Journal of Pharmacological and Toxicological Methods 84 (2017) 37–43

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

Research article

Cortical and spinal assessment - a comparative study using encephalography and the nociceptive withdrawal reflex

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ARTICLE INFO

Article history:
Received 19 May 2016
Received in revised form 20 October 2016
Accepted 27 October 2016
Available online 29 October 2016

Keywords:
Methods
Electroencephalography
Cold pressor
Opioids
Nociceptive withdrawal reflex

ABSTRACT

Background: Standardized objective methods to assess the analgesic effects of opioids, enable identification of underlying mechanisms of drug actions in the central nervous system. Opioids may exert their effect on both cortical and spinal levels. In this study actions of morphine at both levels were investigated, followed by analysis of a possible correlation between the cortical processing and spinal transmission.
Methods: The study was conducted after a double-blinded, two-way crossover design in thirty-nine healthy participants. Each participant received 30 mg morphine or placebo as oral solution in randomized order. The electroencephalogram (EEG) was recorded during rest and during immersion of the hand into ice-water. Electrical stimulation of the sole of the foot was used to elicit the nociceptive withdrawal reflex and the reflex amplitude was recorded.
Results: Data from thirty subjects was included in the data analysis. There was no change in the activity in resting EEG ($P > 0.05$) after morphine administration as compared to placebo. During cold pressor stimulation, morphine significantly lowered the relative activity in the delta (1–4 Hz) band ($P = 0.03$) and increased the activity in the alpha (8–12 Hz) band ($P = 0.001$) as compared to placebo. The reflex amplitudes significantly decreased after morphine administration ($P = 0.047$) as compared to placebo. There was no correlation between individual EEG changes during cold pressor stimulation and the decrease in the reflex amplitude after morphine administration ($P > 0.05$).
Conclusions: Cold pressor EEG and the nociceptive reflex were more sensitive to morphine analgesia than resting EEG and can be used as standardized objective methods to assess opioid effects. However, no correlation between the analgesic effect of morphine on the spinal and cortical assessments could be demonstrated.
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1. Introduction

Standardized methods to objectively assess drug effects in clinical trials are needed to identify the underlying mechanisms of action in the central nervous system.

Electroencephalography (EEG) objectively reflects cortical processing in the brain and can be used to assess pain (Schulz et al., 2015; Schmidt et al., 2012; Tiemann et al., 2015) and drug-induced changes in brain activity (Granmo et al., 2013). EEG during resting state has been used extensively in opioid research, but as pointed out in a review, results have not been consistent (Malver et al., 2014). Tonic pain stimuli, such as cold pressor (CP) (i.e. hand immersed in cold water) mimics the clinical condition due to the unpleasantness and long duration of the stimulus rendering different central mechanisms to be activated (Rainville, Feine, Bushnell, & Duncan, 1992). It has been shown that tonic pain stimulation is sensitive to opioid analgesia in experimental pain research (Olesen, Brock, Sverrisdóttir, Larsen, & Drewes, 2014). Furthermore, EEG assessed during tonic pain is a valid experimental pain model both in terms of reliability between days and in connection between cortical activity and pain perception (Gram, Graversen, Olesen, & Drewes, 2015b). Therefore, EEG during tonic cold pain is of interest as a biomarker for analgesic effect.

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http://dx.doi.org/10.1016/j.vascn.2016.10.008
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The nociceptive withdrawal reflex (NWR), quantified by the electromyography (EMG) amplitude elicited by electrical stimulation on the sole of the foot, is another method to objectively assess drug-induced effects on pain processing. It represents spinal pain transmission although under control of the brain. However, the degree to which EMG amplitudes are related to the cortical level of pain processing is not known (Skljarevski & Ramadan, 2002) and correlation between electrophysiological changes at the spinal and cortical levels have not yet been investigated.

It was hypothesized that in healthy subjects EEG recorded during tonic pain stimulation is more sensitive to detect the effect of morphine than EEG recorded during resting state. Furthermore, it was hypothesized that a correlation between the analgesic effect of morphine on the spinal (NWR) and cortical (EEG) structures exists.

The aims were therefore to evaluate a) the analgesic effect of morphine on the cortical level in terms of spectral content, both during resting state and tonic pain stimulation, b) the analgesic effect of morphine on the NWR and c) correlation between the EEG (reflecting the cortical level) and the NWR (mainly reflecting the spinal level).

