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SHORT COMMUNICATION

Effect of food on systemic exposure to niflumic acid following postprandial administration of talniflumate

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Abstract
Purpose Talniflumate was designed as a prodrug of niflumic acid, a potent analgesic and anti-inflammatory drug, which is widely prescribed for treating rheumatoid diseases. The prandial effect on talniflumate absorption remains unclear; therefore, this study investigated the effect of food on the systemic exposure to niflumic acid in healthy volunteers.
Methods Volunteers received a single 740-mg dose of talniflumate 30 min after consuming a high-fat breakfast, a low-fat breakfast, or no food (fasting condition). Plasma concentrations of both talniflumate and niflumic acid were measured using validated high-performance liquid chromatography coupled to tandem mass spectrometry.
Results The maximum concentration of niflumic acid was 224±193 ng/ml at ~2.7 h in the fasted condition compared with 886±417 ng/ml ($p<0.05$) at 1.8 h and 1,159±508 ng/ml ($p<0.01$) at 2.2 h with the low- and high-fat meals, respectively. The mean area under the curve from zero to infinity (AUC_{inf}) values after the low- and high-fat meals were four- and fivefold, respectively, the value while fasting ($p<0.05$).
Conclusions It is strongly recommended that talniflumate be taken after a meal to increase systemic exposure to its active metabolite. Our results suggest a reduction in the daily dosage of talniflumate when taken with food.

Keywords Talniflumate · Niflumic acid · Food · Systemic exposure

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Introduction

Talniflumate was designed as a prodrug of niflumic acid, a potent analgesic and anti-inflammatory drug, which is widely prescribed for treating rheumatoid diseases. It is synthesized by esterification of the carboxyl group of niflumic acid with a phthalidyl moiety, and it exerts its activity in the body through conversion to niflumic acid [1]. The prandial effect on the absorption of talniflumate remains unclear despite worldwide clinical use of the drug. This study investigated the effect of food on the systemic exposure to niflumic acid in healthy volunteers.

Materials and methods

Subjects

This study protocol was approved by the Institutional Review Board of the College of Medicine of Kyoungpook National University, and the eight male participants provided written informed consent before commencing the study. The mean ± standard deviation values of age and the body weight were 24.9±2.0 years (range=21~27 years) and 69.9±4.2 kg (range=63~75 kg), respectively. Candidates with health problems, drug or alcohol abuse, or laboratory abnormalities on screening were excluded.

Study design

The study was a randomized, three-way crossover trial in which a single oral dose of talniflumate was administered on three occasions, with a 1-week washout period between each drug administration. The volunteers were divided randomly into two groups and received a single 740-mg dose of talniflumate with 240 ml of water 30 min after consuming a high-fat breakfast, a low-fat breakfast, or no food (fasting condition) early in the morning of the study day. The low-fat meal consisted of kimbap, a popular traditional Korean food composed of rice, vegetables, and seaweed. The high-fat meal was hamburger. Although the total calories are similar between kimbap (726 kcal) and hamburger (770 kcal), the fat content of kimbap is one third that of hamburger. Fat, carbohydrate, and protein contents of the meals were 10.5 g (3.1%), 128.3 g (38.5%), and 18.3 g (6.6%) for kimbap and 26.0 g (8.0%), 85 g (25.3%), and 50.0 g (15.4%) for hamburger based on information provided on the Web sites www.jongrokimbap.co.kr and www.mcdonald.co.kr, respectively.

