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ORIGINAL ARTICLE

Aprepitant when added to a standard antiemetic regimen consisting of ondansetron and dexamethasone does not affect vinorelbine pharmacokinetics in cancer patients

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Abstract
Purpose Aprepitant, a selective neurokinin-1 (NK-1) receptor antagonist approved for the treatment and prevention of emesis caused by moderately and highly emetogenic chemotherapy, is an inhibitor, inducer, and substrate of the cytochrome P450 3194 pathway. The CYP3A4 pathway is the major pathway of the metabolism of vinorelbine, a vinca alkaloid frequently used in combination with cisplatin. Therefore, we studied the potential interaction of the aprepitant 3-day antiemetic regimen on the pharmacokinetics of vinorelbine.
Patients and methods Fourteen patients with metastatic solid tumors were included in this open-label, balanced, 2-period crossover study. In treatment arm A, vinorelbine (25 mg/m^2 weekly) was administered alone, while in treatment arm B the same dose of vinorelbine was administered following the administration of the aprepitant antiemetic regimen on day 1 and alone on day 8. The antiemetic regimen of aprepitant was comprised of the following; on day 1: 125 mg aprepitant, 12 mg dexamethasone, and 32 mg ondansetron; on days 2 and 3: 80 mg aprepitant and 8 mg dexamethasone and on day 4: 8 mg dexamethasone. Blood samples for vinorelbine pharmacokinetic analysis were collected over 96 h.
Results Two patients discontinued the study due to adverse events that were judged not to be drug-related. Complete pharmacokinetic data of vinorelbine administered alone and with the aprepitant antiemetic regimen were obtained in 12 patients. The mean plasma concentration profile of vinorelbine administered with aprepitant was identical to that following vinorelbine administered alone, with geometric mean vinorelbine plasma AUC ratios of treatment B day 1/treatment A day 1 and of treatment B day 8/treatment A day of 1.01 (0.93, 1.10) and 1.00 (0.92, 1.08), respectively.
Conclusion As the aprepitant antiemetic regimen has no detectable inhibitory or inductive effect on the pharmacokinetics of vinorelbine, aprepitant when added to a standard antiemetic regimen consisting of ondansetron and dexamethasone can be safely combined with vinorelbine at clinically recommended doses.

Keywords Aprepitant · Vinorelbine · CYP3A4 · Interaction · Pharmacokinetics

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Introduction

One of the most common adverse effects of cytotoxic agents is nausea and vomiting, both of which have a considerable impact on the quality of life of cancer patients. Aprepitant (Emend®), an orally available, selective neurokinin-1 (NK-1) receptor antagonist, has recently been approved in the USA and Europe for the treatment of moderately and highly emetogenic chemotherapy. Aprepitant is effective for both acute and delayed chemotherapy-induced nausea and vomiting and is used in combination with a 5-hydroxytryptamine-3 ($5HT_3$) antagonist (e.g., ondansetron) and a

corticosteroid (e.g., dexamethasone) [1, 2]. In randomized placebo controlled clinical trials, the addition of aprepitant to ondansetron and dexamethasone significantly improved the protection against emesis [3–5]. The recommended dose-regimen of aprepitant is 125 mg prior to the chemotherapy on day 1 and 80 mg on days 2 and 3 [1, 2].

Aprepitant is metabolized by cytochrome P450 (CYP) isozymes 1A2, 2C19, and 3A4, yielding *N*- and *O*-dealkylation products, and was shown to be a moderate inhibitor of CYP3A4 in vitro and a very weak inhibitor of CYP2C19 and CYP2C9 [6]. In a pharmacokinetic study in healthy volunteers, using midazolam as probe drug, aprepitant moderately inhibited CYP3A4 activity [7]. As dexamethasone, which is part of the standard antiemetic regimen, is also subject to CYP3A4-mediated metabolism, and aprepitant was found to interact with the pharmacokinetics of dexamethasone, a dose reduction of dexamethasone is applied when combined with aprepitant. The same holds true for methylprednisolone, a corticosteroid also used to prevent chemotherapy-induced nausea and vomiting [8]. No clinically significant effects of aprepitant have been observed on the pharmacokinetics of the $5HT_3$ antagonists, ondansetron and granisetron [9] and more recently dolasetron [10]. Many cytotoxic agents are known to be substrates of CYP3A4 [11], and therefore caution should be taken when combining those drugs with aprepitant. If the metabolic clearance (Cl) would be reduced, this could impact the exposure and toxicity of the chemotherapy.

