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Comparative study of anti-inflammatory, ulcerogenic and cytotoxic activities of racemate and S-ibuprofen

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ABSTRACT

Ibuprofen is widely commercialized in racemic form. Although metabolic chiral inversion occurs through the conversion of *R*(-)-ibuprofen to *S*(+)-ibuprofen and the latter enantiomer is considered the active form, clinical trials involving the administration of a racemate to *S*-enantiomer dosage ratio of 1:0.5 have demonstrated that *S*(+)-ibuprofen is as efficacious as the racemic formulation. Moreover, the *R*(-)-enantiomer has been implicated in adverse gastrointestinal effects found with the racemic form, but the mechanisms involved in this process are not yet fully understood. The aim of the present study was to evaluate the anti-inflammatory activity of a racemate to *S*(+)-ibuprofen dosage ratio of 1:0.5 using the carrageenan air pouch model of inflammation and determine both ulcerogenic activity and the chiral conversion rate in rats. An *in vitro* study of the cytotoxicity of racemate and *S*(+)-ibuprofen in gastric cells was also performed. Although the plasma level of *S*(+)-ibuprofen was raised after racemate administration, no significant difference was found in anti-inflammatory activity, as assessed by exudate formation, PGE_2 production and leukocyte migration to the air pouches. Fewer gastric lesions were found after *S*(+)-ibuprofen administration, despite the low gastric PGE_2 content. In the *in vitro* study, the racemic compound proved more cytotoxic than *S*(+)-ibuprofen. The present findings suggest that the *S*-enantiomer of ibuprofen could be considered a therapeutic alternative to minimize gastrointestinal side effects, since the chiral inversion of *R*(-)-ibuprofen to *S*(+)-ibuprofen did not result in an improved anti-inflammatory response.

Keywords: Ibuprofen. Enantiomers. Air pouch model. PGE_2. Gastric ulcers.

INTRODUCTION

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that is widely used in its racemic form, i.e., similar quantities of *R*(-)-ibuprofen and *S*(+)-ibuprofen. Ibuprofen was the first non-aspirin NSAID to be commercialized as an over-the-counter drug and its main action mechanism is non-selective COX inhibition. Although some studies report that *R*- enantiomers of the "profen" class of drugs are involved in gastrointestinal toxicity, racemates are still extensively used worldwide (Hardikar, 2008). Studies have suggested that *R*-enantiomers are unable to inhibit COX activity, but could have adverse gastrointestinal effects by inducing changes in neutrophil function, glutathione homeostasis and intestinal permeability (Wechter et al., 1998; Alarcon de La Lastra et al., 2002).

The *S*(+)-ibuprofen isomer has been found to be more potent than the racemic mixture as an analgesic and anti-inflammatory drug in experimental models (Bonabello et al., 2003). Moreover, clinical trials involving a racemate to *S*-enantiomer dosage ratio of 1:0.5 report that *S*(+)-ibuprofen is at least as efficacious as the racemic form (Mayrhofer, 2001; Phleps, 2001; Kollenz et al., 2009). Pharmacokinetics and metabolism are also stereoselective for this drug, i.e., *R*(-)-ibuprofen undergoes metabolic chiral inversion to its antipode through the formation of the acyl CoA thioester of ibuprofen, but not vice versa (Hao et al., 2005). Kinetic analyses of the chiral inversion of ibuprofen have shown that the rate and extent of chiral inversion *in vivo* varies from species to species (Lee et al., 1985; Tan et al., 2002; Doki et al., 2003; Bonabello, 2003), with reports of a 50 to 60% inversion rate of *R*(-)-ibuprofen to *S*(+)- ibuprofen in humans (Lee et al., 1985; Neal, 1998). As chiral inversion occurs *in vivo*, the administration of a racemate to *S*(+)-ibuprofen dosage ratio of 1:0.5 should result in a better anti-inflammatory performance of the racemate despite the greater risk of gastrotoxicity.

The aims of the present investigation were to perform a comparative study of the anti-inflammatory activity of racemate and *S*(+)-ibuprofen at a dosage ratio 1:0.5 using a well-established inflammation model in rats and evaluate gastric ulcerogenic activity in the same animals. The relative bioavailability of *R*(-)-ibuprofen and *S*(+)-ibuprofen following the oral administration of *S*(+)-ibuprofen or racemate was also evaluated and an *in vitro* cytotoxicity assay was performed using gastric cells.

