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Effect of nizatidine on paracetamol and its metabolites in human plasma

Hiroki Itoh, Toshiaki Nagano and Masaharu Takeyama

Abstract

The effect of the histamine H_2-receptor antagonist, nizatidine, on plasma concentrations of paracetamol has been investigated with respect to hepatic metabolism. Paracetamol (1000 mg) together with 300 or 150 mg nizatidine or placebo was orally administered to five healthy male volunteers. Venous blood samples were taken before and after administration. Plasma paracetamol and paracetamol conjugates (glucuronide and sulfate) were measured by high-performance liquid chromatography. The pharmacokinetic parameters were calculated from the plasma paracetamol concentration–time curves of each volunteer. The plasma nizatidine concentration was highest (2420.0 ± 192.4 and 996.0 ± 54.6 ng mL^{-1}) in the sample taken 1 h after administration of 300 mg nizatidine (high dose) and 150 mg nizatidine (low dose), respectively. Plasma paracetamol concentrations with nizatidine (high and low doses) were increased significantly at 45–120 min and 45–60 min, respectively, compared with placebo. The total area under the plasma paracetamol concentration–time curve from 0 to 180 min (2361.5 ± 146.4 and 2085.75 ± 73.5 μg min mL^{-1}) significantly increased after coadministration of nizatidine (high and low doses), respectively ($P < 0.01$ vs placebo). Paracetamol glucuronide concentrations with nizatidine (high and low doses) were decreased significantly at 30–45 min and 30 min, respectively, compared with placebo. However, plasma paracetamol sulfate concentrations with nizatidine (high and low doses) were not significantly altered. The coadministration of nizatidine (150 and 300 mg) dose-dependently reduces plasma paracetamol glucuronide concentrations and increases plasma paracetamol concentrations. The effects of nizatidine could result from the inhibition of glucuronyltransferase. Thus, care is necessary when paracetamol and nizatidine are coadministered.

Introduction

Paracetamol has analgesic and antipyretic effects and is widely used to treat pain and fever. The side-effects are hepatitis, renal failure, agranulocytosis, anaemia, dermatitis, allergy, sterile pyuria and thrombocytopenia (Clissold 1986). Paracetamol is poorly absorbed from the stomach, but rapidly absorbed from the small intestine. The major metabolic pathways of a therapeutic dose of paracetamol in humans are glucuronidation and sulfation, which account for about 60% and 30% of its metabolism, respectively (Shibasaki et al 1968). Peak plasma concentrations are usually reached 30–60 min after oral administration, and the half-life in plasma is approximately 120 min in a therapeutic dose. However, acute overdosage causes fatal hepatic damage.

The histamine H_2-receptor antagonist, nizatidine, which is widely used clinically to treat peptic ulcers, gastroesophageal reflux diseases and gastritis, is a potent

Department of Clinical Pharmacy, Oita Medical University, Hasama-machi, Oita 879-5593, Japan

Hiroki Itoh, Toshiaki Nagano, Masaharu Takeyama

Correspondence: H. Itoh, Department of Clinical Pharmacy, Oita Medical University, Hasama-machi, Oita 879-5593, Japan. E-mail: Itoh@oita-med.ac.jp

inhibitor of gastric acid secretion (Lin et al 1986; Price & Brogden 1988). The dysfunction of gastrointestinal motility is responsible for some upper abdominal symptoms, nausea, vomiting, dyspepsia and epigastric pain. Bachmann et al (1994) and Filingeri et al (1990) reported that there are significant pharmacokinetic interactions between nizatidine and some drugs. Nizatidine is frequently given in combination with paracetamol.

We recently reported that coadministration of paracetamol with ranitidine reduced plasma paracetamol glucuronide formation (Itoh et al 2000). However, to our knowledge there are no reports of the effects of other H_2-antagonists on the metabolites of paracetamol in man. In this study, we examined the effect of nizatidine on paracetamol metabolism by measuring the plasma concentrations of paracetamol and its conjugates before and after administration of paracetamol with nizatidine in five healthy male subjects.

Materials and Methods

Materials

Paracetamol (Calonal tablets; Showa Yakuhin Kako Co., Ltd, Tokyo, Japan) and nizatidine (Acinon capsules; Zeria Pharmaceutical Co., Ltd, Osaka, Japan) were used. Lactose (Merck hoei Co., Ltd, Osaka, Japan) was used as placebo. Standard paracetamol and paracetamol glucuronide were purchased from Sigma Chemical Co. (St Louis, MO). Standard paracetamol sulfate was supplied by Hokuriku Seiyaku Co., Ltd (Fukui, Japan). All other reagents were of analytical reagent grade from commercial sources.