Vinorelbine is a vinca alkaloid approved either as single agent or in combination with cisplatin for the treatment of unresectable, advanced non-small cell lung cancer and advanced breast cancer. Vinorelbine is subject to CYP3A4 mediated metabolism and therefore its exposure might be altered when combined with aprepitant. Although vinorelbine itself is a moderately emetogenic agent, it is frequently used in combination with cisplatin, which is known to be highly emetogenic [12].

Therefore, we studied the potential interaction of the 3-day antiemetic regimen of aprepitant, combined with ondansetron and dexamethasone, on the pharmacokinetics of vinorelbine.

Patients and methods

Patient selection criteria

Patients with advanced malignant solid tumors for whom single agent vinorelbine was a treatment option were eligible for the study. Patients over 18 years of age with a Karnofsky performance score $\geq$60 and a predicted life expectancy of $\geq$3 months could be included in the study. Other inclusion criteria included: no previous radiotherapy or chemotherapy for at least 4 weeks prior to study entry, absolute neutrophil count $\geq 1.5 \times 10^9$/L, serum bilirubin $\leq$2.0 mg/dL and serum creatinine within the normal institutional limits. Female patients of childbearing potential were required to have a negative urine pregnancy test and to agree to use adequate contraception throughout the study. Medication and herbals known to interfere with CYP3A were not allowed from 1 to 2 weeks prior to study start (depending on the drug or herbal), until completion of the study. The study was approved by the Ethics Committee of the Erasmus Medical Center and conducted in accordance with the principles of the Declaration of Helsinki. All patients gave written informed consent.

Study design

The study was an open-label, balanced, two-period crossover study over two consecutive cycles of vinorelbine (Navelbine®, GlaxoSmithKline, Zeist, The Netherlands). Vinorelbine was administered as a 20 min intravenous infusion either in the absence (treatment arm A) or in the presence of the aprepitant regimen (treatment arm B). Vinorelbine was administered at a dose of 25 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. In treatment arm A, vinorelbine was administered alone, while in treatment arm B on day 1 vinorelbine was administered following the oral administration of aprepitant (125 mg, 1 h prior to vinorelbine dosing), oral administration of dexamethasone (12 mg; concomitant with aprepitant) and intravenous administration of ondansetron (32 mg; 30 min; starting 0.5 h prior to vinorelbine dosing). On days 2 and 3 of treatment arm B patient received 80 mg aprepitant and 8 mg dexamethasone, while on day 4 a single dose of 8 mg dexamethasone was administered. On day 8 of treatment arm B vinorelbine was administered alone. Vinorelbine dose adjustments were not allowed during the study. The sequence of treatments (arm A followed by arm B or vice versa) was determined by a randomized, open, and balanced allocation schedule.

The study was designed to enroll 8–12 patients in order to exclude a clinically significant higher exposure to vinorelbine between days 1 of treatment arm B compared to treatment arm A, defined as the geometric mean AUC-vinorelbine ratio of day 1 of both treatment courses $\leq$1.43 (i.e., AUC vinorelbine in combination treatment/AUC vinorelbine alone). Secondly, it was hypothesized that the exposure of vinorelbine following a single dose of vinorelbine given 8 days after

co-administration of vinorelbine with the antiemetic regimen (i.e., day 8 of treatment arm B) was clinically not less than the exposure when vinorelbine given alone (i.e., day 1 of treatment arm A), defined as the geometric mean AUC-vinorelbine ratio ≥0.70 (i.e., day 8 treatment arm B/day 1 treatment arm A).

Pharmacokinetic sampling procedure and analysis

Blood samples for vinorelbine pharmacokinetic analysis were collected in 7-mL tubes containing the anticoagulant lithium heparin on day 1 of treatment A (i.e., cycle without antiemetic regimen) and on days 1 and 8 of treatment B (cycle with antiemetic regimen). Blood samples were collected prior to the start of the vinorelbine infusion, at 10 min after the start of the infusion, at the end of the 20 min infusion and at 0.5, 1, 2, 4, 6, 10, 24, 48, 72, and 96 h after the start of the infusion. Blood samples were centrifuged, at bed-site, immediately after sampling at 2,200*g* for 15 min at T <10°C. The plasma supernatant was directly transferred into 3.6 mL Nunc-CryoTube Vials, and frozen at T <−20°C for a maximum of 24 h, where after the samples were stored at T <−70°C until analysis.

