Effect of Aprepitant on Etoposide Pharmacokinetics in Patients with Testicular Cancer: A Pharmacokinetic Study to Determine the Absence of a Clinically Relevant Interaction

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All patients treated with anticancer agents should receive the most effective anti-emetic regimen. Anti-emetic guidelines provide recommendations but do not take into account possible drug–drug interactions between anti-emetics and anticancer drugs. This study determines the clinical relevance of the potential drug–drug interaction of the neurokinin-1 receptor antagonist, aprepitant, on the pharmacokinetics of etoposide. Aprepitant is a moderate CYP3A4 inhibitor and may increase the systemic exposure of etoposide which is partly metabolized by cytochrome P450 enzyme 3A4 (CYP3A4). In this prospective observational study, the pharmacokinetics of etoposide with and without concomitant use of aprepitant was determined in 12 patients receiving first-line chemotherapy for testicular cancer. The geometric mean (95% confidence interval (CI)) area under the plasma concentration-time curve 0–24 hour (AUC_{0-24h}) of etoposide with aprepitant was 86.2 (79.7–93.2) mg/L*hour vs. 83.7 (75.8–92.4) mg/L*hour without aprepitant. Geometric mean ratios (90% CIs) of AUC_{0-24h} and maximum plasma concentration (C_{max}) for etoposide with and without aprepitant were 1.03 (0.96–1.10) and 0.96 (0.89–1.03), respectively. This study confirms the absence of a clinically relevant interaction between etoposide and aprepitant. Both drugs can be safely combined without affecting etoposide exposure.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Aprepitant is a highly active anti-emetic drug that adds maximum benefit to the anti-emetic-drug regimen for high-emetic-risk chemotherapy. Aprepitant is a moderate CYP3A4 inhibitor and therefore has a potential pharmacokinetic interaction with etoposide which is partly metabolized by CYP3A4.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Is there a clinically relevant pharmacokinetic interaction between the moderate CYP3A4 inhibitor aprepitant and the anticancer drug etoposide?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study confirms the absence of a clinically relevant interaction between aprepitant and etoposide.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Aprepitant can be safely used in combination with etoposide without affecting etoposide systemic exposure.

Etoposide is a topoisomerase II inhibiting anticancer drug that is used in the treatment of various cancers, including testicular cancer (TC), non-small cell lung cancer, and Hodgkin's lymphoma. The initial treatment of TC is based on clinical staging following radical inguinal orchiectomy. When chemotherapy is indicated as a curative treatment option, the recommended first-line treatment consists of etoposide and cisplatin with or without bleomycin (BEP).[1] Cisplatin-based chemotherapy is classified as highly emetogenic chemotherapy (HEC).[2,3] Chemotherapy-induced nausea and vomiting can negatively affect quality of life and can lead to dose reductions, discontinuation of chemotherapy, and reduced survival.[4,5] According to the current anti-emetic guideline of the

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American Society of Clinical Oncology, the anti-emetic regimen for HEC consist of a four-drug combination, including a neurokinin-1 receptor antagonist (NK-1 RA), a serotonin receptor antagonist, dexamethasone, and olanzapine.[2] However, anti-emetic guidelines do not take into account potential pharmacokinetic drug–drug interactions (DDIs), causing uncertainty in clinical practice.[2,3] Especially NK-1 RAs are suspect for pharmacokinetic DDIs, because these drugs can both inhibit and induce cytochrome P450 enzyme 3A4 (CYP3A4).[6] Aprepitant, an NK-1 RA, is highly effective in combination with ondansetron and dexamethasone to prevent and reduce nausea in patients receiving high-dose cisplatin-based chemotherapy.[7–10] For BEP, the percentage of patients with a complete response, defined as no emesis and no rescue therapy, significantly increased from 13% in the placebo group to 42% in the aprepitant group.[10]

