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ORIGINAL ARTICLE

Impact of casopitant, a novel NK-1 antagonist, on the pharmacokinetics of ondansetron and dexamethasone

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Abstract
Introduction Pharmacokinetic interactions between casopitant (a substrate and weak to moderate inhibitor of CYP3A), dexamethasone (a substrate and weak inducer of CYP3A), and ondansetron (a mixed CYP substrate) were evaluated in a two-part, three-period, single-sequence study in two groups of healthy subjects.
Materials and methods Part 1: subjects received oral casopitant (regimen A); oral dexamethasone and IV ondansetron (regimen B); and oral casopitant, a reduced dose of oral dexamethasone, and IV ondansetron (regimen C). Part 2: subjects received oral casopitant (regimen D); IV dexamethasone and oral ondansetron (regimen E); and oral casopitant, IV dexamethasone, and oral ondansetron (regimen F). Each regimen was separated by 14 days.
Results Casopitant AUC in regimen C was increased 28% on day 1 but decreased 34% on day 3 compared to casopitant alone in regimen A. When given with casopitant and ondansetron in regimen C, dexamethasone AUC was 17% lower on day 1, but similar on day 3, compared to regimen B (representing dose-normalized increases in exposure of 39% and 108%, respectively). Ondansetron exposure was equivalent in regimens B and C. Casopitant AUC in regimen F was similar to regimen D on days 1 and 3. Dexamethasone AUC increased 21% when given with oral casopitant and oral ondansetron (regimen F compared to regimen E). Ondansetron exposure was equivalent in regimens E and F.
Conclusion When repeat-dose oral dexamethasone is to be coadministered with oral casopitant, a reduction in dexamethasone dose may be considered; however, no change in casopitant dose is required. Ondansetron exposure was not affected by coadministration with casopitant.

Keywords Casopitant · Dexamethasone · Ondansetron · CINV

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) remains one of the most feared side effects of chemotherapy among cancer patients [25]. Several studies have reported a gap between healthcare providers' awareness of CINV and the actual incidence of CINV in patients, with most healthcare

providers underestimating the actual prevalence of delayed nausea and vomiting [9, 15].

Failure to prevent CINV can negatively affect patient outcome by contributing to low adherence to and withdrawal from potentially effective chemotherapy [20, 21] and optimal prevention of CINV in the first cycle of chemotherapy can decrease the likelihood of CINV in subsequent cycles [4]. Furthermore, preventing CINV during all cycles lowers the probability of developing anticipatory CINV, a conditioned response that occurs prior to administration of chemotherapy [20, 23].

Emesis is an autonomic reflex controlled by multiple neurotransmitter systems; two of the most important systems are the serotonin/5-hydroxytryptamine receptor 3 (5-HT_3) and substance P/neurokinin-1 receptor (NK-1) systems [13]. Blocking both the 5-HT_3 and NK-1 neurotransmitter receptors has been demonstrated to reduce CINV in patients receiving chemotherapy [5, 17, 26]. According to guidelines established by the Multinational Association for Supportive Care in Cancer, patients who will receive a moderately emetogenic chemotherapy (MEC) regimen should receive a 5-HT_3 receptor antagonist and dexamethasone, while patients who will receive a MEC regimen that includes anthracycline and cyclophosphamide or a highly emetogenic chemotherapy (HEC) regimen should receive a 5-HT_3 receptor antagonist, a corticosteroid, and an NK-1 receptor antagonist [10, 12, 22].

A three-drug antiemetic regimen including a novel NK-1 receptor antagonist, casopitant, in combination with ondansetron and dexamethasone has recently demonstrated efficacy for the prevention of CINV in phase II [2] and phase III clinical trials [3, 8, 11, 24].

An important consideration when combining medications for therapeutic benefit is the potential for drug–drug interactions, particularly when the medications share metabolic pathways. Clinical and in vitro studies have demonstrated that the major enzymes involved in the metabolism of the NK-1 receptor antagonist casopitant are from the CYP3A family and that casopitant (and a major circulating metabolite) can result in weak to moderate inhibition of CYP3A.

