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Comparative assessment of ocular tissue distribution of drug-related radioactivity after chronic oral administration of ^{14}C-levofloxacin and ^{14}C-chloroquine in pigmented rats

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Abstract

Fluoroquinolones have been reported to have a high affinity for melanin. The ocular tissue distribution and accumulation of radioactivity was compared after repeated oral administration of ^{14}C-levofloxacin and ^{14}C-chloroquine at daily doses of 20 mg (0.054 mmol) kg^{-1} and 28 mg (0.054 mmol) kg^{-1}, respectively, in pigmented rats for 84 days. The mean serum level at 24 h following each dose of ^{14}C-levofloxacin was almost constant in the range of 0.33–0.45 nmol equiv mL^{-1} after the 14th dose and thereafter. The melanin-containing ocular tissues, such as iris ciliary body and stratum pigment chorioides sclera, showed a much higher concentration of radioactivity than other non-pigmented ocular tissues. The respective concentration in iris ciliary body and stratum pigment chorioides sclera after the 1st dose was 126.47 and 74.91 nmol equiv g^{-1}, and gradually increased with increasing dose number, reaching 1261.81 and 447.45 nmol equiv g^{-1} after the 84th dose, which was ca. 10 and 6 times higher, respectively, than after the 1st dose. The mean serum level following each dose of ^{14}C-chloroquine was almost constant in the range 0.51–0.87 nmol equiv mL^{-1} after the 7th dose and thereafter. The respective concentration in iris ciliary body and stratum pigment chorioides sclera after the 1st dose was 572.10 and 709.41 nmol equiv g^{-1}, and gradually increased with increasing dose number, reaching 33 317.92 and 12 322.90 nmol equiv g^{-1} after the 84th dose, which was ca. 58 and 17 times higher, respectively, than after the 1st dose. The concentration in aqueous humour, cornea, lens, vitreous body and retina after the 84th dose was 1.84, 6.33, 0.48, 5.60 and 11.42 nmol equiv g^{-1} for ^{14}C-levofloxacin and 18.84, 264.99, 27.26, 158.43 and 1020.89 nmol equiv g^{-1} for ^{14}C-chloroquine (ca. 10, 42, 57, 28 and 89 times higher, respectively, than for ^{14}C-levofloxacin). Especially, the concentration in the retina was markedly higher after ^{14}C-chloroquine administration than after ^{14}C-levofloxacin administration. The concentration and the extent of accumulation of radioactivity not only in melanin-containing ocular tissues but also in other non-pigmented ocular tissues, such as retina, after chronic oral administration of ^{14}C-levofloxacin once daily for 84 days were much lower than those after multiple dosing with ^{14}C-chloroquine under the same conditions. These results indicate that levofloxacin would have a much lower risk for ocular toxicity than chloroquine after chronic dosing.

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Introduction

Fluoroquinolones represent a major class of antibacterials with great therapeutic potential. Modification of first-generation quinolones, such as nalidixic acid, has led to a considerable increase in their intrinsic antibacterial activity. The pharmacokinetic properties of these new fluoroquinolones are characterized by excellent oral bioavailability, extensive tissue penetration, low protein binding and long elimination half-life. Levofloxacin is a fluoroquinolone antibiotic, which is the active *S*-(−)-isomer of ofloxacin, and has a broad range of activity against Gram-positive and -negative organisms and anaerobes (Hurst et al 2002).

Chloroquine is an antimalarial agent that is also used in the management of systemic lupus erythematosus and rheumatoid arthritis. Chloroquine is associated with benign corneal deposits and pigmentary retinopathy, which can lead to decreased visual acuity,

decreased visual field and colour-vision defects, as well as electroretinogram and electro-oculogram abnormalities (Jones 1999). Chloroquine has been shown to have distinct affinity for melanin-containing ocular tissues in pigmented animals (Lindquist & Ullberg 1972; Kasuya et al 1976). Tissues such as iris, skin, hair, inner ear and substantia nigra contain melanin. The observation that long-term, high-dose chloroquine therapy produced chorioretinopathy (Hobbs et al 1959) led to the awareness of an association between the toxic effects of some drugs and their high affinity for melanin. Since these early observations, melanin binding of drugs has been implicated not only in ocular toxicity, but also in ototoxicity and pigment disturbances of skin and hair (Ings 1984; Larsson 1993; Salazar-Bookaman et al 1994). The drug's accumulation in these pigmented tissues is of considerable interest from both a pharmacological and a toxicological point of view.

