A Randomized, Double-Blind, Four Treatment, Four Period, Crossover Study, with Placebo, Tizanidine Immediate-Release and Diphenhydramine to Study Effect of Tizanidine Extended-Release on Simulated Driving Performance, Cognitive, and Psychomotor Functioning

Published: 15-12-2015
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To investigate effect of tizanidine ER 12 mg on simulated driving performance, cognitive and psychomotor functions compared with placebo, tizanidine IR 8 mg (two 4 mg doses given 6.5 hours apart) and active-control in healthy subjects

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

Summary

ID

NL-OMON42658

Source
ToetsingOnline

Brief title
Tizanidine

Condition

- Other condition

Synonym
the possible sedative effects of the medication

Health condition

gezonde proefpersonen; slaperigheid bij rijden na inname medicatie

Research involving
Human

Sponsors and support

Primary sponsor: Sun Pharma Advanced Research Company (SPARC) limited
Source(s) of monetary or material Support: Sun pharma Advanced Researcg Company (SPARC) Limited

Intervention

Keyword: alertness, driving performance, extended release tablet, Tizanidine

Outcome measures

Primary outcome

Driving simulator measurement at baseline and at four scheduled time points

post dose of standard deviation lateral position (SDLP) in centimeters

Secondary outcome

* Psychomotor and cognitive function- at baseline and at four scheduled time

points post dose. Reaction time to:

o Visual stimulus on psychomotor vigilance task (PVT) in milliseconds

o Visual stimulus on vigilance and tracking (VigTrack) task in milliseconds

o Light emitting diode (LED) in milliseconds

* Driving simulator measurement at baseline and at four scheduled time points

post dose of:

o Lateral position in centimeters

o Standard deviation of speed (SDSP) in miles per hour

o Distance headway (DHW) in kilometers

o Time-to-collision (TTC) in seconds

o Time headway (THW) in seconds

* Subjective assessment of sleepiness:

A subjective rating with scores 1 to 9 for alertness using Karolinska

Sleepiness Scale (KSS)

Study description

Background summary

Sun Pharma Advanced Research Company (SPARC) Limited has developed a new formulation of tizanidine hydrochloride. It is an extended release (ER) tablet (Tizanidine ER), 12 mg strength, in development for the treatment of acute musculoskeletal pain. The new formulation is developed with the purpose to provide patients with the benefit of less frequent dosing and, more importantly, to minimize adverse effects of central nervous system as a result of lower peak plasma concentrations of drug.

The hypothesis of lower effect on cognition and psychomotor function with tizanidine ER will be evaluated in the proposed clinical study. Tizanidine ER tablets will be evaluated and compared with Zanaflex® (tizanidine IR tablets), diphenhydramine, and placebo on simulated driving and cognitive tests. Driving a vehicle is a complex task that requires sufficient cognitive, visual, and motor skills. Simulated driving is a valid tool for the assessment of cognitive and psychomotor performance in a setting that is almost similar to actual driving.18,19 The clinical facility (TNO), in the Netherlands, conducts a wide variety of driving simulator studies ranging from a focus on fundamental perceptual questions to cognitive research questions.18,19,20
SPARC plans to conduct the proposed study in the TNO*s high-fidelity moving-base driving simulator settings. This study will be conducted in well-controlled testing conditions. TNO*s simulator has previously shown sensitivity to drug-induced impairment.21-26

Study objective

To investigate effect of tizanidine ER 12 mg on simulated driving performance, cognitive and psychomotor functions compared with placebo, tizanidine IR 8 mg (two 4 mg doses given 6.5 hours apart) and active-control in healthy subjects

Study design

This is a randomized, double blind, active and placebo-controlled, four treatment, four period, crossover study

Intervention

In a crossover design all subjects will receive :
- Tizanidine extended release (ER) tablet, (single 12 mg dose) followed by placebo dose after 6.5 hours
- Placebo tablet (two doses separated by 6.5 hours)
- Diphenhydramine 50 mg tablet (single dose) followed by placebo after 6.5 hours
- Tizanidine immediate release tablet (IR), 8 mg (two 4 mg doses separated by 6.5 hours)

all test sessions are one week apart

Study burden and risks

Volunteers have to visit the institute for screening, training on the tasks, and have to undergo the assessments on 4 separate test trial days. Each trail day lasts 11 hours. Before and after the test sessions there is a physical examination, clinical laboratory assessments, a 12-lead ECG, and urine samples at each visit. A measurement of systolic and diastolic blood pressure, to assess orthostatic hypotension, will be scheduled pre-dose, 1, 2.5, 4, and 7 hours post dose.

In clinical studies, most frequently reported adverse effects with tizanidine were dry mouth, somnolence/sedation, asthenia (weakness, fatigue and/or tiredness) and dizziness. In the controlled clinical studies, adverse events that caused discontinuation treatment were asthenia [(weakness, fatigue and/or tiredness) (3%)], somnolence (3%), dry mouth (3%), increased spasm or tone (2%), and dizziness (2%). The detailed description for safety profile of tizanidine is available on lablel information for Zanaflex®.

