An exploratory Phase I randomized, single-site, double-blind, active-controlled, parallel-group, single-administration, dose-escalation trial to investigate the safety and tolerability of neosaxitoxin alone and in combination with bupivacaine (with and without epinephrine), in perineural administrations for brachial plexus blockade in healthy subjects.

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The purpose of this study is to investigate the safety and tolerability of different doses of neosaxitoxin when it is administered to healthy male volunteers alone and in combination with bupivacaine (with and without epinephrine) in perineural...

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

Summary

ID

NL-OMON46410

Source
ToetsingOnline

Brief title
Trial to investigate safety and tolerability of neosaxitoxin

Condition

- Other condition

Synonym
Brachial plexus blockade

Health condition

plexus-brachialisblokkade

Research involving
Human

Sponsors and support

Primary sponsor: Grünenthal GmbH
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Neosaxitoxin, Safety, Tolerability

Outcome measures

Primary outcome

Evaluate the systemic and local safety and tolerability of ascending doses of Neosaxitoxin (NeoSTX) alone and in combination with fixed doses of bupivacaine (BUPI) (with and without epinephrine (EPI)), following brachial plexus blockade in healthy male subjects.

Secondary outcome

Evaluate the pharmacodynamics of ascending doses of Neosaxitoxin, alone and in combination with fixed doses of bupivacaine (with and without epinephrine), following brachial plexus blockade.

Characterize the pharmacokinetics of Neosaxitoxin and bupivacaine after

brachial plexus blockade with Neosaxitoxin alone or different drug

combinations: Neosaxitoxin+epinephrine, Neosaxitoxin+bupivacaine, or

Neosaxitoxin+bupivacaine+epinephrine.

Study description

Background summary

Neosaxitoxin is a new compound that is in clinical development as local anesthetic for surgical anesthesia and postoperative analgesia. Such anesthesia are often performed in hospitals when people are being operated on. At that time anesthesia can be done in addition to narcosis. These anesthetics are also called 'regional anesthesia', 'nerve block' or simply 'blockade'. The nerves that run to the area that is being operated on are then numbed. This is done by an injection with a local anesthetic in the area of those nerves (perineural injection).

Neosaxitoxin is a member of a group of molecules known as sodium channel blockers. Sodium channels are membrane proteins that form ion channels, conducting sodium ions through a cell's plasma membrane. Neosaxitoxin produces reversible conduction blockade of the sodium channels and in this way stops the distribution of the nerve impulse. As a result no initiation or conduction of a pain signal can occur. This effect of blockade is similar to what local anesthetics are doing, e.g., at the dentist. Neosaxitoxin is produced by marine microorganisms such as dinoflagellates. Fresh water cyanobacteria can also produce neosaxitoxin.

Local anesthetics, such as lidocaine, bupivacaine, levobupivacaine, and ropivacaine, are currently the most commonly used local anesthetics. However, these local anesthetics do usually not provide reliable analgesia beyond 8 hours. Furthermore, in case of high blood concentrations these local anesthetics may cause significant toxic effects, mainly cardiovascular toxicity (cardiac arrhythmias and depression) and toxicity in the central nervous system (convulsions and coma). In very rare cases local anesthetics can also cause direct local cytotoxicity on neurons, cartilage, and muscle cells near sites of injection. Neosaxitoxin in combination with bupivacaine and/or epinephrine is being developed to provide local anesthesia with a prolonged duration.

Study objective

The purpose of this study is to investigate the safety and tolerability of different doses of neosaxitoxin when it is administered to healthy male

volunteers alone and in combination with bupivacaine (with and without epinephrine) in perineural administrations for brachial plexus blockade. In section 5, under the heading *Administration of study compound*, it is explained what this administration method entails.

It will also be investigated how quickly and to what extent neosaxitoxin and bupivacaine are absorbed and eliminated from the body (this is called pharmacokinetics). In addition, the effect of neosaxitoxin, bupivacaine and epinephrine on the body function will be investigated (this is called pharmacodynamics).

