# The relative bio-availability of oral and oromucosal melatonin in different formulations in healthy human volunteers - a three-phased cross-over study.

Published: 23-08-2011
Last updated: 28-04-2024

This study, a three-phased cross-over study, aims to define a proper formulation for oral and oromucosal melatonin by investigating the Tmax and relative bioavailability derived from melatonin levels in salivary samples of healthy volunteers after...

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

## Summary

### ID

NL-OMON37529

**Source**
ToetsingOnline

**Brief title**
MELAFORM

### Condition

- Other condition

**Synonym**
sleep onset Insomnia, sleeping disorder

**Health condition**

Slaapstoornissen

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Universiteit Utrecht
**Source(s) of monetary or material Support:** Hoofdonderzoeker fininancieert het onderzoek zelf. De tabletten van Tiofarm worden gratis geleverd. Met apotheek UMCU heeft de hoofdonderzoek een contract afgesloten wat betreft de kosten voor de capsules en het etiketteren/uitvullen door apotheek umcu.

## Intervention

**Keyword:** Bioavailability, Insomnia, Melatonin, Saliva

## Outcome measures

### Primary outcome

The Tmax and relative bioavailability of oral and oromucasol melatonin derived

from melatonin levels in salivary samples of healthy volunteers.

### Secondary outcome

not applicable.

# Study description

### Background summary

The circadian rhythm, the sleep-wake cycle, is mainly regulated by melatonin. The synthesis of melatonin is stimulated by the absence of light, leading to peak serum levels before bedtime. In humans, this endogenous "signaling" neurohormone induces sleep.
Exogenous melatonin can be beneficial in different sleep disturbances including delayed sleep phase insomnia (Dahlitz et al. 1991, Regestein et al. 1995), melatonin- deficiency-related insomnia (especially in elderly) (Garfinkel 1995, Etzioni et al. 1995) and shift work sleep disorder (Folkard et al. 1993, Skene et al. 1996).
A randomized controlled trial of van Geijlswijk et al. (van Geijlswijk 2010) showed that no relationship could be demonstrated between melatonin dose (0.05-0.15 mg/kg) and shift of sleep onset time (SOT), shortening of sleep onset latency (SOL) and shift of dim light melatonin (DLMO). On the other hand,

the timing of melatonin administration did have a clinically and statistically significant effect on all three parameters. Timing of melatonin administration in relation to baseline DLMO determines the phase advance, as can be measured by the shift of DLMO and SOT to an earlier time in the evening, resulting also in a shorter SOL. Melatonin must be administered in a closely defined time-slot before endogenous DLMO and before bedtime. The phase advance occurs when melatonin is administered 1-2 hours before DLMO and bedtime (van Geijlswijk et al. 2010). This trial demonstrated that low dosage of melatonin (0.05mg/kg) is effective in children when given at least 1-2 hours before the individual DLMO and the desired bedtime. This means that the release of melatonin from any pharmaceutical formulation should occur fast enough in order to achieve predictive high levels within the desired time-slot before the occurrence of (baseline) DLMO to induce a phase advance. These high maximum serum levels shortly after administration (Tmax) means the release rate of melatonin from the formulation needs to be as fast as possible and the bioavailability needs to be as high as possible.
Melatonin is known for its low and variable bioavailability in humans due to a high first pass effect and variable pharmacokinetics and short half-life. In order to prevent exposure of patients with unnecessary high dosages of melatonin and in order to achieve a short Tmax and high bio-availability of melatonin, a proper formulation needs to be defined. Thereby, the bioavailability must be made less variable in order to understand the biologic effects of melatonin (Di 1997).

## Study objective

This study, a three-phased cross-over study, aims to define a proper formulation for oral and oromucosal melatonin by investigating the Tmax and relative bioavailability derived from melatonin levels in salivary samples of healthy volunteers after administration of melatonin in different formulations: 2,5mg melatonin immediate release capsule (produced by Apotheek UMCU), 1mg melatonin immediate release tablet (produced by Tiofarma) and the low-dose (0,1mg) Sleepzz melatonin original tablet (geproduceerd door Vemedia Manufacturing BV). The defined formulation for melatonin must work properly in the treatment of sleep onset insomnia.

