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# Photosensitivity to lomefloxacin. A clinical and photobiological study

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**Photosensitivity is an uncommon but characteristic side effect of quinolones, with a variable incidence for the different drugs. Several cases, considered either phototoxic or photoallergic, have been described with lomefloxacin use.**

**During the last 4 years we studied 8 patients (mean age 69.4 years) with eczematous or acute sunburn-like lesions in photo-exposed areas, after taking lomefloxacin for a period of one week to several months. After drug withdrawal and systemic and/or topical corticosteroids, lesions cleared within one week to two months, with dischromia in one patient.**

**Six to eight weeks thereafter, a photobiological study was performed. Minimal erythema dose (MED) for UVA and UVB were normal and photopatch tests with lomefloxacin, ofloxacin, ciproflaxacin and norfloxacin, tested at 1%, 5% and 10% in petrolatum and irradiated with 5 and 10 J/cm$^2$ UVA were negative in 7 patients and 20 controls. Patient 1 had a positive photopatch test with lomefloxacin. One patient, who inadvertently reintroduced the drug before photopatch testing, developed a sharply limited erythematous reaction at 48 h in all irradiated areas, without aggravation at the sites of the quinolones patches.**

**Our patients illustrate the polymorphism of clinical photosensitivity to lomefloxacin and represent the largest series in which photobiological studies have been performed. As in previous reports there are arguments favouring photoallergy, but phototoxicity appears to be the main mechanism of photosensitivity to quinolones, particularly in older patients with concomitant diseases and long-term use of the drug.**

*Key words:* **drug reaction; photosensitivity; phototoxicity; quinolones; lomefloxacin.**

Cutaneous photosensitivity is an uncommon but characteristic side effect of quinolones, considered to be caused by either a phototoxic or photoallergic mechanism. Nalidixic acid, the standard drug of the group, is known as a photosensitiser and has been registered since 1964 in the European drug-surveillance systems as one of the major causes of systemic drug photosensitivity (1, 2). Cutaneous lesions, mainly of the pseudoporphyria type (3, 4), have been attributed to a phototoxic reaction in which free radicals and singlet oxygen seem to be involved (5–7).

Several cases of photosensitivity have also been described with most of the chemically related fluorquinolones, such as enoxacin (8, 9), pefloxacin (10), ofloxacin (10), ciprofloxacin (11), norfloxacin (12), sparfloxacin (13, 14) and, also, lomefloxacin (15–17), with varied clinical aspects: erythema, eczematous or bullous lesions, pseudoporphyria, onycholysis and subcorneal pustules. In some of these cases there are arguments that support photoallergy: the eczematous appearance of the lesions and their histological features (16); the long interval between starting treatment and the beginning of the reaction (8, 9, 15, 16); positive photopatch tests with low drug concentration and low-dose irradiation, and cross-reactions between some quinolones (16). However, in other cases there are strong arguments pointing towards phototoxicity: short latency period; sudden appearance after intense sun exposure (17); frequent negative photopatch tests (15); high incidence of these reactions (13) and its clinical polymorphism (18).

Several *in vitro* tests such as photohaemolysis (5), photosensitised oxidation of histidine, photosensitised inhibition of DNA synthesis in human lymphocytes (11, 12), active neutral red dye uptake by irradiated cultured human fibroblasts (19) and photo-dependent lipid peroxidation (20) have revealed a high phototoxic potential for all quinolones. This effect occurs mainly in the ultraviolet A (UVA) range, is much higher for nalidixic acid than for the fluorquinolones (5, 11, 12), and depends on the drug dosage (11, 19) and irradiance of UV light (11, 12). Also,

Table 1. Patient and clinical data

| | Sex/Age | Clinical aspect | Latency period | Sun exposure | Associated diseases | Biopsy | Photopatchtest LMX |
|---|---|---|---|---|---|---|---|
| Case 1 | M/68 | Acute eczema | 3 days | – | Vt, Alopecia totalis | No | + |
| Case 2 | F/64 | Sunburn-like | 2 days | ++ | Atopy | No | – |
| Case 3 | M/76 | Subacute eczema | 10 days | ++ | CRF, BPH | Yes | – |
| Case 4 | M/76 | Sunburn-like | Long intermitent treatment | ++ | BPH | Yes | – |
| Case 5 | M/35 | Sunbun-like | 5 days | ++ | | No | – |
| Case 6 | M/75 | Subacute eczema | 3.5 months | + | BPH | Yes | – |
| Case 7 | M/79 | Sunbun-like | 4 days | + | BPH | Yes | – |
| Case 8 | M 82 | Sunbun-like | 2 days | + | Vt, Chronic bronchitis | No | – |

