Effect of voriconazole on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam

Objective: **Our objective was to assess the effect of the antimycotic voriconazole on the pharmacokinetics and pharmacodynamics of oral and intravenous midazolam.**

Methods: **We used a randomized, crossover study design. Ten healthy male volunteers were given either no pretreatment (control phase) or voriconazole (voriconazole phase) orally, 400 mg twice daily on the first day and 200 mg twice daily on the second day. Midazolam was given, either 0.05 mg/kg intravenously or 7.5 mg orally, 1 hour after the last dose of voriconazole and during the control phase. Plasma concentrations of midazolam, α-hydroxymidazolam, and voriconazole were determined for 24 hours and pharmacodynamic variables measured for 12 hours.**

Results: **Voriconazole reduced the clearance of intravenous midazolam by 72% ($P < .001$) and increased its elimination half-life from 2.8 to 8.3 hours ($P < .001$). Voriconazole increased the peak concentration and the area under the plasma concentration–time curve of oral midazolam by 3.8- and 10.3-fold, respectively ($P < .001$). The bioavailability of oral midazolam was increased from 31% to 84% ($P < .001$). Voriconazole profoundly increased the psychomotor effects of oral midazolam ($P < .001$) but only weakly increased the effects of intravenous midazolam.**

Conclusion: **When midazolam is given as small intravenous bolus doses, its effect is not increased to a clinically significant degree by voriconazole. The use of large midazolam doses increases the risk of clinically significant interactions also after its intravenous administration. The use of oral midazolam with voriconazole should be avoided, or substantially lower doses should be used. (Clin Pharmacol Ther 2006;79:362-70.)**

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Voriconazole is a novel triazole antifungal agent used for the treatment of severe fungal infections including *Aspergillus* and *Candida* species.[1] It is available as both oral and intravenous formulations. Voriconazole is rapidly and almost completely absorbed from the gastrointestinal tract.[2,3] Voriconazole undergoes an extensive oxidative metabolism involving cytochrome P450 (CYP) enzyme isoforms CYP2C9, CYP2C19, and, to a lesser extent, CYP3A4.[4] Although voriconazole has been shown to inhibit several CYP enzymes, such as CYP2C9 (eg, warfarin[5]), CYP2C19 (eg, omeprazole[6]), and CYP3A4 (eg, sirolimus[7]), the interaction potential of voriconazole is poorly characterized.

Midazolam is a short-acting benzodiazepine widely used for preoperative sedation, induction, and maintenance of anesthesia, as well as sedation of patients in intensive care units. It undergoes extensive first-pass metabolism with an oral bioavailability lower than 50%. The hepatic biotransformation of midazolam is mediated mainly by CYP3A, and midazolam can be used as a probe substrate for this enzyme.[8,9] Previous studies have shown that the concomitant use of CYP3A inhibitors such as ketoconazole, itraconazole, saquinavir, and erythromycin significantly increases the plasma concentrations and pharmacologic effects of both oral and intravenous midazolam.[10-12] We, therefore, found

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The study was supported by EVO Grant No. 13821 from the Hospital District of Southwest Finland and the Sigrid Juselius Foundation.

Received for publication Oct 13, 2005; accepted Dec 20, 2005.

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0009-9236/$32.00

doi:10.1016/j.clpt.2005.12.305

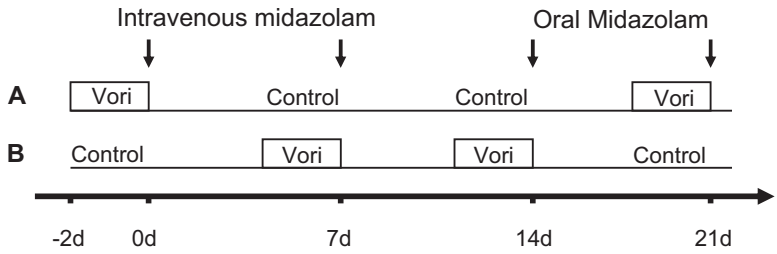

Fig 1. A 4-phase randomized crossover study design at intervals of 1 week was used. Before oral or intravenous midazolam administration, 10 healthy volunteers were given, in a randomized order (sequence A or B), either no pretreatment (control) or oral voriconazole (Vori) for 2 days. The dose of voriconazole was 400 mg twice daily on the first day and 200 mg twice daily on the second day.

it important to study the possible effect of voriconazole on the pharmacokinetics of oral and intravenous midazolam in healthy volunteers.

METHODS

Study design. The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland, as well as by the National Agency of Medicines, Finland. Written informed consent was obtained from 10 healthy volunteers, all men (age range, 23-29 years; weight range, 65-100 kg). Before entering the study, the volunteers were ascertained to be in good health by medical history, clinical examination, and standard hematologic and blood chemistry tests. None of the volunteers was receiving any continuous medication or was a smoker.

