A study to investigate the analgesic effects of buprenorphine and milnacipram in healthy volunteers.

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• To determine if the analgesic effects of co-administration of a single oral dose of milnacipran with a single intravenous dose of buprenorphine are higher than those of buprenorphine alone (potentiation) or higher than those of buprenorphine alone...

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

Summary

ID

NL-OMON37273

Source
ToetsingOnline

Brief title
Interaction pain study between buprenorphine and milnacipran.

Condition

- Other condition

Synonym
neuropathic pain, nociceptive pain

Health condition

pain (neuropathic and acute)

Research involving
Human

Sponsors and support

Primary sponsor: Dr. Reddy's Laboratories Ltd.
Source(s) of monetary or material Support: Industry.

Intervention

Keyword: buprenorphine, milnacipran, pain, synergy

Outcome measures

Primary outcome

Pharmacodynamics

• Pupil size (pupil:iris ratio) [opioid sensitive] (2 min)

Pain threshold and tolerance levels for each nociceptive test:

o Pressure pain (muscle) (kPa), [fibromyalgia model] (4 min)

o Electrical pain (skin) (mA) single stimulus [SNRI sensitive] (4 min)

o Cold pressor test (seconds) (6 min)

• Tolerance time (s)

• Intensity x time AUC (%*s)

o Diffuse Noxious Inhibitory Control (difference of electrical pain before and

after cold pressor task) (4 min)

Other CNS effects

o Saccadic eye movement [SNRI sensitive] (3 min)

o Body sway (postural stability) [opioid, SNRI sensitive] (3 min)

o Adaptive Tracking (Motor Co-ordination/Attention) [opioid, SNRI sensitive] (4

min)

Pharmacokinetics

• Buprenorphine and nor-buprenorphine PK (LLOQ 0.2 ng/mL)

• Milnacipran PK (1-1000 ng/mL, no separation of enantiomers)

Safety & Tolerability

Change from baseline:

• vital signs (supine blood pressure [BP] and HR, SpO2 (saturation)) and body weight;

• ECG variables;

• clinical laboratory tests including urinalysis.

• simple breath count/flow spirometry

Treatment-emergent

• ECG abnormalities 24 hours after study drug administration in each treatment period.

• AEs up to 96 hours after study drug administration in each treatment period.

• SAEs from (first) study drug administration up to EOS.

Secondary outcome

NA

Study description

Background summary

Buprenorphine is a full μ opioid agonist for analgesia. In human pain models, opioids play a complex role by contributing to both analgesia and anti-hyperalgesia. Pharmacokinetic parameters (mean (range)): T* = 36 (20-70) hours, *due in part to reabsorption of buprenorphine after intestinal

hydrolysis of the conjugated derivative, and in part to the highly lipophilic nature of the molecule*.

Milnacipran is a specific inhibitor of both noradrenaline (NA) and serotonin (5-HT) reuptake systems, used for the treatment of fibromyalgia. In this regard, it is similar to other SNRI compounds; however, its inhibitory action is more balanced between serotonin and noradrenalin than other SNRIs. Milnacipran is a racemate of two enantiomers: F2695 and F2696. F2695 had slightly higher potency than milnacipran, whereas F2696 was less potent or inactive. Pharmacokinetic parameters (mean ±SD) after 50 mg oral milnacipran HCl (N=12): Tmax=2 (0.7-6) hours, T*= 6.1 ± 1.4 hours, F=0.85±0.03.

Non-clinical studies suggest that the combination of buprenorphine and milnacipran shows a synergistic analgesic effect in the Bennett model. In the MIA osteoarthritis animal model there is a trend toward a synergistic analgesic effect. In animal studies, the antihyperalgesic effects (CCI model) of milnacipran are able to be blocked by naloxone, suggesting possible opioidergic mechanism of action. Potentiation of the analgesic effects of sub-therapeutic doses of buprenorphine by naltrexone have been shown previously. A PK interaction is not anticipated.

Study objective

• To determine if the analgesic effects of co-administration of a single oral dose of milnacipran with a single intravenous dose of buprenorphine are higher than those of buprenorphine alone (potentiation) or higher than those of buprenorphine alone plus milnacipran alone (synergy) in healthy subjects.

• To determine if the analgesic effects of co-administration of multiple-doses of milnacipran in combination with a single administration of buprenorphine are higher than those of buprenorphine alone (potentiation) or higher than those of buprenorphine alone plus multiple doses of milnacipran alone (synergy) in healthy subjects

• To investigate the safety and tolerability of co-administration of intravenous buprenorphine and oral milnacipran in healthy subjects.