LMX: Lomefloxacin; Vt: Vitiligo; CRF: Chronic renal failure; BPH: Benign prostatic hypertrophy.

after systemic use of ciprofloxacin and norfloxacin in healthy volunteers, there was a minimal erythema dose (MED) decrease, in particular in the 335–365 nm range (11, 12), that affected 50% of the individuals taking ciprofloxacin. In another study enrolling 42 healthy human volunteers the average decrease of the MED at 365 nm, after 5 days of treatment with standard doses of trovafloxacin, ciprofloxacin and lomefloxacin, was respectively 42%, 62% and 76% (21).

The two theoretical models for drug photosensitivity – phototoxicity and photoallergy – were defined by Epstein in 1939 (22). Despite their general usefulness, there is a wide superimposing of these two classic patterns, as regards photosensitivity to systemic drugs. Actually, only photo-active drugs, therefore with phototoxic potential, are able to induce photoallergy. Nevertheless, the distinction between these two patterns seems justified provided that the therapeutic response is different and that photoallergy can cause persistent photosensitivity.

During the last 4 years we studied 8 cases of photosensitivity to lomefloxacin in order to understand better the mechanism responsible for its photosensitivity.

## Clinical cases

We observed 8 patients, 7 males and 1 female, aged between 35 and 82 years (mean 69.4 years), with cutaneous lesions exclusively localised in the photo-exposed areas of the face, V-shaped area of the neck, dorsum of the hands and, in the fourth case, also in the dorsum of the feet (Table 1). These lesions were well limited although with varied clinical aspects: eczematous lesions, with scaly erythema or even exudation (case 1, Fig. 1); acute oedematous sunburn-like lesions that spared the facial folds (cases 2, 4, 5, 7 and 8, Fig. 2); and subacute or chronic eczema with a violaceous hue (cases 3 and 6, Fig. 3), with ectropion and thick hyperkeratotic scaling.

Patients were taking 200–400 mg of lomefloxacin, once a day for periods that varied between one week and several months, for the treatment of respiratory, urinary tract or cutaneous infection (case 1, 2, 5, 7 and 8, respectively) and for infection prophylaxis during urinary catheter replacement (cases 3, 4 and 6). Lesions appeared two days to several months after beginning therapy, specifically following prolonged sun exposure in 4 patients. After drug withdrawal and systemic and/or topical treatment with corticosteroids, lesions cleared within one week to two months. In patient 4 there were persistent residual hypo- and hyperpigmented macules on affected areas and this dischromia remained unchanged for more than six months.

Two patients had vitiligo (cases 1 and 8), the first also with alopecia totalis and a healed leg ulcer with stasis dermatitis; case 3 had chronic renal failure and cases 3, 4, 6 and 7 had benign prostatic hypertrophy (with permanent urinary catheter in patients 3, 4 and 6). General and laboratory examinations were normal except for elevated blood urea nitrogen (58 mg/dl) and creatinine (2.4 mg/dl) in the patient with chronic renal failure.

Histology performed in cases 3, 4, 6 and 7 showed a perivascular lymphomononuclear inflammatory infiltrate, with vasodilatation in the superficial dermis and pigmentary incontinence. In the epidermis there was a variable degree of architectural disturbance, vacuolisation of basal cells and typical sunburn cells with eosinophilyc cytoplasm and picnotic nuclei (Fig. 4). In case 7 there were also intra-epidermal vesicles with exocytotic lymphocytes and red blood cells.

Six to eight weeks after clearing of the cutaneous lesions, patients were submitted to a photobiological study.

