PHARMACOKINETICS AND DRUG DISPOSITION

Effects of the neurokinin$_1$ receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone

Background: **Aprepitant is a neurokinin$_1$ receptor antagonist that, in combination with a corticosteroid and a 5-hydroxytryptamine$_3$ receptor antagonist, has been shown to be very effective in the prevention of chemotherapy-induced nausea and vomiting. At doses used for the management of chemotherapy-induced nausea and vomiting, aprepitant is a moderate inhibitor of cytochrome P4503A4 and may be used in conjunction with corticosteroids such as dexamethasone and methylprednisolone, which are substrates of cytochrome P4503A4. The effects of aprepitant on the these 2 corticosteroids were evaluated.**

Methods: **Study 1 was an open-label, randomized, incomplete-block, 3-period crossover study with 20 subjects. Treatment A consisted of a standard oral dexamethasone regimen for chemotherapy-induced nausea and vomiting (20 mg dexamethasone on day 1, 8 mg dexamethasone on days 2 to 5). Treatment B was used to examine the effects of oral aprepitant (125 mg aprepitant on day 1, 80 mg aprepitant on days 2 to 5) on the standard dexamethasone regimen. Treatment C was used to examine the effects of aprepitant on a modified dexamethasone regimen (12 mg dexamethasone on day 1, 4 mg dexamethasone on days 2 to 5). All subjects also received 32 mg ondansetron intravenously on day 1 only. Study 2 was a double-blind, randomized, placebo-controlled, 2-period crossover study with 10 subjects. Subjects in one group received a regimen consisting of 125 mg methylprednisolone intravenously on day 1 and 40 mg methylprednisolone orally on days 2 to 3. Subjects in the other group received oral aprepitant (125 mg aprepitant on day 1, 80 mg aprepitant on days 2 to 3) in addition to the methylprednisolone regimen.**

Results: **In study 1, the area under the concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24}$) of oral dexamethasone on days 1 and 5 after the standard dexamethasone plus ondansetron regimen (treatment A) was increased 2.2-fold ($P < .010$) with coadministration of aprepitant (treatment B). Coadministration of aprepitant with the modified dexamethasone plus ondansetron regimen (treatment C) resulted in an $AUC_{0\text{-}24}$ for dexamethasone similar to that observed after the standard dexamethasone plus ondansetron regimen (treatment A). In study 2, aprepitant increased the $AUC_{0\text{-}24}$ of intravenous methylprednisolone 1.3-fold on day 1 ($P < .010$) and increased the $AUC_{0\text{-}24}$ of oral methylprednisolone 2.5-fold on day 3 ($P < .010$).**

Conclusions: **Coadministration of aprepitant with dexamethasone or methylprednisolone resulted in increased plasma concentrations of the corticosteroids. These findings suggest that the dose of these corticosteroids should be adjusted when given with aprepitant. (Clin Pharmacol Ther 2003;74:17-24.)**

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Aprepitant (also known as MK-0869, L-754030, and EMEND, a registered trademark of Merck & Co, Inc, Whitehouse Station, NJ) is a potent, selective, and brain-penetrant nonpeptide neurokinin$_1$ receptor antagonist[1] that has been shown to be effective for the prevention of highly emetogenic chemotherapy–induced nausea and vomiting.[2,3] A standard recommended dosing regimen for the prevention of chemotherapy-induced nausea and vomiting consists of dual therapy with a 5-hydroxytryptamine$_3$ receptor antagonist (most commonly, ondansetron) and a corticosteroid (usually dexamethasone).[4,5] Added to this standard regimen, use of aprepitant further reduces the number of patients with chemotherapy-induced nausea and vomiting,[6] the benefit apparently being sustained over multiple cycles of chemotherapy.[7]

Results of in vitro studies with human liver microsomes have suggested that aprepitant is a moderate inhibitor of cytochrome P4503A4 (CYP3A4). In humans, in vivo effects on CYP3A4 were confirmed in a pharmacokinetic study in which midazolam was used as a probe substrate of CYP3A4 activity.[8] Because dexamethasone is metabolized by CYP3A4[9,10] and is intended to be administered in conjunction with aprepitant, there is potential for an interaction between the 2 drugs. We therefore investigated the effects of aprepitant on dexamethasone pharmacokinetics in a triple-therapy dosing regimen (aprepitant, dexamethasone, and ondansetron). In addition, we investigated the effects of aprepitant on the pharmacokinetics of orally and intravenously administered methylprednisolone, a corticosteroid also used as part of a regimen for the management of chemotherapy-induced nausea and vomiting.[4] Methylprednisolone also is metabolized by CYP3A4.[11,12]