An HPLC-assay for the determination of vinorelbine in human lithium heparinized plasma was developed and validated, in accordance with the Guidance for Industry, Bioanalytical Method Validation, as specified by the Food and Drug Administration, Center for Drug evaluation and Research (http://www.fda.gov/cder/guidance/4252fnl.htm). Briefly, plasma samples for the quantitation of vinorelbine were processed by extraction of 500 μL aliquots with 3 mL diethyl ether. Subsequently, vinorelbine was back-extracted in 10 mM ammonium acetate (pH 3.0), the water phase evaporated and dissolved in 150 μL mobile phase. Aliquots of 100 μL were injected into the HPLC-system (Agilent 1100 series, Agilent Technologies Netherlands BV, Amstelveen, The Netherlands). Chromatographic separations were achieved on a Zorbax Eclipse XDB-C8 column (4.6 × 150 mm, 5 μm particle size; Agilent). The mobile phase was composed of 10 mM ammonium acetate pH = 3.0/acetonitrile (65:35, v/v), delivered at a flow rate of 0.70 mL/min. The column was maintained at 50°C and the column effluent was monitored at excitation and emission wavelengths of 280 and 360 nm, respectively. Vinorelbine and the Internal Standard vinblastine eluted at 4 and 6 min, respectively, while the overall run time was 20 min. Weighted (1/concentration) linear regression analysis of peak height ratios of vinorelbine and the Internal Standard, versus concentration of vinorelbine were used for the quantitation using the software package ChemStation as implemented in the HPLC-system. Peak height ratios of vinorelbine versus the Internal Standard were a linear function of the concentration from 2.00 to 200 ng/mL, with the lower limit of quantitation established at 2.00 ng/mL. The within and between-run precisions at five tested concentrations, including the lower limit of quantitation, were ≤6.36 and ≤5.75%, respectively, while the average accuracy ranged from 96.5 to 103.3%.

Individual pharmacokinetic parameter estimates of vinorelbine were derived from three-compartmental analysis of the observed plasma concentrations. Pharmacokinetic parameters of interest included the vinorelbine plasma exposure extrapolated to infinity ($AUC_{0-\infty}$), maximum vinorelbine plasma concentration ($C_{\text{end of infusion}}$), vinorelbine plasma Cl, vinorelbine volume of distribution (V_{ss}) and the vinorelbine elimination half-life ($t_{½}$).

Statistical evaluation

To test the hypothesis of no clinically relevant effect of aprepitant on the AUC of vinorelbine, individual vinorelbine AUC data were natural log transformed and evaluated with an analysis of variance (ANOVA) model having factors for subject within treatment sequence, treatment, period, and day within treatment. To compare vinorelbine pharmacokinetics with and without the aprepitant antiemetic regimen on day 1 (i.e., treatment B day 1/treatment A day 1) and to compare vinorelbine pharmacokinetics when given 8 days after the co-administration with the aprepitant antiemetic regimen to vinorelbine pharmacokinetics when given alone (i.e., treatment B day 8/treatment A day 1), two-sided 90% confidence intervals (CI; equivalent to one-sided 95% confidence limits) for the true mean between-treatment difference in natural log-AUC were calculated using the mean square error. The confidence limits were exponentiated to obtain the corresponding 90% CI for the true ratios.

Plasma clearance and $C_{\text{end of infusion}}$ of vinorelbine were analyzed using the same statistical method as described above for AUC, whereas, descriptive summary statistics were computed for the vinorelbine half-life and volume of distribution.

Assuming a true within-subject variance for natural log transformed AUC of 0.06, 12 patients completing the study, and $\alpha = 0.05$, there was 0.96 probability that the upper limit of the 90% CI for the true ratio treatment B day 1/treatment A day 1 would be ≤1.43 and 0.96 probability that the lower limit of the 90% CI for the ratio treatment B day 8/treatment A day 1 would be ≥0.70, given true ratios of one.

