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Dose of midazolam should be reduced during diltiazem and verapamil treatments

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1 The effects of diltiazem and verapamil on the pharmacokinetics and pharmacodynamics of midazolam were investigated in a double-blind randomized cross-over study of three phases.

2 Nine healthy volunteers were given orally diltiazem (60 mg), verapamil (80 mg) or placebo three times daily for 2 days. On the second day they received a 15 mg oral dose of midazolam, after which plasma samples were collected and performance tests carried out for 17 h.

3 The area under the midazolam concentration-time curve was increased from 12 ± 1 μg ml^{-1} min to 45 ± 5 μg ml^{-1} min by diltiazem ($P < 0.001$) and to 35 ± 5 μg ml^{-1} min by verapamil ($P < 0.001$). The peak midazolam concentration was doubled ($P < 0.01$) and the elimination half-life of midazolam prolonged ($P < 0.05$) by both diltiazem and verapamil treatments.

4 These changes in the pharmacokinetics of midazolam were also associated with profound and prolonged sedative effects.

5 If the administration of midazolam cannot be avoided, the dose of midazolam should be reduced during concomitant treatment with diltiazem and verapamil.

Keywords midazolam diltiazem verapamil drug interaction pharmacokinetics

Introduction

The calcium channel blockers, diltiazem and verapamil, are much used in the treatment of hypertension, angina pectoris and other cardiovascular disorders. Diltiazem and verapamil have been reported to interact probably by enzyme inhibition with many therapeutic agents, including carbamazepine, propranolol, theophylline and cyclosporine [1, 2].

Midazolam is a widely used short acting hypnotic. It has an extensive first-pass metabolism mediated by a hepatic cytochrome P-450 IIIA enzyme and its oral bioavailability is less than 50% [3, 4]. During treatment with erythromycin 500 mg three times daily the area under the midazolam concentration-time curve is increased more than fourfold and peak midazolam concentration almost threefold, which leads to profound and prolonged sedation [5]. Enzyme inhibition by erythromycin is the probable main mechanism of this interaction. *In vitro* the hydroxylation of midazolam is inhibited, in addition of erythromycin, by verapamil and many other drugs [6]. Because midazolam is often used by patients on diltiazem or verapamil therapy, and there seemed to be theoretical basis for the interaction of these drugs, we have studied the effects of diltiazem and verapamil on the pharmacokinetics and pharmacodynamics of midazolam in healthy volunteers.

Methods

Nine healthy female volunteers aged 19 to 28 years and weighing 55 to 80 kg participated in the study. Each subject was ascertained to be in good health by a medical history, a clinical examination and a 12-lead electrocardiogram before entering the study. Six of the subjects were using contraceptive steroids. The subjects had no other continuous medications. The study protocol was approved by the Ethics Committee of the Department

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of Clinical Pharmacology of the Helsinki University Central Hospital. All the subjects gave their written informed consent after full explanation of the protocol before participating in the study.

Study design

A randomized double-dummy cross-over design of three treatment phases was used. The phases were separated by an interval of at least 7 days. The subjects received three pretreatments: 60 mg diltiazem (Dilzem 60 mg tabl., Orion Pharmaceutical Company Ltd, Espoo, Finland), 80 mg verapamil (Verpamil 40 mg tabl., Orion Pharmaceutical Company Ltd) or matched placebo three times daily for 2 days (a total of five doses). The pretreatment doses were administered at 14.30 h and 22.30 h on the first day, and 06.30 h, 14.30 h and 22.30 h on the second day. A 12-lead electrocardiogram was done for all the subjects three times during each pretreatment to look for possible cardiac conduction abnormalities.

On the second day the subjects ingested 15 mg midazolam (Dormicum 15 mg tablets, Hoffmann-La Roche Ltd, Basel, Switzerland) with 150 ml of water at 15.30 h i.e. 1 h after the previous administration of diltiazem, verapamil or placebo. The volunteers fasted 3 h before the administration of midazolam and had a light standard meal 4 h afterwards. They were not allowed to smoke or ingest alcohol, coffee, tea and cola during the test days.

