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# Analysis of a new fluoroquinolone derivative (Q-35) in human scalp hair as an index of drug exposure and as a time marker in hair

**Toshihiko Uematsu[1], Yasutsugu Ohsawa[2], Atsuhiro Mizuno[1], Mitsuyoshi Nakashima[1]**

[1] Department of Pharmacology, Hamamatsu University School of Medicine, Hamamatsu 431-31, Japan
[2] Assay Technology Research Center, Chugai Pharmaceutical Co., Ltd., Tokyo 171, Japan

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**Summary.** Scalp hair samples were obtained every month for three months after administration from healthy male volunteers who participated in the phase I study of a new antimicrobial fluoroquinolone derivative (Q-35). Hairs were cut into 1 cm long pieces successively from the scalp end. Corresponding pieces of 5 hair strands were dissolved in 1 *M* NaOH and assessed for Q-35 by HPLC. The drug was detectable in the hairs of all subjects taking either a single (400 mg, $n = 6$) or repeated oral doses of Q-35 (400 mg/day for 6.5 days, total 2600 mg, $n = 6$). The hair portions containing the drug were shown in most subjects to move outwards along the hair shafts month by month in proportion to the hair growth rate of about 1 cm/month. Q-35 (600 mg/day) was also given to 6 healthy male volunteers for 6.5 days (total 3900 mg) and hair samples were obtained 1 and 3 months after administration. When Q-35 was analyzed along a single hair shaft, the drug was detectable only in 1–2 consecutive 1 cm long pieces, which were also shown to move outwards along the hair shaft with time. A detailed analysis revealed that the drug was contained only in 2–4 consecutive 2.5 mm long pieces of a single hair collected after 3 months, showing that there was no significant axial diffusion of the drug along the hair shaft with time. These findings indicate the utility of measuring this fluoroquinolone derivative in human scalp hair as an index of drug exposure and as a time marker for analyzing other drug(s) in hair.

**Key words:** Scalp hair – Fluoroquinolone – Q-35 – Index of exposure – Time marker

**Zusammenfassung.** Kopfhaarproben wurden über einen Zeitraum von 3 Monaten monatlich von gesunden männlichen freiwilligen Versuchspersonen erhalten, welche in Verbindung mit einer Phase I-Studie ein neues antimikrobielles Fluorochinolon-Derivat (Q-35) erhalten hatten. Die Haare wurden sukzessive in 1 cm lange Stücke zerschnitten. Korrespondierende Teile von insgesamt 5 Haarsträngen wurden in 1 *M* NaOH gelöst und mittels einer HPLC-Methode auf Q-35 untersucht. Die Verbindung war erkennbar in den Haaren aller Versuchspersonen nachzuweisen, welche entweder eine einzelne (400 mg, $n = 6$) oder wiederholte orale Dosen von Q-35 (400 mg/Tag für 6,5 Tage, insgesamt 2.600 mg, $n = 6$) erhalten hatten. Die Haarabschnitte, welche die Substanz enthielten, erwiesen sich bei den meisten Versuchspersonen als auswärts wandernde Haarschäfte, welche entsprechend zur Haarwuchsgeschwindigkeit ungefähr 1 cm pro Monat nach außen wuchsen. Q-35 (600 mg/Tag) wurde auch 6 gesunden männlichen freiwilligen Probanden für die Dauer von 6,5 Tagen gegeben (insgesamt 3.900 mg) und Haarproben über einen Zeitraum von 1–3 Monaten nach der Gabe gesammelt. Wurde Q-35 entlang eines einzelnen Haarschaftes analysiert, war die Substanz nur in 1–2 konsekutiven, 1 cm langen Stücken detektierbar; auch diese zeigten eine Auswärtsbewegung des Haarschafts über die Zeit. Weitergehende Analysen zeigten, daß die Droge nur in 2–4 konsekutiven, 2,5 mm langen Stücken des Haares enthalten war, welches 3 Monate gesammelt worden war; hierdurch wird gezeigt, daß keine bedeutsame zeitabhängige axiale Diffusion der Substanz entlang des Haarschafts stattfindet. Diese Befunde zeigen die Anwendbarkeit dieses Fluorochinolon-Derivats in menschlichen Kopfhaarproben als Index für eine Substanzaufnahme und als Zeitmarker für die Analyse anderer Drogen im Haar an.