Sample collection and niflumic acid measurement

Blood samples (5 ml) were collected in heparinized tubes at various times up to 12 h after drug administration, and plasma was separated and stored at −70°C until analysis. Talniflumate is a prodrug that is rapidly converted into niflumic acid, its major active metabolite, following oral administration. Therefore, we measured the plasma concentrations of both talniflumate and niflumic acid using validated high-performance liquid chromatography coupled to tandem mass spectrometry (LC-MS-MS) [2]. An internal standard, 900 μl of ramipril acetonitrile solution (50 ng/ml), was added to 0.1 ml of plasma. The sample was mixed on a vortexer for 10 s and centrifuged at 13,200 rpm for 10 min. The supernatant was further diluted threefold with acetonitrile, and 1 μl was injected onto the column. Concentrations of talniflumate and niflumic acid in human plasma were quantified using LC-MS-MS with a PE SCIEX API 4000 LC/MS/MS system (Applied Biosystems, Foster City, CA, USA) equipped with an electrospray ionization interface used to generate positive ions of talniflumate and the internal standard and negative niflumic acid ions. The compounds were separated on an Xterra RP_{18} reversed-phase column (50×2.1 mm i.d., 3.5-μm particle size; Waters, USA), with an isocratic mobile phase consisting of acetonitrile/0.1% formic acid (aq) (75:25, v/v). The mobile phase was eluted at 0.3 ml/min using an HP 1100 Series pump (Agilent).

Multiple-reaction monitoring (MRM) was used to quantify the deprotonated precursor ion and related product ions for talniflumate and niflumic acid using the internal-standard method with peak-area ratios. The mass transitions used for talniflumate, niflumic acid, and ramipril were m/z 415.1→132.9, 280.9→236.5, and 417.2→234.1, respectively. Quadrupoles Q1 and Q3 were set at unit resolution. Analytical data were processed using Analyst software (version 1.4.1; Applied Biosystems).

Data analysis

The time course of the plasma niflumic acid level was used to determine the maximum plasma concentration (C_{max}) and the time (T_{max}) to reach C_{max}. The elimination rate constant (k) was obtained from the linear regression of the terminal phase, and the calculated elimination half-life ($t_{1/2}$) was $0.693/k$. The area under the plasma concentration-versus-time curve (AUC) was calculated using the trapezoidal rule and extrapolated to infinity (AUC_{inf}).

Statistical analysis

Analysis of variance (ANOVA) was used to test statistical significance among parameters for niflumic acid following administration of talniflumate after a high-fat or low-fat meal or while fasting.

Results

No unchanged talniflumate was found in plasma, even at the lower limit of quantification (10 ng/ml). The plasma niflumic acid concentration increased significantly after administration of talniflumate following consumption of the low- or high-fat meal compared with the fasting condition. The maximum concentration of niflumic acid was 224±193 ng/ml at ~2.7 h in the fasted condition compared with 886±417 ng/ml ($p<0.05$) at 1.8 h and 1,159±508 ng/ml ($p<0.01$) at 2.2 h with the low- and high-fat meals, respectively (Table 1). Interestingly, the plasma niflumic acid concentration plateaued from 2 or 3 to 5 h after the

Table 1 Pharmacokinetic parameters of niflumic acid following a single oral dose of talniflumate while fasting and after low- and high-fat meals (mean ± standard deviation, $n=8$)

Parameter	Fasting	Low-fat meal	High-fat meal
C_{max} (ng/ml)	224±193	886±417*	1,159±508*
T_{max} (h)	3.1±1.6	3.0±0.8	3.8±1.5
AUC_{inf} (ng·h/ml)	1,087±719	4,016±2,000*	5,287±1,535**
$t_{1/2}$ (h)	2.7±1.1	1.8±0.2	2.2±0.6

C_{max} maximum plasma concentration, T_{max} maximum time to reach C_{max}, k elimination time constant, $t_{1/2}$) elimination half-life, (AUC_{inf}) area under the plasma concentration-versus-time curve to infinity
*$p<0.05$, ** $p<0.01$ compared with the fasting condition

meal (Fig. 1). The mean AUC_{inf} values after the low- and high-fat meal were four- and fivefold, respectively, the value while fasting ($p<0.05$). Systemic exposure to niflumic acid seemed to be greater after the high-fat meal than after the low-fat meal, but the difference was not statistically significant. Although the half-life of niflumic acid after a meal tended to be shorter than that while fasting, the difference was not significant.

Discussion

The effect of food on bioavailability has been investigated for various classes of drugs, including anticoagulants [3], immunosuppressants [4], antihistamines [5], and nonsteroidal anti-inflammatory drugs (NSAIDs). As it is recommended that NSAIDs be taken with food to prevent gastrointestinal upset, the influence of food on their absorption should be considered.