Determination of plasma midazolam, diltiazem and verapamil

On the second day of each pretreatment a forearm vein was cannulated with a plastic cannula and timed samples (10 ml) were drawn into EDTA tubes immediately before the administration of midazolam and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 17 h after it. Plasma was separated within 30 min and stored at −40° C until analysis.

Plasma midazolam concentration was determined by a specific gas chromatographic method with NP-detection using methoxydiazepam as an internal standard [7]. The sensitivity of the method was 1 ng ml^{-1} and the coefficient of variation was 4.5% at mean 30 ng ml^{-1} ($n = 17$) and 2.8% at mean 45 ng ml^{-1} ($n = 10$).

Plasma diltiazem concentrations were determined using high performance liquid chromatography [8]. The coefficient of variation of the method was 2.7% (mean 157 ng ml^{-1}; $n = 6$). Plasma verapamil concentrations were quantified by a high performance liquid-chromatographic method [9]. The coefficient of variation was 2.4% (mean 95 ng ml^{-1}; $n = 7$).

Pharmacokinetics

The areas under the midazolam concentration-time curves (AUC(0–∞)) were calculated using the trapezoidal rule with extrapolation to infinity. Peak concentrations (C_{max}) and concentration peak times (t_{max}) of midazolam were also registered. The terminal log-linear phase of the plasma concentration-time curve was identified visually for each subject. The elimination rate constant (k) was determined by regression analysis of the log-linear part of the curve. The elimination half-life ($t_{½}$) was calculated from $t_{½} = \ln 2/k$ [10]. The areas under the diltiazem and verapamil concentration-time curves (AUC(0–17 h)) were calculated using the trapezoidal rule.

Pharmacodynamic measurements

The effect of midazolam on performance was assessed at each blood sampling time using performance tests. The volunteers were trained to do the tests ten times on two separate days before the study. The Maddox wing test was used to measure the coordination of extraocular muscles [11]. The result was expressed as heterophoria in diopters. The number of digits correctly substituted by simple symbols in 3 min was recorded in the digit symbol substitution test (DSST) [12]. Seventeen 100 mm long horizontal visual analogue scales (VAS) were used to record subjective effects. The opposing ends of the scales were in subject's own native language: alert–drowsy, calm–excited, strong–feeble, muzzy–clear-headed, well-coordinated–clumsy, lethargic–energetic, contented–discontented, troubled–tranquil, mentally slow–quick-witted, tense–relaxed, attentive–dreamy, incompetent–proficient, happy–sad, antagonistic–friendly, interested–bored, withdrawn–sociable, very good–very bad performance [13]. Subjective drowsiness (alert–drowsy) was used as the primary result. Side-effects were taken down on a questionnaire.

For each pharmacodynamic variable the areas under the response-time curves were determined by the trapezoidal rule for 0–7 h (AUC(0–7 h)) and 0–17 h (AUC(0–17 h)). The maximum effects (E_{max}) over 0–17 h were also registered.

Statistical analysis

The pharmacokinetic variables, the areas under the response-time curves and the maximum effects of midazolam during the three different pretreatments were compared using analysis of variance followed by Tukey's test. Tukey's test was also used to compare the performance test results between treatments at different time points after midazolam administration. The correlation of the AUC(0–17 h) of diltiazem and verapamil to the change in the pharmacokinetic variables of midazolam was evaluated using Pearson's correlation coefficient. All the data were analysed by use of the Systat System for Statistics [14]. Results are expressed as mean values ± s.e. mean. The chosen significance level was $P < 0.05$.

Results

During the diltiazem phase, the AUC(0–∞) of midazolam was almost four times higher ($P < 0.001$) than during the placebo phase (Figure 1, Table 1). Diltiazem pretreatment doubled the C_{max} of midazolam ($P = 0.004$) and increased the elimination $t_{½}$ of midazolam by 49% ($P = 0.003$) compared with placebo pretreatment. Verapamil admini-

stration doubled the C_{max} of midazolam ($P = 0.007$) and increased the AUC(0–∞) of midazolam threefold ($P < 0.001$). The elimination $t_{½}$ of midazolam was prolonged by 41% by verapamil ($P = 0.012$). The changes in the means of the pharmacokinetic variables caused by verapamil were smaller than the changes caused by diltiazem, but the difference between these two calcium channel blockers was not statistically significant. Neither of the drugs caused statistically significant changes in the t_{max} of midazolam.