We used a randomized, open, 4-phase crossover study design at intervals of 1 week (Fig 1). Before the administration of midazolam (intravenously in the first part of the study and orally in the second part of the study), the volunteers were given, in a randomized order, either no pretreatment (control phase) or oral voriconazole (voriconazole phase) for 2 days. The dose of voriconazole (Vfend tablet; Pfizer, New York, NY) was 400 mg every 12 hours for 1 day and then 200 mg every 12 hours for 1 additional day. The last dose of voriconazole was given at 8 AM with 150 mL of water by the investigators in the research facility, and those volunteers not receiving any pretreatment were given 150 mL of water.

In the first part of the study, on 2 occasions at an interval of 1 week, all volunteers received 0.05 mg/kg intravenous midazolam (Dormicum, 1-mg/mL injection; Roche, Basel, Switzerland) in a 2-minute period, 1 hour after the last dose of voriconazole or water. In the second part of the study, on 2 occasions at an interval of 1 week, all subjects received 7.5 mg oral midazolam (Dormicum, 7.5-mg tablet; Roche) with 150 mL of water 1 hour after the last dose of voriconazole or water. The volunteers had been instructed to take the pretreatment dose at home with a meal, and adherence with the drug-dosing schedule was assessed by use of mobile telephone text messages. The volunteers fasted for 12 hours before the administration of midazolam. They were given standard meals at 4 hours and 8 hours after midazolam administration. They were not allowed to smoke or to drink grapefruit juice, alcohol, coffee, tea, or cola on the test days.

Blood sampling and drug analysis. On the test days, a forearm vein of each subject was cannulated, and timed blood samples were drawn into ethylenediaminetetraacetic acid–containing tubes immediately before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after midazolam administration. An additional blood sample was drawn 0.25 hour after intravenous midazolam administration. Plasma was separated within 30 minutes and stored at −40°C until analysis. In the first part of the study, another venous cannula was inserted into the opposite forearm for the intravenous administration of midazolam.

Concentrations of midazolam and α-hydroxymidazolam were determined by HPLC.[13] The quantitation limit was 2 ng/mL for midazolam and 1 ng/mL for α-hydroxymidazolam. The interday coefficient of variation (CV) for midazolam was 10.3%, 3.8%, and 3.1% at 2.75 ng/mL, 60.4 ng/mL, and 141 ng/mL, respectively (n = 12). The CV for α-hydroxymidazolam was 6.3%, 2.5%, and 1.9% at 3.00 ng/mL, 60.7 ng/mL, and 140 ng/mL, respectively (n = 12). Concentrations of voriconazole were determined by HPLC.[14,15] The quantitation limit was 20 ng/mL, and the CV was 10.3%, 1.8%, and 1.8% at 50.3 ng/mL, 953 ng/mL, and 9923 ng/mL, respectively (n = 9).

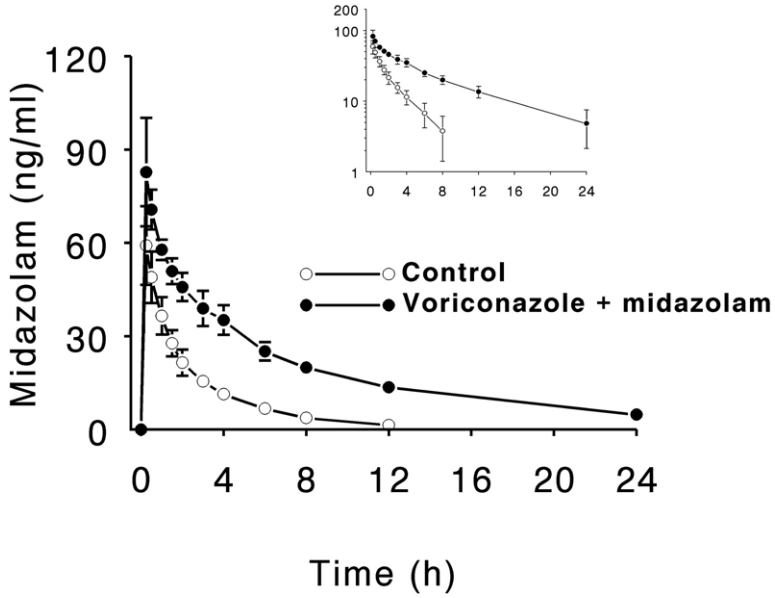

Fig 2. Plasma concentrations (mean ± SD) of midazolam in 10 healthy volunteers after intravenous dose of 0.05 mg/kg midazolam without pretreatment (*open circles*) or after pretreatment with oral voriconazole (400 mg twice daily on first day and 200 mg twice daily on second day) (*solid circles*). The concentrations are shown both on an arithmetic and on a semilogarithmic plot (*inset*).

