PAIN® 154 (2013) 1413–1418

PAIN®

www.elsevier.com/locate/pain

Oxycodone alters temporal summation but not conditioned pain modulation: Preclinical findings and possible relations to mechanisms of opioid analgesia

Erica Suzan [a,b,*], Ayelet Midbari [b], Roi Treister [a,c], May Haddad [b,c], Dorit Pud [c], Elon Eisenberg [a,b]

[a] Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel
[b] Institute of Pain Medicine, Rambam Health Care Campus, Haifa, Israel
[c] Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa, Israel

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 1 January 2013
Received in revised form 11 March 2013
Accepted 19 April 2013

Keywords:
Analgesia
Conditioned pain modulation
Experimental pain
Oxycodone
Temporal summation

ABSTRACT

Opioid analgesia is mediated primarily by modulating (inhibiting and enhancing) pain mechanisms at the spinal and supraspinal levels. Advanced psychophysical paradigms of temporal summation (TS) and conditioned pain modulation (CPM) likely represent pain mechanisms at both levels. Therefore, the study of opioid effects on TS and CPM can shed light on their analgesic mechanisms in humans. The current randomized, double-blind study tested the effects of oxycodone on the magnitude of both TS and CPM in 40 healthy subjects.

TS was tested by measuring increments in pain intensity in response to 10 repetitive painful phasic heat stimuli. CPM was assessed by subtracting the response to a painful phasic heat stimulus administrated simultaneously with a conditioning cold pain stimulus from a painful phasic heat stimulus alone. These paradigms were tested before and at 60, 120, and 180 minutes after administration of a single oral dose of either oxycodone or an active placebo. Repeated-measures analysis of variance revealed significant effects of oxycodone, but not placebo, on the magnitude of TS ($F = 7.196$, $P < .001$). Pairwise comparisons revealed that relative to baseline, TS was significantly reduced at 60 minutes ($P = .008$) and at 180 minutes ($P = .017$) after oxycodone administration. In contrast, no significant effects of either oxycodone ($F = 0.871$, $P = .458$) or placebo ($F = 2.086$, $P = .106$) on the magnitude of CPM were found. These results suggest that under the current experimental conditions, oxycodone exerted spinal, rather than supraspinal, analgesic effects. Furthermore, compared with CPM, TS seems more suitable for studying the mechanisms of opioid analgesia in humans.

1. Introduction

It is generally considered infeasible to routinely access the site (brain vs spinal cord) in humans at which opioids produce analgesia. However, recent advanced methods of dynamic psychophysics allow, at least indirectly, the study of phenomena that are believed to represent spinal and supraspinal pain mechanisms. This is achieved by using the paradigms of temporal summation (TS) and conditioned pain modulation (CPM), which presumably originate from the spinal and supraspinal levels of the central nervous system, respectively [7,14,20,24]. TS constitutes an increased pain response to repetitive (>0.3 Hz) or prolonged nociceptive stimulation at C-fiber–activating intensity. It is regarded as the experimental correlate of the electrophysiological "wind-up" phenomenon in the superficial dorsal horn neurons of the spinal cord [20,23,24]. CPM refers to a phenomenon in which the response to a given painful test stimulus is attenuated by another conditioning painful stimulus simultaneously administered in a remote area of the body [16]. CPM is believed to be the human equivalent of diffuse noxious inhibitory control (DNIC) in animals [33].

Evidence suggests that a variety of chronic pain conditions may be associated with impaired TS or CPM. For example, temporomandibular disorder and fibromyalgia have been linked to increased TS [18,29], whereas post-thoracotomy pain syndrome, irritable bowel syndrome, headache, chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder were found to be associated with reduced CPM [28,34]. Therefore, our understanding of the degree to which analgesic drugs, including opioids, affect TS and CPM, can

* Corresponding author. Address: Institute of Pain Medicine, Rambam Health Care Campus, P.O. Box 9602, Haifa 31096, Israel. Tel.: +972 4 854193; fax: +972 4 8542880.
E-mail address: Erica.dol@gmail.com (E. Suzan).

0304-3959/$36.00
http://dx.doi.org/10.1016/j.pain.2013.04.036

have clinical relevance for their use in treating various clinical conditions.

Regardless of the debate on their use for chronic nonmalignant pain, opioids remain a cornerstone in treating moderate to severe acute and cancer pain [2]. Opioids exhibit their analgesic effect by acting primarily on the central nervous system, at both the spinal and supraspinal levels [3,4,26,32]. At the spinal level, opioids act at both pre- and postsynaptic sites to inhibit nociceptive transmission in the superficial dorsal horn [6]. At the supraspinal level, opioids enhance pain modulation by activating the descending inhibitory pathways [12]. Indeed, animal studies have demonstrated that both wind up and DNIC are affected by opioids [14–17]. In humans, the effects of opioids on TS and CPM have also been tested. However, these studies have yielded inconclusive results, with some indicating a decline in TS or CPM after opioid administration [9,11,25,31], whereas others suggest the opposite [1,5]. Additional studies, both animal and human, have claimed no effect of opioids on either of the 2 phenomena [8,27]. Although TS and CPM have been studied separately in humans, to the best of our knowledge, they have not been tested together in a single population of subjects. Hence, the current study aimed to test the effects of the administration of a single oral dose of oxycodone on the magnitude of both TS and CPM in 1 group of healthy subjects, using a randomized, double-blind, placebo-controlled design.

