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Communication

Cisapride raises the bioavailability of paracetamol by inhibiting its glucuronidation in man

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Abstract

The effect of cisapride on plasma concentrations of paracetamol was investigated with respect to hepatic metabolism. Paracetamol (1 g) together with cisapride (7.5 mg) or placebo was orally administered to five healthy male volunteers. Venous blood samples were taken before and after administration. Plasma paracetamol and its glucuronide and sulfate conjugates were measured by HPLC. The pharmacokinetic variables were calculated from the plasma concentration–time curves of each volunteer. The area under the plasma paracetamol concentration–time curve from 0 to 180 min (mean $\pm$ s.d.) increased from 1875.0 $\pm$ 112.8 μg min mL^{-1} (placebo coadministration) to 2238.8 $\pm$ 125.8 μg min mL^{-1} (cisapride coadministration) ($P < 0.01$). The mean maximum plasma paracetamol concentration (18.2 μg mL^{-1}) with placebo was reached 30 min after administration, whereas mean maximum plasma paracetamol concentration (21.2 μg mL^{-1}) with cisapride occurred 45 min after administration. The plasma paracetamol concentrations with cisapride were significantly greater at 45 to 120 min after administration compared with placebo. Plasma paracetamol glucuronide conjugate concentrations with cisapride were decreased at 15 to 60 min compared with placebo ($P < 0.05$), whereas plasma paracetamol sulfate conjugate concentrations did not change significantly. Hence the coadministration of paracetamol with cisapride reduced plasma paracetamol glucuronide concentrations and increased plasma paracetamol concentrations, presumably due to inhibition of paracetamol metabolism via paracetamol glucuronyltransferase. Thus, care is necessary when paracetamol and cisapride are coadministered.

Introduction

Paracetamol is widely used as an analgesic and antipyretic agent. The side-effects are agranulocytosis, anaemia, dermatitis, allergy, hepatitis, renal failure, sterile pyuria and thrombocytopenia (Clissold 1986). Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract (Shibasaki et al 1968). Its concentration in plasma reaches a peak 30 to 60 min after oral administration, and the half-life of a therapeutic dose in plasma is approximately 2 h. Acute overdosage can cause fatal hepatic damage. The major metabolic pathways of a therapeutic dose of paracetamol in man are glucuronidation and sulfation, which account for approximately 60 and 30% of its metabolism, respectively (Nelson 1982).

Cisapride, a drug with prokinetic actions on the gastrointestinal tract, is widely used to treat dyspepsia, gastroparesis and constipation (Reboa et al 1984; Reyntjens et al 1986). It is frequently given in combination with other drugs. Satoh et al (1996) reported that there are significant pharmacokinetic interactions between cisapride and some other drugs.

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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 cisapride on paracetamol glucuronide concentrations in man. In this study, we examined the effect of cisapride on paracetamol metabolism by measuring the plasma concentrations of paracetamol and its conjugates before and after administration of paracetamol with cisapride in five healthy male subjects.

Materials and Methods

Materials

Paracetamol (Calonal tablets; Showa Yakuhin Kako Co., Ltd, Tokyo, Japan) and cisapride (Acenalin tablets, Kyowa Co. Ltd, Tokyo, Japan) were used. Lactose (Merck Hoei Co., Ltd, Osaka, Japan) was used as placebo. Pure paracetamol and its glucuronide were purchased from Sigma Chemical Co. (St Louis, MO). Paracetamol sulfate was supplied by Hokuriku Seiyaku Co., Ltd (Fukui, Japan), and pure cisapride was supplied by Kyowa Co. Ltd (Tokyo, Japan). All other reagents were of analytical reagent grade from commercial sources.

Subjects

Five healthy male volunteers, aged 23–28 years (median 26 years), 53–68 kg (median 63 kg), participated in the study. Each subject received information about the scientific purpose of the study, which was approved by the Ethics Committee of Oita Medical University, Oita, Japan, and gave informed consent. The subjects did not receive any medication one week before the study, and fasted during the experiment and for 12 h before the study commenced.

Study schedule

Paracetamol (1 g) together with a therapeutic dose of cisapride (7.5 mg) or placebo (0.3 g) were administered orally with 100 mL water. 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 between 0800 h and 1100 h.

Determination of cisapride concentrations in plasma

Cisapride was measured by a modification of the method of Cisternino et al (1998). A 200 μL plasma sample was mixed with 50 μL methanol and 700 μL phosphate buffer (pH 7.9, 0.05 M), and centrifuged at 1500 g for 10 min. The supernatant was loaded onto a Sep-Pak C_{18} column (Millipore Corporation, Milford, MA), washed with 800 μL phosphate buffer, and the cisapride was eluted with 1 mL methanol. The eluate was evaporated to dryness, reconstituted in 150 μL methanol, and subjected to HPLC using a C_{18} column (Cosmosil 5C18-AR; Nacalai Tesque, Kyoto, Japan) at 20°C and UV detection at 276 nm. Acetonitrile/methanol/0.015 M phosphate buffer pH 2.2–2.3 (680:194:126, v/v/v) was used as the mobile phase at a flow rate of 0.8 mL min^{-1}. The concentrations of cisapride were proportional to the peak area over the range 1–150 ng mL^{-1}.

