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Effect of Alcoholic Beverages on Drug Absorption: Blood Concentration Profile of Ibuprofen in Mice

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Abstract

Consumption of alcohol concomitantly with a drug may increase absorption of the active ingredients, leading to dose dumping. In this study, ibuprofen was administered to mice along with rice wine or beer. Blood concentrations of ibuprofen were lower when taken with alcohol than when taken with water. The ibuprofen formulation was suspended in rice wine, beer, 15% ethanol, or 20% mannitol, and then administered to male ddY mice. In a separate experiment, mice were pretreated with rice wine per os (p.o.) or loperamide (p.o.) 30 min before administering ibuprofen with water. Ibuprofen doses for oral administration and tail vein injection were 40 mg/kg and 0.75 mg/kg, respectively. Maximum blood concentrations (C_{max}) were lower in mice pretreated with rice wine or beer. There were no significant differences in ibuprofen clearance between animals pretreated with rice wine by tail vein injection and controls. Pretreatment with 20% mannitol or loperamide lowered the blood concentration of ibuprofen. These results suggest that alcoholic beverages affect drug pharmacokinetics. In particular, absorption may be affected by an increase in osmotic pressure and inhibition of gastrointestinal transit.

Keywords: Alcoholic beverage; Ibuprofen; Blood concentration; Osmotic pressure; Gastrointestinal transit

Introduction

Consumption of Over-The-Counter (OTC) formulations with beverages other than water is not uncommon. There are many routine scenarios involving consumption of medications, especially during dinner, when drugs are taken along with alcoholic beverages. Some of our patients have reported taking medications with alcoholic beverages such as beer (e.g., during a business meeting). Consumption of medications with an alcoholic beverage can increase solubility of the active ingredients; the active ingredients are then largely dissolved in ethanol, resulting in a condition that has been termed as "dose dumping".

The effects of dose dumping on the absorption of active ingredients have been previously described [1,5]. Two of these reports are studies on agents affecting the central nervous system [3,4] and one examined controlled-release formulations such as hydromorphone [4]. The review by Lennernas discussed ethanol-drug absorption and cited many studies using an ethanol solution [5], but few examining the effects or mechanisms associated with consumption of an alcoholic beverage. In this report, we focus on alcoholic beverages and discuss their effects on ibuprofen absorption in mice.

Ibuprofen was developed more than 50 years ago as an anti-inflammatory drug and is widely used to treat pain, with dosages ranging from ≤ 1200 mg/d for ≤ 10 days to high anti-rheumatic dosages of ≤ 2400 mg/day. Low-dose ibuprofen is used in more than 80 countries as an OTC medication [6]. Ibuprofen is classified as a class II (low solubility, high permeability) drug in the Biopharmaceutics Classification System (BCS); therefore, it is considered to have poor water solubility and good absorption in the digestive tract [7]. In products that are required to show an immediate effect, such as analgesic agents, ibuprofen is used to improve solubility and potentiate their effect. Consequently, we performed our experiments using ibuprofen, since it is extremely versatile and can be consumed with alcoholic beverages.

Materials and Methods

Materials

BRUFEN® tab 200 mg was purchased from Kaken Pharmaceutical. Co., Ltd. (Tokyo, Japan). Rice wine (containing ~14% ethanol) and beer (containing ~5% ethanol) were chosen as the alcoholic beverages to be used in this study. The rice wine and beer were purchased from Hakutsuru Sake Brewing Co., Ltd. (Hyogo, Japan) and Kirin Brewery Company, Ltd. (Tokyo, Japan), respectively. The 20% mannitol injection 300 ml solution was obtained from Yoshindo, Inc. (Toyama, Japan). Ibuprofen, loperamide hydrochloride, ethyl benzoate, ethanol (special grade), and acetonitrile (high performance liquid chromatography (HPLC)-grade) were obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan).

