Effect of sapropterin on variations of blood phenylalanine and tyrosine over 24 hours and from day to day in patients with phenylketonuria

Published: 05-03-2014
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Primary objective- To measure the effect of sapropterin on diurnal and day to day variations of blood phenylalanine concentrations.Secondary objective- To measure the effect of sapropterin on diurnal and day to day variations of blood tyrosine...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Inborn errors of metabolism
Study type	Interventional

Summary

ID

NL-OMON44967

Source
ToetsingOnline

Brief title
Phenylalanine and tyrosine variation and sapropterin

Condition

- Inborn errors of metabolism

Synonym
phenylketonuria, PKU

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Biomarin Pharmaceutical Inc.

Intervention

Keyword: phenylalanine, sapropterin, tetrahydrobiopterin (BH4), tyrosine

Outcome measures

Primary outcome

The mean standard deviations of the blood phenylalanine concentrations measured four times a day of 2 consecutive days and once a day on the 6 consecutive days of all participants compared between the sapropterin + diet treatment period and the diet alone treatment period.

Secondary outcome

- The standard deviation of the blood tyrosine concentrations measured once a day on 8 consecutive days of all participants compared between the sapropterin + diet treatment period and the diet alone treatment period.
- The mean standard deviations of the blood tyrosine concentrations measured four times a day of 2 consecutive days of all participants compared between the sapropterin + diet treatment period and the diet alone treatment period.
- The standard deviations of the blood phenylalanine/tyrosine ratios measured once a day on 8 consecutive days of all participants compared between the sapropterin + diet treatment period and the diet alone treatment period.
- The mean standard deviations of the blood phenylalanine/tyrosine concentrations measured four times a day of 2 consecutive days of all participants compared between the sapropterin + diet treatment period and the diet alone treatment period.

Study description

Background summary

Patients with phenylketonuria (PKU) treated by diet only may have large fluctuations in plasma concentrations of both phenylalanine (Phe) and tyrosine (Tyr). Increased plasma phenylalanine, increased phenylalanine/tyrosine ratio, and fluctuations in these values may negatively influence brain functions. Apart from decreasing plasma phenylalanine concentrations, sapropterin may influence positively plasma tyrosine concentrations, and by that also normalize phenylalanine/tyrosine ratios. As a consequence, brain function may also be improved. The question is whether sapropterin also stabilizes fluctuations of especially phenylalanine. Some preliminary data suggest such stabilization of phenylalanine concentrations. In addition, it is the question whether sapropterin also stabilizes fluctuations of tyrosine, and the phenylalanine/tyrosine ratio. There are no data to suggest or deny such an influence on the fluctuations of tyrosine and the phenylalanine/tyrosine ratio. The purpose of the study is to investigate the effect of sapropterin on fluctuations of especially blood phenylalanine in children with PKU. The study is hypothesis generating. Does sapropterin not only decrease the plasma phenylalanine concentrations and increase the plasma tyrosine concentrations, but also decreases the fluctuations in the plasma phenylalanine and tyrosine concentrations and the phenylalanine/tyrosine ratio.

Study objective

Primary objective
- To measure the effect of sapropterin on diurnal and day to day variations of blood phenylalanine concentrations.

Secondary objective
- To measure the effect of sapropterin on diurnal and day to day variations of blood tyrosine concentrations.
- To measure the effect of sapropterin on diurnal and day to day variations of blood phenylalanine/tyrosine ratio.

Study design

Open label randomized longitudinal crossover intervention study.

Intervention

16 PKU patients who use sapropterin as part of the treatment, males and females 4 to 12 years of age incl. and 18 years and above will be tested twice with blood phenylalanine concentrations within therapeutic range. The two treatment

periods consists of a period of 8 consecutive days not using sapropterin (only diet) and a period of 8 consecutive days using sapropterin + diet. Prior to each treatment period, there will be a stabilization period of at least 15 days in which patients already start with the treatment tested to achieve a stable situation before testing. In the period without Kuvan®, a stricter diet with respect to phenylalanine intake is prescribed to ensure comparable blood phenylalanine concentrations. In both treatment periods the diet prescribed will be comparable for total protein and energy intake, as well as for meal frequency and fasting periods, but differentiating in the balance between natural protein and protein substitute.

Study burden and risks

The study will be performed ambulatory. Parents/patients will sample blood at home and participation in the study includes no extra visits to the hospital. Instruction about the study will be realized by a research dietician at the regular visits in the clinic, when preferred home visits and/or via mail and telephone. In both study periods blood sampling is scheduled for the first two days four times daily (7-8 am, 12-1 pm, 5-6 pm and bedtime) and once a day (7-8 am) on the six consecutive days thereafter, in total 28 samples per patient. The sampling is done as routinely usual for the patient by finger puncture collecting blood on filter paper. All samples of all participating patients will be sent by mail to the UMCG laboratory Metabolic Diseases (Dr. R. Heiner-Fokkema). During the sampling days 1 and 2 plus the day before the sampling starts (in total 6 days) patients (or patient's* caretakers) perform a detailed food record of all their food and beverages.
Both groups will enter the study at random. The stabilization period will be used to create a stable situation before testing.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

- Males and females from 4 to 12 years of age incl. and 18 years and above.
- Diagnosed with phenylketonuria by newborn screening.
- Use of sapropterin as part of the treatment.
- Under good metabolic control; defined as 2/3 or 67% of the blood phenylalanine levels within target ranges during the last year.

Exclusion criteria

- Concomitant disease which may preclude the participation in the study in the judgment of the investigator.
- Intercurrent illness which might influence the blood phenylalanine levels.
- Concomitant medication as mentioned in the Kuvan® SPC.
- Known hypersensitivity to Kuvan® or its excipients.
- Known hypersensitivity to other approved or non-approved formulations of tetrahydrobiopterin.
- Non-compliance with study procedures in the judgement of the investigator.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-06-2014
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kuvan
Generic name:	sapropterin dihydrochloride
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	05-03-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	21-03-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	25-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	11-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-021343-41-NL
CCMO	NL45110.042.13
Other	trialregister.nl

Study results

Date completed:	01-04-2019
Actual enrolment:	13