Dexamethasone and ondansetron are commonly employed as part of an antiemetic regimen for the prevention of CINV. Dexamethasone is also metabolized by CYP3A and is a weak inducer of CYP3A after prolonged exposure or repeat-dose administration [7, 18]. Ondansetron, much like other 5-HT_3 receptor antagonists, is metabolized by several CYP enzymes, primarily CYP1A2, CYP2D6, and CYP3A [6]. Consequently, there is a potential for casopitant to impact the pharmacokinetics of dexamethasone and ondansetron, and dexamethasone also may impact the pharmacokinetics of casopitant.

The purpose of the current study was to evaluate the potential pharmacokinetic interactions between casopitant, dexamethasone, and ondansetron using three drug regimens that may be employed for the prevention of CINV resulting from MEC or HEC. The dose of casopitant employed in the current study is the highest oral dose regimen currently under clinical investigation (employed in a phase III study examining the efficacy of casopitant for the prevention of CINV resulting from MEC [8]) and is a 3-day oral regimen of 150 mg on day 1, followed by 50 mg on days 2 and 3. Phase III studies (in both the HEC and MEC settings) also examined the efficacy of a 3-day regimen of casopitant where the day 1 oral dose was replaced by an IV dose of 90 mg casopitant, selected to provide a similar casopitant exposure to the 150 mg oral dose form. The results of the current study are therefore applicable to 3-day regimens of oral/oral or IV/oral casopitant, as well as a single-dose oral regimen consisting of 150 mg casopitant on day 1 only.

Materials and methods

Study population

Healthy male and female subjects not undergoing chemotherapy, 18 to 55 years of age, with a body mass index of ≥19 to ≤37 kg/m^2 and adequate organ function were eligible to enter the study. All females of childbearing potential were required to use birth control from 14 days before the first dose of study medication, throughout the study and for 14 days after the last dose of study medication. Exclusion criteria were designed to ensure that subjects were in good health and not receiving concomitant medications that may interfere with the pharmacokinetics of study medications.

The study protocol and informed consent documents were reviewed and approved by the institutional review board at the Buffalo Clinical Research Center. Subjects provided written consent prior to participation in the trial. All investigators were required to abide by Good Clinical Practices, International Conference on Harmonization guidelines, Declaration of Helsinki principles, and local laws and regulations.

Study design

This open-label, two-part, fixed-sequence study was conducted at one center in the USA. Subjects were only eligible to participate in one part of the study. Each part consisted of three treatment periods (regimens), with at least 14 days between each period. In part 1, which was representative of a 3-day treatment regimen for the prevention of CINV resulting from HEC, subjects received oral casopitant in regimen A, oral dexamethasone and IV ondansetron in regimen B, and oral casopitant, a reduced

dose of oral dexamethasone, and IV ondansetron in regimen C (Table 1). In part 2, which was representative of a 3-day treatment regimen that may be employed for the prevention of CINV resulting from MEC, subjects received oral casopitant in regimen D, IV dexamethasone and oral ondansetron in regimen E, and oral casopitant, IV dexamethasone, and oral ondansetron in regimen F (Table 1). All oral doses were taken with water after at least a 4 h fast, and when subjects were to receive multiple study medications, all doses were taken at the same time.

Blood samples for PK analysis were collected over a 24-h period on day 1 and day 3 of each treatment period at the following times: pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, and 24 h post-dose. When dexamethasone was administered twice daily (part 1, regimen B), samples were collected pre-dose, and 0.25, 0.5, 1, 1.5, 2, 3, 5, 8, and 12 h after the morning and evening doses. This schedule allowed comparison of the 24 h exposure of dexamethasone after twice daily dosing of dexamethasone alone to that observed after once daily dosing when combined with casopitant. Adverse events (AEs) were reported and clinical laboratory values, ECGs, and vital signs were assessed.

Pharmacokinetics

Plasma samples were analyzed for casopitant, dexamethasone, and ondansetron using validated analytical methods based on protein precipitation, followed by HPLC/MS/MS analysis. Using a 50 μL aliquot of human plasma the lower limit of quantification (LLQ) for casopitant was 1.50 ng/mL and the higher limit of quantification (HLQ) was 1,500 ng/mL; the LLQ for dexamethasone was 1.0 ng/mL and the HLQ was 500 ng/mL. Using a 20 μL aliquot of human plasma, the LLQ for ondansetron was 0.5 ng/mL and the HLQ was 500 ng/mL. Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the QC results were to deviate from the nominal concentration by more than 15% and at least 50% of the results from each QC concentration should be within 15% of nominal. The applicable analytical runs met all predefined run acceptance criteria.