Study protocol

Male mice (ddY; 6-7 weeks old) were obtained from Shimizu Laboratory Supplies Co. Ltd. (Kyoto, Japan) and were fasted for three hours before beginning the experiments. Ibuprofen (40 mg/kg) suspended in water, rice wine, beer, 15% ethanol, or 20% mannitol was orally administered (5 ml/kg) to mice. There were more than six mice in each treatment group. For experiments involving pretreatment with rice wine or loperamide hydrochloride, 20 ml/kg rice wine (2.8 g/kg

ethanol) and 2.5 mg/5 ml/kg (in purified water) loperamide were orally administered 30 min before administering ibuprofen with water. Ibuprofen dissolved in phosphate-buffered saline (pH 7.4) was administered by tail vein injections (2.5 mg/5 ml/kg). Pretreatment for analysis of blood samples was carried out based on method described by Komori et al. [8]. Blood samples were collected 0, 10, 15, 30, 60, 120, 180, and 240 min after administration of ibuprofen. Ethanol (15 µl) and ethyl benzoate (5 µL, as an internal standard in ethanol) were added to the blood samples (10 µl), and the mixture was centrifuged for 10 min (12000 × g). The supernatant was analyzed by HPLC. Because sample quantities were small, we analyzed whole blood.

These experiments were conducted in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals and were accomplished per the Guiding Principles of Animal Experimentation of Setsunan University (Grant number K14-23).

Ibuprofen assay using mouse blood

Ibuprofen concentrations were determined by the HPLC method described by Lalande et al., with minor modifications [9]. No interfering peaks were observed from blank blood samples. Ibuprofen concentrations in blood were calculated by comparing the peak height ratio of ibuprofen with that of the internal standard using previously prepared standard curves. A series of standard blood samples containing ibuprofen were prepared with a final concentration of 2.5–40 µg/ml. All standard curves were linear over the range examined and passed close to the origin. The regression coefficients were 0.999 or better. Reproducibility of the experiment was determined by performing 5 repetitions. The coefficient of variation was less than 10%, except at a concentration of 2.5 µg/ml, in which it was 13.9%.

HPLC conditions for ibuprofen analysis

Blood samples (5 µL) were loaded into a reversed-phase column (COSMOSIL 5C18-AR-2 150 × 4.6 mm i.d.) with monitoring at a wavelength of 220 nm (Shimadzu SPD-10A detector). The flow rate was set at 1.0 ml/min with a Shimadzu LC-10 AD pump. The mobile phase, acetonitrile-water-trifluoroacetic acid (600:400:1, v/v/v), was run at 40°C with a Shimadzu CTO-10A column oven.

Pharmacokinetic parameters

Parameter analyses from the oral administrations, including maximum blood concentration (C_{max}) and time to peak concentration (T_{max}), were estimated from the actual concentrations measured in the experiments. Time of elimination half-life ($t_{1/2}$) and area under the concentration-time curve from time 0 to 240 min (AUC_{0-240}) were calculated by the least-squares method and standard linear trapezoidal integration, respectively. For tail vein injections, initial concentration (C_0), total clearance (CL_{tot}), $t_{1/2}$, and AUC from time 0 to infinity (AUC_∞) were calculated by performing statistical moment analyses. Statistical evaluations were analyzed by the student's t-test or Dunnet's test. Significant differences were defined as $p<0.05$.

Results

Blood concentration profile of ibuprofen when taken with beverages

Comparison of ibuprofen concentration profiles administered with rice wine or beer

C_{max} was observed 30 min after administering ibuprofen concomitantly with water, rice wine, and beer; C_{max} with water was 17.9 µg/ml. The drug was eliminated rapidly, and its concentration after 240 min was 10 µg/ml. In contrast, the concentrations of ibuprofen administered with rice wine or beer were lower at all-time points, and the profiles for the two scenarios were very similar. The C_{max} with rice wine or beer was ~13 µg/ml. The concentration of ibuprofen administered with rice wine was significantly lower than that of ibuprofen administered with the other test beverages, and the concentration after 240 min was close to that of water at the same time point (Figure 1a).