The MED for UVB, tested on the back with doses increasing from 20 to 200 mJ/cm$^2$ (Waldmann UV 800), was superior to 120 mJ/cm$^2$ in all patients and none of them reacted to 15 J/cm$^2$ of UVA (Waldmann 7001K). Photopatch tests were performed with a photoallergen series and several pure quinolone antibiotics supplied by the pharmaceutical industry, lomefloxacin, ofloxacin, ciprofloxacin and norfloxacin, tested at 1%, 5% and 10% in petrolatum. Three sets of tests were applied on the back for 48 h. Afterwards one set was shielded from light whereas the other two were irradiated with 5 and 10 J/cm$^2$ of UVA (PUVA cabin Waldmann 7001K). A positive test

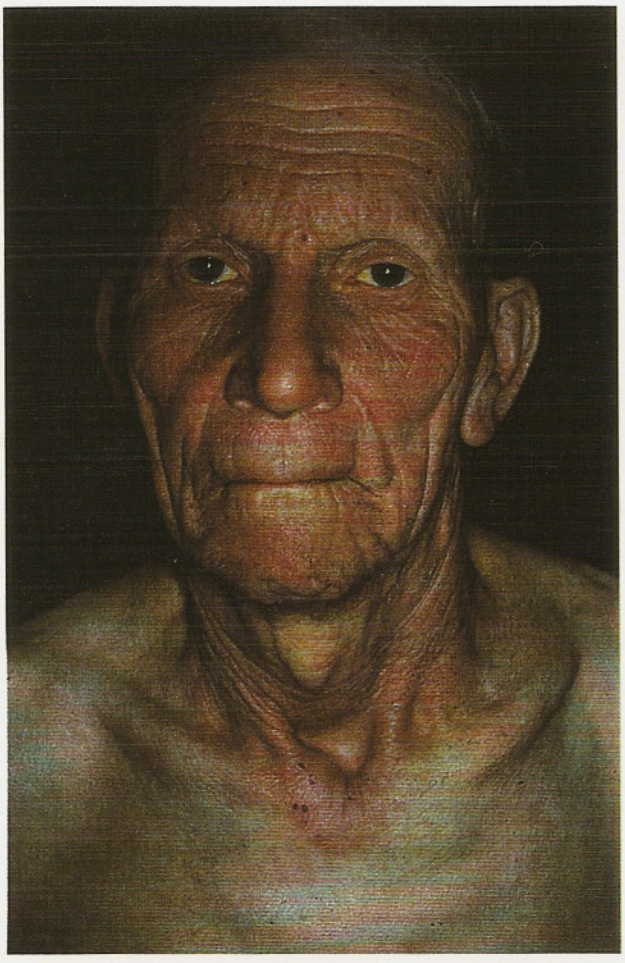

*Fig. 1.* Eczematous scaly erythema (patient 1).

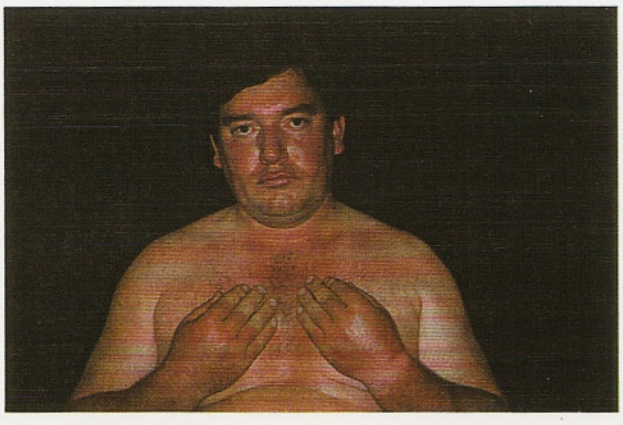

*Fig. 2.* Sunburn aspect, sparing photo-protected areas (patient 5).