METHODS

Study 1: Effects of aprepitant on the pharmacokinetics of dexamethasone

Subjects. The subjects were 20 healthy persons (12 men and 8 women) between the ages of 20 and 46 years (mean age, 34 years). The protocol and its consent form were reviewed by the institutional review board of the participating institution (Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, NY). All subjects gave written informed consent.

Design. The study had an open-label, randomized, incomplete-block, 3-period crossover design. Each subject received, in a randomized sequence, 3 of 5 possible 5-day treatment regimens with a washout period of at least 14 days between each regimen. In this design, 12 subjects received each treatment regimen. Treatment A consisted of a standard oral dexamethasone treatment regimen (20 mg dexamethasone on day 1, 8 mg dexamethasone once daily on days 2 to 5) and was the reference against which the other treatment regimens were compared. Treatment B was used to examine the effects of oral aprepitant (125 mg aprepitant on day 1, 80 mg aprepitant once daily on days 2 to 5) on the standard oral dexamethasone regimen (20 mg dexamethasone on day 1, 8 mg dexamethasone once daily on days 2 to 5). Preliminary results of an earlier study indicated that aprepitant increased plasma levels of dexamethasone. Accordingly, treatment C was used to examine the effects of oral aprepitant on a modified oral dexamethasone regimen (12 mg dexamethasone on day 1, 4 mg dexamethasone once daily on days 2 to 5). The intention was to compensate for the anticipated interaction and thereby match dexamethasone concentrations with those in treatment A. All subjects also received 32 mg ondansetron intravenously on day 1 only. The other 2 treatment regimens consisted of aprepitant alone (125 mg aprepitant on day 1, 80 mg aprepitant once daily on days 2 to 5) or a low-dose aprepitant regimen (40 mg aprepitant on day 1, 25 mg aprepitant once daily on days 2 to 5 plus the standard dexamethasone and ondansetron treatments) not optimal for the management of chemotherapy-induced nausea and vomiting. Data on these 2 treatment regimens were not relevant for the purposes of this discussion and are not presented. The sequence of treatment administration on day 1 for the standard dexamethasone plus ondansetron regimen (treatment A) was oral dexamethasone followed immediately by the start of the intravenous infusion of ondansetron, which lasted for 15 minutes. In treatment groups B and C, oral aprepitant was given 30 minutes before oral dexamethasone and intravenous ondansetron on day 1, and on days 2 to 5 oral aprepitant and dexamethasone were coadministered. On each day of dosing, subjects consumed a standard light breakfast approximately 15 minutes before taking the oral dose of aprepitant.

Pharmacokinetic assessment. Blood was drawn for measurement of the plasma concentration of dexamethasone on day 1 before administration of aprepitant and at 1, 1.25, 1.5, 2, 2.5, 4, 6, 8, 12, 18, and 24 hours after administration and, on day 5, before administration of aprepitant and at 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 18, and 24 hours after administration. The plasma samples were assayed for dexamethasone by Cedra Corporation (Austin, Tex) with liquid chromatography–tandem mass spectrometry. The lower limit of quantitation was 0.25 ng/mL. Plasma containing dexamethasone and the internal standard, beclomethasone (INN, beclometa-

sone), was extracted with 10% cyclohexane in ethyl acetate solution. The dried extract was reconstituted in mobile phase, and an aliquot was injected into a Sciex API III-Plus liquid chromatography–tandem mass spectrometry system (PerkinElmer, Shelton, Conn) equipped with an HPLC column in enhanced ion focusing mode. The calibration spiking solutions were prepared with target concentrations ranging from 0.25 to 500 ng/mL, and the low-, medium-, and high-quality control samples were prepared at 1.0, 25.0, and 250 ng/mL. The interday deviation of the mean from the theoretic concentration ranged from 1.0% to 8.1%. The interday coefficient of variation ranged from 0.97% to 7.1%. The following plasma dexamethasone pharmacokinetic parameters were calculated: $AUC_{0\text{-}24}$, maximum concentration of drug observed in the plasma (C_{max}), time to reach C_{max} (t_{max}), and apparent terminal half-life ($t_{1/2}$).

