Aprepitant: drug–drug interactions in perspective

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The implications of chemotherapeutic drug–drug interactions can be serious and thus need to be addressed. This review concerns the potential interactions of the antiemetic aprepitant, a neurokinin-1 receptor antagonist indicated for use (in Europe) in highly emetogenic chemotherapy and moderately emetogenic chemotherapy (MEC) in combination with a 5-hydroxytryptamine-3 (5-HT3) receptor antagonist and corticosteroids and (in the United States) in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy including high-dose cisplatin. When considering use of aprepitant for prevention of chemotherapy-induced nausea and vomiting, its potential drug–drug interaction profile as a moderate inhibitor of cytochrome P-450 isoenzyme 3A4 (CYP3A4) has been a source of concern for some physicians and other health care professionals. We explore in this paper how real those concerns are. Our conclusion is that either no interaction or no clinically relevant interaction exists with chemotherapeutic agents (intravenous cyclophosphamide, docetaxel, intravenous vinorelbine) or 5-HT3 antagonists (granisetron, ondansetron, palonosetron). For relevant interactions, appropriate measures, such as corticosteroid dose modifications and extended International Normalized Ratio monitoring of patients on warfarin therapy, can be taken to effectively manage them. Therefore, the concern of negative interactions remains largely theoretical but needs to be verified with new agents extensively metabolized through the 3A4 pathway.

Key words: antiemetic, aprepitant, CINV, drug interaction

introduction

While drug–drug interactions are a valid concern in all patients, it should be recognized that not all potential drug interactions have clinical consequences and many are manageable [1]. The use of multiple drugs at once is a common feature of care for cancer patients; not only are these patients likely taking more than one chemotherapeutic agent but they are also in need of supportive care and thus rely on several other drugs for analgesia, anemia, neutropenia, depression, etc, as well as prevention of nausea and vomiting which may involve a three-drug combination that may include a 5-HT3 (serotonin-3) receptor antagonist, a corticosteroid, and a neurokinin (NK)-1 receptor antagonist, presently aprepitant. The various metabolic pathways involved in drug metabolism account for many important drug interactions and therefore, it is important to consider both the number of drugs that patients take as well as the specific metabolic pathways of each.

The cytochrome P-450 isoenzyme 3A4 (CYP3A4) is a major metabolic pathway for drugs in the human body including many of the drugs used by patients to treat the symptoms caused by cancer and its treatment as well as their other illnesses including cardiovascular disease. CYP3A4 can be both inhibited and induced by drugs, leading to many complex and important drug interactions. Potent inhibitors of CYP3A4 have the potential to interact with cytotoxic agents to cause adverse effects. It is essential to understand the clinical impact of drug–drug interactions affecting chemotherapy treatment to provide patients with the best possible care.

the need for aprepitant

Nausea and vomiting are frequently cited as the most distressing side-effects of chemotherapy [2, 3]. Up to 75% of all cancer patients will experience chemotherapy-related emesis with increased risk associated with specific chemotherapeutic agents used, female gender, age <50 years, and history of nausea or vomiting (including during pregnancy, prior chemotherapy use, motion sickness) [4, 5]. The introduction of antiemetic therapy with a corticosteroid and a 5-HT3 receptor antagonist significantly improved the control rate of chemotherapy-induced nausea and vomiting (CINV) in the 1990s. Two important neuropeptide receptors involved in the mechanism of emesis following chemotherapy treatment have been identified. Serotonin receptors in the gastrointestinal (GI) tract and in the central nervous system are important in the early development of emesis; 5-HT3 receptor antagonists in particular have been shown to provide relief from emesis in
Aprepitant is an NK-1 receptor antagonist that crosses the blood–brain barrier to exert its antiemetic effect [10] and has been approved for the prevention of CINV in patients receiving highly emetogenic chemotherapy and MEC. Aprepitant has been initially evaluated in four phase III double-blind randomized studies, three of which involved high-dose cisplatin and one with chemotherapy containing an anthracycline plus cyclophosphamide for breast cancer [13, 17–19]. The standard therapy arms contained ondansetron and dexamethasone; in the experimental arm, aprepitant in the currently approved dose and schedule was added to ondansetron and dexamethasone. The addition of aprepitant resulted in an absolute difference in complete response (CR; absence of retching or vomiting and no use of an ‘as-needed’ antiemetic) of 14%–21% in the cisplatin trials and a difference of 9% with MEC. The lesser difference with MEC was attributed to a lack of effect on nausea with aprepitant; however, for retching or vomiting alone, a similar difference with aprepitant among all phase III studies was demonstrated with a 17% difference achieved with MEC and a 14.3%–22.7% difference with cisplatin. Furthermore, significant improvement with aprepitant was observable in both the acute (first 24 h) and delayed phase [14], much needed improvement of CINV management came with the introduction of the NK-1 receptor antagonists, a new class of antiemetics, as well as of palonosetron, a long-acting 5-HT3 receptor antagonist [16].

