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Celecoxib does not induce convulsions nor does it affect $GABA_A$ receptor binding activity in the presence of new quinolones in mice

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Abstract

We sought to determine whether celecoxib would induce convulsions when coadministered with new quinolone antimicrobial agents in mice. The oral administration of celecoxib (500 mg/kg) alone or in combination with enoxacin (500 mg/kg), lomefloxacin (1000 mg/kg), ciprofloxacin (1000 mg/kg), or levofloxacin (1000 mg/kg) induced no convulsions in mice. In contrast, some nonsteroidal anti-inflammatory drugs (NSAIDs), fenbufen (200 mg/kg), indomethacin (500 mg/kg), and naproxen (500 mg/kg) induced convulsions in combination with the majority of the new quinolones tested. γ-Aminobutyric acid $(GABA)_A$ receptor blockade-mediated neuronal excitation is assumed to be involved in these toxic convulsions. Enoxacin (100 μM) and lomefloxacin (100 μM) only slightly reduced [^{3}H]muscimol binding to $GABA_A$ receptors in mouse whole brain membrane. However, these reductions were markedly enhanced by the addition of fenbufen (100 μM), indomethacin (100 μM), or naproxen (100 μM). Conversely, celecoxib (100 μM) had no apparent effect on [^{3}H]muscimol binding when applied alone or in combination with enoxacin or lomefloxacin. These results suggest that celecoxib may be a more desirable anti-inflammatory agent with respect to drug interactions with new quinolones compared with some conventional NSAIDs.

Keywords: New quinolone; Nonsteroidal anti-inflammatory drug; Drug interaction; Convulsion; $GABA_A$ receptor

1. Introduction

A series of fluorinated nalidixic acid derivatives, termed new quinolones, are among the most frequently used antimicrobial agents because of their wide spectra of antibacterial activities and excellent tissue permeability (Andriole, 1993). At present, they are prescribed for many conditions, including respiratory and urinary tract infections. They are also occasionally used together with anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs (NSAIDs; Brouwers, 1992; Janknegt, 1990). However, new quinolones have been shown to possess excitatory side effects on central nervous system, such as headache, dizziness, and tremor (Simpson and Brodie, 1985; Anastasio et al., 1988; Slavich et al., 1989; Kushner et al., 2001). Although the incidence of their side effects on central nervous system is quite low, serious convulsions have been reported in patients taking certain combinations of new quinolones with NSAIDs, e.g., enoxacin and fenbufen, and ciprofloxacin and ketoprofen (Pharmaceuticals and Chemicals Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare of Japan, 1986, 1989). In practice, these combinations of new quinolones with NSAIDs are contraindicated in Japan. The mechanisms of action involved in the toxic convulsions are not clearly understood; however, the combined application of new quinolones and NSAIDs has been shown to attenuate ligand-binding affinity at the γ-aminobutyric acid $(GABA)_A$ receptor (Akahane et al., 1994a, 1989; Motomura et al., 1991), which mediates inhibitory neurotransmission in the

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mammalian central nervous system. In addition, some quinolone derivatives are demonstrated to act as antagonists at both central and peripheral $GABA_A$ receptors (Blandizzi et al., 1991). Furthermore, GABA-induced current response in Xenopus oocytes injected with mouse brain messenger RNA was demonstrated to be abolished by a combined application of enoxacin with 4-biphenylacetic acid, an active metabolite of fenbufen (Kawakami et al., 1997). These data suggest that blockade of the $GABA_A$ receptor by these compounds results in a functional reduction in GABA-ergic neuronal transmission. Therefore, the inhibition of GABA-ergic signals, which may lead to neuronal excitation, is assumed to be one of the mechanisms involved in the generation of new quinolone/NSAID-induced convulsions.

Celecoxib is one of the novel class of anti-inflammatory agents, the coxibs (Penning et al., 1997), that selectively inhibit the inducible enzyme, cyclooxygenase-2, while sparing cytoprotective prostanoids produced via the action of the cyclooxygenase-1 enzyme isoform. As a consequence of its cyclooxygenase-1 sparing properties, celecoxib has been shown to be associated with a lower incidence of gastrointestinal events than conventional NSAIDs (Silverstein et al., 2000). Celecoxib is classified as a diaryl-substituted pyrazole (diarylheterocyclic) and thus is structurally distinct from those NSAIDs reported to cause convulsions in combination with new quinolones (Fig. 1).