Statistical analysis. The $AUC_{0\text{-}24}$ of dexamethasone was the primary pharmacokinetic variable of interest. An ANOVA appropriate for a 5-treatment, 3-period balanced incomplete-block design was used to analyze the natural log–transformed dexamethasone $AUC_{0\text{-}24}$ data. The ANOVA model contained factors for sex, subject within sex, period, treatment, and sex-by-treatment interaction. The 90% confidence intervals (CIs) were calculated from the differences in the least squares means between relevant treatments with the mean square error from the ANOVA referencing a *t* distribution. The estimated difference in means and 90% CIs were back-transformed to obtain the corresponding geometric mean ratios between treatments (treatment B/treatment A, treatment C/treatment A) and corresponding CIs for the geometric mean ratios. Similar methods were followed for the analysis of C_{max} except that 95% CIs were calculated. For $t_{1/2}$, an ANOVA model similar to that described here was applied to inverse-transformed individual values, and the least squares treatment means were back-transformed for estimation of the harmonic mean. The median t_{max} also was calculated.

Study 2: Effects of aprepitant on the pharmacokinetics of methylprednisolone

Subjects. The subjects were 10 healthy persons (8 men and 2 women) between the ages of 20 and 44 years (mean age, 31 years). The protocol and consent form were approved by the institutional review board of the participating institution (PharmaKinetics Laboratories, Baltimore, Md). All subjects gave written informed consent.

Design. This study had a double-blind, randomized, placebo-controlled, 2-period crossover design with a washout period of at least 12 days between regimens. One treatment regimen consisted of oral placebo and 125 mg methylprednisolone hemisuccinate administered intravenously on day 1, followed by oral placebo and 40 mg methylprednisolone administered orally on days 2 and 3. In the other treatment regimen, subjects received oral aprepitant (125 mg aprepitant on day 1, 80 mg aprepitant on days 2 and 3) in addition to the methylprednisolone regimen. The sequence of treatment administration on day 1 was oral aprepitant or placebo followed 30 minutes later by the start of the intravenous infusion of methylprednisolone, which lasted for 10 minutes. On days 2 and 3, oral aprepitant or placebo and oral methylprednisolone were coadministered. Ondansetron was not used in this study. On each day of dosing, subjects consumed a standard light breakfast approximately 60 minutes before taking the oral dose of aprepitant or placebo.

Pharmacokinetic assessments. On day 1, blood samples for measurement of plasma methylprednisolone concentration were obtained before the start of the intravenous methylprednisolone infusion and at 10 (end of infusion), 20, 30, and 45 minutes and 1, 1.5, 2, 4, 6, 8, 10, 12, 14, and 24 hours thereafter. The plasma samples were assayed for methylprednisolone by BAS Analytics (West Lafayette, Ind) with liquid chromatography–tandem mass spectrometry. The lower limit of quantitation was 5 ng/mL. Methylprednisolone was extracted from the ethylenediaminetetraacetic acid–treated human plasma with methyl *tert*-butyl ether. Before extraction, dexamethasone was added as an internal standard. The dried extract was reconstituted with the mobile phase and injected into a liquid chromatography–tandem mass spectrometry system with an Eclipse XDB-C8 (Agilent, Palo Alto, Calif) column with an acetonitrile/water/acetic acid mobile phase. The calibration standards ranged from 5 to 300 ng/mL. The interassay accuracy of the calibration standards and the intra-assay and interassay accuracy of the quality control samples were between 85% and 115%. Interassay and intra-assay precision was $\pm$15% or less. The accuracy and precision for the low quality control samples and any calibration standards with concentrations equal to or less than the nominal low quality control samples were allowed to increase to 80% to 120% and $\pm$20%, respectively. The following plasma methylprednisolone pharmacokinetic parameters were calculated for day 1: $AUC_{0\text{-}24}$, concentration of drug in the plasma at the end of infusion (C_{eoi}), and $t_{1/2}$. Although not prespecified in the study protocol, volume of distribution at steady