MATERIALS AND METHODS

Animals

Male Wistar rats (320 to 390 g) free of specific pathogens were obtained from the Multidisciplinary Center

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for Biological Investigation of the State University of Campinas (Campinas, SP, Brazil). The experiments were performed in accordance with the principles outlined by the Brazilian College for Animal Experimentation and this study received approval from the Ethics Committee of São Francisco University (Bragança Paulista, SP, Brazil) under protocol number 006.009.11. The rats were maintained in a room with a 12-hour light-dark cycle and controlled temperature and humidity. Twelve hours prior to an experiment, the animals were deprived of food (standard chow), but not water. All studies were carried out using five rats per group.

Carrageenan air-pouch model

Air pouches were induced as described elsewhere (Martin et al., 1994). Briefly, air cavities were produced by the subcutaneous injection of 20 ml of sterile air into the dorsal skin of the rats, with an additional injection of 10 ml of sterile air at the same site after three days to maintain the space open. On the sixth day, 2 ml of a 1% solution of carrageenan dissolved in PBS was injected directly into the pouch to produce a local inflammatory response. In one group of rats, sterile PBS (2 ml) was injected into the air pouches instead of carrageenan (negative control group). All injections were performed after the rats had been lightly anaesthetized with ketamine/xylazine (1:1 v/v). Six hours after the carrageenan injection, the animals were anaesthetized again and the pouches were carefully opened with a small incision. The exudate was collected and transferred to a sterile tube. The volume of exudate was measured gravimetrically and the exudate was stored for subsequent PGE_2 quantification. Moreover, an aliquot of exudate was used for the quantification of leukocytes in a CellM counter (model 550; Brazil).

Ibuprofen administration

One hour prior to the injection of carrageenan into the air pouches, one group was pretreated orally with vehicle (1% carboxymethylcellulose) and considered the positive control for the air-pouch model. Other groups received 3 and 10 $mg.kg^{-1}$ of racemic ibuprofen or 1.5 and 5 mg/kg of *S*(+)-ibuprofen (both Sigma, St Louis, MO, USA). For the bioavailability studies, rats received racemic ibuprofen or *S*(+)-ibuprofen at 300 mg/kg or 150 mg/kg of body weight, respectively, and were killed after 0.5 or 1 h. Blood was drawn from the inferior vena cava using EDTA as anticoagulant and centrifuged for the separation of the plasma.

Evaluation of gastric ulcerogenic activity and prostaglandin E2 content

After blood and exudate collection under anesthesia, animals were killed and the stomachs were removed and opened along the greater curvature. The ulcerative lesion index of each animal was calculated by adding the following values (Gamberini et al., 1991): loss of normal morphology (1 point), discoloration of mucosa (1 point), hemorrhage (1 point), petechial points (1 to 3 points), ulcers up to 1 mm (n × 2 points) and ulcers > 1 mm (n × 3 points). The stomachs were then weighed, put in a tube with phosphate buffer (pH 7.0), homogenized and centrifuged for 10 min at 4 °C. The supernatant of each sample was used for the determination of PGE_2 using an enzyme immunoassay kit (GE Healthcare, UK).

Quantification of R(-)- and S(+)-ibuprofen in rat plasma

Following the addition of a hydrochloric acid solution (50 µl, 1 M), plasma (200 µl) was extracted with hexane-ether (80:20, v/v 1.0 ml). The extraction process was repeated and the extracts were combined. The organic layer was transferred, dried under nitrogen and suspended in hexane (20 µl). An aliquot (1 µl) was taken for gas chromatography/flame ionizer detection in a chromatograph equipped with a chiral column (RT - BetaDex - SM, 30 m × 0.32 mm × 0.25 µm, Restek). H_2 was used as the carrier gas with a pressure of 75 kPa. The injector and detector temperature was 350 ºC. Initial and final column temperatures were 180 and 200 ºC, respectively, with the temperature was increased at a rate of 3 $ºC.min^{-1}$. Retention times for *S*(+)-ibuprofen and *R*(-)-ibuprofen were 5.3 and 5.8 min, respectively. Linear calibration curves over the range of 0.5 to 150 µg/mL with correlation coefficients of 0.989 were produced for each set of samples. S-ibuprofen standards were prepared with concentrations of 10, 20, 30, 40, 80 and 100 µg/ml in rat plasma. Replicate samples (n = 3) were assayed at 20, 40 and 80 µg/ml for validation of the accuracy and precision of the assay.

