British Journal of Anaesthesia **110** (6): 1010–16 (2013)
Advance Access publication 5 February 2013 · doi:10.1093/bja/aes578

BJA

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Influence of ketamine and morphine on descending pain modulation in chronic pain patients: a randomized placebo-controlled cross-over proof-of-concept study

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Editor's key points

- Dysfunction of central inhibition of pain processing has been implicated in the pathogenesis of chronic pain states.
- The effects of morphine and ketamine on conditioned pain modulation (CPM) were studied in 10 adults with chronic peripheral neuropathic pain.
- Morphine, ketamine, and placebo all provided CPM in proportion to their analgesic effects, suggesting a role for CPM in the treatment of chronic pain.

Background. Descending inhibition of pain, part of the endogenous pain modulation system, is important for normal pain processing. Dysfunction is associated with various chronic pain states. Here, the effect of ketamine and morphine on descending inhibition is examined using the conditioned pain modulation (CPM) paradigm in chronic neuropathic pain patients.

Methods. CPM responses were obtained in 10 adult neuropathic pain subjects (two men/eight women). All subjects had peripheral neuropathy as defined by abnormal quantitative sensory testing. The effects of *S*(+)-ketamine (0.57 mg kg^{-1} h^{-1} for 1 h) and morphine (0.065 mg kg^{-1} h^{-1} for 1 h) were tested in a randomized, placebo-controlled double-blind study. CPM was measured at baseline and 100 min after the start of treatment and was induced by immersion of the leg into a cold-water bath. The test stimulus was a 30 s static thermal stimulus to the skin of the forearm.

Results. Without treatment, no CPM was detectable. Treatment with ketamine, morphine, and placebo produced CPM responses of 40.2 (10.9)%, 28.5 (7.0)%, and 22.1 (12.0)%, respectively (for all treatments, CPM effect $P<0.05$), with no statistical difference in the magnitude of CPM among treatments. The magnitude of CPM correlated positively with the magnitude and duration of spontaneous pain relief.

Conclusions. The observed treatment effects in chronic pain patients suggest a role for CPM engagement in analgesic efficacy of ketamine, morphine, and placebo treatment.

Keywords: diffuse noxious inhibitory control; ketamine; morphine; peripheral nervous system diseases; placebo effect

Accepted for publication: 17 December 2012

Normal pain processing involves modulation of pain signals in the central nervous system by the activation of endogenous inhibitory (analgesic) or facilitatory (algesic) mechanisms.[1–3] These modulatory mechanisms allow optimal functionality in response to an acute painful insult.[4] For example, activation of endogenous inhibition of pain allows for an evolutionary well-preserved fight or flight response;[5 6] facilitation of pain responses puts the emphasis on tissue damage and forces an individual to seek rest, medical attention, or both.[6] In recent years, various experimental (surrogate) expressions of endogenous modulation of pain gained increasing interest in chronic pain research.

Conditioned pain modulation (CPM, formerly known as diffuse noxious inhibitory controls or DNIC) has been investigated most intensively and induces central inhibition of a focal pain stimulus by administering a second noxious stimulus at a remote area.[7 8] In contrast to animals, where endogenous inhibition involves activation of spinal–medullary–spinal feedback loops (e.g. DNIC),[9] in humans more complex supraspinal mechanisms also play an important role (e.g. CPM).[7 10] Absent or impaired CPM responses have been observed in several chronic pain states.[8 11–13] Defects in CPM possibly reflect an inability to engage descending inhibition, either causing perseverance of pain symptoms or possibly even leading to the development of chronic pain. For example, recent animal data show that less efficient descending inhibition is associated with a high probability of chronic pain development after peripheral nerve injury.[14 15]

Few studies address the effect of analgesic medication on CPM responses in chronic pain patients. It can be

hypothesized that chronic pain patients would benefit from analgesics that enhance descending inhibition as measured by CPM.[14 16] A recent study showed that duloxetine-induced improvement of CPM responses correlated with drug efficacy in patients with painful diabetic neuropathy.[16] Hence, the positive effect of analgesics on CPM might have a predictive effect on their ability to cause (long-term) analgesia. In the current study, we assessed the effect of morphine and ketamine on CPM responses in a group of patients with chronic painful peripheral neuropathy. Both treatments are effective in chronic pain patients, but their effects on CPM responses have only been tested in volunteers, but not in chronic pain patients. We hypothesized that both drugs enhance CPM responses and that the magnitude of these responses correlates positively with the magnitude and duration of spontaneous pain relief.