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Aprepitant is used in combination with corticosteroids and 5-HT3 receptor antagonists to prevent CINV associated with highly emetogenic chemotherapy and MEC. Aprepitant improves acute and delayed phase control of vomiting and maintains its efficacy over multiple cycles of chemotherapy [13, 17, 25]. Aprepitant is an oral formulation with ~65% bioavailability; it also has a prodrug, fosaprepitant, which is available as an i.v. preparation. Following oral administration, peak plasma concentrations are achieved in 4 h, and its absorption is not affected by food. Aprepitant is recommended for once-a-day (QD) administration as it has a terminal half-life of 9–13 h. It is indicated for use for a maximum of three consecutive days per chemotherapy cycle at a recommended oral dose of 125 mg on day 1 of treatment 1 h before chemotherapy and 80 mg QD on days 2 and 3. Mild hepatic or renal insufficiency does not affect dosage and adjustments are not required on the basis of age, race, or gender. On the basis of publicly available data, oral aprepitant (125 mg) and i.v. fosaprepitant (115 mg) have similar mean plasma concentrations at 24 h after dose and fosaprepitant up to 150 mg is generally well tolerated [26]. The primary pathway of aprepitant elimination is the CYP3A4 [27]. CYP3A is the most abundant isoenzyme expressed in the human liver and small intestine and is involved in the metabolism of various anticancer drugs [28]. In addition to being a substrate, aprepitant has been shown to moderately inhibit CYP3A4 and mildly induce CYP2C9 [29, 30]. These findings indicate that possible drug–drug interactions may occur when aprepitant is coadministered with drugs, including anticancer agents, metabolized by either of these enzymes. However, it has been noted through a number of pharmacokinetic studies that the impact of most of these interactions is not clinically significant and leads to dose adjustments in few circumstances (Table 1).

Aprepitant drug interactions put into perspective

The idea that drug–drug interactions with aprepitant are mostly of little clinical importance may seem contradictory.
Table 1. Pharmacokinetics of drug–drug interactions with aprepitant

