Time effects of food intake on the pharmacokinetics and pharmacodynamics of quazepam

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Aims There is little information on interaction between food and the hypnotic agent quazepam. We therefore studied the effects of food and its time interval on the pharmacokinetics and pharmacodynamics of quazepam.

Methods A randomized three-phase crossover study with 2-week intervals was conducted. Nine healthy male volunteers took a single oral 20 mg dose of quazepam under the following conditions: 1) after fasting overnight; 2) 30 min after eating standard meal; or 3) 3 h after eating the same meal. Plasma concentrations of quazepam and its metabolite, 2-oxoquazepam and psychomotor function using the Digit Symbol Substitute Test (DSST), Stanford Sleepiness Scale (SSS) and Visual Analogue Scale were measured up to 48 h.

Results During the food treatments at 30 min and 3 h before dosing, the peak concentrations ($C_{\max}$) were 300% (95% CI 260, 340%; $P < 0.001$) and 250% (95% CI 210, 290%; $P < 0.01$) of the corresponding value during the fasting phase. For quazepam, the area under the plasma concentration–time curve from 0 to 8 h measured at 30 min and 3 h before dosing was significantly increased, with the food treatments by 2.4-fold (95% CI 2.0; 2.8-fold; $P < 0.001$) and 2.1-fold (95% CI 1.7; 2.4-fold; $P < 0.01$), respectively. In response to pharmacokinetic changes, some of the pharmacodynamics (DSST, $P < 0.05$; SSS, $P < 0.05$) differed significantly between fasted status and fed status. No difference was found in any pharmacokinetic or pharmacodynamic parameters between the two food treatment phases.

Conclusions A food effect on quazepam absorption is evident and continues at least until 3 h after food intake. The dosing of quazepam after a long period of ordinary fasting might reduce its efficacy because a 3 h interval between the timing of the evening meal and bedtime administration of hypnotics is regarded as normal in daily life.

Keywords: food effect, pharmacokinetics, quazepam, time interval

Introduction

Quazepam is a trifluorinated benzodiazepine with long-acting hypnotic effects in humans [1, 2]. Classical pharmacokinetic studies have shown that quazepam is well-absorbed, and reaches a maximum plasma concentration at about 1.5 h. Bioavailability of quazepam is assumed to be 29–35% based on calculating the ratio of

the dose-normalized cumulative amount excreted in Japanese subjects (personal communication, Esuesu Pharmaceuticals, Tokyo, Japan). Quazepam is extensively metabolized in the liver, and the major metabolites of quazepam, 2-oxoquazepam and N-desmethyl-2-oxoquazepam, (both of which are pharmacologically active although the involvement of the metabolites in quazepam efficacy has not been proven yet), have been identified in plasma. Plasma elimination half-lives for quazepam and 2-oxoquazepam are 25–40 h and that of N-desmethyl-2-oxoquazepam is 70–75 h [3, 4].

Administration of drugs with food may reduce [5, 6], delay [7, 8], increase [9, 10] or have no effect on drug absorption [11–13]. Food can affect GI physiological factors such as gastric emptying time [14, 15], acid secre-

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tion [16–18], blood flow [19, 20], intestinal motility [21], bile secretion [22, 23] and enzyme secretion [24]. To our knowledge, however, there is no information about the effect of food on pharmacokinetics and pharmacodynamics of quazepam, although unpublished data suggest that the plasma concentration of quazepam with food is higher than that without food in a small group of individuals (personal communication, Esuesu Pharmaceuticals).

This study was therefore designed to examine the effect of food on the pharmacokinetics of quazepam after a single oral dose administration, with particular attention to the effect of timing of dosing and fasting on the interaction between food and quazepam. In addition, the pharmacodynamics of quazepam as a hypnotic agent were evaluated by means of psychomotor function tests.

Methods

Study design

Nine male healthy volunteers (age range, 22–44 years; weight range, 58–90 kg) participated in the study after each gave written informed consent. The protocol was approved by the Ethics Committee of Hiroasaki University School of Medicine. A randomized, crossover study design in three phases was used at intervals of 2 weeks. The volunteers fasted for more than 12 h overnight before receiving quazepam under three separate experimental conditions: 1) fasting phase; 2) meal phase 30 min before drug administration; and 3) meal phase 3 h before drug administration. For each phase of the study, including the fasting phase, which served as a baseline control for the meal phases of the study, each subject ingested a 20-mg oral dose of quazepam (Doral, Welfide Pharmaceutical, Osaka, Japan) with 200 ml of tap water at 09.00 h. For the fasting phase, subjects were administered quazepam after the overnight fast. For the randomized meal phases, subjects took two slices of bread with 30 g of butter and 200 ml of apple juice at 08.30 h (30 min before quazepam administration) or took the same meal at 06.00 h (3 h before quazepam administration). No meal was allowed until 4 h after the dosing (13.00 h). The use of alcohol, tea, coffee and cola was forbidden during the test days.