Study design

The actual study will consist of 1 period during which the volunteer will stay in the PRA research center in Groningen at the location of the Martini Hospital from Day -2 to Day 3. The stay of the volunteer can be prolonged with a maximum of 4 additional days (from Day 4 to Day 7) if the sensation and the possibility to move volunteers the arm are not yet recovered.

Day 1 is the day of administration of the study compound(s). The volunteers are expected at the PRA research center at 14:00 h in the afternoon of Day -2 (2 days prior to the day of administration of the study compound(s)). The volunteer will leave the PRA research center in the afternoon of Day 3 of the study. If the stay of the volunteer will be prolonged, the volunteer will leave the PRA research center at the maximum on Day 7 of the study.

A combination of all or some of the study compounds neosaxitoxin, bupivacaine and epinephrine will be given as a single perineural injection on Day 1. A perineural injection is an injection around the nerves. This takes place at the lateral side of the neck to locally anesthetize the network of nerves (the so-called plexus) that run from the cervical spinal cord to the arm (the so-called plexus brachialis). The injection site is located between the 2 neck muscles (the so-called interscalenus muscles) and therefore this technique is called the interscalene brachial plexus blockade. The study compound(s) will give local anesthesia of the arm by induction of a blockade of the nerves running to the arm which means that temporarily the sensation of the arm and ability to move the arm is blocked (sensory block and motor block). Administration of the study compound(s) (interscalene brachial plexus blockade) will be done by an anesthesiologist from the Department of Anesthesiology of the UMCG with extensive experience in this technique. To make the site of the injection as precise and safe as possible, an ultrasound imaging technique is used to see where the nerves and other structures are located. Also, very small electrical currents are sent through the needle to test how close it is to the nerve and thus increase safety. It may be that the volunteer notices these little currents briefly because a muscle moves or because the volunteer feels a small tingling sensation. The interscalene brachial plexus blockade will be done at the non dominant arm. Before the blockade will performed, 2 cannulas

(tubes) will be inserted. The first cannula will be inserted in the contralateral (opposite side) arm and will be used for blood sampling. The second cannula will be inserted in the foot and will be used for fluid and drug administration in emergency cases.
The volunteer will receive a short acting subcutaneous local anesthesia (1% lidocaine) at the injection site prior to the brachial plexus blockade, if deemed necessary by the anesthesiologist. During the interscalene brachial plexus blockade, the volunteer can experience an unpleasant tingling sensation or an electric shock in the arm and often in the fingers. This can cause stress or anxiety. The arm becomes numb after injection of the study compound(s) and the volunteer can also no longer lift and bend the arm and this can also cause an uncomfortable feeling. The hand and the fingers can also be numb with this nerve block. If the volunteer feel uncomfortable or experience stress or anxiety, the anesthesiologist can give the volunteer in steps a sedative (midazolam) through a cannula until the volunteer do not feel stressed or anxious anymore.

Before administration of the study compound(s), the volunteer should have fasted for at least 6 hours (no eating and drinking). Also after administration of the study compound(s), the volunteer will be required to fast for 4 additional hours. Then the volunteer will be served lunch. During fasting the volunteer is allowed to drink water or a carbohydrate-rich drink designed for pre-operative use (e.g., Nutricia preOp®) with the exception of 2 hours prior to administration of the study compound(s).

Intervention

Part A
Part A of the study will be performed in 8 groups each consisting of 5 healthy male volunteers. Two additional groups of 5 healthy male volunteers each may be added to the study based on the results of previous groups. Thus, in Part A there will be a maximum of 10 groups with a total of 50 healthy male volunteers that will be dosed. The volunteer will participate in 1 of these 8 to 10 groups. There will be 1 treatment period for each volunteer.

The starting dose of neosaxitoxin for the first group will be 1.25 microgram. For the rest of the groups the dose level of neosaxitoxin is not known yet and will be determined later based on the results of the previous group(s). The maximum dose of neosaxitoxin will not be higher than 60 microgram.