The effects of midazolam were more profound during both the diltiazem and the verapamil phase than during the placebo phase (Figure 1). The changes in test results were in proportion to the changes in plasma midazolam levels caused by diltiazem and verapamil. During both the diltiazem and the verapamil treatment the AUC (0–7 h) for all three tests differed ($P < 0.01$) from the placebo treatment (Table 2). During diltiazem treatment the AUC (0–17 h) for all the tests was changed statistically significantly from placebo treatment, but during verapamil treatment the AUC(0–17 h) was statistically significantly changed only for heterophoria. The maximum effects in digit symbol substitution test and heterophoria were more profound during both the diltiazem and the verapamil phase than during the placebo phase ($P < 0.05$). Compared with placebo verapamil increased ($P = 0.026$) the maximum subjective drowsiness, but diltiazem did not.

During the diltiazem phase, the results of digit symbol substitution test and heterophoria differed significantly from the placebo phase up to 6 h as assessed by Tukey's test. During the verapamil phase digit symbol substitution test results were different compared with placebo up to 3 h and heterophoria up to 5 h after the administration of midazolam ($P < 0.05$). Subjective drowsiness was significantly increased up to 4 h by both diltiazem and verapamil treatments. No statistically significant differences were observed between diltiazem and verapamil treatments in any of the performance tests using Tukey's test.

Compliance was documented by plasma diltiazem and verapamil concentrations (Figure 1). No statistically significant linear correlation was seen between the AUC(0–17 h) of diltiazem or verapamil and the change in the pharmacokinetic variables of midazolam caused by the drug.

All the subjects completed the study. One of the subjects forgot to take the third dose of verapamil. She had lower plasma verapamil concentrations than the others. Another subject experienced nausea and vomiting 3 to 4 h after the fourth dose of verapamil. During diltiazem and verapamil treatments, but not during placebo treatment, most of the subjects were too drowsy to do any performance tests at the 1 h and 1.5 h time points after midazolam administration.