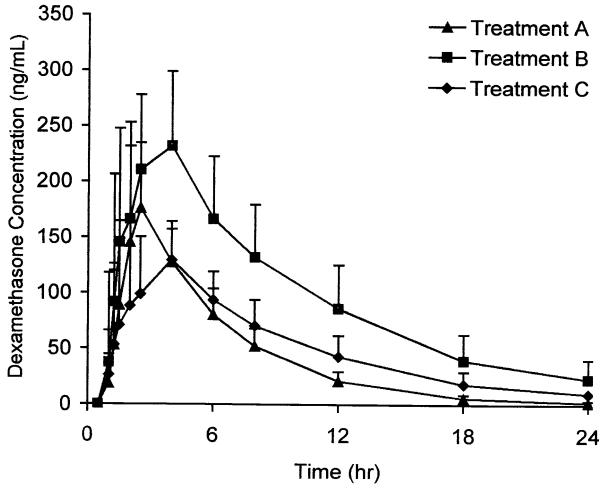

Fig 1. Mean plasma concentration profiles of dexamethasone on day 1. Treatment A: 20 mg dexamethasone orally plus 32 mg ondansetron intravenously. Treatment B: 125 mg aprepitant orally, 20 mg dexamethasone orally, and 32 mg ondansetron intravenously. Treatment C: 125 mg aprepitant orally, 12 mg dexamethasone orally, and 32 mg ondansetron intravenously. *Error bars* show standard deviation.

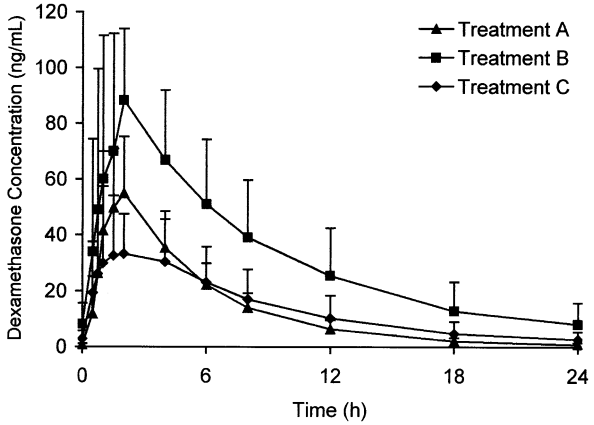

Fig 2. Mean plasma concentration profiles of dexamethasone on day 5. Treatment A: 20 mg dexamethasone orally plus 32 mg ondansetron intravenously on day 1; 8 mg dexamethasone orally on days 2 to 5. Treatment B: 125 mg aprepitant orally, 20 mg dexamethasone orally, and 32 mg ondansetron intravenously on day 1; 80 mg aprepitant orally plus 8 mg dexamethasone orally on days 2 to 5. Treatment C: 125 mg aprepitant orally, 12 mg dexamethasone orally, and 32 mg ondansetron intravenously on day 1; 80 mg aprepitant orally plus 4 mg dexamethasone orally on days 2 to 5. *Error bars* show standard deviation.

state (V_{ss}), clearance (CL), and mean residence time for methylprednisolone were calculated on a post hoc basis for methylprednisolone given with placebo. Apparent plasma CL also was calculated for methylprednisolone given with aprepitant. The other pharmacokinetic values were not calculated for methylprednisolone given with aprepitant because of difficulties in interpreting the data (CL during inhibition by aprepitant may be variable over time, and assumptions about linear kinetics may not have been met). On day 3, blood samples for plasma methylprednisolone assay were obtained at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after oral dosing with methylprednisolone. $AUC_{0\text{-}24}$, C_{max}, t_{max}, and $t_{1/2}$ were calculated for each subject. The bioavailability of methylprednisolone after the 40-mg oral dose given with placebo was calculated. The bioavailability of methylprednisolone given with aprepitant was not calculated because CL was likely different between the intravenous and the oral treatment arms. Therefore an estimate using the ratio of dose-adjusted oral AUC to intravenous AUC would not be appropriate.

