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Preliminary report

Differential anti-inflammatory and analgesic effects by enantiomers of zaltoprofen in rodents

Ig Jun Cho [a], Chang Woo Lee [a], Myeong Youl Lee [a], Moo Rim Kang [a], Jieun Yun [a], Soo Jin Oh [a], Sang-Bae Han [b], Kiho Lee [c], Song-Kyu Park [c], Hwan Mook Kim [d], Sang-Hun Jung [e], Jong Soon Kang [a,*]

[a] Bioevaluation Center, Korea Research Institute of Bioscience and Biotechnology, Ochang, Cheongwon, Chungbuk 363-883, Republic of Korea
[b] Collage of Pharmacy, Chungbuk National University, Heungdeok, Cheongju, Chungbuk 361-763, Republic of Korea
[c] College of Pharmacy, Korea University, Jochiwon, Yeongi, Chungnam 339-700, Republic of Korea
[d] College of Pharmacy, Gachon University of Medicine and Science, Yeonsu, Incheon 406-799, Republic of Korea
[e] College of Pharmacy, Chungnam National University, Yuseong, Daejon 305-764, Republic of Korea

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ABSTRACT

In the present study, we investigated the effect of zaltoprofen enantiomers on inflammation and pain and compared their effect with racemic zaltoprofen. S(+)-zaltoprofen potently inhibited the inflammatory response in carrageenan-induced paw edema model, whereas R(−)-zaltoprofen did not. Moreover, the anti-inflammatory effect of S(+)-zaltoprofen was stronger than that of racemic zaltoprofen, suggesting that S(+)-zaltoprofen is an active component of racemic zaltoprofen in terms of anti-inflammatory activity. In contrast, the results of acetic acid-induced writhing model demonstrated that no significant analgesic effect was observed by racemic zaltoprofen and zaltoprofen enantiomers at doses used in carrageenan-induced paw edema model. However, racemic zaltoprofen and zaltoprofen enantiomers all exerted an analgesic effect at higher doses, which is inconsistent with the result of carrageenan-induced paw edema model. Gastric ulcers induced by racemic zaltoprofen and zaltoprofen enantiomers were minimal. Taken together, these results suggest that S(+)-zaltoprofen is a potent and active anti-inflammatory component of racemic zaltoprofen, but both S(+)-zaltoprofen and R(−)-zaltoprofen might seem to contribute to the analgesic effect of racemic zaltoprofen.

1. Introduction

Zaltoprofen, (±)-2-(10,11-dihydro-10-oxodibenzo[*b,f*]thiepin-2-yl) propionic acid (Fig. 1), is a derivative of 2-arylpropionic acids and belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs). It has been reported that the anti-inflammatory and analgesic effects of zaltoprofen are mediated by inhibiting prostaglandin synthesis and blocking bradykinin B_2 receptor-mediated pathways [1–4]. Zaltoprofen has been used in the treatment of rheumatoid arthritis and osteoarthritis as well as for inflammation/pain relief after surgery, injury and tooth extraction [5]. In addition, recent double-blind study to evaluate the antipyretic and analgesic effects of a single administration of zaltoprofen in patients with acute upper respiratory tract infection provided scientific evidence on the possible application of zaltoprofen in the therapy of this disease [6].

The 2-arylpropionic acids are known to contain at least one chiral center and exhibit optical activity. It is well-known that enantiomers have very similar physicochemical properties, but they frequently show quite different pharmacological and pharmaceutical properties [7]. Enantiomers are also considered to differ in terms of their absorption, distribution, metabolism and excretion [8]. Most of chiral NSAIDs have been marketed as racemic mixtures except for naproxen [9] and recently, dexibuprofen (S(+)-isomer of ibuprofen) was marketed for the treatment of arthritis, pain, inflammation and fever [10,11]. Treatment with dexibuprofen was shown to exert improved analgesic and anti-inflammatory effects and reduced gastric damage compared to racemic ibuprofen in rodents [12] and humans [10]. At present, zaltoprofen is commercially available as a racemic mixture. Moreover, enantiospecific pharmacological activity of zaltoprofen has not been reported until now although analytical methods and pharmacokinetic properties of zaltoprofen enantiomers were studied previously [13]. Here, we examined the effect of zaltoprofen enantiomers on inflammation and pain in rodents.