**Schlüsselwörter:** Kopfhaare – Fluorochinolon – Q-35 – Aufnahme-Indikator – Zeitmarker

## Introduction

Human scalp hair is useful for therapeutic drug monitoring as well as for forensic or toxicological analysis (Airey 1983; Balabanova et al. 1987; Baumgartner et al. 1981;

*Correspondence to:* T. Uematsu

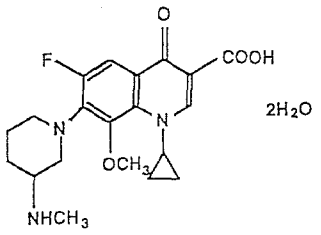


**Fig. 1.** Chemical structure of Q-35

Suzuki et al. 1984). However, the rate of hair growth is known to vary both within and between subjects, ranging approximately from 0.5 to 2 cm/month (Montagna and Parakkal 1974). Moreover, hair has a growth cycle of 2–8 years or more consisting of the growing, intermediate and resting stages. Therefore information about the hair cycle and growth rate is essential. We have previously shown that ofloxacin, an antimicrobial fluoroquinolone derivative widely used in Japan, is detectable in hair after a short exposure (Miyazawa et al. 1991) and that the hair growth rate can be roughly evaluated from the axial distribution of the drug along the hair shaft (Uematsu et al. 1991).

Q-35 [1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-aminopiperidin-1-yl)-4-oxoquinoline-3-carboxylic acid dihydrate ($C_{20}H_{24}FN_3O_4 \cdot 2H_2O$; M.W. 425.46); water-insoluble; Fig. 1] is one of the antimicrobial fluoroquinolone derivatives currently under development in Japan. In the present study, hair samples were collected periodically from subjects participating in a phase I study of Q-35 and analyzed for the drug to evaluate whether Q-35 in hair acts as an index of exposure or not.

## Materials and methods

*Subjects.* Hairs were collected at 1 month intervals for 3 months after the oral administration of Q-35 from each of 12 healthy male volunteers participating in the 1st half of the phase I study [single dose of 400 mg ($n = 6$) and repeated doses of 200 mg twice daily for 6.5 days, total 2600 mg ($n = 6$)]. The age of the subjects ranged from 27 to 49 (mean 35.8) years and body weight from 52.0 to 74.2 (mean 63.2) kg. Hair samples were also obtained from 6 healthy male volunteers (age: 24–52, mean 36.7 years; body weight: 52.7–76.7 mean 67.2 kg), who had taken 300 mg of Q-35 twice daily for 6.5 days (total 3900 mg) in the 2nd half of the phase I study, at 1 and 3 months after administration. All subjects gave their informed consent to taking the drug and to hair sampling. The protocol was approved by the local ethics committee.

*Preparation of hair samples.* In the 1st half of the study 5 strands of hair were sectioned together into 1 cm lengths successively from the scalp ends. A single hair was sectioned into 0.25 or 1 cm long pieces in the 2nd half of the study. The hair samples were washed with distilled water several times, blotted between 2 sheets of a paper towel and allowed to dry at room temperature. The hair samples were weighed and dissolved in 0.5 ml of 1 *M* NaOH by heating at 80° C for 30 min. The weight of a single 1 cm long piece of hair was approx 0.1 mg. To this solution, 0.5 ml of 1 *M* HCl solution, 1 ml of 0.5 *M* phosphate buffer (pH 7.0), 0.1 ml solution containing Q-36, 1-cyclopropyl-6,8-fluoro-1, 4-dihydro-7-(3-methyl-aminopiperidin-1-yl)-4-oxoquinoline-3-carboxylic acid (0.5 μg/ml), as internal standard (I.S.) and 5 ml of dichloromethane were successively added. The mixture was agitated for 10 min on a shaker and centrifuged at 1,700 × g for 5 min. The organic layer was transferred and evaporated under a stream of nitrogen gas at 40° C in a water bath. The residue was dissolved in 0.1 ml of a mobile phase for HPLC and aliquots (25 μl) were injected onto the HPLC. The stability of Q-35 in 1 M NaOH at 80°C was ascertained by adding 10 ng of Q-35 and 0.5 mg of blank hair to 0.5 ml of 1 M NaOH and by changing the heating time (0, 15, 30, 45, 60, 120 and 180 mins). The recovery of Q-35 (%) was 98.5–107.9% in the range 0–180 min, showing that there was no actual degradation of Q-35 under these conditions.