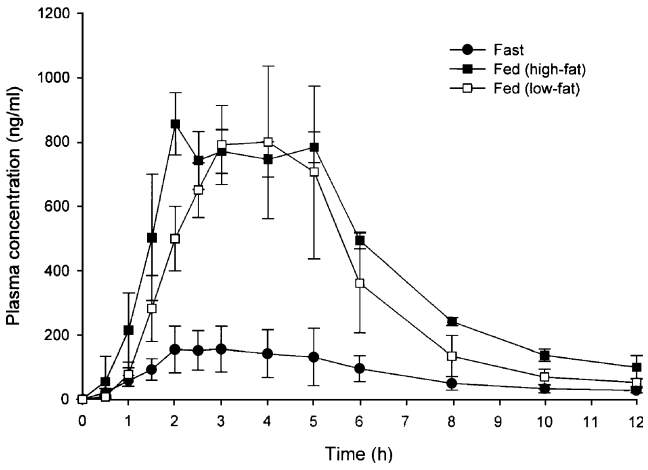

Fig. 1 Plasma concentration of niflumic acid in healthy male volunteers after a single oral dose of talniflumate (740 mg) while fasting or after a low-fat or high-fat meal (mean ± standard deviation, $n=8$)

Many studies have reported a prandial effect on the absorption and metabolism of NSAIDs. The maximum concentrations of diclofenac [6], ketoprofen [7], flurbiprofen [8], and piroxicam [9] are lower and delayed when they are taken with food, although the total amount entering the systemic circulation is not reduced. Le Liboux et al. revealed that absorption of a slow-release form of ketoprofen was increased with the intake of low-fat, low-calorie food compared with absorption with the intake of high-fat, high-calorie food [10]. Thus, individuals who eat a diet high in calories and fat may require an adjustment in the daily dose of ketoprofen and may experience greater benefit by switching to a low-fat, low-calorie diet to improve bioavailability. Taking ketorolac with a high-fat breakfast slowed the speed of drug absorption by about 1 h but did not affect the overall blood level of the drug [11].

Food may decrease the oral absorption of NSAIDs. The peak plasma bromfenac concentration for fed patients was only 28% of that for fasted patients, and its analgesic effect was reduced by food intake. Therefore, Forbes et al. suggested that the results of analgesic studies that do not consider the patients' food status might be misleading [12].

By contrast, the C_{max} and AUC of 6-methoxy-2-naphthylacetic acid, a major active metabolite of nabumetone, were increased significantly when nabumetone was coadministered with food or milk [13], and those of tolfenamic acid were increased significantly after meal [14], suggesting that the absorption of both nabumetone and tolfenamic acid is increased with food intake.

To our best knowledge, this is the first report of prandial effects on the absorption of talniflumate. Meal consumption did not delay the time to C_{max}, which is generally attributed to the fact that the presence of food in the stomach delays the rate of gastric emptying [15]. However, systemic exposure to niflumic acid was significantly increased, by four- to fivefold, with postprandial administration. Four possible mechanisms could explain this phenomenon: (1) Elevation of gastric pH due to food intake may increase the solubility of talniflumate and/or niflumic acid; although there has been no report on the pH dependency on the solubility of those compounds as yet, one may get a clue from the previous literature regarding the effect of magnesium hydroxide on the oral absorption of tolfenamic acid, which has fenamate moiety, the similar structure to niflumic acid [16]. (2) Consumption of food enhances biliary activity in response to dietary fat, and the increased activity of bile salts induced by the meal improves stability of the emulsion phase within the gut lumen, which increases the absorption of drugs [17]. (3) Food may also act as a physical barrier that prevents drug access to the mucosal surface of the gastrointestinal tract, affecting both active and passive absorption of drugs. (4) Increased splanchnic blood flow may influence absorption of drugs

that are extensively metabolized as a result of changes in the clearance of drugs during the first pass through the hepatoportal system [18].

In conclusion, consumption of food before administration of talniflumate caused a significant increase in the bioavailability of niflumic acid. Therefore, it is strongly recommended that talniflumate be taken after a meal to increase systemic exposure to its active metabolite. Our results suggest a reduction in the daily dosage of talniflumate when taken with food.

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