Methods

Approval of the study was obtained from the local human ethics committee, and written informed consent was obtained from all subjects. The study was registered in the Dutch Trial Register (www.trialregister.nl) under trial number NTR2005.

Subjects

Ten patients with chronic pain were recruited to participate in the study. They were diagnosed with chronic peripheral neuropathic pain and were included on the basis of their symptoms, the results of quantitative sensory testing (QST), and a neurological examination.[17–19] Subjects were required to have at least two of the following symptoms in legs, arms, or both (in a stocking-glove distribution): (i) symmetrical dysesthesias or paresthesias; (ii) burning or painful feet with night-time worsening; or (iii) peripheral tactile allodynia. With respect to the QST, subjects were included if they had an abnormal warm and cold detection threshold, an abnormal warm and cold pain threshold, or allodynia.

Before participation, all subjects underwent physical examination. Exclusion criteria for the study were: age <18 or >80 yr; presence or history of a medical disease such as renal, cardiac, vascular (including hypertension), or infectious disease; presence or history of a neurological and psychiatric disease such as increased cranial pressure, epilepsy or psychosis; glaucoma; pregnancy; obesity (BMI>30); or use of strong opioid medication. Subjects were allowed to continue the following pain medications as long as they used a constant dose for at least 3 months before the start of the study and could be kept constant during the whole study period: acetaminophen, non-steroidal anti-inflammatory drugs, amitriptyline, gabapentin, and pregabalin.

Pain assessment and CPM

As examined by Pud and colleagues,[7] noxious cold water is the most used pain modality as a conditioning stimulus combined, with different pain modalities used as test stimulus. We applied a heat pain stimulus as test stimulus and cold water as conditioning stimulus, in agreement with earlier studies from our laboratory and from King and colleagues.[8 20]

The test stimulus was a noxious thermal stimulus applied to clinically normal skin of the volar side of the dominant forearm (with normal warm and cold thresholds). The skin was stimulated with a 3×3 cm thermal probe of the Pathway Neurosensory Analyzer (Medoc Ltd, Ramat Yishai, Israel). During the heat pain stimulus, subjects continuously quantified the pain intensity level of the stimulus using a slider on a computerized potentiometer that ranged from 0 (no pain) to 100 (worst pain imaginable), which allowed continuous, electronic monitoring of the visual analogue scale (eVAS). To overcome sensitization, a 3 min interval was incorporated between tests and the volar side of the arm was divided into three zones.[8] The thermode was moved from zone to zone between stimuli. The test stimulus was obtained by gradually increasing the thermode temperature from baseline (32°C) to the test temperature (at 1.5°C s^{-1}). When the test temperature was reached, it remained constant for 30 s. Next, the temperature was rapidly decreased (at 6°C s^{-1}) to baseline. Before the test, individual test and conditioning temperatures were determined. For the test stimulus, a series of heat stimuli was applied. Baseline temperature was set at 32°C after which temperature increased by 1.5°C s^{-1} to temperatures ranging from 42°C to 49°C for 10 s. The temperature evoking an eVAS of at least 50 mm was set as test temperature and used during the remainder of the study for the experimental stimulus. Before testing, the thermode was calibrated using a surface thermometer (K-Thermocouple thermometer, Hanna Instruments, Woonsocket, RI, USA).

The conditioning stimulus was cold water immersion in a cold-water bath which was filled and temperature adjusted using a rapid-water cooling system (IcyDip, IcySolutions BV, Delft, The Netherlands).[20] The subject's foot and lower leg were immersed into the cold water reservoir, which could be set at temperatures ranging from 6°C to 18°C. The temperature that produced an eVAS of at least 30 mm was used in the study for the conditioning stimulus. After exposure to cold water, the subject's extremity was immediately warmed to normal temperature using the warm water reservoir of the IcyDip system.

To measure CPM, eVAS responses to the test stimulus were obtained without ($n=3$) and with the conditioning stimulus ($n=3$). The conditioning stimulus was applied 25 s before the start of the test stimulus and ended simultaneously with the end of the test stimulus. The subject was instructed to only rate the pain intensity level of the test stimulus with the eVAS slider.

Study design

Each subject visited the laboratory on 3 days, at least 2 weeks apart, in which placebo, morphine, and ketamine were tested using a double-blind, randomized cross-over study design. Initially, CPM was measured without treatment (baseline values). After a break, i.v. treatment was given (infusion duration 1 h),