Pharmacokinetic parameters were determined in parts 1 and 2 on both day 1 and 3 in periods 1, 2, and 3 using standard non-compartmental methods (WinNonlin, version 4.1, Pharsight Corp, Mountain View CA, USA). AUC was calculated using the linear up-log down method, with AUC(0-τ) being calculated for repeat-dose study medications [AUC(0-24) was calculated for twice daily dexamethasone] and AUC(0-∞) being calculated for single-dose IV ondansetron or dexamethasone administration. Cmax, tmax, and half-life were also determined.

Statistics

For the assessment of the interactions between casopitant, dexamethasone, and ondansetron pharmacokinetics, log(e)-transformed AUC and Cmax parameters were statistically analyzed by performing an analysis of variance (ANOVA) for each analyte (casopitant, dexamethasone, or ondansetron), day (1 or 3) and part (1 or 2) separately. The ANOVA used a mixed-effects model with subject as a random effect and treatment as a fixed effect. For assessment of the effect of dexamethasone and/or ondansetron on casopitant pharmacokinetics, regimen A or D was the reference treatment and regimen C or F was the test treatment, respectively. For assessment of the effect of casopitant on dexamethasone and ondansetron pharmacokinetics, regimen B or E was the reference treatment and regimen C or F was the test treatment, respectively. Point estimates and 90% confidence intervals for the differences of interest were constructed using the residual variance for each part. Point and interval estimates were then exponentially back transformed to

Table 1 Casopitant, dexamethasone, and ondansetron dosing regimens for parts 1 and 2

Part	Regimen	Day 1	Days 2 and 3
1 (HEC regimen)	Regimen A	150 mg oral casopitant once daily	50 mg oral casopitant once daily
	Regimen B	20 mg oral dexamethasone once daily 32 mg IV ondansetron single-dose	8 mg oral dexamethasone twice daily
	Regimen C	150 mg oral casopitant once daily 12 mg oral dexamethasone once daily 32 mg IV ondansetron single-dose	50 mg oral casopitant once daily 8 mg oral dexamethasone once daily
2 (MEC regimen)	Regimen D	150 mg oral casopitant once daily	50 mg oral casopitant once daily
	Regimen E	8 mg IV dexamethasone single-dose 8 mg oral ondansetron twice daily	8 mg oral ondansetron twice daily
	Regimen F	150 mg oral casopitant once daily 8 mg IV dexamethasone single-dose 8 mg oral ondansetron twice daily	50 mg oral casopitant once daily 8 mg oral ondansetron twice daily

Table 2 Demographic characteristics of enrolled subjects

	Part 1 (n=23)	Part 2 (n=21)
Age, years		
Median (min−max)	27.0 (20–54)	29.0 (18–55)
Gender, n (%)		
Female	7 (30)	6 (29)
Male	16 (70)	15 (71)
Weight, kg		
Median (range)	78.90 (61.2–100.2)	75.30 (50.4–103.4)
BMI, kg/m^2		
Median (range)	24.40 (20.0–32.3)	25.70 (20.2–32.7)
Ethnicity, n (%)		
Hispanic or Latino	2 (9)	0
Not Hispanic or Latino	21 (91)	21 (100)
Race		
African American/African heritage	6 (26)	10 (48)
Asian–East Asian heritage	1 (4)	0
White–White/Caucasian/ European heritage	16 (70)	11 (52)

construct point and interval estimates for the ratios of interest. As comparisons of dexamethasone exposure in regimens A and C were made with different dexamethasone dose levels, dose-normalized comparisons were also made, where the dose-normalized fold-change was determined by the ratio of the two dose levels (per day) multiplied by the point estimate.

A sufficient number of subjects were enrolled to ensure that at least 18 evaluable subjects completed each part of the study. Based on the within-subject coefficients of variation for casopitant, dexamethasone, and ondansetron AUC and Cmax observed in previous studies (34.2% being the highest value), a sample size of 18 subjects should result in the lower and upper bounds of the 90% CI to be within 22% of the point estimates. This calculation was based on a symmetric two-tailed procedure on the log(e) scale and a type I error rate of 5% in each tail.