In vitro *cytotoxicity assays: MTT and cell proliferation*

Cell toxicity was estimated using the tetrazolium salt reduction test (MTT assay) on gastric PG 100 cells (Rio de Janeiro Cell Bank, RJ, Brazil) after exposure to equivalent molar masses of the drugs. Briefly, cells (10 000 cells/well) were incubated with either racemic ibuprofen or *S*(+)-ibuprofen for 24 h at 37 °C in a 5% CO_2 atmosphere in triplicate using 96-well plates. The culture medium was removed and each well received MTT (100 µl/well; 5 mg/ml in PBS). The cells were allowed to incubate for 3 h at 37 °C in a 5% CO_2 atmosphere, after which 100 µl of 10% sodium dodecyl sulfate in 0.01 M HCl were added to each well. The cell samples were then incubated for 18 h at 37 °C in a 5% CO_2 atmosphere and absorbance was measured at 540 nm in a microplate reader (Multiscan MS, Labsystems, USA). The cell proliferation assay was carried out using sulforhodamine B (SRB) protein staining. PG 100 cells (5 000 cells/well) were incubated with either racemic ibuprofen or S-ibuprofen for 48 h at 37 °C in a 5 % CO_2 atmosphere in triplicate using 96-well plates. Trichloroacetic acid (50% wt/vol) was added (50 ul/well), followed by incubation for 60 minutes at 4 °C. The supernatant was removed and 100 ul of SRB (0.4% wt/vol in a 1% acetic acid solution) were added. Unbound SRB was removed by washing five times with 1% acetic acid and Tris buffer was added to the wells. Absorbance was measured at 515 nm.

Statistical analysis

All data were expressed as the mean ± standard error of the mean (SEM). Comparisons among groups were performed using one-way ANOVA followed by the Dunnett multiple comparisons test. An associated probability of less than 5% was considered significant ($p < 0.05$).

RESULTS

Anti-inflammatory, ulcerogenic and cytotoxic activity

The oral administration of racemate (3 or 10 $mg.kg^{-1}$) and *S*(+)-ibuprofen (1.5 or 5 $mg.kg^{-1}$) at a dosage ratio of 1:0.5 to rats resulted in exudate and PGE_2 reduction in the air pouches when carrageenan was administered (Figure 1A and C). Leukocyte migration to the air pouches was reduced only in rats that received a dosage of 10 or 5 $mg.kg^{-1}$ (Figure 1B).

Interestingly, *S*(+)-ibuprofen administration resulted in a lower ulcerative lesion index in comparison to racemate (Figure 2A), despite the greater inhibition of gastric PGE_2 with the *S*(+)-enantiomer (Figure 2B). Cell assays were performed to confirm the greater toxicity of racemate in comparison to the *S*-enantiomer. In gastric cells, racemic ibuprofen proved to be cytotoxic at dose from 100 μM, whereas S-ibuprofen had no toxic effect at the highest dose tested (1000 μM; Figure 3A), as analyzed by the MTT assay. The same was observed when the sulforhodamine B assay was performed (Figure 3B).

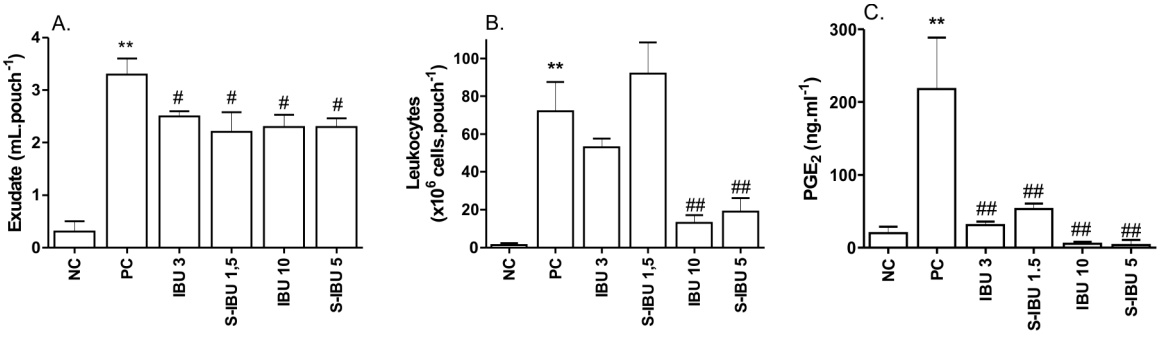

Figure 1. Effects of 1:0.5 ratio of racemate (IBU) and *S*(+)-ibuprofen (S-IBU) on carrageenan-induced exudate formation (panel A), leukocyte influx (panel B) and PGE_2 production (panel C) in air pouches; results expressed as mean ± SEM of data obtained from 5 animals; ∗∗ $p < 0.01$ in comparison of positive control (PC) to negative control (NC); # $p < 0.05$ and ## $p < 0.01$ in comparison of treated groups to PC.

