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Structure–phototoxicity relationship in Balb/c mice treated with fluoroquinolone derivatives, followed by ultraviolet-A irradiation

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Abstract

We examined the structure–phototoxicity relationship for fluoroquinolone antimicrobial agents (quinolones) using female albino Balb/c mice. First of all, to obtain an optimum dosage level for induction of phototoxicity, the prototype phototoxicant sparfloxacin was intravenously administered once at 10 mg/kg, 30 mg/kg or 100 mg/kg to female mice, followed immediately by ultraviolet-A (UVA) irradiation for 4 h (21.6 J/cm^2). The auricular thickness was measured at pre-dose (0 h), 4, 24, 48, 72 and 96 h post-dose, and then the histopathological examination of the auricle was performed. As results, the auricular thickness increased from 30 mg/kg, in conjunction with edema, cellular infiltration, epidermal necrosis and focal loss of the auricle. On the basis of these information, ciprofloxacin, enoxacin, fleroxacin, gatifloxacin, lomefloxacin, norfloxacin and ofloxacin were given intravenously to mice at a fixed dose of 100 mg/kg to compare their potential phototoxicities. Certain quinolones caused the auricular lesions in the following rank order (from lowest to highest): vehicle control (non-phototoxicity) = gatifloxacin = ofloxacin < ciprofloxacin = norfloxacin < enoxacin = fleroxacin < lomefloxacin = sparfloxacin.
From the viewpoint of the structure–phototoxicity relationship, quinolones possessing the C-8 substituent with a fluorine or hydrogen and 1,8-naphthyridine derivative evoked phototoxicity in the mouse auricle. These results demonstrate that phototoxicity induced by quinolones would be related to the property of the eighth position.

Keywords: Fluoroquinolone antimicrobials; Phototoxicity; Mouse; Ultraviolet-A

1. Introduction

Fluoroquinolone antimicrobial agents (quinolones) have been widely used in clinical fields because of their broad spectra and bactericidal activity. Some of the quinolones placed on the market, however, have been reported to evoke photosensitivity in humans

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(Ferguson, 2003). Clinical manifestations include erythema in sun-exposed areas and extensively severe bullous eruptions (Lipsky and Baker, 1999). These adverse reactions have been considered phototoxic rather than photoallergic (Ferguson, 2003; Lipsky and Baker, 1999). The incidence of phototoxicity has been recognized to be approximately 10% of patients receiving fleroxacin, lomefloxacin and sparfloxacin (Ferguson, 2003). In contrast, the incidence of phototoxicity of ciprofloxacin, enoxacin, norfloxacin and ofloxacin has been reported to be less than 2.4% (Ferguson, 1995; Ferguson and Dawe, 1997).

In experimental studies, Wagai et al. (1989) and Wagai and Tawara (1991b) have developed a method to detect phototoxicity using female albino Balb/b mice. This procedure has been used as a useful tool for predicting the phototoxic potential of quinolone derivatives because the in vivo system incorporates all the physiological aspects (Domagala, 1994). Nevertheless, there is little information dealing with the structure–phototoxicity relationship for quinolones in the in vivo systems under the same experimental conditions. In the present study, ciprofloxacin, enoxacin, fleroxacin, gatifloxacin, lomefloxacin, norfloxacin, ofloxacin and sparfloxacin were given intravenously to Balb/c mice, followed immediately by ultraviolet-A (UVA) irradiation to assess the possible structure–phototoxicity relationship.

2. Materials and methods

2.1. Drugs

Eight quinolones (ciprofloxacin, enoxacin, fleroxacin, gatifloxacin, lomefloxacin, norfloxacin, ofloxacin and sparfloxacin) used for the present study were synthesized at Daiichi Pharmaceutical Co. Ltd. (Tokyo, Japan). These drugs were dissolved in 0.1N NaOH solution to obtain a constant administration volume of 10 ml/kg.

2.2. Animals

Five-week-old female albino Balb/c mice (17–22 g) were purchased from Japan Charles River (Kanagawa, Japan). They were housed four to six animals per plastic cage in an air-conditioned room (temperature, $23 \pm 2\,^{\circ}C$; relative humidity, $55 \pm 20\%$; lighting cycle, 12 h) with free access to commercial laboratory chow (F-2, Funabashi Farm, Chiba, Japan) and tap water. After a 3-day acclimation, the animals were used for examinations. They were treated humanely, and the study protocol was in accordance with the institutional guidelines of Daiichi Pharmaceutical Co. Ltd. for use of laboratory animals.

2.3. Optimum dosage level of sparfloxacin for induction of phototoxicity

Sparfloxacin as a prototype phototoxicant was intravenously administrated once at 10 mg/kg, 30 mg/kg or 100 mg/kg to groups of six mice each. Additional mice ($n = 4$) given 0.1N NaOH solution in the same way served as the vehicle control. The number of animals per group used in this experiment was selected on the basis of previous published data in our laboratory (Wagai et al., 1989; Wagai and Tawara, 1991a,b, 1992), and the intravenous administration was chosen as a dosing route capable of providing quinolone exposure at an identical level without bias due to a difference in the gastrointestinal absorption. The reproducibility of this test system has been confirmed in numerous experiments so far (Takayama et al., 1995; Wagai et al., 1989; Wagai and Tawara, 1991a,b, 1992). Immediately after administration, the animals were placed individually in partitioned chambers (4 cm × 8 cm × 4 cm) covered with a 3 mm pane of glass (Floatglass, Asahi Glass, Tokyo, Japan) to eliminate wavelength below 320 mm and irradiated with UVA at 1.5 mW/cm^2 for 4 h (21.6 J/cm^2) as described previously (Wagai et al., 1989). The light source was a bank of 10 black light tubes (FL20SB, diameter: 32.5 mm, length: 58 cm, Toshiba, Tokyo, Japan) emitting radiation within 300–400 nm (a peak: 352 nm). The irradiation condition was nearly equivalent to sunbathing for 4–5 h in the summer in Tokyo (latitude 35°40′). The intensity of UVA was measured at 365 nm with a UVX digital radiometer fitted with a UVX-36 sensor (UVP Inc., CA, USA). The auricular thickness was measured with a digital thickness micrometer gauge (IDC 543, Mitsutoyo, Tokyo, Japan) at pre-dose (0 h), and 4, 24, 48, 72 and 96 h post-dose. At termination (96 h), all animals were euthanized under the ether anesthesia. The auricular specimens were excised, fixed in 10% buffered formalin, embedded in paraffin wax, sectioned at 4 μm thickness,