Randomized, double-blind, placebo-controlled, three way crossover, double dummy, single centre study evaluating the effect of haloperidol 2 mg and lorazepam 1 mg on posturography and underlying systems involved in standing balance in 12 healthy elderly subjects.

Published: 22-05-2014
Last updated: 21-04-2024

• To assess the effect of lorazepam compared to placebo on stability (Body Sway) in relation to stabilizing subsystems (BalRoom) in healthy elderly.• To assess the effect of haloperidol compared to placebo on stability (Body Sway) in relation to...

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

Summary

ID

NL-OMON40805

Source
ToetsingOnline

Brief title
BalRoom study

Condition

- Other condition

Synonym
Balance disorders

Health condition

evenwichtsproblemen

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Leiden University Medical Centre

Intervention

Keyword: Balance control, Elderly, Medication

Outcome measures

Primary outcome

1. Pharmacodynamics

BalRoom assessment:

• Sensory weights (weighting factors of proprioceptive, visual and vestibular system).

• Active dynamics of ankle joint (time delay (s), active stiffness (Nm/rad) and active damping (Nm/rad/s)).

• Active dynamics of hip joint (time delay (s), active stiffness (Nm/rad) and active damping (Nm/rad/s)).

• Force feedback (time constant (s) and stiffness (Nm/rad))

• Passive dynamics of ankle joint (passive stiffness (Nm/rad) and passive damping (Nm/rad/s)).

• Passive dynamics of hip joint (passive stiffness (Nm/rad) and passive damping (Nm/rad/s)).

Neurocart assessment:

• Saccadic Eye Movements (saccadic reaction time, saccadic peak velocity (deg/sec), and saccadic inaccuracy).

• Body Sway (antero-posterior sway (mm/2min)).

• Smooth Pursuit (percentage of time the eyes of the subjects are in smooth pursuit of the target (%)).

• Bond and Lader VAS (alertness, calmness, mood subscales (mm)).

• Bowdle VAS (internal & external perception, feeling high)(mm))

• Adaptive Tracking (%).

• Pharmaco-EEG ((α, β, δ, γ and * *power)

Short physical performance battery:

• Ability to maintain standing balance (yes/no)

• 4-meter walking speed (m/s)

• Sit-to-stand transfer (s)

Other:

• Serum prolactin concentrations

• Handgrip strength (kg)

2. Pharmacokinetics

• Cmax, Tmax, AUClast, AUC24, AUCinf, CL/F, Vz/F, t1/2.

3. Tolerability / safety

Adverse events, vital signs measurements, 12-lead ECGs, physical examination

findings and clinical safety laboratory measurement.

Secondary outcome

Not applicable

Study description

Background summary

Impaired balance is a common problem among the elderly, has a significant impact on the health and quality of life, and is one of the main causes of falls. Impaired balance can have several causes as different underlying systems interact with each other to maintain standing balance. Current clinical balance tests do not give information about the underlying cause of impaired balance, due to the interaction between the underlying systems involved in standing balance and used compensation strategies.

Using the Balance test Room (BalRoom) it is possible to make a distinction between the underlying systems involved in standing balance using a method based on a control engineering approach. By applying specific and unpredictable disturbances to the underlying systems during stance and determining the reaction of the body on those disturbances, a distinction can be made between the underlying systems involved in standing balance and therefore can help to detect the underlying cause of impaired balance. In the future, the BalRoom can be applied as a diagnostic tool to detect the underlying cause of impaired balance in elderly. A better diagnosis of impaired standing balance gives the possibility to apply targeted interventions, which will improve standing balance and finally prevents falling.

Previous research showed that medication, such as antipsychotics and benzodiazepines, results in impaired standing balance and increases the risk of falls in elderly (antipsychotics odds ratio (OR), 1.59 (95% CI: 1.37; 1.83) and benzodiazepines OR, 1.57 (95% CI: 1.43; 1.72)). Those drugs affect the Dopamine 1 (D1) and D2-receptors and gamma-aminobutyric acid (GABA) A receptors, respectively, which are involved in the basal ganglia-thalamocortical systems and therefore affect fine tuning of motor commands. Antipsychotics and benzodiazepines are both frequently prescribed to elderly to treat psychoses. Haloperidol is an atypical antipsychotic, blocks D1 and D2 receptors and therefore has extra pyramidal side effects resulting in more stiffness and less ability to modulate the size of postural responses and less integration of sensory information. Haloperidol is previously used in studies investigating