Blood samplings and psychomotor function tests

Blood samples (10 ml each) for determination of quazepam and its metabolite 2-oxoquazepam were taken into heparinized tubes just before and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24 and 48 h after the administration of quazepam. Plasma was separated immediately and stored at -30°C until analysis.

Assay

Plasma concentrations of quazepam and its metabolites 2-oxoquazepam and N-desmethyl-2-oxoquazepam were determined by high performance liquid chromatography (HPLC) methods developed in our laboratory. Quazepam, 2-oxoquazepam, N-desmethyl-2-oxoquazepam and alprazolam as an internal standard were supplied by Welfide Pharmaceutical (Osaka, Japan) and Upjohn Company (Kalamazoo, Mich., USA), respectively. All solvents used were of HPLC grade, and all reagents were purchased from Wako Pure Chemical Industries (Kyoto, Japan). After sample alkalization with 0.5 ml of NaOH (0.5 mol l^{-1}), the test compound and internal standard, alprazolam, were extracted from plasma using chloroform-toluene (15 : 85 v/v). The organic phase was evaporated to dryness and the residue was dissolved with 800 μl of mobile phase. An aliquot of the solution (500 μl) was injected into a C_{18} STR ODS-II analytical column (5 μl , 150×4.6 mm internal diameter). The mobile phase consisted of phosphate buffer (0.02 mol l^{-1} , pH 4.6) and acetonitrile (63 : 37 v/v) for quazepam and phosphate buffer (0.02 mol l^{-1} , pH 4.6), perchloric acid (6 mol l^{-1}) and acetonitrile (57.95 : 0.05 : 42 v/v) for metabolite and was delivered at a flow-rate of 0.6 ml min^{-1} . The peak was detected using a UV detector set at 286 nm for quazepam and 254 nm for metabolites. The method was validated for the concentration range $1\text{--}100\text{ ng ml}^{-1}$. Intra- and inter-day relative standard deviations were less than 3.6% at 20 ng ml^{-1} of the concentrations. The limit of quantification was 0.8 ng ml^{-1} .

Data analyses of pharmacokinetics

As the N-desalkyl-2-oxoquazepam in plasma was not washed out fully for 2 weeks because of its long half-life, data for this metabolite were not included in this study. The peak concentrations (C_{max}) and concentration peak time (t_{max}) were obtained directly from the original data. The AUC(0,8 h) and AUC(0,48 h) and AUC(0,8 h) (with extrapolation from the last detectable concentration obtained to infinity) were calculated with use of the trapezoidal rule. The terminal rate constant (k_e) used for the extrapolation was determined by regression analysis of the log-linear part of the concentration–time curve for each subject. The elimination half-life was determined by $0.693/k_e$.

Data analyses of pharmacodynamics

At the same times as the blood samples, psychomotor function status was evaluated with use of the Digit Symbol Substitution Test (DSST), which is an item of

the Wechsler Adult Intelligence Scale in 90 s, the Visual Analogue Scale (VAS) of mood and subjective states [25] and the Stanford Sleepiness Scale (SSS) [26]. The DSST variables were assessed by changed scores from baseline. The areas under the response–time curves were determined by the trapezoidal rule for 0–8 h and for 0–48 h for each pharmacodynamic variable.

Statistical analysis

Data are expressed as geometric mean values and CV or median and range. Statistical analysis was performed with the statistical program Stat View for Windows (version 5.0; Hulinks, Tokyo, Japan). Two-way ANOVA followed by Tukey's test were used for pharmacokinetic analyses based on log-transformed data, except $t_{\max}$, which was measured by nonparametric Tukey-type multiple comparison. Nonparametric Tukey-type multiple comparison was also used for pharmacodynamic values. A P value of <0.05 was regarded as statistically significant. The 95% confidence interval of population geometric means between fed and fasted treatments was calculated.