<table>
<thead>
<tr>
<th>Chemotherapeutic agents</th>
<th>Change in AUC from baseline with the addition of aprepitant</th>
<th>Aprepitant effect and recommended adjustments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide i.v.</td>
<td>No clinically significant effect</td>
<td>No effect on adverse events; slight increase in autoinduction; dose adjustments not required</td>
<td>[31, 32]</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>0.97-fold (90% CI 0.86–1.10)</td>
<td>No effect on pharmacokinetics or toxicity, dose adjustment not required</td>
<td>[33]</td>
</tr>
<tr>
<td>Vinorelbine i.v.</td>
<td>1.01-fold (day 1; 90% CI 0.93–1.10); 1.00-fold (day 8; 90% CI 0.92–1.08)</td>
<td>No effect on plasma concentration</td>
<td>[34]</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>No data</td>
<td>Possible increased incidence of encephalopathy, not proven to be aprepitant related</td>
<td>[35, 36]</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>2.2-fold</td>
<td>Requires up to 50% dose reduction</td>
<td>[37, 38]</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>2.5-fold</td>
<td>Requires 50% dose reduction</td>
<td>[37, 39, 40]</td>
</tr>
<tr>
<td>i.v.</td>
<td>1.3-fold</td>
<td>Requires 25% dose reduction</td>
<td></td>
</tr>
<tr>
<td>5-HT3 antagonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granisetron</td>
<td>No significant effect</td>
<td>No effect on pharmacokinetics</td>
<td>[41, 42]</td>
</tr>
<tr>
<td>Ondansetron (i.v.)</td>
<td>~15% increase ($P = 0.019$) with 375 mg aprepitant</td>
<td>Supratherapeutic aprepitant dose slightly increases plasma concentration; not expected with therapeutic aprepitant dose</td>
<td>[43–46]</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>No significant effect</td>
<td>No effect on pharmacokinetics</td>
<td>[47]</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oral contraceptives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>43% decrease</td>
<td>Secondary barrier contraceptive recommended</td>
<td>[48]</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>8% decrease</td>
<td>Secondary barrier contraceptive recommended</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>No significant effect (day 3); 34% reduction in S-enantiomer (day 5); 14% decrease in prothrombin time (day 5)</td>
<td>Requires 2 weeks of INR monitoring</td>
<td>[49]</td>
</tr>
<tr>
<td>CYP probes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral midazolam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>3.3-fold ($P &lt; 0.01$)</td>
<td>Moderate effect on plasma concentration</td>
<td>[29, 30]</td>
</tr>
<tr>
<td>i.v.</td>
<td>1.24-fold (day 4, $P &lt; 0.01$); 0.81-fold (day 8, $P &lt; 0.01$); 0.96-fold (day 15, $P = 0.646$)</td>
<td>Moderate effect on plasma concentration</td>
<td></td>
</tr>
<tr>
<td>Tolbutamid (oral)</td>
<td>0.77-fold (day 4, $P &lt; 0.01$); 0.72-fold (day 8, $P &lt; 0.01$); 0.85-fold (day 15, $P = 0.05$)</td>
<td>Moderate effect on plasma concentration</td>
<td>[30]</td>
</tr>
</tbody>
</table>

AUC, area under the concentration–time curve; CI, confidence interval; 5-HT3, 5-hydroxytryptamine-3; INR, International Normalized Ratio; CYP, cytochrome P-450 isoenzyme.
considering that aprepitant is known to modify key isoenzymes and is coadministered with several medications that are substrates of those enzymes. Indeed, the required dose reduction of dexamethasone when given with aprepitant indicates a clinically relevant potential for significant interactions. Thus, the assumption has been that there is a potential risk of drug–drug interactions with its use. However, not only is it important to determine which aprepitant interactions are clinically relevant but it is also necessary to put those interactions into clinical perspective with other drugs that are isoenzyme modifiers.