Determination of paracetamol and its metabolites

The concentrations of paracetamol, paracetamol glucuronide and paracetamol sulfate were determined by a 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 supernatants were filtered through a membrane filter (Millipore, Sample 4-LH, 0.45 μm), and then subjected to HPLC using a C_{18} column (Cosmosil 5C18-AR; Nacalai Tesque, Kyoto, Japan) at 45°C and 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 plasma paracetamol, paracetamol glucuronide and paracetamol sulfate with this extraction procedure was 91.8 ± 2.28, 94.8 ± 4.60 and 92.4 ± 4.51 % (means $\pm$ s.d., $n = 5$), respectively.

Statistical analysis

The area under the plasma concentration–time curve (AUC) was calculated using the trapezoidal method. AUC and the maximum concentration (C_{max}) represent the mean $\pm$ s.d. of concentrations in five tests. The time to maximum concentration (t_{max}) represents median range. The values were analysed using the Wilcoxon Signed Rank for paired samples. A statistically significant difference was considered at $P < 0.05$.

Results

The profile of average plasma cisapride concentration against time after coadministration of paracetamol with cisapride (7.5 mg) is shown in Figure 1. The plasma concentration (40 ng mL^{-1}) was greatest in the 60-min sample.

The concentration–time curves of paracetamol, paracetamol glucuronide and paracetamol sulfate in plasma from the five male volunteers are shown in Figures 2–4. The mean peak plasma paracetamol concentration (18.2 μg mL^{-1}) with placebo was reached 30 min after administration, whereas the mean maximum plasma paracetamol concentration (21.2 μg mL^{-1}) with cisapride was reached 45 min after administration (Table 1). The plasma paracetamol concentration with cisapride increased from 45 to 120 min compared with placebo. The $AUC_{0-180\ min}$ of paracetamol was increased from 1875.0 ± 112.8 μg min mL^{-1} (placebo coadministration) to 2238.8 ± 125.8 μg min mL^{-1} (cisapride coadministration) ($P < 0.01$).

The plasma paracetamol glucuronide concentrations with cisapride were reduced at 15 to 60 min, compared with placebo. The mean maximum plasma paracetamol glucuronide concentration (28.4 μg mL^{-1}) with placebo was reached 60 min after administration, whereas the mean maximum plasma paracetamol glucuronide concentration (25.5 μg mL^{-1}) with cisapride was reached 90 min after administration (Table 1).

Plasma paracetamol sulfate concentrations with cisapride were not significantly changed after administration compared with placebo.

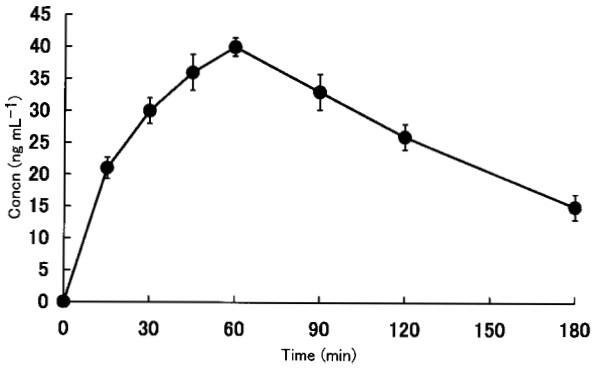

Figure 1 Plasma cisapride concentrations after coadministration of paracetamol with cisapride. Each value represents the mean ± s.d. of concentrations from five volunteers.

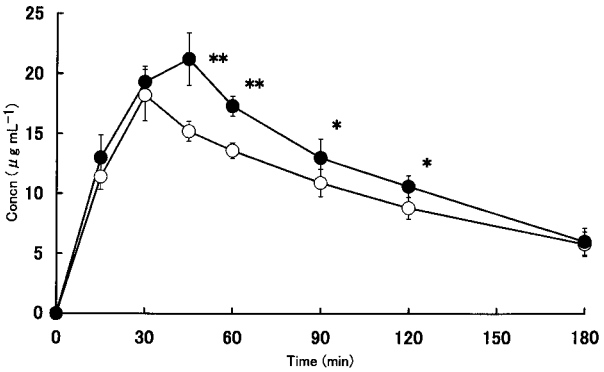

Figure 2 Plasma paracetamol concentrations after cisapride (●) or placebo (○) coadministration. Each value represents the mean ± s.d. of concentrations from five volunteers. $*P < 0.05$ and $**P < 0.01$ compared with placebo.

