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A simple extemporaneous oral suspension of aprepitant yields sufficient pharmacokinetic exposure in children

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Abstract

Introduction: Aprepitant is used for the treatment of chemotherapy induced nausea and vomiting. A liquid formulation is needed for treatment of young children. However, the commercial (powder for) suspension was not available worldwide for a prolonged period of time and, therefore, a 10 mg/mL aprepitant oral suspension was extemporarily prepared to prevent suboptimal antiemetic treatment. The current pharmacokinetic study was developed to investigate whether this extemporaneous oral suspension offers an appropriate treatment option.

Methods: From 49 pediatric patients (0.7–17.9 years) 235 plasma concentrations were collected. Patients were either treated with our extemporaneous oral suspension (n = 26; 53%), commercially available capsules (n = 18; 37%), or the intravenous prodrug formulation of aprepitant (fosaprepitant, n = 5; 10%). Pharmacokinetic analyses were performed using nonlinear mixed effects modelling.

Results: A one-compartment model adequately described the pharmacokinetics of aprepitant in children. The bioavailability of the extemporaneous oral suspension was not significantly different to that of the capsules (P = 0.26). The observed bioavailability throughout the total population was 83% (95% CI 69%-97%). The absorption of the extemporaneous oral suspension was 39.4% (95%CI 19.5–57.4%) faster than that of capsules (mean absorption time of 1.78 h (95% CI 1.32–2.35), but was comparable to that of the commercial oral suspension. The median area under the curve after (fos)aprepitant was 22.2 mg/L*h (range 8.9–50.3 mg/L*h) on day 1.

Conclusion: Our extemporaneous oral suspension is an adequate alternative for the commercially (un)available oral suspension in young children. An adequate exposure to aprepitant in children was yielded and the bioavailability of the extemporaneous suspension was comparable to capsules.

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Introduction

Aprepitant is a selective neurokinin-1 (NK-1) receptor antagonist, which is orally available. Aprepitant enhances its effect by blocking the NK-1 receptor, preventing substance P from binding to the NK-1 receptors and, thereby, preventing chemotherapy induced nausea and vomiting (CINV).[1] Later, fosaprepitant, an intravenous formulation, was developed.[2] Fosaprepitant is a water soluble prodrug of aprepitant, which is rapidly converted to aprepitant after administration.

Aprepitant and fosaprepitant (hereafter, (fos)aprepitant) are used in children and adults for the treatment of CINV.[3,4] (Fos)aprepitant is added to the antiemetic regimen when high emetogenic chemotherapy is given. The standard prophylaxis for highly emetogenic agents consists of a 5-HT3 receptor antagonist, dexamethasone and aprepitant. Fosaprepitant is used in cases were oral administration is not possible. Aprepitant and fosaprepitant are administered in a 3-day regimen using a dosing schedule of 3 mg/kg (aprepitant max 125 mg, fosaprepitant 115 mg) at day 1 and 2 mg/kg (aprepitant and fosaprepitant max 80 mg) at day 2 and 3.[1,2] In the Netherlands, dexamethasone is dosed four times daily 3 mg/m^2 (intravenous or oral) when combined with (fos)aprepitant, according to the national guideline of the Dutch Childhood Oncology Group (DCOG).

For aprepitant treatment of younger children (below 12 years of age) the required doses of 2 or 3 mg/kg cannot be administered using commercially available capsules of 40, 80 and 125 mg as lower individual weight-based doses are needed. For this purpose, a powder for suspension was developed by Merck Sharp & Dohme B.V.[1] Aprepitant has low water solubility (Log P 4.8 at pH 7.0.[5]) To improve the bioavailability of aprepitant, a nano-particle formulation was developed by the manufacturer. The commercially available capsules and oral suspension both contain these aprepitant nano-particle-coated beads.[6,7] The pharmacokinetics (PK) of aprepitant in children, administered orally using commercially available capsules and commercially available oral suspension and intravenously using fosaprepitant, have been studied before.[8] The absorption of aprepitant was delayed in the case of capsules, but not when the oral suspension was used. The difference in bioavailability between capsules and commercial suspension was not tested.

