Effects of aprepitant on cytochrome P450 3A4 activity using midazolam as a probe

Background: **Aprepitant is a neurokinin$_1$ receptor antagonist that enhances prevention of chemotherapy-induced nausea and vomiting when added to conventional therapy with a corticosteroid and a 5-hydroxytryptamine$_3$ (5-HT$_3$) antagonist. Because aprepitant may be used with a variety of chemotherapeutic agents and ancillary support drugs, which may be substrates of cytochrome P450 (CYP) 3A4, assessment of the potential of this drug to inhibit CYP3A4 activity in vivo is important. The effect of aprepitant on in vivo CYP3A4 activity in humans with oral midazolam used as a sensitive probe of CYP3A4 activity was evaluated in this study.**

Methods: **In this open-label, randomized, single-period study, 16 healthy male subjects were enrolled. Subjects received one of two oral aprepitant regimens for 5 days (8 subjects per regimen): (1) 125 mg aprepitant on day 1 and then 80 mg/d on days 2 to 5 or (2) 40 mg aprepitant on day 1 and then 25 mg/d on days 2 to 5. All subjects also received a single oral dose of midazolam, 2 mg, at prestudy (3 to 7 days before aprepitant treatment) and on days 1 and 5 (1 hour after aprepitant administration).**

Results: **Coadministration of midazolam and 125/80 mg aprepitant increased the midazolam area under the plasma concentration–time curve by 2.3-fold on day 1 ($P < .01$) and by 3.3-fold on day 5 ($P < .01$), as compared with midazolam alone (prestudy). The 125/80-mg regimen of aprepitant also increased the midazolam maximum observed concentration by 1.5-fold on day 1 ($P < .05$) and by 1.9-fold on day 5 ($P < .01$). The midazolam half-life values increased from 1.7 hours (prestudy) to 3.3 hours on both day 1 and day 5. Coadministration of 40/25 mg aprepitant and midazolam did not result in significant changes in the midazolam area under the plasma concentration–time curve, maximum observed concentration, and half-life at either day 1 or day 5.**

Conclusions: **The 5-day 125/80-mg regimen of aprepitant produced moderate inhibition of CYP3A4 activity in humans, as measured with the use of midazolam as a probe drug. (Clin Pharmacol Ther 2003;74:150-6.)**

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Aprepitant (also known as MK-0869, L-754030, and EMEND [registered trademark of Merck & Co, Inc, Whitehouse Station, NJ]) is the first of a new class of antiemetic agents called the neurokinin$_1$ receptor antagonists.[1] By blocking the neurokinin$_1$ receptor, these agents antagonize a dysregulation in central nervous system substance P activity, which is thought to contribute to emesis. When administered concomitantly with a corticosteroid and a 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist, aprepitant effectively improves the control of nausea and vomiting associated with highly emetogenic chemotherapy.[2,3] The mean oral bioavailability of aprepitant is approximately 60% to 65%, and the mean peak plasma concentrations are reached at approximately 4 hours. The apparent terminal half-life ranges from approximately 9 to 13 hours. Aprepitant is unlikely to interact with drugs that are substrates for the P-glycoprotein transporter, as shown by the lack of interaction of aprepitant with digoxin in a clinical drug interaction study.[4] In vitro studies in human liver microsomes have shown that aprepitant inhibits cytochrome P450 (CYP) 3A4 (unpublished ob-

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servations). The CYP3A4 isozyme is involved in the metabolic clearance of many clinically used medications and can give rise to a variety of metabolic drug-drug interactions.[5] Because aprepitant will potentially be administered in conjunction with chemotherapeutic and antiemetic agents, as well as therapy for concurrent medical illnesses, it is important to quantify the potential for this drug to inhibit CYP3A4 activity in vivo.