Statistical analysis. The $AUC_{0\text{-}24}$ of methylprednisolone was the primary pharmacokinetic variable of interest. An ANOVA appropriate for a 2-treatment, 2-period, 2-treatment sequence crossover study was used to analyze the natural log–transformed methylprednisolone data separately for day 1 (intravenous methylprednisolone dosing) and day 3 (oral methylprednisolone dosing). For days 1 and 3 separately, a 2-sided 95% CI was calculated (equivalent to a 1-sided 97.5% CI), with the within-subject error from the ANOVA model, for the true difference between the mean log-transformed methylprednisolone $AUC_{0\text{-}24}$ with aprepitant and the mean log-transformed methylprednisolone $AUC_{0\text{-}24}$ alone. The estimated difference in mean values and 95% CI was back-transformed to obtain the corresponding geometric mean $AUC_{0\text{-}24}$ ratio (methylprednisolone with aprepitant/methylprednisolone with placebo) and corresponding 95% CIs. The Bonferroni correction was incorporated into the statistical methods by calculation of 2-sided 95% CIs (equivalent to 1-sided 97.5% CIs) for geometric mean $AUC_{0\text{-}24}$ ratios instead of the usual 2-sided 90% CIs (equivalent to 1-sided 95% CIs). Similar methods were followed for the analysis of C_{eoi} and C_{max}. For $t_{1/2}$, an ANOVA model similar to that described earlier was applied to inverse-transformed individual values, and the least squares treatment mean values were back-transformed to obtain estimates of the harmonic mean. Median t_{max} also was calculated. Pharmacokinetic parameters for 2 subjects on day 1 were not calculated because of an anomaly in the assayed plasma concen-

Table I. Summary of dexamethasone pharmacokinetics on day 1 and day 5 with and without aprepitant

Variable	*Day*	*Treatment A: Standard dex.*	*Treatment B: Standard dex. plus aprepitant*	*Treatment C: Modified dex. plus aprepitant*	*Ratio: B versus A*	*P value*	*Ratio: C versus A*	*P value*
AUC_{0-24} (ng · h/mL)*	1	896.7 (762.6-1054.5)	1943.0 (1652.8-2248.0)	1160.4 (986.8-1364.4)	2.17 (1.95-2.40)	<.010	1.29 (1.17-1.44)	<.010
	5	292.4 (233.0-366.8)	641.8 (511.8-805.0)	302.5 (241.1-379.6)	2.20 (1.89-2.55)	<.010	1.03 (0.89-1.20)	>.250
C_{max} (ng/mL)*	1	178.7 (151.2-210.8)	241.7 (205.0-285.0)	152.2 (129.1-179.5)	1.35 (1.12-1.64)	<.010	0.85 (0.70-1.03)	.099
	5	58.1 (47.7-70.7)	88.2 (72.5-107.4)	45.9 (37.7-55.8)	1.52 (1.21-1.90)	<.010	0.79 (0.63-0.99)	.040
$t_{1/2}$ (h)†	1	3.6 (3.1-4.1)	5.4 (3.3-9.5)	5.2 (3.2-7.1)	—	<.010	—	<.010
	5	3.9 (2.8-5.1)	5.6 (3.6-9.4)	5.3 (3.4-8.8)	—	<.010	—	<.010
t_{max} (h)‡	1	2.5 (1.5-4.0)	2.5 (1.3-4.0)	4.0 (1.5-4.0)	—	—	—	—
	5	1.5 (1.0-4.0)	2.0 (0.8-4.0)	1.8 (0.5-4.0)	—	—	—	—

Treatment A: 20 mg dexamethasone orally plus 32 mg ondansetron intravenously on day 1; 8 mg dexamethasone orally on days 2 to 5. Treatment B: 125 mg aprepitant orally plus 20 mg dexamethasone orally plus 32 mg ondansetron intravenously on day 1; 80 mg aprepitant orally plus 8 mg dexamethasone orally. on days 2 to 5. Treatment C: 125 mg aprepitant orally plus 12 mg dexamethasone orally plus 32 mg ondansetron intravenously on day 1; 80 mg aprepitant orally plus 4 mg dexamethasone orally on days 2 to 5.

dex., Dexamethasone; AUC_{0-24}, area under the concentration-time curve from 0 to 24 hours; C_{max}, maximum concentration in plasma; $t_{1/2}$, terminal half-life; t_{max}, time to reach C_{max}.

