy volunteers (28 males, four females) of mean age 33.3 years (range 18–54 years) took part in this study. All were Caucasian, lived in the Tayside area of the UK and had no previous history of allergy to quinolones or clinical photosensitivity and no recent use of concomitant medication. Exclusion criteria were hepatic or renal impairment, a history of seizure disorders, previous participation in other grepafloxacin trials, or use of any other investigational drug or device within 4 months before the study. The study was approved by the Tayside Committee on Medical Ethics, and written informed consent was obtained from all subjects.

Study design

The study was a randomized, double-blind, comparative trial carried out at a single centre. All subjects underwent phototesting within 21 days before treatment in order to establish that their baseline sensitivity to ultraviolet and visible radiation was within the normal range. Phototesting was performed by means of standard monochromator techniques,^{15–17} and baseline sensitivity expressed as the minimal erythral dose (MED, i.e. the minimum amount of irradiation at a waveband capable of producing a faint but definite erythema within the area of irradiation). The subjects were then randomized into four groups (eight subjects in each group) and treated with either grepafloxacin 400 or 600 mg once daily, ciprofloxacin 500 mg bd, or placebo; subjects who received grepafloxacin received the active medication in the evening and a placebo in the morning. Treatment was continued for 7 days and phototesting was repeated towards the end of the treatment period (days 5–7). If an abnormal phototest result (defined as a reduction in MED of >40% from baseline) was obtained, phototesting was repeated between days 14 and 16, and again between days 24 and 26, if necessary. Patients with abnormal results were followed until the MED returned to pre-treatment levels.

Phototesting

Baseline phototesting was performed over 3 days. On the first day, each subject was tested on the mid-upper back skin with a large step series of doses at a range of wavebands

chosen to represent the UVB (280–315 nm), UVA (315–400 nm) and visible (>400 nm) spectra. The doses used are shown in Table I. Skin reactions were assessed visually 1, 2, 5 and 30 min and 1, 4, 24 and, if possible, 48 h after exposure to monitor for abnormal immediate and delayed erythema. Assessment at 24 h provided an approximate measure of the MED; a more precise measurement was then obtained by phototesting with a narrow step series of exposures, based on the preliminary MED, on the second day. Again, skin reactions were assessed up to 24 h after exposure. The skin was also examined for other clinical signs of photosensitivity, such as blistering, photo-onycholysis, milia and increased pigmentation.

Phototesting was repeated during drug treatment, beginning on day 5 or 6. The results of the large step phototest were recorded, and narrow step testing performed on the next day and the 24 h MED from the narrow step test determined on the following day (day 7 or 8). The clinical evaluation of the skin was also repeated to identify any skin reactions occurring during treatment.