Results

A total of 44 subjects were enrolled in the study, 23 in part 1 and 21 in part 2. The majority of subjects in part 1 were White, while approximately half of the subjects in part 2 were African American. Demographic characteristics were otherwise similar in parts 1 and 2 and are summarized in Table 2. Forty subjects completed the study (four subjects withdrew during the conduct of part 1, none due to adverse events).

Pharmacokinetics

Part 1: highly emetogenic chemotherapy regimen

Casopitant Single-dose administration (day 1) showed that coadministration of 150 mg oral casopitant with 12 mg oral dexamethasone (reduced-dose dexamethasone regimen compared to the standard dose of 20 mg) and 32 mg IV ondansetron resulted in a 28% increase in mean casopitant plasma AUC(0-τ) when compared to casopitant administered alone (Table 3 and Fig. 1). After 3 days coadministration of oral casopitant (150 mg day 1, 50 mg days 2 and 3) and the reduced-dose regimen of oral dexamethasone (12 mg day 1, 8 mg once daily days 2 and 3), casopitant AUC(0-τ) and Cmax decreased by 34% and 18%, respectively, compared to 3 days of administration of casopitant alone (Table 3).

Dexamethasone On day 1, coadministration 12 mg oral dexamethasone and 150 mg oral casopitant and 32 mg IV ondansetron resulted in a lower mean dexamethasone AUC(0-τ) and Cmax, by 17% and 35%, respectively, when compared to administration of 20 mg oral dexamethasone

Table 3 Comparison of casopitant, dexamethasone, and ondansetron AUC and Cmax from parts 1 and 2

Part	Analyte (regimen comparison)	Day	AUC Geometric mean ratio (90% CI)	Cmax Geometric mean ratio (90% CI)
1 (HEC regimen)	Casopitant (Reg C: Reg A)	1	1.28 (1.14, 1.44)	1.06 (0.95, 1.2)
		3	0.66 (0.598, 0.73)	0.82 (0.74, 0.91)
	Dexamethasone (Reg C: Reg B)	1	0.83 (0.77, 0.91)	0.65 (0.59, 0.73)
		3	1.04 (0.97, 1.11)	1.37 (1.20, 1.57)
	Ondansetron (Reg C: Reg B)	1	1.09 (1.02, 1.16)	0.96 (0.83, 1.11)
		3	NA	NA
2 (MEC regimen)	Casopitant (Reg F: Reg D)	1	1.16 (1.07, 1.26)	1.27 (1.16, 1.39)
		3	0.92 (0.83, 1.01)	0.90 (0.81, 1.01)
	Dexamethasone (Reg F: Reg E)	1	1.21 (1.14, 1.28)	0.95 (0.88, 1.04)
		3	NA	NA
	Ondansetron (Reg F: Reg E)	1	1.02 (0.94, 1.11)	0.96 (0.85, 1.08)
		3	1.11 (1.06, 1.17)	1.00 (0.93, 1.08)