2. Methods

The study was conducted in the outpatients' clinic at the Department of Gastroenterology, Aalborg University Hospital Denmark between November 2010 and April 2012. The study protocol was approved by The North Denmark Region Committee on Health Research Ethics (N-20100046) and the Danish Health and Medicines Authority (reference no. 2612–4319). Participants were informed verbally and in writing before deciding to participate. Subsequently, an informed consent form was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and ICH-GCP guidelines. The trial was registered on ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01245244, EUDRACT no. 2010-020894-17). Regular monitoring was performed by the GCP-unit, Aalborg and Aarhus University Hospitals, Denmark. Other data from the study have previously been reported (Olesen et al., 2014; Sverrisdóttir et al., 2014; Kristiansen et al., 2014; Hansen, Olesen, Graversen, Drewes, & Frøkjaer, 2015; Hansen, Olesen, Simonsen, Drewes, & Frøkjær, 2014a; Hansen et al., 2014b; Gram et al., 2015b; Lelic et al., 2014; Gram, Graversen, Olesen, & Drewes, 2015a). This report includes data on the effect of morphine and placebo on resting EEG, EEG recorded during a tonic pain stimulus and EMG amplitude from the NWR. Furthermore, quantitative sensory testing (QST) data from the reflex threshold (RT) and area under the curve (AUC) while the subjects hand is immersed in cold water is reported.

2.1. Study protocol

A double blinded, randomized, two-way crossover, placebo-controlled single dose study was conducted. At least one-week washout intervals were included. Each participant fasted at least 4 h prior to the study. Prior to first dosing day, a training session, including all experimental pain procedures was conducted, in order to familiarize the participants to the laboratory environment and to verify that the participants could tolerate the comprehensive experimental pain testing procedure included in the full protocol. Well-trained experimenters performed all testing in a quiet room. The same experimenters tested each participant at the same time of the day on both study days. Assessments were performed at baseline (before drug administration) and repeated sixty minutes after drug administration, since the pharmacodynamic effect is at its maximum at this time point (Staahl et al., 2008).

2.2. Participants

Thirty-nine healthy opioid-naive Caucasian participants (eighteen females and twenty-one males; average age: 26.9 ± 6.5 years) were enrolled in this study. Medical history and physical examination including measurement of blood pressure and oxygen saturation verified each subject to be healthy. Individuals with a history of alcohol, opioids or other drugs abuse were not considered eligible for inclusion, neither were individuals with a history of abuse in the near family. Individuals with previous somatic or psychiatric diseases were excluded. Female participants used contraceptives during their participation and were investigated in the same phase of their individual menstrual cycle. Additionally, a pregnancy test was performed before initiation of each dosing day. Participants were barred from using strong analgesics during their enrolment. In addition, the use of over the counter analgesics was not allowed 24 h prior to the experiment.

2.3. Randomization, blinding and medication

A randomization list was generated via www.randomization.com. Mirror randomization was employed in case of participant drop-outs. To ensure blinding of the investigator, staff and participants the medicine was prepared by a pharmacist with no other involvement in the study. Thirty mg of morphine (morphine oral liquid mixture 2 mg/ml Hospital Pharmacies, Denmark) or 15 ml placebo oral liquid mixture, pure water, (Hospital Pharmacies, Denmark) were administered. The morphine was not titrated for its anti-nociceptive effect across subjects or adjusted accordingly to bodyweight. All subjects received the same dose (30 mg morphine).

All medications were masked in color and taste by 5 ml orange juice concentrate and had a volume of 20 ml. The mixture was administered orally immediately after baseline recordings.

2.4. Pain rating

During the cold pressor stimulation, the volunteers were asked to evaluate the pain intensity continuously using Medoc's computerized visual analogue scale. The subjects were instructed to evaluate both innocuous sensation and noxious sensation, as both innocuous as well as noxious ranges were included in the utilized scale. VAS was defined as: 0 = no perception, 1 = vague perception of mild sensation, 2 = definite perception of mild sensation, 3 = vague perception of moderate sensation, 4 = definite perception of moderate sensation, 5 = the pain detection threshold, 6 = mild pain, 7 = moderate pain (PTT), 8 = pain of medium intensity, 9 = intense pain and 10 = unbearable pain (Drewes, Gregersen, & Arendt-Nielsen, 2003).

2.5. Cold pressor test

The CP test was performed using circulated water bath (Grant, Fischer Scientific, Slangerup, Denmark). The water was cooled to 2 °C and the subjects immersed their left hand for 2 min while water was circulated. During this test, the subject was asked to remain quiet. The subjects rated the perceived pain continuously on the electronic handheld device.

2.6. EEG recordings

EEG was recorded in a dimly lit room, first during a resting period and then during CP test. During the 2.5 min resting state recordings, subjects were instructed to keep their eyes open and minimize eye blinking. EEG recordings during CP were started as the subject immersed the hand into water. EEG was recorded from a standard 62-channel cap (Quick-Cap International, Neuroscan, El Paso, TX, USA), amplified digitally on a Synamps 2 system (Neuroscan Compumedics, El Paso, TX, USA) and saved for later analysis (Neuroscan 4.3.1, Neuroscan, El Paso, TX, USA).

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