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Effect of Fenbufen on the Entry of New Quinolones, Norfloxacin and Ofloxacin, into the Central Nervous System in Rats

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Abstract—The entry of two new quinolone antibacterial agents, norfloxacin and ofloxacin, into the central nervous system (CNS) of rats, and the effect of fenbufen on this was investigated. At various times after the administration of a bolus intravenous dose of norfloxacin or ofloxacin (10 mg kg^{-1}) with or without fenbufen (20 mg kg^{-1}), serum and cerebrospinal fluid (CSF) samples and whole brain were collected from the rats and the concentration of norfloxacin or ofloxacin in each sample was determined. Serum concentrations of both quinolones declined biexponentially with time and were significantly elevated by coadministration with fenbufen at the terminal phase. The fractions of these quinolones bound to serum protein were not altered by coadministration with fenbufen. Coadministered fenbufen raised the brain concentrations of both quinolones but did not affect their brain to serum unbound concentration ratios. In contrast, CSF to serum unbound concentration ratios as well as CSF concentrations of norfloxacin and ofloxacin were elevated by coadministration with fenbufen. Apparent diffusional clearances between blood and CSF of norfloxacin and ofloxacin estimated by the physiological model analysis increased by 1·9 and 2·6 times, respectively, after coadministration with fenbufen. These findings suggest that coadministered fenbufen may facilitate the entry of norfloxacin and ofloxacin into the CNS.

The quinolonecarboxylic acid antibacterial agents are used in the chemotherapy of various infectious diseases because of their broad and strong antibacterial activity against Gram-positive and Gram-negative bacteria, including those resistant to aminoglycoside and β-lactam antibiotics (Janknegt 1986). They can, however, distribute into the central nervous system (CNS) and cause serious neurotoxic side-effects, such as convulsions (Simpson & Brodie 1985; Anastasio et al 1988).

It has been reported that the concomitant use of these quinolones and the non-steroidal anti-inflammatory drug, fenbufen (Sloboda et al 1980), induces severe convulsions in man as well as laboratory animals (Ministry of Health & Welfare of Japan 1986, 1989; Hirai et al 1989; Takeo et al 1989). The mechanism for induction of the convulsions by the coadministration of both drugs is unclear but is very important for effective and rational drug therapy.

We have investigated the possible pharmacokinetic interactions between some of the new quinolones and fenbufen in experimental animals. In our previous reports (Katagiri et al 1989a, b; Naora et al 1990a, b), we showed that coadministered fenbufen elevated plasma concentrations of enoxacin, norfloxacin, ofloxacin and ciprofloxacin, in rats. Our most recent study (Naora et al 1991) demonstrated that fenbufen facilitated the entry of ciprofloxacin into the CNS thus elevating the concentrations of this quinolone in the brain and cerebrospinal fluid (CSF).

However, further screening of other new quinolones is essential to determine the interaction between the new quinolones and fenbufen in the CNS. In the present paper we have studied the entry of two other quinolones, norfloxacin and ofloxacin, into the brain parenchyma and CSF of rats and investigated the effect of fenbufen on CNS entry.

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Materials and Methods

Materials

Norfloxacin and ofloxacin were supplied by Kyorin Yakuhin Co. Ltd (Tokyo, Japan) and Daiichi Seiyaku Co. Ltd (Tokyo, Japan), respectively. Fenbufen was supplied by Lederle Japan Ltd (Tokyo, Japan). All other chemicals were commercial products and of analytical or liquid chromatographic grade.

Animals

Male Wistar rats (Japan SLC, Inc., Hamamatsu, Japan), 300–360 g, 10–11 weeks old, were used. The right jugular vein was cannulated (Upton 1975) at least 15 h before drug administration and then the animals were housed individually with free access to food and water.