Pharmacokinetic analysis. The peak plasma concentrations (C_{max}) and corresponding C_{max} times (t_{max}) were observed directly from the data. The areas under the midazolam and α-hydroxymidazolam plasma concentration–time curves were estimated by means of the trapezoidal rule with extrapolation to infinity [AUC(0-∞)]. We used the linear trapezoidal rule when successive concentration values were increasing and the logarithmic trapezoidal rule when successive concentration values were decreasing after the peak concentration value. For voriconazole, we calculated the area under the voriconazole plasma concentration–time curve from 0 to 24 hours [AUC(0-24)]. For each subject, the terminal log-linear phase of the midazolam plasma concentration–time curve was identified visually and the elimination rate constant (k_e) was determined by regression analysis. The elimination half-life ($t_{½}$) was then calculated from the following equation: $t_{½} = \ln 2/k_e$.

After intravenous administration of midazolam, plasma clearance (CL) and steady-state volume of distribution (V_{ss}) of midazolam were calculated by use of noncompartmental methods based on statistical moment theory. The oral bioavailability of midazolam (F) was calculated as follows: $F = [AUC(0\text{-}\infty)_{oral} \cdot Dose_{intravenous}]/[AUC(0\text{-}\infty)_{intravenous} \cdot Dose_{oral}]$.

After oral administration of midazolam, we calculated the apparent clearance (CL/F) and the apparent volume of distribution of midazolam during elimination (V_z/F). The pharmacokinetic data were analyzed with the use of the WinNonlin pharmacokinetic program (version 4.1; Pharsight, Mountain View, Calif).

Pharmacodynamic measurements. The effects of midazolam were assessed with the Maddox wing test and 3 visual analog scales at the time of blood sampling up to 12 hours after midazolam administration. The Maddox wing test was used to measure the effect of midazolam on the coordination of the extraocular muscles, and the result was given in diopters.[16] Subjective effects (no effects of the drug to very strong effects of the drug, alert to drowsy, very good performance to very poor performance) were recorded with 100-mm horizontal visual analog scales.[17] For each pharmacodynamic variable, the area under the response-time curve was determined by use of the trapezoidal rule for 12 hours.

Statistical analysis. The results are expressed as mean ± SD. The Student paired *t* test was used, and differences were regarded as significant at $P < .05$. We also calculated the geometric mean ratios with 90% confidence intervals and 95% confidence intervals for the differences between the control and voriconazole

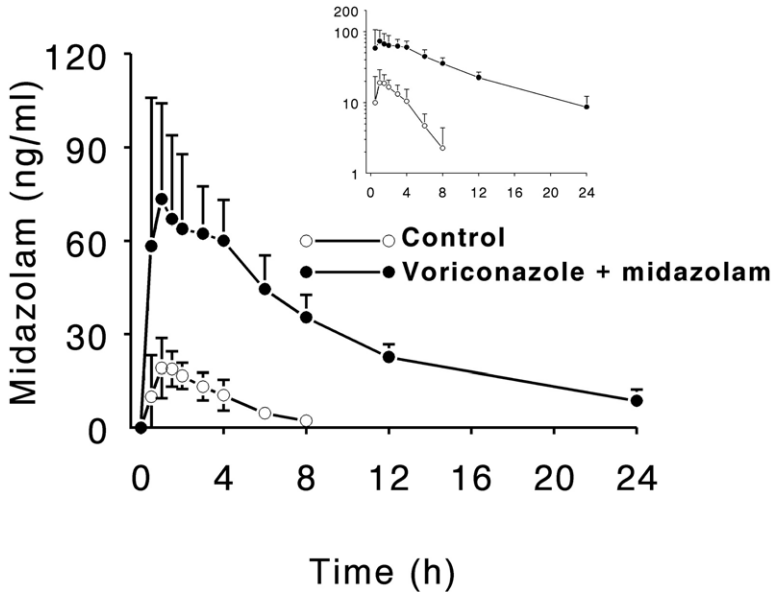

Fig 3. Plasma concentrations (mean ± SD) of midazolam in 10 healthy volunteers after oral dose of 7.5 mg midazolam without pretreatment (*open circles*) or after pretreatment with oral voriconazole (400 mg twice daily on first day and 200 mg twice daily on second day) (*solid circles*). The concentrations are shown both on an arithmetic and on a semilogarithmic plot (*inset*).

Table I. Pharmacokinetic parameters of midazolam and α-hydroxymidazolam after intravenous administration of 0.05 mg/kg midazolam without pretreatment (control) or after pretreatment with oral voriconazole (400 mg twice daily on first day and 200 mg twice daily on second day) to 10 healthy volunteers

