The feasibility of using a subtherapeutic dose of piracetam as a marker of adherence to therapy

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To assess the feasibility of using a subtherapeutic dose of piracetam as a marker of adherence to therapy by determining whether this subtherapeutic dose produces a detectable concentration in the urine

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON53199

Source
ToetsingOnline

Brief title
Subtherapeutic dose of piracetam as a therapy adherence marker

Condition

- Other condition

Synonym
n.v.t. (zie uitleg onder vraag C21)

Health condition

De studie wordt uitgevoerd in gezonde vrijwilligers met als doel te onderzoeken of er een meetbare concentratie piracetam in de urine ontstaat na subtherapeutisch dosering piracetam. Er wordt dus geen effect op een aandoening onderzocht.

Research involving

Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: adherence tracer, Drug adherence, quantitative urinalysis, subtherapeutic dosing

Outcome measures

Primary outcome

Verifying the detectability of piracetam in urine after administration of the

planned doses using an in-house High-Performance Liquid Chromotography-tandem

Mass Spectrometry (HPLC-MS/MS) assay

Secondary outcome

To determine the piracetam urine concentrations after nonadherence of two days

Study description

Background summary

This study with healthy volunteers will test a subtherapeutic dose of piracetam as an adherence marker to assess the feasibility of its use in a multicenter, randomized, double-blind, placebo-controlled study of the efficacy of dexamfetamine in cocaine use disorder (CUD) with comorbid opioid use disorder (REDUCE-trial).

Adherence to the study medication in the REDUCE-trial will be assessed by urinanalysis twice weekly for the presence of dexamfetamine. To determine adherence in the placebo group, the tablets must be formulated with a marker detectable in urine. It is necessary to assess adherence in the REDUCE-trial since stimulants will be provided to patients who are dependent on stimulants. Moreover, monitoring adherence ensures that efficacy is established when the medication is taken at the correct dose and frequency.[1] Non-adherence to study medication is especially a problem in trials involving the addicted population, with 10% of participants never taking a dose.[2] In addition,

relatively low adherence rates (39-42%) are common for this population.[3][4] Efficacy and safety effects may be underestimated as a result of nonadherence to study medication. Since adherence to placebo was found to be a predictor of better treatment outcomes, it is important to assess this as well.[5]

Several markers for assessing medication adherence are described in the literature.[1][7-12] However, none of these previously used markers were eligible for use within the clinical trial design. First, the measurement of adherence for some markers was based on urine staining (methylene blue, phenol red, fluorescein, phenazopyridine) that would be visible to patients enrolled in the trial. Second, some markers (riboflavin, quinine) are interfered with by dietary or vitamin intake.[1] In addition, some markers are limited by the occurrence of side effects (phenobarbital).[10][11] Finally, the long half-life of the adherence markers bromide and digoxin would not fit the twice weekly urinalysis, where non-compliance of several days would be masked.[7-9] Therefore, a suitable marker for the REDUCE-trial was searched.

The ideal marker is nontoxic and potentially detectable in urine at a subtherapeutic dose. Therefore, a drug with a relatively high therapeutic dose, high bioavailability, high unchanged renal clearance and low hepatic metabolism is favourable. Thus, detectable amounts in urine at subtherapeutic dose would be likely. Moreover, the half-live of the marker must match the twice weekly assessments of adherence. Of all the authorised drugs in the Netherlands, piracetam was found to meet the most of the criteria. Piracetam is a well-tolerated therapy and registered in the Netherlands for the treatment of vertigo. Daily therapeutic intake is 2400 mg with complete bioavailability, no hepatic metabolism and a renal clearance of about 90%.[13] The likelihood of interference with prescribed piracetam is low, as only 740 patients used the drug in the Netherlands in 2021.[14]

The subtherapeutic dose of piracetam was calculated using the EMA guidelines on shared manufacturing facilities.[15] This guideline contains acceptance limits of cross-contamination between drugs in multipurpose manufacturing processes. These limits are based on the absence of a therapeutic or toxicological effect of the residues of an active drug.[15] The permitted daily exposure (PDE) is calculated using all available pharmacological and toxicological data, including both non-clinical and clinical data, to derive safe thresholds. The PDE represents a substance-specific dose that is unlikely to cause adverse effects if a person is exposed to or below this dose for a lifetime. The PDE for piracetam was calculated to be 8 mg (Appendix I). As patients in the REDUCE-trial receive one, two or three placebo tablets per day, the intention is to add 2.5 mg of piracetam to the placebo tablets. If the urine concentration of piracetam known in the literature at daily intake of 800 mg is extrapolated to 2.5 mg, a measurable urine concentration of 200 ng/ml is expected.[16] However, it should first be confirmed in healthy volunteers whether detectable piracetam concentrations are actually excreted in the urine.

The references can be found on pages 25-26 of the study protocol.

Study objective

To assess the feasibility of using a subtherapeutic dose of piracetam as a marker of adherence to therapy by determining whether this subtherapeutic dose produces a detectable concentration in the urine

Study design

Prospective, single center, open-label, uncontrolled study in 10 healthy volunteers who will receive various subtherapeutic doses of piracetam

Intervention

All included participants will administer the investigational product once weekly according to the following scheme:

Week 1 (day 1): 7.5 mg (6 tablets)
Week 2 (day 1): 5 mg (4 tablets)
Week 3 (day 1): 2.5 mg (2 tablets)
Week 4 (day 1): 1.25 mg (1 tablet)

Urine samples will be collected 24 and 72 hours after administration of the weekly dose

Study burden and risks

As described under E9, the risks to participants within this study are negligible.

Participants themselves do not benefit from taking part in this study. But by participating, participants help to reliably investigate whether a drug works well in a study in the future. This may act as motivation for participants to participate in the study and be perceived as a benefit. Taking part in this study may have disadvantages. The burden of this study includes 10 visits to the treatment site. The intake of six and four tablets respectively (in week 1 and week 2) may be perceived as burdensome by the participants. In addition, the participants may find the submission of urine unhygienic or uncomfortable. Participating in the study will cost participants extra time and they will have to follow the arrangements associated with the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

To be considered eligible to participate in this study, all of the following requirements must be
met:
1. Age >= 18 years;
2. Able and willing to give written informed consent;
3. Able and willing to undergo urine sampling for analysis;
4. Able and willing to digest multiple tablets at day one of each study week (6 tablets of
1.25 mg in week 1; 4 tablets of 1.25 mg in week 2; 2 tablets of 1.25 mg in week 3 and 1 tablet of 1.25 mg in week 4)

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
1. Current prescribed treatment with piracetam;
2. Pregnant or breastfeeding;
3. Criteria regarding the following contra-indications for piracetam:
- Cerebral haemorrhage;
- Huntington's chorea;
- Hypersensitivity to pyrrolide derivatives.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	04-07-2023
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nootropil
Generic name:	Piracetam
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	22-06-2023
Application type:	First submission
Review commission:	METC NedMec

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	EUCTRn.v.t.ziedocum-NL
Other	In afwachting van NCT nummer (clinicaltrials.gov), voor registratie zie document K6. 'Protocol Registration and Results System (PRS) Receipt'
CCMO	NL84344.041.23

Study results

Date completed:	31-08-2023
Results posted:	29-08-2024
Actual enrolment:	10

First publication
29-08-2024