Drug administration and sample collection

Norfloxacin or ofloxacin was dissolved in phosphate-buffered 0·9% NaCl (saline) containing 0·1 M sodium hydroxide with or without fenbufen. A bolus dose of 10 mg kg^{-1} of each quinolone was injected through the cannula with or without 20 mg kg^{-1} fenbufen. The volume of solution injected was 2 mL kg^{-1}. At designated times after drug administration, each rat was lightly anaesthetized with ether and a CSF specimen (approx. 50–100 μL) was obtained by cisternal puncture (Naora et al 1991). Immediately after CSF collection, blood (approx. 1–2 mL) was withdrawn from the jugular vein and the rat was killed by microwave irradiation focused on its skull for 0·8–1·0 s at an output of 5 kW, using a microwave applicator model TMW-6402A (Toshiba, Tokyo, Japan). A 200 μL sample of the blood was haemolysed with

an equal volume of distilled water for the determination of the drug concentration in whole blood. The serum was immediately separated from the blood by centrifugation with a serum separator (Fibrichin; Takazono Sangyo Co. Ltd, Tokyo, Japan), and a portion of it was ultrafiltered with Amicon Centrifree (Amicon Div., W. R. Grace & Co., Danvers, MA) by centrifugation at 4000 rev min^{-1} for 15 min (model KR-20000T, Kubota, Tokyo, Japan). The brain was quickly excised and weighed after the careful removal of the dural and subarachnoidal vessels.

Assay

Norfloxacin and ofloxacin concentrations in whole blood, serum, ultrafiltrate, brain and CSF were determined by HPLC. Sample pretreatment was as previously developed for ciprofloxacin (Naora et al 1990b; Katagiri et al 1990) with some modifications in the chromatographic conditions. A Shimadzu LC-4A pump (Kyoto, Japan) was used, equipped with a Shimadzu RF-530 or RF-535 fluorescence spectromonitor with excitation and emission wavelengths of 278 and 445 nm for norfloxacin, and 340 and 460 nm for ofloxacin, respectively. Separation was achieved using a reversed phase column (150 mm × 4·6 mm i.d.) packed with Wakosil 5C18 (Wako Pure Chemical Industries Ltd, Osaka, Japan) and a mobile phase of CH_3OH:0·02 M KH_2PO_4 (60:40 for norfloxacin, or 55:45 for ofloxacin; pH 2·5) containing 2 mM sodium lauryl sulphate. Under the above conditions, the sensitivities of the assay were as follows: brain, 10 ng g^{-1} for norfloxacin and 50 ng g^{-1} for ofloxacin; CSF, 2·5 ng mL^{-1} for norfloxacin and 20 ng mL^{-1} for ofloxacin; serum, ultrafiltrate and whole blood, below 0·1 μg mL^{-1} for both quinolones. The coefficients of variation of both drugs were within 10% for all samples.

The net drug concentration in the brain parenchyma was calculated by subtracting the intravascular concentration in brain from the measured brain concentration. Intravascular drug concentration was obtained from the product of cerebral blood volume and whole blood concentration. Cerebral blood volume was estimated to be 0·0243 mL g^{-1} from the calculation based on regional cerebral blood volume (Rapoport et al 1979) and regional brain weight (Glowinski & Iversen 1966).

Data analysis

After intravenous injection of the quinolones, serum total concentration (C_t) vs time (t) data was represented by the following biexponential equation:

$$C_t = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$

where A, B, α and β are hybrid parameters.

The transport of quinolones into CSF was analysed based on a physiological model which includes passive diffusion, convective removal by CSF turnover and unidirectional active efflux processes. Assuming no biotransformation in the CSF and no exchange between brain tissue and CSF, the rate of change of the quinolone concentration in the CSF is given as follows:

$$V_c \cdot dC_c/dt = PA_c(C_f - C_c) - Q_c \cdot C_c - CL_{eff} \cdot C_c$$

where C_c and C_f are CSF and serum unbound concentrations of the quinolone, respectively; V_c is the volume of CSF; PA_c is apparent diffusional clearance of the quinolone between blood and CSF; Q_c is the rate of CSF turnover and CL_{eff} is the active efflux clearance of the quinolone from CSF to blood. The value of V_c was estimated to be 0·18 mL from the relationship between the estimate by Sato et al (1988) and the body weight of the animals. Q_c was reported to be 0·0022 mL min^{-1} in rats (Cserr 1965).

The data on the concentrations of the quinolone in serum and CSF were fitted according to the model equations given above by a non-linear least squares regression program, MULTI (Yamaoka et al 1981), to estimate the kinetic parameters A, B, α, β, PA_c and CL_{eff}. A weighting factor of reciprocal of the concentration was used in all of the regression analyses.

Statistics

The Student's *t*-test for unpaired data was used to evaluate the significant differences between two groups. $P < 0.05$ was considered to be statistically significant.

