W-2 [15:00～15:40]

Drug Interactions on NSAIDs
- Synergism of New Quinolone-Induced Convulsions -

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INTRODUCTION

New quinolone antibiotics (NQs) are prescribed generally for treatment of various infections, but neurotoxicity is known to be their major adverse reactions and some serious cases of convulsions have been reported. It is also reported that non-steroidal anti-inflammatory drugs (NSAIDs), which are commonly used in rheumatoid patients, synergize this convulsive potency. In Japan, these two types of drugs are concomitantly used under precautions and some pairs are contraindicated.

We have been performing experiments to elucidate the mechanisms of the convulsive effects of NQs and the influence of NSAIDs, and to evaluate it quantitatively.

1. Quantitative evaluation of the influence of NSAIDs on convulsive potent of NQs

First, enoxacin was administrated to mice intravenously at different dose rates. At the onset of convulsion, brain concentration of enoxacin was same, although plasma concentrations varied. This revealed that the concentration in the brain, not in plasma, would be an index for convulsive potency. Next, ciplofloxacin, enoxacin, norfloxacin, and ofloxacin were coadministrated intravenously with felbinac to mice at various dose rates. As shown in Fig. 1, brain concentration of NQs at the onset of convulsions were greatly lower with felbinac coadministration compared to NQs alone. On the other hand, NSAIDs did not affect the systematic pharmacokinetics of NQs (Fig. 2). Furthermore, when NQs were administrated to rats by

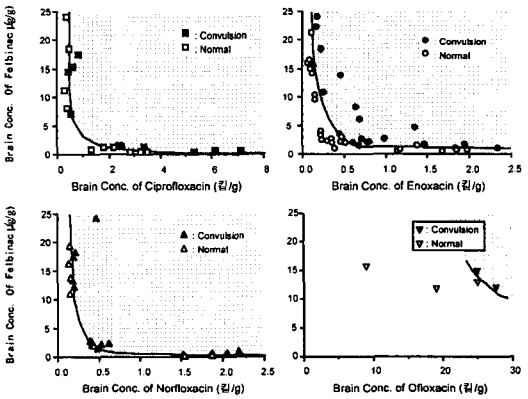

Fig. 1. Brain-Concentration Isobologram for the Convulsive Interactions between New Quinolones and Felbinac after Intravenous Injection in Mice.
Solid lines are threshold level for the occurrence of clonic convulsion.
Shadow areas present the concentration range of both new quinolones and felbinac for the convulsion group.

intracerebral infusion, the threshold dose for convulsions were lower with felbinac coadministration compared to NQs alone. From these findings, it was suggested that convulsions induced by NQs occurs via the central nervous system (CNS), and that its potency rises by pharmacodynamic interactions with NSAIDs.

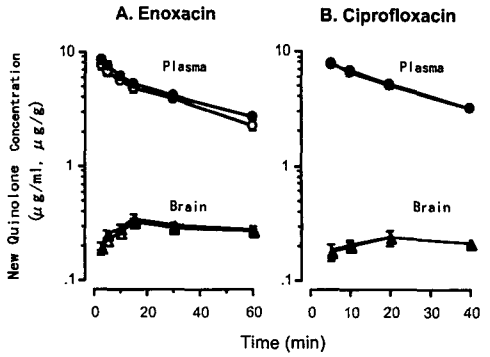

Fig. 2 . Effect of Felbinac on Plasma and Brain Concentration of New Quinolones after Concomitant Intravenous Administration in Mice.
Panel A: enoxacin (25mg/kg) and felbinac (15mg/kg). and
Panel B: ciprofloxacin (20mg/kg) and felbinac (50mg/kg).
Open symbols: new quinolone alone, and
Closed symbols: new quinolone with felbinac. (n=4, mean ±S.D.)

2. Mechanisms of synergistic effects of NSAIDs on NQs induced convulsions

We investigated the inhibitory effects of NQs on various neurotransmitters [ACh, serotonin (5-HT), GABA, glycine (Gly), NMDA, kainic acid (KA), and quisqualic acid (QA)]- induced currents and the effect of felbinac in *Xenopus* oocytes injected with mouse-brain mRNA (Fig. 3). Inhibitory effects of NQs on GABA were observed. In addition, NSAIDs itself did not modulate the GABA response although it synergized the inhibitory effects of NQs to the GABA-induced current. IC_{50} of NQs for the GABA response correlated well with brain concentrations at the onset of convulsion in mice after intravenous administration of NQs. These results suggested that the convulsive effect of NQs *in vivo* may be predicted from the blockade of GABA-ersic neurotransmission *in vitro*. The inhibitory effects on GABA response were examined in *Xenopus* oocytes injected with brain mRNA of rats, rabbits, dogs, and monkeys as well as mice, and small differences between species were observed.