Subjects

Five healthy male volunteers, aged 23–29 years (median 26 years), weighing 55–68 kg (median 62 kg), participated in the study. Each subject received information about the scientific purpose of the study, which was approved by our Ethics Committee at Oita Medical University, and gave informed consent. The subjects did not receive any medication one week before the study, and fasted for 12 h before the study commenced and during the experiments.

Study schedule

Paracetamol (1000 mg) together with 300 mg nizatidine, 150 mg nizatidine or placebo were administered orally with 100 mL water. Each subject was administered these drugs at an interval of three weeks. The dose of nizatidine in this study was the same as a daily dose in clinical therapy. Venous blood samples (10 mL) were taken from a forearm vein before and at 15, 30, 45, 60, 90, 120 and 180 min after paracetamol administration. The study was carried out from 0800 to 1100 h.

Determination of nizatidine concentration in plasma

Nizatidine was measured by a modification of the method of Aronoff et al (1988) and Knadler et al (1986). A 0.5-mL plasma sample was mixed with 1 mL saturated Na_2CO_3, nizatidine was extracted into 5 mL methylene chloride. The eluate was evaporated to dryness, reconstituted in 200 μL 0.1 M HCl/mobile phase (1:1, v/v), and subjected to high-performance liquid chromatography (HPLC) using a C18 column (Cosmosil 5C18-AR; Nacalai Tesque, Kyoto, Japan) and UV detection at 313 nm. The mobile phase was 0.1 M ammonium acetate/methyl alcohol/diethanolamine pH 7.5 (76:24:1), at a flow rate of 1.4 mL min^{-1}. The concentration of nizatidine was proportional to the peak area over the range 20–600 ng mL^{-1}. The recovery of nizatidine in plasma using this extraction procedure was $>93\%$.

Determination of paracetamol and paracetamol metabolites

The concentrations of paracetamol, paracetamol glucuronide and paracetamol sulfate were determined by the modified method of Mineshita et al (1986) and Brunner & Bai (1999). The plasma samples were deproteinized with 5% perchloric acid and centrifuged at 5000 *g* for 2 min. The supernatant was filtered through a membrane filter (Sample 4-LH, 0.45 μm; Millipore) and then applied onto the HPLC. HPLC was carried out using a C18 column (Cosmosil 5C18-AR, Nacalai Tesque) at 45°C with UV detection at 254 nm. The mobile phase was 1% acetic acid/0.1 M potassium dihydrogen phosphate (3:97), at a flow rate of 1.0 mL min^{-1}. The recovery of paracetamol, paracetamol glucuronide and paracetamol sulfate in plasma using this extraction procedure was $91.8\pm2.28\%$, $94.8\pm4.60\%$ and $92.4\pm4.51\%$ (n = 5), respectively.

Statistical analysis

The area under the plasma concentration–time curve (AUC) was calculated using the trapezoidal method. AUC and C_{max} represent the means$\pm$s.d. of concentrations in five tests. T_{max} represents the median range.

Table 1 Pharamacokinetic parameters of paracetamol, paracetamol glucuronide and paracetamol sulfate after 300 mg nizatidine, 150 mg nizatidine, or placebo coadministration.

	Placebo coadministration	Nizatidine (300 mg) coadministration	Nizatidine (150 mg) coadministration
Paracetamol			
$AUC_{0-180\,min}$ (μg min mL^{-1})	1889.0±132.6	2361.5±146.4**	2085.8±73.5**
C_{max} (μg mL^{-1})	18.3±2.3	21.0±2.8	20.2±0.9
T_{max} (min)	15–45	15–45	15–45
Paracetamol glucuronide			
$AUC_{0-180\,min}$ (μg min mL^{-1})	3427.5±462.0	3290.3±148.5	3418.5±95.6
C_{max} (μg mL^{-1})	28.0±2.7	26.9±0.7	28.0±0.9
T_{max} (min)	45–90	45–90	45–90
Paracetamol sulfate			
$AUC_{0-180\,min}$ (μg min mL^{-1})	1487.3±425.0	1528.5±86.4	1531.5±117.0
C_{max} (μg mL^{-1})	11.7±2.5	11.4±3.8	11.6±0.8
T_{max} (min)	45–90	45–90	45–90

$AUC_{0-180\,min}$, area under the plasma concentration–time curve from 0 to 180 min; C_{max}, maximum concentration; T_{max}, time to maximum concentration. AUC and C_{max} represent the mean±s.d. of concentrations in five tests. T_{max} represents the median range. $^{**}P < 0.01$ significantly different compared with placebo.

