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Offset Analgesia and The Impact of Treatment with Oxycodone and Venlafaxine

- A Placebo Controlled, Randomized Trial in Healthy Volunteers

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Short running title: Offset analgesia - oxycodone and venlafaxine effect

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Abstract: Offset analgesia (OA) is a pain-modulating mechanism described as a disproportionately large decrease in pain intensity evoked by a discrete decrease in stimulus temperature. The role of the opioidergic, serotonergic and noradrenergic systems on OA remains unclear. The aim of the present study was to evaluate whether OA is modulated by an opioid (oxycodone) and a serotonin and noradrenaline reuptake inhibitor (venlafaxine) in terms of psychophysical assessments.

In this randomised, double-blinded, placebo-controlled cross-over study, 20 healthy male participants (mean age: 24.6±2.5 years) received 10 mg oxycodone, 37.5 mg venlafaxine or placebo twice daily for five days in three periods. OA was induced by noxious thermal stimulation on the forearm at baseline and last day of treatment. A control session of constant stimulus intensity was included for comparison.

OA magnitude was unaffected by oxycodone and venlafaxine (P=0.20 and P=0.90, respectively). Oxycodone affected the control paradigm where a decreased rating of pain intensity was observed compared to placebo (P=0.001).

OA could not be modulated by oxycodone or venlafaxine and may be a robust phenomenon in healthy volunteers and not suitable for exploring pharmacological mechanisms of analgesia in humans.

Keywords: offset analgesia, oxycodone, venlafaxine, pain modulation

The trial was registered at EU Clinical Trials Register (EudraCT number: 2013-000170-30).

Modulation in central nervous system pain processing due to nociceptive input plays an important role in chronic pain states. Pain is modulated by complex endogenous systems that facilitate and inhibit painful stimuli. One pain-modulating mechanism is offset-analgesia (OA) which is described as a disproportionately large decrease in pain intensity evoked by a discrete decrease in stimulus temperature[1]. OA has been investigated in a variety of different experimental set-ups in healthy volunteers to explore the underlying mechanisms[2,3] and in chronic pain patients where OA was found to be abnormal [4–6].

Results from several fMRI studies have demonstrated that the pain-modulating regions of the brainstem are activated during assessment of OA in healthy individuals[7–10]. Many of these regions, such as the periaqueductal grey, are involved in opioidergic analgesia. Moreover, areas consistent with serotonergic and noradrenergic nuclei were activated during assessment of OA[8]. Serotonin and noradrenaline reuptake inhibitors (SNRI) like e.g. venlafaxine modulate the serotonergic and noradrenergic pathways simultaneously, likely by involvement of enhancement of descending pain inhibitory activity. Thus, theoretically, OA may be modulated by SNRIs and opioids.

Pharmacological modulation of OA has been investigated but the magnitude of offset analgesia was not altered by tapentadol, morphine, remifentanil, naloxone or ketamine in either healthy volunteers or patients [2–5]. However, methodological challenges, as e.g. few pain ratings over time, lack of control paradigm or the use of absolute changes instead of relative changes in pain scores, may lead to inconclusive results on the pharmacological modulation and the role of the opioidergic, noradrenergic and serotonergic systems on pain modulation remains unclear. Due to limitations in previous studies and the heterogeneous picture about the suitability of OA in analgesic drug studies, reassessment and detailed analysis of the method is warranted.

It was hypothesized that an opioid (oxycodone) and an SNRI (venlafaxine) would increase OA as compared to placebo. To test this hypothesis, the aim of the present study was to evaluate the effects of oxycodone and venlafaxine on OA in terms of relative changes in psychophysical assessments and compare the effects to a control paradigm.

Methods

A double-blinded, randomised placebo-controlled, cross-over study was performed. The study was designed and conducted to investigate different mechanisms of oxycodone and venlafaxine. Other endpoints have previously been published[11,12]. The study was approved by The North Denmark Region Committee on Health Research Ethics and the Danish Medicines Agency (N-20130011 and EudraCT number: 2013-000170-30) and registered at EU Clinical Trials Register.

The study was carried out according to the principles of Good Clinical Practice (GCP) and monitored by the GCP unit at Aalborg and Aarhus University Hospitals, Denmark. Recommendations of the Helsinki declaration (2013) were followed. Data were collected in the research laboratories at Mech-Sense, Department of Gastroenterology, Aalborg University Hospital, Denmark, from November 2013 to December 2014. Written informed consents were obtained from participants before the study procedures.

