Influence of S(+)-ketamine on Diffuse Noxious Inhibitory Control (DNIC) and offset analgesia (OA) in chronic pain patients (neuropathic pain, complex regional pain syndrome type 1, fibromyalgia) and healthy volunteers

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1. Measure DNIC and offset analgesia in CRPS-1 patients, fibromyalgia patients and neuropathic pain patients;2. Compare DNIC and offset analgesia in chronic pain patients with DNIC and offset analgesia in healthy volunteers;3. Assess the effect of...

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

Summary

ID

NL-OMON33040

Source
ToetsingOnline

Brief title
DNIC study

Condition

- Peripheral neuropathies

Synonym
chronic pain, pain

Research involving

Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: analgesia, chronic pain, pain

Outcome measures

Primary outcome

The effect of ketamine on pain measurements assessed using DNIC and offset

analgesia paradigms (see background of the study)

Secondary outcome

na

Study description

Background summary

DNIC and offset analgesia. Pain perception is modulated via facilitatory and inhibitory control systems. Inhibitory control is most important to chronic pain patients as there are strong indications that failed inhibition constitutes a predisposition to acquired chronic pain. Various systems involved in inhibitory control have been demonstrated over the years. Two systems seem important: (1) top-down inhibition of afferent noxious information by endogenous analgesia originating in the periaquaductal grey (PAG) and affecting pain perception via descending pathways; (2) bottom-up activation of pain modulatory systems via activation of spino-bulbo-spinal loops originating in the dorsal horn of the spinal cord. The effect that the latter system has on pain perception is called Diffuse Noxious Inhibitory Control (DNIC). The two systems are interconnected and DNIC is considered a bottom-up activation of the pain modulatory mechanism, as part of the descending endogenous analgesia system. DNIC dysfunctions or is less efficacious in various complex chronic pain states, such as irritable bowel syndrome, chronic headache, fibromyalgia and temporomandibular disorder. Little is known on DNIC in other evenly complex chronic pain states such as neuropathic pain and Complex Regional Pain Syndrome

type 1 (CRPS-1).

Offset analgesia is another expression of the endogenous opioid system and is evoked by noxious stimulation, in order to reduce (or control) the perception of the noxious event. Offset analgesia becomes apart when an even more painful stimulus occurs briefly during prolonged painful stimulation. Due to activation of the endogenous opioid system the prolonged stimulation is perceived less painful after the intense noxious stimulus than therefore. In day-to-day life this exemplified by putting ones hand or foot in a warm bath. The heat perception is reduced when taking out the extremity for just a short moment. The activation of the endogenous opioid system now reduces pain perception.

CRPS-1 and neuropathic pain. Complex Regional Pain Syndrome Type-1 (CRPS-1) is a chronic pain syndrome typically affecting an extremity after a local trauma or surgical intervention. The initial phase of the syndrome is characterized by pain, edema, changes in skin temperature and color, and hyperhydrosis. Although the recovery rate of CRPS is unknown, a substantial number of patients develop chronic disease with severe pain, disability, and loss of quality of life. In the Netherlands the incidence of CRPS-1 is 26 per 100,000 person years, with predominance in women. At present, the pathophysiology of CRPS-1 remains largely unknown. In contrast to neuropathic chronic pain syndromes there is no proof of a clinically evident nerve lesion as a causative factor in CRPS-1. Neuropathic pain is due to an evident nerve lesion from trauma (incl. surgical trauma), diabetes (small fiber neuropathy), infection (incl. HIV), chemotherapy, etc. The primary sensation is a burning pain coinciding with areas of hyperalgesia and allodynia.
S(+)-ketamine. We recently showed significant and long-lasting pain relief in CRPS-1 patients using low-dose S(+)-ketamine treatment (Protocol P05.100). Ketamine is an antagonist of the N-methyl-D-aspartate receptor (NMDAR). The NMDAR is implicated in the development and maintenance of chronic pain states. In several chronic pain states the NMDAR is activated and upregulated in the spinal cord (central sensitization). This results in enhanced signal transmission in the pain circuitry from the spinal cord to the cortex leading to spontaneous pain, allodynia (pain perception from a non-noxious stimulus) and hyperalgesia (increased pain sensitivity). Our observation in CRPS-1 patients suggests that ketamine*s beneficiary effect (that is, dechronification of pain) is caused by desensitization of the NMDAR. How this relates to DNIC and offset analgesia is unknown. While it has been suggested that DNIC and offset analgesia are involved in the endogenous opioid-receptor system, a role for the NMDAR is not excluded. In fact, the close relation between chronic pain (with a causal role for an activated/upregulated NMDAR) and a reduced DNIC implicitly suggests a role for the NMDAR in DNIC/offset analgesia.

Study objective

1. Measure DNIC and offset analgesia in CRPS-1 patients, fibromyalgia patients and neuropathic pain patients;

2. Compare DNIC and offset analgesia in chronic pain patients with DNIC and offset analgesia in healthy volunteers;

3. Assess the effect of low-dose S(+)-ketamine on DNIC and offset analgesia.

Study design

Open-label, observational study design

Intervention

A 1-h infusion with low dose S(+)-ketamine

Study burden and risks

Nausea. There is a chance that the subjects become nauseated. In that case they will receive 4 mg iv ondansentron (Zofran), a potent antiemetic. This will not end the study.

Psychomimetic side effects (ketamine). S(+)-ketamine may cause psychedelic side effects such as hallucinations, vivid dreams, feeling of inebriation, confusion, drowsiness, and dizziness. All of these side effects are temporarily and will disappear spontaneously or after discontinuation of the S(+)-ketamine infusion. We are currently performing a S(+)-ketamine study (08.075) and have now some additional knowledge on the psychomimetic effects of the S(+)-variant of ketamine. The psychomimetic effects of S(+)-ketamine are minimal with some dizziness as most pronounced side effect. If side effects occur they do so only after prolonged infusion. Hence we do not expect serious problems from S(+)-ketamine with respect to psychomimetic side effects in our current study. We cannot exclude, however, that some hallucinations or vivid dreams during the ketamine infusion occur. They will dissappear upon the termination of the infusion. In case such side effect does occur in our study, the infusion of ketamine will immediately be terminated and the study will continue without further drug infusion.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
2333 ZA Leiden
NL
Scientific

Leids Universitair Medisch Centrum

Albinusdreef 2
2333 ZA Leiden
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patient inclusion criteria. (i) Patients diagnosed with CRPS-1, small-fiber neuropathy or fibromyalgia, according to the guidelines of the IASP or other professional pain societies (eg., Netherlands Society of Anesthesiologists); (ii) a pain score of 5 or higher; (iii) age between 18 and 75 years; (iv) being able to give written informed consent.
Volunteer inclusion criteria. Healthy volunteers in the age range 18-75 years of either sex.

Exclusion criteria

Patient and volunteer exclusion criteria. (i) Unable to give written informed consent; (ii) medical disease such as renal, liver, cardiac, vascular (incl. hypertension) infectious disease; (iii) increased intracranial pressure; (iv) epilepsy; (v) psychosis; (vi) glaucoma; (vii) a history of cerebro-vascular accident < 1 year; (viii) pregnancy; and (ix) obesity (BMI > 30).

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-08-2010
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ketanest-S
Generic name:	S(+)-ketamine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-06-2009
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	27-08-2009
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	EUCTR2009-012586-55-NL
CCMO	NL28179.058.09