For a longer period of time, the commercial (powder for) suspension was not available worldwide creating an urgent need for an alternative liquid formulation in order to treat younger patients with aprepitant. Therefore, we extemporized a 10 mg/mL aprepitant oral suspension using the commercially available capsules and a standard commercially available suspension base. Similar attempts with commercially available capsules and Orablend have been made. The relative bioavailability of this extemporaneous suspension, compared to capsules, was 82.3% in healthy adults.[9,10] Since the suspension is mainly used for treatment of young children, it is important to study the PK properties (e.g. bioavailability) of the extemporaneous suspension in a pediatric population, in order to investigate whether our extemporaneous oral suspension offers an appropriate alternative for young children.

Methods

Patients and sampling

Patients 0.5–18 years, treated with (fos)aprepitant and with a central venous line in situ for blood collection were included in a prospective observational study, studying the PK of aprepitant and dexamethasone, at the Princess Máxima Center for pediatric oncology in the Netherlands. There were no restrictions for chemotherapeutic treatment. Patients with Down syndrome were excluded. The use of CYP3A4 substrates and/or inhibitors within seven days or CYP3A4 inducers within 30 days before the start of antiemetic therapy was also reason for exclusion. Patients were included after written informed consent was obtained. Ethical approval by the institutional Medical Ethics Committee of the Erasmus MC was obtained. The study was registered in the Dutch Trial Registry as NTR7720. The current study describes the aprepitant part of this prospective observational study.

Patients were treated with (fos)aprepitant according to local protocol (doses as described in the introduction). Patients that could not be treated with the standard capsule formulation (80 mg or 125 mg) were treated with an extemporaneous oral suspension of 10 mg/mL, produced using the commercially available capsule filling[1] (Emend, Merck Sharp & Dohme B.V.) and a suspension base (Fagron). The suspension was prepared by grinding the aprepitant capsule filling, before mixing it with the suspension base as described by Dupuis et al.[9] Excipients of the suspension base were sucrose, colloidal magnesium-aluminum silicate, carboxymethylcellulose sodium salt, citric acid, methylparaben, propylparaben and banana essence. The self-life of the extemporaneous suspension was 1 month at room temperature.[9] Fosaprepitant was assumed to rapidly and completely convert to aprepitant after intravenous administration.

After administration of (fos)aprepitant on day 1, 2 or 3, a maximum of 6 blood samples of 1 mL over a time period of 24 h (at t = 0.5, 1.5, 4, 6, 12, 24 h) were taken from the central venous line. When samples were taken on day 2 or 3, a trough level sample before (fos)aprepitant administration was added. Plasma concentrations of aprepitant were measured using a validated liquid chromatography mass spectrometry method, with a lower limit of quantification (LLOQ) of 0.1 ng/mL, as described by Nijstad et al.[11] The first samples below LLOQ were included as a plasma concentration of 0.05 ng/mL (1/2 LLOQ).

Model development

Starting point for model development for aprepitant was a one-compartment model with first order absorption. Allometric scaling using body weight (BW) was a priori included on all parameters.[12] Subsequently, a two-compartment model was tested.

Since an absorption lag-time was found by Chain et al.,[8] a transit compartment model was implemented to describe aprepitant drug absorption.[13] The number of transit compartments was optimized manually. The mean absorption time (MAT) was estimated.

Interindividual variability (IIV) was evaluated for all parameters, according to equation (1):

$$P_i = P_{pop} \times e^{(\eta_i)} \quad (1)$$

where P_i represents the individual parameter estimate for individual i, P_{pop} represents the typical population parameters estimate, and η_i is assumed to be normally distributed with a mean of zero and a variance of ω^2.