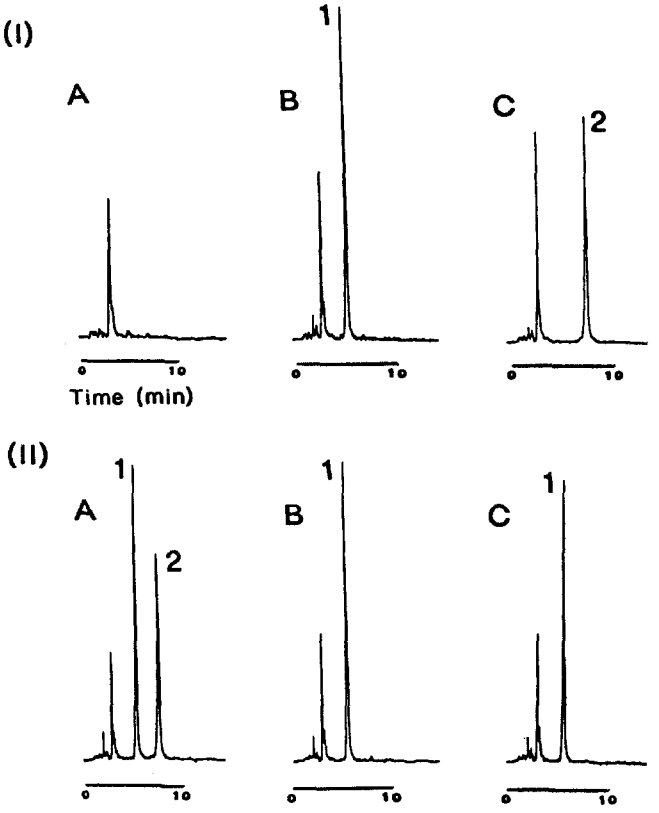


**Fig. 2.** Representative chromatograms of Q-35 and Q–36 (internal standard: I.S.) in hair sample. (I) Chromatograms of (A) blank hair (0.5 mg) treated in the same way as described in the text for the actual hair sample, (B) blank hair supplemented with 50 ng of I.S. and (C) blank hair supplemented with 50 ng of Q-35. (II) Chromatograms of actual hair samples collected 1 month after administration from a subject having taken a single oral dose of Q-35 (400 mg). Five strands of hair were sectioned into 1-cm lengths successively from the scalp ends. The chromatogram of the hair portions of 0–1 cm from the scalp end showed a peak for Q-35 (A), while those of 1–2 cm (B) and 2–3 cm (C) showed no corresponding peak. Peaks 1 and 2 are I.S. and Q-35, respectively

*Analytical procedures.* Q-35 was measured by HPLC using a Shimadzu (Kyoto, Japan) HPLC system composed of a pump (LC-9A), an auto-sampler (SIL-6B) and a system controller (Chromatopac C–R6A) together with a fluorescence spectrophotometer (F–1000, Hitachi, Tokyo, Japan; Excitation and emission wavelengths: 295 and 500 nm). An ODS analytical column (YMC AM–301–3, YMC, Kyoto, Japan) was used. The mobile phase was a mixture of water, acetonitrile and triethylamine (81:19:1, v/v), adjusted to pH 4.5 by adding phosphoric acid. The solution was filtered through a membrane filter (pore size: 0.45 μm) and degassed before use. The HPLC system was operated at ambient temperature and the flow rate was 1.0 ml/min. Under these conditions there were no peaks which interfered with the measurements of Q-35 and I.S. (Fig. 2 upper panel).

The calibration curve was prepared as follows: Q-35 (1, 5, 10, 50 and 100 ng) was added to the blank hair (0.5 mg) and treated in