Twenty healthy male participants were randomized to five-day, three-arm treatment with oxycodone, venlafaxine or placebo in a double-blinded, randomized sequence, in three periods. Each period began on day 1 with baseline OA assessments and ended on day 5 with new OA assessment. Between treatments, a washout period of minimum 7 days was inserted. Inclusion criteria for the study were: 1) age between 20 and 35 years; 2) ability to read and understand Danish; 3) Scandinavian origin; 4) clinical examination ruling out any diseases and 5) male.

Exclusion criteria were: 1) known allergy towards study medication; 2) participation in other studies within two weeks prior to first visit; 3) expected need of medical/surgical treatment during the course of the study; 4) history of psychiatric illness; 5) history of persistent or recurring pain conditions; 6) history of substance abuse; 7) family history of substance abuse; 8) use of any analgesic medication within 24 hr prior to and during the study; 9) use of prescribed medicine and/or herbal medicine and 10) need to drive motor vehicle within the treatment periods.

Study medication

Oxycodone, venlafaxine and placebo were administered orally as extended release tablets and capsules, respectively. The tablets and capsules were further encapsulated and masked so all administered capsules looked identical. These capsules were produced and packed by the Hospital Pharmacy, Central Denmark Region, Denmark, where a randomization list was generated bywww.randomization.com. Participants and study personnel were blinded to interventions.

The dosages for oxycodone were 10 mg extended release, and for venlafaxine the dosages were 37.5mg extended release. These are the lowest clinical, therapeutic dosages (pro.medicin.dk). A steady-state plasma concentration is reached within 24 hr for oxycodone and within 72 hr for venlafaxine treatment. Hence, 4 days of treatment was considered appropriate. On study day 1 and day 5, medications were administered once daily (QD), and on study day 2-4 twice daily (BID); thus, a total of eight doses were administered.

Experimental procedure

Prior to study enrolment, a screening session was performed to familiarize participants with the experimental procedures.

The contact heat stimulation was induced by using the PATHWAY Pain and Sensory Evaluation System (Medoc Ltd, Ramat Yishai, Israel). The standard thermode (contact heat-evoked potential stimulator) stimulated a surface area of 6.6 cm^2 using a computer-controlled OA stimulus paradigm. The temperature was increased from 35ºC, with 1.5ºC/second to determine individual pain tolerance thresholds ($PTT_{individual}$). The PTT was determined three times, and the average temperature was used in the following OA/CS stimulation paradigms.

The OA paradigm consisted of three contiguous phases (Figure 1): T1) an initial noxious stimulus temperature ($PTT_{individual}$ – 1°C, 5-sec. duration); T2) a 1°C increase to a second temperature ($PTT_{individual}$, 5-sec. duration), and then T3) a decrease back to the temperature used in T1 ($PTT_{individual}$ – 1 °C, 20-sec. duration). After T3, the temperature decreased back to baseline (1.5 ºC/sec.). The control paradigm consisted of a constant stimulus (CS) paradigm ($PTT_{individual}$ - 1°C for 30 sec.).

During the contact heat stimulation, the participants were asked to evaluate and report the pain intensity continuously using Medoc's computerized scale. The participants were instructed to evaluate both innocuous and noxious sensations on a modified visual analogue scale (VAS). VAS scores were 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, 8 = pain of medium intensity, 9 = intense pain and 10 = unbearable pain [13].

The OA and CS paradigms were performed in randomized order. After the OA/CS paradigms had been performed at baseline, drugs were administered twice daily for five consecutive days. Hereafter, the OA/CS paradigms were repeated.

Statistical analysis

The results are listed as mean values with standard deviations (SD) unless otherwise indicated. Before statistical analyses, the following parameters were calculated for each participant: Peak (maximum VAS rating within T2); Nadir (minimum VAS rating within T3); ΔVAS (decrease in pain ratings that occurred between peak and nadir (Peak – Nadir)) and $\Delta VAS_{corrected}$ as a measure of OA magnitude (ΔVAS normalized with respect to peak value ((ΔVAS/peak)*100)) (Fig. 1).