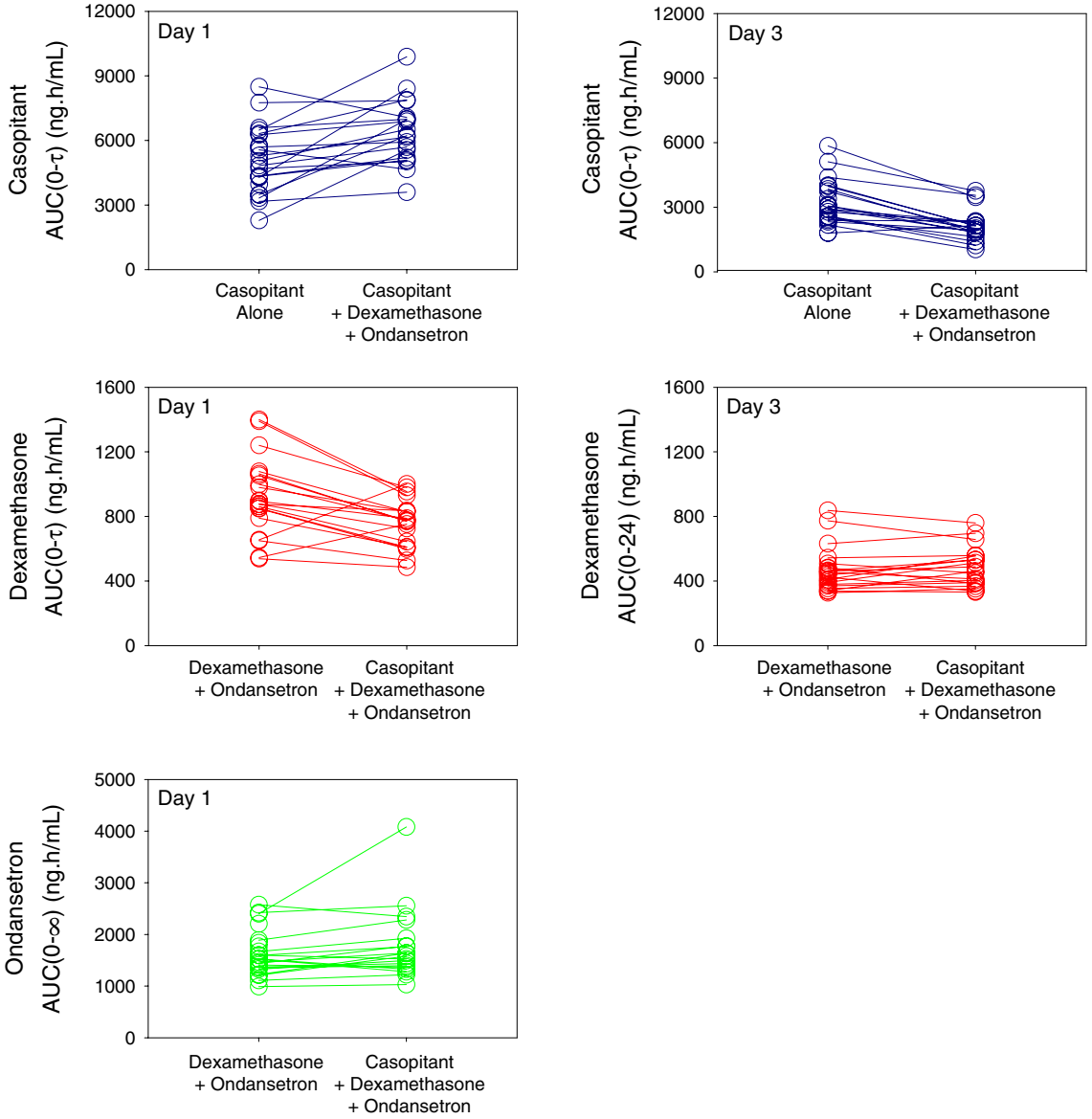

Fig. 1 Changes in individual casopitant (*top*), dexamethasone (*middle*), and ondansetron (*bottom*) AUC parameters after administration of casopitant alone, dexamethasone + ondansetron, and casopitant + dexamethasone + ondansetron, from part 1 (HEC regimen)

and 32 mg IV ondansetron (Table 3 and Fig. 1). Dose-normalization of the pharmacokinetic parameters showed that casopitant increased the AUC(0-τ) of oral dexamethasone by 39%. After 3 days of coadministration, the 24 h AUC resulting from 8 mg once daily oral dexamethasone combined with 50 mg oral casopitant was similar to that resulting from 8 mg twice daily oral dexamethasone alone, and represented a dose-normalized increase in dexamethasone exposure of 108%. The mean increase in the Cmax of 8 mg oral dexamethasone on day 3 was 37%.

Ondansetron Plasma exposures of 32 mg IV ondansetron were not affected by coadministration with casopitant (Table 3 and Fig. 1).

Part 2: moderately emetogenic chemotherapy regimen

Casopitant Single-dose administration (day 1) showed coadministration of a single-dose of 150 mg oral casopitant with 8 mg IV dexamethasone and 8 mg twice daily oral ondansetron resulted in an increase in mean plasma casopitant AUC(0-τ) and Cmax of 16% and 27%, respectively (Table 3 and Fig. 2). The exposure of 50 mg oral casopitant was not affected by 3 days of coadministration with 8 mg twice daily oral ondansetron.