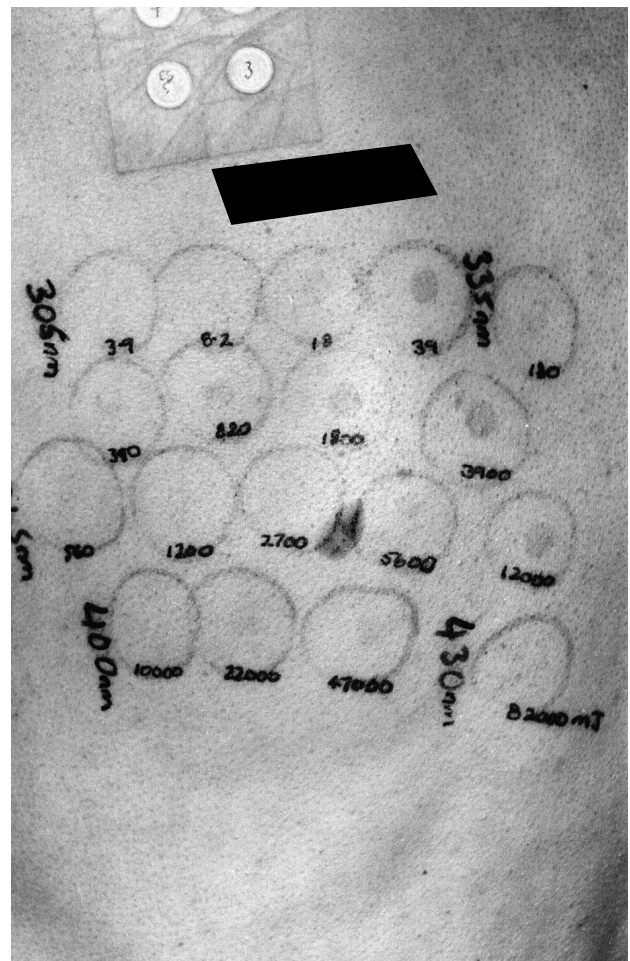


Figure. Ultraviolet and visible wavelength testing showing erythema responses to different doses of selected ultraviolet wavelengths. This represents the first day of testing, when large increments were used. The following day, narrowing down of the minimal erythral dose and no-response dose is achieved.

Phototoxicity of fluoroquinolones

Table I. Monochromator phototest doses (mJ/cm²) used in baseline assessment. The 460 ± 30 nm waveband was available but only used if the 430 ± 30 nm waveband produced an abnormality.

305 ± 5	335 ± 30	Waveband (nm)			
		365 ± 30	400 ± 30	430 ± 30	460 ± 30
4.7	220	1200	10,000	22,000	22,000
10	470	2700	22,000	47,000	47,000
22	1000	5600	47,000	82,000	82,000
47	4700	12,000	82,000		
100	10,000	22,000			

Clinical assessment

Before entry to the study, a full medical history was taken and a physical examination performed. Blood was taken for routine haematology and clinical chemistry, measurement of porphyrins (plasma fluorescence scan), anti-Ro and anti-La tests for lupus erythematosus, and measurement of plasma grepafloxacin concentrations. Blood testing was repeated at the end of treatment (day 8), and the physical examination was repeated between days 14 and 16 if further phototesting was not required; the examination was performed again 7 days later if phototesting was required. Information about adverse events and skin reactions was obtained by direct questioning throughout the study.

Statistical methods

The significance of changes in MED at each waveband within each treatment group was assessed by means of the Wilcoxon signed rank test. Differences in MED between groups were assessed by means of the Wilcoxon rank sum test.

Results

All 32 subjects completed the trial. Before treatment, all subjects showed normal 24 h MEDs at all wavebands, as defined by the Dundee Photobiology Unit normal subject phototest database (Table II). In all subjects who showed a change in MED of >40% during treatment, MED returned to baseline levels within 1 week of stopping treatment. MED values at baseline and during drug treatment are summarized in Table III.

Placebo

Changes in MED in placebo-treated subjects showed wide inter-individual variation. In all but one subject, however, changes were confined to one or two dose steps i.e. ≤40% in either direction. In the remaining subject, reductions in MED of between 61% and 69% occurred at wavelengths of

Table II. Dundee Photobiology Unit normal subject minimal erythemal dose (MED) database

Waveband (nm)	Range for 70% of normal subjects (mJ/cm ²)	Lower limit of normal (mJ/cm ²)
305 ± 5	47–82	27
335 ± 30	3300–6800	1800
365 ± 30	12,000–22,000	8200
400 ± 30	47,000–>47,000	47,000
430 ± 30	>82,000	>82,000
460 ± 30	>82,000	>82,000

305, 335 and 365 nm. In no case did the MEDs fall below the lower limit of the normal range (Table II). The mean changes in MED during placebo treatment were –5.4%, –21.5%, –8.6% and +7.5%, at wavelengths of 305, 335, 365 and 400 nm, respectively. None of these were statistically significant.

Grepafloxacin 400 mg once daily

The MED at 305 nm increased by a mean of 8.3% (range –43% to +110%) in patients treated with grepafloxacin, 400 mg once daily. There was a large amount of inter-subject variation, including one subject who had an increase in MED of +110%. Since this increase represented only three exposure steps during testing, it could have been due to observer error. All changes at this wavelength represented a small number of exposure steps, and none reached statistical significance. Another subject showed a significant decrease of –43%, but this did not reach an abnormal level, and returned to baseline within 1 week after treatment.

