Pain 139 (2008) 431–438

PAIN

www.elsevier.com/locate/pain

Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain – New perspective of opioid-induced hyperalgesia

Kerstin Carlin Ram [a], Elon Eisenberg [b,c], May Haddad [b], Dorit Pud [a,*]

[a] *Faculty of Social Welfare and Health Sciences, University of Haifa, Mount Carmel, Haifa 31905, Israel*
[b] *Pain Relief Unit, Rambam Medical Center, Haifa, Israel*
[c] *The Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Israel*

Received 25 January 2008; received in revised form 12 May 2008; accepted 22 May 2008

Abstract

Opioids can elicit unexpected changes in pain sensitivity, known as opioid-induced hyperalgesia (OIH). The aim of this study was to explore whether OIH exists in patients with chronic pain treated with oral opioids (OP) versus non-opioid (NOP) analgesics. The sensitivity to cold pain and the magnitude of diffuse noxious inhibitory control (DNIC) were evaluated in 73 OP and 37 NOP treated patients. Pain threshold, intensity and tolerance in response to the cold pressor (1 °C) were measured. DNIC was tested by co-administrating conditioned heat stimulation (47 °C) to the left forearm and a conditioning stimulation of 12 °C for 30 s to the right hand. The results showed no differences between the two groups in any of the cold pain measures. In contrast, the magnitude of DNIC was significantly larger in the NOP than in the OP treated patients ($p = 0.003$). A gender based analysis showed a significant difference in DNIC between OP and NOP treated men only. However, a mixed model ANOVA demonstrated a significant effect of treatment (OP versus NOP) ($F = 5.928$, $p = 0.017$) rather than gender on DNIC. A regression analysis showed that opioid dosage and treatment duration had a significant negative effect on the magnitude of DNIC in OP treated men ($\beta = -2.175$, $p = 0.036$ and $\beta = -2.061$, $p = 0.047$, respectively). In conclusion, oral opioids usage for the treatment of chronic pain does not result in abnormal sensitivity to cold pain, but seems to alter pain modulation. The use of 'advanced' psychophysics tests such as evaluation of DNIC can help understanding the phenomenon of OIH.

Keywords: Cold pressor test; Diffuse noxious inhibitory control (DNIC); Descending analgesia; Hyperalgesia; Gender

1. Introduction

It is well accepted that opioids are the most efficacious analgesics for the treatment of moderate to severe pain. However, growing evidence shows that opioids can elicit unexpected changes in pain sensitivity, resulting in opioid induced hyperalgesia (OIH) both in animals [4,5,27,28,40,41,44] and in humans [7,11,18,21]. In humans, much of this evidence is based on studies on intraoperative infusions of short-acting opioids, (i.e., fentanyl or remifentanil) [7,11,18,19]. Interestingly, opioid addicts also show alterations in pain perception [10,13,32]. At the same time, little is known of this phenomenon in patients with chronic pain who are treated with opioids. Two large studies failed to show evidence of OIH: Fillingim et al. [15] examined 240 patients with chronic back pain, classified as opioid and non-opioid users and showed no differences between the groups with regard to the back pain severity and to experimental ischemic pain tolerance. In another recent study we found no differences in threshold pain for punctuate,

* Corresponding author. Tel.: +972 4 8288006; fax: +972 4 8288017.
E-mail address: doritpud@research.haifa.ac.il (D. Pud).

0304-3959/$34.00
doi:10.1016/j.pain.2008.05.015

pressure and heat as well as the intensity of suprathreshold heat pain in opioids compared to non-opioids treated patients [34]. In contrast, two small human studies support the concept of OIH in patients with chronic pain: one early report of 4 cases suggested that chronic non-malignant pain was exacerbated by chronic administration of opioids, a phenomenon that was reversed by cessation of opioids use [1]. Another preliminary prospective study in 6 patients showed that they became hyperalgesic to cold but not to heat pain after 4 weeks of morphine treatment compared to baseline [9]. However, no firm conclusions could be drawn from these two studies due to the very small sample size.