The effect of aprepitant on CYP3A4 and CYP2C9 has been studied using established probes to each of these enzymes [29, 30]. Interactions with aprepitant appear to be more pronounced with oral drugs compared with i.v. drugs, and hence CYP3A4 in the gut may be more important for drug interactions. Midazolam is a benzodiazepine that undergoes extensive first-pass metabolism by both hepatic and intestinal CYP3A4. Midazolam given i.v. is an established probe to measure CYP3A4 in the liver, whereas midazolam given orally is useful for CYP3A4 measurement in the gut and liver. The pharmacokinetics of midazolam has been correlated with the activity of CYP3A4 and can be used to detect changes in the activity of the enzyme. This is helpful for determining the extent to which a drug of interest affects CYP3A4. This information can be used to classify the drug of interest as a CYP3A4 inhibitor or inducer in vivo [50]. Findings that a 5-day regimen of aprepitant coadministration with oral midazolam in healthy male subjects resulted in a significant increase (3.3-fold; \( P < 0.01 \)) in area under the concentration–time curve (AUC) plasma concentration and maximum observed concentration (1.9-fold; \( P < 0.01 \)) of midazolam confirmed aprepitant as an inhibitor of CYP3A4 [29]. An additional study reported a 25% increase (versus placebo) of i.v. midazolam AUC [30]. However, a 25% increase is of marginal clinical significance in comparison with other drugs that modify CYP3A4 to a much greater degree. For example, a strong metabolic inducer like rifampin caused a 96% reduction in midazolam AUC [51] and both ketoconazole and itraconazole increased the midazolam AUC 10–15 times (\( P < 0.001 \)) and the mean peak concentrations three to four times (\( P < 0.001 \)) [52]. Therefore, on the basis of the midazolam classification scale, aprepitant inhibition of CYP3A4 is considered moderate and is comparable with inhibition by two calcium channel blockers, diltiazem and verapamil [50].

Few, if any, chemotherapeutic agents are metabolized by CYP2C9 and therefore, the inductive effect of aprepitant on this enzyme could be considered less important. However, some of the additional drugs used for comorbid conditions or supportive care may be metabolized by CYP2C9. Oral tolbutamide was used as a CYP2C9 probe drug to examine the effect of aprepitant on this enzyme in healthy subjects [30]. Aprepitant had a small but statistically significant effect on the pharmacokinetics of tolbutamide but was not considered clinically relevant as this effect was weak and transient. For agents that have a small therapeutic index, like warfarin, this interaction needs to be considered [53]. However, for most other drugs metabolized by CYP2C9, such as some nonsteroidal anti-inflammatory drugs (e.g. diclofenac), a slight decrease in plasma concentration is unlikely to be of clinical importance.

**Aprepitant impact on chemotherapeutic agents**

Anticancer drugs known to be metabolized by CYP3A4 include vinca alkaloids (vincristine, vinblastine, and vinorelbine), docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, gefitinib, and dasatinib. Cyclophosphamide autoinduces its own metabolism through several isoenzyme pathways, and CYP3A4 does not play a major role in its metabolism to the 4-OH active metabolite. The concern is for inducing elevated plasma concentrations of such chemotherapeutic drugs through interactions with CYP3A4 modifiers, resulting in increased toxic effects. Clinical trials of aprepitant with anticancer drugs, including cyclophosphamide, etoposide, taxanes, and vinca alkaloids, failed to produce any clinically significant interaction; however, pharmacokinetic analysis was not always evaluated in the clinical studies [54].

Vinorelbine is a vinca alkaloid that is regularly administered with cisplatin [55] and is particularly sensitive to changes in CYP3A4 activity and thereby drugs that are able to inhibit or induce CYP3A4 activity [56]. Coadministration of aprepitant with vinorelbine could potentially decrease its metabolism, thereby increasing exposure to the active agent and toxicity. Yet a pharmacokinetic drug interaction study investigating potential interactions found that aprepitant had no clinically significant effect on i.v. vinorelbine pharmacokinetics; the geometric mean vinorelbine plasma AUC ratio was the same on day 1 [1.01; 90% confidence interval (CI) 0.93–1.10] as on day 8 (1.00; 90% CI 0.92–1.08), indicating no clinically relevant inhibiting or inductive effect of the 3-day aprepitant regimen combined with dexamethasone and ondansetron [34].