The following treatments will be administered to each group of volunteers. The volunteer will receive only one of these treatments:
- Test Treatment: a single dose of increasing dose levels of neosaxitoxin (between 1.25 microgram and 60 microgram) combined with bupivacaine (low dose: 40 milligram) and epinephrine
- Reference Treatment 1: a single dose of bupivacaine (low dose: 40 milligram) combined with epinephrine

- Reference Treatment 2: a single dose of bupivacaine (high dose: 100 milligram) combined with epinephrine
Whether the volunteer will receive the Test Treatment, Reference Treatment 1 or Reference Treatment 2 will be determined by chance. Within each group, 3 volunteers will receive the Test Treatment, 1 volunteer will receive Reference Treatment 1 and 1 volunteer will receive Reference Treatment 2.

Part B
Part B of the study will be performed in 8 groups each consisting of 5 healthy male volunteers. The volunteer will participate in 1 of these 8 groups. There will be 1 treatment period for each volunteer. Part B will be performed in a maximum of 40 healthy male volunteers that will be dosed.

The dose levels of neosaxitoxin for Part B are not known yet and will be determined based on the results of Part A and during the conduct of Part B based on the previous groups of Part B of the study. The range of the dose levels for neosaxitoxin that will be given in Part A of the study will be 1.25 to 60 microgram. The starting dose of neosaxitoxin in Part B will not be higher than half of the maximum dose of neosaxitoxin given in Part A of the study at that time point (resulting in a maximum starting dose of 30 microgram neosaxitoxin). The maximum dose of neosaxitoxin in Part B of the study will not be higher than the maximum dose given in Part A of the study.

The following treatments will be administered to each group of volunteers. The volunteer will receive only one of these treatments:
- Test Treatment: a single dose of increasing dose levels of neosaxitoxin combined with bupivacaine (low dose: 10-80 milligram)*
- Reference Treatment 1: a single dose of bupivacaine (low dose: 10-80 milligram)*
- Reference Treatment 2: a single dose of bupivacaine (high dose: 100 milligram)
* The dose level of bupivacaine is not known yet, but the dose level will not be lower than 10 milligram and not higher than 80 milligram. The actual dose level of bupivacaine that will be given during Test Treatment and Reference Treatment 1 will be decided before the start of Part B of the study.

Whether the volunteer will receive the Test Treatment, Reference Treatment 1 or Reference Treatment 2 will be determined by chance. Within each group, 3 volunteers will receive the Test Treatment, 1 volunteer will receive Reference Treatment 1 and 1 volunteer will receive Reference Treatment 2.

Part C
Part C of the study will be performed in 4 groups. The volunteer will participate in 1 of these 4 groups. There will be 1 treatment period for each volunteer. Part C will be performed in up to 21 healthy male volunteers that will be dosed.

The following treatments will be administered. The volunteer will receive only

one of these treatments:
- Test Treatment 1: a single dose of neosaxitoxin combined with bupivacaine and epinephrine
- Test Treatment 2: a single dose of neosaxitoxin combined with bupivacaine
- Test Treatment 3: a single dose of neosaxitoxin
- Test Treatment 4: a single dose of neosaxitoxin combined with epinephrine

The dose level of neosaxitoxin will be the same for all 4 test treatments. The dose level of bupivacaine will be the same for Test Treatments 1 and 2. The dose levels of neosaxitoxin and bupivacaine are not known yet and will be determined based on the results of Part B of the study. The possible range of the dose level for neosaxitoxin will be 1.25 to 60 microgram and for bupivacaine 10 to 80 milligram. Up to 6 volunteers will receive Test Treatment 1, a maximum of 3 volunteers will receive Test Treatment 2, 6 volunteers will receive Test Treatment 3, and 6 volunteers will receive Test Treatment 4.

Study burden and risks

Study compound(s)
All drugs can potentially cause adverse reactions; the extent to which this occurs differs. The study compound(s) may also have side effects that are still unknown.