Dexamethasone The day 1 single-dose IV AUC(0-∞) of dexamethasone was increased by 21% when coadministered with 150 mg oral casopitant and 8 mg twice daily

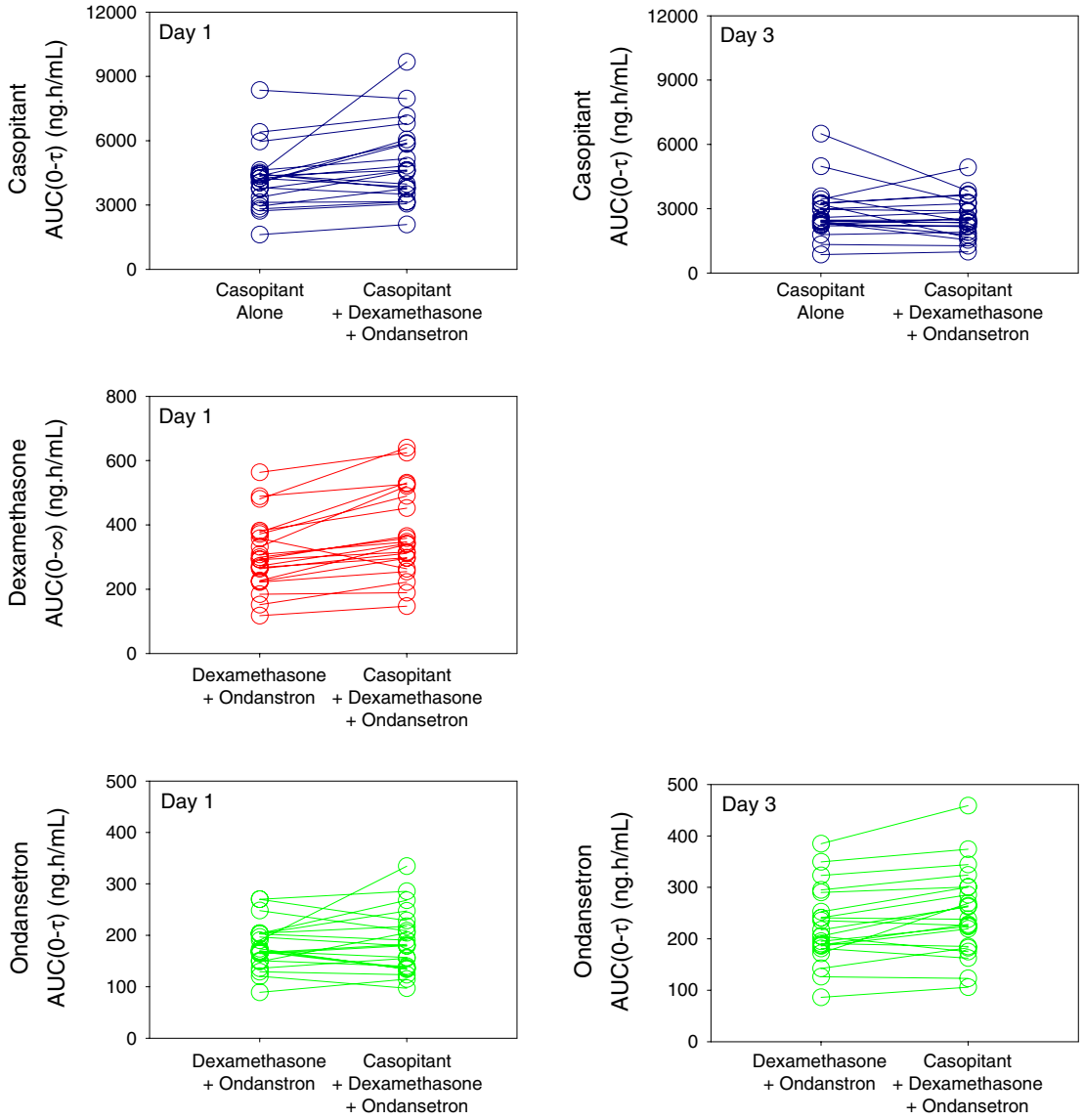

Fig. 2 Changes in individual casopitant (*top*), dexamethasone (*middle*), and ondansetron (*bottom*) AUC parameters after administration of casopitant alone, dexamethasone + ondansetron, and casopitant + dexamethasone + ondansetron, from part 2 (MEC regimen)

ondansetron, but there was no change in dexamethasone Cmax (Table 3 and Fig. 2).

Ondansetron The day 1 and day 3 oral ondansetron AUC(0-τ) and Cmax were not affected by coadministration with casopitant (Table 3 and Fig. 2).