All subjects showed a decrease in MED at 335 and 365 nm. The mean reduction at 335 nm was 64.1% (reduction range 44–82%), which was statistically significant ($P = 0.008$) (Table IV). All subjects showed reductions of >40%, and MEDs decreased to below normal baseline levels in three subjects. Smaller reductions were seen at 365 nm (mean reduction 42.6%, range 17–86%), but the

Table III. MED values (mJ/cm²) at baseline and during study period (days 5–7).

	Waveband (nm)							
	305 ± 5 nm		335 ± 30 nm		365 ± 30 nm		400 ± 30 nm	
	baseline	study period	baseline	study period	baseline	study period	baseline	study period
Placebo								
Mean ± s.d.	65.1 ± 24.2	57.0 ± 17.9	5175 ± 4251	3175 ± 1286	16,500 ± 6803	14,100 ± 6201	70,125 ± 17,208	71,625 ± 16,300
Median	62.0	51.5	3900	3300	15,000	13,500	82,000	82,000
Grepafloxacin, 400 mg once daily								
Mean ± s.d.	56.3 ± 22.1	56.6 ± 23.2	7413 ± 6002	2450 ± 1816	21,750 ± 15,818	10,525 ± 6843	61,750 ± 14,109	67,250 ± 21,332
Median	51.5	47.0	5600	2200	15,000	8400	56,000	82,000
Grepafloxacin, 600 mg once daily								
Mean ± s.d.	60.5 ± 25.2	58.6 ± 26.4	8750 ± 8255	2415 ± 2026	23,000 ± 15,325	10,863 ± 9716	77,625 ± 12,374	75,875 ± 12,654
Median	51.5	47.0	5150	1850	16,500	7800	82,000	82,000
Ciprofloxacin 500 mg bd								
Mean ± s.d.	84.3 ± 29.2	83.6 ± 23.8	10,225 ± 3236	4525 ± 1946	29,250 ± 11,671	13,075 ± 5137	82,000	82,000
Median	100.0	82.0	10,000	4700	27,000	12,000	82,000	82,000

Table IV. Summary of statistical analysis of MED (mJ/cm²) at wavebands of 335 ± 30 nm and 365 ± 30 nm

	Waveband (nm)								
	335 ± 30		365 ± 30		365 ± 30				
	grepafloxacin 400 mg od	grepafloxacin 600 mg od	ciprofloxacin 500 mg bd	placebo	grepafloxacin 400 mg od	ciprofloxacin 500 mg bd	grepafloxacin 600 mg od	ciprofloxacin 500 mg bd	placebo
Mean value pre-treatment	7413	8750	10,225	5175	21,750	23,000	29,250	29,250	16,500
Mean value at visit 2	2450	2415	4525	3175	10,525	10,863	13,075	13,075	14,100
Mean % change from pre-treatment to visit 2	-64.1	-63.0	-51.7	-21.5	-42.6	-53.7	-48.5	-48.5	-8.6
P value	0.008	0.016	0.016	0.13	0.008	0.008	0.008	0.008	0.77

changes were still statistically significant ($P = 0.008$). MEDs decreased by $>40\%$ in four subjects.

The change in MED at 400 nm varied markedly, from a decrease of 30% to an increase of 46% (mean change $+8.25\%$). In each case, the change in dose was within two exposure steps. At 430 nm, MEDs before and during treatment were above the maximum dose ($82,000 \text{ mJ/cm}^2$) in all subjects.

Grepafloxacin 600 mg once daily

At 305 nm, MED was unchanged during treatment with grepafloxacin 600 mg once daily, in all but two subjects. These subjects showed a reduction of 15–16% in MED (equivalent to one exposure step). Overall, there was no significant change in MED in this group.

At 335 nm, MED decreased significantly in all but one subject, in whom MED was unchanged. The mean decrease was 63% (range 0–88%, $P = 0.016$). A similar reduction was seen at 365 nm (mean 53.7%, range 30–78%, $P = 0.008$). Decreases of $>40\%$ occurred in six subjects, of whom four had MEDs below the lower limit of normal (Table IV).

At 400 nm, MEDs were unchanged in all except one subject, in whom the MED decreased but remained within the normal range. At 430 nm, all MEDs were above the maximum dose level.

Ciprofloxacin 500 mg bd

At 305 nm, there was marked inter-individual variation in the change in MED in ciprofloxacin-treated subjects. The mean change was $+7.8\%$ (range -44% to $+74\%$), which was not significant. One subject showed a decrease of 44%; no other changes of more than three dose steps were observed.

