Fluoroquinolone phototoxicity: a comparison of moxifloxacin and lomefloxacin in normal volunteers

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Moxifloxacin, a broad-spectrum fluoroquinolone with the methoxy group at position 8 of the quinolone structure that is believed to confer reduced phototoxicity, was investigated in 32 healthy human male volunteers by a randomized double-blind placebo and positive control (lomefloxacin) phototest technique. A comparison of pre- and on-drug photosensitivity levels tested with an irradiation monochromator using relevant sunlight wavelengths, failed to demonstrate phototoxicity after administration of either placebo or moxifloxacin (200 mg or 400 mg/day) for 7 days. As expected, lomefloxacin (400 mg/day) phototoxicity was revealed at the UVA wavebands 335 ± 30 nm and 365 ± 30 nm (maximal at 24 h), with a phototoxic index of 3–4. The susceptibility to this effect rapidly normalized within 48 h of stopping the drug. No special protection from UVA wavelengths is necessary for those taking moxifloxacin.

Introduction

Drug-induced photosensitivity represents an abnormal reaction of the skin to natural or artificial light sources. While a wide range of reactions are known to occur, phototoxicity is the commonest. This reaction will arise in any individual, providing there is enough of the phototoxic drug within the skin followed by an appropriate dosage of irradiation. Other less common idiosyncratic reactions include induction of porphyria, lupus erythematosus and photoallergy.

The quinolone antibiotics are used for the treatment of a wide range of bacterial infections, but are recognized as a group to be associated with drug-induced phototoxicity. This was anticipated since the closely related molecule, nalidixic acid, is known to produce photosensitivity skin reactions in humans. However, rather than the skin fragility and blistering of exposed sites (pseudoporphyria) in the presence of normal porphyrin values that is seen with nalidixic acid, some fluoroquinolones are associated with skin erythema and blistering with subsequent peeling following irradiation with UVA wavelengths (often described as an exaggerated sunburn reaction).

The early fluoroquinolones, i.e. ciprofloxacin, norfloxacin and ofloxacin, have been associated with a low incidence of mild photosensitivity. As a result, it was felt that the group as a whole were mild photosensitizers, capable of severe photosensitivity only when a patient was exposed to high drug dosages and unusually high levels of sunlight.

However, with the development of second-generation agents, the initial impression has given way to the understanding that some members of the group have a much greater phototoxic potential than others. In particular it seems that lomefloxacin, sparfl oxacin and fleroxacin have a greater phototoxic effect when tested in humans. In-vivo studies in healthy volunteers have shown that phototoxicity is a dose-related effect, predominantly associated with the UVA part of the electromagnetic spectrum (315–400 nm). Monochromatic test equipment has shown the effect to be rapidly reversible, with each subject returning to their pre-drug baseline sensitivity within 1 week of stopping the drug.

Moxifloxacin is a new fluoroquinolone antibacterial agent, structurally similar to other recently developed fluoroquinolones. It possesses a methoxy group at position 8 of the quinolone system and this is believed to confer reduced phototoxicity upon the molecule. The aim of the present study was to assess the potential of moxifloxacin to induce phototoxicity when compared with lomefloxacin and placebo.

Materials and methods

Subjects

Thirty-two healthy male volunteers of mean age 27.6 years (range 18–45 years) took part in the study. All were Caucasian and lived in the Tayside region of Scotland.
None had a history of allergy to quinolones or clinical photosensitivity or were using other medication. Standard exclusion criteria included hepatic or renal impairment, history of seizures, previous participation in another moxifloxacin trial or any drug investigation over the previous 3 months. The study was approved by the Tayside Committee on Medical Research Ethics and written informed consent was obtained from all subjects.

Study design

The study was a randomized double-blind placebo- and positive-controlled investigation conducted in a single centre.