Safety

The most commonly reported AEs were headache and dizziness. In part 1, subjects who received oral dexamethasone and IV ondansetron demonstrated a virtually identical frequency of AEs, 58% and 59%, respectively, in the presence (regimen C) or absence (regimen B) of casopitant. Casopitant alone (regimen A) produced an AE frequency of 17% with no headache or dizziness (Table 4).

In part 2, the frequency of subjects with AEs following administration of casopitant plus IV dexamethasone and oral ondansetron (regimen F) was similar to the frequency of AEs with casopitant alone (regimen D) with 24% each and the number of AEs following administration of IV dexamethasone and oral ondansetron without casopitant (regimen E) was actually numerically higher (43%) than the other two regimens (Table 4). No statistical analyses of the safety data were performed.

The majority of AEs were considered not related to study medication and were considered to be mild in nature.

Table 4 Adverse events reported by two or more subjects

Adverse event	Number of subjects (%)					
	Part 1			Part 2		
	Regimen A (*N*=23)	Regimen B (*N*=22)	Regimen C (*N*=19)	Regimen D (*N*=21)	Regimen E (*N*=21)	Regimen F (*N*=21)
Headache	0	5 (22%)	1 (4%)	2 (10%)	2 (10%)	2 (10%)
Dizziness	0	6 (26%)	5 (22%)	0	0	0
Disorientation	0	2 (9%)	0	0	0	0
Dyspepsia	0	0	2 (9%)	0	0	0
Fatigue	0	2 (9%)	1 (4%)	0	0	0
Hiccups	0	2 (9%)	1 (4%)	0	0	0
Insomnia	0	2 (9%)	0	0	1 (5%)	0
Paraesthesia	0	0	0	0	2(10%)	0
Tachycardia	0	1 (4%)	2 (9%)	0	0	0
Back pain	1 (4%)	1 (4%)	1 (4%)	0	0	0
Abdominal pain (upper)	0	0	0	0	1 (5%)	1 (5%)
Diarrhea	0	0	0	1 (5%)	1 (5%)	0
Myalgia	0	1 (4%)	1 (4%)	0	0	0
Nasopharyngitis	0	0	1 (4%)	0	0	1 (5%)
Vasovagal syncope	1 (4%)	0	0	1 (5%)	0	0
Abdominal pain	0	0	0	1 (5%)	0	0

All AEs resolved. There were no deaths on the study. One subject, who experienced a serious adverse event of pulmonary embolism (considered by the investigator to be possibly related to study medication) 2 days after completing part 1, withdrew from the study. Warfarin therapy was instituted and the AE resolved prior to hospital discharge. Follow-up assessments of this subject after completion of warfarin therapy show the subject has an underlying diagnosis of type II protein C deficiency where antigen levels are normal but activity is decreased.

Discussion

Part 1 of this study was designed to examine the potential pharmacokinetic interactions of the addition of casopitant to a corticosteroid/5-HT_3 receptor antagonist regimen that would be used for the prevention of CINV resulting from HEC [10, 19]. As data from earlier studies suggested some potential for casopitant to increase the exposure of coadministered oral dexamethasone, the three-drug combination of casopitant, dexamethasone, and ondansetron utilized a reduced-dose regimen of dexamethasone, with the objective of showing that this three-drug regimen (regimen C) provided approximately the same dexamethasone exposure as a standard-dose two-drug regimen of dexamethasone and ondansetron (regimen B). Part 1 showed that casopitant exposure was modestly affected by coadministration with dexamethasone and ondansetron, with a 28% increase in exposure on day 1 and a 34% decrease in exposure on day 3. These changes in casopitant exposure when combined with repeat-dose dexamethasone would not be considered clinically important given the patient to patient variability in the pharmacokinetics of CYP3A substrates, like casopitant, where exposures can vary between subjects by as much as 50% to 80%, or higher depending on the substrate [14]; in addition, a 3-day regimen of casopitant combined with repeat-dose oral dexamethasone has recently been shown to be effective in the prevention of CINV resulting from HEC [24].