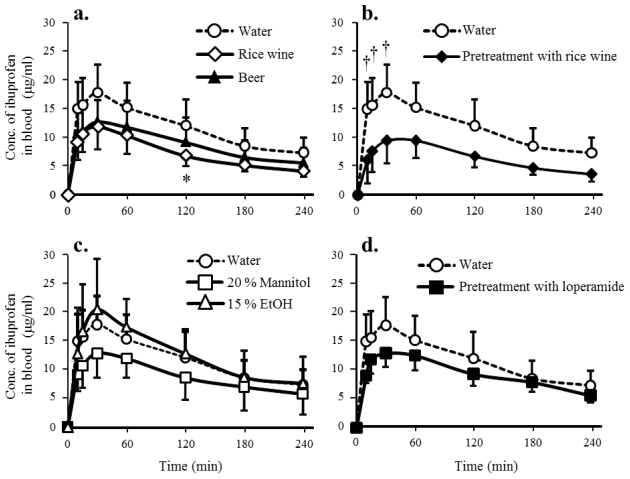

Figure 1: Blood concentration profile of ibuprofen under various conditions. a) Administration with rice wine or beer, b) pretreatment with rice wine, c) administration with 20% mannitol or 15% ethanol, and d) pretreatment with loperamide hydrochloride. *$p<0.05$ for rice wine vs. water, †$p<0.05$ for pretreatment with rice wine vs. water.

Effect of pretreatment with rice wine

Thirty minutes before ibuprofen was orally administered with water, the mice were pretreated with rice wine (approximately 2.8 g/kg ethanol). C_{max} (10.2 µg/ml) was reached 30 min after administration; this concentration was significantly lower than that of ibuprofen taken with water at the same time point. The concentration profile was very similar to that of ibuprofen taken with rice wine at the same time (Figure 1b).

Comparison of ibuprofen concentration profile with administration of 20% mannitol or 15% ethanol

Ibuprofen levels in the blood were not lower when taken with 15% ethanol than when taken with water at all-time points examined.

Ibuprofen levels were slightly higher 30 min after administration with ethanol than after administration with water. In contrast, when concomitantly taken with 20% mannitol, ibuprofen concentrations were lower than when taken with water. These results are similar to those observed when ibuprofen was taken with rice wine at the same time (Figure 1c).

Effects of pretreatment with loperamide hydrochloride

Thirty minutes before ibuprofen was orally administered with water, the mice were pretreated with loperamide hydrochloride (2.5 mg/kg as loperamide, p.o.). Under these conditions, the C_{max} of ibuprofen at 30 min was 13.3 μg/ml, which was lower than that observed with water. Ibuprofen levels in the blood were decreased at all-time points examined; however, the results were not significant (Figure 1d).

Influence of administration method on the pharmacokinetic parameters of ibuprofen

The C_{max} and $AUC_{0\text{-}240}$ values for ibuprofen in mice pretreated with rice wine, as well as in mice simultaneously administered beer or rice wine, were lower than those obtained when ibuprofen was consumed with water; however, these results were only significant in mice pretreated with rice wine. In particular, the C_{max} of ibuprofen was lower in mice pretreated with 20% mannitol or loperamide than when it was administered with water; however, the C_{max} of ibuprofen administered with 15% ethanol was slightly higher than when administered with water. For each condition, $AUC_{0\text{-}240}$ values from ibuprofen administered with water and 15% ethanol were the highest, whereas those in mice pretreated with rice wine were the lowest. T_{max} for all conditions was approximately 34–50 min, with no significant differences. The $t_{1/2}$ after pretreatment with 20% mannitol or loperamide was slightly prolonged, and the $t_{1/2}$ after pretreatment with rice wine was shortened (Table 1).

Parameters				
Treatment (n=the number of mice)	**T_{max} min**	**C_{max} μg/mL**	**$t_{½}$ min**	**$AUC_{0\text{-}240}$ μg min/mL**
Water (n=7)	34.3 ± 10.2	17.91 ± 4.82	170.0 ± 52.8	2815.7 ± 880.2
Rice Wine (n=8)	36.4 ± 15.6	11.58 ± 3.90	159.5 ±52.8	1727.1 ± 465.0
Beer (n=6)	37.5 ± 16.8	13.11 ± 4.38	166.7 ± 36.0	2117.8 ± 852.0
Pretreatment with rice wine (n=6)	50.0 ± 14.4	*10.20 ± 3.93	136.0 ± 22.8	*1567.2 ± 502.2
20% mannitol (n=6)	50.0 ± 33.6	13.38 ± 4.25	196.0 ± 120.0	2112.8 ± 784.2
15% EtOH (n=7)	42.9 ± 15.0	21.34 ± 8.17	175.7 ± 114.0	3025.7 ± 1063.2
Pretreatment with loperamide (n=6)	42.5 ± 18.0	13.26 ± 2.10	188.1 ± 47.4	2253.3 ± 384.0
Mean S.D. *p<0.05 vs. "water"				

Table 2: Pharmacokinetic parameters of orally administered ibuprofen.