Neosaxitoxin
The following adverse reactions can occur when neosaxitoxin (with or without epinephrine) is administered:
• Oral paresthesia (an abnormal sensation, typically tingling or pricking of the mouth)
• Oral hypoesthesia (reduced sense of touch or sensation of the mouth; numbness).
The frequency of these side effects is currently not known. It is however expected that more events occur at increasing doses.

In this study, epinephrine is used in a low dose (a usual dose as adjunct to local anesthesia) in combination with neosaxitoxin. When it is used as recommended, no adverse effects are expected from the use of epinephrine in addition to those of neosaxitoxin. In case of overdose or inadvertent intravenous (in a vein) injection, epinephrine can however potentially cause serious effects induced by a sharp rise in blood pressure due to vasoconstriction and cardiac arrhythmias.

Bupivacaine (with or without epinephrine)
The adverse reactions that can occur after administration of bupivacaine with or without epinephrine are summarized in the SmPCs (Summary of Product Characteristics) of the marketed products. Both SmPCs include the same adverse reactions. Addition of epinephrine in the low dose used in this combination does not lead to additional adverse reactions. Effects that are related to

spinal chord/epidural anesthesia in the respective SmPCs are not mentioned here, as they are not applicable to the interscalene route of administration (the method of study compound administration that is used in this study).

Very common adverse reactions (which may affect more than one person in every 10):
• Nausea
• Low blood pressure

Common adverse reactions (which may affect more than one person in every 100 and less than one person in every 10):
• Paresthesia (an abnormal sensation, typically tingling or pricking)
• Dizziness
• Vomiting
• Bradycardia (slow heart rate)
• High blood pressure

Uncommon adverse reactions (which may affect more than one person in every 1000 and less than one person in every 100):
• Signs and symptoms of central nervous system toxicity ranging from signs generally regarded as *prodromal symptoms* (including hypoaesthesia oral [reduced sense of touch or sensation of the mouth; numbness], paraesthesia oral [an abnormal sensation, typically tingling or pricking of the mouth], dizziness), over hyperacusis [hearing disorder with an increased sensitivity to certain frequency and volume ranges], visual disturbances, tinnitus, tremor, muscle twitching and dysarthria up to severe symptoms* (including loss of consciousness and seizures)

Rare adverse reactions (which may affect more than one person in every 10000 and less than one person in every 1000):
• Allergic reactions, anaphylactic reaction/shock
• Neuropathy (damage or disease of nerves)
• Peripheral nerve injury
• Paresis (weakness, partial loss or impaired movement)
• Diplopia (double vision)
• Cardiac arrest*, cardiac arrhythmias
• Respiratory depression**(hypoventilation)

* In case of high blood concentrations that typically may occur after unintentional intravascular injection or overdose, serious systemic adverse reactions concerning the central nervous system or the heart (such as seizures, loss of consciousness, cardiac arrest) may occur. The anesthesiologist performing the blocking procedure is trained and equipped to treat such conditions. He will perform the block using certain precautions to minimize the risk of unintentional intravascular injection.
** Block of phrenicus nerve, often observed during brachial plexus block (mainly the interscalene route) may lead to transient unilateral diaphragm

palsy usually with minor impact on respiration in healthy subjects. If, by accident, the medication is administered via subarachnoid injection (a certain tissue in the spinal canal) during a brachial plexus block, this can lead to very high spinal anesthesia possibly with apnea (suspension of breathing) and severe hypotension (low blood pressure).

Neosaxitoxin combined with bupivacaine (with or without epinephrine)
The adverse drug reactions of neosaxitoxin (oral paresthesia and oral hypoesthesia) are already included in those known for bupivacaine. Therefore, the adverse reactions that can occur after administration of this combination(s) are the same as for bupivacaine (with or without epinephrine) as given above. The frequency of the adverse reactions in this combination is however currently not known.