Parameter	*Control phase*	*Voriconazole phase*	*95% CI of difference between phases*	*Geometric mean ratio (90% CI)*
Midazolam				
CL (mL · min^{-1} · kg^{-1})	5.9 ± 1.5	1.6 ± 0.3*	−5.3 to −3.3	0.28 (0.25 to 0.31)
% of control and range	100	28 (20-35)		
V_{ss} (L · kg^{-1})	1.2 ± 0.2	1.0 ± 0.2‡	−0.4 to −0.1	0.81 (0.72 to 0.91)
% of control and range	100	82 (60-110)		
AUC(0-∞) (ng · mL^{-1} · h)	151 ± 40	534 ± 88*	334 to 433	3.61 (3.20 to 4.08)
% of control and range	100	369 (283-495)		
$t_{½}$ (h)	2.8 ± 1.1	8.3 ± 3.5*	3.6 to 7.3	2.93 (2.64 to 3.26)
% of control and range	100	298 (229-376)		
α-Hydroxymidazolam				
C_{max} (ng · mL^{-1})	3.8 ± 0.9	3.1 ± 1.2‡	−1.2 to −0.1	0.80 (0.69 to 0.93)
% of control and range	100	82 (53-107)		
t_{max} (h)	0.75 (0.25-1.5)	2.0 (1.0-3.0)†		
AUC(0-∞) (ng · mL^{-1} · h)	16.1 ± 3.2	27.0 ± 13.1‡	3.0 to 18.8	1.53 (1.20 to 1.95)
% of control and range	100	164 (79-222)		
AUC ratio	0.11 ± 0.04	0.05 ± 0.03*	−0.07 to −0.05	0.42 (0.35 to 0.52)
% of control and range	100	45 (28-68)		

Data are given as mean ± SD, except for t_{max} data, which are given as median and range. Percent of control was calculated individually for each subject, and the mean and range of these individual values are reported.

CI, Confidence interval; CL, plasma clearance of midazolam; V_{ss}, steady-state volume of distribution; AUC(0-∞), area under midazolam or α-hydroxymidazolam plasma concentration–time curve extrapolated to infinity; $t_{½}$, elimination half-life; C_{max}, peak plasma concentration; t_{max}, time to peak plasma concentration; AUC ratio, ratio of α-hydroxymidazolam AUC(0-∞) to midazolam AUC(0-∞).

*Significantly different from control at $P < .001$.

†Significantly different from control at $P < .01$.

‡Significantly different from control at $P < .05$.

Table II. Pharmacokinetic parameters of midazolam and α-hydroxymidazolam after oral administration of 7.5 mg midazolam without pretreatment (control) or after pretreatment with oral voriconazole (400 mg twice daily on first day and 200 mg twice daily on second day) to 10 healthy volunteers

Parameter	*Control phase*	*Voriconazole phase*	*95% CI of difference between phases*	*Geometric mean ratio (90% CI)*
Midazolam				
C_{max} (ng · mL^{-1})	24.1 ± 7.2	86.6 ± 26.2*	44.5 to 80.5	3.56 (2.85 to 4.44)
% of control and range	100	380 (193-648)		
t_{max} (h)	1.0 (0.5-3.0)	1.0 (0.5-6.0)		
AUC(0-∞) (ng · mL^{-1} · h)	91 ± 30	855 ± 104*	698 to 831	9.85 (8.23 to 11.79)
% of control and range	100	1028 (601-1546)		
CL/F (mL · min^{-1} · kg^{-1})	20.1 ± 8.1	1.9 ± 0.3*	−23.8 to −12.5	0.10 (0.08 to 0.12)
% of control and range	100	11 (6-17)		
V_z/F (L · kg^{-1})	3.7 ± 0.8	1.4 ± 0.4*	−2.8 to −1.8	0.36 (0.31 to 0.42)
% of control and range	100	38 (26-67)		
$t_{½}$ (h)	2.5 ± 1.2	8.8 ± 4.0*	4.1 to 8.5	3.57 (3.09 to 4.12)
% of control and range	100	367 (227-536)		
F	0.31 ± 0.06	0.84 ± 0.08*	0.45 to 0.60	2.73 (2.38 to 3.12)
% of control and range	100	280 (210-436)		
α-Hydroxymidazolam				
C_{max} (ng · mL^{-1})	8.2 ± 2.7	7.7 ± 3.8	−3.5 to 2.5	0.89 (0.64 to 1.23)
% of control and range	100	101 (33-171)		
t_{max} (h)	1.0 (0.5-2.0)	1.0 (0.5-6.0)		
AUC(0-∞) (ng · mL^{-1} · h)	24.4 ± 5.7	60.8 ± 22.1*	23.6 to 49.1	2.39 (2.09 to 2.73)
% of control and range	100	245 (179-323)		
AUC ratio	0.30 ± 0.13	0.07 ± 0.03*	−0.07 to −0.04	0.24 (0.20 to 0.30)
% of control and range	100	26 (13-39)		

Data are given as mean ± SD, except for t_{max} data, which are given as median and range. Percent of control was calculated individually for each subject, and the mean and range of these individual values are reported.
CL/F, Apparent oral clearance; V_z/F, apparent volume of distribution during elimination; F, oral bioavailability.
*Significantly different from control at $P < .001$.

phases. The Pearson product-moment correlation coefficient was used to investigate the possible relationship between the ratio of the AUC(0-∞) of midazolam during the voriconazole phase with the AUC(0-∞) of midazolam during the control phase and the AUC(0-24) of voriconazole. Correlation analysis was also used to study the possible relationship between midazolam plasma concentrations and effects. All data were analyzed by use of the statistical program SPSS for Windows, version 11.0 (SPSS, Chicago, Ill).