*Values are given as geometric mean and 95% CI except for AUC_{0-24} ratios, which are geometric mean and 90% CI.

†Values are given as harmonic mean and range.

‡Values are given as median and range.

trations (concentrations at 10 minutes were lower than concentrations at 20 minutes for both subjects, a finding inconsistent with the expected peak concentrations at the end of the 10-minute infusion), but both subjects were included in the day 3 oral methylprednisolone analyses.

RESULTS

Study 1

The mean plasma concentration profiles of dexamethasone on day 1 of each treatment regimen are shown in Fig 1, and those on day 5 are shown in Fig 2. The AUC_{0-24}, C_{max}, $t_{1/2}$, and t_{max} of oral dexamethasone for each treatment regimen on days 1 and 5 are summarized in Table I. The AUC_{0-24} of dexamethasone on days 1 and 5 after the standard dexamethasone plus ondansetron regimen (treatment A) increased approximately 2.2-fold with coadministration of aprepitant (treatment B). Coadministration of aprepitant with a modified (lower) dose of dexamethasone plus ondansetron (treatment C) resulted in an AUC_{0-24} of dexamethasone on days 1 and 5 similar to the AUC_{0-24} of dexamethasone after the standard dexamethasone plus ondansetron regimen (treatment A). There was no significant sex-by-treatment interaction ($P > .05$), and there was no sex effect ($P > .05$) for the AUC_{0-24} of dexamethasone. The C_{max} of dexamethasone on days 1 and 5 after the standard dexamethasone plus ondansetron regimen (treatment A) increased approximately 1.5-fold with the addition of aprepitant (treatment B). Coadministration of aprepitant with a modified (lower) dose of dexamethasone plus ondansetron (treatment C) resulted in a slightly lower C_{max} of dexamethasone on days 1 and 5 in relation to the $C_{max}$of dexamethasone after the standard dexamethasone plus ondansetron regimen (treatment A). Aprepitant increased the $t_{1/2}$ of dexamethasone by approximately 1.5 to 2 hours (Table I).

Study 2

The mean plasma concentration profiles of methylprednisolone without aprepitant and with aprepitant on day 1 are shown in Fig 3, and those on day 3 are shown in Fig 4. Pharmacokinetic measures for each treatment regimen on day 1 and day 3 are summarized in Table II. On day 1, the AUC_{0-24} of intravenous methylprednisolone increased 1.3-fold, and the $t_{1/2}$ increased approximately 1.5 hours when methylprednisolone was

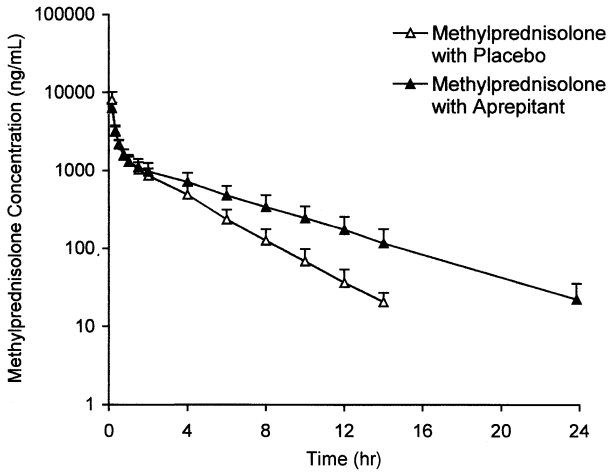

Fig 3. Mean plasma concentration profiles of methylprednisolone on day 1. Methylprednisolone with placebo regimen: oral administration of placebo and intravenous administration of 125 mg methylprednisolone. Methylprednisolone with aprepitant regimen: 125 mg aprepitant orally plus 125 mg methylprednisolone intravenously. The measurement at the 24-hour time point in the methylprednisolone group was below the lower limit of quantitation of 5 ng/mL. *Error bars* show standard deviation.