Results

Pharmacokinetics

Plasma concentrations of quazepam from 2 to 5 h after the administration of quazepam in the fed state (food intake 30 min and 3 h before quazepam administration) were higher than those in the fasted state, while plasma quazepam concentrations among the three treatment phases were unchanged from 6 to 48 h after administration (Figure 1). Consequently, food at 30 min and 3 h before the dosing significantly increased $C_{\max}$ by 3.0-fold (95% CI 2.6; 3.4-fold; $P < 0.001$) and 2.5-fold (95% CI 2.1; 2.9-fold; $P < 0.01$), AUC(0;8 h) by 2.4-fold (95% CI 2.0; 2.8-fold; $P < 0.001$) and 2.1-fold (95% CI 1.7; 2.4-fold; $P < 0.01$), and AUC(0;48 h) by 1.6-fold (95% CI 1.4; 1.9-fold; $P < 0.01$) and 1.5-fold (95% CI 1.3; 1.8-fold; $P < 0.05$), respectively, of quazepam, but did not prolong elimination half-life (Table 1). These parameters were increased in each of the nine subjects during each of the two food phases. The $t_{\max}$ of quazepam 30 min after food was significantly ($P < 0.01$) shorter than that without food intake (Table 1).

Likewise, plasma concentrations of 2-oxoquazepam were increased with both food treatments between 2 and 8 h after quazepam administration (Figure 1). Food significantly increased $C_{\max}$ by 2.4-fold (95% CI 2.0; 3.1-fold; $P < 0.01$) and 2.1-fold (95% CI 1.8; 2.4-fold; $P < 0.01$), AUC(0;8 h) by 2.1-fold (95% CI 1.7; 2.6-fold; $P < 0.001$) and 1.8-fold (95% CI 1.6; 2.0-fold; $P < 0.001$), and AUC(0;48 h) by 1.7-fold (95% CI 1.4; 2.2-

Figure 1 The geometric mean plasma quazepam concentration–time curve from 0 to 48 h (a) and the mean plasma 2-oxoquazepam concentration–time curve from 0 to 24 h (b) after a single oral dose of 20 mg quazepam to nine healthy volunteers. ○, variables with no food; ●, variables at 30 min after food intake and △, variables at 3 h after food intake.

fold; $P < 0.01$) and 1.6-fold (95% CI 1.4; 1.7-fold; $P < 0.01$), respectively, of quazepam, but did not prolong elimination half-life (Table 1). The $t_{\max}$ of 2-oxoquazepam was significantly ($P < 0.05$) shortened by food intake 30 min before the administration (Table 1). The ratio of 2-oxoquazepam to quazepam in $C_{\max}$, AUC(0, C_{last}) or AUC(0,8h) did not differ between the fasted and the two fed states, where C_{last} indicates plasma concentrations at 48 h for quazepam and at 24 h for 2-oxoquazepam after the administration.

Mean plasma concentrations of quazepam and 2-oxoquazepam were almost same when food was served 30 min and 3 h before drug administration (Figure 1). As a result, there were no differences in any pharmacokinetic parameters of quazepam or 2-oxoquazepam [$C_{\max}$, $t_{\max}$, AUC(0,48 h), AUC(0,8 h) or $t_{1/2}$] between the two food treatments (Table 1).

Pharmacodynamics

As quazepam is regarded as a hypnotic agent, pharmacodynamic parameters from 0 to 8 h and those from 0 to

Table 1 Pharmacokinetic variables of 20 mg quazepam to 9 healthy volunteers with no food and 30 min and 3 h after food intake.

Variables	Fasted status	Fed status 30 min after food	3 h after food
Quazepam			
C _{max} (ng mL ⁻¹)	28.0 (45)	81.2 (19)***	67.9 (34)**
t _{max} (h)	3.0 (2.0–4.0)	2.0 (1.0–3.0)**	2.0 (2.0–3.0)
AUC(0–8) (ng h ⁻¹ mL ⁻¹)	131 (44)	302 (20)**	261 (35)**
AUC(0–48) (ng h ⁻¹ mL ⁻¹)	291 (38)	468 (21)**	431 (30)*
AUC(0–8) (ng h ⁻¹ mL ⁻¹)	318 (37)	500 (22)*	453 (30)
Elimination t _{1/2} (h)	14.3 (19)	15.5 (22)	13.4 (10)
2-oxoquazepam			
C _{max} (ng mL ⁻¹)	8.8 (28)	21.5 (22)**	18.2 (20)**
t _{max} (h)	3.0 (2.0–5.0)	2.0 (1.0–4.0)*	3.0 (2.0–4.0)
AUC(0–8) (ng h ⁻¹ mL ⁻¹)	46 (27)	94 (15)***	82 (17)***
AUC(0–24) (ng h ⁻¹ mL ⁻¹)	95 (28)	160 (12)**	148 (19)**
AUC(0–8) (ng h ⁻¹ mL ⁻¹)	151 (39)	216 (24)	192 (27)
Elimination t _{1/2} (h)	17.8 (40)	14.4 (38)	12.0 (28)

Data are geometric mean (CV(%)) and t_{max} are expressed as median (range). C_{max}, peak concentration; t_{max}, peak concentration time; AUC, area under the plasma concentration–time curve; t_{1/2}, half-life. *p<0.05, **p<0.01, ***p<0.001 compared with no food.