It has been reported that fluoroquinolones such as ofloxacin, levofloxacin, lomefloxacin and moxifloxacin showed high affinity to melanin and pigmented tissues (Fukuda & Sasaki 1989, 1990; Kurata et al 1991; Siefert et al 1999; Fukuda et al 2000; Perez et al 2002).

We have previously reported the in-vitro binding characteristics of fluoroquinolones to synthetic melanin (Ono & Tanaka 2003) and the in-vivo binding of drug-related radioactivity to melanin-containing ocular tissues in pigmented rats after single oral administration of ^{14}C-levofloxacin and ^{14}C-chloroquine (Ono et al 2003; Tanaka et al 2004). During the course of these studies, we found that levofloxacin had a much lower affinity and capacity to synthetic melanin and melanin-containing tissues than chloroquine after single doses. However, to our best knowledge, there is no report on the ocular tissue distribution of levofloxacin and chloroquine after chronic administration of ^{14}C-labelled drugs in pigmented rats.

In this study, the ocular tissue distribution and accumulation was compared in pigmented rats after repeated oral administration of ^{14}C-levofloxacin and ^{14}C-chloroquine at daily doses of 20 mg (0.054 mmol) kg^{-1} and 28 mg (0.054 mmol) kg^{-1}, respectively, for 84 days.

Materials and Methods

Test materials

^{14}C-Levofloxacin hemihydrate with specific activity of 2.12 MBq mg^{-1} was radiosynthesized at Daiichi Pure Chemicals Co. Ltd (Ibaraki, Japan). A radiochemical purity of more than 98% was established by thin-layer chromatography. Non-radiolabelled levofloxacin hemihydrate was synthesized by Daiichi Pharmaceutical Co. Ltd (Tokyo, Japan). [Quinoline-3-^{14}C]chloroquine diphosphate with specific activity of 3.72 MBq mg^{-1} was radiosynthesized at Amersham Biosciences Corp. (NJ). A radiochemical purity of more than 97% was established by thin-layer chromatography. Non-radiolabelled chloroquine diphosphate was purchased from Sigma-Aldrich Fine Chemicals (MO). Other reagents were of analytical grade and used without further purification.

Animals

Pigmented male BN/Crj rats, 138–173 g, aged 7 weeks ($n = 3$ per time point) were purchased from Charles River Japan, Inc., Kanagawa, Japan).

The rats were acclimatized to the laboratory conditions for more than 1 week before the study at a temperature of 23 ± 2°C and 55 ± 15% humidity. Rats were housed in stainless-steel cages. A solid laboratory diet (MF; Funabashi Farm Co. Ltd, Chiba, Japan) and tap water were available to all rats throughout the course of the study. All experimental procedures were performed in accordance with the guidelines of the Institutional Animal Care and Use Committee of Daiichi Pure Chemicals Co. Ltd (Ibaraki Japan).

Dose formulation and administration

^{14}C-labelled and non-labelled levofloxacin hemihydrate was dissolved in water for injection (JP standard; Otsuka Pharmaceutical Factory, Tokushima, Japan), to achieve 10 mg mL^{-1}. ^{14}C-labelled and non-labelled chloroquine diphosphate was dissolved in water for injection to achieve 14 mg mL^{-1}. The dosing volume administered was 2 mL kg^{-1}. The dose of radioactivity was 0.70 MBq kg^{-1} daily. The dosing solution was given to rats via oral gavage.