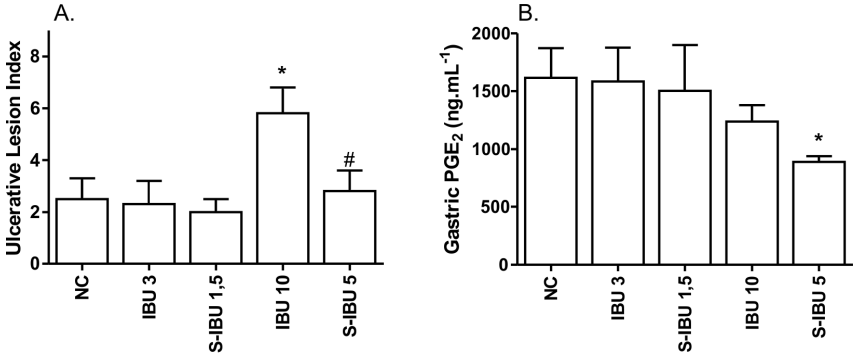

Figure 2. Ulcerative lesion index (panel A) and gastric PGE_2 content (panel B) following administration of 1:0.5 (w/w) of racemate (IBU) and *S*(+)-ibuprofen (S-IBU); results expressed as mean ± SEM of data obtained from 5 animals; ∗ $p < 0.05$ in comparison of treated groups to negative control (NC); # $p < 0.05$ in comparison of IBU 10 to S-IBU 5 group.

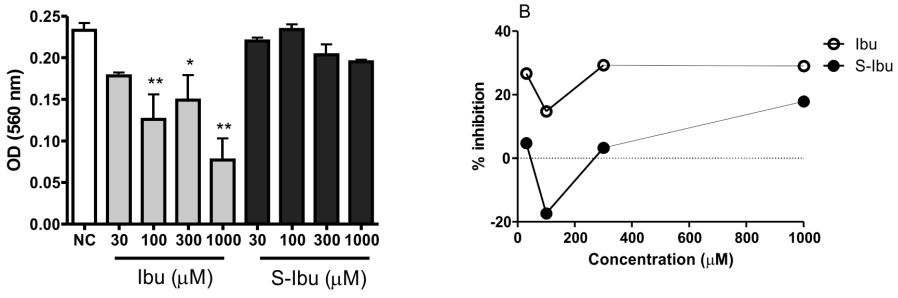

Figure 3. Effect of racemate (IBU) and *S*(+)-ibuprofen (S-IBU) on viability of gastric cells; A. MTT assay; B. Sulforhodamine B assay; data expressed as mean ± SEM of triplicate experiment; * $p < 0.05$ and ** $p < 0.01$ in comparison to non-treated cells (negative control)

Comparative bioavailability of S(+)-ibuprofen and R(-)-ibuprofen

Figure 4 displays the plasma concentration of *S*(+)-ibuprofen and *R*(-)-ibuprofen 0.5 and 1 h after oral administration at a racemate (100 mg/ kg) to *S*(+)-ibuprofen (50 mg/ kg) dosage ratio of 1:0.5. In the analysis of the plasma samples, the *R*(-)-enantiomer was not detected following the administration of *S*(+)-ibuprofen (Figure 4A). Following the administration of racemic ibuprofen, plasma levels of *R*(-)-enantiomer were detected and the level of *S*(+)-enantiomer also increased by 67% and 82% after 0.5 and 1 h, respectively, in comparison to plasma samples from animals that received a half dosage of *S*(+)-ibuprofen (Figure 4B).