Before further statistical analysis, average baseline values were calculated, as a mean of three single values, for each participant. Data were analysed using repeated measures regression with treatment as random effect using the "xtmixed command" in Stata. Sample size calculation was based on previous studies in healthy volunteers. However, as no previous study has investigated venlafaxine effect on OA, the calculation was an estimate. Stata 12.1 (Stata Corporation, College Station, Texas, USA) was used in the statistical analysis. *P*-values <0.05 were considered significant.

Results

Twenty opioid-naïve, male participants with mean age of 24.6±2.5 years were included. Due to technical issues, baseline values were not assessed during all sessions for two participants. In these two cases, the average baseline was calculated based on two measures instead of

three. Thus, complete data were available for analysis from all twenty participants. Mean $PTT_{individual}$ used for the OA and CS paradigm was 48.8±1.2°C.

The effect of oxycodone and venlafaxine on OA

Results on OA endpoints are presented in Table 1. The average magnitude of OA ($\Delta VAS_{corrected}$) at baseline was 68.3±19.0%. There were no significant differences in the magnitude of OA after treatment with either oxycodone or venlafaxine compared to placebo (*P*=0.20 and *P*=0.90, respectively). Moreover, no other OA endpoints (Peak, Nadir, ΔVAS) were affected by oxycodone or venlafaxine compared to placebo (Peak: *P*=0.32 and *P*=0.39; Nadir: *P*=0.23 and 0.81; ΔVAS: *P*=0.40 and 0.88, respectively).

The effect of oxycodone and venlafaxine on control paradigm

Results on the control paradigm are presented in Table 1. The average decrease in pain rating during the control session at baseline was 29.8±16.8%. This decrease in pain rating was unaffected by oxycodone and venlafaxine compared to placebo (*P*=0.30 and *P*=0.41, respectively). Oxycodone treatment resulted in a reduced peak pain rating (VAS) in the control paradigm compared to placebo (-11.4±15.5, *P*=0.001) whereas no effect of the venlafaxine treatment was found (-2.0±12.0, *P*=0.31).

Discussion

In the present study, no modulatory effects of oxycodone and venlafaxine on OA were found, and thus involvement of central mechanisms via modulation by opioidergic, serotonergic or noradrenergic pathways could not be demonstrated.

The brain regions associated with pain perception during OA are known to be rich in opioid receptors[14]. Thus, it was hypothesized that modulation of OA is dependent on the opioidergic system. This could, however, not be confirmed by results from the present study. Supporting this, it has been shown that OA persists despite administration of naloxone[2]. Furthermore, results from previous studies indicate that OA was unaltered after administration of the opioid agonists morphine, hydromorphone and remifentanil[2,5,15]. Together, these findings defy that the opioidergic system is involved in the modulation of OA. Other pharmacological agents have also been tested in the OA paradigm. For example, it has been demonstrated that ketamine infusion did not affect OA in healthy volunteers or patients[3,5]. Ketamine antagonizes the N-methyl-D-aspartate receptors (NMDA) within the spinal cord, consequently decreasing ascending input to higher order structures[16]. Thus, it appears that the underlying mechanisms of OA are independent on NMDA receptors as well as the opioidergic, serotonergic and noradrenergic pathways. However, it cannot be excluded that OA is dependent on these pathways as several factors may affect outcomes and lead to misleading conclusions. In the OA testing paradigm, different parameters can reveal changes in pain sensitivity as well as in the magnitude and duration of OA. ΔVAS, also known as the magnitude of OA[2,17,18], is the test parameter which classically contains information about the OA modulation as it comprises information of the peak- and the nadir values. In this study, the ΔVAS was normalized ($\Delta VAS_{corrected}$) with respect to peak value in order to circumvent a potential artefact arising from variability in peak VAS scores between individuals [3]. This normalized value is probably more robust and suitable to detect subtle pharmacological modulations of OA due to reduced variability. Another factor that may affect the outcome is the study population. For example, one previous study included a rather small number of patients and type I error cannot be excluded[5]. Additionally, the estimated OA effect may be affected by adaptation. Thus, a control session with a constant stimulus paradigm was

included in the present study, and it was demonstrated that pain ratings decreased approximately 30% ($\Delta VAS_{corrected}$) in a constant stimulus paradigm (CS) as an indication of adaptation to the stimulation intensity. Heat stimuli have been shown to primarily affect C-fibres[19]. Peak pain intensity score was reduced in the control paradigm after treatment with oxycodone, indicating analgesia on the tonic thermal stimulation due to attenuation of C-fibre activated pain by the opioid [20].