Lidocaine
If deemed necessary, the volunteer will receive a short-acting subcutaneous local anesthesia (1% lidocaine) at the injection site prior to the interscalene brachial plexus blockade.
The following adverse reactions can occur according to the SmPC of the marketed product (no frequencies are given in the SmPC):
• Allergic or anaphylactoid reactions, anaphylactic shock
• Dizziness or light-headedness, nervousness, tremor, paresthesia (an abnormal sensation, typically tingling or pricking), tongue numbness, drowsiness, convulsions, coma
• Blurred vision, diplopia (double vision) and transient amaurosis (vision loss)
• Tinnitus, hyperacusis (hearing disorder with an increased sensitivity to certain frequency and volume ranges)
• Hypotension, bradycardia (slow heart rate), myocardial depression, cardiac arrhythmias and possibly cardiac arrest or collapse of blood circulation
• Dyspnea (shortness of breath), bronchospasm (sudden constriction of the muscles in the walls of the bronchioles), respiratory depression (hypoventilation), respiratory arrest
• Nausea, vomiting
• Rash, urticaria, angioedema (swelling), face edema (swelling of the face)

Please note, that only a very small dose is necessary for the anesthesia of the skin at the injection site, so that most of the adverse reactions are unlikely to occur.

Midazolam
If the volunteer finds the tingling and numbing sensation after the interscalene brachial plexus blockade uncomfortable to the point of distress or anxiety, intravenous (in a vein) midazolam administration will be allowed. Midazolam will be given in steps until the volunteer do not feel distressed or anxious anymore.
The following adverse reactions can occur according to the SmPC of the marketed product (no frequencies are given in the SmPC):

• Hypersensitivity, anaphylactic shock, angioedema (swelling)
• Confusional state, euphoric mood, hallucination, agitation, hostility, rage, hyperactivity, aggressiveness, excitement, physical drug dependence and withdrawal syndrome, abuse
• Involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, sedation (prolonged and postoperative), alertness decreased, somnolence, headache, dizziness, ataxia (lack of voluntary coordination of muscle movements), anterograde amnesia, convulsions have been reported in premature infants and neonates, drug withdrawal convulsions
• Cardiac arrest, bradycardia (slow heart rate), cardiovascular disorder
• Hypotension, vasodilation (widening of blood vessels), thrombophlebitis (vein inflammation related to a thrombus, which is a blood clot), thrombosis
• Respiratory depression (hypoventilation), apnea (suspension of breathing), respiratory arrest, dyspnea (shortness of breath), laryngospasm uncontrolled/involuntary muscle contraction of the vocal folds), hiccups, bronchospasm (sudden constriction of the muscles in the walls of the bronchioles)
• Nausea, vomiting, constipation, dry mouth
• Rash, urticaria, pruritus, skin reactions
• Fatigue, injection site erythema (redness), injection site pain
• Falls, fractures
• Assault

Technique and discomforts of the interscalene brachial plexus blockade
During this study the volunteer will receive the study compound(s) as an injection around the nerves. This takes place at the lateral side of the neck to locally anesthetize the network of nerves (the so-called plexus) that run from the cervical spinal cord to the arm (the so-called plexus brachialis). The injection site is located between the 2 neck muscles (the so-called interscalenus muscles) and therefore this technique is called the interscalene brachial plexus blockade. To make the site of the injection as precise and safe as possible, an ultrasound imaging technique is used to see where the nerves and other structures are located. Also, very small electrical currents are sent through the needle to test how close it is to the nerve and thus increase the safety. It may be that the volunteer notices these little currents briefly because a muscle moves or because you feel a small tingling sensation.
The study compound(s) will give local anesthesia of the arm by induction of a blockade of the nerves running to the arm which means that temporarily the sensation of your arm and ability to move your arm is blocked (sensory block and motor block). The volunteer may feel tingling and numbing sensation. If the volunteers find the tingling and numbing sensation uncomfortable to the point of distress or anxiety, the volunteer will receive intravenous (in a vein) midazolam bolus administration to treat these. The blocking procedure will include disinfection of the skin area at the neck in order to minimize the risk of infection.
One of the risks of the interscalene brachial plexus blockade is a prolonged sensory block (no sensation of the arm) and prolonged motor block (no ability