Specimen collection

For collection of blood, serum and ocular tissue samples, 7 groups of 3 male pigmented rats received repeated oral doses of ^{14}C-levofloxacin hemihydrate (20 mg or 0.054 mmol kg^{-1} daily) or ^{14}C-chloroquine diphosphate (28 mg or 0.054 mmol kg^{-1} daily) to investigate differences in distribution and accumulation of drug-related radioactivity in the tissues after chronic dosing. The rats were killed by ether inhalation at 24 h after the 1st, 3rd, 7th, 14th, 28th, 56th and 84th dose and exsanguinated following incision of an abdominal aorta. Serum was obtained by centrifugation of blood samples. The eyes were removed, weighed immediately, then dissected and aqueous humour, cornea, lens, vitreous body, iris ciliary body, retina and stratum pigment chorioides sclera were separated. Aqueous humour, cornea, lens, vitreous body and retina samples from three rats per group were pooled for analysis of radioactivity.

Radioactivity analysis

The measurement of radioactivity concentration in the blood, serum and tissues was conducted by the combustion method. The samples were combusted using an auto combustor ACS-113 (Aloka Co. Ltd, Tokyo, Japan) and the radioactivity absorbed to Oxisorp-CO_2 (6 mL; Du Pont NEN Research Products, MA) was mixed with Oxiprep-2 (12 mL; Du Pont NEN Research Products) and quantified by liquid scintillation counter (LSC-903; Aloka Co. Ltd) using an external standard method.

Data analysis

The concentration of radioactivity was expressed as nmol equivalents (nmol equiv) of levofloxacin hemihydrate or chloroquine diphosphate per mL of fluid or g of tissue. The net d min^{-1} were determined as the d min^{-1} minus the background d min^{-1}. Samples having a net d min^{-1} less than the background value were considered to contain an amount of radioactivity below the limit of quantification (LOQ). Where required, the difference between treatments was analysed using a Mann–Whitney *U*-test ($P < 0.05$ denoted significance).

Results

The concentration of radioactivity in the blood, serum and ocular tissues after repeated oral administration of ^{14}C-levofloxacin hemihydrate and ^{14}C-chloroquine diphosphate to pigmented rats at daily doses of 0.054 mmol kg^{-1} for 84 days is shown in Tables 1 and 2, respectively.

The concentration of radioactivity in serum after the 1st and 3rd dose of ^{14}C-levofloxacin was, respectively, below the LOQ and 0.18 ± 0.04 nmol equiv mL^{-1} and gradually increased with multiple dosing. The mean serum levels following the 14th dose and thereafter were almost constant in the range of 0.33–0.45 nmol equiv mL^{-1}. Eyes were dissected and aqueous humour, cornea, lens, vitreous body, iris ciliary body, retina and stratum pigment chorioides sclera were separated. The concentration in vitreous body and retina after the 1st dosing was 0.87 and 1.83 nmol equiv g^{-1}, respectively, and the levels increased with increasing dose numbers to reach 5.60 and 11.42 nmol equiv g^{-1} after the 84th dose, which was ca. 6 times the concentration after the 1st dose. The concentration in aqueous humour, cornea and lens after the 1st dose was below the LOQ and became measurable after the 14th dose and thereafter to reach 1.84, 6.33 and 0.48 nmol equiv g^{-1}, respectively, after the 84th dose. The melanin-containing ocular tissues, such as iris ciliary body and stratum pigment chorioides sclera, showed markedly higher radioactivity concentrations than other ocular tissues. The respective concentration in iris ciliary body and stratum pigment chorioides sclera after the 1st dose was 126.47 ± 16.97 and 74.91 ± 24.68 nmol equiv g^{-1}, and the level gradually increased with increasing dose number to reach 1261.81 ± 58.73 and 447.45 ± 96.23 nmol equiv g^{-1} after the 84th dose, which was ca. 10 and 6 times the concentration after the 1st dose.