Results

Serum concentration vs time profile

Fig. 1 shows the semilogarithmic plot of mean serum total concentration of norfloxacin or ofloxacin vs time after a bolus intravenous injection with or without fenbufen to rats. Serum concentrations of both quinolones declined rapidly and biexponentially with time. Coadministration with fenbufen caused a significant elevation of serum concentrations of the quinolones during the terminal phase. Mean serum concentration vs time data were fitted according to the equation which expressed biexponential function. The hybrid parameters estimated by least squares regression of the mean data and the elimination half-lives at the terminal phase obtained from the hybrid parameter are listed in Table 1. The elimination half-life of norfloxacin increased by about 1·2 times after the coadministration with fenbufen. Similar results were also found in our previous report with rat plasma (Katagiri et al 1989b).

Serum protein binding

Bound fractions of norfloxacin and ofloxacin ranged from 0·25 to 0·33 and from 0·28 to 0·36, respectively. There was no effect of coadministered fenbufen on the bound fraction of either quinolone.

Brain and CSF concentration vs time profiles

Brain concentration vs time profiles for norfloxacin and ofloxacin after intravenous injection with or without fenbufen to rats are shown in Fig. 2. Brain concentration of norfloxacin rose rapidly after drug administration and then declined slowly. Brain concentration of ofloxacin was found to be higher than that of norfloxacin. For both quinolones, significant elevation of brain concentration was observed at several time points after the coadministration with fenbufen. CSF concentration vs time profiles for norfloxacin and ofloxacin after intravenous injection with or without fenbufen to rats are shown in Fig. 3. CSF concentrations of norfloxacin and ofloxacin attained their peaks at 3–5 min

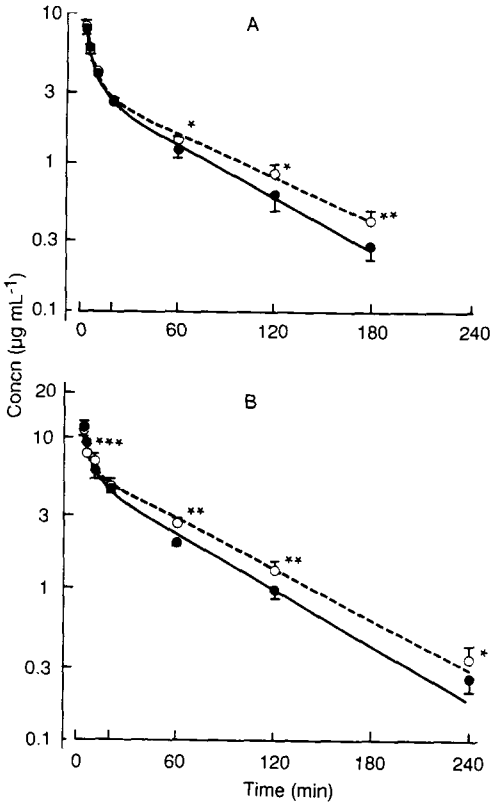

FIG. 1. Serum total concentration vs time data of norfloxacin (A) and ofloxacin (B) after intravenous administration (10 mg kg^{-1}) with (○) or without (●) fenbufen (20 mg kg^{-1}) in rats. Each point represents the mean ± s.d. of five rats. Each line indicates the simulation curve for the mean data by the computer program MULTI. Significant difference from quinolone alone at $*P<0.05$, $**P<0.01$ or $***P<0.001$.