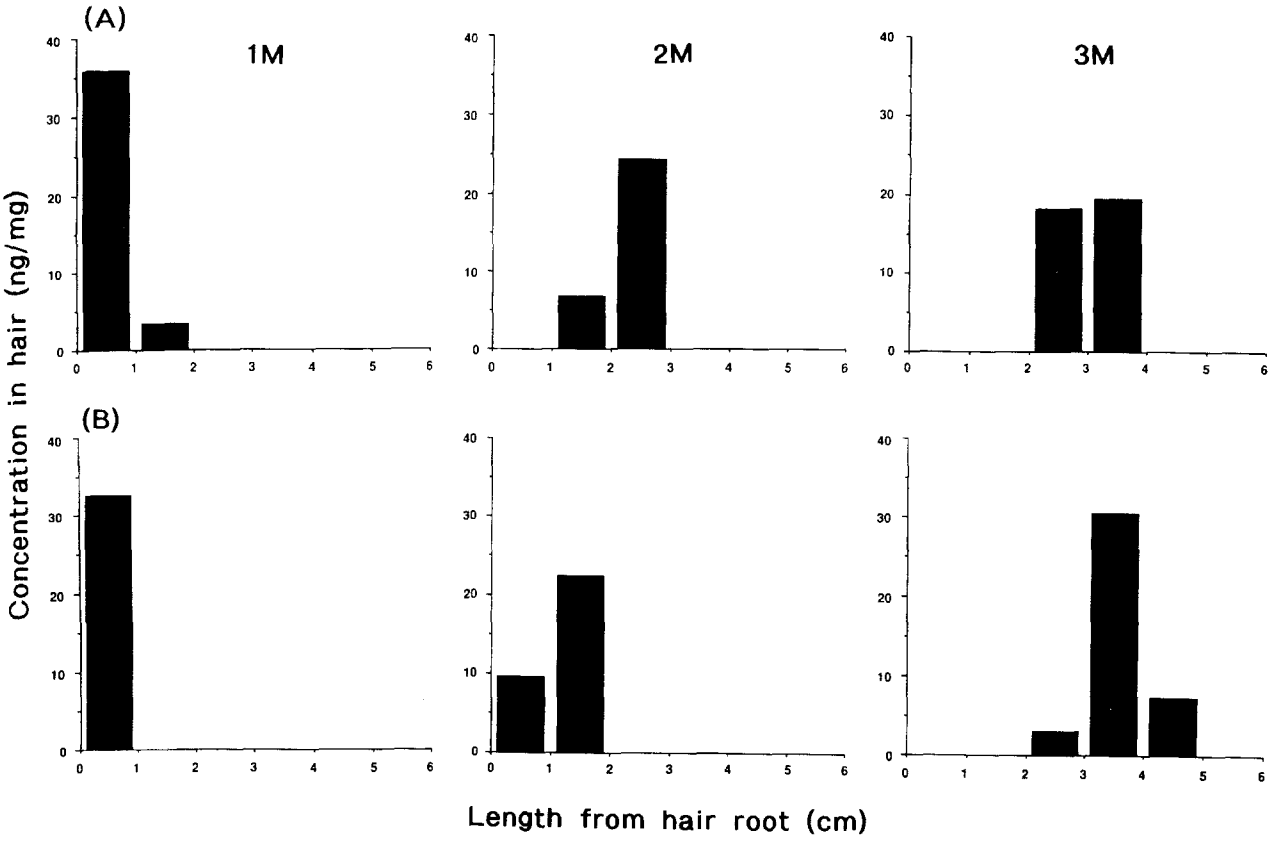


**Fig. 3.** Distribution of Q-35 along the hair shafts collected at 1, 2, and 3 months (1M, 2M, 3M) after a single oral dose of 400 mg. Each panel shows the distribution of Q-35 examined cm by cm along the entire 6 cm long portion (0–6 cm in abscissa) of 5 hair strands from the scalp ends. The results from 2 representative subjects (A and B) are shown. The height of black column shows the concentration of Q-35 (ordinate)

the same way as described above for actual hair samples. As the final residue was dissolved by 0.1 ml of the mobile phase for HPLC, the concentration of added Q-35 was expressed as 10, 50, 100, 500 and 1000 ng/ml, respectively. The calibration curve thus obtained was linear within this concentration range ($r = 0.9994$). The coefficient of variation of the assay was 3.3 and 2.2% at the concentrations of 10 and 1000 ng/ml ($n = 5$/each), respectively. Therefore, the detection limit was considered to be less than 10 ng/ml.

## Results

In the subjects who had taken either a single dose (400 mg) or repeated doses (total 2600 mg) of Q-35 in the first half of the study, 5 strands of hair were used for each measurement. The drug was detected in at least 1 out of 3 hair samples collected from each subject 1, 2 and 3 months after administration (Fig. 2 lower panel). In most cases the hair portions containing the drug was shown to move along the hair shafts month by month at a relatively constant rate after the administration of a single (Fig. 3) and repeated doses of Q-35 (Fig. 4). However, in some cases the drug could not be detected in the earlier samples and/or the month-by-month movement was not uniform. Hairs in the resting-stage might have been sampled in such cases.

In 6 subjects (A–F in Figs. 5–7), to whom Q-35 (total 3900 mg) had been also administered in the 2nd half of the study, a single hair was analyzed in the same way as mentioned above. It was ascertained in these subjects that growing-stage hairs were collected by cutting closest to the scalp in the frontal area. The hair strands were cut by pulling tightly in order to exclude loose hairs that might be in the resting stage and easily shed. When a single hair was sectioned into 1 cm long pieces successively from the scalp side, the drug was detected only in 1–2 consecutive pieces and the distance from the scalp end ranged from 0 to 2 cm at 1 month and from 1 to 5 cm at 3 months (Figs. 5 and 6). In one subject (F in Fig. 6) each of 3 hair strands collected at 3 months was separately analyzed, showing that the variability of hair growth rate was rather small within a subject. The 3–4 cm long portion of the hair, which had the 1–2 cm long hair portion containing the drug in the middle section, was cut out from the other single hair shaft of the same subject and sectioned further into 2.5 mm long pieces successively from the scalp end for drug analysis. The results obtained from 5 subjects (B–F) are shown in Fig. 7. As the weight of a 2.5 mm long piece of hair was only 0.02–0.03 mg, the concentration of Q-35 was expressed as ng/segment of hair in Fig. 7. Although the hair length analyzed could not fully cover the entire length containing the drug, (E in Fig. 7), only 2–4 consecutive 2.5 mm long pieces of hair contained the drug. Since the hair samples were obtained exactly 3 months after the completion of drug administration, the