The concentration of radioactivity in the serum after the 1st dose of ^{14}C-chloroquine was 0.16 ± 0.06 nmol equiv mL^{-1} and gradually increased with multiple dosing. The mean serum level following the 7th dose and thereafter was almost constant in the range of 0.51– 0.87 nmol equiv mL^{-1}. The concentration in the cornea, vitreous body and retina after the 1st dose was 11.30, 7.49 and 73.65 nmol equiv g^{-1}, and increased with multiple dosing to reach 264.99, 158.43 and 1020.89 nmol equiv g^{-1}, respectively, after the 84th dose, which was ca. 23, 21 and 14 times the level after the 1st dose, respectively. The concentration in the aqueous humour and lens after the 1st dose was below the LOQ and the level became measurable at 24 after the 3rd dose and thereafter to reach 18.84 and 27.26 nmol equiv g^{-1}, respectively, after the 84th dose, which was ca. 22 and 13 times the level after the 3rd dose, respectively. The concentration in the iris ciliary body and stratum pigment chorioides sclera after the 1st dose was 572.10 ± 97.34 and 709.41 ± 58.91 nmol equiv g^{-1}, and gradually increased with increasing dose number to reach $33\,317.92 \pm 5624.52$ and $12\,322.90 \pm 2164.39$ nmol equiv g^{-1}, respectively, after the 84th dose, which was ca. 58 and 17 times the level after the 1st dose, respectively.

There were marked differences in the concentration of ^{14}C-levofloxacin and ^{14}C-chloroquine and the extent of accumulation of radioactivity, not only in melanin-containing ocular tissue but also other ocular tissue

Table 1 Radioactivity concentration in tissues at 24 h after repeated oral administration of ^{14}C-levofloxacin hemihydrate at daily doses of 20 mg (0.054 mmol) kg^{-1} under non-fasting conditions in pigmented rats for 84 days

Tissue	Radioactivity concn (nmol equiv g^{-1} or nmol equiv mL^{-1})						
	1st dose	3rd dose	7th dose	14th dose	28th dose	56th dose	84th dose
Serum	< LOQ	0.18 ± 0.04	0.21 ± 0.03	0.33 ± 0.06	0.39 ± 0.14	0.45 ± 0.10	0.40 ± 0.08
Blood	< LOQ	0.17 ± 0.03	0.19 ± 0.05	0.24 ± 0.06	0.33 ± 0.08	0.35 ± 0.05	0.26 ± 0.05
Aqueous humour[a]	< LOQ	< LOQ	< LOQ	1.01	0.63	1.26	1.84
Cornea[a]	< LOQ	3.04	< LOQ	2.73	2.94	8.25	6.33
Lens[a]	< LOQ	< LOQ	< LOQ	0.39	0.47	0.59	0.48
Vitreous body[a]	0.87	2.25	2.30	6.10	4.36	5.02	5.60
Iris ciliary body	126.47 ± 16.97	427.70 ± 223.50	374.10 ± 106.88	453.96 ± 50.58	750.75 ± 80.95	780.64 ± 214.99	1261.81 ± 58.73
Retina[a]	1.83	3.65	3.09	2.98	3.60	6.10	11.42
Stratum pigment chorioides sclera	74.91 ± 24.68	154.18 ± 19.61	270.08 ± 79.24	294.13 ± 67.10	339.77 ± 103.73	396.76 ± 54.47	447.45 ± 96.23

LOQ, limit of quantification. Concentration is expressed as mean ± s.d., n = 3. [a]Samples from 3 rats per group were pooled for radioactivity analysis.

