

PHARMACOKINETICS OF APREPITANT AND DEXAMETHASONE

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON24991

Source

NTR

Brief title

n/a

Health condition

The relevance for childhood cancer in the light of this current pilot study is very clear. Prophylaxis on chemotherapy induced nausea and vomiting is still a major problem in children receiving highly emetogenic therapy. Compared to adults we achieve almost 30% less control of CINV in children. This emphasizes the urgent need for novel strategies in the prophylaxis of CINV in children.

With these study results we can build a PK model which will be used for the optimization of the aprepitant and dexamethasone dosing schedule according to different age levels. Data from this pilot study will be used to subsequently perform a randomized controlled trial to assess the optimal dose, frequency and duration of aprepitant treatment in children with CINV.

Sponsors and support

Primary sponsor: Princess Maxima Center for pediatric oncology

Source(s) of monetary or material Support: Stichting kinderen kankervrij (KIKa)

Intervention

Outcome measures

Primary outcome

The primary objective of this study is to define the recommended dose of aprepitant given in combination with dexamethasone by constructing a population PK model in children according to different age groups

Secondary outcome

1. The feasibility of using the validated PeNAT score on nausea intensity in clinical practice
2. To describe possible interaction of dexamethasone and aprepitant with concurrent chemotherapy

Study description

Background summary

Rationale: Children treated with moderate to high emetogenic chemotherapy appear to have worse anti-emetic control when compared to adults (i.e. approximately 50% compared to 70-80% in adults), which has important consequences for quality of life during chemotherapy administration. One potential explanation for the inferior efficacy of regular anti-emetic therapy in children is that suboptimal doses and duration of combined aprepitant and dexamethasone in children are used, which - together with a 5-HT₃ antagonist - is the gold standard of current anti-emetic therapy. Aprepitant and dexamethasone show a mutual drug-drug interaction, which has been studied in adults, but this has not been studied in children. As a rule of thumb in children 50% dose-reduction of dexamethasone is applied with treatment is combined with aprepitant, which was extrapolated from findings in adults. This may result in sub-optimal dosing in children and may at least partly explain the differences in anti-emetic control between adults and children. Therefore, this pharmacokinetic interaction (PK) also needs to be characterized in children. Moreover, children of different age groups use different formulations which may also impact on drug exposure. Another important aspect is that aprepitant exposure is known to be influenced by chemotherapy, as summarized by Patel et al. 2017.¹ There is almost no data of aprepitant in chemotherapy regimens frequently used in children.

Primary Objective: To assess the recommended dose of aprepitant and dexamethasone in children using both antiemetic agents at the same time, given their PK-interaction.

Explorative secondary objective:

1. The feasibility of using the validated PeNAT score on nausea intensity in clinical practice.
2. To describe possible interaction of dexamethasone and aprepitant with concurrent chemotherapy

Study design: prospective observational study

Study population: Patients aged 0-19 years treated in the Princess Máxima Center (PMC) who will receive intravenously administered chemotherapy and are treated with aprepitant and/or dexamethasone plus granisetron/ondansetron as standard of care, who have a central line in place to sample blood for pharmacokinetics. We will enroll six different patient groups in the study: 1) age between 6 months to 6 years and dexamethasone only; 2) age between 6 months to 6 years and dexamethasone and aprepitant; 3) age 6 years and above to 12 years and dexamethasone only; 4) age 6 years and above to 12 years and dexamethasone and aprepitant; 5) age 12 years or above and dexamethasone only; 6) age 12 years or above and dexamethasone and aprepitant.

Main study parameters/ endpoints:

Pharmacokinetic parameters (i.e. clearance and volume of distribution) will be assessed using non-linear mixed effects modelling (NONMEM). Influence of relevant co-variables will be assessed by standard model building methods.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

The patient has no direct benefit from participating in this study. The data obtained in this study will be used to assess the population PK to develop an optimized dosing regimen of aprepitant and dexamethasone in children. Participation in this pilot study is minimally invasive and will include additional blood samples (maximum of 6 samples of 1 ml) and questionnaires on nausea and vomiting. The blood samples will be taken from the central line, which is inserted as standard of care in the context of chemotherapeutic treatment. The volume of blood that is withdrawn for the study does not exceed the recommended maximum. Sampling, using a flexible time scheme, will only be requested during regular hospital visits.

Study objective

Given the poor control of chemotherapy induced nausea and vomiting (CINV) in the delayed phase of CINV and the lower aprepitant exposure in terms of AUC and C₂₄ we suggest room for dose-optimization of aprepitant treatment in children.

Study design

START of the study: 01-02-2019

END of the study: 01-02-2020

Intervention

n/a

Contacts

Public

Scientific

Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Planned to receive chemotherapy intravenously as regular treatment (standard of care);
2. Receiving granisetron/ondansetron; dexamethasone and/or aprepitant as standard of care
3. Age $\geq$ 6 months and $\leq$ 18 years;
4. Signed Informed consent form (ICF) prior to participation in the study;
5. A present central line to sample blood for pharmacokinetics;
6. No Down syndrome or other syndromes that may influence regular dosing or no other disease/circumstances that may influence the participation of the subject in a negative way;
7. No use of strong CYP3A4 substrates or inhibitors within 7 days or CYP3A4 inducers within 30 days of treatment (appendix 2)

Exclusion criteria

see eligibility criteria above

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL	
Recruitment status:	Pending
Start date (anticipated):	01-02-2019
Enrollment:	99
Type:	Anticipated

Ethics review

Positive opinion	
Date:	23-01-2019
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 48783
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL7478
NTR-old	NTR7720
CCMO	NL67072.078.18
OMON	NL-OMON48783

Study results

Summary results

Kang HJ, Loftus S, Taylor A, DiCristina C, Green S, Zwaan CM. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial. The Lancet. Oncology. Apr 2015;16(4):385-394