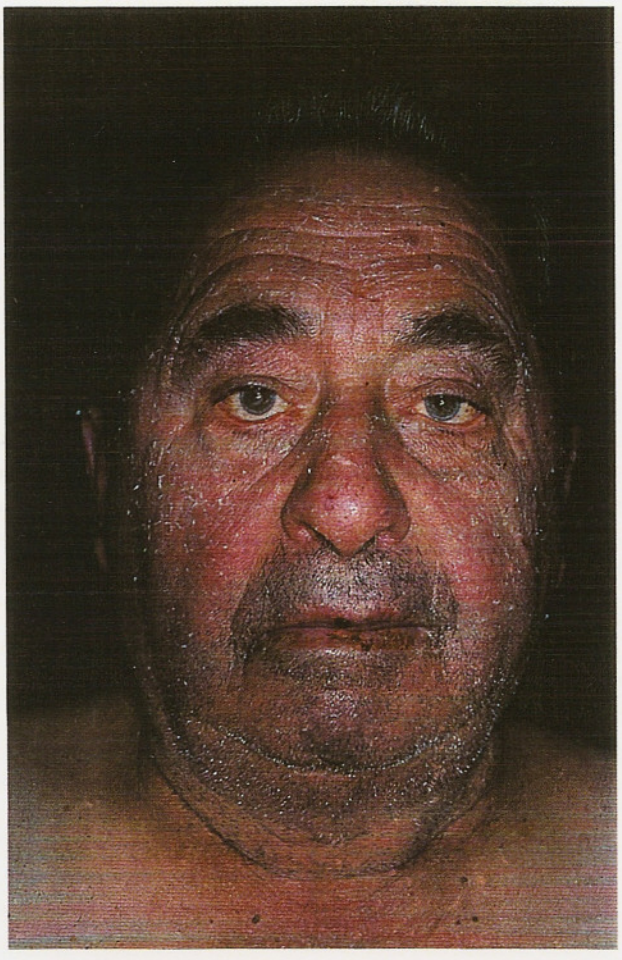

*Fig. 3.* Subacute eczema, with a violaceous hue (patient 3).

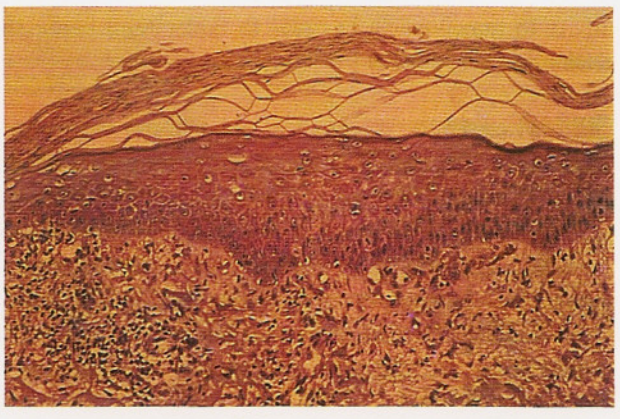

*Fig. 4.* Epidermal architecture disturbance with vacuolisation of basal cells and typical sunburn-like cells.

was obtained only in case 1, with lomefloxacin at 5% and 10% in petrolatum and with the same intensity when irradiated with 5 or 10 J/cm$^2$. No other positive reactions were observed in these patients nor in 20 controls (8 men, 12 women, mean age 37 years) tested with the same protocol. In patient 5, who inadvertently reintroduced the drug before photopatch testing at a dosage of 200 mg/d, all the areas irradiated with 5 and 10 J/cm$^2$ of UVA developed a sharply limited erythematous reaction at 48 h, with the same intensity following the two doses of irradiation and

without aggravation on the sites where the quinolones patches had been placed.

Epicutaneous patch tests with the Portuguese Contact Dermatitis Group standard series and topical and systemic antibiotic series performed in all patients revealed only positive results (++) to lanolin, amerchol L101 and neomycin in patient 1, probably related to previous treatments for his stasis dermatitis, and positive results to thiuran mix (+++) and Peru balsam (++) in patient 8.

## Discussion

Although photosensitivity reactions occurred in 1.7% of the 2869 patients enrolled in controlled clinical trials with lomefloxacin in the USA (17), only 7 cases of photosensitivity were studied and published in a detailed manner, mainly in Japanese patients (15). Our cases represent the largest series of patients in whom photobiological studies have been performed, and as in previous reports we can find arguments favouring photoallergy in some patients (case 1) and others that clearly support phototoxicity in patients 2, 5, 7 and 8.

Although clinical and pathological arguments are individually fallible in distinguishing photoallergy from phototoxicity (6), they are the basis for the pathophysiological discussion, resembling the current debate between irritant and allergic contact dermatitis. We know now that only moderately irritant substances are able to induce the active process of contact sensitisation in allergic contact dermatitis (23), which may also be the case in systemic photosensitivity.

