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# Absence of pharmacokinetic interaction between ofloxacin and fenbufen in rats

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**Abstract**—The possible pharmacokinetic interaction between a new quinolone and fenbufen was investigated by comparing the plasma concentration-time profiles and serum protein binding of ofloxacin, fenbufen and its active metabolite, felbinac, in rats. The rats were administered intravenous doses of ofloxacin (5 mg $kg^{-1}$), fenbufen (10 mg $kg^{-1}$) alone or concomitantly. The plasma elimination half-lives were about 55 min in both groups. A slight elevation of plasma concentration of ofloxacin and a small decrease of its total body clearance were observed after its coadministration with fenbufen. The extent of ofloxacin binding to rat serum tended to be slightly reduced by fenbufen which coexisted at relatively high concentrations. Plasma concentration-time curves, pharmacokinetic parameters and serum protein binding of fenbufen and felbinac were not affected by the coadministration with ofloxacin. These results suggest that any substantive pharmacokinetic interaction may be unlikely after the concomitant administration of ofloxacin and fenbufen.

The quinolonecarboxylic acids (quinolones) are antibacterial agents with a broad spectrum of activity (Neuman 1988) and are known to possess neurotoxic side reactions including convulsions (Janknegt 1986). It has been predicted that these side reactions may be due to the inhibitory effect of the new quinolones on the binding of γ-aminobutyric acid (GABA) to its receptor site in brain (Tsuji et al 1988a). A severe convulsion was also induced in several cases when a quinolone, enoxacin, and a non-steroidal anti-inflammatory agent, fenbufen, were administered concomitantly (Ministry of Health & Welfare of Japan 1986; Morita et al 1988). Therefore, this convulsion is likely to be induced or enhanced by an increase of enoxacin level in the cerebrospinal fluid (CSF) due to possible pharmacokinetic interaction with fenbufen. Similar cases may be presumed for other quinolones if coadministered with fenbufen. Basic investigation of the pharmacokinetics of the quinolone when coadministered with fenbufen is required to clarify or predict the possible interaction between both drugs, but it has not been carried out in detail for any quinolone in any animal species yet.

In the present paper, we employed ofloxacin (OFLX), which possessed great diffusibility into the CSF (Stübner et al 1986), as the model drug of quinolones and investigated the possible pharmacokinetic interaction between OFLX and fenbufen by comparing the plasma concentration-time profiles and serum protein binding of OFLX, fenbufen and its active metabolite, felbinac, in rats.

## Materials and methods

*Materials.* Ofloxacin (OFLX) was kindly supplied by Daiichi Seiyaku Co., Ltd (Tokyo, Japan) and fenbufen and felbinac by Lederle Japan Co., Ltd (Tokyo, Japan). All other reagents were commercially available and of analytical grade.

*Animals.* Male Wistar rats (Japan SLC Inc., Hamamatsu, Japan), 250–290 g, were allowed free access to food and water during the experiments. Under light ether anaesthesia, each rat was cannulated in the right jugular vein in the same manner as reported previously (Upton 1975) about 20 h before the drug administration.

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*Pharmacokinetic study.* A bolus dose of 5 mg $kg^{-1}$ of OFLX and 10 mg $kg^{-1}$ of fenbufen, which was prepared in isotonic phosphate buffer solution containing 0·1M sodium hydroxide, was administered alone or coadministered intravenously via the jugular vein cannula to the rat. After the drug administration, about 0·13 mL of blood was withdrawn periodically from the cannula into the heparinized (1 unit per 0·1 mL of the blood) tube. Plasma was immediately separated by centrifugation, and a 50 μL aliquot used for the analysis.

*Serum protein binding study.* The rats were administered drugs in the same manner as described above, and about 2·5 mL of blood was withdrawn 3 and 45 min after the administrations. The serum was immediately separated by centrifugation with serum separator (Fibrichin, Takazono Sangyo Co., Ltd, Osaka, Japan). The binding of the three drugs was determined by ultrafiltration using a micropartition system MPS-3 (Amicon Corp., Danvers, MA, USA).

*Analytical procedure.* The concentrations of OFLX, fenbufen and felbinac in each sample (i.e. plasma, serum, or filtrate) were simultaneously determined by the high-performance liquid chromatographic method of Katagiri et al (1988).