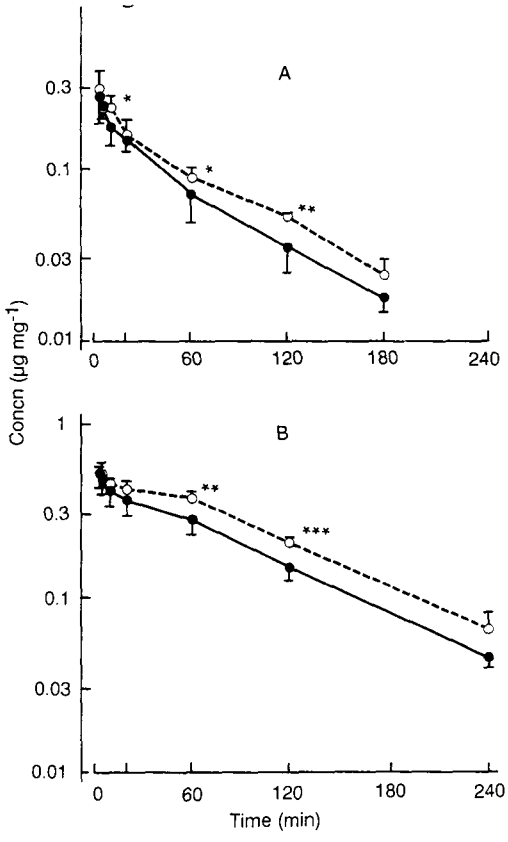

FIG. 2. Brain concentration vs time data of norfloxacin (A) and ofloxacin (B) after intravenous administration (10 mg kg^{-1}) with (○) or without (●) fenbufen (20 mg kg^{-1}) in rats. Each point represents the mean ± s.d. of five rats. Significant difference from quinolone alone at $*P<0.05$, $**P<0.01$ or $***P<0.001$.

after drug injection. CSF concentration of ofloxacin at each time point was approximately ten times as high as that of norfloxacin. For ofloxacin, significant elevation of CSF concentration was caused by coadministration with fenbufen at all time points, even 3 min after the injection.

Brain to serum unbound concentration (C_b/C_f) ratios of norfloxacin and ofloxacin are shown in Fig. 4. The C_b/C_f ratio of norfloxacin was relatively small and almost constant during 20 to 180 min after drug administration, while C_b/C_f ratio of ofloxacin gradually increased from 0·06 at 3 min to 0·28 at 240 min. The change in the C_b/C_f ratios of both quinolones was observed only at a few time points after coadministration with fenbufen. CSF to serum unbound concentration (C_c/C_f) ratios of both quinolones after intravenous injection with and without fenbufen are shown in Fig. 5. A significant increase of the C_c/C_f ratio was observed in both quinolones after the coadministration with fenbufen.

Table 1. Pharmacokinetic parameters of norfloxacin and ofloxacin obtained from serum concentration–time data after a bolus intravenous administration (10 mg kg^{-1}) with or without fenbufen (20 mg kg^{-1}) in rats.

Drug		Parameter	Alone	With fenbufen
Norfloxacin	A	(μg mL^{-1})	8·29 ± 0·97	10·1 ± 1·9
	B	(μg mL^{-1})	3·11 ± 0·37	3·10 ± 0·41
	α	(min^{-1} × 10^{-2})	19·0 ± 3·7	23·0 ± 5·8
	β	(min^{-1} × 10^{-2})	1·39 ± 0·14	1·14 ± 0·16*
	$t_{\frac{1}{2}\beta}$	(min)	49·7	61·0
Ofloxacin	A	(μg mL^{-1})	12·1 ± 2·2	8·21 ± 2·71*
	B	(μg mL^{-1})	5·31 ± 0·70	5·91 ± 0·90
	α	(min^{-1} × 10^{-2})	21·0 ± 5·8	20·1 ± 10·7
	β	(min^{-1} × 10^{-2})	1·41 ± 0·17	1·25 ± 0·18
	$t_{\frac{1}{2}\beta}$	(min)	49·0	55·6

Parameters were estimated from the mean data of five rats by the computer program, MULTI [weight(i) = 1/C_i, where C was serum concentration of the quinolone]. Hybrid parameters (A, B, α and β) are expressed as the mean ± s.d. of the estimate. The elimination half-life at the terminal phase ($t_{\frac{1}{2}\beta}$) was calculated from the mean value of β. $*P<0.05$ compared with quinolone alone.

The values of the area under concentration–time curve for serum unbound concentration (AUC_f), brain concentration (AUC_b) and CSF (AUC_c) were calculated by the estimated hybrid parameters or trapezoid method. Table 2 shows these AUC values and the ratios of them for the control and for coadministered rats.