In the clinic, venlafaxine does not exert a robust effect on depression until after 2-4 weeks of treatment[21]. However, effects on venlafaxine on the pain system have been observed already after a few days[11,22]. Despite this, no analgesic effect of venlafaxine was found in the present study indicating that venlafaxine at the current dose does not affect acute C-fibre-activated pain. None of the study treatments affected adaptation in the control paradigm, and therefore our results suggest that opioidergic, serotonergic and noradrenergic mechanisms are not involved in OA or adaptation. The results indicated that adaptation may account for 40% of the OA effect (CS ΔVAS=23.9 compared to OA ΔVAS=57.9), indicating the importance of including a control paradigm in future studies to distinguish between OA and adaptation. Most studies have used thermal stimulus to evoke OA[23] but one study induced OA with a visceral pressure stimulus, indicating that OA is not specific to thermal pain[24]. Since no gold standard exists, small differences in protocols are present [23] and more studies are needed for further evaluation of OA mechanisms and specificity.

In previous studies, the classical VAS has been used. The classical VAS is a 10-cm continuous line with two extremes as endpoints only evaluating painful sensation going from no pain to the most intense pain imaginable[25]. Thus, the nadir cannot be less than zero (no pain) and hereby the OA magnitude cannot be influenced by innocuous sensations. In contrast, the pain scale used in the present study was a modified VAS, which has been tested

for reliability and robustness in a variety of pharmacological experiments in healthy participants and in different patient groups[13] and also previously used in the OA testing paradigm[26]. This version included both the innocuous and noxious sensory ranges. However, despite a wider dynamic range, the present study could not demonstrate any treatment effects on OA.

As this study was conducted in healthy volunteers, it cannot be excluded that the opioidergic system and the serotonergic and noradrenergic systems are involved in OA in patients with chronic pain, as different pharmacological effects may be found in the sensitized pain system[27] and there are indications for decreased OA in neuropathic pain patients[5,23]. Studies have also investigated if offset analgesia was disrupted during sensitized states in healthy volunteers. The magnitude of OA remained intact after both capsaicin-heat and heat only sensitization in zones of both primary and secondary mechanical allodynia[17]. Moreover, it was recently demonstrated that OA is not modulated by exercise[28]. One study found that conditioned pain modulation (CPM) may modulate OA non-pharmacologically as an additive effect of CPM and OA on pain inhibition was found in healthy males [29]. However, study limitations as for example group-averaged pain ratings obtained from 6 predefined time points, and OA magnitude calculated in reference to constant (at T3 time point) and not to corrected to T2 temperature may have affected results and further studies are warranted to confirm this relationship.

In conclusion, the present study in a homogeneous group of healthy volunteers, using the $\Delta VAS_{corrected,}$ a VAS with a wider dynamic range and a control paradigm for evaluation of adaption, found no effect of oxycodone or venlafaxine on OA. As it appears that pharmacological agents do not affect the part of the pain modulatory behaviour as revealed

by OA, OA may be a robust phenomenon in healthy volunteers and unsuitable for exploring pharmacological mechanisms of analgesia in healthy volunteers.

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Figure legends:

Figure 1. Graph depicting the offset analgesia and control stimulus paradigms

The offset analgesia (OA) paradigm (black, dashed line) consists of three phases. Initially, the temperature increases and stabilizes to a plateau previously defined (T1). Then, the temperature increases 1°C (T2) whereafter temperature decreases to T1 level (T3). The control stimulus (CS) paradigm (grey line) is single phasic where the temperature increases and stabilizes to a plateau, which is kept until the end of stimulation. The corresponding pain intensities for OA (red, dashed line) and CS (blue line) are illustrated. Also depicted (triangles) are Peak (maximum VAS rating within T2); Nadir (minimum VAS rating within T3) and ΔVAS (decrease in pain ratings that occurred between peak and nadir (Peak – Nadir)). $\Delta VAS_{corrected}$ is not depicted but used in the analysis as a measure of OA magnitude ((ΔVAS/Peak)*100)..