Table 2 Pharmacodynamic variables of 20 mg quazepam to nine healthy volunteers with no food and 30 min and 3 h after food intake.

Variables	Fasted state	Fed state 30 min after food	3 h after food
DSST			
AUC (0,8 h) (score × h)	–11 (–29–140)	–39 (–227–(–2))*	–35 (–136–11)*
AUC(0,48 h) (score × h)	139 (15–948)	–70 (–199–50)*	27 (–887–141)*
SSS			
AUC (0,8 h) (score × h)	22 (16–29)	23 (16–51)*	26 (16–42)*
AUC(0,48 h) (score × h)	102 (96–113)	104 (96–145)	110 (96–132)
VAS (Thinking speed)			
AUC (0,8 h) (mm × h)	313 (187–451)	283 (110–397)	283 (151–371)
AUC(0,48 h) (mm × h)	1658 (661–2933)	2142 (1388–2787)	2329 (1153–3651)
VAS (Fatigue)			
AUC (0,8 h) (mm × h)	414 (268–503)	319 (110–437)	317 (151–437)
AUC(0,48 h) (mm × h)	2312 (1980–3297)	2143 (1388–2787)	2324 (1153–3651)

Data are median (range). *P<0.05 compared with no food.

48 h after quazepam administration were evaluated for hypnotic effect and for hangover side-effects, respectively. As shown in Figure 2, quazepam had CNS-depressant effects assessed by several psychomotor function tests from 1 to 8 h and the recovery from the effects was evident 12 h after drug administration.

For 0–8 h, there were significant differences in the pharmacodynamic parameters [AUC(0,8h)] of DSST and SSS between the fasted and fed state in response to pharmacokinetic changes (Table 2). In addition, the variables in DSST for 0–48 h [AUC(0,48h)] differed between fasted and fed state (Table 2). No differences were found in AUC for any pharmacodynamic variables in VAS including the items of 'thinking speed' or 'fatigue' (Table 2). There were no differences in any pharmacody-

namic variables of quazepam between the two meal phases (30 min before and 3 h before drug administration).

Discussion

The plasma concentrations of quazepam in the two fed states were higher than those in the fasted state between 2 and 5 h after quazepam administration, and the plasma concentrations of quazepam between the three phases were similar between 8 and 48 h (Figure 1). Consequently, food significantly increased C_{max} and AUC of quazepam by 2.5-fold, but not elimination half-life (Table 1). These findings suggest that food does not inhibit the metabolism of quazepam, but enhances the absorption of quazepam.

Figure 2 The median score of change in Digit Symbol Substitution Test (DSST)–time curve (a), the mean Stanford Sleepiness Score (SSS)–time curve (b), the mean scale in item ‘thinking speed’ in Visual Analogue Scale (VAS)–time curve (c) and the mean scale in item ‘fatigue’ in VAS–time curve (d) from 0 to 48 h after a single oral dose of 20 mg quazepam to nine healthy volunteers. ○, variables with no food; ●, variables at 30 min after food intake and △, variables at 3 h after food intake.

The absorption rate after administration of quazepam dissolved in alcohol, propylene glycol, glycerin, sorbitol and water was found in a previous study to be 87.5% as measured by calculating the radioactivity of the excreted dose in urine and faeces in Americans [27]. However, the absorption rate of the quazepam tablet is lower (33–40%) than dissolved quazepam, as mentioned above, based on the dose measured in urine in Japanese subjects. Therefore, the bioavailability of the quazepam tablet is assumed to be about 29–35% (personal communication, Esuesu Pharmaceuticals). The increase in C_{max} and AUC of quazepam in this study were 150–200% and 60–130%, respectively. These values are reasonable because the potential increase is expected to be 200% if the bioavailability was increased to about 100% with food intake.

Non-ionizable drugs classified with low solubility and high permeability, for example cyclosporin, carbamazepine, griseofulvin, danazol, repirinast, several of the retinoid drugs and spironolactone show increased absorption with high-fat meals [28]. For many of these drugs,

the extent of absorption is determined by the limited dissolution of high doses, and the promotion of dissolution by high-fat meals serves to elevate the extent of drug absorption [28, 29]. Meals increase bile secretion and gastrointestinal fluid volume, providing a better dissolution medium for poorly dissolving drugs. On the other hand, some drugs classified as possessing high solubility and low permeability show decreased absorption with food, for example captopril, frusemide, alendronate and bidisomide. Some drugs classified as possessing high solubility and high permeability show no change in absorption with food intake and some classified as low solubility and low permeability show low absorption with or without food. As quazepam is also characterized by low solubility and high permeability, the absorption of quazepam is most likely to be influenced by food intake.