to move the arm). If on Day 3 the sensory and motor block are not yet recovered, volunteers stay in the research center can be prolonged until Day 7 of the study to watch the recovery under supervision and to minimize the risk of injuries. This loss of feeling and movements of the arm can cause anxiety and some panic.
Besides the intended transient block of nerves of the plexus brachialis to provide anesthesia in the shoulder/arm, other nerves of the surrounding neural tissue can be blocked due to their proximity. Using typical volumes of local anesthetics commonly leads to block of the phrenic nerve with the result of a block-sided diaphragm palsy. The fact that the diaphragm cannot move transiently has usually only a minimal impact on breathing of a healthy person. Less often a stellate ganglion (a part of the sympathetic autonomic nervous system) block is leading to the so called Horner syndrome (characterized by miosis (small pupils), ptosis (the upper eyelid droops over the eye), enophthalmos (posterior displacement of the eyeball). Hoarseness resulting from blocking the nerve innervating the vocal cord may also occur. As the block wears off, these side effects usually resolve.
It can happen that arteries or veins are hit, causing a bruise or swelling.
Also the nerve tissue can in principle be damaged by the needle itself or due to toxicity of the local anesthetic potentially leading to neurological deficits, such as a longer lasting numbness in the arm. A permanent complication such as permanent numbness of the arm or permanent loss of strength or paralysis of the arm is rare. Because the interscalene brachial plexus blockade occurs in the vicinity of the lung, a collapsed lung (also called pneumothorax) can occur. A collapsed lung is a condition in which there is free air in the chest cavity next to the lung. This air presses on the internal organs, so also on the lung. The occurrence of a collapsed lung due to the blockade is rare.

Study procedures
Blood draw
The insertion of the needle for drawing blood and/or insertion of the indwelling cannula may cause pain, bleeding or mild infection where the needle goes into the arm. Another possible reaction is feeling dizzy or light-headed. Rare complications during or after a blood draw include fainting, blood clot, infections, inflammation of the vein, scarring of the vein, nerve injuries, and accidental puncture of an artery. In total, we will take about 200 mL of blood from the volunteer. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time. Additional blood draws may be necessary for medical reasons.

ECG electrodes
To monitor the heart rate, electrodes (small, plastic patches) will be pasted at specific locations on the chest and abdomen. Prolonged use of these electrodes can cause skin irritation (rash and itching).

Quantitative Sensory Testing

The other procedures used to detect touch, cold, and warm sensation, and to induce pain in this study, such as mechanical, cold and heat pain assessments, have been used extensively in studies with healthy volunteers. Even though they are painful, they are generally well tolerated and of sufficiently short duration to avoid any risk to the health or well-being of healthy volunteer.

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

- Male subject, aged 18 years to 55 years, inclusive.;- Body mass index between 20.0 kg/m2 and 30.0 kg/m2 inclusive, with a minimal body weight of 60.0 kg.;- Subject must be in good health as determined by the prior/concomitant diseases, physical and laboratory examinations.;- Non-smoking or not more than 10 sigarettes, 2 cigars or 2 pipes per day

Exclusion criteria

Suffering from hepatitis B, hepatitis C, or HIV/AIDS. In case of participating in another drug study withing 1 month prior to the screening visit, donated 100 mL or more of blood between the screening visit and entry into the PRA research center excluding blood taken for this clinical study, donated 500 mL or more of blood within 3 months prior to the screening viist.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-11-2016
Enrollment:	111
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Neosaxitoxin
Generic name:	N/A

Ethics review

Approved WMO

Date:	06-12-2017

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-01-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-07-2018
Application type:	Amendment
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	EUCTR2016-003958-33-NL
CCMO	NL63010.056.17