Docetaxel is primarily metabolized by CYP3A4 and patients with the lowest CYP3A4 activity experience lower clearance of the drug and consequently greater toxicity, manifested as longer and/or more severe neutropenia and other adverse events [33]. Coadministration of docetaxel with drugs that induce, inhibit, or are metabolized by CYP3A4 is only recommended with caution. Aprepitant has not been shown to cause any clinically significant alterations in pharmacokinetics of docetaxel or its toxicity (adverse events and neutropenia) compared with administration of docetaxel alone in cancer patients [33]. The geometric mean AUC ratio of docetaxel plus aprepitant (3.17 mg·h/ml) versus docetaxel alone (3.26 mg·h/ml) was 0.97 (90% CI 0.86–1.10). Furthermore, even as 95% of patients in the phase III studies received other concomitant chemotherapeutic agents that are CYP3A4 substrates, such as etoposide and paclitaxel, doses were not adjusted to account for potential drug interactions [13, 17, 18]. These findings indicate that although aprepitant is a moderate inhibitor of CYP3A4, it does not necessarily significantly increase the plasma levels or otherwise alter the pharmacokinetics of other i.v. chemotherapeutic agents that are also CYP3A4 substrates.

Cyclophosphamide is a prodrug that is metabolized to its active metabolite of 4-OH-cyclophosphamide primarily via CYP2B6 and is metabolized to toxic and inactive metabolites
600 mg/m²) is currently being investigated by Walko et al. in the effect of aprepitant on the pharmacokinetics of cyclophosphamide. The influence of aprepitant on the pharmacokinetics of cyclophosphamide in this study was analyzed using a population pharmacokinetic analysis including a reference population of 49 patients receiving the same chemotherapy regimen without aprepitant and sampled under the same conditions. The rates of cyclophosphamide autoinduction and thiotepa clearance were significantly reduced by 23% (P = 0.04) and 33% (P < 0.001), respectively. There was large interindividual (45.8% thiotepa; 54.0% cyclophosphamide) and intraindividual variability in clearance of these drugs; however, the effect of aprepitant was considered small and of minor clinical importance [31].

The effect of aprepitant on the pharmacokinetics of cyclophosphamide as part of the breast cancer regimen called AC (doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m²) is currently being investigated by Walko et al. in a randomized, double-blind, two-period crossover study. Patients received cyclophosphamide plus aprepitant (125 mg on day 1 and 80 mg on days 2 and 3) or placebo in the two periods. Seventeen patients have completed two cycles. There was no statistically significant change in the AUC of the active metabolite of cyclophosphamide (4-OH metabolite) when cyclophosphamide was given with aprepitant [32].

Ifosfamide is another prodrug that requires activation by CYP3A4 enzyme. Metabolism results in both the active metabolite (4-hydroxy-ifosfamide [4OH-Ifo]) as well as inactive but neurotoxic metabolites (2- and 3-dechlooroethyl-ifosfamide [2d-Ifo and 3d-Ifo]) [35]. A report of an individual developing acute encephalopathy following ifosfamide infusion and aprepitant administration [35] and a retrospective observation of a series of patients receiving ifosfamide [36] indicate a possible interaction which can lead to an increased risk of encephalopathy. These data should prompt a prospective pharmacokinetic evaluation. It should be noted that encephalopathy is a rare but well-known adverse reaction to ifosfamide [59].

The importance of understanding potential drug–drug interactions between antiemetics and cytotoxins cannot be overstated. At present, there is no evidence that such interactions with aprepitant are of major clinical importance. Scope remains to understand the consequences of drug–drug interactions in patients taking multiday chemotherapy, in new combinations of cytotoxics and targeted agents for cancer therapy.

### Management of Aprepitant Effect on Corticosteroids

Both dexamethasone and methylprednisolone are metabolized by CYP3A4 [39,40,60] and the impact of aprepitant on the pharmacokinetics of these drugs is clinically relevant. In a phase IIB study, the addition of aprepitant to the standard oral dexamethasone (20 mg dexamethasone on day 1, 8 mg dexamethasone on days 2–5) plus ondansetron (32 mg i.v. on day 1 only) regimen resulted in a 2.2-fold increase in the area under the concentration–time curve from 0 to 24 h (AUC₀–2₄). The results were similar when a modified regimen of oral dexamethasone was used (12 mg on day 1, followed by 4 mg on days 2–5). Methylprednisolone is also used for CINV management and its metabolism is sensitive to aprepitant. Aprepitant increased the AUC₀–₂₄ of i.v. methylprednisolone 1.3-fold on day 1 (P < 0.010) and of oral methylprednisolone 2.5-fold on day 3 (P < 0.010) [37]. Therefore, it is recommended to dose-reduce i.v. and oral methylprednisolone by 25% and 50%, respectively, when coadministered with aprepitant.