In the present study, we evaluated whether celecoxib would provoke convulsions when administered together with new quinolones in mice compared with conventional NSAIDs. In addition, the influence of the simultaneous application of celecoxib and new quinolones on $GABA_A$ receptor binding activity was also examined using mouse whole brain membranes.

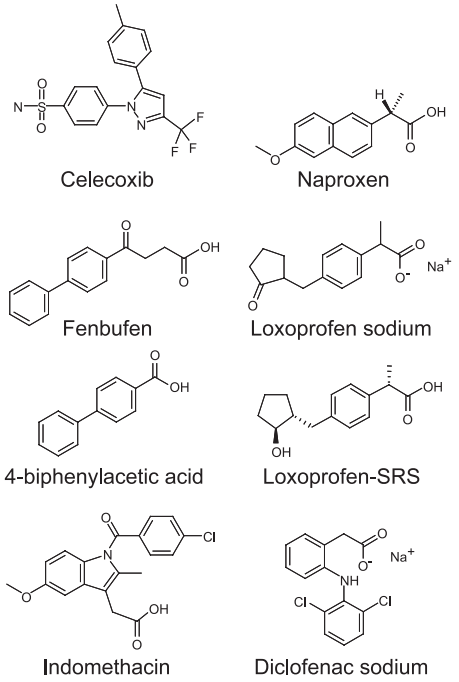

Fig. 1. Chemical structures of celecoxib and conventional NSAIDs.

2. Materials and methods

2.1. Animals

Five-week-old male ddy mice were obtained from Japan SLC (Shizuoka, Japan). Animals were maintained in cages with 12-h light/dark intervals with water and food available ad libitum. All animal experiments were performed in compliance with the regulations of the institutional Animal Ethics Committee of Yamanouchi Pharmaceutical.

2.2. Drugs and reagents

Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide) was obtained from Pfizer (New York, NY, USA). Loxoprofen sodium (monosodium 2-[4-(2-oxocyclopentylmethyl)phenyl]propanoate dihydrate) was obtained from Shiono Chemical (Tokyo, Japan). Loxoprofen-SRS (an active metabolite of loxoprofen, (2S)-2-{4-[(1R,2S)-2-hydroxycyclopentylmethyl]phenyl}-propanoic acid) was synthesized by Yamanouchi Pharmaceutical (Tokyo, Japan). Enoxacin, lomefloxacin hydrochloride, fenbufen, 4-biphenylacetic acid, indomethacin, naproxen, diclofenac sodium, and GABA were purchased from Sigma-Aldrich (St. Louis, MO, USA). [^{3}H]Muscimol was purchased from Perkin-Elmer Life Sciences (Boston, MA, USA). For in vivo experiments, new quinolone antimicrobial agents were purchased as the following commercial drugs: FLUMARK® (enoxacin, Dainippon Pharmaceutical, Osaka, Japan), Lomebact® (lomefloxacin hydrochloride, SHIONOGI, Osaka, Japan), Cravit® (levofloxacin, Daiichi Pharmaceutical, Tokyo, Japan), and Ciproxacin® (ciprofloxacin hydrochloride, Bayer Yakuhin, Osaka, Japan). Other reagents used were obtained from standard commercial suppliers. For in vitro [^{3}H]muscimol binding studies, test drugs were dissolved in dimethylsulfoxide, except that enoxacin and lomefloxacin hydrochloride were first dissolved with 40% volume of 0.1N NaOH and then added with 60% volume of dimethylsulfoxide. For in vivo experiments, test drugs were dissolved or suspended in a solution of 0.5% methylcellulose containing 0.025% Tween-20 to give 0.1 ml/10 g animal body weight.

2.3. Convulsion-inducing activity in mice

Mice were fasted for approximately 18 h prior to experiments. New quinolones, NSAIDs, celecoxib, or vehicle was administered orally, and mice were placed in observational cages. After drug administration, observations were continued for 8 h to determine the occurrence of clonic and tonic convulsions and death. Total numbers of deaths in the 24 h