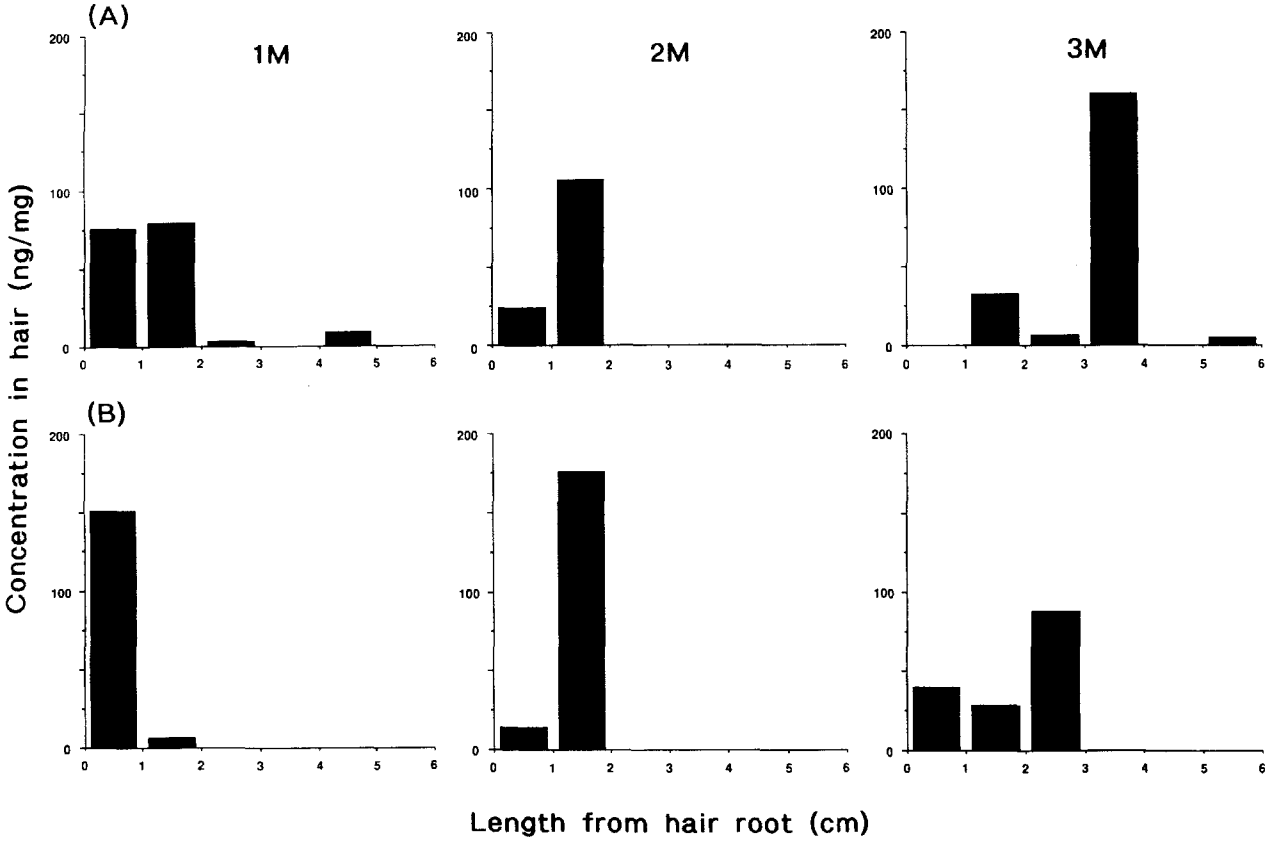


**Fig. 4.** Distribution of Q-35 along the hair shafts collected at 1, 2, and 3 months (1M, 2M, 3M) after repeated oral doses of 200 mg twice daily for 6.5 days. Each panel shows the distribution of Q-35 examined cm by cm over the entire 6 cm-long portions of 5 hair strands as shown in Fig. 2. The results of two representative subjects (A and B) are shown