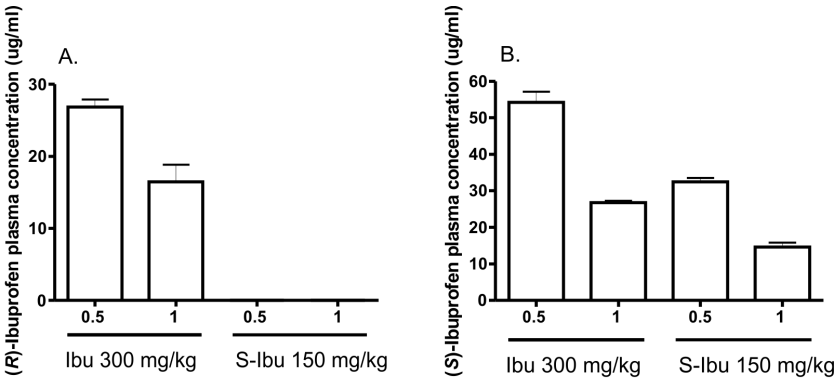

Figure 4. Comparative bioavailability of *R*(-)- and *S*(+)-ibuprofen in rat plasma 0.5 and 1 h after oral administration of racemate (300 mg.kg) or *S*(+)-ibuprofen (150 mg.kg)

DISCUSSION

Gastrointestinal tolerability is an important consideration when a nonselective NSAID is prescribed (Mallen et al., 2011). Racemic ibuprofen seems to be two-to-fourfold more ulcerogenic in enantiomerically equivalent doses than *S*(+)-ibuprofen (Wechter et al., 1993), but cytotoxicity seems not to be related to COX inhibition. Moreover, *S*(+)-ibuprofen seems to have the same anti-inflammatory activity as racemic ibuprofen, as no significant difference was found when the 1:0.5 ratio of racemate to *S*(+)-ibuprofen was employed in the present investigation. In a previous study, *S*(+)-ibuprofen was found to be more potent than the racemic formulation in carrageenan-induced paw edema when administered orally, but not after intravenous administration, which suggests differences in the absorption rate of the compounds (Bonabello et al., 2003). In another study involving an air pouch model, *S*(+)-ibuprofen was delivered directly to the air pouch and was able to inhibit the synthesis of PGE_2, but other parameters, such as cellular influx and exudate, were not evaluated; moreover, no comparison was made between *S*(+)-ibuprofen and the racemic form regarding the inhibition of PGE_2 synthesis (Martin et al., 1994).

In the present investigation, an independent mechanism of gastric PGE_2 inhibition confirmed that racemic ibuprofen was more ulcerogenic than *S*(+)-ibuprofen. A previous study employing different NSAIDs found no correlation between the severity of mucosal damage and the inhibition of prostaglandin E_2 synthesis in the stomach, suggesting that the specific chemical and pharmacokinetic properties of each drug could be more important with regard to ulcerogenic effects (Ligumsky et al., 1990). Prostaglandin inhibition in the small intestine has been evaluated in rats treated with racemic, R- and S-flurbiprofen at the same dosage (10 mg/kg) and the authors found that racemic and S-flurbiprofen led to the same degree of inhibition of PGE_2 synthesis, whereas R-flurbiprofen proved ineffective (Mahmud et al., 1998). However, another study carried out with racemic ketoprofen and S-ketoprofen at dosage ratio of 1:0.5 found that S-ketoprofen produced less intestinal damage (which is in agreement with the present findings), but had the same PGE_2 inhibition activity in the intestinal mucosa at dosages of 50 and 25 mg/kg (Alarcon de La Lastra et al., 2002).

Greater PGE_2 inhibition in the gastric mucosa was found using 10 and 5 mg/kg of *S*-ibuprofen, suggesting better COX inhibition, while no ulcerogenic activity was found with the use of the *S*-enantiomer. There are no any previous reports involving a comparative study of cytotoxicity in gastric cells using racemic and isolated enantiomers of ibuprofen. Racemic, *R*- and *S*-enantiomers of flurbiprofen and ketoprofen were found not to be cytotoxic to chondrocytes at doses of 1 and 10 μM (Panico et al., 2005). Employing higher doses, the present data demonstrate that the racemate is clearly more cytotoxic to gastric cells than the *S*-enantiomer of ibuprofen, which supports the notion that the administration of *S*-ibuprofen could be safer to the gastrointestinal tract while achieving the same anti-inflammatory activity. Due to the ability of *S*(+)-ibuprofen to reduce edema, no reduction in leukocyte infiltration or PGE_2 synthesis was found in the site of focal inflammation (air pouch).