In this study the potential for aprepitant to inhibit CYP3A4 activity in humans in vivo was assessed by using oral midazolam as a sensitive probe substrate.[6-8] Midazolam undergoes extensive first-pass metabolism by both hepatic and intestinal CYP3A4 and is rapidly converted to 1'-hydroxymidazolam.[7,9] Measurement of midazolam pharmacokinetics can, therefore, be a sensitive probe by which to detect changes in CYP3A4 activity in humans resulting from CYP3A4 inhibitors or inducers.[10] The effects of aprepitant on midazolam pharmacokinetics were determined in healthy male subjects after administration of a 5-day dose regimen similar to the 3-day regimen recommended for prevention of chemotherapy-induced nausea and vomiting (ie, the same doses were used but with an additional 2 days of treatment) and a low-dose aprepitant regimen, which was less effective in an early clinical trial.[11]

METHODS

Subjects. A total of 16 healthy male volunteers were studied, all of whom were nonsmokers, were between 20 and 43 years old (mean, 30 years), and were within 20% of the ideal height and weight range (mean weight, 77 kg [range, 59-99 kg]; mean height, 175 cm [range, 168-185 cm]). Subjects were in good general health according to routine medical history, physical examination, and laboratory data, and all agreed to refrain from consumption of grapefruit or grapefruit juice (a CYP3A4 inhibitor) 2 weeks before and during the study. Subjects were excluded if they had clinically significant abnormalities on prestudy examination, had a history of drug or food allergies or drug or alcohol abuse, had intolerance or hypersensitivity to high-dose steroids or 5-HT_3 antagonists, had donated blood or received an investigational drug within 4 weeks, or were habitual heavy coffee drinkers.

The study was conducted at The Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, NY. The protocol was approved by the institutional review board of the study center. The protocol was conducted in accordance with the guidelines on good clinical practice and with ethical standards for human experimentation established by the Declaration of Helsinki. Every subject gave written informed consent.

Design. This was an open-label, randomized, single-period study designed to evaluate the effects of aprepitant on CYP3A4 activity. A total of 16 subjects were randomly assigned to receive 1 of 2 aprepitant dosing regimens, each lasting a total of 5 days (days 1 through 5). The 125/80-mg regimen of aprepitant was similar to that used in phase III trials of the prevention of chemotherapy-induced nausea and vomiting, except that in those trials aprepitant dosing continued for only 3 days. A low-dose 40/25-mg regimen of aprepitant, which is not optimal for the treatment of chemotherapy-induced nausea and vomiting, was also studied (the optimal treatment regimen was not known at the time the study was performed). All aprepitant doses were in capsule formulations. Subjects in the 125/80-mg aprepitant group ($n = 8$) received a single oral dose of 125 mg aprepitant on day 1 and then 80 mg/d on days 2 through 5; subjects in the 40/25-mg aprepitant group ($n = 8$) received a single oral dose of 40 mg aprepitant on day 1 and then 25 mg/d on days 2 through 5. For each treatment regimen, aprepitant was administered at 8 AM, approximately 15 minutes after a light breakfast, with 250 mL of water. Subjects in both aprepitant groups received single oral doses of midazolam, 2 mg, in syrup form (VERSED; Roche Laboratories, Nutley, NJ) on 3 separate occasions, as follows: at prestudy (3 to 7 days before aprepitant treatment) and on days 1 and 5. Midazolam was administered with at least 250 mL of water 1 hour after aprepitant administration (on days 1 and 5) and 1.25 hours after a standard light breakfast in the morning.

For determination of plasma midazolam concentrations, blood was collected at 0, 1, 2, 3, 4, 8, 12, and 24 hours relative to midazolam dosing. Plasma concentrations of midazolam were determined by liquid chromatography–tandem mass spectrometry. The method was linear from 0.5 ng/mL to 100 ng/mL and used $^{13}C_3$-midazolam for the internal standard. The analyte and internal standard were isolated from the plasma by use of a liquid/liquid extraction. The organic extract was dried under nitrogen and reconstituted to a final volume of 150 μL, consisting of 40% methanol and 60% aqueous buffer. Liquid chromatographic separation was conducted with the use of a gradient under reversed phase condition. The analytic column used was a Keystone BetaBasic C18 (100 × 2 mm, 5 μm), fitted with a Keystone Basic C18 guard column (Thermo Hypersil-Keystone, Waltham, Mass). Detection was performed with HPLC–tandem mass spectrometry with the use of positive ion atmospheric pressure chemical ionization.