## Study design

Three-phase cross-over study.

## Intervention

The intervention will consist of three intervention days with intervals of 6 days. During each intervention day the participant will administer one of the formulations, respectively a 2,5mg melatonin immediate release capsule, a 1mg melatonin immediate release tablet and a 0,1mg melatonin sublingual tablet.

This means that each participant is his or her own control. The intervention days of a group will take place in following weeks to minimize possible season effects on the endogenous levels of melatonin.
The intervention starts between 10:00 and 11:00 am when the participant flushes his mouth with water, waits 15 minutes and starts to chew on a cotton plug during 1 minute. Directly after that the participant will administer one of the IMP*s according to the instructions. The tablet and capsule will be swallowed. The sublingual tablet will be administered sublingual. 10 minutes after administration the subjects will drink one glass of water and subsequently try to swallow as much liquid (including saliva), in order to prevent contamination of the saliva sample with the remaining exogenous melatonin. At 15 minutes, 30 min, 1 hour, 1.5 hour, 2 hours and 3 hours after oral administration the participant will chew on new cotton plugs during 1 minute. After administration of the sublingual tablet saliva samples will be collected at 25 minutes, 40 minutes, 60 minutes, 1.5 hour, 2 hours and 3 hours after sublingual administration. 15 minutes before each sampling the subject will flush his mouth with water. The cotton plugs with salivary will be preserved in a test-tube in the freezer and will be analyzed by Ziekenhuis Gelderse Vallei. Each participant will fill in a checklist during each intervention day.

**Study burden and risks**

As mentioned before, melatonin is well tolerated and is not reported to have a hangover effect. Its rarely occurring side effects include fatigue, dizziness, nausea, mild drowsiness, hypothermia and headache (Wagner 1998, Waldhauser 1990, Dahlitz 1991, Garfinkel 1995, Dollins 1994). Besides that, the participants will be asked to perform simple actions during 3 intervention days for only 3 hours.
The low dose (0,1mg melatonin) sublingual tablet is available without prescription in drugstores in the Netherlands. The tablet will also contain low dosage of melatonin, respectively 1mg and the capsule will contain a regular dose
of melatonin (2,5mg). These dosages are safe for adults and children. A few reports have been published on the consequences of long-term treatment with melatonin in humans. (Severe) adverse events were not described in these reports. (Van Geijlswijk 2011, Jan et al. 1996, Jan et al. 1994, Gilberg et al. 1997, Smits et al. 2001, Arendt 2000).

# 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

healthy volunteers (male) aged 18 to 35 years old without insomnia.

## Exclusion criteria

Exclusion criteria
• Lactose intolerance.
• Hepatic disease
• Kidney disease
• Auto-immune disease
• Depression
• Neurological disorders
• Oromucosal diseases.
Volunteers will not be enrolled if they are receiving medication during the study period, and within 4 weeks before the first intervention day, that are known inducers or inhibitors of melatonin metabolism or have farmacodynamic interactions with melatonin. ;Other exclusion criteria:
• Use of stimulants, neuroleptics, benzodiazepines, antidepressants, hypnotics, beta-blokkers and clonidin within 4 weeks before the first intervention day and during the study.

• Inhibitors of melatonin metabolism:
o Fluvoxamin (CYP1A2, 2C19, 2C9 inhibitor),
o 5- or 8 methoxypsoralen,
o Cimetidin (CYP1A2 inhibitor),
o Quinolones (1A2 inhibitor).
• Inducers of melatonin metabolism:
o Carbamazepin (substrate and inductor of CYP1A2)
o Rifampicin (CYP2C9 inducer).
o Omeprazol.
• Oral anticoagulants

# Study design

## Design

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| 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): | 25-02-2012 |
| Enrollment: | 10 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Melatonin 1mg tablet |
| Generic name: | Melatonin |
| Product type: | Medicine |
| Brand name: | Melatonin 2,5mg capsule |
| Generic name: | Melatonin |

# Ethics review

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| Approved WMO Date: | 23-08-2011 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 29-02-2012 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |

# 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 | EUCTR2011-003068-61-NL |
| CCMO | NL37716.041.11 |