All subjects underwent baseline photosensitivity testing to UV and visible radiation, by means of a standard monochromator technique. The end-point used at each wavelength tested was the minimal erythema dose (MED), i.e. the minimum amount of irradiation capable of producing a faint but definite erythema within the area of irradiation. The subjects underwent randomization into one of four treatment groups (eight subjects in each group), to be treated with moxifloxacin 200 mg/day, moxifloxacin 400 mg/day, lomefloxacin 400 mg/day or placebo for 7 days. Medication was blinded by encapsulation and given orally bd. On treatment days 5–7, phototesting was repeated. If an abnormal response (as defined by a reduction in MED of >40% from baseline) was revealed, phototesting was repeated 2 days later to assess if the MED level had returned to that seen at baseline.

Baseline (pre-drug) phototesting was performed over a period of 3 days. The test site was the skin of the mid upper back, avoiding the paravertebral area. On the first day, a large incremental step series of dosages at a range of wavelengths was used (Table I). The wavelengths were chosen to represent shorter wavelength terrestrial sunlight, UVA and the visible region. Responses at the test sites were assessed visually 1, 2, 5, 30 min as well as 1, 4, 24 h and, when possible, 48 h after exposure. Thus the technique was designed to reveal immediate and delayed erythema patterns. Assessment at 24 h allowed identification of the preliminary MED value (Figure 1). The same day, further testing was performed with a narrow step series of exposures based upon the preliminary MED value achieved at the 24 h reading. Thereafter, the assessment programme followed in an identical fashion. The skin was also examined for other clinical signs of photosensitivity such as blistering, photo-onycholysis, milia and increased pigmentation. These reactions were not anticipated as all subjects were residential in a UV-protected environment provided by Drug Development (Scotland) Ltd., Dundee, Scotland.

Phototesting was repeated during treatment beginning on day 5. The results of the preliminary MED were confirmed by testing on day 6. Clinical evaluation of photoexposed sites was also repeated to identify any skin reactions during the study period.

A phototoxic index (PI) can be derived for individuals or median values by simple division of the baseline MED by the on-drug MED at a particular waveband. This indicates the degree of photosensitization with a particular UV or visible source emission spectrum. A calculation can reveal how long an individual would need to be exposed to give rise to erythema. For example, a PI of 3 (Figure 2) indicates that, while taking the drug, an individual will react to one-third of the amount of irradiation needed to elicit a response before taking the agent.

### Table I. Monochromator phototest doses (mJ/cm²) used in baseline assessment

<table>
<thead>
<tr>
<th>Waveband (nm)</th>
<th>305 ± 5</th>
<th>335 ± 30</th>
<th>365 ± 30</th>
<th>400 ± 30</th>
<th>430 ± 30</th>
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<tbody>
<tr>
<td>4.7</td>
<td>220</td>
<td>1200</td>
<td>10,000</td>
<td>22,000</td>
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<td>10</td>
<td>470</td>
<td>2700</td>
<td>22,000</td>
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<tr>
<td>22</td>
<td>1000</td>
<td>5600</td>
<td>47,000</td>
<td>82,000</td>
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</tr>
<tr>
<td>47</td>
<td>4700</td>
<td>12,000</td>
<td>82,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>10,000</td>
<td>22,000</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Figure 1.** Monochromator phototesting responses to the test range of UV and visible wavebands showing abnormal erythema (24 h reading) at 335 ± 30 nm and 365 ± 30 nm in a volunteer taking lomefloxacin.
Quinolone phototoxicity

Clinical assessment
Before study entry, a physical examination was conducted and a full medical history was taken. Blood was taken for routine haematology and clinical chemistry, measurement of plasma porphyrins (fluorescent scan), anti-Ro, anti-La and ANA tests for lupus erythematosus and measurement of moxifloxacin plasma concentrations. These investigations were repeated on days 5, 7, 9 and 21. Physical examination was reassessed after the treatment period. All subjects were given enough sunblock to cover exposed sites until the follow-up visit. They were also instructed to clothe exposed areas where possible and to wear sunglasses when outside.

Statistical procedure
The phototoxicity analysis was performed on percentage change of MED values. Pair-wise comparisons between the groups were made by the Wilcoxon rank sum test.