2. Materials and methods

2.1. Chemicals and animals.

All reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA) unless otherwise stated. Racemic zaltoprofen, S(+)-zaltoprofen and R(−)-zaltoprofen were synthesized and supplied by Prof. Sang-Hun Jung at Chungnam National University. The estimated content of S(+)-zaltoprofen and R(−)-zaltoprofen within racemic zaltoprofen is

* Corresponding author. Tel.: +82 43 240 6524.
E-mail address: kanjon@kribb.re.kr (J.S. Kang).

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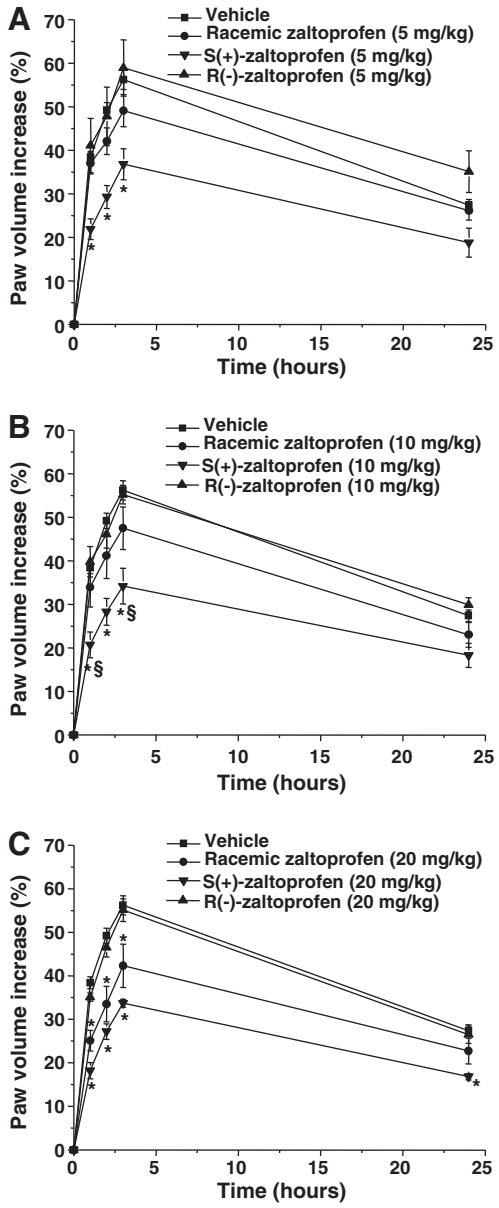

Fig. 1. The anti-inflammatory effect of racemic zaltoprofen and zaltoprofen enantiomers in carrageenan-induced paw edema model. SD rats were pretreated with vehicle (VH) or (A) 5 mg/kg, (B) 10 mg/kg or (C) 20 mg/kg of racemic zaltoprofen, S(+)-zaltoprofen or R(−)-zaltoprofen. After 30 min, 0.1% carrageenan was subcutaneously injected into the left hind paw and paw volume was measured using plethysmometer. Each column shows the mean ± S.E.M. of five determinations. $^{*}p < 0.05$ vs. vehicle, $^{\S}p < 0.05$ vs. racemic zaltoprofen.

50:50. Racemic zaltoprofen, S(+)-zaltoprofen and R(−)-zaltoprofen were dissolved in distilled water containing 10% ethanol and 5% Tween 80 for in vivo experiments. Specific pathogen-free SD rats (male, 6 weeks old) and ICR mice (male, 5 weeks old) were purchased from Koatech (Pyungtaek, Gyeonggi, Republic of Korea) and allowed to acclimate to the local environment for at least 1 week before use. All animal experiments were approved by the Institutional Animal Care and Use Committee at Korea Research Institute of Bioscience and Biotechnology.