For some patients, data of multiple doses was available, so interoccasion variability (IOV) was implemented similarly as IIV, with each dose and subsequent sampling defined as a separate occasion. This variability was evaluated for all parameters to diagnose potential time-dependent trends and to allow for random unaccounted variability between dosing moments.

Residual unexplained variability was modelled as a proportional error model.

Covariate analysis

The influence of formulation on the absorption related PK parameters was evaluated. Furthermore, age, as measure of maturation, was evaluated as covariate on clearance (CL), because Chain et al. found this to be a significant covariate on CL.[8]

Model evaluation

Discrimination between models was guided by physiological plausibility, goodness-of-fit (GOF) plots, precision of parameter estimates and change in objective function value (dOFV). A drop of ≥3.84 points, corresponding to a $P < 0.05$ (χ2-distribution with 1 degree of freedom (df)), was considered a significant improvement of the fit for hierarchical nested models. The adequacy of the models was assessed by GOF plots and visual predictive checks (VPC).[14] Parameter precision was assessed by the sampling importance resampling (SIR) procedure.[15]

Exposure

Using the given dose and the estimated individual CL, an area under the curve (AUC) was calculated, according to equation (2):

$$AUC_i = \frac{F_i \times Dose_i}{CL_i} \quad (2)$$

where AUC_i represents the area under the curve for individual i, F_i represents the estimated individual bioavailability, $Dose_i$ represents the given dose to individual i, and CL_i represents the estimated individual CL.

Software

Nonlinear mixed-effects modeling was performed using NONMEM (version 7.3.0, ICON development Solutions, Ellicott City, MD, USA) and Pearl-speaks-NONMEM (PsN, version 4.7.0) with First-Order Conditional Estimation with interaction (FOCE-I) as estimation method.[16,17] Pirana (version 2.9.9) was used as graphical user interface for NONMEM.[18] R (version 3.4.3) was used for data handling and visualization.[19]

Results

Patients and sampling

In total, 49 patients with a median age of 10.0 years (range 0.7–17.9) were available for inclusion in the aprepitant part of this study. 26 patients (53%) were treated with our extemporaneous oral suspension. In total, 235 aprepitant samples were available for analysis, of which 2 were below LLOQ. 86% of the patients were sampled during day 1 of (fos)aprepitant. Figure 1 displays the observed plasma concentrations over time. Detailed patient characteristics are shown in Table 1.

Model development and evaluation

A linear one-compartment model was appropriate to describe the PK of aprepitant. BW was a priori included as covariate using allometric scaling on all PK parameters. The exponents for BW on clearance (CL) and volume of distribution (V) were fixed to 0.75 and 1, respectively, prior to covariate analyses. A two-compartment model

was tested based on a previously published model,[8] but this did not improve the model, so further optimization was performed using a one-compartment model.

Transit compartments were implemented to describe a delay in absorption of aprepitant. The optimal number of transit compartments was three. The MAT was estimated to be 1.78 h (95% CI 1.32−2.35 h), multiplied by 0.61 (95% CI 0.43−0.81) in the case of the extemporaneous oral suspension (absolute MAT of 1.08 h). This represents a faster absorption of the oral suspension compared to the capsules.

The absolute bioavailability (F1) for the whole population (capsules and extemporaneous oral suspension together) was estimated to be 83% (95% CI 69%−97%). The relative bioavailability of the oral suspension compared to the capsules was tested and estimated to be 87% (95% CI 71%−108%, p = 0.26). This indicates that the bioavailability of the extemporaneous oral suspension is comparable to the bioavailability of the capsules.