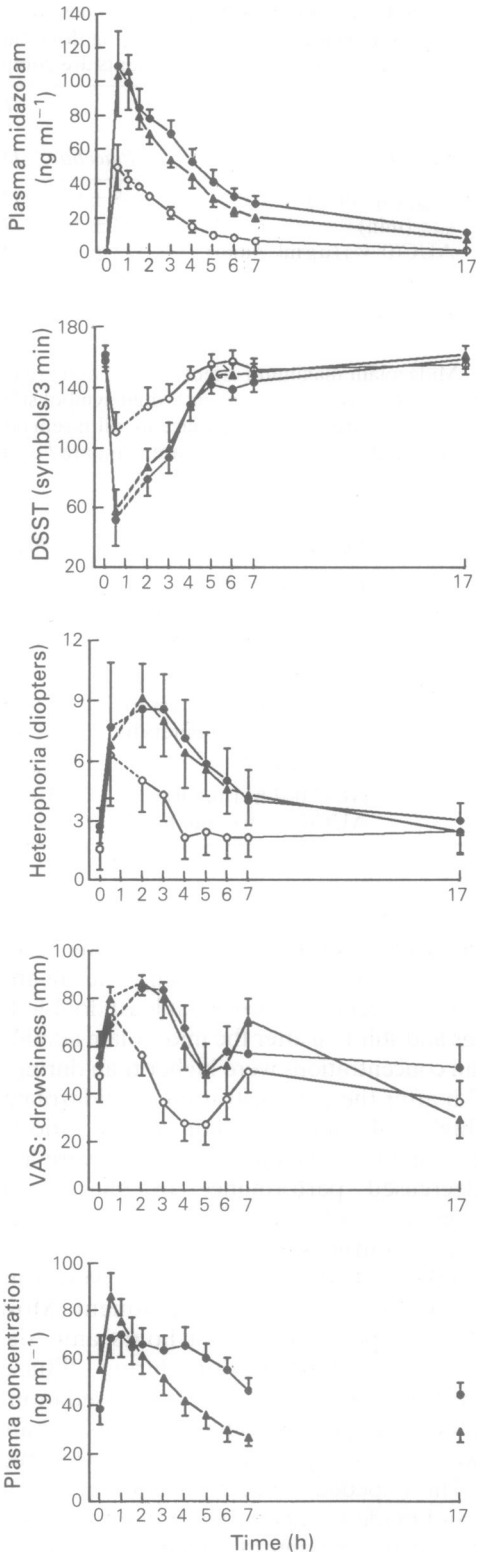

Figure 1 Plasma concentrations of midazolam and results of performance tests (mean ± s.e. mean): digit symbol substitution test (DSST), Maddox wing test (Heterophoria) and subjective drowsiness (VAS), after an oral 15 mg dose of midazolam following pretreatment with diltiazem 60 mg (●), verapamil 80 mg (▲) or placebo (○) three times daily for 2 days in nine healthy volunteers. Plasma concentrations (mean ± s.e. mean) of diltiazem (●) and verapamil (▲) are shown on the bottom. The fourth dose of diltiazem or verapamil was taken 1 h before the 0 h blood sample and the fifth dose immediately after the 7 h blood sample.

Discussion

In this study, treatment with diltiazem 60 mg and verapamil 80 mg three times daily considerably changed the pharmacokinetics of orally given midazolam and

Table 1 The pharmacokinetic variables (mean ± s.e. mean) of midazolam after pretreatment with placebo, diltiazem 60 mg and verapamil 80 mg three times daily for 2 days in nine healthy volunteers. Pharmacokinetic variables during different treatments are compared using Tukey's test (*P* values)

	Treatment			*Placebo* vs *diltiazem*	*Placebo* vs *verapamil*	*Diltiazem* vs *verapamil*
Variable	*Placebo*	*Diltiazem*	*Verapamil*	P	P	P
C_{max} (ng ml^{-1})	65 ± 9	133 ± 11	128 ± 16	0.004	0.007	0.965
t_{max} (min)	67 ± 16	73 ± 21	43 ± 5	0.948	0.533	0.364
AUC(0–∞) (μg ml^{-1} min)	12 ± 1	45 ± 5	35 ± 5	<0.001	<0.001	0.063
$t_{½}$ (h)	4.9 ± 0.6	7.3 ± 0.5	6.9 ± 0.5	0.003	0.012	0.734

Table 2 Midazolam maximum effects (E_{max}) and areas under the response-time curves [AUC(0–7 h), AUC(0–17 h)] for results of performance tests (mean ± s.e. mean): digit symbol substitution test (DSST), Maddox wing test (Heterophoria) and subjective drowsiness after pretreatment with placebo, diltiazem 60 mg and verapamil 80 mg three times daily for 2 days in nine healthy volunteers. Variables during different treatments are compared using Tukey's test (*P* values)

		Treatment			*Placebo* vs *diltiazem*	*Placebo* vs *verapamil*	*Diltiazem* vs *verapamil*
Test	*Variable*	*Placebo*	*Diltiazem*	*Verapamil*	P	P	P
DSST	E_{max} (symbols)	93 ± 10	29 ± 9	50 ± 10	<0.001	0.007	0.222
	AUC(0–7 h) (symbols h)	978 ± 49	773 ± 32	820 ± 54	<0.001	0.001	0.310
	AUC(0–17 h) (symbols h)	2517 ± 114	2369 ± 84	2378 ± 105	0.003	0.067	0.277
Heterophoria	E_{max} (diopters)	7 ± 1	11 ± 2	10 ± 2	0.002	0.018	0.267
	AUC(0–7 h) (diopters h)	24 ± 8	47 ± 12	45 ± 10	0.003	0.007	0.738
	AUC(0–17 h) (diopters h)	47 ± 17	82 ± 22	78 ± 20	0.003	0.007	0.782
Drowsiness	E_{max} (mm)	80 ± 6	89 ± 3	92 ± 3	0.103	0.026	0.735
	AUC(0–7 h) (mm h)	310 ± 39	472 ± 37	469 ± 41	0.003	0.004	0.996
	AUC(0–17 h) (mm h)	743 ± 116	1012 ± 101	973 ± 83	0.024	0.055	0.902

increased its effects in healthy subjects. Diltiazem and verapamil treatments greatly increased the AUC(0–∞), the C_{max} and the $t_{½}$ of midazolam. The mean plasma midazolam concentrations were at least doubled by both the drugs and still 17 h after the midazolam administration the mean concentrations were higher than during placebo phase 7 h after the administration of midazolam.