Ibuprofen elimination in mice pretreated with rice wine

Mice were pretreated with rice wine (ethanol ~2.8 g/kg, p.o.) 30 min before administering ibuprofen by tail vein injection (2.5 mg/5 ml/kg). Elimination profiles for no-treatment and rice wine pretreatment conditions were similar. The elimination rate constants for no-treatment and rice wine pretreatment conditions were -0.0136 and -0.0132, respectively, and the R values for both were >0.97 (Figure 2).

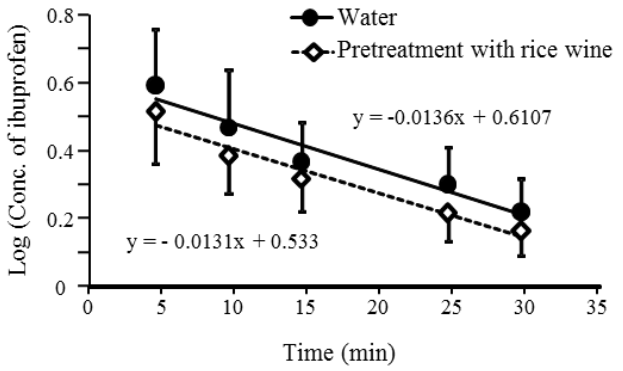

Figure 2: Blood concentration and elimination process after pretreatment with rice wine under (open triangle) and no-treatment (closed circle).

Pharmacokinetic parameters of ibuprofen are shown in Table 2. The AUC_∞ and C_0 were lower for mice pretreated with rice wine than for mice that did not receive treatment. Further, CL_{tot} was higher in rice wine-treated mice than that of mice that did not receive treatment; however, the differences were not significant. $T_{1/2}$ values were approximately 52–53 min, with no significant differences between the two conditions.

Parameters				
Treatment (n=the number of mice)	**$C_{(0)}$**	**CL_{tot}**	**$t_{½}$**	**AUC_∞**
	μg/mL	**mL/min**	**min**	**μg min/mL**
Water (n=6)	4.45 ± 1.77	11.97 ± 2.23	51.78 ± 21.0	216.66 ± 42.0
Pretreatment with rice wine (n=7)	3.68 ± 1.55	13.31 ± 2.10	53.02 ± 12.6	192.27 ± 2.28
Mean ± S.D.				

Table 2: Pharmacokinetic parameters of ibuprofen injected in the tail vein.

Discussion

Administration of drugs concomitantly with alcoholic beverages or after the consumption of alcoholic beverages is thought to affect drug pharmacokinetics. The mannitol and loperamide used in these experiments did not reproduce the conditions observed in mice pretreated with alcoholic beverages. Although ibuprofen clearance increased slightly, there were no major differences in mice pretreated with rice wine. Therefore, it is likely that changes in osmotic pressure and inhibition of gastrointestinal transit lowered the blood concentration of ibuprofen in this study. The fasted time when we assumed may have not been sufficient to compare significant influence in administering orally. These experiments were conducted in mice; however, they are applicable to humans who may be similarly influenced.

To date, several studies have reported that drug pharmacokinetics is affected by ingestion of ethanol. Fagerberg et al. predicted that changes in blood concentration would occur *in silico* when nine drugs were taken with a 20% ethanol solution [10]. This prediction was based on improvements in the solubility of indoprofen by addition of 20% ethanol in Fasted-State Simulated Gastric Fluids (FaSSGFs). The ibuprofen used in our study is slightly acidic, and mimics indoprofen well. Our results support the work of Fagerberg et al. [10]. When ibuprofen was administered with 15% ethanol, the ibuprofen concentration in blood increased slightly. However, the blood concentration was low when ibuprofen was taken with rice wine containing approximately 15% ethanol. Lennernas and Franke et al. pointed out that alcoholic beverages are not pure ethanol solutions [5,11], and we suggest that this consideration supports our results. Franke et al. compared beer, wine, and whiskey with an equal concentration of ethanol in terms of gastric emptying [11]. They reported that fermented alcoholic beverages, such as beer and red wine, affect gastric emptying more than that of ethanol. They considered osmotic pressure as an important factor, based on a report that hypertonic solutions delay gastric emptying [12]. The osmotic pressure of ethanol is high; however, ethanol is absorbed immediately in the gastrointestinal tract, resulting in decreased osmotic pressure. As alcoholic beverages are not pure ethanol solutions, Lennernas and

Franke et al. suggested that fermented alcoholic beverages containing a lot of sugar tend to maintain osmotic pressure [5,11]. Therefore, whiskey, which is distilled liquor, inhibits gastric emptying at the same level as 40% ethanol [11]. In our study, Tmax was prolonged for 20% mannitol, an effect that was not significant. Therefore, gastric emptying did not appear to be influenced. These results may be attributable to the experimental timeline, which we shortened to reduce animal stress.