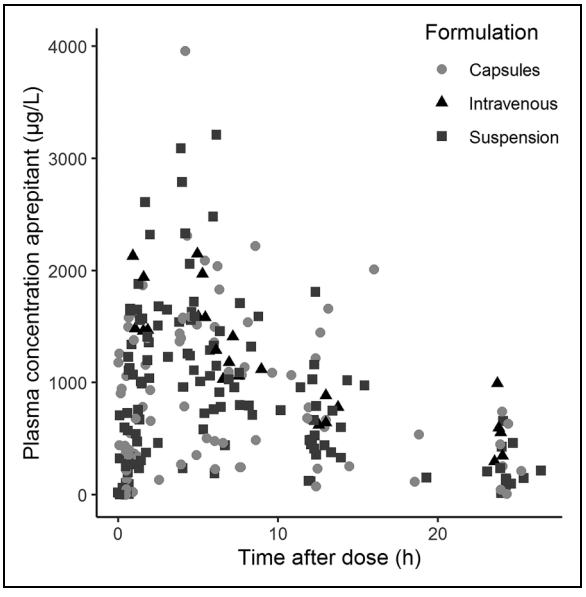

Figure 1. Aprepitant plasma concentrations versus time after dose.

In line with the published model of Chain et al.,[8] maturation was tested as covariate on CL, but this did not improve our model. In addition, no trend for an age effect was found looking at (ETA) plots.

In the final model, IIV was included on CL, MAT and F1. IOV was included on CL. The final estimates and 95% confidence intervals (CI) are shown in Table 2.

The GOF plots (Figure on request) showed accurate population and individual predictions, without any signs for over- or underprediction. Conditional weighted residuals (CWRES) are evenly distributed over the whole plasma concentration range and time interval. The VPC demonstrated that the median and the 95% CI of the observed data were in line with those from the simulation-based predictions from the model (Supplemental figure S1).

Exposure

The median AUC after (fos)aprepitant was 22.2 mg/L*h (range 8.9–50.3 mg/L*h) on day 1 and 10.4 mg/L*h (range 4.3–35.3 mg/L*h) on day 2 or 3. The median AUC of day 1 was 24.3 mg/L*h (range 8.9–50.3 mg/L*h) for patients treated with capsules. Patients treated with the extemporaneous suspension achieved a median AUC of 20.1 mg/L*h (range 11.7–42.3 mg/L*h) on day 1. Intravenously administered fosaprepitant yielded a median aprepitant AUC of 28.4 mg/L*h (range 23.4–45.9 mg/L*h) on day 1.

Discussion

This study describes the characterization of PK properties of aprepitant, administered as an extemporaneous oral suspension, by developing a population PK model of (fos)aprepitant in children. The bioavailability of the extemporaneous oral suspension was shown to be comparable to the bioavailability of commercially available aprepitant capsules and therefore offers an appropriate treatment option for young children. Extemporaneous preparation of an oral aprepitant suspension in the hospital pharmacy secures the availability of a highly needed drug in pediatric oncology, and solves supply continuity issues with the manufacturer. Eventually, this can be combined with dose

Table 1. Patient characteristics, median (range).

	Aprepitant capsules N = 18 (37%)	Aprepitant suspension N = 26 (53%)	Fosaprepitant N = 5 (10%)	Total N = 49
Patient characteristics				
Female sex [n (%)]	4 (22%)	15 (58%)	1 (20%)	20 (41%)
Age, years	14.4 (10.4–17.9)	6.0 (0.7–14.1)	13.3 (4.4–13.8)	10.0 (0.7–17.9)
Body weight, kg	50.7 (40.5–66.3)	22.1 (8.4–41.7)	41.7 (19.5–52.4)	32.5 (8.4–66.3)
Available data				
Total no. of PK samples [n]	88	123	24	235
No of samples per patient	5 (2–7)	5 (1–7)	5 (4–5)	5 (1–7)

Table 2. Final population PK parameter estimates of aprepitant.