• To examine the potential pharmacokinetic interactions between intravenous buprenorphine and oral milnacipran in healthy subjects.

Study design

Double blind milnacipran, double blind buprenorphine, 4-way, placebo-controlled cross over design
Subjects will receive either 0 mg (placebo), 25 mg or 50 mg BID milnacipran in combination with buprenorphine, or 50 mg BID milnacipran alone (double-blinded,

randomised, Williams square design,). At the start and end of the milnacipran dosing period, a buprenorphine (or placebo) infusion will be administered. There will be a washout period of at least 14 days between the last buprenorphine (or placebo) dose of a period and the first of the next period.

Milnacipran, 25 mg BID p.o. and 50 mg BID p.o. (10:00 and 22:00, ± 1hr) c.f 100 mg (but up to 200 mg) per day. Upper dose limited to avoid side-effects (incidence >= 5%: constipation, hot flush, hyperhidrosis, vomiting, palpitations, heart rate increased, dry mouth, and hypertension). Acute dosing pharmacology studies have used up to 300 mg BID in healthy subjects.

Buprenorphine
The following dosing regimens provide suitable PK and PD (electrical pain) during the 1.5-2.0 hours after dosing:
30 minute i.v. infusion: 0.5 µg/kg (sub-therapeutic) [35 µg/70 kg]
30 minute i.v. infusion: 1.0 µg/kg (minimum analgesic dose) [70 µg/70 kg]
30 minute i.v. infusion: 3.0 µg/kg (analgesic dose) [210 µg/70 kg])

Intervention

NA

Study burden and risks

NA

Contacts

Public
Dr. Reddy's Laboratories Ltd.

Dr. Reddy's Laboratories, Ltd. Door No 8-2-337, Road No 3, Banjara Hills, Hyderabad 500034 Andhra Pradesh
IN
Scientific
Dr. Reddy's Laboratories Ltd.

Dr. Reddy's Laboratories, Ltd. Door No 8-2-337, Road No 3, Banjara Hills, Hyderabad 500034 Andhra Pradesh
IN

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed informed consent prior to any study-mandated procedure.
2. Caucasian (white) males aged between 18 and 45 years (inclusive) at screening.
3. Body mass index (BMI) between 18 and 30 kg/m2 (exclusive) at screening.
4. No clinically significant findings on the physical examination at screening.
5. Ability to communicate well with the investigator in the local language and to understand and comply with the requirements of the study.
6. Systolic blood pressure (SBP) between 100 and 140 mmHg (inclusive).
7. Diastolic blood pressure (DBP) between 45 and 90 mmHg (inclusive).
8. Heart rate (HR) between 45 and 100 b.p.m. (inclusive).
9. Haematology and clinical chemistry results within normal range (to a clinically relevant extent at screening).
10. Negative results for urine drug tests at screening.
11. 12-lead electrocardiogram (ECG) normal or to have no clinically significant alterations.

Exclusion criteria

1. Known hypersensitivity to buprenorphine and/or milnacipran.
2. Previous treatment with any prescribed or OTC medications (including herbal medicines such as St John*s Wort), within 7 days prior to screening.
3. Treatment with another investigational drug within 3 months prior to screening.
4. History or clinical evidence of alcoholism or drug abuse.
5. Treatment with or consumption of inducers or inhibitors of CYP3A4 (e.g. grapefruit (juice), star fruit) or CYP2C8 within 7 days prior to screening.
6. Smoking within 3 months prior to screening and inability to refrain from smoking during the course of study. Excessive caffeine consumption, defined as >= 800 mg per day at screening.
7. History or clinical evidence of any disease, and/or existence of any surgical or medical

condition, which might interfere with the absorption, distribution, metabolism or excretion of the study drugs.
8. Loss of 250 mL or more of blood within 3 months prior to screening.
9. Positive results from the hepatitis serology at screening.
10. Positive results from the HIV serology at screening.
11. Any circumstances or conditions, which, in the opinion of the investigator, may affect full participation in the study or compliance with the protocol.
12. Legal incapacity or limited legal capacity at screening.;All clinical judgments will be done by the study physician and he or she will decide eligibility of the subjects based on individual evaluation for each case. Any vital signs or laboratory values which are out of the normal range for the age group should be excluded unless the study physician and/or the principal investigator deems not to be clinically significant.

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):	11-06-2012
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ixel
Generic name:	milnacipran
Product type:	Medicine
Brand name:	Temgesic

Generic name:	buprenorphine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	30-05-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-06-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2012-002302-43-NL
CCMO	NL40777.056.12