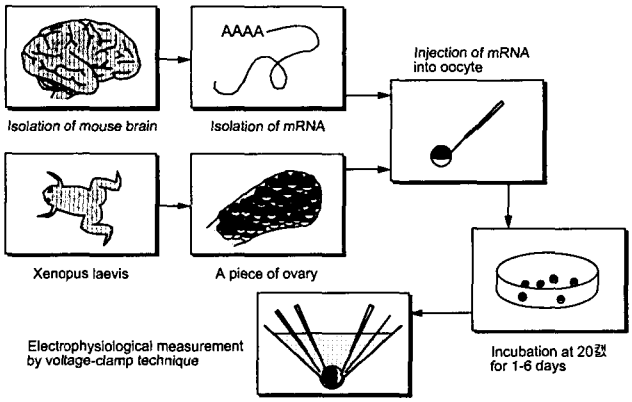

Fig. 3. Schematic Diagram Indicating the Principal Steps Involved in the Extraction, Injection of Mouse Brain mRNA into *Xenopus* Oocytes, Incubation and Electrophysiological Measurement.

3. Comparison between various NSAIDs on synergistic effects on NQs induced convulsion

The GABA response *in vitro* was investigated on various NSAIDs and NQs. As a result, it was revealed that a piperazinyl or 3-aminopyrrolidinyl substituent at the 7 position of the parent nuclei in NQs molecules acts mostly against GABA response, and the phenylacetic or indolacetic acid moiety of NSAIDs synergizes this effect (Fig. 4 and 5).

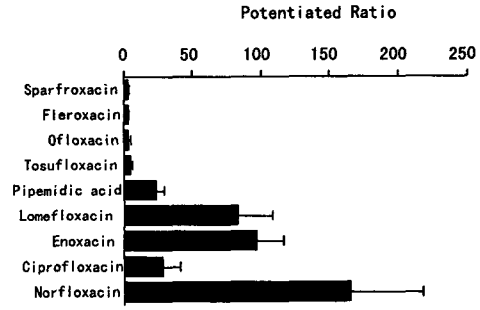

Fig. 4. Potentiated Ratio by Felbinac for Inhibition of GABA Response among Quinolones in *Xenopus* Oocytes Injected with Mouse-brain mRNA

Potential ratio was calculated by dividing IC_{50} in the absence of felbinac by that in the presence of felbinac.
(n = 3, mean±S.D.)

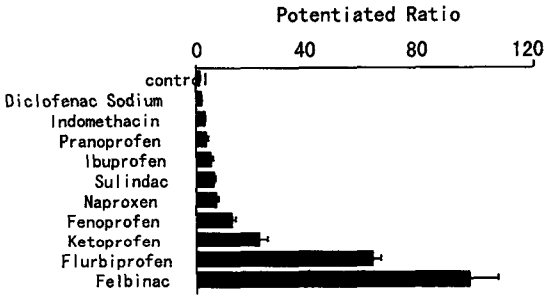

Fig. 5. Potentiated Ratio of Enoxacin for Inhibition of GABA(10 μM)-induced Current Response for NSAIDs in *Xenopus* Oocytes injected with Mouse-brain mRNA (n = 3, mean±S.D.)

Potential ratio was calculated by dividing IC_{50} in the absence of enoxacin by that in the presence of enoxacin.

CONCLUSIONS

The above data shows that the synergism of NSAIDs on the convulsive potency of NQs could be quantitatively predicted by *in vitro* experiments. Thus, this affords us information for rheumatoid patients on the optimal use of NSAIDs.

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REFRENCES

1) Kita H., *et al.* In vivo and in vitro toxicodynamic analyses of new quinolone-and nonsteroidal anti-inflammatory drug-induced effects on the central nervous system. *Antimicrob. Agents Chemother.* 43:1091-7, 1999.
2) Kawakami J., *et al.* Inhibitory effect of new quinolones on GABA(A) receptor-mediated

response and its potentiation with felbinac in Xenopus oocytes injected with mouse-brain mRNA: correlation with convulsive potency *in vivo*. *Toxicol. Appl. Pharmacol.* 145:246-54, 1997.

3) Kawakami J., *et al.* Effect of acute renal failure on neurotoxicity of enoxacin in rats. *Biol. Pharm. Bull.* 20:931-4, 1997.
4) Ohtani H., *et al.* Lack of potentiation with felbinac patch on the convulsive toxicity of enoxacin in rats. *Biol. Pharm. Bull.* 19:995-7, 1996.
5) Kawakami J., *et al.* Prediction of brain delivery of ofloxacin, a new quinolone, in the human from animal data. *J. Pharmacokin. Biopharm.* 22:207-27, 1994.
6) Kawakami J., *et al.* Inhibition of GABAA receptor-mediated current responses by enoxacin (new quinolone) and felbinac (non-steroidal anti-inflammatory drug) in *Xenopus* oocytes injected with mouse-brain messenger RNA. *Biol. Pharm. Bull.* 16:726-8, 1993.