PK parameter	Estimate	95% CI
CL_{70kg} (L/h)	5.83	5.02–7.20
V_{70kg} (L)	86.8	74.2–98.1
MAT (h)	1.78	1.32–2.35
Effect of suspension on MAT	0.606	0.426–0.805
F1 (%)	83	69–97
IIV CL (%)	25.1	7.2–39.5
IIV MAT (%)	58.9	47.3–72.5
IIV F1 (%)	33.0	24.7–41.9
IOV CL (%)	30.2	15.8–47.2
Proportional residual error (%)	33.2	28.8–37.0

PK pharmacokinetics *CI* confidence interval obtained by sampling importance resampling, *CL* clearance, *V* volume of distribution, *MAT* mean absorption time, *F1* bioavailability, *IIV* interindividual variability, *IOV* interoccassion variability.
Population estimates CL_{70kg}, V_{70kg} correspond to a subject weighing 70 kg and are adjusted to an individual value using allometric scaling.

banding strategies to enable safe and efficient administration of this important drug.

A one-compartment model was found to best describe the data. This is in line with a previous population PK model in adults,[20] but in contrast to a large PK study in children by Chain et al.[8] However, a two-compartment model was inferior to describe our data and we did not find any trends in our GOF plots that would suggest that a two-compartment model would fit our data better. Another discrepancy between the model of Chain et al. and our model is that we could not find an effect of CYP3A4 maturation within our dataset. This could be explained by the fact that we included only 3 patients (6%) below the age of 2 years. Chain et al. included 30 patients (20%) <2 years.[8]

Using a transit compartment modelling approach, we observed that absorption of aprepitant from capsules is slower than absorption of aprepitant from our extemporaneous suspension (MAT of 1.78 h for capsules compared to a MAT of 1.08 h for the extemporaneous suspension). This is as expected, as the dissolution step is faster in case of treatment with suspension. This is also in accordance with previous literature.[8,20] However, both previous studies used lag-time to correct for the delayed absorption, which represents an abrupt increase in the absorption rate from a value of zero. From a physiological approach, one would expect a rather slow increase starting from time point zero. Using transit compartments, a more physiological drug absorption process is described by a multistep process.[13]

Furthermore, we can conclude that the bioavailability of aprepitant within our population is 83%. We observed that the bioavailability of our extemporaneous suspension is comparable to the bioavailability of the capsules. Previous studies showed a bioavailability range of 59–67% for the commercially available capsules, which is increased when administered in fed state.[1] We observed a higher bioavailability than the described range. However, we did not have data on the fed state of our patients, so that might explain the slightly higher bioavailability. Data on the bioavailability of the commercially available oral suspension is not available, but the previous study that investigated the bioavailability of an extemporaneous aprepitant suspension observed a relative bioavailability of 82%, which is comparable with our results.[10] Furthermore, we detected an IIV of 33% for F1, so variability throughout our population seems to be moderate.

This study has several limitations. Firstly, within this PK study, we did not investigate the antiemetic effect of aprepitant. This means that within the current study, we were only able to compare the aprepitant AUC to historical cohorts, described in literature. The AUC that was found within our population was comparable with ranges described in literature.[1,3,8] Furthermore, as mentioned before, we did not collect data on fed state of the patients. The study protocol did not specify any dietary restrictions. Nevertheless, in the summary of product characteristics, the difference in exposure between fed and unfed state, was not considered clinically relevant.[1] Moreover, the acceptability of the extemporaneous suspension was not tested. However, we did not note any complaints about intake during the clinical study, so this may indicate that there were no problems with administration. Lastly, we did not investigate the chemical stability and the state of the nanoparticles in our extemporaneous formulation. The chemical stability of a similar extemporaneous suspension was investigated previously and appeared stable for at least 90 days by 4°C and 65 days at 4°C.[9] Information on stability of the aprepitant nanoparticles was not available, but since we did not experience any significant decline in bioavailability, we assume that the nanoparticles were still intact.