RESULTS

Midazolam. Voriconazole decreased the plasma CL of intravenous midazolam by 72% ($P < .001$) and increased its $t_{½}$ from 2.8 hours to 8.3 hours ($P < .001$) (Fig 2 and Table I). Voriconazole increased the mean C_{max} and AUC(0-∞) of oral midazolam by 3.8- and 10.3-fold, respectively ($P < .001$). The AUC(0-∞) of oral midazolam was increased in all subjects by voriconazole, with the greatest increase being 15.5-fold. The $t_{½}$ of oral midazolam was prolonged from 2.5 hours to 8.8 hours, and the oral bioavailability was increased from 31% to 84% ($P < .001$) by voriconazole (Fig 3 and Table II).

α-Hydroxymidazolam. Voriconazole increased the AUC(0-∞) of α-hydroxymidazolam after oral ($P < .001$) and intravenous ($P < .05$) midazolam. The ratio of α-hydroxymidazolam AUC(0-∞) to midazolam AUC(0-∞) was significantly higher ($P < .001$) during the control phase, as compared with the voriconazole phase, after both oral and intravenous midazolam (Tables I and II).

Pharmacodynamics. There was a linear correlation between midazolam concentration and effect in all pharmacodynamic variables ($P < .001$). During the voriconazole phase, the high concentrations of midazolam after oral administration were associated with profound sedative effects. The area under the plasma concentration–time curve (AUC) from 0 to 12 hours for all pharmacodynamic tests during the voriconazole phase differed significantly ($P < .001$) from that in the control phase (Fig 4). After intravenous administration of