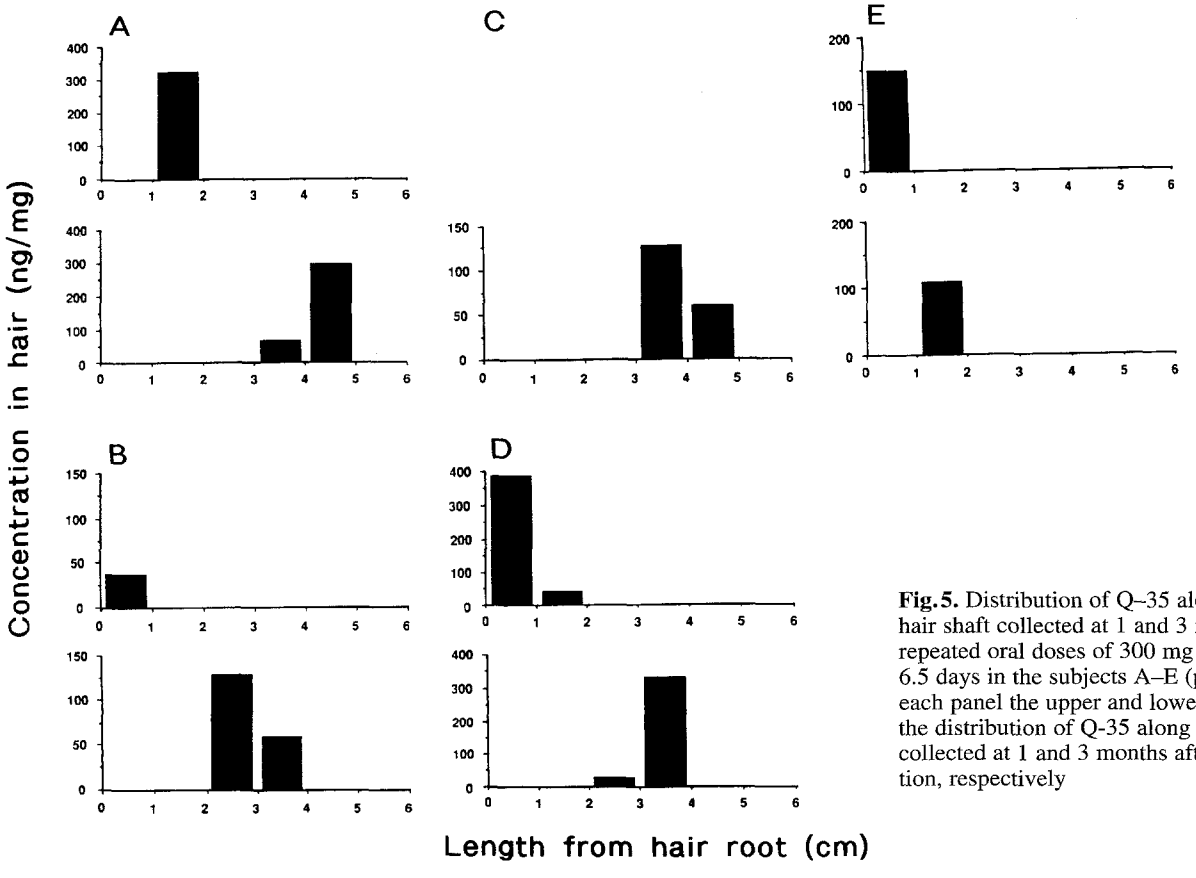


**Fig. 5.** Distribution of Q–35 along a single hair shaft collected at 1 and 3 months after repeated oral doses of 300 mg twice daily for 6.5 days in the subjects A–E (panels A–E). In each panel the upper and lower graphs show the distribution of Q-35 along single hairs collected at 1 and 3 months after administration, respectively

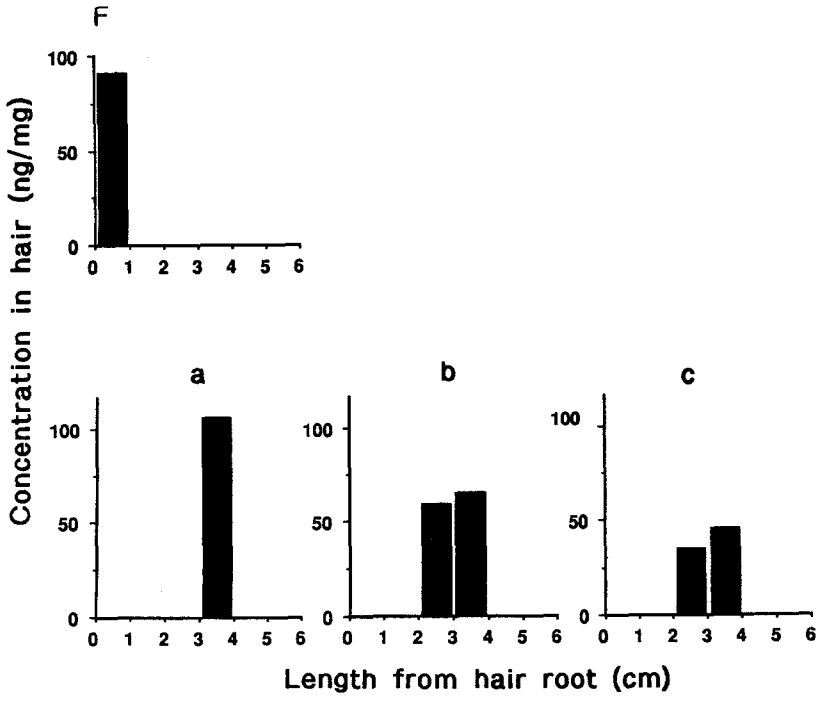


**Fig. 6.** Distribution of Q-35 along a single hair shaft collected at 1 (upper panel) and 3 months (lower panels) after repeated oral doses of 300 mg twice daily for 6.5 days in subject (F). The upper panel shows the distribution of Q-35 along a single hair collected at 1 month. Each of the lower 3 panels shows the distribution of Q-35 along a single different hair shaft collected at 3 months