Transport parameters into CSF

The pharmacokinetic parameters of these quinolones for transport into the CSF are listed in Table 3. These parameters were estimated by applying the mean data shown in Fig. 3 to the model equations. The apparent clearances of norfloxacin and ofloxacin for the bidirectional diffusion between blood and CSF (PA_c) were 0·133 ± 0·012 and 0·721 ± 0·089 for the control rats, and 0·258 ± 0·061 and 1·86 ± 0·22 for the coadministered rats, respectively. The PA_c values of norfloxacin and ofloxacin were increased by about

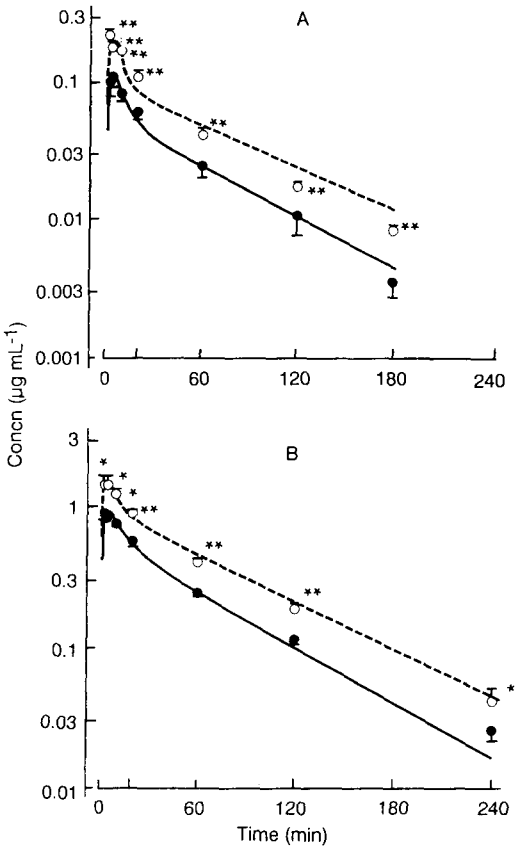

FIG. 3. CSF concentration vs time data of norfloxacin (A) and ofloxacin (B) after intravenous administration (10 mg kg^{-1}) with (○) or without (●) fenbufen (20 mg kg^{-1}) in rats. Each point represents the mean ± s.d. of five rats. Each line indicates the simulation curve for mean data by the computer program MULTI. Significant difference from quinolone alone at $*P<0.01$ or $**P<0.001$.

1·9 and 2·6 times after the coadministration, respectively, whereas a significant change in CL_{eff} on coadministration of fenbufen was not observed for either norfloxacin or ofloxacin.

Discussion

Brain and CSF concentrations of ofloxacin were higher than those of norfloxacin (Figs 2, 3) and ofloxacin had considerably larger C_b/C_f and C_c/C_f ratios than norfloxacin (Fig. 3) suggesting that ofloxacin penetrates into the CNS more readily than norfloxacin. The C_b/C_f ratio of norfloxacin remained constant after 20 min indicating that the diffusion of norfloxacin between blood and brain has attained equilibration at this time point whereas the C_b/C_f ratio of ofloxacin increased with time from 3 to 240 min after intravenous injection suggesting that the elimination of ofloxacin from the brain may be slower than that from the blood so that it accumulates in the brain.

CSF concentration vs time data were analysed by the following model equation (Naora et al 1991):

$$V_c \cdot dC_c/dt = PA_c(C_f - C_c) + Q_c(C_f - C_c) - CL_{eff} \cdot C_c$$

The entry of drug into CSF on the process of CSF formation is estimated as the first term of the equation. Q_c represents the

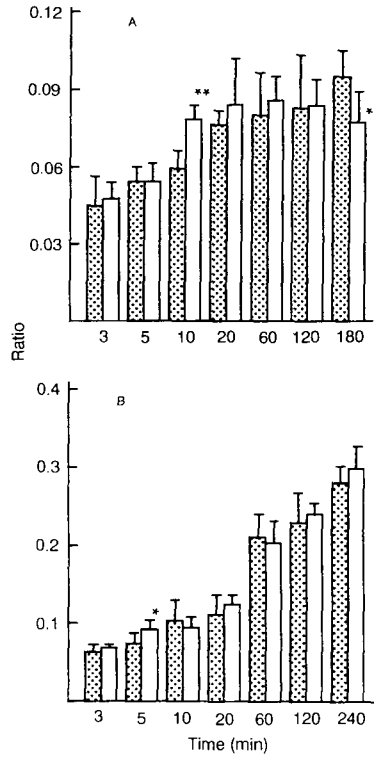

FIG. 4. Ratios of brain concentration to serum unbound concentration of norfloxacin (A) and ofloxacin (B) after intravenous administration (10 mg kg^{-1}) with (□) or without (▩) fenbufen (20 mg kg^{-1}) in rats. Each bar represents the mean ± s.d. of five rats. Significant difference from quinolone alone at $*P<0.05$ or $**P<0.01$.