Results
Thirty of the 32 subjects completed the trial. Two subjects withdrew and were excluded from the efficacy analysis. One left to take up employment and the other withdrew for personal reasons, both after 3 days of treatment.

At baseline, all subjects showed normal 24 h MEDs, as defined by the Dundee Photobiology Unit normal subject phototest database, at all wavebands (Table II).

For the wavelengths 305 ± 5 nm, 400 ± 30 nm and 430 ± 30 nm the overall treatment group comparisons were not statistically significant ($P > 0.05$). For the wavelengths 335 ± 30 nm and 365 ± 30 nm the overall treatment group comparisons were significantly different (Table III). None of the subjects experienced photosensitivity skin reactions or other significant adverse effects. Porphyrin scan and lupus erythematosus studies were negative pre- and post-irradiation in all volunteers.

Placebo
Changes in the placebo-treated subjects comparing baseline with on medication showed a wide inter-individual variation. At no wavelength, however, did the median change exceed 17.6%, i.e. the changes were confined to one or two dosage steps, i.e. $<40\%$, in either direction (Table III). None of the changes seen were of statistical significance.

Moxifloxacin 200 mg/day
At 305 ± 5 nm there was no significant change in MED. Insignificant changes (0–15.4%) were also seen at the other wavelengths tested (Table III). There was no statistical difference, either, comparing baseline or on-drug values with those in the placebo recipients. During phototesting pharmacokinetic studies showed a geometric mean $C_{max}$ of moxifloxacin of 1.3 mg/L and an AUC of 13.86 mg·h/L.
## Table III. Summary of 24 h MED values

<table>
<thead>
<tr>
<th>Treatment:</th>
<th>Waveband (nm)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>305 ± 5</td>
<td>335 ± 30</td>
<td>365 ± 30</td>
<td>400 ± 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>On</td>
<td>Pre</td>
<td>On</td>
<td>Pre</td>
<td>On</td>
</tr>
<tr>
<td>Placebo (n = 8)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Median</td>
<td>56</td>
<td>56</td>
<td>6800</td>
<td>5150</td>
<td>24500</td>
<td>20000</td>
</tr>
<tr>
<td>IQR</td>
<td>56–68</td>
<td>51.5–75</td>
<td>6200–7500</td>
<td>4700–6900</td>
<td>15000–33000</td>
<td>15000–33000</td>
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<tr>
<td>Median % change</td>
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<td>17.6</td>
<td>24500</td>
<td>20000</td>
<td>82000</td>
<td>82000</td>
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<tr>
<td>Moxifloxacin 200 mg (n = 7)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>47</td>
<td>56</td>
<td>3900</td>
<td>4700</td>
<td>18000</td>
<td>15000</td>
</tr>
<tr>
<td>Median % change</td>
<td>+14</td>
<td>+20.5</td>
<td>3300–11000</td>
<td>3000–11000</td>
<td>16500–47000</td>
<td>12000–27000</td>
</tr>
<tr>
<td>Moxifloxacin 400 mg (n = 8)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>73.5</td>
<td>73.5</td>
<td>4750</td>
<td>6450</td>
<td>20000</td>
<td>24000</td>
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<tr>
<td>IQR</td>
<td>36–100</td>
<td>43–110</td>
<td>3300–11000</td>
<td>3000–11000</td>
<td>16500–47000</td>
<td>12000–27000</td>
</tr>
<tr>
<td>Median % change</td>
<td>0</td>
<td>+35</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lomefloxacin (n = 7)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>47</td>
<td>56</td>
<td>4700</td>
<td>1200</td>
<td>22000</td>
<td>6800</td>
</tr>
<tr>
<td>IQR</td>
<td>39–100</td>
<td>27–100</td>
<td>3900–8200</td>
<td>1200–27000</td>
<td>15000–33000</td>
<td>3300–12000</td>
</tr>
<tr>
<td>Median % change</td>
<td>+14</td>
<td>−69.2</td>
<td>+14</td>
<td>−72.5</td>
<td>+14</td>
<td>−72.5</td>
</tr>
</tbody>
</table>