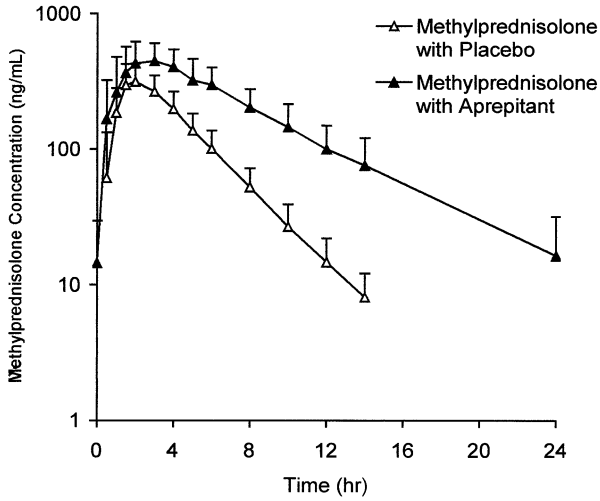

Fig 4. Mean plasma concentration profiles of methylprednisolone on day 3. Methylprednisolone with placebo regimen: oral administration of placebo plus intravenous administration of 125 mg methylprednisolone on day 1; oral administration of placebo plus oral administration of 40 mg methylprednisolone on days 2 and 3. Methylprednisolone with aprepitant regimen: 125 mg aprepitant orally plus 125 mg methylprednisolone intravenously on day 1; 80 mg aprepitant orally plus 40 mg methylprednisolone orally on days 2 and 3. The measurement at the 24-hour time point in the methylprednisolone group was below the lower limit of quantitation of 5 ng/mL. *Error bars* show standard deviation.

given with aprepitant. In contrast, the C_{eoi} of intravenous methylprednisolone decreased approximately 22% with aprepitant coadministration. The following geometric mean values were observed in the post hoc analysis of additional pharmacokinetic measures for methylprednisolone given with placebo on day 1: V_{ss}, 42.0 L (95% CI, 35.3-49.9 L); CL, 306.4 mL/min (95% CI, 259.3-362.0 mL/min); mean residence time, 2.3 hours (95% CI, 1.8-2.9 hours). The apparent plasma CL for methylprednisolone given with aprepitant was 229.5 mL/min (95% CI, 194.2-271.2), the 25% reduction being consistent with the increase of one third in the AUC_{0-24}. On day 3, the AUC_{0-24} of oral methylprednisolone increased 2.5-fold, C_{max} increased 1.5-fold, and $t_{1/2}$ increased by approximately 1.5 hours with aprepitant coadministration. The geometric mean bioavailability of the oral dose of 40 mg methylprednisolone given with placebo was 65% (95% CI, 50%-83%).

DISCUSSION

These studies showed that plasma concentrations (AUC_{0-24}) of typical therapeutic doses of the corticosteroids dexamethasone and methylprednisolone for the prevention of chemotherapy-induced nausea and vomiting increased when the drugs were coadministered with aprepitant. The increase was approximately 2-fold for oral dexamethasone and methylprednisolone and 1.3-fold for intravenous methylprednisolone. The mechanism by which aprepitant increases plasma levels of dexamethasone and methylprednisolone most likely involves inhibition of CYP3A4. The metabolism of both corticosteroids by CYP3A4 has been demonstrated in drug interaction studies with CYP3A4 inhibitors such as itraconazole and ketoconazole[9,11,12] and by in vitro evaluations.[10] Administered at the doses used in this study, aprepitant is a moderate inhibitor of CYP3A4, as shown by its ability to increase the plasma concentration of oral midazolam 2-fold to 3-fold.[8] The increase in concentration of oral dexamethasone and methylprednisolone was similar to that observed previously for oral midazolam. Thus the increase in plasma concentration of dexamethasone and methylprednisolone observed with aprepitant is consistent with aprepitant inhibition of the CYP3A4-mediated metabolism of these corticosteroids. It is important to note that the pharmacokinetics of ondansetron, which is

Table II. Summary of methylprednisolone pharmacokinetics on day 1 and day 3 with and without aprepitant