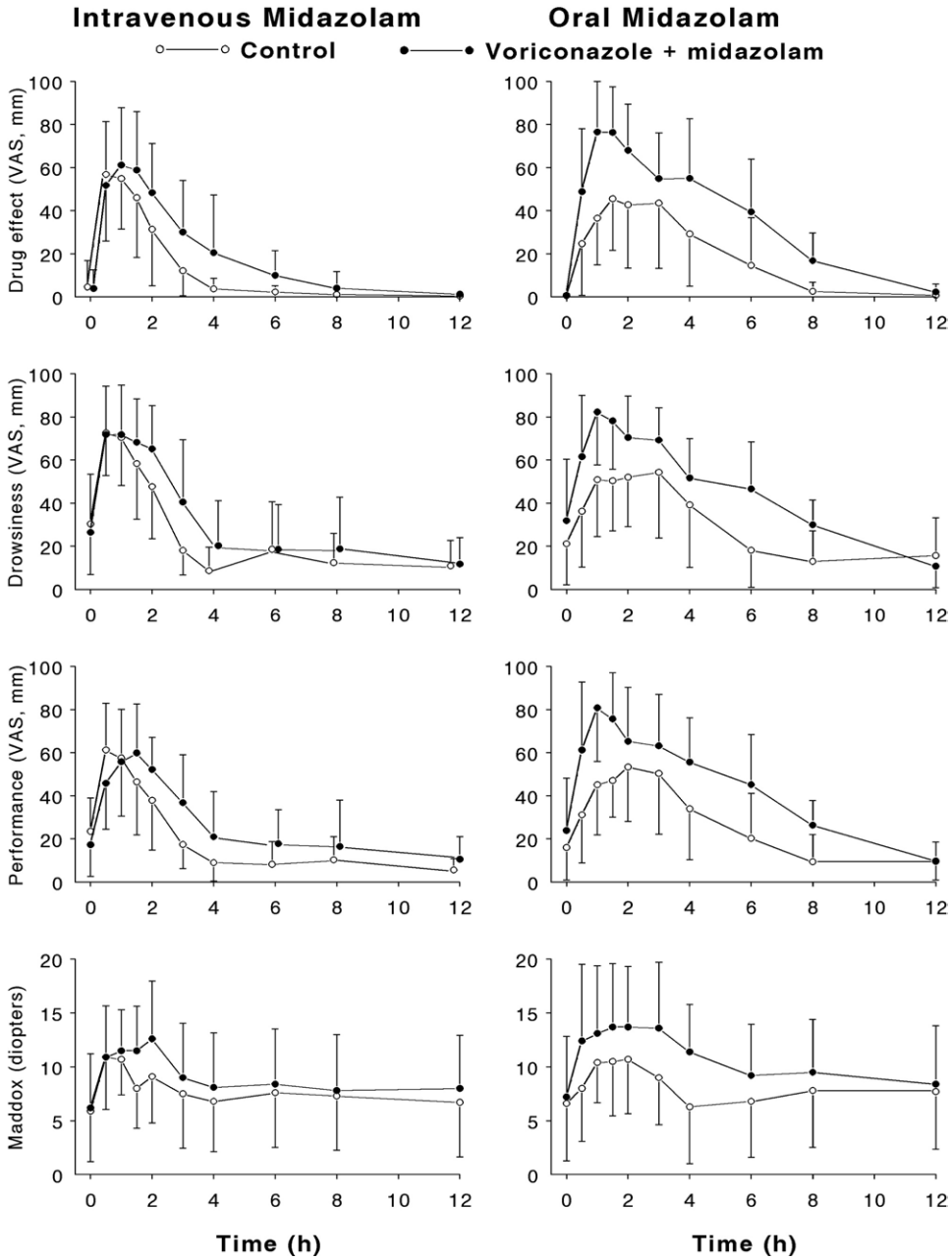

Fig 4. Results (mean ± SD) of Maddox wing test and recordings of subjective drug effect, drowsiness, and performance from visual analog scales (VAS) after intravenous dose of 0.05 mg/kg (*left*) and after oral dose of 7.5 mg (*right*) of midazolam without pretreatment (*open circles*) or after pretreatment with oral voriconazole (400 mg twice daily on first day and 200 mg twice daily on second day) (*solid circles*) to 10 healthy volunteers.

midazolam, voriconazole increased only the AUC from 0 to 12 hours for overall drug effect by 71% ($P < .05$).

Plasma voriconazole. The plasma concentration profile of voriconazole was similar during both voriconazole phases (Fig 5). The mean plasma concentration of voriconazole before the administration of midazolam was 397 ng/mL (range, 243-1502 ng/mL) in the first part of the study and 492 ng/mL (range, 217-826

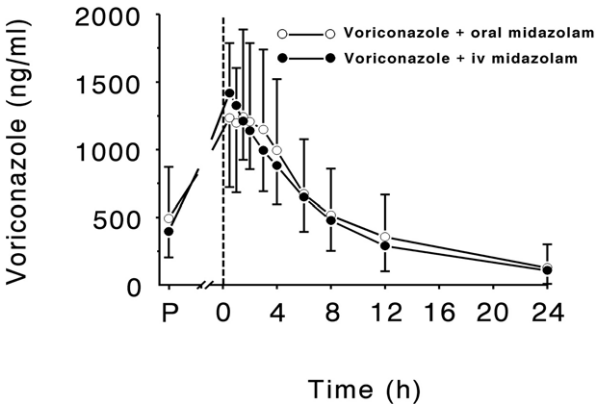

Fig 5. Plasma concentrations (mean ± SD) of voriconazole in 10 healthy volunteers during voriconazole phases. The dose of oral voriconazole was 400 mg twice daily on the first day and 200 mg twice daily on the second day. The *vertical dotted line* denotes the time when either 0.05 mg/kg intravenous midazolam or 7.5 mg oral midazolam was administered. P, Time point before administration of last dose of voriconazole.

ng/mL) in the second part. The AUC(0-24) of voriconazole was 12,201 ± 5734 ng · mL^{-1} · h (mean ± SD) in the first part of the study and 13,776 ± 10,758 ng · mL^{-1} · h in the second part (Table III). In addition, C_{max}, t_{max}, and $t_{½}$ of voriconazole were similar during both voriconazole phases (Table III). In the control phase the plasma voriconazole concentrations were undetectable on the test days. There was no significant linear correlation between the change in the AUC(0-∞) of midazolam and the AUC(0-24) of voriconazole after the intravenous ($r = 0.13$, $P = .73$) or oral ($r = -0.24$, $P = .5$) administration of midazolam.

Adverse effects. All volunteers completed the study, but visual adverse events were reported by 6 of 10 volunteers. They had transient altered perception of light, chromatopsia, and photophobia shortly after taking voriconazole. No other adverse effects were reported.

DISCUSSION

Voriconazole profoundly affected the pharmacokinetics of both intravenous and oral midazolam. After intravenous midazolam administration, voriconazole reduced the mean plasma CL of midazolam by 72%. Because values for V_{ss} remained essentially unaffected, the change in CL was associated with a significant prolongation of the $t_{½}$. After oral administration, the C_{max} of midazolam was increased by 3.8-fold and the AUC(0-∞) was increased by 10.3-fold. These changes resulted from an increase in oral bioavailability and a decrease in the plasma CL of midazolam. During the voriconazole phase, the mean plasma concentration of midazolam at 12 hours after oral ingestion was still higher than the C_{max} of midazolam when no voriconazole was administered.

Midazolam is metabolized mainly by CYP3A4, yielding α-hydroxymidazolam and, to a lesser extent, 4-hydroxymidazolam.[9] The observed decreases in the C_{max} values of α-hydroxymidazolam and in the ratio of α-hydroxymidazolam AUC(0-∞) to midazolam AUC(0-∞) reflect the inhibition of midazolam hydroxylation during voriconazole treatment. Because CYP3A4 is expressed both in the gut wall and in the liver,[18] the inhibition of CYP3A4 by voriconazole can occur in both sites. Accordingly, it is not surprising that the mean AUC(0-∞) of oral midazolam was increased by more than 10-fold by voriconazole compared with the 3.7-fold increase after intravenous midazolam.

There was a considerable interindividual variation in the AUC(0-24) of voriconazole. It is mainly the saturable metabolism that increases interindividual variability in plasma voriconazole concentrations.[3] Another important factor increasing the variability of voriconazole concentrations is the genetic polymorphism in the activity of CYP2C19, which plays a major role in the elimination of voriconazole.[19] However, the crossover study design allowed us to evaluate the effect of voriconazole on the pharmacokinetics of midazolam reliably.