The effects of aprepitant on CYP3A4 activity has been investigated in pharmacokinetic studies using midazolam as a probe.[11–13] Co-administration of aprepitant on 5 consecutive days increased the systemic exposure to orally administered midazolam by 2.3-fold on day 1 and by 3.3-fold on day 5.[11] The effect of aprepitant on intravenously (i.v.) administered midazolam is much smaller. When midazolam is i.v. administered 1 hour after 125 mg aprepitant, the systemic exposure to midazolam is increased with 50%.[12] Systemic exposure to midazolam i.v. increases with only 25% when administered 1 day after completing a 3-day treatment with aprepitant. Five days after a 3-day aprepitant regimen, the systemic exposure to midazolam decreased with 19%, reflecting the CYP3A4 induction potential of aprepitant after cessation. On day 12 after the last dose of aprepitant, the effect on CYP3A4 activity is no longer present.[13] Therefore the interaction potential can be considered irrelevant for the following cycles of chemotherapy. The larger effect of aprepitant on orally administered midazolam compared to i.v. administered midazolam can be explained by inhibition of presystemic (intestinal and hepatic) CYP3A4 metabolism which can be relevant for orally administered CYP3A4 probes but not for i.v. administered drugs.

Although patients benefit from the addition of a NK-1 RA, aprepitant potentially increases the exposure to drugs metabolized by CYP3A4 directly after start of aprepitant. Etoposide is partly metabolized by CYP3A4, which may also make etoposide susceptible to interact with aprepitant.[14] As a result of this interaction, the exposure to etoposide might be increased during simultaneous use of aprepitant. The drug label of aprepitant states that no dosage adjustment is needed when aprepitant is combined with etoposide.[15] On the other hand, the use of netupitant, another NK-1 RA and also an inhibitor of CYP3A4, increases systemic exposure to i.v. administered etoposide by 28%.[16] The drug label of netupitant-palonosetron combination advises caution and monitoring for chemotherapeutic-related adverse reactions when netupitant is combined with etoposide.[16]

As a result of the potential interaction between aprepitant and etoposide, patients who are treated with this drug combination might be overexposed to etoposide. At the same time, if aprepitant is avoided, patients receive inferior anti-emetic therapy. Both situations potentially harm patients' outcome. Pharmacokinetic DDI studies can provide essential information that is required to assess the clinical relevance of DDIs and helps to overcome these dilemmas in clinical practice.

The purpose of this study is to determine the clinical relevance of the interaction between etoposide and aprepitant in patients with TC treated with i.v. etoposide as part of BEP. The results of this study will provide insight if there is a clinically relevant interaction between aprepitant and etoposide that should be taken into account when these drugs are simultaneously used.

METHODS

The interaction between aprepitant and etoposide was investigated in a prospective, paired study in patients with TC treated with etoposide according to the BEP protocol. The study was approved by the regional ethics committee Arnhem Nijmegen and was registered at the European Clinical Trials Database (EudraCT 2021-000342-17) and clinicaltrials.gov (NCT04935255). Written informed consent was obtained from all patients before entering the study.

A schematic representation of the study is shown in **Table S1**. The patients were treated with anti-emetics including aprepitant (125 mg on day 3, 80 mg on days 4–7) as part of standard care. Pharmacokinetic sampling was performed on day 2 (without aprepitant) and on day 4 (with aprepitant) of treatment with etoposide.

An indwelling peripheral i.v. catheter was placed from which 10 samples per pharmacokinetic curve were collected for pharmacokinetic assessment. These samples were collected at $t = 0$ hours (prior to dose), $t = 1$ hour (at the end of infusion of etoposide), and 2, 3, 4, 5, 7, 9, 11, and 24 hours after the start of infusion. The pharmacokinetic parameters area under the plasma concentration-time curve 0–24 hour (AUC_{0-24h}), maximum plasma concentration (C_{max}), and terminal half-life ($t_{1/2}$) were determined. The effect of aprepitant on etoposide pharmacokinetics was investigated by paired observation.

