Pharmacokinetics in Plasma and Saliva of a Single Dose Immediate- or Extended-Release Methylphenidate in Healthy Volunteers.

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To establish the pharmacokinetic profiles of saliva and plasma concentration of 10 mg MPH-IR and 18 mg MPH-OROS in healthy volunteers; to investigate whether there is a correlation between saliva- and plasma levels of MPH-IR and MPH-OROS, and if...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cognitive and attention disorders and disturbances
Study type	Interventional

Summary

ID

NL-OMON34088

Source
ToetsingOnline

Brief title
MPH PK in healthy volunteers.

Condition

- Cognitive and attention disorders and disturbances

Synonym
ADHD, attention-deficit/hyperactivity disorder (PK study)

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research

Source(s) of monetary or material Support: Interne studie CHDR.

Intervention

Keyword: Healthy volunteers, Methylphenidate, Pharmacokinetics, Plasma/saliva ratio

Outcome measures

Primary outcome

Saliva methylphenidate concentrations (and effect of saliva pH); plasma methylphenidate concentrations; relationship between measured saliva and plasma concentrations

Secondary outcome

Relationship between hCE1 (and other nuclear enzymes) polymorphism(s) and methylphenidate clearance.

Study description

Background summary

Despite frequent use of methylphenidate in children with attention deficit/hyperactivity disorder (ADHD), very little is known about its metabolism or the relationship between the time-course of effects related to blood levels. Recently, a study was performed in children with ADHD in which acute effects of one dose immediate-release (IR) methylphenidate (MPH) were measured non-invasively using the Neurocart. As blood sampling is undesirable in children in the setting of a non-therapeutic study, saliva samples were collected to measure MPH concentration. By combining these data with pharmacokinetic data in blood, a PK model can be build that provides us with estimated plasma drug levels in children needed for population PK/PD analysis. However, only limited data have been published on the PK of MPH in serum and/or saliva, and if published, data were pooled. Therefore, a study in healthy volunteers is needed in which both plasma and saliva samples will be obtained prior and post administration of medication.
The aim of the proposed study is to elucidate pharmacokinetic plasma and saliva profiles of 10 mg MPH-IR, and to describe the relationship between plasma and saliva concentrations (for use in the analysis of data in the previous study).
In addition, the possible effect of saliva pH (and saliva flow) on MPH saliva

concentration will be investigated as previous studies on drugs in saliva have shown that other weak bases tend to concentrate in saliva. As another planned study involves investigation of medication levels and observed acute effects of MPH in an osmotic controlled-release oral delivery system (OROS) in ADHD children, these steps will also be performed for 18 mg MPH-OROS. In addition, blood samples will be collected for future study in more subjects on potential gene polymorphism affecting MPH PK. With exception of one recent small study by Nemoda and colleagues (2009), genetic analyses of drug metabolizing enzymes have not been carried out in relation to MPH. Human liver carboxylesterase 1A1 (hCE1A1) might be a good candidate for genetic analysis in our study, as it is responsible for the hydrolysis of both the D- and L-isomer of MPH, and for the resulting first-pass, stereoselective metabolism of the drug (Sun et al. 469-76). Expression and activity of hCE1 is age-related and CES enzymes are regulated by nuclear receptor enzymes. It is (yet) unknown which nuclear receptor enzymes are responsible for the regulation of hCE1.

Study objective

To establish the pharmacokinetic profiles of saliva and plasma concentration of 10 mg MPH-IR and 18 mg MPH-OROS in healthy volunteers; to investigate whether there is a correlation between saliva- and plasma levels of MPH-IR and MPH-OROS, and if present, to describe this relationship; to determine the effect of saliva pH on MPH saliva concentration; to explore the potential influence of a hCE1A1 (human carboxylesterase 1A1) polymorphism on the plasma concentration time profile of MPH. If indicated, polymorphisms of regulator enzymes, like nuclear receptor enzymes, will also be explored in the future.

Study design

Randomized open label cross-over study.

Intervention

10 mg MPH-IR or 18 mg MPH-OROS.

Study burden and risks

Negligible burden and minimal risk.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

18-35 years of age
BMI 18-30 kg/m2, body weight 50-90 kg
Healthy

Exclusion criteria

Pregancy or breast feeding
Alcohol or substance abuse
Smoking > 5 cig/day
Previous exposure to stimulant compounds past 6 months
Disallowed concomittant medication within one week from first study day

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):	14-05-2010
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Concerta
Generic name:	Methylphenidate hydrochloride
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Ritalin
Generic name:	Methylphenidate hydrochloride
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-04-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-05-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2010-020014-28-NL
CCMO	NL32377.058.10