When midazolam was given orally, its higher plasma concentrations after previous voriconazole administration were also reflected in pharmacodynamics. During the control phase, midazolam caused a short-lasting hypnotic and sedative effect only. In contrast to this, administration of midazolam along with voriconazole resulted in deep and long-lasting hypnotic effects. All pharmacodynamic measurements showed a statistically significant difference between the control and voriconazole phases up to 8 hours after administration of oral midazolam. However, because no double-blind study design was used, the pharmacodynamic findings should be interpreted cautiously, but they do support the observed changes in pharmacokinetics demonstrating a forceful interaction between voriconazole and oral midazolam. There was a high rate of mild reversible visual disturbances after the administration of voriconazole. Because the volunteers were medical students who were well informed about the side effects of voriconazole, even a double-blind study design would hardly have increased the validity of the pharmacodynamic results.

Table III. Pharmacokinetic parameters of oral voriconazole (400 mg twice daily on first day and 200 mg on second day) in 10 healthy volunteers during oral and intravenous dosing of midazolam

Parameter	*Intravenous administration*	*Oral administration*	*95% CI of difference between oral and intravenous dosing*	*Geometric mean ratio (90% CI)*
C_{max} (ng · mL^{-1})	1495 ± 609	1441 ± 329	−244 to 135	1.02 (0.89 to 1.17)
t_{max} (h)	1 (0.25-3)	0.5 (0.5-1)		
AUC(0-24) (ng · mL^{-1} · h)	13,776 ± 10,758	12,201 ± 6044	−4603 to 1454	0.97 (0.84 to 1.12)
$t_{½}$ (h)	6.9 ± 2.5	6.5 ± 1.8	−1.06 to 0.24	0.99 (0.57 to 1.72)

Data are given as mean ± SD, except for t_{max} data, which are given as median and range.
AUC(0-24), Area under voriconazole plasma concentration–time curve from 0 to 24 hours.

The pharmacokinetics of midazolam after intravenous administration were not affected to the same extent as after oral ingestion. However, during the voriconazole phase, the concentration of intravenous midazolam was still, 24 hours after its administration, higher than during the control phase at 8 hours. The pharmacodynamic changes paralleled the changes in pharmacokinetics, and consequently, only minor changes in pharmacodynamics were observed. Because voriconazole changes the pharmacokinetics of oral midazolam both by reducing the first-pass metabolism and by reducing elimination, it affects the pharmacokinetics of oral midazolam more than that of intravenous midazolam.

Voriconazole has been shown to have significant interactions with several substrates of CYP3A4. For example, voriconazole increases the concentrations of cyclosporine (INN, ciclosporin),[20] sirolimus,[7] and tacrolimus[21] to a clinically significant degree. However, the extent of the interaction can depend greatly on the pharmacokinetic properties of the substrate drug. Itraconazole, fluconazole, and erythromycin decrease the mean plasma CL of intravenous midazolam by 69%, 51%, and 54%, respectively, and increase the AUC of oral midazolam by 6.6-, 3.6-, and 4.4-fold, respectively.[11,22] Ketoconazole has caused a 15.9-fold increase in the AUC of oral midazolam.[10] Thus voriconazole decreases the plasma CL of midazolam to the same extent as itraconazole but more than fluconazole or erythromycin. Regarding oral midazolam, voriconazole increases its plasma concentrations more than itraconazole, fluconazole, and erythromycin but less than ketoconazole.

A strong inhibition of CYP3A4 may carry a risk of earlier unrecognized drug interactions. For example, a recent pharmacoepidemiologic study has found a more than 5-fold incidence ratio in the adjusted rate of sudden death from cardiac diseases among those patients who concurrently used strong inhibitors of CYP3A4 and erythromycin.[23] Accordingly, it is prudent to also avoid the concomitant use of voriconazole and erythromycin.

The interaction of orally administered midazolam with voriconazole is clearly of clinical significance. The clinical implication of this study is that clinicians should know that voriconazole increases and prolongs the effects of common hypnotic doses of oral midazolam to the extent that its hypnotic and sedative effect can no longer be regarded as being short in duration. Prescription of oral midazolam to patients receiving voriconazole should be avoided, or substantially lower doses should be used. On the other hand, the interaction of intravenous midazolam with voriconazole is probably of less clinical significance. Voriconazole considerably decreases the CL of midazolam. However, after small bolus doses, it is mainly the redistribution of midazolam that determines the duration of action. Therefore, on the basis of this study in healthy young volunteers, it can be concluded that major adjustments of the dose are most likely not necessary. Unfortunately, we have not studied the interaction of voriconazole and midazolam in other groups, such as elderly patients or patients with renal or liver dysfunction. Thus our results may not be extrapolated uncritically to clinical practice. If high doses of intravenous midazolam are used, it is prudent to adjust doses of intravenous midazolam and to monitor patients closely. Long-term infusions of midazolam to patients receiving systemic voriconazole (eg, during intensive care treatment) may result in undesirably long-lasting hypnotic effects if the dose is not titrated according to the effect.