*Pharmacokinetic analysis.* The plasma concentration (C), vs time (t) data of OFLX and fenbufen in an individual rat were fitted to the equation for the bi-exponential decline ($C = Ae^{-\alpha t} + Be^{-\beta t}$), where A, B, α and β are hybrid parameters. Pharmacokinetic parameters of OFLX and fenbufen were determined by using the conventional equations (Clark & Smith 1986). To analyse the plasma concentration-time data of felbinac, a one-compartment model with first-order metabolism was applied as follows: $C = K_m \cdot D \cdot M_m(e^{-k_{(m)}t} - e^{-k_m t})/[M_p \cdot V_d(k_m - k_{(m)})]$, where $k_m$ and $k_{(m)}$ are the rate constants for formation and elimination of felbinac, respectively; $V_d$ is the distribution volume; D is the dose of parent drug; and $M_p$ and $M_m$ are molecular weights of parent drug and metabolite, respectively. Because more than 95% of fenbufen administered to rats is metabolized directly to felbinac (Chiccarelli et al 1980a), the fraction of the dose metabolized was assumed to be 1·0 in the present model. All of the individual plasma concentration-time data were analysed by a non-linear least squares regression program MULTI (Yamaoka et al 1981).

## Results and discussion

*Plasma concentration data for OFLX, fenbufen and felbinac.* Plasma concentration-time curves of OFLX after bolus intravenous administration of OFLX with or without fenbufen are shown in Fig. 1A. The plasma OFLX levels declined bi-exponentially with time in both groups of the rats. Slight, but significant, elevation of plasma level of this drug was observed at

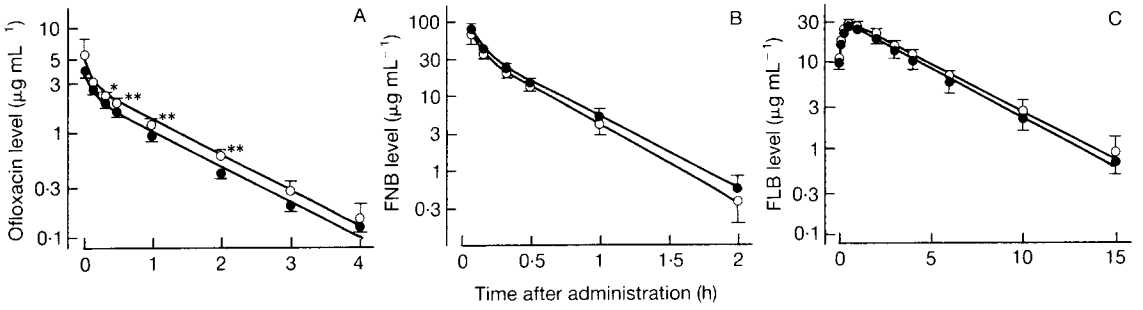


FIG. 1. Plasma concentration-time courses of OFLX with (○) and without (●) fenbufen (A), fenbufen (FBN) with (○) and without (●) OFLX (B) and felbinac (FLB) after fenbufen with (○) and without (●) OFLX(C) by bolus intravenous administration of OFLX (5 mg $kg^{-1}$) and fenbufen (10 mg $kg^{-1}$) in rats. Each point and vertical bar indicate the mean and s.d. of five rats. The solid lines represent the computer-fitted curves for the mean data [Weight(i) = 1/Ci, where C is the drug concentration]. There are significant differences (A) from OFLX alone, $*P<0.05$, $**P<0.01$.

Table 1. Pharmacokinetic parameters for OFLX after bolus intravenous administration of OFLX with and without coadministration of fenbufen in rats.

| Parameter[a] | OFLX alone | OFLX and fenbufen |
|---|---|---|
| A (μg $mL^{-1}$) | 4·50 ± 3·86 | 15·5 ± 21·6 |
| B (μg $mL^{-1}$) | 2·03 ± 0·34 | 2·66 ± 0·36[b] |
| α ($min^{-1}$) | 0·143 ± 0·092 | 0·234 ± 0·117 |
| β ($min^{-1}$) | 0·0126 ± 0·0015 | 0·0126 ± 0·0020 |
| $t_{\frac{1}{2}\beta}$ (min) | 55·5 ± 6·9 | 55·9 ± 9·2 |
| AUC (μg min $mL^{-1}$) | 190·8 ± 14·5 | 260·8 ± 55·1 |
| CL (mL $min^{-1}kg^{-1}$) | 26·3 ± 2·1 | 19·8 ± 3·9[b] |
| $V_c$ (mL $kg^{-1}$)[c] | 924 ± 334 | 649 ± 446 |
| $V_p$ (mL $kg^{-1}$)[d] | 737 ± 124 | 907 ± 210 |

Each value represents the mean ± s.d. of five rats.
[a] Estimated by program MULTI [Weight(i) = 1/Ci, where C is the OFLX concentration].
[b] Significant difference from OFLX alone, $P<0.05$.
[c] Distribution volume of central compartment.
[d] Distribution volume of peripheral compartment.