Overall, the results of the PK study show that the bioavailability of the extemporaneous oral suspension is comparable to capsules and that the extemporaneous oral suspension is an adequate alternative for the commercially available oral suspension in young children.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

References

1. Sharp M and Dohme BV. Summary of product characteristics: emend, https://www.ema.europa.eu/en/documents/product-information/emend-epar-product-information_en.pdf (2008, accessed 5 November 2021).
2. Sharp M and Dohme BV. Summary of product characteristics: ivemend, https://www.ema.europa.eu/en/documents/product-information/ivemend-epar-product-information_en.pdf (2013).
3. Kang HJ, Loftus S, Taylor A, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2015; 16: 385–394.
4. Dupuis LL, Sung L, Molassiotis A, et al. 2016 Updated MASCC/ESMO consensus recommendations: prevention of acute chemotherapy-induced nausea and vomiting in children. *Support Care Cancer* 2017; 25: 323–331.
5. Olver I, Shelukar S and Thompson KC. Nanomedicines in the treatment of emesis during chemotherapy: focus on aprepitant. *Int J Nanomedicine* 2007; 2: 13–18.
6. European Medicines Agency. Emend: EPAR - scientific discussion, https://www.ema.europa.eu/en/documents/scientific-discussion/emend-epar-scientific-discussion_en.pdf (2006).
7. European Medicines Agency. Emend-H-C-527-X-0049/G: EPAR - assessment report - extension, https://www.ema.europa.eu/en/documents/variation-report/emend-h-c-527-x-0049/g-epar-assessment-report-extension_en.pdf (2016).
8. Chain A, Wrishko R, Vasilinin G, et al. Modeling and simulation analysis of aprepitant pharmacokinetics in pediatric patients with postoperative or chemotherapy-induced nausea and vomiting. *J Pediatr Pharmacol Ther* 2020; 25: 528–539.
9. Dupuis LL, Lingertat-Walsh K and Walker SE. Stability of an extemporaneous oral liquid aprepitant formulation. *Support Care Cancer* 2009; 17: 701–706.
10. Patel P, Nathan PC, Walker SE, et al. Relative bioavailability of an extemporaneously prepared aprepitant oral suspension in healthy adults. *J Oncol Pharm Pract* 2019; 25: 1907–1915.
11. Nijstad AL, Tibben MM, Gebretensae A, et al. Development and validation of a combined liquid chromatography tandem-mass spectrometry assay for the quantification of aprepitant and dexamethasone in human plasma to support pharmacokinetic studies in pediatric patients. *J Chromatogr B Anal Technol Biomed Life Sci* 2021; 1171: 122639.
12. West GB, Brown JH and Enquist BJ. A general model for the origin of allometric scaling laws in biology. *Science* 1997; 276: 122–126.
13. Savic RM, Jonker DM, Kerbusch T, et al. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. *J Pharmacokinet Pharmacodyn* 2007; 34: 711–726.
14. Bergstrand M, Hooker AC, Wallin JE, et al. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J* 2011; 13: 143–151.
15. Dosne AG, Bergstrand M and Karlsson MO. An automated sampling importance resampling procedure for estimating parameter uncertainty. *J Pharmacokinet Pharmacodyn* 2017; 44: 509–520.
16. Lindbom L, Ribbing J and Jonsson EN. Perl-speaks-NONMEM (PsN)–a perl module for NONMEM related programming. *Comput Methods Programs Biomed* 2004; 75: 85–94.
17. Boeckmann AJ, Sheiner LB and Beal SL. NONMEM User guide. *NONMEM Part V* 2011; 2–169.
18. Keizer RJ, van Benten M, Beijnen JH, et al. Piraña and PCluster: a modeling environment and cluster infrastructure for NONMEM. *Comput Methods Programs Biomed* 2011; 101: 72–79.
19. RC Team. R: a language and environment for statistical computing. *R Found Stat Comput Vienna*.
20. Nakade S, Ohno T, Kitagawa J, et al. Population pharmacokinetics of aprepitant and dexamethasone in the prevention of chemotherapy-induced nausea and vomiting. *Cancer Chemother Pharmacol* 2008; 63: 75–83.