A double blind, placebo controlled, double dummy, randomized, crossover trial to investigate the pharmacokinetics, pharmacodynamics and tolerability of a novel intranasal midazolam formulation in healthy adult subjects

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• To determine the onset of action of IN MDZ as compared to IV MDZ.• To determine extend and duration of the sedative effects of 2.5 mg and 5 mg IN MDZ. • To estimate the absolute and relative bioavailability and dose proportionality of single doses...

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

Summary

ID

NL-OMON34288

Source
ToetsingOnline

Brief title
Intranasal Midazolam

Condition

- Other condition
- Seizures (incl subtypes)

Synonym
epilepsy, procedural sedation

Health condition

Introduction of conscious sedation

Research involving
Human

Sponsors and support

Primary sponsor: Medir B.V.
Source(s) of monetary or material Support: Medir B.V.

Intervention

Keyword: intra-nasal, midazolam, saccadic eye movement

Outcome measures

Primary outcome

Pharmacodynamics:

• Peak Saccadic Velocity

• Visual Analogue Scale (Bond and Lader) for sedation

• Observer*s Assessment of Alertness/Sedation Scale

• Simple Reaction Time Task

Pharmacokinetics:

• AUC 0-t: The area under the plasma concentration time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.

• AUC0-*: The area under the plasma concentration time curve from time 0 to infinity.

• AUCextrap: Percent of the AUC located from the last quantifiable plasma concentration to infinity.

• CL: Total systemic clearance.

• V: Volume of distribution.

• F: Bioavailability.

• Cmax: Maximum measured plasma concentration over the time span specified.

• Tmax: Time of the maximum measured plasma concentration.

• t*: The apparent first-order terminal elimination half-life.

• kel: apparent first-order terminal elimination rate constant.

Safety and tolerability:

• Adverse events, vital signs, ECG, blood hematology and chemistry, pulse

oxymetry and ENT-examination.

Secondary outcome

N.A.

Study description

Background summary

Benzodiazepines elicit their pharmacological effects through non-selective modulation of GABAA-receptors. Midazolam (MDZ) is a short-acting benzodiazepine. MDZ solution for parenteral use has been administered nasally in studies for epilepsy and conscious sedation in both patients and healthy volunteers. These studies showed that parenteral solution is less suitable for nasal administration because of a low pH and too low concentrations, which necessitates high volumes to be administered leading to nasal run-off. To avoid swallowing and gastrointestinal absorption of excess fluid reaching the oropharynx, the maximal volume of nasal application is ideally restricted to approximately 100 µL, requiring the dose of MDZ to be solubilized within this volume. Therefore, highly concentrated solutions with a high bioavailability are essential to achieve clinically relevant serum concentrations. Availability of nasal MDZ formulations would offer clinical benefits in conscious sedation and in lay treatment of patients with epileptic seizures, saving important time

until IV access can be established. There appears to be an unmet need for an adequate MDZ formulation for nasal delivery.

Study objective

• To determine the onset of action of IN MDZ as compared to IV MDZ.
• To determine extend and duration of the sedative effects of 2.5 mg and 5 mg IN MDZ.
• To estimate the absolute and relative bioavailability and dose proportionality of single doses of IN MDZ 2.5 and 5 mg.
• To determine the inter-subject variability of IN MDZ pharmacokinetics.
• To evaluate the safety and tolerability of IN MDZ.
• Optional: to determine possible associations between genetic variation and the observed pharmacokinetic characteristics.

Study design

This study will be a four way cross over, randomized, double blind, double dummy study in 16 healthy subjects. For each study subject, the whole study-period, screening and follow-up visit included, will last at least five weeks and maximally ten weeks.

A randomized, double blind, double dummy study is selected to avoid bias and to reduce symptoms arising from the subjects* knowledge of treatment. Placebo administration is selected to obtain reference data and to avoid bias. Male and female healthy subjects are chosen to enhance the generalization of the study results. The four-way crossover plan is designed to balance the carry-over effects of different medication orders and meet the requirement for power with a relatively small group of subjects.

The administration of a single dose with at least 6 days apart from the next treatment will minimize the carry-over effects from previous treatments. 6 days is longer than expected to be needed for MDZ to be virtually absent in plasma, based on the known T1/2 el.