Exposure to high doses of corticosteroids has not been studied for its antiemetic properties [14]. Usage of steroids, such as dexamethasone, at higher doses may be associated with a higher incidence of febrile neutropenia and serious infections compared with standard therapy [38]. Accordingly, in the subsequent phase III trials, the oral dexamethasone dose when coadministered with aprepitant was reduced by 50% to achieve exposures similar to those obtained without aprepitant and is the current dosage adjustment recommended by the aprepitant prescribing information. It is worth noting that there were no further reports of febrile neutropenia following the dose reduction of dexamethasone in the phase III studies.

Recent data indicate that while oral dexamethasone should be decreased by 50%, this might be not necessary for i.v. dexamethasone since there is less CYP3A4 gut effect involved [61]. Thus, the pharmacokinetic impact of aprepitant on corticosteroids used in the antiemetic regimens can be easily managed using dose adjustments.

### Lack of Clinical Effect by Aprepitant on 5-HT3 Antagonists

Ondansetron and granisetron are two commonly used first-generation 5-HT3 receptor antagonists in the prevention of CINV and both are metabolized by the CYP system. Ondansetron is metabolized by numerous CYP enzymes, including CYP1A2, CYP2D6, and CYP3A4 [62], while granisetron appears to be metabolized by the CYP3A family [41]. Although there are very few clinically relevant interactions listed for ondansetron, it has been shown to have interactions at supratherapeutic doses with a number of agents, including cyclophosphamide, antidepressants, and analgesics [43–46]. In healthy subjects, a supratherapeutic dose (three times the recommended dose) of aprepitant caused a small but
of palonosetron and thus, palonosetron did not require a dose
aprepitant was found to have no effect on the pharmacokinetics
elimination [66]. In clinical pharmacokinetic interaction studies,
CYP2D6 and, to a lesser extent, by CYP1A2 and CYP3A with both
combination with dexamethasone and aprepitant [65].
hydrodolasetron pharmacokinetics was found in healthy
volunteers irrespective of metabolizer type [63].
Palonosetron is a second-generation 5-HT3 receptor
antagonist with a prolonged duration of action and higher
receptor-binding affinity than first-generation antagonists like
ondansetron and granisetron [16, 64]. It has also been studied in
combination with dexamethasone and aprepitant [65]. In vitro,
palonosetron has been shown to be primarily metabolized by
CYP2D6 and, to a lesser extent, by CYP1A2 and CYP3A with both
renal and hepatic clearance being equally important to its
elimination [66]. In clinical pharmacokinetic interaction studies,
aprepitant was found to have no effect on the pharmacokinetics
of palonosetron and thus, palonosetron did not require a dose
adjustment when coadministered with aprepitant [47].