Table 2 Radioactivity concentration in tissues at 24 h after repeated oral administration of ^{14}C-chloroquine diphosphate at daily doses of 28 mg (0.054 mmol) kg^{-1} under non-fasting conditions in pigmented rats for 84 days

Tissue	Radioactivity concn (nmol equiv g^{-1} or nmol equiv mL^{-1})						
	1st dose	3rd dose	7th dose	14th dose	28th dose	56th dose	84th dose
Serum	0.16 ± 0.06	0.33 ± 0.07	0.67 ± 0.04	0.51 ± 0.05	0.67 ± 0.08	0.87 ± 0.21	0.78 ± 0.19
Blood	0.62 ± 0.02	1.04 ± 0.07	1.63 ± 0.12	1.32 ± 0.08	1.78 ± 0.15	2.33 ± 0.28	2.03 ± 0.38
Aqueous humour[a]	< LOQ	1.45	3.52	3.18	3.89	10.34	18.84
Cornea[a]	11.30	42.03	45.86	51.96	96.28	149.13	264.99
Lens[a]	< LOQ	1.23	2.09	3.60	6.64	10.63	27.26
Vitreous body[a]	7.49	20.64	20.95	29.44	78.16	97.42	158.43
Iris ciliary body	572.10 ± 97.34	2643.38 ± 1169.13	3722.33 ± 208.47	7386.11 ± 523.05	12 698.05 ± 5291.98	12 482.25 ± 5006.33	33 317.92 ± 5624.52
Retina[a]	73.65	160.13	184.48	169.23	255.94	296.99	1020.89
Stratum pigment chorioides sclera	709.41 ± 58.91	1998.80 ± 139.43	3169.48 ± 307.41	9716.48 ± 1394.09	6488.34 ± 1852.81	6698.39 ± 2558.75	12 322.90 ± 2164.39

LOQ, limit of quantification. Concentration is expressed as mean ± s.d., n = 3. [a]Samples from 3 rats per group were pooled for radioactivity analysis.

containing no melanin, after chronic administration. The concentration in iris ciliary body and stratum pigment chorioides sclera after the 84th dose of ^{14}C-chloroquine was ca. 26 and 28 times higher, respectively, than after ^{14}C-levofloxacin dosing. The level in aqueous humour, cornea, lens, vitreous body and retina after the 84th dose of ^{14}C-chloroquine was ca.10, 42, 57, 28 and 89 times higher, respectively, than after ^{14}C-levofloxacin administration.

Discussion

Melanin in animals and man is synthesized entirely within melanocytes as melanosomes, which are found in both external and internal tissues (eye, skin, ear, brain and hair) (Ings 1984). The remarkable affinity and capacity of melanin to bind various chemicals, including drugs, are proposed as one of the strongest retention mechanisms of the body. Melanins are polyanions with a relatively high content of negatively charged carboxyl groups and *o*-semiquinones (Ings 1984; Salazar-Bookaman et al 1994). Electrostatic forces have been reported to play an important role in the binding of drugs to melanin; however, non-electrostatic contributions, including hydrophobic and van der Waals' interactions and charge transfer reactions would also contribute to the binding for such drugs as chlorpromazine and chloroquine (Larsson & Tjälve 1979; Tjälve et al 1981; Stepien & Wilczok 1982). Covalent binding has been suggested as the means for the strong and partly irreversible binding of chlorpromazine and chloroquine to melanin (Ings 1984; Larsson & Tjälve 1979).

It has been reported that fluoroquinolones, such as ofloxacin, levofloxacin, lomefloxacin, grepafloxacin and moxifloxacin, show a high affinity for melanin and pigmented tissues (Fukuda & Sasaki 1989, 1990; Kurata et al 1991; Siefert et al 1999; Fukuda et al 2000; Perez et al 2002). We have previously reported on the binding characteristics of fluoroquinolones, including levofloxacin, to synthetic melanin in-vitro (Ono et al 2003). During the course of this study, we found that electrostatic force mainly participated in the formation of the chloroquine–melanin complex, whereas van der Waals' and hydrophobic interactions were involved in the levofloxacin–melanin complex in addition to electrostatic force. We have also previously reported on the in-vivo binding characteristics of ^{14}C-chloroquine and ^{14}C-levofloxacin to melanin-containing tissues, such as uveal tract, in pigmented rats after single oral dosing (Ono et al 2003; Tanaka et al 2004). It was found that the binding mechanisms of chloroquine and levofloxacin to melanin in-vitro and in-vivo were similar and that ^{14}C-chloroquine showed a much higher concentration of radioactivity in melanin-containing ocular tissues than ^{14}C-levofloxacin. The concentration of ^{14}C-chloroquine and ^{14}C-levofloxacin-related radioactivity in uveal tracts declined very slowly with the terminal half lives being 187 days and 19.5 days, respectively. The turnover of ocular melanin is very low (Ings 1984). Therefore, it is highly possible that chloroquine and levofloxacin accumulate in melanin-containing ocular tissues after multiple dosing. However, no report has been published on ocular tissue distribution and accumulation of drug-related radioactivity after chronic administration of ^{14}C-levofloxacin and ^{14}C-chloroquine in pigmented rats.