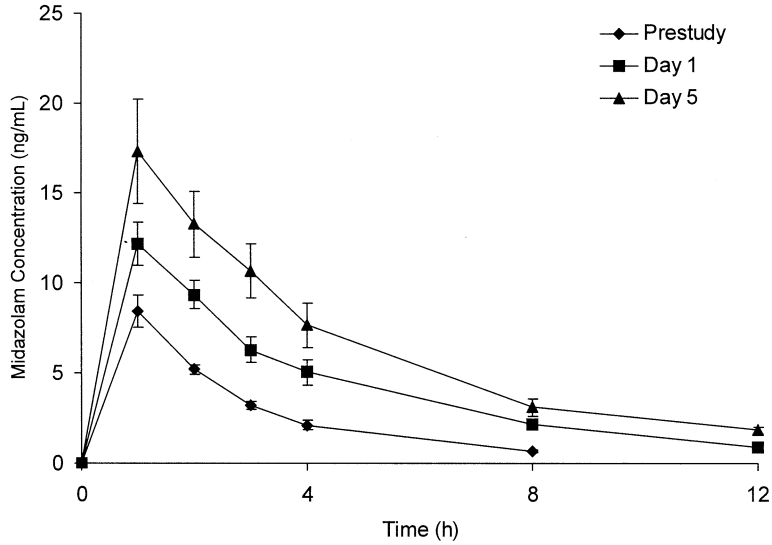

Fig 1. Plasma concentration–time profiles of midazolam before (prestudy) and during (on days 1 and 5) administration of 125 mg aprepitant on day 1 and then 80 mg on days 2 to 5. Midazolam was administered as a single oral 2-mg dose on each of the periods assessed (prestudy, day 1, and day 5). Data represent mean values in 8 healthy male subjects. The 12-hour measurement at the prestudy visit was below the limit of quantitation. *Error bars* represent standard error.

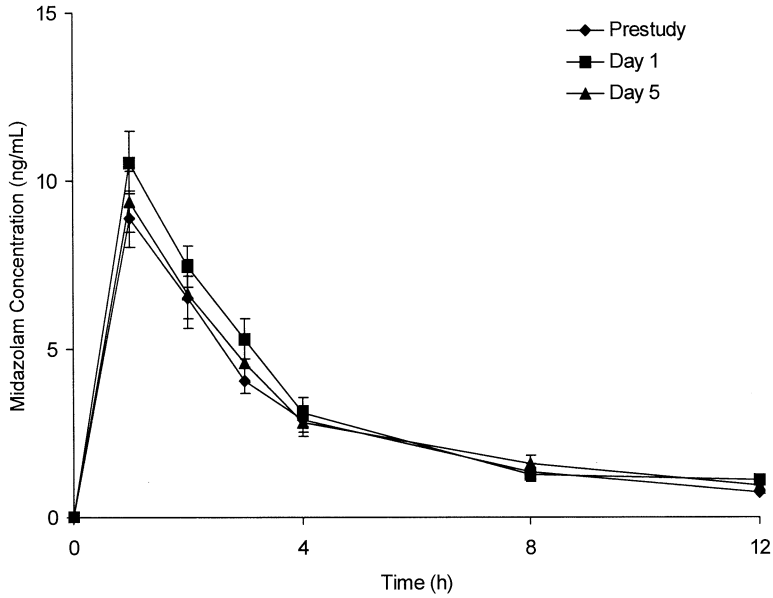

Fig 2. Plasma concentration–time profiles of midazolam before (prestudy) and during (on days 1 and 5) administration of 40 mg aprepitant on day 1 and then 25 mg on days 2 to 5. Midazolam was administered as a single oral 2-mg dose on each of the periods assessed (prestudy, day 1, and day 5). Data represent mean values in 8 healthy male subjects. *Error bars* represent standard error.

For internal standards, the intrarun precision (percent coefficient of variation) was less than or equal to 12.8% and the accuracy (percent bias) ranged from −8.50% to 4.60%. For quality controls, the corresponding values were 9.11% and 1.20% to 7.00%, respectively. The lower limit of quantitation was 0.5 ng/mL.