We thank Mrs Elina Kahra, Mrs Eija Mäkinen-Pulli, and Mr Jouko Laitila for skillful determinations of the drug plasma concentrations and technical assistance.

There are no conflicts of interest.

References

1. Boucher HW, Groll AH, Chiou CC, Walsh TJ. Newer systemic antifungal agents. Pharmacokinetics, safety and efficacy. Drugs 2004;64:1997-2020.

2. Purkins L, Wood N, Greenhalgh K, Eve MD, Oliver SD, Nichols D. The pharmacokinetics and safety of intravenous voriconazole—a novel wide-spectrum antifungal agent. Br J Clin Pharmacol 2003;56(Suppl 1):2-9.
3. Purkins L, Wood N, Greenhalgh K, Allen MJ, Oliver SD. Voriconazole, a novel wide spectrum triazole: oral pharmacokinetics and safety. Br J Clin Pharmacol 2003; 56(Suppl 1):10-6.
4. Hyland R, Jones BC, Smith DA. Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. Drug Metab Dispos 2003;31:540-7.
5. Purkins L, Wood N, Kleinermans D, Nichols D. Voriconazole potentiates warfarin-induced prothrombin time prolongation. Br J Clin Pharmacol 2003;56(Suppl 1): 24-9.
6. Wood N, Tan K, Purkins L, Layton G, Hamlin J, Kleinermans D, et al. Effect of omeprazole on the steady-state pharmacokinetics of voriconazole. Br J Clin Pharmacol 2003;56(Suppl 1):56-61.
7. Sádaba B, Campanero MA, Quetglas EG, Azanza JR. Clinical relevance of sirolimus drug interactions in transplant patients. Transplant Proc 2004;36:3226-8.
8. Allonen H, Ziegler G, Klotz U. Midazolam kinetics. Clin Pharmacol Ther 1981;30:653-61.
9. Wandel C, Böcker R, Böhrer H, Browne A, Rügheimer E, Martin E. Midazolam is metabolized by at least three different cytochrome P450 enzymes. Br J Anaesth 1994; 73:658-61.
10. Olkkola KT, Backman J, Neuvonen PJ. Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole and itraconazole. Clin Pharmacol Ther 1994;55:481-5.
11. Palkama VJ, Ahonen J, Neuvonen PJ, Olkkola KT. Effect of saquinavir on the pharmacokinetics and pharmacodynamics of oral and intravenous midazolam. Clin Pharmacol Ther 1999;66:33-9.
12. Olkkola KT, Aranko K, Luurila H, Hiller A, Saarnivaara L, Himberg JJ, et al. A potentially hazardous interaction between erythromycin and midazolam. Clin Pharmacol Ther 1993;53:298-305.
13. Ha HR, Rentsch KM, Kneer J, Vonderschmitt DJ. Determination of midazolam and its 1-hydroxymetabolite in human plasma and urine by high-performance liquid chromatography. Ther Drug Monit 1993;15:338-43.
14. Gage R, Stopher DA. A rapid HPLC assay for voriconazole in human plasma. J Pharm Biomed Anal 1998;17: 1449-53.
15. Pennick GJ, Clark M, Sutton DA, Rinaldi MG. Development and validation of HPLC assay for voriconazole. Antimicrob Agents Chemother 2003;7:2348-50.
16. Hannington-Kiff JG. Measurements of recovery from outpatient general anaesthesia with a simple ocular test. BMJ 1970;3:132-5.
17. Bond A, Lader M. The use of analogue visual scales in rating subjective feelings. Br J Med Psychol 1974;47: 211-8.
18. Lown KS, Kolars JC, Thummel KE, Barnett JL, Kunze KL, Wrighton SA, et al. Interpatient heterogeneity in expression of CYP3A4 and CYP3A5 in small bowel: lack of prediction by the erythromycin breath test. Drug Metab Dispos 1994;22:947-55.
19. Ikeda Y, Umemura K, Kondo K, Sekiguchi K, Miyoshi S, Nakashima M. Pharmacokinetics of voriconazole and cytochrome p450 2C19 genetic status. Clin Pharmacol Ther 2004;75:586-8.
20. Romero AJ, Le Pogamp P, Nilsson L-G, Wood N. Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant patients. Clin Pharmacol Ther 2002; 71:226-34.
21. Venkataramanan R, Zang S, Gayowski T, Singh N. Voriconazole inhibition of the metabolism of tacrolimus in a liver transplant recipient and in human liver microsomes. Antimicrob Agents Chemother 2002;46:3091-3.
22. Olkkola KT, Ahonen J, Neuvonen PJ. The effect of the systemic antimycotics, itraconazole and fluconazole, on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. Anesth Analg 1996;82:511-6.
23. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and the risk of sudden death from cardiac causes. N Engl J Med 2004;351:1089-96.