Our patients illustrate the polymorphism of clinical photosensitivity to systemic drugs, which was already apparent in previous cases with quinolones: bullous sunburn in a 25-year-old woman, occurring after an intense sun exposure in the snow (17), or erythematous and oedematous lesions with vesicles and/or bullae appearing a few days after beginning of treatment, mainly in old patients (15, 16). This is certainly dependent on the complex mechanisms of photosensitivity, with acute phototoxic situations resembling acute sunburn reactions, even with bullae, as in the case described by Poh-Fitzpatrick (17) and in our patients 2, 5, 7 and 8; more eczematous lesions in cases where photallergy is suspected as in cases reported by Kurumaji and Shono (15) and Correia et al. (16) and in our case 1. It seems also that the duration of quinolone treatment affects the clinical aspect because the patients with chronic drug use had infiltrated violaceous lesions with hyperkeratotic scaling, lesions that in one of our patients healed with persistent dischromia.

Pathology performed in 4 of our patients clearly supports a phototoxic reaction with sunburn-like keratinocytes. In the case reported by Correia et al. (16), however, histopathology and the study of the inflammatory cells of the liquid of the bullae (revealing a high percentage of T-helper lymphocytes) favours an immunologic reaction, with positive photopatch tests, with a cross-reaction with ciprofloxacin supporting photoallergy (16). Kurumaji and Shono had to perform a prior scarification in order to obtain positive reactions to this high molecular weight drug (15), which was not necessary in our case 1. Negativity of all but one of the photopatch tests and the clinical aspect of the systemic photoprovocation test suggest a phototoxic mechanism.

As it is not possible to distinguish between photoallergy and phototoxicicty on clinical grounds, lomefloxacin has been the object of *in vivo* and *in vitro* studies in order to clarify its photosensitivity mechanism. In two Japanese studies using Balb/c mice, lomefloxacin proved to be the most phototoxic of the fluorquinolones, even superior to nalidixic acid in the first study (24, 25). Using guinea pigs, Horio et al. also demonstrated the phototoxicity of all quinolones tested, after a single oral administration of the drugs (26). Interestingly, they were able, for the first time, to induce experimentally a photoallergic reaction to the quinolones lomefloxacin and nalidixic acid.

Lomefloxacin is highly photoactive, being easily photodegraded by UVA radiation, which might be partially related to the presence of the fluorine atom at position 8 of the quinoline ring. Substitution of this fluorine or a hydrogen atom at this position by a metoxy group provides photostability to quinolones and completely inhibits their *in vitro* phototoxic activity (25). After photolysis of lomefloxacin (and fleroxacin) with loss of its fluorine atom as a fluoride, a highly reactive carbene at C-8 is generated (27), which could explain the greater photomutagenic and photocarcinogenic properties of these quinolones, and eventually also their greater phototoxicity compared to others in which C-8 does not bear a fluorine atom.

So far and in contrast to its high *in vivo* and *in vitro* phototoxic potential, clinical photosensitivity to lomefloxacin has not been frequently reported, probably because, as with other phototoxic drugs, it is necessary to have the simultaneous occurrence of high tissue drug levels and sun exposure, together with the failure of the defence and repair mechanisms against phototoxic aggression (6). This conjuncture might have occurred in our patients with renal failure and benign prostatic hypertrophy or in the one with vitiligo and alopecia universalis. In accordance with our results, Arata et al., who investigated photosensitivity to lomefloxacin in terms of patient background and treatment factors (28), also found correlations with age (60 years and older, as in our patients 1–4 and 6–8), concomitant diseases (as patients 1, 3, 4 and 6–8), total amount of the drug (20 g and more, as patients 4 and 6)) and duration of treatment (30 days or longer, as patients 4 and 6).

In its regular therapeutic use, the association of these factors should be avoided, by forbidding direct or indirect UV exposure during treatment and a few days thereafter. Alternatively, adverse reactions can be minimised by taking the drug at the end of the day. Although this last recommendation was not sufficient in our patient 5, who took it regularly at 11 p.m., in a prospective study it was observed that whereas an evening dose of lomefloxacin induced no modification of the MED for UVA (tested at day time), a statistically significant reduction was observed when the drug was taken in the morning (29).

Due to its wide antibacterial spectrum and low incidence of side effects, second generation fluorquinolones are increasing their share of the antibiotics market. Lomefloxacin, which was introduced in Portugal in 1991, has shown a gradual increase of its sales and represented 7.9% of the quinolones market in 1998. Taking into account its phototoxic potential, it is predictable that without the necessary precautions it may join the group of the major photosensitiser drugs in sunny countries like Portugal.

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