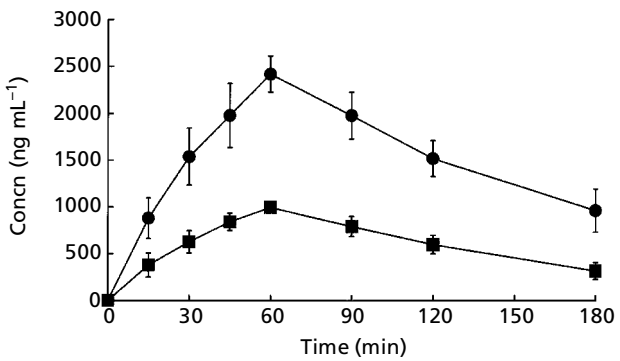

Figure 1 Plasma nizatidine concentrations in healthy male subjects after oral administration of 300 mg nizatidine (●) and 150 mg nizatidine (■). Each value represents the mean±s.d., n = 5.

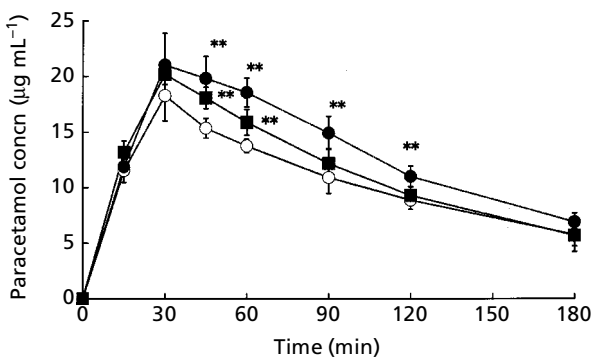

Figure 2 Plasma paracetamol concentrations after coadministration of 300 mg nizatidine (●) and 150 mg nizatidine (■), or placebo coadministration (○). Each value represents the mean±s.d. of concentrations in five volunteers. $^{**}P < 0.01$ significantly different compared with placebo.

Comparison of mean values (Figures 2, 3, 4; Table 1) were made by a one-way analysis of variance and $P < 0.05$ was considered statistically significant.

Results

Figure 1 shows the profiles of average plasma nizatidine concentrations against time, after the oral administration of nizatidine (300 and 150 mg). The plasma concentration was highest at 1 h after administration of nizatidine (2420.0±192.4 and 996.0±54.6 ng mL^{-1} for 300 and 150 mg nizatidine, respectively). The concentration–time curves of paracetamol, paracetamol glucuronide and paracetamol sulfate in plasma from the five male volunteers are shown in Figures 2–4.

Effects of 300 mg nizatidine on plasma concentrations of paracetamol, paracetamol glucuronide and paracetamol sulfate

Mean peak plasma paracetamol concentrations were elevated from 18.3±2.3 μg mL^{-1} (placebo coadministration) to 21.0±2.8 μg mL^{-1} (nizatidine coadministration) 30 min after administration, and $AUC_{0-180\,min}$ of paracetamol was correspondingly increased from

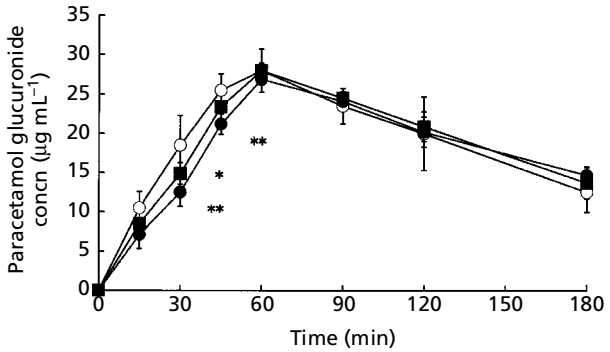

Figure 3 Plasma paracetamol glucuronide concentrations after co-administration of 300 mg nizatidine (●) and 150 mg nizatidine (■), or placebo coadministration (○). Each value represents the mean±s.d. of concentrations in five volunteers. $^{*}P < 0.05$ and $^{**}P < 0.01$, significantly different compared with placebo.

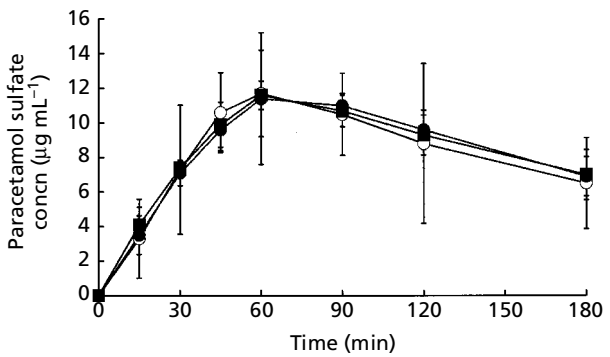

Figure 4 Plasma paracetamol sulfate concentrations after co-administration of 300 mg nizatidine (●) and 150 mg nizatidine (■), or placebo coadministration (○). Each value represents the mean±s.d. of concentrations in five volunteers.