A limited sample size of four patients was required to demonstrate equivalent exposure with a power of 80%, a significance level of 0.05%, and a within-subject coefficient of variation of 9.3%.[17] Based on US Food and Drug Administration (FDA) guidance for statistical approaches to establish bioequivalence, a minimum of 12 patients to be included was retained.[18] Male patients could participate in this study if they were at least 18 years old, willing and able to give informed consent, blood sampling was possible, and were treated with BEP for TC. Participation was not possible if patients were taking drugs that interact with the metabolism of etoposide (including moderate or strong CYP3A4 inhibitors and inducers),[19] had an eGFR of < 40 mL/minute using the modification of diet in renal disease formula or a total bilirubin level >17 mmol/L. Plasma concentrations of etoposide were analyzed using a validated ultraperformance liquid chromatography-fluorescence method (**Supplementary Methods**). Geometric means and the geometric mean ratio (GMR) of exposure over time (AUC_{0-24h}) of etoposide with and without aprepitant was calculated. When the 90% confidence interval (CI) of the GMR falls within the 0.8–1.25 limits, this interaction is considered non-clinically relevant in line with the FDA guideline "Clinical Drug Interaction studies – Cytochrome P450 enzyme- and transporter-mediated drug interactions guidance for industry".[20] Pharmacokinetic parameters and descriptive statistics were performed by noncompartmental analysis using Phoenix WinNonlin 8.3.4.295.

RESULTS

A total of 17 patients were included in the study from October 2021 to June 2022 in the Radboudumc, Nijmegen, The Netherlands. Five patients dropped out due to withdrawal of consent ($n = 3$) or due to obstruction of the peripheral i.v. catheter preventing sequential blood drawn ($n = 2$). In the end, 236 samples from 12 patients were collected and analyzed. The characteristics

of the evaluable patients are presented in **Table S2**. The median age of the patients was 34 years (range: 24–59 years), the majority of patients ($n = 10$) had a Karnofsky Performance Score of 100 at baseline.

The geometric mean plasma concentration-time curves of etoposide with and without aprepitant are shown in **Figure 1**. The etoposide exposure with and without aprepitant for the individual patients is shown in **Figure S1**. Concomitant use of aprepitant did not result in a statistically significant difference in systemic exposure to etoposide (**Table 1**). When etoposide was used without aprepitant, the AUC_{0-24h} was 83.7 mg/L*hour (95% CI: 75.8–92.4) and 86.2 mg/L*hour (95% CI: 79.7–93.2) when combined with aprepitant. The C_{max} was 19.7 mg/L (95% CI: 18.6–20.9) when etoposide was administered alone, and in combination with aprepitant the C_{max} was 18.9 mg/L (90% CI: 88.8–103.1). The $t_{1/2}$ of etoposide was 4.7 (95% CI: 4.2–5.3) hours without aprepitant, and 5.1 (95% CI: 4.5–5.7) in combination with aprepitant. The GMR for AUC_{0-24h} was 1.03 (90% CI: 0.96–1.10) and for C_{max} 0.96 (90% CI: 0.89–1.03).

DISCUSSION

In this study, we demonstrated that aprepitant has no clinically relevant effect on etoposide exposure. Etoposide and aprepitant can therefore be safely combined. Patients who are treated with BEP for TC should receive optimal anti-emetic therapy, including the use of aprepitant or another NK-1 RA.

The patient population included in this study is representative for the TC population. Based on the $t_{1/2}$ of etoposide no carryover effects are expected between the two pharmacokinetic sampling days. The systemic exposure to etoposide found in our study is comparable to earlier findings. Thomas and colleagues observed an AUC_{0-24h} of 85 mg/L*hour to etoposide after a dose of 100 mg/m^2, which is in line with the AUC_{0-24h} of 83.7–86.2 mg/L*hour, as reported in our study after an equal dose.[20] Based on dose-proportional pharmacokinetics of etoposide over a dose range of 100–600 mg/m^2, it is not expected that a different effect will be observed at other dose levels.[21] Therefore, the results of this study are expected to be applicable to other patient populations treated with etoposide containing HEC regimens, for example, patients with lung carcinoma treated with a combination of cisplatin (or carboplatin) and etoposide.