Plasma midazolam concentrations were used to calculate midazolam pharmacokinetic parameters (area under the plasma concentration–time curve [AUC], maximum observed concentration [C_{1h}], and half-life [$t_{1/2}$]) at prestudy and on days 1 and 5. C_{1h} is the maximum observed concentration, which may approximate the C_{max} (maximum plasma drug concentration). The first-order terminal rate constant (λ_z) was calculated from the terminal natural log–linear portion of the plasma concentration–time curve by use of a weighting of 1/*y* with the commercial software package WinNonlin (version 3.1A; Pharsight Corporation, Mountain View, Calif). The terminal $t_{1/2}$ was set at $\ln(2)/\lambda_z$. $AUC_{0\text{-}\infty}$ (AUC from time 0 to infinity) was calculated from $AUC_{last} + C_{last}/\lambda_z$ by use of the linear up/log down trapezoidal rule to calculate AUC_{last} up to the last measurable concentration (C_{last}).

Although not a primary purpose of the study, the $AUC_{0\text{-}24}$ (AUC from 0 to 24 hours) of aprepitant was also calculated on days 1 and 5.

Physical examinations, 12-lead electrocardiography, and routine hematologic, serum chemical, and urinalysis testing were performed before and after the study. Subjects were assessed for adverse experiences throughout the study. Any adverse experiences were rated by the investigator as to seriousness (regulatory definition), relatedness to study drug, and severity.

Statistical analysis. Because fold change rather than change from prestudy was of interest, the data were natural log–transformed before analysis, with arithmetic mean differences on the log scale leading to geometric mean ratios (or fold change) on the original scale. Thus individual natural log–transformed midazolam AUC values for each of the 125/80-mg and 40/25-mg regimens of aprepitant were evaluated in separate ANOVA models (with factors for subject and day). Estimates of the midazolam AUC geometric mean ratios (day 1/prestudy and day 5/prestudy) were obtained by exponentiation of the relevant between-day differences in least-squares means for the 125/80-mg and 40/25-mg regimens of aprepitant. Ninety-five percent confidence intervals (CIs) for the mean difference (on the log scale) were calculated by use of the mean square error from the ANOVA, referencing a *t* distribution. The 95% CIs for the true ratios were calculated by exponentiation of the limits of the intervals described. Statistical significance was reported if *P* values were less than .05 (2-tailed test). C_{1h} was analyzed by methods similar to those used for AUC. Differences in $t_{1/2}$were not formally analyzed.

RESULTS

All 16 subjects completed the study. The treatment regimens were generally well tolerated, with none of the subjects reporting serious clinical, laboratory, or other adverse experiences. No subjects reported sedation as an adverse experience.

Figs 1 and 2 show the mean midazolam plasma concentration–time profiles after administration of midazolam before and during (on days 1 and 5) administration of aprepitant. The 125/80-mg regimen of aprepitant increased the plasma concentrations of midazolam on day 1 compared with prestudy values (Fig 1). Further increases in plasma midazolam concentrations were apparent after aprepitant administration for a total of 5 days. In contrast, administration of 40/25 mg aprepitant did not significantly alter the plasma concentration–time profiles of midazolam determined on either day 1 or day 5 as compared with that on the prestudy day (Fig 2).

The effects of coadministration of 125/80 mg or 40/25 mg aprepitant on the key pharmacokinetic parameters of oral midazolam are summarized in Table I. Coadministration of oral midazolam with 125/80 mg aprepitant increased the geometric mean midazolam AUC from 23.0 ng · h/mL at prestudy to 52.1 ng · h/mL on day 1 and 75.7 ng · h/mL on day 5. This corresponds to AUC geometric mean ratios of 2.27 (95% CI, 1.64-3.14) on day 1 and 3.30 (95% CI, 2.39-4.56) on day 5.