1889.0±132.6 μg min mL^{-1} (placebo coadministration) to 2361.5±146.4 μg min mL^{-1} (nizatidine coadministration) ($P < 0.01$). Plasma paracetamol concentrations with nizatidine were increased significantly at 45–120 min ($P < 0.01$). The plasma paracetamol glucuronide with nizatidine was significantly reduced at 30–45 min compared with placebo ($P < 0.01$). Plasma paracetamol sulfate concentrations with nizatidine were not significantly changed after administration compared with placebo.

Effects of 150 mg nizatidine on plasma concentrations of paracetamol, paracetamol glucuronide and paracetamol sulfate

Mean peak plasma paracetamol concentrations were elevated from 18.3±2.3 μg mL^{-1} (placebo coadministration) to 20.2±0.9 μg mL^{-1} (nizatidine coadministration) 30 min after administration, and $AUC_{0-180\,min}$ of paracetamol was correspondingly increased from 1889.0±132.6 μg min mL^{-1} (placebo coadministration) to 2085.8±73.5 μg min mL^{-1} (nizatidine coadministration) ($P < 0.01$). Plasma paracetamol concentrations with nizatidine were increased significantly at 45–60 min ($P < 0.01$). The plasma paracetamol glucuronide with nizatidine was significantly reduced at 30 min compared with placebo ($P < 0.05$). Plasma paracetamol sulfate concentrations with nizatidine were not significantly changed after administration compared with placebo.

Discussion

Coadministation of paracetamol with nizatidine increased paracetamol concentrations and delayed paracetamol glucuronide transformation. We found a pharmacokinetic interaction between paracetamol and nizatidine when both drugs were coadministered.

Paracetamol is clinically effective as an analgesic and antipyretic treatment. Its absorption appears to be negligible from the stomach, but very rapid from the small intestine (Heading et al 1973). The conventional oral dose of paracetamol is 300–500 mg, with a total daily dosage not exceeding 4 g. Although paracetamol produces fewer side-effects than aspirin in therapeutic doses, skin rashes and other allergic reactions occur occasionally (Clissold 1986). Paracetamol is mainly metabolized by the liver to glucuronide and sulfate conjugates.

Nizatidine is widely used as an effective therapy for peptic ulcer diseases, gastroesophageal reflux diseases, gastritis and hypersecretory states (Lin et al 1986). Nizatidine has anti-acetylcholinesterase activity, and stimulates gastrointestinal motility and gastric emptying (Ueki et al 1993).

We have previously confirmed that coadministration of ranitidine significantly reduces concentrations of paracetamol glucuronide and increases concentrations of paracetamol in human plasma (Itoh et al 2000). Emery et al (1985) investigated the effects of ranitidine on paracetamol metabolism. Inhibition of paracetamol glucuronyltransferase activity by ranitidine reduced paracetamol conjugation. However, there are no reports on the effects of nizatidine on paracetamol metabolism. Therefore we examined the effects of nizatidine on the hepatic metabolism of paracetamol.

Peak plasma nizatidine concentrations were obtained 60 min after the coadministration of paracetamol with nizatidine (300 and 150 mg). The profiles of plasma paracetamol, paracetamol glucuronide and paracetamol

sulfate concentrations are shown in Figure 2–4. In our study, plasma paracetamol concentrations were affected by nizatidine coadministration. Coadministration of nizatidine significantly increased plasma paracetamol concentrations and the $AUC_{0-180\,min}$ of paracetamol (Table 1). Nizatidine at doses of 150 and 300 mg significantly increased the $AUC_{0-180\,min}$ of paracetamol to 2085.8 ± 73.5 and 2361.5 ± 146.4 $\mu g\ min\ mL^{-1}$, respectively, in a dose-dependent manner. Plasma paracetamol glucuronide concentrations with nizatidine (300 and 150 mg) were decreased significantly at 30–45 min and 30 min, respectively, compared with placebo. Thus, plasma paracetamol concentrations would be increased during the process of absorption in the presence of nizatidine, probably owing to the inhibition of paracetamol glucuronyltransferase by nizatidine, similar to ranitidine coadministration (Itoh et al 2000).

This study showed the coadministration of paracetamol with nizatidine causes a dose-dependent, significant decrease in plasma paracetamol glucuronide concentrations and increases in plasma paracetamol concentrations. Thus, nizatidine may prevent the first-pass hepatic metabolism of paracetamol and delay the extent of paracetamol glucuronyltransferase activity during the process of absorption in the presence of nizatidine. These findings are potentially important clinically, particularly if nizatidine can increase the toxicity of paracetamol.

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