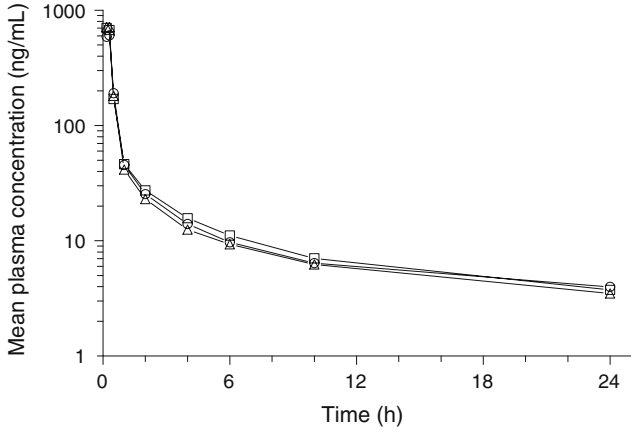

Fig. 1 Mean (n = 12) plasma concentration curves of vinorelbine given alone on day 1 of treatment arm A (*circles*) and given in combination with aprepitant antiemetic regimen on day 1 of treatment arm B (*squares*) and on day 8 of treatment arm B (*triangles*). Data are presented for the first 24 h, as concentrations were frequently below the LLQ of 2.00 ng/mL thereafter

Results

Patient population

Fourteen patients were included in the study between February and September 2005. Of the 14 patients started, 12 patients (four males, eight females; median age 56 years) completed the study. One patient discontinued treatment after cycle 1 and one patient during cycle 2, both due to adverse events not considered to be related to study drug. Cancer diagnoses included, among five miscellaneous carcinomas, five patients with breast cancer, and four patients with a carcinoma of unknown primary site. Only 1 of 12 patients was chemo naive.

Vinorelbine pharmacokinetics

Complete preliminary PK data of vinorelbine administered alone and with the aprepitant antiemetic regimen in 12 cancer patients were obtained. As shown in Fig. 1, identical mean plasma concentration time curves of vinorelbine, either administered alone, or in combination with the aprepitant antiemetic regimen, were observed. Paired individual vinorelbine plasma exposures (i.e., $AUC_{0-\infty}$) of vinorelbine after treatment alone and in combination with aprepitant antiemetic regimen are shown in Fig. 2. In Table 1, the summary of the vinorelbine plasma pharmacokinetics is given. As the geometric mean (90% CI) vinorelbine plasma AUC ratio of treatment B day 1/treatment A day 1 was 1.01 (0.93, 1.10) and the geometric mean (90% CI) vinorelbine plasma AUC ratio of treatment B day 8/treatment A day 1 was 1.00 (0.92, 1.08), no clinically relevant inhibiting nor inductive effect of the 3-day aprepitant regimen on the vinorelbine pharmacokinetics was observed.

Discussion

Aprepitant, an orally available, selective NK-1 receptor antagonist is mainly metabolized by CYP3A4 and was shown to be a moderate inhibitor and weak and transient inducer of CYP3A4 [6]. The cytochrome CYP3A4 is abundantly expressed in the liver and small intestine and involved in the metabolism of numerous exogenous compounds, including anticancer agents. Several cytotoxic agents are known to be substrates of

