Phase I pharmacokinetic interaction study of dextromethorphan with supplementation of grape seed extract

Published: 21-03-2012
Last updated: 01-05-2024

To determine the potential pharmacokinetic interaction between GSE and dextromethorphan in healthy volunteers.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON37784

Source
ToetsingOnline

Brief title
Interaction study of dextromethorphan and grape seed extract

Condition

- Other condition

Synonym
Not applicable.

Health condition

gezonde vrijwilligers

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: KWF Kankerbestrijding

Intervention

Keyword: dextromethorphan, grape seed extract, interaction, pharmacokinetics

Outcome measures

Primary outcome

Dextromethorphan (DM) to dextrorphan (DX) metabolic ratio (MR) in urine

collected up to 8 h after dextromethorphan administration.

MR = (0-8 h urinary output of DM) / (0-8 h urinary output of DX).

Secondary outcome

Incidence of dextromethorphan-related adverse events.

Study description

Background summary

Nowadays, the antiestrogenic agent tamoxifen is widely used for the treatment of breast cancer. Tamoxifen becomes pharmacologically active after metabolism to its most abundant active metabolite endoxifen. CYP2D6 is the major enzyme involved in this biotransformation of tamoxifen.
In vitro data revealed that the herbal supplement grape seed extract (GSE, Vitis vinifera) inhibited CYP2D6. CYP2D6 inhibition by GSE has also been demonstrated in our laboratory at Utrecht University (unpublished data). In our experiment GSE showed to be a potent inhibitor of CYP2D6, as its half maximal inhibitory concentration (IC50) was even lower than the IC50 of the potent CYP2D6 inhibitor and positive control quinidine. Thus theoretically, concomitant use of GSE and tamoxifen might lead to decreased endoxifen plasma levels, possibly leading to a decreased therapeutic effect of tamoxifen. Accordingly, the specific CYP2D6 inhibitor paroxetine did lower endoxifen plasma levels in breast cancer patients taking tamoxifen.
According to the FDA Guideline *Drug Interaction Studies*, the interaction potential of a compound (in this case GSE) should first be investigated using specific CYP substrates. For CYP2D6, one of the recommended substrates is

dextromethorphan. Interestingly, dextromethorphan has shown to be an adequate predictor of endoxifen exposure in breast cancer patients taking tamoxifen (27). Therefore, and because no clinical interaction study with GSE and dextromethorphan has been executed yet, our aim is to perform the first clinical study which assesses the effect of GSE on dextromethorphan pharmacokinetics. Results of this study would provide valuable data regarding concomitant use of GSE and tamoxifen.

Study objective

To determine the potential pharmacokinetic interaction between GSE and dextromethorphan in healthy volunteers.

Study design

Included subjects will be randomized to cohort A (dextromethorphan alone, followed by dextromethorphan + grapeseed extract) or cohort B (dextromethorphan + grapeseed extract, followed by dextromethorphan alone).

Intervention

- Administration of 15 mL 2 mg/mL dextromethorfan cough syrup on day 1 and 10.
- Ingestion of 3 times daily 1 capsule of grapeseed extract during 2 days, followed by 1 ingestion in the morning of the third consecutive day.

Study burden and risks

Burden:
- Administration of 15 mL 2 mg/mL dextromethorfan cough syrup on day 1 and 10.
- Ingestion of 3 times daily 1 capsule of grapeseed extract during 2 days, followed by 1 ingestion in the morning of the third consecutive day.
- Keeping a diary for registration of times of grapeseed extract intake.
- Visit the research center three times: screening visit (1x), administration of dextromethorphan and collection of urine (2x).
- Venapunction for CYP2D6 genotyping.

Risks:
Dextromethorphan:
Incidentally, dextromethorphan can cause the following side effects: constipation, nausea, vomiting, drowsiness and dizziness. Rarely, confusion, excitement and allergic skin reactions can occur.

Grapeseed extract:
No adverse effects of grapeseed extract have been reported.

Venapunction:

Venapunction may cause discomfort, hemorrhage or bruising on the injection site. Incidentally, infection of a vein can occur or the subject can lose consciousness.

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

1. Healthy volunteer;
2. Age 18 years or older;
3. Able and willing to give written informed consent;
4. Able and willing to undergo blood sampling for CYP2D6 genotyping;
5. Able and willing to swallow and retain oral medication;
6. Able and willing to collect urine for pharmacokinetic analysis;
7. Willing to comply to the protocol and to follow dietary restrictions.

Exclusion criteria

1. Concomitant medication known to be moderate or strong inhibitors of CYP2D6 for at least two weeks prior to study start, including bupropion, cinacalcet, fluoxetine, paroxetine, quinidine, duloxetine, sertraline, terbinafine, amiodarone and cimetidine.
2. Concomitant medication known to be moderate or strong inducers of inhibitors of CYP3A for at least two weeks prior to study start, including indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, saquinavir, telithromycine, aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil, diltiazem, rifampicin, St. John*s wort and carbamazepine.
3. Any treatment with investigational drugs within two weeks prior to receiving the first dose of investigational treatment;
4. Use of alcohol (max. 2 units per day allowed), grapefruit or grapefruit juice for at least two weeks prior to study start until handing in collected urine on day 10.
5. Contra-indications for dextromethorphan use (e.g. treatment with MAO inhibitors, severely impaired liver function).

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):	30-05-2012
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bisoltussin

Generic name:	dextromethorphan
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-03-2012
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	05-04-2012
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)

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	EUCTR2012-001274-28-NL
CCMO	NL40062.048.12