The 125/80-mg regimen of aprepitant also increased the midazolam C_{1h}, from a prestudy geometric mean of 8.1 ng/mL to 11.8 ng/mL on day 1 and 15.7 ng/mL on day 5. These increases correspond to C_{1h} geometric mean ratios of 1.46 (95% CI, 1.01-2.09) on day 1 and 1.94 (95% CI, 1.35-2.7) on day 5. Moreover, 125/80 mg aprepitant increased the midazolam harmonic mean $t_{1/2}$ from 1.69 hours (prestudy) to 3.27 hours (day 1) and 3.32 hours (day 5).

In contrast to increases in pharmacokinetic parameters produced by 125/80 mg aprepitant, coadministration of midazolam with the 40/25-mg regimen of aprepitant resulted in no significant change in the midazolam pharmacokinetics either on day 1 or day 5 (Table I).

The geometric mean $AUC_{0\text{-}24}$ of aprepitant was 22.0 μg · h/mL and 28.5 μg · h/mL on day 1 and day 5, respectively, after the 125/80-mg regimen of aprepitant and 5.3 μg · h/mL and 4.0 μg · h/mL on day 1 and day 5, respectively, after the 40/25-mg regimen.

DISCUSSION

In this study 2 dose regimens of the neurokinin$_1$ receptor antagonist aprepitant were evaluated for their

Table I. Summary of midazolam pharmacokinetics (2-mg oral dose) with aprepitant (days 1 and 5) and without aprepitant (prestudy)

Parameter	*Prestudy*	*Day 1*	*Day 5*	*GMR: Day 1/ prestudy*	*P value*	*GMR: Day 5/ prestudy*	*P value*
125/80 mg aprepitant							
$AUC_{0-\infty}$ (ng · h/mL) (mean* and 95% CI)	23.0 (17.7-29.7)	52.1 (40.2-67.6)	75.7 (58.4-98.1)	2.27 (1.64-3.14)	<.01	3.30 (2.39-4.56)	<.01
C_{1h} (ng/mL) (mean* and 95% CI)	8.1 (6.0-10.8)	11.8 (8.8-15.7)	15.7 (11.7-20.9)	1.46 (1.01-2.09)	.043	1.94 (1.35-2.78)	<.01
$t_{1/2}$ (h) (mean† and range)	1.69 (1.0-2.5)	3.27 (2.7-4.5)	3.32 (2.2-4.5)	—	—	—	—
40/25 mg aprepitant							
$AUC_{0-\infty}$ (ng · h/mL) (mean* and 95% CI)	30.8 (22.0-43.1)	37.7 (26.9-52.7)	31.4 (22.5-43.9)	1.22 (0.93-1.61)	NS	1.02 (0.77-1.35)	NS
C_{1h} (ng/mL) (mean* and 95% CI)	8.6 (7.0-10.5)	10.4 (8.4-12.7)	9.0 (7.4-11.1)	1.21 (0.91-1.61)	NS	1.05 (0.79-1.40)	NS
$t_{1/2}$ (h) (mean† and range)	2.26 (1.2-3.7)	2.59 (1.2-5.2)	2.00 (1.0-4.6)	—	—	—	—

GMR, Geometric mean ratio, 125/80 mg aprepitant, 125 mg on day 1 and then 80 mg/d on days 2 to 5, $AUC_{0-\infty}$, area under plasma concentration–-time curve from time 0 to infinity, C_{1h}, maximum observed concentration, $t_{1/2}$, half-life; 40/25 mg aprepitant, 40 mg on day 1 and then 25 mg/d on days 2 to 5; CI, confidence interval; NS, not statistically significant ($P > .05$).

*Geometric mean.

†Harmonic mean.

potential to inhibit CYP3A4 activity in vivo with oral midazolam used as a sensitive probe substrate. The plasma concentrations and pharmacokinetics of single-dose midazolam were determined on day 1 and on day 5, after administration of aprepitant once daily for a total of 5 days. The following 2 regimens of aprepitant were studied: a 125/80-mg regimen similar to that shown to be effective for the prevention of chemotherapy-induced nausea and vomiting in phase III clinical trials (except with 5 days of dosing instead of 3 days) and a low-dose 40/25-mg regimen, which was less effective in an early clinical trial.[11] This design allowed assessment of potential interactions during the course of aprepitant dosing for the treatment of chemotherapy-induced nausea and vomiting and evaluation of the dose-effect relationship for such interactions.