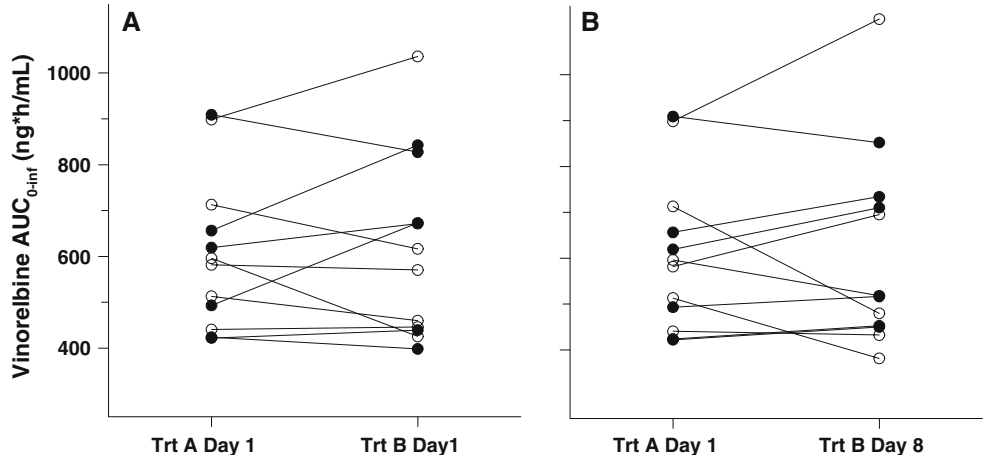

Fig. 2 **a** Paired individual vinorelbine plasma exposures of vinorelbine after treatment alone (Trt A day 1) and in combination with aprepitant antiemetic regimen (Trt B day 1). **b** Paired individual vinorelbine plasma exposures of vinorelbine after treatment alone (Trt A day 1) and alone 8 days after aprepitant antiemetic regimen (Trt B day 8)

Table 1 Summary of pharmacokinetic parameters for vinorelbine

	Geometric mean (90% CI)			Geometric mean ratio (90% CI)	
	Treatment A day 1	Treatment B day 1	Treatment B day 8	Treatment B day 1/treatment A day 1	Treatment B day 8/treatment A day 1
$AUC_{0-\infty}$ (ng/h/mL)	584.8 (497.9, 687.0)	589.4 (501.8, 692.3)	582.3 (495.7, 683.9)	1.01 (0.93, 1.10)	1.00 (0.92, 1.08)
$C_{\text{end of infusion}}$ (ng/mL)	631.9 (551.0, 724.9)	733.3 (639.3, 841.1)	747.6 (651.8, 857.5)	1.16 (1.01, 1.33)	1.18 (1.03, 1.36)
Cl (L/h)	78.0 (65.5, 92.8)	77.4 (65.0, 92.1)	79.1 (66.4, 94.2)	0.99 (0.90, 1.09)	1.01 (0.92, 1.11)
V_{ss} (L)[a]	1,330.3 (474.1)	923.5 (230.0)	1,061.3 (430.3)		
Alpha half-life (h)[b]	0.07 (0.02)	0.06 (0.01)	0.06 (0.02)		
Beta half-life (h)[b]	1.1 (0.3)	1.2 (0.5)	1.1 (0.4)		
Gamma half-life (h)[b]	21.4 (8.8)	17.1 (7.0)	18.7 (8.7)		

Treatment A = Vinorelbine alone

Treatment B = Vinorelbine + Aprepitant + Ondansetron + Dexamethasone

AUC mean square error (log-scale) = 0.0143

Ceoi mean square error (log-scale) = 0.0390

Cl mean square error (log-scale) = 0.0176

[a] Arithmetic mean (SD)

[b] Harmonic mean (Pseudo SD)

CYP3A4, including, but not limited to, epipodophylotoxins, taxanes, vinca alkaloids, and molecularly targeted anticancer agents [11]. We here studied the potential interaction of the antiemetic regimen of aprepitant, ondansetron, and dexamethasone on the pharmacokinetics of vinorelbine, which is subject to CYP3A4 mediated metabolism and is frequently used in combination with emetogenic anticancer agents.

As the geometric mean (90% CI) vinorelbine plasma AUC ratio of treatment B day 1/treatment A day 1 was 1.01 (0.93, 1.10) and the geometric mean (90% CI) vinorelbine plasma AUC ratio of treatment B day 8/treatment A day 1 was 1.00 (0.92, 1.08), the antiemetic regimen of aprepitant plus dexamethasone and ondansetron had no detectable impact on the pharmacokinetics of vinorelbine.

This resembles the experience concerning the pharmacokinetics and the adverse effects of docetaxel [13], a taxane extensively metabolized by CYP3A4 [14]. The exposure to docetaxel, expressed as the AUC_{0-last}, in the absence or presence of aprepitant was similar with a geometric mean (90% CI) of the ratio of 0.97 (0.86, 1.10). Thus, our study and the one of Nygren et al [13] demonstrate that it is very unlikely that antiemetic regimens including aprepitant will have a clinically relevant effect on the pharmacokinetics of intravenously administered anticancer agents subject to CYP3A4 mediated metabolism.

In conclusion, there was no interaction with the pharmacokinetics of both docetaxel and vinorelbine, suggesting that clinically relevant interactions of aprepitant, when added to a standard antiemetic regimen consisting of ondansetron and dexamethasone, with other intravenously administered anticancer agents subject to CYP3A4 mediated metabolism may be extremely unlikely.

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