The paradoxical phenomenon of OIH can be related to the altered balance between pro-nociceptive and anti-nociceptive (i.e., endogenous inhibitory modulation) processes [6,28,29]. The latter is commonly evaluated by the 'diffuse noxious inhibitory control' (DNIC) test paradigm [23]. Previous reports showed that morphine blocks DNIC effects in rats [2,3] and in healthy humans [25] in a naloxone reversible fashion [24,42].

Based on these findings we hypothesized that if OIH is indeed a result of opioid treatment in patients with chronic pain, it might be related to opioids' capacity to block DNIC. This study is aimed to explore in a controlled fashion if (1) oral opioid treatment results in a paradoxical response to cold pain in patients with chronic pain, as compared to non-opioid analgesic treatment and (2) the magnitude of DNIC differs between these two groups of patients.

2. Methods

2.1. Patients

The study population consisted of patients with either cancer or non-cancer-related pain who were referred to the Pain Relief Unit at Rambam Medical Center in Haifa, Israel for pain control between September 2006 and September 2007. The patients were enrolled in the study after meeting the following criteria: (1) adults (>18 years of age); (2) ability to communicate and understand the purpose and instructions of the study; (3) presence of either chronic non-malignant or cancer-related pain for at least three months; (4) use of analgesic medications, either opioids or other analgesics including non-steroidal anti-inflammatory drugs (NSAIDs). Non-opioid treated patients were selected as a control group because they resembled the study group in many ways and therefore reduced any potential bias that might have been associated, for example, with a control group of healthy subjects. Exclusion criteria were (1) pregnancy; (2) evidence of peripheral neuropathy per history or clinical examination; (3) diabetes; (4) pain involving the upper extremities; (5) treatment with repeated injections, infusions, or spinal opioids. The study was approved by the institutional Ethics Committee. Written informed consent was obtained from all patients. All tests were conducted in the morning, within several hours following the morning dose of the analgesic drugs.

2.2. Instruments

2.2.1. Assessment of pain history and treatment

Patients who were willing to participate in the study underwent an initial evaluation which included: (a) a study questionnaire on demographic data, diagnosis, duration of the painful condition, consumption of analgesics with special emphasis on the exact dosage, and duration of treatment; (b) measurements of the average and worst pain intensity that patients felt during the week prior to referral using a 10-cm blank visual analogue scale (VAS).

2.2.2. Assessment of cold pain perception

The cold pressor test (CPT) apparatus (Heto CBN 8-30 Lab equipment, Allerod, Denmark) is a temperature-controlled water bath with a maximum temperature variance of ± 0.5 °C, which is continuously stirred by a pump. Subjects were asked to place their right hand in the CPT (1 °C) in a still position with their fingers spread wide apart, according to the standard protocol [43]. A stopwatch was simultaneously activated, and subjects were requested to maintain their hand in the cold water for as long as they could. A cut-off time of 180 s was set for safety reasons. Subjects were instructed to indicate the exact point in time when the cold sensation began to elicit pain. This time until the pain was first perceived was defined as the threshold of cold pain (s). Immediately after hand withdrawal, subjects were asked to mark their maximal pain intensity on a 0–100 visual analogue scale (VAS), where 0 represents 'no pain' and 100 represents the 'worst pain one can imagine.' The latency of intolerability (spontaneous hand removal) was defined as pain tolerance (s). Tolerance for subjects that did not withdraw their hand for the entire 180 s was recorded as 180 s.

2.2.3. Assessment of DNIC

In order to induce DNIC effect, heat stimulations were given and considered as the 'test stimulation' (or 'conditioned' stimulation), whereas cold stimulation was used as a 'conditioning' stimulation.