The high-fat meal is the most frequently used meal in food-effect studies. To examine the effect of food intake on drug absorption, US Food and Drug Administration's Division of Bioequivalence recommends a high-fat meal

(~36 g fat) such as one fried egg, one buttered English muffin, one slice of bacon, one slice of cheese, one serving of hash brown potatoes, 240 ml whole milk, and 180 ml orange juice. The 30.2 g fat used in the present study might be somehow lower than the dietary fat content in high-fat meals used in previous studies [30]. It might be possible that very high levels of fat (60–100 g) in meals would cause a greater increase in $C_{\max}$ and AUC of quazepam. However, a similar impact of a low-fat meal on the pharmacokinetics and pharmacodynamics of quazepam has been observed to that of a medium-high-fat meal [31], suggesting that food intake has an effect on quazepam absorption even when meals have a low fat content. It means that even a light meal, e.g. snack and fruit juice, causes significant interaction with quazepam.

Some constituents of food may inhibit metabolism in the small intestine [32, 33]. Several compounds in grapefruit juice increase the absorption of many drugs based on inhibition of CYP3A4 in the lumen of the small intestine [32, 33]. Although apple juice has not been evaluated with respect to an inhibitory effect on drug metabolism, meals including apple juice significantly increased $C_{\max}$ and AUC of 2-oxoquazepam by three-fold in this study. However, since there was no difference in ratio of AUC(0,24 h) of 2-oxoquazepam to AUC(0,48 h) of quazepam between the three phases, it is concluded that food does not inhibit the metabolism of quazepam in the small intestine. The higher plasma concentration of 2-oxoquazepam in the two fed conditions compared with the fasted state might be attributable to elevation of quazepam concentration in the fed states, resulting from the enhanced absorption of quazepam caused by food intake. In addition, the effect of food on the metabolism of 2-oxoquazepam is unlikely, based on the present study showing an unchanged elimination half-life of 2-oxoquazepam by food.

The pharmacokinetic interaction between quazepam and food was significant. In fact, administration of quazepam with food has been contraindicated in Japan based on only a pharmacokinetic interaction study (unpublished data), which was conducted in a small group, but not in a crossover manner. Moreover, several pharmacodynamic parameters indicating sedative effect in response to pharmacokinetic data were increased with food intake in this study. This might support the position in Japan that quazepam administration is contraindicated at the time of food intake.

However, it should be noted that there were no differences in any pharmacokinetic or pharmacodynamic parameters observed between the two meal phases (30 min before and 3 h before the administrations) in the present study. These findings indicate that the effect of food continues until at least 3 h after food intake. This is

probably explained by the amount of time that food, particularly fat, remains in the gastrointestinal tract (3–4 h) [28, 29]. With respect to the time interval between the evening meal and administration of hypnotics, the 3-h difference adopted in this study is a reasonable simulation of the normal situation. It is therefore suggested that taking quazepam at the usual dinnertime results in greater absorption and hence higher drug concentrations than when taken in the fasted state. In contrast, a 2–3-times higher dose than normal might be required in order to achieve a therapeutic concentration range and sufficient efficacy when the normal dose of quazepam is given in the fasted condition. In particular, a very small hypnotic effect of quazepam on DSST was observed after 20 mg quazepam without food despite being a normal or higher dose for insomnia (Figure 2a). Therefore, the administration of quazepam after fasting for a long time might reduce its efficacy.

Since the plasma concentrations and psychomotor function parameters overlapped from 8 to 48 h after a single dose of quazepam in the three phases and the desirable hypnotic duration is regarded as 6–8 h, AUC(0,8 h) was evaluated for these parameters. Although the AUC(0,48h) in DSST differed between quazepam dosing with and without food in the present study, AUC(8,48 h) in DSST was unchanged. Therefore, the significant difference in the AUC(0,48 h) in DSST is attributed to the relatively large difference in the AUC(0,8h) in DSST. Furthermore, these findings suggest that administration of quazepam with food is unlikely to induce a hangover effect.

In conclusion, the present study suggests that the food effect on quazepam absorption is evident and continues for at least 3 h after taking food. The dosing of quazepam after long time fasting might reduce its efficacy because the 3-h interval between the evening meal and administration of hypnotics at bedtime is regarded as normal in daily life.

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