In this study, the concentration of radioactivity in ocular tissues was measured after repeated oral administration of ^{14}C-levofloxacin and ^{14}C-chloroquine (0.054 mmol kg^{-1} daily) to pigmented rats for 84 days to investigate the differences in distribution and accumulation of drug-related radioactivity in the tissues after chronic dosing. The concentration of radioactivity in melanin-containing ocular tissues, such as the iris ciliary body and stratum pigment chorioides sclera, was much higher than in other non-pigmented ocular tissues (Tables 1 and 2). This difference in the distribution pattern was interpreted as reflecting the high affinity of levofloxacin and chloroquine to melanin. However, the concentration of radioactivity and the half-life in melanin-containing ocular tissues after single oral administration of ^{14}C-levofloxacin was found to be much lower and shorter, respectively, than ^{14}C-chloroquine. The half-life of uveal tract radioactivity after ^{14}C-levofloxacin was 19.5 days, which was approximately one-tenth of that after ^{14}C-chloroquine (187 days) (Ono et al 2003; Tanaka et al 2004). The mean C_{max} in uveal tract for ^{14}C-levofloxacin was 26.33 μg equiv g^{-1}, which was ca. one-sixth that of ^{14}C-chloroquine (158.42 μg equiv g^{-1}). The concentration in melanin-containing ocular tissues increased with multiple dosing and did not reach plateau even after the 84th oral dose, especially in the case of chloroquine (Figure 1). The concentration and extent of accumulation of radioactivity in melanin-containing ocular tissues after chronic dosing with ^{14}C-chloroquine was markedly higher than those after ^{14}C-levofloxacin dosing. At 24 h after the 84th dose, ^{14}C-chloroquine showed ca. 26 and 28 times higher concentrations in iris ciliary body and stratum pigment chorioides sclera, respectively, compared with ^{14}C-levofloxacin. These results reflect the differences in the uveal tract

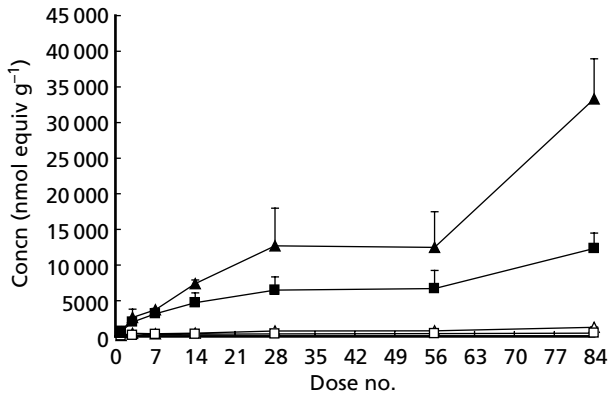

Figure 1 Mean concentration of radioactivity in melanin-containing ocular tissues (iris ciliary body (triangle) and stratum pigment chorioides sclera (square)) at 24 h after repeated oral administration of ^{14}C-levofloxacin (open symbols) or ^{14}C-chloroquine (solid symbols) at daily doses of 20 mg (0.054 mmol) kg^{-1} and 28 mg (0.054 mmol) kg^{-1}, respectively, under non-fasting conditions in pigmented rats for 84 days. Each value represents mean + s.d. for three rats.

concentrations and the half-lives of drug-related radioactivity after single oral administration of these two dugs (Ono et al 2003; Tanaka et al 2004).