Test stimulation: A TSA thermode of 30 × 30 mm (Medoc TSA-2001 device Israel) was attached to the skin above the left thenar eminence. Four heat pain stimuli of 47 °C (starting from 37 °C in an increasing and decreasing rate of 10 °C/s), each lasting 4 s, with inter-stimulus interval of 12 s were delivered. After each stimulus the patient was asked to report the pain intensity he or she felt, using a 0–10 numeric pain scale (NPS). The NPS was chosen because patients were required to make rapid rating of pain intensity during the test stimulation, with one hand occupied by the CPT.

Conditioning stimulation: The right hand was immersed into the CPT (12 °C) for 30 s.

The DNIC test paradigm was the following: first heat stimulation was delivered and the patients verbally reported the level of pain intensity (NPS) at the point when the temperature reached 47.0 °C. This was considered as 'baseline test stimulation' (baseline). Patients were then asked to immerse their right hand into the CPT. Following 15 s of immersion, while the hand was still in the CPT, the second test stimulation was delivered and pain intensity was recorded again (test 1). Patients were asked to remove their hand from the CPT 15 s later (with total time of hand immersion in the CPT of 30 s).

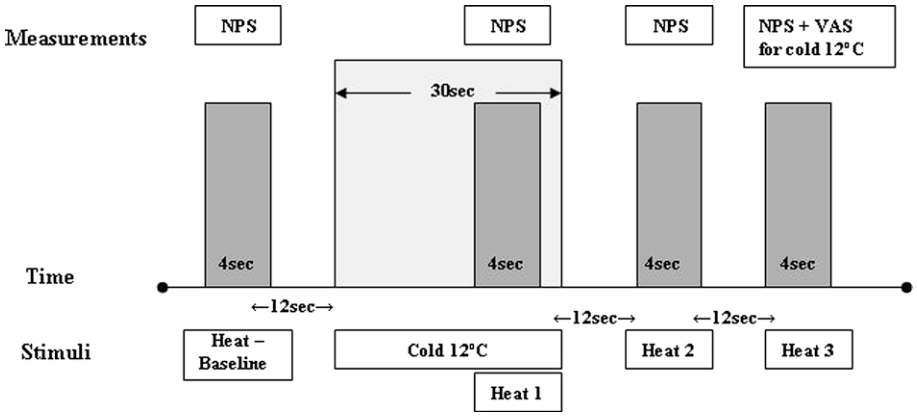

Fig. 1. DNIC test paradigm (see text). NPS, Numeric Pain Scale; VAS, Visual Analogue Scale.

Two additional heat stimulations were conducted 15 and 30 s subsequent to the removal of the hand from the CPT (test 2 and test 3, respectively). Upon completion of the session, patients were instructed to report the intensity of the pain (VAS) that was caused by immersing the hand in the CPT (conditioning induced pain intensity). The DNIC test paradigm is depicted in Fig. 1.

2.3. Statistical analysis

Statistical analyses were performed with SPSS version 14. Comparisons of demographic data and pain measures between the OP and the NOP treated groups were calculated using the Student's *t*-test. The magnitude of DNIC (ΔNPS) was determined by decreasing the baseline heat pain intensity from each of the subsequent pain intensity measurements during and after the conditioning stimulation (tests 1, 2, and 3).

All used opioids were converted to their equianalgesic dosages of oral morphine according to the previously published tables. Accordingly, oral oxycodone preparations were multiplied by 1.5 (e.g., 10 mg of oxycodone was converted to 15 mg of oral morphine); fentanyl were multiplied by 2; codeine was divided by 10; propoxyphene was divided by 3; tramadol was divided by 5 [35]. Notably, although not regarded as a 'classical' opioid, tramadol was included in the analyses because its analgesic effect is mediated in part by opioid mechanisms [33].

Mixed model ANOVA was used to determine the effect of the group (OP vs. NOP) and gender on heat pain ratings (baseline vs. test 1), while controlling the age as a covariate. Regression analysis was conducted to determine the contribution of opioid dosage and treatment duration to the magnitude of DNIC in OP treated males. Data are presented as means ± SD. Results were considered significant at the 0.05 level.