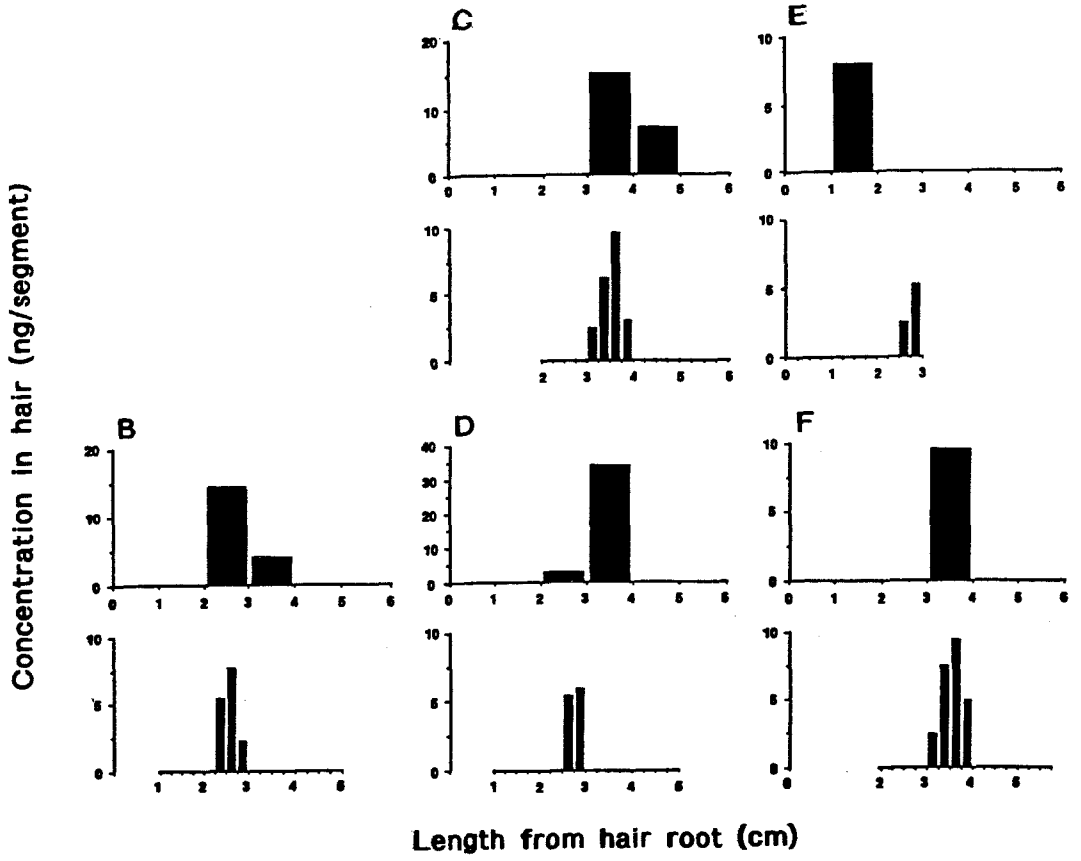


**Fig. 7.** Distribution of Q-35 along a single hair shaft collected from each of 5 subjects (B–F; the same symbols as in Fig. 4) 3 months after administration. The upper graph of each panel shows the cm-by-cm analysis over the 6 cm from the scalp end, which corresponds to the lower graph of Fig. 4. The lower panel shows the result of the detailed analysis: a single hair was cut into 2.5 mm lengths successively from the scalp end over the entire length depicted on the abscissa. As the weight of a 2.5 mm long piece of hair was only 0.02–0.03 mg, the concentration of Q-35 was expressed as ng/segment of hair on the ordinates of both upper and lower panels for comparison

growth rate was calculated in each subject by dividing the hair length, where the drug peaked, by 3: about 0.88, 1.2, 0.92, 0.96 and 1.2 cm/month in the subjects B, C, D, E and F of Fig. 7, respectively.

## Discussion

The present study shows the following: (1) A newly developed fluoroquinolone derivative, Q-35, is deposited in hair and quantitatively detectable even after exposure to a single dose of 400 mg. (2) The hair portion(s) containing the drug moved outwards along the hair shaft month by month at different rates in different subjects, depending on the different hair growth rates. (3) There was little axial diffusion of the drug along a single hair shaft with time, showing that the discriminative power for analyzing Q-35 along the hair length was 5–10 mm after the repeated administrations over a 7-day period.

Q-35 incorporated in hair was shown to move along the hair shaft month by month up to 3 months after administration. The speed of movement varied among subjects in relation to the hair growth rate. Where the movement was not uniform the sampled hairs might have been in the resting stage. In addition, when 5 strands of hair were used together for the analysis, the axial distribution of Q-35 along the hair shafts tended to be broader with time as shown in Fig. 4. This phenomenon was perhaps due to the difference in growth rate and/or cycle stage among the 5 hair strands used. In the 2nd half of the study, therefore, a single hair in the growing stage, was used for the analysis. Thus, the growth rate of hair was revealed to be less variable within a subject as shown in Fig. 6. Using a single hair in the growing stage, a detailed analysis of drug distribution along the shaft enabled us to calculate the hair growth rate. The growth rate was calculated to be about 0.88–1.2 cm/month by dividing the hair length, where the drug peaked, by the interval between the dates of drug ingestion and hair sampling (Fig. 7). Since reliable and quantitative measurement of hair growth rate is essential for assessing treatments intended to increase hair growth (Barth 1986; Price and Menefee 1990), the measurement of a fluoroquinolone derivative such as Q-35 along a hair shaft may provide a useful tool for such an assessment.