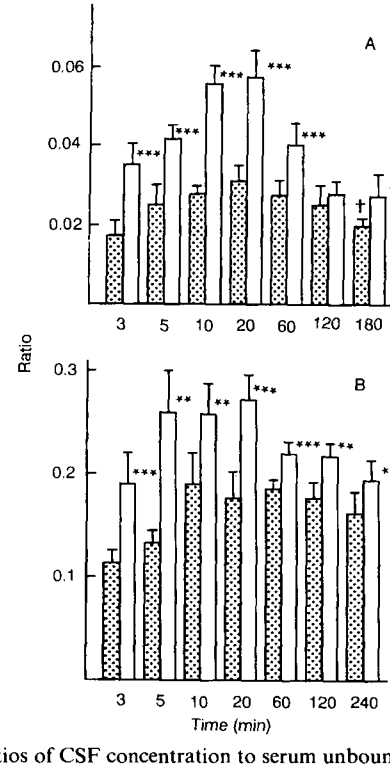

FIG. 5. Ratios of CSF concentration to serum unbound concentration of norfloxacin (A) and ofloxacin (B) after intravenous administration (10 mg kg^{-1}) with (□) or without (▩) fenbufen (20 mg kg^{-1}) in rats. Each bar represents the mean ± s.d. of five (†four) rats. Significant difference from quinolone alone at $*P<0.05$, $**P<0.01$ or $***P<0.001$.

Table 2. AUC values for serum unbound, brain and CSF concentrations of norfloxacin and ofloxacin after bolus intravenous administration (10 mg kg^{-1}) with or without fenbufen (20 mg kg^{-1}) in rats.

	Norfloxacin		Ofloxacin	
	Alone	With fenbufen	Alone	With fenbufen
AUC_f (μg min mL^{-1})	180·9	202·9	284·9	339·2
AUC_b (μg min g^{-1})	12·5	15·4	44·8	58·0
AUC_c (μg min mL^{-1})	4·69	8·45	48·9	80·4
AUC_b/AUC_f	0·0693	0·0761	0·157	0·171
AUC_c/AUC_f	0·0260	0·0416	0·172	0·237
AUC_c/AUC_b	0·375	0·547	1·10	1·39

Each AUC value was estimated from zero to the last time of sampling. AUC_f was calculated from hybrid parameters for serum unbound concentration-time data, and AUC_b and AUC_c were calculated by the trapezoid method.

Table 3. Pharmacokinetic parameters of norfloxacin and ofloxacin for transport in CSF after bolus intravenous administration (10 mg kg^{-1}) with or without fenbufen (20 mg kg^{-1}) in rats.

Drug		Parameter	Alone	With fenbufen
Norfloxacin	PA_c	(mL $min^{-1} \times 10^{-2}$)	0·133 ± 0·012	0·258 ± 0·061*
	CL_{eff}	(mL $min^{-1} \times 10^{-2}$)	5·14 ± 0·60	5·69 ± 1·62
Ofloxacin	PA_c	(mL $min^{-1} \times 10^{-2}$)	0·721 ± 0·089	1·86 ± 0·22**
	CL_{eff}	(mL $min^{-1} \times 10^{-2}$)	3·78 ± 0·63	5·86 ± 0·86*

Parameters were estimated from the mean data of five rats by the computer program, MULTI [Weight(i) = $1/C_i$, where C was CSF concentration of the quinolone]. Values are expressed as the mean ± s.d. of the estimated parameters. *$P < 0·01$ or **$P < 0·001$ compared with quinolone alone.

rate of CSF bulk flow. The second term should express the drug elimination from the CSF by the bulk flow. In this equation, however, PA_c may be underestimated by the presence of $Q_c \cdot C_f$ in the second term. The negative value of PA_c was estimated when CSF concentration vs time data of norfloxacin was analysed by the previous equation. In the present analysis of CSF concentration vs time data, therefore, the model equation was constructed by adding the active efflux process from CSF to blood to the diffusion and flow model described by Karol et al (1983). The analysis of CSF concentration data yielded reasonable estimates for both PA_c and CL_{eff}.