The present findings are in agreement with the unidirectional chiral inversion for ibuprofen described by different research groups (Tan et al., 2002; Itoh et al., 1997; Uno et al., 2008). However, the most interesting question remains: If inactive *R*-ibuprofen is converted to active *S*-ibuprofen, why is the racemate not more effective when administered at a dosage ratio of 1:0.5? Pharmacokinetic

characteristics following racemate administration are different from those following the administration of individual enantiomers, i.e., plasma protein binding is different due to enantiomer-enantiomer interactions and could result in an increased distribution volume and total body clearance when racemate is administered (Itoh et al., 1997). Although chiral inversion contributes to the generation of an active anti-inflammatory enantiomer of ibuprofen, as demonstrated in the present study, the maintenance of an adequate plasma level could be impaired and the anti-inflammatory performance may not differ when racemic or *S*(+)-ibuprofen is administered at a dosage ratio of 1:0.5.

Based on the present findings, racemic and *S*(+)-ibuprofen administered orally to rats at a dosage ratio of 1:0.5 provide the same anti-inflammatory activity, but the racemate is more ulcerogenic than the *S*(+)-enantiomer. The harmful gastric effects of racemate are not related to PGE_2 inhibition in the stomach, but are rather due a direct cytotoxic effect. Although the unidirectional chiral inversion of *R*- to *S*-ibuprofen occurs, it is not enough to result in a better anti-inflammatory profile for racemic ibuprofen.

RESUMO

Estudo comparativo da atividade antiinflamatória, ulcerogênica e citotóxica do S-ibuprofeno e ibuprofeno racêmico

O Ibuprofeno é normalmente comercializado na forma racêmica. Embora ocorra inversão quiral convertendo a forma *R*(-)- em *S*(+)-ibuprofeno e, a última seja considerada a forma ativa, a administração da proporção 1:0,5 (racemato:*S*-enantiômero) demonstrou que o *S*(+)-ibuprofeno é mais eficaz que a formulação racêmica. Adicionalmente, o *R*(-)-enantiômero está envolvido nos efeitos adversos gastrintestinais descritos para a formulação racêmica, embora os mecanismos não sejam complemente compreendidos. O objetivo deste estudo foi avaliar a atividade antiinflamatória da proporção 1:0,5 (racemato:*S*-ibuprofeno) utilizando o modelo experimental de bolsa de ar, a atividade ulcerogênica e a taxa de conversão quiral em ratos. Também estudamos *in vitro,* a citotoxicidade provocada pelo racemato e *S*(+)-ibuprofeno em células gástricas. Embora os níveis plasmáticos de *S*(+)-ibuprofeno tenham aumentado após a administração do racemato, a atividade antiinflamatória avaliada pela formação de exsudato, produção de PGE_2 e migração de leucócitos para a bolsa de ar não foram diferentes. As lesões gástricas foram reduzidas após a administração de *S*(+)-ibuprofeno, apesar da inibição de PGE_2 gástrica. *In vitro*, o composto racêmico foi mais citotóxico que o *S*(+)-ibuprofeno. Nossos resultados sugerem que o *S*-enantiômero do ibuprofeno pode ser considerado uma alternativa terapêutica visando a redução dos efeitos colaterais gastrintestinais, visto que a inversão quiral do *R*(-)- para o *S*(+)-ibuprofeno não resultou em melhora do efeito antiinflamatório observado.

Palavras-chave: Ibuprofeno. Enantiômeros. Modelo experimental de bolsa de ar. PGE_2. Úlceras gástricas.

REFERENCES

Alarcón de La Lastra C, Nieto A, Martín MJ, Cabré F, Herrerías JM, Motilva V. Gastric toxicity of racemic ketoprofen and its enantiomers in rat: oxygen radical generation and COX-expression. Inflamm Res. 2002;51(2):51-7.

Bonabello A, Galmozzi MR, Canaparo R, Isaia GC, Serpe L, Muntoni E, Zara GP. Dexibuprofen (S+-isomer ibuprofen) reduces gastric damage and improves analgesic and antiinflammatory effects in rodents. Anesth Analg. 2003;97(2):402-8.

Doki K, Hayakawa T, Lin W, Yanaguimoto H, Ding G, Inotsume N. Effects of absorption rate on the pre-systemic chiral inversion of ibuprofen in rabbits. Journal of Pharm Pharmacol. 2003;55(8):1091-7.