standing balance in elderly with a dosage of 2 or 3 mg. Lorazepam is a benzodiazepine, a full agonist of the GABA A receptors and therefore results in decrease levels of muscle tone. Lorazepam is frequently used as active comparator in studies investigating new partial subtype selective GABA-A receptor agonists and is previously used in studies investigating standing balance in elderly with a dosage of 1 mg. The BalRoom could be used to detect those underlying changes in standing balance that result from the use of specific medication.

Study objective

• To assess the effect of lorazepam compared to placebo on stability (Body Sway) in relation to stabilizing subsystems (BalRoom) in healthy elderly.
• To assess the effect of haloperidol compared to placebo on stability (Body Sway) in relation to stabilizing subsystems (BalRoom) in healthy elderly.
• To assess the effect of lorazepam compared to haloperidol on stability (Body Sway) in relation to stabilizing subsystems (BalRoom) in healthy elderly.
• To assess the relationship between BalRoom and NeuroCart subtests in healthy elderly.
• To assess the sensitivity of BalRoom and NeuroCart parameters for drug effects in healthy elderly.

Study design

This is a randomized, double-blind, placebo-controlled, three way crossover, double dummy, single centre study evaluating the effect of haloperidol 2 mg and lorazepam 1 mg on posturography and underlying systems involved in standing balance in 12 healthy elderly subjects.

Intervention

- 1 mg lorazepam
- 2 mg haloperidol
- placebo

Study burden and risks

No exceptional severe adverse drug reactions are expected and burden/convenience for the subjects are considered relatively mild.

Side-effects haloperidol:
- expected: sleepiness, lightheadedness (upon standing), dizziness: these effects usually disappear within a couple of hours.
- rare: dystonia: for this rare side-effect there will be biperideen (Akineton®). The effect of biperideen occurs rapidly, usually within 20 minutes.

Side-effects lorazepam:
- expected: daytime drowsiness, dizziness, muscle weakness, and ataxia.

During the experiments with the BalRoom the subject has to perform an active task. To avoid fatigue the subject can rest during the experiments. The risk of the measurements is minimally. No invasive procedures are included. Safety is performed by software and hardware of the device. The subject wears a safety harness during the measurement to avoid falling.

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 male and/or female subjects of non-childbearing potential over the age of 70 years (inclusive; healthy is defined as no clinically relevant abnormalities identified by a detailed

medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG, and clinical laboratory tests).;2. Body Mass Index (BMI) of 17.5 to 35 kg/m2; and a total body weight =>50 kg.;3. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.;4. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. ;5. Mini-Mental State Examination (MMSE) score > 26 points at screening.

Exclusion criteria

1. Evidence or history of clinically significant haematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing).;2. Subjects presenting with orthostatic hypotension, in which orthostatic hypotension is defined as a decrease of 20 mmHg for systolic blood pressure or 10 mmHg for diastolic blood pressure 2 minutes after standing from a supine position.;3. Any condition possibly affecting drug absorption (eg, gastrectomy).;4. A positive urine drug screen.;5. History of regular alcohol consumption exceeding 14 drinks/week for females or 21 drinks/week for males (1 drink = 150 mL of wine or 360 mL of beer or 45 mL of hard liquor) within 6 months of Screening.;6. Treatment with an investigational drug within 3 months prior to screening or having participated in more than 4 investigational drug studies within 1 year prior to screening.;7. Use of (non-)prescription medications that are believed to affect subject safety or the overall results of the study following judgment by the investigator.;8. Loss or donation of blood over 500 mL within three months (males) or four months (females) prior to screening;9. Unwilling or unable to comply with the Lifestyle Guidelines described in this protocol.;10. Physically unable to perform BalRoom tests, e.g. walking and standing tests.;11. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.;12. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or subjects directly involved in the conduct of the study.;13. Clinical significant abnormalities on ECG and or QTcF > 500ms.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-08-2014
Enrollment:	12
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	22-05-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	02-07-2014
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	EUCTR2014-001545-25-NL
CCMO	NL48985.058.14