The higher plasma midazolam concentrations caused by diltiazem and verapamil treatments were associated with decreased performance in pharmacodynamic measurements. It was almost impossible for the subjects to stay awake during the first 1.5 h after the administration of midazolam during diltiazem and verapamil treatments, but not during placebo treatment. Most of the subjects also experienced several hours' amnesia following midazolam administration during diltiazem and verapamil treatments. The profound sedation caused missing values in pharmacodynamic tests at 1 and 1.5 h, which was near the expected time of maximum midazolam effects. This impeded the determination of the maximum effects and made it impossible to determine accurately the times of the maximum effects of midazolam. This probably also reduced the differences in the E_{max} values between the phases.

The hypnotic effects of midazolam were also much prolonged by the calcium channel blocker treatments. During diltiazem treatment the decrease of performance from placebo treatment was still statistically significant 6 h after the administration of midazolam. During verapamil treatment a significant difference in performance test results was seen up to 5 h after midazolam administration. Thus, patients taking 15 mg midazolam orally during diltiazem or verapamil treatment are probably incapable of doing tasks requiring skills (e.g. car driving) up to 6 h after midazolam administration. It is questionable whether they would be capable of tasks even 8–10 h after midazolam administration, since mean midazolam concentrations at 7 h time point were 3–5 times higher during concomitant diltiazem or verapamil treatments than during placebo treatment.

The considerable increases in the AUC(0–∞), the C_{max} and the $t_{½}$ of midazolam caused by diltiazem and verapamil are most probably the result of increased oral bioavailability and decreased clearance of midazolam, since it is not likely that the volume of distribution of midazolam would have changed. Unfortunately, the oral administration of midazolam did not allow the calculation of the volume of distribution. It is known that midazolam is extensively metabolised in liver by a cytochrome P-450 IIIA enzyme and that its bioavailability is normally less than 50% [3, 4]. Thus, reducing the metabolism of midazolam could well increase its bioavailability and decrease its clearance. Both diltiazem and verapamil inhibit hepatic cytochrome P-450 enzymes and may increase hepatic blood flow [1, 2, 15]. Increased hepatic blood flow would reduce first pass metabolism, but it is clear that enzyme inhibition reduces metabolism during elimination, too. Both these mechanisms are probably responsible for the altered pharmacokinetics of midazolam observed in this study. It has been suggested that the reduction in hepatic metabolism caused by diltiazem and verapamil is dose and time dependent [2]. Although we did not find any linear concentration dependence in the interaction of these calcium channel blockers with midazolam, it is possible that the changes in the pharmacokinetics and pharmacodynamics of

midazolam would be even greater during a higher dose or long term diltiazem or verapamil therapy.

Midazolam appears to be susceptible to drug interactions involving its cytochrome P-450 IIIA mediated metabolism. *In vitro* its metabolism is inhibited by many drugs, including cimetidine, ranitidine, erythromycin and verapamil [6]. Cimetidine and ranitidine have been reported to increase the bioavailability of midazolam by 25 to 30% in humans [16]. Erythromycin 500 mg three times daily has been demonstrated to increase distinctly the AUC, C_{max} and $t_{½}$ of midazolam and therefore to potentiate its psychomotor actions even dangerously [5]. The effect of diltiazem and verapamil on the pharmacokinetics and pharmacodynamics of midazolam observed in this study is of the same magnitude as the effect of erythromycin.

The implication of this study is that clinicians should know that diltiazem and verapamil treatments distinctly increase the plasma concentrations and the actions of orally administered midazolam. To avoid unnecessary deep sleep and prolonged hypnotic effect, the usual dose of midazolam should be reduced by at least 50% during concomitant diltiazem and verapamil treatment. It should also be kept in mind that the elimination $t_{½}$ of midazolam is increased by these calcium channel blockers, which may lead to prolonged effects of midazolam regardless of its dose.

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