other aprepitant interactions to consider

warfarin
Warfarin is an oral coumarin-based anticoagulant prescribed
for the treatment and prophylaxis of various thromboembolic
diseases such as deep venous thrombosis and pulmonary
embolism [67]. Warfarin is frequently prescribed for cancer
patients for the prevention of venous access thrombosis as well as
the treatment of hypercoagulation conditions. It is a rac
mixture of its R- and S-enantiomers, but most of the
pharmacological activity resides with the S-enantiomer [68].
Warfarin enantiomers are extensively metabolized in the liver
by different CYP enzymes: CYP3A4 and CYP1A2 primarily
metabolize the R-enantiomer, whereas the S-enantiomer is
mainly metabolized by CYP2C9 [69]. Drug interactions with
this anticoagulant are important as enhanced exposure may be
associated with an increased risk of hemorrhage and reduced
exposure can diminish its anticoagulant effect.
Several drugs, including prescription, over-the-counter, and
herbal medicines, are known to have significant interactions with
warfarin, requiring their discontinuation or dose adjustments
[70]. As cancer patients could likely require warfarin and
aprepitant concomitantly and aprepitant is a mild inducer of
CYP2C9, its effect on warfarin pharmacokinetics and
pharmacodynamics was investigated in healthy patients
stabilized on chronic warfarin therapy [49]. Aprepitant was
administered at its recommended 3-day regimen and on day 3,
no significant effect on the plasma AUC of R- or S-enantiomers
was found. Five days after the completion of aprepitant dosing,
a significant reduction (34%) in the plasma S-enantiomer
concentration in conjunction with a 14% decrease in
prothrombin time [reported as International Normalized Ratio
(INR)] was demonstrated. The S-enantiomer is primarily
responsible for the anticoagulant effect of warfarin and these
results are consistent with aprepitant induction of CYP2C9.
Consequently, it is recommended that in patients on chronic
warfarin therapy, the INR be closely monitored for the 2-week
period following the 3-day regimen, particularly for 7–10 days. It
should be noted that once-monthly monitoring is indicated as
standard protocol in all patients with stable INR on warfarin
therapy [71] and guidelines are available to help physicians adjust
warfarin dosages if needed [72] as an extensive list of drugs,
herbal products and food are known to interact with warfarin.

oral contraceptives
Contraception is recommended during, and for 1 month
following, aprepitant treatment. It was noted that when given
QD 100 mg for 14 days, with an oral contraceptive containing
35 μg of ethinyl estradiol and 1 mg of norethindrone, aprepitant
decreased the AUC of ethinyl estradiol and norethindrone
by 43% and 8%, respectively. In combination with ondansetron
dexamethasone, a 3-day regimen of aprepitant given during
days 8–10 of a 21-day oral contraceptive cycle decreased
trough concentrations of ethinyl estradiol and norethindrone
by ~60% during days 9 through 21 [48]. Using alternate
methods of contraception during aprepitant treatment is
appropriate. Moreover, secondary barrier contraceptive
methods should be used with any chemotherapy regimens as
most chemotherapeutic agents are known teratogens.

conclusions
The addition of aprepitant to standard therapy has improved
emesis in both the acute and delayed phases of CINV, thereby
addressing this unmet need in CINV patients as chemotherapy
compliance and quality of life are enhanced with its use.
Accordingly, major antiemesis guidelines, such as the European
Society for Medical Oncology, the Multinational Association
for Supportive Care in Cancer and the American Society of
Clinical Oncology, now recommend aprepitant as part of
standard antiemetic therapy in high-risk patients (a category
which comprises cisplatin-based regimens and female patients
treated with anthracycline–cyclophosphamide-based
combinations) [73–75]. It has been shown that patients on
high-dose chemotherapy regimens who experienced substantial
nausea and vomiting were not treated according to any
guideline [76], indicating that incomplete CINV management
is not necessarily due to the lack of efficacious treatments but
rather the lack of drug use by health care providers.
Any apprehension about using aprepitant for combination
CINV management should be eased with the knowledge that
most drug–drug interactions with aprepitant have little or no
clinical consequence (Table 1). Dose adjustments required with
dexamethasone and methylprednisolone use have been proven
to appropriately modify drug exposures and not result in
further drug toxicity. It is important that these drug
interactions be put into perspective to help clarify the
usefulness of and need for aprepitant in patients at high or
moderate risk from CINV.
disclosure

M.S. Aapro has indicated that he is an advisor to Merck and several other manufacturers of antiemetics. C.M. Walko is currently conducting an investigator-initiated industry-sponsored trial with Merck.

references

48. Data on file, Merck Inc.