The concentration of drug-related radioactivity in non-pigmented ocular tissue, such as aqueous humour, cornea, lens, vitreous body and retina, was much lower than that in melanin-containing ocular tissue. However, there were also differences in the concentration and the extent of accumulation of radioactivity in these non-pigmented ocular tissues between ^{14}C-levofloxacin and ^{14}C-chloroquine. The extent of accumulation of radioactivity in these ocular tissues was much lower for ^{14}C-levofloxacin than for ^{14}C-chloroquine (Figure 2). The concentration in aqueous humour, cornea, lens, vitreous body and retina after the 84th dose of ^{14}C-chloroquine was ca. 10, 42, 57, 28, and 89 times higher, respectively, than after ^{14}C-levofloxacin. Especially, the concentration in the retina was markedly higher after dosing with ^{14}C-chloroquine than after ^{14}C-levofloxacin.

It has been reported that prolonged high dosage (0.25 g or more daily for several years) is usually necessary before ocular toxicity of chloroquine develops (Böke et al 1967). The low dosage associated with antimalarial treatment does not normally produce noticeable ocular changes (Goldman & Preston 1957; Hobbs et al 1959). Initially, the chloroquine-induced retinopathy was believed to be related to high and sustained drug concentration in the pigmented eye as a consequence of melanin binding. However, Leblanc et al (1998) reported that the drug-related toxic effects on the retina described in man and animals were unrelated to melanin binding and that melanin binding and retinal toxicity were two separate entities, the latter being related to the intrinsic toxicity of the compound rather than its ability to bind. While a causal relationship between drug–melanin binding and ocular toxicity has not been established yet, levofloxacin would have a lower risk of causing ocular toxicity because of the much lower exposure in the pigmented and non-pigmented ocular tissues after chronic dosing as well as shorter duration of therapy, compared with chloroquine.

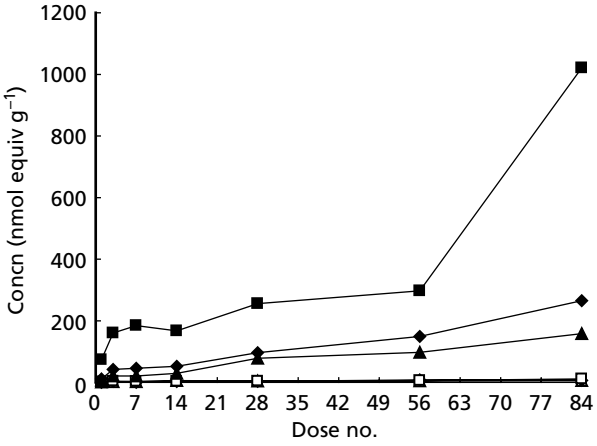

Figure 2 Mean concentration of radioactivity in retina (square), cornea (diamond) and vitreous body (triangle) at 24 h after repeated oral administration of ^{14}C-levofloxacin (open symbols) and ^{14}C-chloroquine (solid symbols) at daily doses of 20 mg (0.054 mmol) kg^{-1} and 28 mg (0.054 mmol) kg^{-1}, respectively, under non-fasting conditions in pigmented rats for 84 days.

Conclusion

The ocular tissue distribution and accumulation after chronic oral administration of ^{14}C-levofloxacin and ^{14}C-chloroquine to pigmented rats once daily for 84 days has been investigated. The melanin-containing ocular tissues such as iris ciliary body and stratum pigment chorioides sclera showed much higher radioactivity concentrations than other non-pigmented ocular tissues after dosing of both drugs. The extent of accumulation and total exposure in pigmented and non-pigmented ocular tissues after chronic administration of ^{14}C-levofloxacin was found to be much lower, compared with ^{14}C-chloroquine. These results indicated that levofloxacin would have a much lower risk for ocular toxicity than chloroquine.

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