The PA_c is a parameter related to the passive diffusion between blood and CSF at the choroid plexus. Therefore, the value of PA_c might be affected by the lipophilicity of the drug diffused. Thus, the relationship between the values of PA_c and the lipophilicity of the new quinolones was examined. In order to compare the PA_c values of norfloxacin and ofloxacin with that of ciprofloxacin, the previous data concerning CSF concentration of ciprofloxacin after bolus intravenous administration (Naora et al 1991) were re-analysed by the present model equation. It was reported that the apparent partition coefficients (P_{app}) between *n*-octanol and phosphate buffer (pH 7·0) of norfloxacin, ciprofloxacin and ofloxacin were 0·069, 0·115 and 0·391, respectively (Tsuji et al 1988a). The PA_c values obtained by the present model were 0·00133, 0·00318 and 0·00721 mL min^{-1} for norfloxacin, ciprofloxacin and ofloxacin, respectively. Thus, the PA_c values of these three quinolones were almost proportional to their P_{app} values. This suggests that the diffusibility of these quinolones between blood and CSF at the choroid plexus may be mainly dependent on the lipophilicities of the drugs.

The ratios of CSF concentration to brain concentration of norfloxacin and ofloxacin, which were calculated in the control rats, ranged from 0·201 to 0·379 and from 0·580 to 1·77, respectively. The AUC_c/AUC_b ratio for ofloxacin was considerably larger than that for norfloxacin (about 3-fold). Thus, less norfloxacin entered the CSF compared with the brain. As shown in Table 3, the CL_{eff} of norfloxacin was about 40-fold larger than the PA_c of this drug. For ofloxacin, however, CL_{eff} was only about five times the PA_c. It is suggested that the remarkably large clearance of norfloxacin for active efflux from CSF to blood may limit the rise of CSF concentration of this drug.

Brain concentrations of norfloxacin and ofloxacin were elevated by coadministration with fenbufen (Fig. 2), but fenbufen did not affect the C_b/C_f ratios of these two quinolones (Fig. 4). Furthermore, the AUC_b/AUC_f ratio in the control rats was approximately the same as that in the coadministered rats. These findings indicate that the elevation in brain concentrations of these quinolones after coadministration with fenbufen may be predominantly due to the change in their serum concentration. Consequently, we concluded that fenbufen does not alter the permeability of these quinolones through the blood–brain barrier.

In contrast, coadministered fenbufen significantly elevated CSF concentrations of norfloxacin and ofloxacin (Fig. 3). In addition, the C_c/C_f ratios also increased after coadministration with fenbufen (Fig. 5), and the AUC_c/AUC_f ratios for the coadministered rats were also larger than those

for the control rats for both quinolones. From these findings, we concluded that the elevation of CSF quinolone concentration may be due to the increased transport of quinolone into the CSF as well as the elevation in the serum concentration.

The model analysis was performed to investigate the mechanism for this enhancement of drug transport into CSF. Coadministered fenbufen enlarged the PA_c values of norfloxacin and ofloxacin markedly, whereas a decrease in CL_{eff} of either quinolone was not observed after the coadministration. These results suggest that the elevation of CSF concentrations of these quinolones by fenbufen may be due to enhancement of diffusion between blood and CSF, but not be due to inhibition of active efflux transport from CSF to blood. This conclusion is supported by the fact that substantial elevation of CSF concentration was observed immediately after drug administration.

Some pharmacodynamic mechanisms for the interaction between the quinolones and fenbufen have recently been clarified by in-vitro experiments. Tsuji et al (1988b) reported that the inhibitory effect of the quinolones on the γ-aminobutyric acid binding to its receptor was promoted by coadministration with fenbufen. Dimpfel et al (1991) demonstrated that the occurrence of epileptogenic seizures following treatment with the quinolones and fenbufen was explained by a primary induction of spontaneous hippocampal activity by fenbufen and its amplification by the quinolones. In the present experiments, we determined that there was a pharmacokinetic interaction between the quinolones and fenbufen. Fenbufen elevates the serum concentration of norfloxacin or ofloxacin and enhances the entry of the quinolones into the CSF, resulting in the elevated concentration of the quinolones in the CNS. Therefore, we can conclude that the pharmacokinetic interaction may result in the neurotoxic side effects observed when the quinolones and fenbufen are administered together.

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