*P < 0.05 (compared with placebo); all other % changes were not significant (Wilcoxon rank sum test). IQR, interquartile range.
Moxifloxacin 400 mg/day

At 305 ± 5 nm the median MED was unchanged during treatment with moxifloxacin 400 mg/day. At the other tested wavelengths, the MED was not significantly reduced although, of note, at 335 ± 30 nm apparent photoprotection was seen (% increase in MED = 35%) \((P < 0.05)\). After 400 mg doses the geometric mean \(C_{\text{max}}\) value was 2.4 mg/L and AUC was 26.73 mg·h/L.

Lomefloxacin 400 mg/day

At 305 ± 5 nm there was no significant difference comparing baseline with on-drug values. At 335 ± 30 nm, however, it was evident that the median MED was significantly reduced (69.2%) and this effect was maximal at 24 h (yet absent at 7 h). Similar results (72.5% reduction) were seen at 365 ± 30 nm. The results at wavelengths 335 ± 30 nm and 365 ± 30 nm (Table IV) were statistically significant compared with those of the placebo.

In all subjects who showed a change in MED of >40% during the treatment phase, their MED value returned to their baseline level within 2 days of stopping treatment.

Discussion

These study results indicate that moxifloxacin has no phototoxic potential at the daily dosages used, producing neither abnormal immediate nor delayed erythema. No difference was seen between placebo and the two moxifloxacin dosages other than demonstration of a minor degree of photoprotection at 365 ± 30 nm with moxifloxacin 400 mg/day \((P < 0.05, \text{Wilcoxon rank sum test})\).

As in previous studies with lomefloxacin, at the wavelengths 335 ± 30 nm and 365 ± 30 nm, the photosensitizing effect is significant and maximal at 24 h. Evidence produced in this study indicates that it is rapidly reversible. The median reduction in MED at the most sensitive waveband (335 ± 30 nm) indicates a near quadrupling of sensitivity as shown by the PI of 3.9 (Figure 2). Previous work conducted in the Photobiology Unit has arbitrarily divided the phototoxic potential of drugs into mild, moderate and severe (PI = 0.4–3 (mild), e.g. ciprofloxacin, amiodarone; PI > 3–6 (moderate), e.g. NSAIDs, lomefloxacin; PI > 6 (severe), e.g. thiazides; BAY 3118).

Previous work with a number of fluoroquinolones has shown a range of phototoxic potential. The in-vitro data which suggest that the possession of a methoxy group at position 8 confers reduced phototoxicity are supported by the moxifloxacin results in this study. When phototoxicity is present, it shows remarkable consistency, appears to be induced by the UVA wavebands, is maximal at 24 h and rapidly clears following cessation of the drug. The fact that the therapeutic effect has a nuclear site of action supports the possibility of cutaneous phototumorigenesis, as has been shown in murine studies using both fleroxacin and lomefloxacin. The fact that these two agents are known to possess significant phototoxicity raises the possibility of a direct relationship between the degree of phototoxicity and phototumorigenic effect. Although, in man, the significance of the mouse studies is unknown, it makes zero phototoxicity an even more desirable characteristic of an agent within this class of compounds.

In conclusion, it has been demonstrated in this double-blind study that moxifloxacin, when taken by healthy Caucasian volunteers at 200 or 400 mg/day for 7 days, has no phototoxic potential. In contrast, lomefloxacin, the positive control, has again shown it has a statistically significant phototoxic potential which requires photoprotection at the time of drug administration and for a short period (48 h) after stopping the drug.

Table IV. Probability values for differences in median percentage change from pre- to on-treatment values

<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>Moxifloxacin 200 mg/day vs placebo</th>
<th>Moxifloxacin 400 mg/day vs placebo</th>
<th>Lomefloxacin vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>335 ± 30</td>
<td>0.11</td>
<td>0.0010*</td>
<td>0.0014</td>
</tr>
<tr>
<td>365 ± 30</td>
<td>0.34</td>
<td>0.87</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

*A statistically significant increase in MED.

References