At 335 nm, there was a mean decrease in MED of 51.7% (range 0–85%, $P = 0.016$); MEDs were reduced in all except one subject, who showed no change. In one subject, MED decreased by 85% to 1500 mJ/cm^2 , but all other values remained within the normal range (Table IV).

The reduction in MED at 365 nm was similar to that at 335 nm (mean 48.5%, range 19–88%, $P = 0.008$) (Table IV). Only one subject showed a reduction in MED to below normal limits. No significant changes in MED at 400 or 430 nm occurred during ciprofloxacin treatment compared with baseline values.

The Wilcoxon rank sum test showed no significant differences between any of the treatment groups in changes in MED during treatment.

Clinical events

No clinical signs of phototoxicity were seen during the study. One subject in the group treated with grepafloxacin 600 mg had mild facial erythema, and one ciprofloxacin-treated subject had mildly increased skin pigmentation, at

the start of the trial. In both cases, these persisted during treatment but did not worsen.

A total of five adverse events were reported by placebo-treated subjects, compared with two each in the ciprofloxacin and grepafloxacin, 400 mg groups and three in the grepafloxacin, 600 mg group. All were mild or moderate in intensity, with the exception of toothache in one subject receiving grepafloxacin 600 mg, and headache in one patient in the placebo group. No clinically significant changes in haematology or clinical chemistry tests were observed, and plasma scans for porphyrins, anti-Ro and anti-La were normal before and after treatment. Mean plasma concentrations of grepafloxacin at the end of treatment were $270.0 \mu\text{g/L}$ and $456.2 \mu\text{g/L}$ in the groups receiving 400 and 600 mg, respectively.

Discussion

The results of this study show that grepafloxacin has a mild photosensitizing effect comparable to that of ciprofloxacin. The degree of ciprofloxacin photosensitivity seen in this study was similar to that previously reported.⁵ Previous studies using the same techniques as were used in this study, indicate that this is an effect shared by other members of the fluoroquinolone group of antibiotics.^{5,7} The effect is greatest 24 h after exposure to UVA radiation, particularly in the wavebands 335 and $365 \pm 30 \text{ nm}$.

As in previous studies with fluoroquinolones,^{5,7} the photosensitizing effect of grepafloxacin is mild and reversible. The mean reduction in MED at the most sensitive wavelength, $335 \pm 30 \text{ nm}$, was 50–70%, which indicates an approximate doubling of sensitivity in most subjects. By contrast, severe photosensitivity would be considered to have occurred when MED is reduced to 5–10% of normal levels. Moreover, few subjects showed MEDs outside the normal range and MEDs consistently returned to normal levels within 1 week of stopping drug treatment.

The findings of this phototest study, along with the normal porphyrin scans and lupus erythematosus serology, point towards phototoxicity as the likely mechanism of grepafloxacin photosensitivity action. Most quinolone photosensitivity cases are believed to be phototoxic in origin. In model systems, this is highly dependent on drug concentrations. In this study, however, the decrease in MED at 335 nm did not appear to be related to dose, as the mean decreases in subjects receiving grepafloxacin 400 and 600 mg were 64.1% and 63%, respectively. At 365 nm, the decrease in MED in subjects receiving the 600 mg dose was greater than that in those receiving the lower dose, but there was no conclusive evidence of dose-dependency. Further studies would be necessary to clarify this issue. The plasma grepafloxacin concentrations did not show a strong correlation with the response to UV light; they did, however, provide a useful check on subject compliance.

In conclusion, the results of this study indicate that

grepafloxacin has a weak photosensitizing effect similar to that seen with ciprofloxacin, which is dependent on UVA wavelengths. Thus, on particularly bright days, sunlight—either direct or transmitted through window glass—could potentially induce a phototoxic reaction similar to sunburn. This photosensitivity is reversible within 1 week of discontinuing treatment. In view of this photosensitivity, it seems prudent to recommend that, as with other quinolones, sunbathing or sunbed use should be avoided while using grepafloxacin. A topical sunscreensing agent protecting against UVA radiation should be used if prolonged exposure to sunlight is unavoidable.

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