Scandinavian Journal of Pain 17 (2017) 107–115

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Original experimental

Quantitative sensory tests fairly reflect immediate effects of oxycodone in chronic low-back pain

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HIGHLIGHTS

- Oxycodone had a significant analgesic effect on low-back pain compared to placebo.
- Oxycodone had significant anti-nociceptive effects on almost all QST modalities.
- Anti-nociceptive effects assessed by QST fairly reflect efficacy of oxycodone.
- QST may be more useful to identify non-responders rather than potential responders.

ARTICLE INFO

Article history:
Received 1 May 2017
Received in revised form 29 June 2017
Accepted 5 July 2017

Keywords:
Quantitative sensory tests
Chronic low-back pain
Oxycodone
Experimental pain
Analgesic effect
Anti-nociceptive effect

ABSTRACT

Introduction: Quantitative sensory tests (QST) can be used for profiling anti-nociceptive effects of analgesics. However, anti-nociceptive effects detected by QST are not necessarily associated with analgesic effects in pain patients. As part of a large investigation on low back pain, this paper describes the immediate analgesic and anti-nociceptive effects of oxycodone in chronic low-back pain and ranks different QST according to their ability to reflect this effect. The results are expected to support the selection of QST for future studies on potential novel opioid agonists in human pain.

Methods: In this randomized, placebo-controlled and double-blinded cross-over study, 50 patients with chronic low-back pain received a single oral dose of oxycodone 15 mg or active placebo, and underwent multiple QST testing. The intensity of low-back pain was recorded during 2 h. The areas under the ROC curves and 95% confidence intervals were determined, whereby responder status (≥30% pain reduction) was set as reference variable and changes in QST from baseline were set as classifiers.

Results: Significant analgesic effect on low-back pain as well as anti-nociceptive effects for almost all QST parameters were observed. The QST with the highest area under the curve were heat pain detection threshold (0.65, 95%-CI 0.46 to 0.83), single-stimulus electrical pain threshold (0.64, 95%-CI 0.47 to 0.80) and pressure pain detection threshold (0.63, 95%-CI 0.48 to 0.79).

Conclusions: The results suggest that anti-nociceptive effects assessed by QST fairly reflect clinical efficacy of oxycodone on low-back pain. Pressure pain detection threshold, heat pain detection threshold and single-stimulus electrical pain threshold may be more suitable to sort out potential non-responders rather than identifying potential responders to opioid medication. Future pre-clinical human research may consider these results when investigating the analgesic effect of opioid agonists by means of QST.

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http://dx.doi.org/10.1016/j.sjpain.2017.07.004
1877-8860/

1. Introduction

Opioid prescription for chronic pain has considerably increased in the past years, particularly for chronic low-back pain [1]. However, long-term use of opioids for non-cancer conditions is controversial because of numerous side effects such as development of tolerance, respiratory depression, constipation or drug misuse. A recent systematic review found opioids to be better than placebo, but not necessarily better than non-opioid analgesics for chronic low-back pain [2].

Most available studies that have examined the short-term effects of opioids did so by means of quantitative sensory tests (QST) in healthy volunteers [3–6]. However, a significant anti-nociceptive effect detected by QST in pain-free volunteers does not necessarily imply that the drug exerts a clinically meaningful analgesic effect in pain patients. Given the broad spectrum of QST modalities, it would be of relevance to know which QST parameter best reflects the clinical effect of a drug in a given patient population.

The present study is part of a larger project that investigated the ability of QST to predict the efficacy of several drugs in chronic low-back pain. This sub-study describes the immediate analgesic effect of oxycodone on chronic low-back pain and its anti-nociceptive effects as assessed by QST. The different QST are ranked according to their ability to reflect these effects. The results are expected to support the selection of QST for future studies on potential novel opioid agonists in human pain.

2. Methods

This was a randomized, double-blinded and placebo-controlled study at the University Department of Anesthesiology and Pain Medicine, Inselspital Bern, Switzerland. It was registered with clinicaltrials.gov (NCT01179828) and approved by the local ethics committee (KEK 213-09). The detailed study protocol [7] and results from another substudy [8] have been published. All participants gave written informed consent prior to enrolment.