Part 1 also demonstrated that the reduced-dose regimen of dexamethasone (from 20 mg to 12 mg on day 1 and from 8 mg twice daily to 8 mg once daily on days 2 and 3) was a suitable adjustment for the pharmacokinetic effect of casopitant on dexamethasone exposure. Although the three-drug combination resulted in a slightly lower dexamethasone exposure on day 1 when compared to the standard-dose two-drug regimen (17% lower), the 24 h dexamethasone exposure on day 3 was similar to the standard regimen. These results indicate that the 3-day regimen of oral casopitant increases dexamethasone by 39% on day 1 and 108% on day 3. The exposure of 32 mg IV ondansetron was not affected by 150 mg casopitant when used in this three-drug regimen and, therefore, no dose adjustment is necessary.

The dose regimens in part 2 were designed to evaluate the potential pharmacokinetic interactions of the addition of casopitant to an IV dexamethasone/oral ondansetron two-

drug regimen for the prevention of CINV resulting from MEC [10, 19]. In this case, no significant drug interactions were expected and therefore no a priori dose reductions were used in the study.

Again, casopitant exposures were only modestly affected by coadministration with 8 mg IV dexamethasone and 8 mg twice daily oral ondansetron on day 1 (16% increase) and were not affected following 3 days of coadministration with oral ondansetron. Addition of casopitant to the two-drug regimen of IV dexamethasone and oral ondansetron resulted in a 21% increase in dexamethasone AUC(0-∞), but no change in ondansetron exposure on day 1 or day 3. These results confirm that no alteration in IV dexamethasone or oral ondansetron dose is necessary when coadministered with 1-day or 3-day regimens of casopitant for the prevention of MEC and this three-drug regimen has recently been shown to be effective in the prevention of CINV resulting from MEC [8]. The lack of interaction between single and repeat doses of oral casopitant and single or repeat-doses of oral doses of the 5-HT_3 antagonists dolasetron or granisetron has also recently been shown [1] suggesting that any of these 5-HT_3 receptor antagonists could be used in a three-drug regimen with casopitant for the prevention of CINV.

Coadministration of repeat oral doses of casopitant with IV ondansetron and oral dexamethasone, or with IV dexamethasone and oral ondansetron, in healthy subjects was generally well tolerated under the conditions of this study. One serious adverse event of severe pulmonary embolism occurred 2 days following completion of treatment in part 1. This event was considered possibly related to treatment with study medication(s); however, follow-up assessments of this subject after the completion of warfarin therapy suggest type II protein C deficiency, an important risk factor for venous thromboembolism. It has been recommended that the subject be followed by a hematologist because of a need for life-long anticoagulation.

The three drug combinations of casopitant, dexamethasone, and ondansetron employed in the current study have been successfully utilized in phase III clinical trials, including study arms that tested a convenient single oral dose of 150 mg casopitant on day 1 only and replacing the day 1 150 mg oral dose of casopitant with a 90 mg IV infusion of casopitant as part of a 3-day IV/oral regimen [3, 8, 11, 24]. These results demonstrate that any of these three-dosage regimens for casopitant can be added to existing two-drug regimens consisting of a corticosteroid and a 5-HT_3 receptor antagonist. In the case of regimens for the prevention of CINV that include repeat-doses of oral dexamethasone (e.g., CINV resulting from HEC), a reduction in the dose of dexamethasone from 20 mg to 12 mg on day 1 and from 8 mg twice daily to 8 mg once daily on days 2 and 3 may be employed to maintain a similar dexamethasone exposure to that of the standard two-drug regimen. If a single day 1 dose of 150 mg casopitant is to be used for the prevention of CINV, only the day 1 dose of dexamethasone would need to be reduced, as no interaction of significance would be expected to occur in the day or days after single-dose casopitant administration (half-life of 17 h, unpublished results). In addition, as supraproportional increases in dexamethasone exposures with increasing dose have not been observed [16], the observations in the current study would be applicable to a dexamethasone dose of 20 mg, i.e., a 40% higher exposure would be expected, and this increase (equivalent to a dexamethasone dose of 28 mg) may not be considered clinically relevant given the variability in exposure of CYP3A substrates [14]. When 1- or 3-day regimens of casopitant are to be added to single-dose IV dexamethasone and repeat-dose ondansetron for the prevention of CINV (e.g., that resulting from MEC), no adjustment in dexamethasone dose is required. This study also showed that casopitant does not impact the pharmacokinetics of oral or IV ondansetron.

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