Intervention

Midazolam nasal spray, injection and placebo.

Study burden and risks

During the screening clinical significant abnormalities might be discovered, while during the study after the administration of midazolam, respiratory depression may occurs.

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. Males and females aged 18-55 years (both inclusive).
2. Females with reproductive potential should agree to remain abstinent or use (and have her partner use) acceptable methods of birth control throughout the study.
3. Voluntary provision of written informed consent prior to any study procedure, indicative of understanding the purpose of the study and willing to participate in the study and comply with the study procedures and restrictions.

Exclusion criteria

1. Subject is unhealthy according to medical history, physical examination, ECG, blood pressure and heart rate, and laboratory profile of blood and urine. A volunteer with a clinical

abnormality may be included only if the investigator or his designee considers that the abnormality will not introduce additional risk factor for the subject's health, or interfere with the study objectives.
2. Presence or history of clinical significant psychiatric diseases, as judged by the investigator.
3. Any clinically relevant acute or chronic diseases which according to the investigator could interfere with the subject*s safety during the trial, or expose them to undue risk, or which could interfere with the study objectives.
4. Presence or history of clinical significant diseases of the renal, hepatic, gastrointestinal, cardiovascular, musculoskeletal system or presence of history of clinical significant immunological, endocrine, metabolic diseases, or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs, as judged by the investigator.
5. Presence or history of clinically significant allergy or known hypersensitivity to any component of the investigational product.
6. Clinically significant upper respiratory infection, common cold or flu -like symptoms and/or rhinitis, as judged by the investigator.
7. Presence or history of clinically significant nasal abnormalities (e.g. polyps or other physical abnormalities), as judged by the investigator.
8. Recent (< 4 weeks) nose bleeds.
9. History of clinically significant nasal surgery that could affect the nasal absorption of midazolam or would result in a reduced tolerability of midazolam, as judged by the investigator.
10. Has a Body Mass Index (BMI) < 18 or > 33 kg/m2.
11. Has positive serology for HIV, hepatitis B (surface antigen), and/or hepatitis C antibodies.
12. Has planned medical treatments (including dental care) between screening and follow-up visit.
13. Use of prescribed medication or over-the-counter (OTC) medication within two weeks prior to dosing, except for paracetamol (up to 1.5 g per day).
14. Enrolment in any investigational study or intake of an investigational drug within 3 months prior to the start of the study or more than 4 times a year.
15. Current regular user of any illicit drugs or history of drug or alcohol abuse and history of any drug use taken intransally (e.g. cocaine). Subjects who have a positive drug screen, or have a positive alcohol breath test at screening will be excluded.
16. Donation of blood/plasma outside limits of Sanquin Blood Supply Foundation guidelines.
17. Unlikely to co-operate in the study, and/or has poor compliance anticipated by the investigator. Or not consistently reachable in case of emergency.
18. Daily consumption of xanthine-containing products more than 8 units. Unwilling or unable to refrain from consumption of xanthine-containing foods or drinks from 1 days prior to admission and during the stay in the research unit. One caffeine unit is contained in the following items: one cup of coffee, two cans of cola, one glass of tea, * cup of energy drink (e.g. Red Bull) or three chocolate bars.
19. Unwilling or unable to refrain from intensive physical exercise from screening until the follow-up visit.
20. Unwilling or unable to refrain from products containing alcohol from 1 days before admission and during the stay in the research unit.
21. Unwilling or unable to refrain from products containing grapefruit and star fruit, from 2 days before admission and during the stay in the research unit.

22. Unwilling or unable to refrain from smoking during admission and the stay in the research unit.
23. Males who are unwilling to abstain from having unprotected sexual intercourse or donating sperm during the study and for 3 months after study.
24. Male*s partner is planning pregnancy within 3 month of last dosing.
25. Is unsuitable, in the opinion of the investigator, to participate in the study for any other reason.
26. Unwilling to refrain from consuming St. Johns Wort, an herbal remedy, from screening until their last assessment.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-01-2011
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Midazolam
Generic name:	Midazolam
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-12-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-01-2011
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	EUCTR2010-023425-38-NL
CCMO	NL34435.058.10