Variable	*Day*	*Methylprednisolone plus placebo*	*Methylprednisolone plus aprepitant*	*Ratio: With versus without aprepitant*	*P value*
$AUC_{0\text{-}24}$(ng · h/mL)*	1	6822.1 (5646.4-8242.6)	9122.8 (7550.6-11,022.4)	1.34 (1.17-1.52)	<.010
	3	1404.8 (1098.5-1796.5)	3462.1 (2707.2-4427.6)	2.46 (2.24-2.72)	<.010
C_{eoi} (ng/mL)*	1	8532.2 (7153.9-10,176.0)	6645.8 (5572.3-7926.2)	0.78 (0.64-0.94)	.018
C_{max} (ng/mL)*	3	341.6 (287.6-405.9)	498.9 (420.0-592.7)	1.46 (1.31-1.63)	<.010
$t_{1/2}$ (h)†	1	2.0 (1.4-2.7)	3.5 (2.0-5.0)	—	<.010
	3	2.1 (1.3-2.5)	3.7 (1.9-6.4)	—	<.010
t_{max} (h)‡	1	—	—	—	—
	3	2.0 (1.0-3.0)	2.5 (1.0-4.0)	—	—

Methylprednisoline plus placebo regimen: placebo orally plus 125 mg methylprednisolone intravenously on day 1; placebo orally plus 40 mg methylprednisolone orally on days 2 and 3. Methylprednisolone plus aprepitant regimen: 125 mg aprepitant orally plus 125 mg methylprednisolone intravenously on day 1; 80 mg aprepitant orally plus 40 mg methylprednisolone orally on days 2 and 3.

C_{eoi}, Plasma concentration at end of infusion. Other abbreviations as in Table I.

*Values are given as geometric mean and 95% CI.

†Values are given as harmonic mean and range.

‡Values are given as median and range.

intended to be used as part of the triple-therapy regimen (aprepitant, dexamethasone, and ondansetron) and which is metabolized by numerous enzymes, including CYP3A4, are not altered by aprepitant.[13]

In addition to increasing the $AUC_{0\text{-}24}$, aprepitant increased the C_{max} and $t_{1/2}$ of both corticosteroids when they were given orally. These data are consistent with aprepitant inhibition of both the first-pass and the systemic clearance of the corticosteroids. Given the high bioavailability of oral dexamethasone (approximately 80%)[14] and methylprednisolone (65% in this study, in agreement with values reported by others[15]), any effect of aprepitant on first-pass elimination of these drugs is likely to be relatively minor, and the observed increase in dexamethasone and methylprednisolone $AUC_{0\text{-}24}$ is more indicative of inhibition of systemic CYP3A4 by aprepitant. The finding that aprepitant increased the C_{max} of dexamethasone and methylprednisolone approximately 50% also suggests a small first-pass effect. In contrast to the increase in C_{max} found when aprepitant was coadministered with oral methylprednisolone, a 22% decrease in the C_{eoi} of intravenous methylprednisolone occurred in the presence of aprepitant. The cause of this small decrease was not apparent. However, because the overall plasma exposure (AUC) and duration of treatment, rather than the C_{eoi}, of intravenous methylprednisolone, are likely the primary determinants of the antiemetic efficacy of intravenous methylprednisolone, this finding is probably not clinically relevant.

From a clinical perspective, it is desirable to avoid unnecessarily high exposure to corticosteroids because of the potential for an increase in acute side effects such as hyperglycemia and increased susceptibility to infection.[16] These findings suggest that, when used for the management of chemotherapy-induced nausea and vomiting, oral doses of dexamethasone or methylprednisolone should be reduced one half to maintain approximately similar exposures to the oral corticosteroids given without aprepitant. The findings also suggest that the intravenous dose of methylprednisolone should be reduced approximately one fourth. Study 1 was a specific investigation of the effect of aprepitant on a modified dexamethasone regimen. The findings in that study confirmed that approximately halving the dexamethasone dose (12 mg on day 1 and 4 mg thereafter) resulted in plasma concentrations of dexamethasone similar to those that occur with a standard dexamethasone regimen (20 mg on day 1, 8 mg thereafter) without aprepitant.

In summary, these findings indicated that the neurokinin$_1$ receptor antagonist aprepitant, at doses intended for the management of chemotherapy-induced nausea and vomiting, alters the pharmacokinetics of the corticosteroids dexamethasone and methylprednisolone, most likely because of moderate inhibition of CYP3A4.

Reduction of the corticosteroid dose by 50% for oral dosing and by 25% for intravenous dosing of methylprednisolone is, therefore, recommended when aprepitant is added to a standard dual-therapy regimen for the management of chemotherapy-induced nausea and vomiting.

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