Table 2. Pharmacokinetic parameters for fenbufen after bolus intravenous administration of fenbufen with and without coadministration of OFLX in rats.

| Parameter[a] | Fenbufen alone | Fenbufen and OFLX |
|---|---|---|
| A (μg $mL^{-1}$) | 180·3 ± 152·8 | 139·7 ± 171·4 |
| B (μg $mL^{-1}$) | 45·8 ± 4·6 | 43·3 ± 3·1 |
| α ($min^{-1}$) | 0·271 ± 0·098 | 0·237 ± 0·084 |
| β ($min^{-1}$) | 0·0385 ± 0·0045 | 0·0402 ± 0·0040 |
| $t_{\frac{1}{2}\beta}$ (min) | 18·2 ± 2·0 | 17·4 ± 1·8 |
| AUC (μg min $mL^{-1}$) | 1786 ± 501 | 1572 ± 335 |
| CL (mL $min^{-1}kg^{-1}$) | 5·99 ± 1·77 | 6·56 ± 1·16 |
| $V_c$ (mL $kg^{-1}$) | 64·5 ± 38·5 | 80·5 ± 37·0 |
| $V_p$ (mL $kg^{-1}$) | 51·8 ± 9·4 | 48·1 ± 8·8 |

Each value represents the mean ± s.d. of five rats.
[a] Estimated by program MULTI [Weight(i) = 1/Ci].

20 to 120 min after its coadministration with fenbufen. Pharmacokinetic parameters for OFLX estimated from the plasma concentration-time data of individual rats are listed in Table 1. The total body clearance (CL) was significantly reduced from about 26 to 20 mL $min^{-1}$ $kg^{-1}$ after the concomitant administration. However, the half-lives at terminal phase ($t_{\frac{1}{2}\beta}$) were about 55 min in both groups. These results indicate that the slight decrease in CL value for OFLX as a result of concomitant administration may not involve the reduction in the elimination rate of this drug from plasma but may result in a slight elevation of the plasma level only at a few time points. Therefore, it was considered that there were no substantive changes in the pharmacokinetics of OFLX on coadministration with fenbufen.

Table 3. Pharmacokinetic parameters for felbinac after bolus intravenous administration of fenbufen with and without coadministration of OFLX in rats.

| Parameter[a] | Fenbufen alone | Fenbufen and OFLX |
|---|---|---|
| $k_m$ ($10^{-3}min^{-1}$)[b] | 81·2 ± 9·8 | 79·7 ± 5·5 |
| $k_{(m)}$ ($10^{-3}min^{-1}$)[c] | 4·70 ± 0·49 | 4·47 ± 0·57 |
| $t_{\frac{1}{2}}$ (min) | 148·6 ± 15·7 | 157·2 ± 23·2 |
| tmax (min) | 37·5 ± 2·8 | 38·5 ± 2·6 |
| Cmax (μg $mL^{-1}$) | 25·5 ± 3·8 | 28·2 ± 2·7 |
| AUC (μg min $mL^{-1}$) | 6516 ± 1216 | 7553 ± 723 |
| CL (mL $min^{-1}kg^{-1}$) | 1·32 ± 0·22 | 1·12 ± 0·10 |
| $V_d$ (mL $kg^{-1}$) | 280 ± 45 | 251 ± 25 |

Each value represents the mean ± s.d. of five rats.
[a] Estimated by program MULTI [Weight(i) = 1/Ci].
[b] Rate constant for formation of felbinac.
[c] Rate constant for elimination of felbinac.

The plasma concentration-time curves of fenbufen and felbinac after bolus intravenous administration of fenbufen with or without OFLX are shown in Fig. 1B and 1C, respectively. The estimated pharmacokinetic parameters for both drugs are listed in Tables 2 and 3. Plasma concentration of fenbufen declined in the bi-exponential fashion, while that of felbinac, which peaked at about 40 min, declined mono-exponentially. The rate constant at terminal phase of plasma felbinac, $k_{(m)}$, after the administration of fenbufen alone (Table 3) was almost identical with the value, 5·10 ± 0·26 ($10^{-3}min^{-1}$), which was estimated for the elimination from plasma after bolus intravenous administration of felbinac to rats (n = 4, unpublished data). This indicates that the present analysis of the plasma concentration-time data of felbinac after bolus intravenous administration of fenbufen according to a one-compartment model with first-order metabolism is appropriate and that the model employed is not "flip-flopped". In both drugs, no change was observed either in plasma concentration-time curves or in pharmacokinetic parameters after the coadministration with OFLX. From these results, it was suggested that the coadministration of OFLX did not affect the distribution, metabolism and elimination of fenbufen and felbinac.