2.2. Carrageenan-induced paw edema.

Paw edema was induced by subcutaneous injection of 0.1 ml of 0.1% carrageenan into the left hind paw of 6-week-old male SD rats. The volume of hind paw was measured by water displacement method using a plethysmometer (Ugo Basile, Comerio, VA, Italy). Racemic zaltoprofen, S(+)-zaltoprofen or R(−)-zaltoprofen were administered 30 min before carrageenan treatment. Paw volumes were measured before the start of experiment and 1, 2, 3, and 24 h after carrageenan treatment.

2.3. Acetic acid-induced writhing test.

Racemic zaltoprofen, S(+)-zaltoprofen or R(−)-zaltoprofen were administered orally to overnight-fasted female ICR mice (6 weeks old) 30 min before intraperitoneal injection of 10 ml/kg of 1% acetic acid. The number of writhing events was recorded for 30 min as described previously [14].

2.4. Gastric ulcer model.

SD rats were treated with vehicle, racemic zaltoprofen, S(+)-zaltoprofen, R(−)-zaltoprofen (100, 200 or 400 mg/kg) or acetylsalicylic acid (200 mg/kg) by oral administration. The animals were sacrificed 3 h after chemical treatment. The stomachs were removed, opened along the greater curvature, rinsed with saline (0.9%) and photographed using digital camera. The gastric lesion area was analyzed using Image-Pro Plus 4.5.1 (Media Cybernetics, Inc., Rockville, MD, USA) and expressed as % of total area.

2.5. Statistical analysis.

GraphPad Prism (GraphPad Software, Inc., San Diego, CA, USA) was used for statistical analysis. A paired *t* test was used to compare two groups, and one-way ANOVA and Dunnett's *t*-test were used for multiple comparisons. The criterion for statistical significance was set at $p < 0.05$.

3. Results

3.1. Effect of racemic zaltoprofen and zaltoprofen enantiomers on carrageenan-induced paw edema in rats.

We evaluated the anti-inflammatory effect of racemic zaltoprofen and zaltoprofen enantiomers using carrageenan-induced paw edema model. As expected, racemic zaltoprofen significantly suppressed carrageenan-induced paw edema in rats (Fig. 1). S(+)-zaltoprofen also inhibited carrageenan-induced paw edema in a dose-dependent manner and the magnitude of anti-inflammatory effect by S(+)-zaltoprofen was greater than that of racemic zaltoprofen (Fig. 1). The inhibition rate of paw edema was 12.7%, 15.6% and 24.8% by 5 mg/kg, 10 mg/kg and 20 mg/kg of racemic zaltoprofen and 34.5%, 39.1% and 40.0% by 5 mg/kg, 10 mg/kg and 20 mg/kg of S(+)-zaltoprofen, respectively, at 3 h after carrageenan treatment. However, R(−)-zaltoprofen had no significant effect on carrageenan-induced paw edema at all doses tested.

3.2. Effect of racemic zaltoprofen and zaltoprofen enantiomers on acetic acid-induced writhing response in mice.

In this study, analgesic effects of racemic zaltoprofen and zaltoprofen enantiomers were evaluated by acetic acid-induced writhing test. As shown in Fig. 2A, racemic zaltoprofen and zaltoprofen enantiomers had no statistically significant effects on writhing response induced by acetic acid at doses used in carrageenan-induced paw edema model. However, there was a tendency of dose-related reduction of acetic acid-induced writhing response after treatment with racemic zaltoprofen and zaltoprofen enantiomers. Therefore, we evaluated the effect of higher doses of racemic zaltoprofen and zaltoprofen enantiomers on acetic acid-induced writhing response. Fig. 2B shows that higher doses of racemic zaltoprofen and zaltoprofen enantiomers significantly inhibited acetic acid-induced writhing response, although