PHARMACOKINETICS OF APREPITANT AND DEXAMETHASONE

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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.

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON24991

Bron
NTR

Verkorte titel
n/a

Aandoening

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.

Ondersteuning

Primaire sponsor: Princess Maxima Center for pediatric oncology
Overige ondersteuning: Stichting kinderen kankervrij (KIKA)

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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

Toelichting onderzoek

Achtergrond van het onderzoek

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 antiemetogenic 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 M¨¢xima 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-variates 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.

Doel van het onderzoek

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.

Onderzoeksopzet

START of the study: 01-02-2019

END of the study: 01-02-2020

Onderzoeksproduct en/of interventie

n/a

Contactpersonen

Publiek

Wetenschappelijk

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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 ≥ 6 months and ≤ 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)

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

see eligibility criteria above

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	01-02-2019
Aantal proefpersonen:	99
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	23-01-2019
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 48783
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

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

Resultaten

Samenvatting resultaten
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