Several clinical studies studies were conducted in Indian population, to evaluate pharmacokinetics of tizanidine ER product. To date, 84 subjects were treated with tizanidine ER product. The medication was tolerated well and reported side effects were similar to those reported for Zanaflex® and no new adverse effects were reported.
Most frequently reported adverse event for diphenhydramine were somnolence, dizziness, sedation. The rare adverse effects reported were irritability, impaired performance (impaired driving performance, poor work performance, incoordination, reduced motor skills and impaired information processing), dryness of nose, tightness of chest, constipation, diarrhoea, dry mouth, hypotension, palpitations, tachycardia, headache and photosensitivity. The detailed description for safety profile of tizanidine is available on lablel

information for Sleepeaze or one a night nightcalm.

Due to the spatial limitations of the driving simulator, perceived discrepancies between the motion of the simulator and that of the virtual vehicle can occur and lead to simulator sickness. Symptoms of simulator sickness include discomfort, apathy, drowsiness, disorientation, fatigue, and vomiting. Occurrence of driving simulator sickness occurs in 5-10% of the population and is reduced by selecting non-urban scenarios with a limited amount of turning/braking events in the scenario.

It is anticipated that all reported adverse effects recover spontaneously after termination of the treatment. It is considered that the possible adverse effects of the study medication and/or simulator conditions are non-health threatening and acceptable. The new medication will allow for less frequent dosing and will lead to lower peak plasma concentrations thereby minimizing adverse effects on the central nervous system.

Contacts

Public
Sun Pharma Advanced Research Company (SPARC) limited

Mahakali Caves Rd Andheri (E); Mahal Industrial Estate 17 B
Mumbai 400 093
IN
Scientific
Sun Pharma Advanced Research Company (SPARC) limited

Mahakali Caves Rd Andheri (E); Mahal Industrial Estate 17 B
Mumbai 400 093
IN

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-The potential participant has given informed and written consent and is able to comply with all study assessments scheduled in the protocol
-Healthy males or females aged 21 to 45 years (both inclusive) with body mass index between 18 and 30 kg/m2 and having normal vision
-Possession of a valid Netherlands driver*s license * 3 years with a reported average annual mileage * 5,000 km during the last 3 years
-Any female surgically sterile (bilateral tubal ligation at least 6 months prior, bilateral oophorectomy, or hysterectomy performed) or any female of child bearing potential should be willing to practice an acceptable method of birth control following screening to completion of study of the study. The acceptable contraceptive methods are condoms, diaphragm, intrauterine device (IUD), same sex partner or partner with vasectomy, (note: hormonal contraception is not permitted as it affects tizanidine pharmacokinetics)
-Potential subjects considered healthy based on medical evaluation, electrocardiogram and laboratory values at screening, all lab values are within normal limits or any value out of normal limits considered by the Investigator to be of no clinical significance. lab tests:(Hematology: hemoglobin [Hb] and leukocytes; Biochemistry: C-reactive protein [CRP], creatinine, gamma-glutamyl transpeptidase [Gamma-GT], aspartate aminotransferase [ASAT], alanine aminotransferase [ALAT], bilirubin

Exclusion criteria

1. History of allergies or hypersensitivity or intolerance to tizanidine or diphenhydramine
2. History or presence of clinically significant or uncontrolled cardiovascular, neurological, psychiatric, hepatic, renal, gastrointestinal, hematological, musculoskeletal or sleep disorder
3. History of surgery within 4 weeks of screening
4. Clinical lab results suggestive of hepatic impairment (ALT or AST or bilirubin > 2 times of ULN) or renal impairment (creatinine > 2 mg/dL)
5. Clinically significant history of alcohol intake (> 21 drinks per week).
6. History of drug abuse with drugs used for recreational purpose within one year of the screening visit
7. Use of any drug known to induce or inhibit hepatic drug metabolism (specifically CPY1A2 inhibitors, fluoroquinolones, zileuton, antiarrythmics, anti-histamines, ticlopidine, anti-virals, oral contraceptives, anti-depressants and any drugs known to cause change in neurological function) within 14 days of screening to end of study
8. Signs or symptoms of narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy or bladder-neck obstruction
9. History of participation in an investigational drug study within the past 30 days
10. History of excessive caffeine consumption (> 5 cups/day) or smoking (*10 cigarettes per

day) during the last six months prior to screening
11. At admission for each period: evidence of pregnancy (urine pregnancy test positive on urine drug screen for women), or demonstrable blood-alcohol concentration (alcohol breath test)
12. Pregnant or lactating females

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-04-2016
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	Tizanidine extended release (ER) tablet 12 mg
Product type:	Medicine
Brand name:	Sleapeaze
Generic name:	Diphenhydramine 50 mg
Product type:	Medicine
Brand name:	Zanaflex
Generic name:	Tizanidine immediate release tablet (IR), 2x 4 mg
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-12-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-01-2016
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-06-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2015-003770-32-NL
CCMO	NL54219.028.15