2. Methods

2.1. Subjects

The study population consisted of 40 healthy paid subjects who were enrolled in the study after meeting the following inclusion criteria: (1) free of pain of any type; (2) no medication use (except for oral contraceptives); and (3) ability to understand the purpose and instructions of the study. Exclusion criteria were (1) pregnancy; (2) allergy to opioids; (3) history of substance abuse; and (4) a diagnosis of Raynaud syndrome. Participants were not allowed to consume alcohol or take any drugs except for the study medication and were instructed to fast for at least 6 hours before the trial.

2.2. Instruments

The following devices were used in the current study: (1) The Thermal Sensory Analyzer (TSA 2001-II; Medoc, Ramat Yishai, Israel), used to administer painful thermal stimuli, is a Peltier surface stimulator of 30 × 30 mm attached to the ventral surface of the left forearm with a Velcro strap and maintained at a baseline temperature of 32°C. (2) The Cold Pressor Test (CPT) apparatus (Cooling Bath CBN 8-30 Lab equipment; HETO, Allerod, Denmark) is a temperature-controlled water bath with a maximum temperature variance of ±0.5°C, which is continuously stirred by a pump.

2.3. Pain measures

2.3.1. Temporal summation

Using the TSA thermode at a starting temperature of 32°C, 10 painful phasic heat stimuli (each lasting 1 second) were applied with an interstimulus interval of 3 seconds. The end temperature was increased by an additional 6°C (from 41°C to 47°C). The increasing and decreasing temperature rate was 10°C/s. The subjects were asked to verbally report the level of pain intensity experienced, using a 0–100 numeric pain scale (NPS), after administration of the first, fifth, and 10th heat stimuli. TS was calculated as the difference between the pain scores obtained after the stimulus that produced the peak effect and the pain scores obtained after the first stimulus. TS was assessed in accordance with the TS test paradigm previously used in our laboratory [10].

2.3.2. Conditioned pain modulation

To induce CPM, heat stimulation was considered the test pain, whereas cold stimulation was used as the conditioning stimulation.

2.3.2.1. Test pain. The TSA 2001-II thermode was attached to the skin above the left thenar eminence. Five heat pain stimuli at 47°C (starting from 37°C at an increasing and decreasing rate of 10°C/s), each lasting 4 seconds, were delivered with an interstimulus interval of 12 seconds. The subjects were asked to verbally report the pain intensity experienced at the end of each stimulus, using a 0–100 NPS.

2.3.2.2. Conditioning stimulation. The subjects' right hand was immersed in the CPT bath (at 12°C) for 30 seconds. CPM was assessed according to the CPM test paradigm previously used in our laboratory [30] and was conducted as follows: First, heat stimulation was delivered, and the subjects were instructed to verbally report their level of pain intensity induced by the first stimulus, using a 0–100 NPS. This was considered the baseline test pain. Then the subjects were requested to immerse their right hand in the CPT bath (at 12°C). After 15 seconds of immersion, while their hand was still in the CPT bath, the second test stimulation was delivered and their pain intensity was recorded again (test 1). The subjects were asked to remove their hand from the CPT bath 15 seconds later (test 2), for a total time of 30 seconds of hand immersion in the CPT bath. Upon hand removal, the subjects were asked to report the intensity of the pain caused by immersing their hand in the CPT bath (conditioning induced pain intensity), using a 0–100 NPS. Two additional heat stimulations were delivered at 15 and 30 seconds after removal of their hand from the CPT bath (test 3 and test 4, respectively). The maximal difference between heat pain intensity reported at baseline (test pain) and in response to the subsequent stimuli (conditioned test pain) was calculated and considered the CPM score.

2.4. Adverse events

Subjects were requested to self-report any adverse events (AEs) that they experienced during the 180 minutes after drug/placebo administration.

2.5. Study medications

Oxycodone hydrochloride (Rafa Laboratories Ltd., Jerusalem, Israel) was administered at a dose of 0.3 mg/kg. Additionally, an active placebo, chlorpheniramine maleate (0.033 mg/kg), was used to mimic the adverse effects of opioids and thus to reduce the risk of unblinding the study medication. All study medications were administered orally in the form of solutions and were diluted with 50 mL of tap water and 5 mL of grape-flavored syrup.

2.6. Study design

This double-blind, crossover, prospective study was approved by the Ethics Committee of Rambam Health Care Campus in Haifa, Israel. All subjects received a detailed explanation of the study design, the study medications, and the pain tests. After signing a written informed consent, the subjects received a short training session to familiarize them with the devices and the perceived sensations. The training tests were not used in the statistical analyses. Thirty minutes later, a second round of pain tests was conducted and regarded as the baseline measurement. Study medications consisted of an identical-looking liquid form of either oral oxycodone hydrochloride or the active placebo prepared by a nurse not involved in the study. Medications were administered