Absorption of ibuprofen was inhibited by an increase in osmotic pressure in the gastrointestinal tract. Lane et al. reported that osmotic pressure increases with absorption of ibuprofen. Further, absorption of ibuprofen is inhibited when the intestinal tract is filled with FeSSIFs, which have high pH values and are hypertonic [13]. High permeability drugs, such as ibuprofen, are affected by the flux of water across the intestinal mucosa. Drug absorption is reduced by inhibition of the intestinal fluid flux by hypertonic media. The osmotic pressure of 20% mannitol (approximately 1500 mOsm), as was used in this study, is higher than that of FeSSIF (635 mOsm), and our results support the hypothesis of Lane et al. [13]. For comparison, the osmotic pressures of beer and rice wine have been shown to be approximately 1,000 mOsm and about 2,000 mOsm, respectively [11].

Ethanol in alcoholic beverages is reported to influence drug dissolubility as well as the gastrointestinal tract. Franke et al. reported that ethanol itself extends gastric emptying, and Scroggs et al. reported that ethanol extends gastrointestinal transit. Thus, ethanol can inhibit the gastrointestinal transit time and may affect drug absorption [11,14]. In our study, there were no significant differences; however, the blood concentration of ibuprofen was decreased. The ethanol concentration of the rice wine used in the pretreatment studies was the same as that used by Scroggs et al. [14]. In addition, when we pretreated mice with a dose of loperamide equivalent to that used by Bianchi et al. (2.0 mg/kg), the increase in ibuprofen blood concentrations was suppressed [15]. Therefore, the membrane transport of highly permeable agents such as ibuprofen may be affected by gastrointestinal transit. However, ethanol modifies membrane fluidity and lowers the barrier function of mucous membranes in the gastrointestinal tract. Ferrando et al. reported that absorption of lipophilic and hydrophilic compounds increases *in situ* [16]. Considering this fact, we cannot say whether alcohol beverages lower the absorption of drugs uniformly; however, it is likely that alcohol beverages cause some changes in absorption. Furthermore, it is thought that the absorption of ibuprofen is strongly affected by pH in the gastrointestinal tract. Tsume et al. predicted that Cmax becomes less than 50% if the pH is two points lower in the gastrointestinal tract *in silico* [17].

In this study, the $t_{1/2}$ was 52–53 min and 136–196 min when ibuprofen was administered by tail vein injection and orally, respectively. It is unlikely that oral administration of ibuprofen with water inhibits metabolism. Extension of the $t_{1/2}$ suggests a flip-flop phenomenon. Thus, there is a high possibility that the $t_{1/2}$ listed in Table 1 expresses a time of absorption half-life. Ibuprofen, a BCS II drug, is highly permeable, with poor solubility. In these experiments, ibuprofen was applied at a high dose of (40 mg/kg); therefore, it is possible that the ibuprofen was not absorbed as a solid in the gastrointestinal tract when taken with the fermented alcohol beverages or in mice pretreated with rice wine.

In conclusion, we determined the blood concentration profile of ibuprofen taken with rice wine and beer. Although we initially imagined a phenomenon such as dose dumping would occur (i.e., solubility of the active ingredient is increased by ethanol), we suggest that the high osmotic pressure caused by fermented alcoholic beverages and gastrointestinal transit time had a greater effect on the whole absorption process than did solubility. This theory is supported by the fact that similar results were obtained for beer, which is a low alcoholic beverage. In particular, it is thought that beverages such as beer, which are often consumed in large quantities, affect the pH of the gastrointestinal tract and influence absorption. When medications are taken with a fermented alcoholic beverage, they are rendered less effective, which explains the lack of significance observed in these experiments. Thus, we recommend consuming water when taking medications.

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