Coadministration of oral midazolam with the 125/80-mg regimen of aprepitant (125 mg on day 1 and then 80 mg on days 2 to 5) resulted in a 2.3-fold increase in midazolam AUC on day 1 and a 3.3-fold increase on day 5, as compared with prestudy values. In addition, 125/80 mg aprepitant increased both the C_{1h} and the $t_{1/2}$ of midazolam, a finding consistent with aprepitant inhibiting both the first-pass metabolism and the systemic clearance of midazolam. The larger fold change in midazolam AUC on day 5 compared with that on day 1 is consistent with a somewhat higher aprepitant AUC on day 5 versus day 1. In contrast to the effects of 125/80 mg aprepitant on midazolam pharmacokinetics, coadministration of the low-dose 40/25-mg regimen of aprepitant (40 mg on day 1 and then 25 mg on days 2 to 5) and midazolam resulted in no change in the midazolam pharmacokinetics on either day 1 or day 5.

As noted previously, the 5-day 125/80-mg regimen of aprepitant used in this study corresponds to that shown to be effective in phase III trials of the prevention of chemotherapy-induced nausea and vomiting, with the exception that dosing with aprepitant continued for only 3 days in the phase III trials. It is unlikely that the level of CYP3A4 inhibition observed over a 3-day period would exceed that observed over a 5-day period in this study. Although moderately effective in early clinical trials, the low-dose 40/25-mg regimen of aprepitant investigated in this study is not intended for clinical use.

The extent to which a drug affects the plasma AUC of orally administered midazolam (typically a single 2-mg oral dose) has been proposed for use as a pharmacologic standard by which to classify CYP3A4 in-

hibitors in vivo.[10] By determination of the midazolam AUC measured in the presence and absence of a suspected CYP3A4 inhibitor, a particular drug can be classified into 1 of 4 CYP3A4 inhibitor categories, as follows: a strong inhibitor (≥5-fold elevation in midazolam AUC), a moderate inhibitor (2- to 4.9-fold elevation in midazolam AUC), a weak inhibitor (<2-fold elevation in midazolam AUC), or a drug with no CYP3A4 inhibitory activity.[10] On the basis of this classification system, the 125/80-mg dose regimen of aprepitant can be considered a moderate inhibitor of CYP3A4 activity in vivo over the 5-day duration of treatment. This degree of CYP3A4 inhibition is of a magnitude similar to that of diltiazem and verapamil (2 commonly used calcium channel antagonists) or 8 oz of grapefruit juice,[10] and it is substantially weaker than the level of inhibition observed with ketoconazole or itraconazole.[10,12]

Our finding that 5 days of treatment with the 125/80-mg dose regimen of aprepitant produced moderate CYP3A4 inhibition in vivo is corroborated by data from 2 recent studies in healthy subjects. These studies showed that 125/80 mg aprepitant increased the AUC of oral dexamethasone and oral methylprednisolone (2 agents metabolized by CYP3A4 and often used as part of a multimodal treatment regimen for chemotherapy-induced nausea and vomiting) by approximately 2-fold.[13] These findings are consistent with moderate inhibition by aprepitant of CYP3A4-mediated metabolism of these steroids and support halving the oral doses of these agents to avoid unnecessarily high corticosteroid exposure. The need for adjustment of doses of other CYP3A4 substrates that a patient might be receiving with aprepitant will depend on the predicted clinical impact of up to a 2- to 3-fold increase in their concentrations after oral administration.

In summary, this study indicates that 5 days of treatment with 125/80 mg aprepitant, a regimen similar to that recommended for the prevention of chemotherapy-induced nausea and vomiting, results in moderate inhibition of CYP3A4 activity. This level of inhibition is comparable to that observed with calcium channel antagonists such as diltiazem or with grapefruit juice. Our findings suggest that the 3-day regimen of aprepitant recommended for the treatment of chemotherapy-induced nausea and vomiting should be used with caution in patients receiving concomitant medicinal products that are primarily metabolized through CYP3A4, because inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these medicinal products.

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