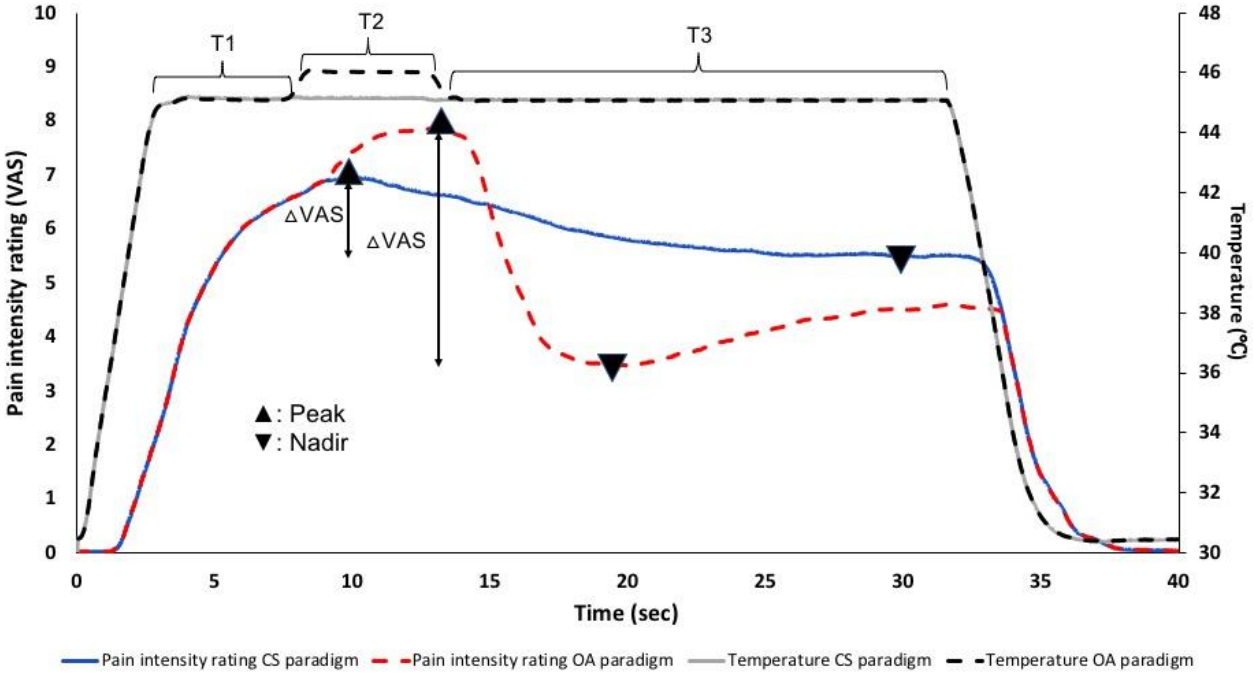

Table 1. Pain perception endpoints during OA and CS paradigms.

	OA paradigm			
	Average baseline	**Placebo**	**Oxycodone**	**Venlafaxine**
Peak	84.4 (9.4)	84.2 (10.3)	81.7 (13.8)	82.0 (12.3)
Nadir	26.5 (16.0)	33.4 (25.0)	26.2 (22.8)	32.0 (20.7)
ΔVAS	57.9 (17.8)	50.9 (25.4)	55.6 (21.7)	50.0 (21.4)
$\Delta VAS_{corrected}$	68.3% (19.0)	60.3% (29.4)	69.3% (25.5)	61.2% (26.0)
	CS paradigm			
	Average baseline	**Placebo**	**Oxycodone**	**Venlafaxine**
Peak	79.2 (9.5)	81.2 (11.8)	67.8 (15.7)*	77.2 (14.1)
Nadir	55.2 (14.5)	56.2 (19.6)	51.7 (19.1)	49.4 (25.5)
ΔVAS	23.9 (15.3)	25.0 (21.3)	16.1 (18.6)	27.8 (24.0)
$\Delta VAS_{corrected}$	29.8% (16.8)	30.1% (23.3)	22.2 % (24.5)	36.4% (29.3)

P <0.05 considered significant: * significant difference between active treatment and placebo. *P*-value. Peak (maximum VAS rating within T2); Nadir (minimum VAS rating within T3); ΔVAS (decrease in pain ratings that occurred between peak and nadir (Peak – Nadir)) and $\Delta VAS_{corrected}$ as a measure of OA magnitude (ΔVAS normalized with respect to peak value ((ΔVAS/peak)*100)).