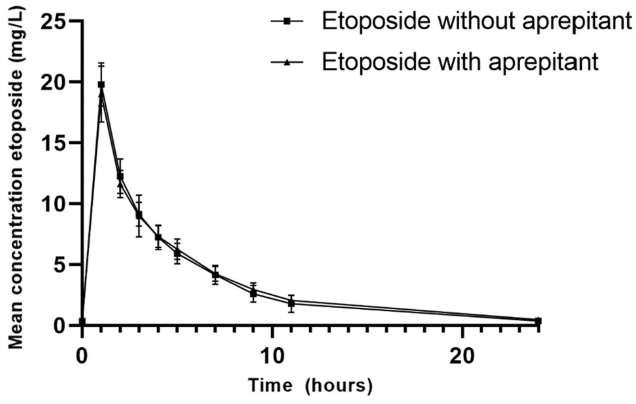

Figure 1 Etoposide plasma concentration-time curves with and without aprepitant. Data are represented as geometric mean and standard deviation.

The effect of aprepitant on systemic exposure to etoposide is significantly smaller compared to the effect on midazolam. The absence of an effect of aprepitant on etoposide exposure could be explained by the fact that etoposide undergoes multiple clearance mechanisms besides CYP3A4 metabolism.[14] In addition to CYP3A4/5 metabolism, etoposide can be converted via prostaglandin synthases or myeloperoxidases to the active metabolites catechol and quinone. Both parental drug and active metabolites can be inactivated by glutathione and glucuronide conjugation mediated by glutathione transferases (GSTT1/GSTP1) and uridine diphosphate glucuronosyltransferases (UGT1A1).[22] Etoposide is excreted by both renal and nonrenal processes. Approximately 56% of a dose is excreted in urine (of which 45% unchanged) and 44% is excreted in feces as unchanged drug and/or metabolites.[21] Aprepitant is not expected to affect renal and biliary excretion of etoposide.

Another important factor that should be taken into account is the route of administration. The bioavailability of oral etoposide is incomplete and variable, which might be due to poor solubility and limited stability of etoposide in gastric and intestinal fluids.[23] However, because the involvement of intestinal and hepatic first-pass metabolism cannot be ruled out, our findings cannot be extrapolated to oral treatment with etoposide.

In addition to aprepitant, according to current guidelines, other NK-1 RAs can also be used in anti-emetic treatment, such as fosaprepitant and netupitant. These NK-1 RAs show comparable or less CYP3A4 inhibitory potential compared to aprepitant, based on interaction studies with midazolam as a model-probe. Systemic exposure to orally administered midazolam was increased 2.4-fold by netupitant and 1.8-fold by fosaprepitant.[24,25] As mentioned earlier, the use of aprepitant increases systemic exposure to orally administered midazolam by 2.3-fold on day 1. Based on these data, it is surprising that netupitant increases systemic exposure to i.v. administered etoposide by 28%, whereas aprepitant has no

Table 1 Pharmacokinetic parameters etoposide with and without aprepitant

PK parameter	Etoposide without aprepitant ($n = 12$)	Etoposide with aprepitant ($n = 12$)	GMR (90% CI)
AUC_{0-24h}, mg/L*hour (95% CI)	83.7 (75.8–92.4)	86.2 (79.7–93.2)	1.03 (0.96–1.10)
C_{max}, mg/L (95% CI)	19.7 (18.6–20.9)	18.9 (17.5–20.4)	0.96 (0.89–1.03)
$t_{1/2}$, hour (95% CI)	4.7 (4.2–5.2)	5.1 (4.5–5.7)	1.08 (0.94–1.24)

AUC_{0-24h}, area under the plasma concentration-time curve 0–24 hours; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetic; $t_{1/2}$, terminal half-life.

effect on etoposide exposure. However, an increase of 28% is considered clinically irrelevant and etoposide can be safely combined with netupitant in clinical practice. It may be possible to translate aprepitant results to both netupitant and fosaprepitant. However, dedicated DDI studies may show small different outcomes as was seen for netupitant.

The results of this study confirm that there is no clinically relevant interaction between aprepitant and etoposide. The concomitant use of aprepitant, and fosaprepitant or netupitant with care, can be used safely in clinical practice in combination with etoposide. Optimal anti-emetic therapy, including the use of a NK-1 RA, should not be withheld in patients treated with etoposide-containing HEC.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

J.St., L.A.W.J., I.M.E.D., and N.P.E. designed the research. J.St., L.J., and J.Si. performed the research. J.St., and L.J. analyzed the data. J.St., and L.J. wrote the manuscript.

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