Gamberini MT, Skorupa LA, Souccar C, Lapa AJ. Inhibition of gastric secretion by a water extract from *Baccharis triptera*, Mart. Mem Inst Oswaldo Cruz. 1991;86(Suppl 2):137-9.

Hao H, Wang G, Sun J, Ding Z, Wu X, Roberts M. Unidirectional inversion of ibuprofen in Caco-2 cells: developing a suitable model for presystemic chiral inversion study. Biol Pharm Bull. 2005;28(4):682-7.

Hardikar MS. Chiral non-steroidal anti-inflammatory drugs--a review. J Indian Med Assoc. 2008;106(9):615-8.

Itoh T, Maruyama J, Tsuda Y, Yamada H. Stereoselective pharmacokinetics of ibuprofen in rats: effect of enantiomer-enantiomer interaction in plasma protein binding. Chirality. 1997;9(4):354-61.

Kollenz C, Phleps W, Kaehler ST. ADIDAC Trial: Analgesia With Dexibuprofen Versus Ibuprofen In Patients Suffering From Primary Dysmenorrhea: A Crossover Trial. Gynecol Obstet Invest. 2009;67(1):25-31.

Lee EJ, Williams K, Day R, Graham G, Champion D. Stereoselective disposition of ibuprofen enantiomers in man. Br J Clin Pharmacol. 1985;9(5):669-74.

Ligumsky M, Sestieri M, Karmeli F, Zimmerman J, Okon E, Rachmilewitz D. Rectal administration of nonsteroidal antiinflammatory drugs. Effect on rat gastric ulcerogenicity and prostaglandin E_2 synthesis. Gastroenterology. 1990; 98(5 Pt 1):1245-9.

Mahmud T, Somasundaram S, Sigthorsson, G, Simpson RJ, Rafi S, Foster R, Tavares IA, Roseth A, Hutt AJ, Jacob M, Pacy J, Scott DL, Wrigglesworth JM, Bjarnason I. Enantiomers of flurbiprofen can distinguish key pathophysiological steps of NSAID enteropathy in the rat. Gut. 1998;43(6):775-82.

Mallen SR, Essex MN, Zhang R. Gastrointestinal tolerability of NSAIDs in elderly patients: a pooled analysis of 21 randomized clinical trials with celecoxib and nonselective NSAIDs. Curr Med Res Opin. 2011;27(7):1359-66.

Martin SW, Stevens AJ, Brennan BS, Davies D, Rowland M, Houston JB. The six-day-old rat air pouch model of inflammation: characterization of the inflammatory response to carrageenan. J Pharmacol Toxicol Methods. 1994;43(6):775-82.

Mayrhofer F. Efficacy and long-term safety of dexibuprofen [S(+)-ibuprofen]: a short-term efficacy study in patients with osteoarthritis of the hip and a 1-year tolerability study in patients with rheumatic disorders. Clin Rheumatol. 2001;20(Suppl 1):S22-9.

Neal MD. Clinical pharmacokinetics of ibuprofen: the first 30 years. Clin Pharmacol. 1998;34(2):101-54.

Panico AM, Cardile V, Gentile B, Garufi F, Avondo S, Ronsisvalle S. "In vitro" differences among (R) and (S) enantiomers of profens in their activities related to articular pathophysiology. Inflammation. 2005;29(4-6):119-28.

Phleps W. Overview on clinical data of dexibuprofen. Clin. Rheumatol. 2001;20(Suppl 1):S15-21.

Tan SC, Patel BK, Jackson SH, Swift CG, Hutt AJ. Stereoselectivity of ibuprofen metabolism and pharmacokinetics following the administration of the racemate to healthy volunteers. Xenobiotica. 2002;32(8):683-97.

Uno S, Uraki M, Komura H, Ikuta H, Kawase A, Iwaki M. Impaired intrinsic chiral inversion activity of ibuprofen in rats with adjuvant-induced arthritis. Xenobiotica. 2008;38(11):1410-21.

Wechter WJ, Bigornia AE, Murray ED Jr, Levine BH, Young JW. Rac-flurbiprofen is more ulcerogenic than its (S)-enantiomer. Chirality. 1993;5(7):492-4.

Wechter WJ, Mccracken JD, Kantoci D, Murray ED, Quiggle D, Leipold D, Gibson K, Mineyama Y, Liu Y. Mechanism of enhancement of intestinal ulcerogenicity of S-aryl propionic acids by their R-enantiomers in the rat. Dig Dis Sci. 1998;43(6):1264-74.

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