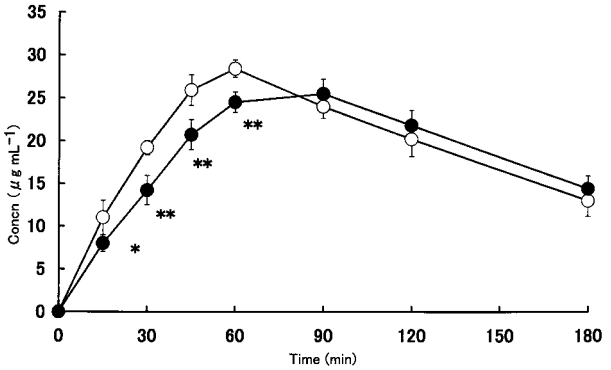

Figure 3 Plasma paracetamol glucuronide concentrations after cisapride (●) or placebo (○) coadministration. Each value represents the mean ± s.d. of concentrations from five volunteers. $*P < 0.05$ and $**P < 0.01$ compared with placebo.

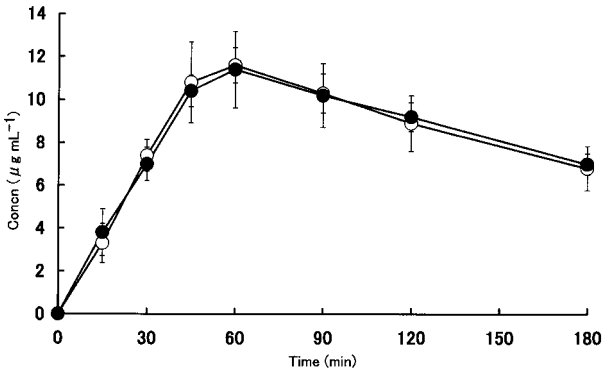

Figure 4 Plasma paracetamol sulfate concentrations after cisapride (●) or placebo (○) coadministration. Each value represents the mean ± s.d. of concentrations from five volunteers.

Table 1 Pharamacokinetic parameters of paracetamol, paracetamol glucuronide and paracetamol sulfate after cisapride or placebo coadministration in healthy volunteers.

	Placebo coadministration	Cisapride coadministration
Paracetamol		
$AUC_{0-180\ min}$ (μg min mL^{-1})	1875.0 ± 112.8	2238.8 ± 125.8**
C_{max} (μg mL^{-1})	18.2 ± 2.1	21.2 ± 2.2*
t_{max} (min)	15–45	30–60
Paracetamol glucuronide		
$AUC_{0-180\ min}$ (μg min mL^{-1})	3499.5 ± 125.5	3372.8 ± 78.3
C_{max} (μg mL^{-1})	28.4 ± 1.0	25.5 ± 1.7**
t_{max} (min)	45–90	60–120
Paracetamol sulfate		
$AUC_{0-180min}$ (μg min mL^{-1})	1497.0 ± 107.8	1504.5 ± 78.5
C_{max} (μg mL^{-1})	11.6 ± 0.8	11.4 ± 1.8
t_{max} (min)	45–90	45–90

$AUC_{0-180\ min}$ is the area under the plasma concentration–time curve from 0 to 180 min; C_{max} is the maximum concentration, and t_{max} is the time to maximum concentration. AUC and C_{max} represent the mean ± s.d. of concentrations in five volunteers; t_{max} represents the median range. *$P < 0.05$ and **$P < 0.01$ compared with placebo.

Discussion

Coadministration of paracetamol with cisapride increased paracetamol concentrations and delayed paracetamol glucuronide transformation. We found a pharmacokinetic interaction between paracetamol and cisapride when both drugs were administered together. Inhibition of paracetamol glucuronyltransferase activity by cisapride would reduce paracetamol conjugation.

Although paracetamol is most commonly used as an analgesic and antipyretic, it has also been used to measure gastric emptying because it appears to be absorbed much more rapidly from the small intestine than from the stomach (Heading et al 1973). The conventional oral dose of paracetamol for adults is 1 g, with total daily dosage not exceeding 4 g.

Cisapride improves deranged gastrointestinal motility and reduces duodenogastric reflux (Testoni et al 1993). It also speeds gastric emptying in normal subjects and in insulin-dependent diabetics with delayed gastric emptying (Horowitz et al 1987; Lazzaroni et al 1987). This stimulation of motility may occur via 5-HT4 receptors (Song et al 1997) or by facilitating acetylcholine release at nerve endings in the myenteric plexus (Van Nueten et al 1984) which acts on muscarinic receptors (Schuurkes et al 1984).

Rowbotham et al (1992) noted that cisapride did not affect paracetamol absorption in man, and Van Wyk et al (1992) reported that cisapride coadministration to normal volunteers caused a transient increase in gastric emptying. Therefore we examined the effects of cisapride on the hepatic metabolism of paracetamol after oral coadministration with cisapride.

Concentrations of plasma paracetamol with cisapride increased in the 45 to 120 min after coadministration, and the glucuronide concentrations were decreased significantly at 15 to 60 min compared with placebo, in accordance with the elevation of plasma cisapride concentrations. Thus, cisapride delayed the extent of paracetamol glucuronyltransferase activity in the process of absorption in the presence of cisapride. These findings are potentially important clinically, particularly if cisapride can increase the toxicity of paracetamol.

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