The measurement of a fluoroquinolone derivative, e.g., ofloxacin (Uematsu et al., 1991) as well as Q-35, along the hair shaft is also expected to serve as a time marker for analyzing other drug(s) in hair. When a single hair was sectioned into smaller portions of 2.5 mm, Q-35 was found to be contained only in 2–4 consecutive sections, i.e., 5.0–10.0 mm long, 3 months after administration over a 7-day period. In addition, the drug peaked in only 1–2 consecutive 2.5 mm lengths and, therefore, the discriminative power of hair analysis is considered to be sufficiently small to serve as a time marker within hair. A 2.5 mm long piece of hair corresponds to the growth over the 7-day period of administration assuming an average hair growth rate of 1 cm/month (Montagna and Parakkal 1974).

We have shown that haloperidol and chlorpromazine are deposited in hairs in proportion to the given dose, and that their axial distribution along a single hair shaft reflects the dosage history from several months up to a year depending on the length of hair (Matsuno et al. 1990; Sato et al. 1989; Sato et al. 1993; Uematsu et al. 1989, 1990; Uematsu and Sato 1990). In addition, the cm-by-cm distribution of nicotine content along the hair shafts represents the month-by-month smoking behavior of an individual (Mizuno et al. 1993). These findings suggest that hair is a potentially useful biopsy material with interdisciplinary relevance. In the case of haloperidol or chlorpromazine, which is usually taken by psychiatric patients over a long period of time, a change in the daily dose was shown to cause the corresponding change of concentration along the hair shaft. The hair portion reflecting such a change of dose was shown to move outwards along the hair shaft month by month (Matsuno et al. 1990; Sato et al. 1989; Sato et al. 1993). Therefore, the hair growth rate can be estimated by the distribution of haloperidol or chlorpromazine concentration along the hair shaft only if a change of dose occurred within several months. These drugs are, however, used only in a limited population with mental disorders. On the other hand, the antimicrobial drug fluoroquinolone may be intermittently and repeatedly administered over a relatively short period of time for treating various infectious diseases independently of the original disease or in the patients with only minor infections. Therefore, hair analysis of a quinolone derivative seems superior to that of haloperidol or chlorpromazine for estimating hair growth rate.

Our previous studies on haloperidol (Uematsu et al. 1990), chlorpromazine (Sato et al. 1993), ofloxacin (Uematsu et al. 1992b) and nicotine determined in hair (Mizuno et al. 1993) suggest that a drug with high affinity for melanin should accumulate in hair to a higher degree. The facts that many quinolone derivatives possess a high affinity for melanin (Uematsu and Nakashima 1992) and that almost Japanese, especially younger ones, have black hair promoted us to measure Q-35 in hair for the purpose of utilizing it as a time marker in hair. The concentration of eumelanin in Japanese black hair is in fact higher than those in European dark brown, medium light brown and dark red hairs, i.e., about 0.6% vs. 0.3, 0.2 and 0.1% of wet weight respectively (Ito and Jimbow 1983; Ito and Fujita 1985; Ortonne and Prota 1993). However, the content of melanin in hair is not the only factor affecting the accumulation of a drug in hair. For example, the concentration of haloperidol in European blond hair is quite comparable to that in Japanese black hair within the same range of daily dose (unpublished observation). The concentration of chlorpromazine in hair was much lower than that of haloperidol in the same subject taking both drugs daily, although the affinity of both drugs for melanin was almost the same and, moreover, the plasma concentration of chlorpromazine was much higher than that of haloperidol (Sato et al. 1993). Therefore, the role of other constituents of hair such as melanosome, the precursor of melanin may be important factors for the incorporation of a drug into hair. It is also true that Japanese black hair is thicker than European hairs and the weight of a single 1 cm long piece of hair used in the present study was around 0.1 mg. However, the sensitivity of the present method for measuring

Q-35 and the absolute amount of Q-35 contained in hair may be sufficient to allow us to quantitate the drug in a single European hair even if the hair color is blond or light brown. This should be clarified in a further study.

## Conclusion

The growth rate of an individual hair could be estimated by analyzing the distribution of Q-35 along the hair shaft. Because there was little axial diffusion of the drug along the hair shaft, a precise measurement of growth rate was possible in a single hair piece several months after the drug ingestion. In addition, the distribution of the drug along the hair shaft may serve as a time marker for therapeutic monitoring of other drugs or chemical substances.

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