Recently, it was reported that quinolones inhibited GABA binding to its receptor site in rat brain in a concentration dependent manner (Tsuji et al 1988a) and this inhibitory effect was promoted by the presence of fenbufen in-vitro (Tsuji et al 1988b). In addition, it was reported that OFLX levels in the CSF and brain changed with serum level (Sato et al 1988). Therefore, a possibility of marked elevation of plasma OFLX levels by coadministered fenbufen would enhance the inhibitory effect on GABA binding to its receptor. In the present pharmacokinetic

Table 4. Effects of concomitant administration of OFLX and fenbufen on binding of OFLX, fenbufen and felbinac to rat serum protein in-vivo.

| Drug | t[a] (min) | Treatment | $C_t$[b] ($\mu g\ mL^{-1}$) | $C_f$[c] ($\mu g\ mL^{-1}$) | Bound fraction (%) |
|---|---|---|---|---|---|
| OFLX | 3 | OFLX alone | 4·65±0·39 | 3·16±0·25 | 32·1±1·8 |
| | | OFLX+fenbufen | 4·76±0·58 | 3·47±0·46 | 27·2±0·9[d] |
| | 45 | OFLX alone | 1·22±0·22 | 0·88±0·13 | 27·7±2·2 |
| | | OFLX+fenbufen | 1·57±0·12 | 1·14±0·09 | 27·3±1·7 |
| Fenbufen | 3 | Fenbufen alone | 74·3±2·4 | 1·18±0·16 | 98·4±0·2 |
| | | Fenbufen+OFLX | 72·1±9·2 | 1·13±0·08 | 98·4±0·2 |
| | 45 | Fenbufen alone | 7·80±1·11 | 0·14±0·03 | 98·2±0·3 |
| | | Fenbufen+OFLX | 7·92±0·98 | 0·13±0·01 | 98·3±0·2 |
| Felbinac | 3 | Fenbufen alone | 8·06±1·53 | 0·09±0·03 | 98·9±0·3 |
| | | Fenbufen+OFLX | 8·36±1·42 | 0·10±0·02 | 98·8±0·2 |
| | 45 | Fenbufen alone | 29·1±1·9 | 0·34±0·07 | 98·8±0·3 |
| | | Fenbufen+OFLX | 28·5±2·8 | 0·32±0·03 | 98·9±0·1 |

Each value represents the mean±s.d. of five experiments by ultrafiltration method.
[a] Time after drug administration.
[b] Total drug concentration in serum.
[c] Unbound drug concentration in serum.
[d] Significant difference from OFLX alone, $P<0·01$.

study, only slight or no change in plasma levels of OFLX and/or fenbufen was observed in the coadministered rats. Consequently, any elevation of OFLX and fenbufen levels in the CSF and brain and the resultant enhancement of GABA binding inhibition may be unlikely to occur after their concomitant administration.

*Binding of OFLX, fenbufen and felbinac to serum protein.* The bound fraction of both fenbufen and felbinac to the human serum protein is known to be more than 99% (Chiccarelli et al 1980b). Therefore, it is likely that either may reduce the bound fraction of other coadministered drugs. We examined the effects of the concomitant administration of OFLX and fenbufen on the binding of OFLX, fenbufen and felbinac to rat serum protein. In the present study, blood serum was used in place of the plasma because it was reported that non-esterified fatty acid, which may influence the binding of various drugs to plasma protein (Spector et al 1973), was increased in the heparinized plasma (Giacomini et al 1980).

The results of serum protein binding experiments are summarized in Table 4. The bound fraction of OFLX at 3 min after the drug administration decreased from about 32 to 27% by the coadministration with fenbufen. At this relatively early time its total concentration was higher than 70 $\mu g\ mL^{-1}$. There was no difference in the extent of OFLX binding at 45 min between two groups. On the other hand, the bound fractions of fenbufen and felbinac were about 98 to 99% at both times and were not altered by coadministered OFLX. These aspects suggest that only OFLX binding may be slightly reduced by the coexistence of a relatively large amount (i.e. at higher concentration) of fenbufen. However, since the unbound concentration of OFLX at 3 min was not significantly elevated by the coadministration with fenbufen, it was considered that there was little effect of the slight change in the OFLX binding to serum protein on its pharmacokinetics. In-vitro serum protein binding experiments yielded similar results to these in-vivo findings (unpublished data).

In conclusion, any pharmacokinetic interaction may be unlikely to occur after the concomitant administration of OFLX and fenbufen.

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