2.1. Patients

Consecutive patients aged 18–80 years with chronic low-back pain of at least 3 months duration were eligible. Pain intensity at the moment of testing had to be ≥3/10 on the numerical rating scale (NRS, 0 = no pain and 10 = worst pain imaginable). Exclusion criteria were: suspected radicular pain (as defined by leg pain associated with an MRI finding of a herniated disc or spinal stenosis), signs or suspicion of neurological dysfunction at the tested sites, pregnancy (as assessed by pregnancy test), breast feeding, treatment with an antidepressant, opioid or anticonvulsant, intake of centrally active substances (including drug or alcohol abuse), allergy or pharmacological contraindications to the tested drugs, systemic inflammatory or rheumatologic disease, and major depression (Beck Depression Inventory short form score > 9). Analgesic medication was stopped one week before the first experiment. Only acetaminophen or ibuprofen were allowed as rescue medication until 24 h before the experiment.

2.2. Medication and measurements

In this cross-over study, oxycodone 15 mg and tolterodine 1 mg (active placebo) were administered in a randomized, double-blinded fashion, after 6 h of fasting and with a minimal wash-out time of 1 week between experiments. Tolterodine was chosen as an active placebo because it is a centrally active anti-cholinergic drug that mimics some of the side-effects of oxycodone (e.g. drowsiness, light sedation), but is devoid of any analgesic effect. Each the verum and the placebo pills were concealed by the hospital pharmacy using identical-looking red gelatin capsules and packed in semi-opaque plastic flasks labelled with subject number, lot number and expiry date. Neither the subject nor the investigators were aware which flask contained which substance. Randomization was performed by the pharmacist using a computer-generated random list.

2.3. Quantitative sensory testing

Quantitative sensory testing (QST) was performed at the leg and arm of the more painful body side (or randomly selected side in case of bilateral/midline pain). Pressure pain detection and tolerance thresholds (PPDT and PPTT) were measured at the second toe using an electronic algometer (Somedic AB, Horby, Sweden) with a probe surface of 1 cm^2. Pressure was increased at a rate of 30 kPa/s until the sensation became painful (PPDT) or intolerable (PPTT).

Electrical single-stimulation pain threshold (ESPT) and electrical repeated-stimulation pain threshold (ERPT with 5 stimuli at 2 Hz inducing temporal summation) were measured using a constant current stimulator (Digitimer Ltd, Welwyn Garden City, UK) and two surface electrodes attached below the lateral malleolus. Bursts of five 1 ms square wave impulses within 25 ms (perceived as one single stimulus) were delivered with current intensity increasing by 0.5 mA until the sensation became painful (ESPT). For ERPT, the stimuli were repeated five times at a frequency of 2 Hz. Current intensity of all 5 stimuli was increased in steps of 0.5 mA until the last 2–3 stimuli were perceived as painful, indicating temporal summation threshold.

Heat pain detection and tolerance thresholds (HPDT and HPTT) and cold pain detection threshold (CPDT) were measured at the leg (L5-dermatome) and at the forearm (C6-dermatome) using a thermode (TSA II, Medoc, Ramat Yishai, Israel). All measurements started at 30.0 °C, the rate of temperature change was 1 °C/s. Subjects stopped the measurements by pressing a button when the warm sensation turned to pain (HPDT) or when the pain became intolerable (HPTT) or when the cold sensation started to become painful (CPDT). In any case, the measurements were stopped at a temperature of 50.5 °C for HPTT or 0 °C for CPDT, respectively. CPDT was dichotomized into patients reaching 0 °C without pain ("CPDT at limit") and patients who reported pain above 0 °C ("CPDT not at limit").

Conditioned pain modulation (CPM) was assessed using the cold pressor test as conditioning stimulus. Electrical train-of-five stimulation was delivered at an intensity 1.2 times stronger than the previously determined ERPT. This was used as test stimulus and its painfulness was rated by the subjects on a 0–10 NRS. After this rating, subjects immersed their contralateral hand into an ice-saturated water bath (1.5 ± 1 °C). Once the cold pain reached an intensity of 7 on the 0–10 NRS, the test stimulus was repeated at the same current intensity. Again, a pain rating of that test stimulus was obtained. The time until cold pain reached 7/10 was recorded. A decrease in pain rating of the test stimulus was considered a measure of CPM.

The normative values of all mentioned QST (except CPM) have been determined in a large sample of 300 healthy volunteers [9] and – with exception of CPDT – have also been shown to have acceptable test-retest reliability [10].

2.4. Outcome measures

Low-back pain intensity 2 h after drug intake was the primary outcome measure. NRS scores for pain in the supine and sitting position were recorded at baseline and in intervals of 30 min for up to 2 h after drug intake. Drug responders were defined as patients having ≥30% pain reduction after 120 min. The patients' global