3. Results

3.1. Study population

Of the 466 patients who were referred for the study, 324 met the inclusion criteria, but 209 of them refused to participate in the study for various reasons (e.g., lack of time, fear of additional pain). Of the 115 patients who entered the study, 5 were unable to complete it. Thus, complete data for this study were available from a total of 110 patients (58 men and 52 women), with a mean of 49.5 ± 16.5 years of age, ranging from 19 to 76 years. Seventy-three patients (38 men, 35 women) received opioids (OP) whereas the other 37 patients (20 men, 17 women) received non-opioid (NOP) analgesics (Table 1). The medications consumed by the patients in each group are listed in Table 2. Of the 73 patients in the OP group, 55 had chronic non-malignant pain and 19 had cancer-related pain. All 37 patients in the NOP group suffered from chronic non-malignant pain. Notably, average and maximal pain intensities of both groups were above 6 and 8 (0–10 VAS), respectively, indicating that in spite of the administered treatment, pain intensity was moderate to severe. With the exception of age, no significant differences between the two groups were found in the duration of pain, duration of treatment, average and worst intensity of the spontaneous pain during the week prior to the examination (Table 1).

3.2. Cold pain perception

No significant differences between the OP and the NOP treated groups were found in the mean pain thresholds, pain intensities or tolerance to the CPT.

Due to the large variations in the treatment duration and in the opioid dosage (reflected by the wide range of equianalgesic doses of morphine), that might have 'hidden' a dose or treatment duration effect on the results of the CPT, a further analysis of the OP treated patients was conducted. The OP treated group was divided into two subgroups according to the median value of the morphine equianalgesic dosage and also according to the median treatment duration. Thus, four subgroups of OP treated patients were defined: low dose opioid group (LDO) that consisted of patients who received less than the equivalent to 45 mg of oral morphine; high

Table 1
Patients' characteristics in each of the two treatment groups (mean±SD)

	OP	NOP	t, p values
	$N = 73$	$N = 37$	
Gender (M/F)	38/35	20/17	
Age (year)			
Mean ± SD	52.6 ± 16.0	43.2 ± 15.9	$t = -2.922$, $p = 0.004$
Median (range)	57 (20–76)	43 (19–75)	
Pain duration (months)			
Mean ± SD	70.5 ± 85.7	93.7 ± 101.4	$t = 1.264$, $p = 0.209$
Median (range)	4–480 (43.5)	60 (4–370)	
Treatment duration (months)			
Mean ± SD	19.5 ± 28.8	16.9 ± 24.1	$t = -0.469$, $p = 0.640$
Median (range)	12 (0.5–180)	9 (0.5–120)	
Mean ± SD pain during the week prior to examination (VAS; 0–10)	6.6 ± 23.3	6.1 ± 2.4	$t = -1.090$, $p = 0.280$
Median (range)	7 (0–10)	6 (0–10)	
Worst pain during the week prior to examination (Mean ± SD VAS; 0–10)	8.3 ± 2.3	7.9 ± 2.1	$t = -0.822$, $p = 0.779$
Median (range)	9 (0–10)	8 (0–10)	
Equianalgesic opioid dosage = mg of oral morphine			
Mean ± SD	100.80 ± 166.46	–	
Median (range)	45 (3–1110)		

dose opioid group (HDO) with patients who received 45 mg of morphine or more; short-treatment duration (STD) of less than 12 months, and long treatment duration (LTD) of 12 or more months of opioid treatment. Yet, the results failed to demonstrate statistically significant differences in any of the cold pain measures between the LDO and HDO subgroups or between the STD and the LTD subgroups (Table 3).

3.3. Assessment of DNIC

3.3.1. Effect of treatment (OP versus NOP) and gender

Exposing the right hand to the conditioning stimulation of 12 °C for 30 s produced cold pain at intensities of 64.2 ± 28.8 and 59.9 ± 31.4 in the NOP and OP treated groups, respectively (VAS; mean ± SD; $p = 0.69$).

Mean ± SD baseline heat pain score recorded from the left thenar (before immersing the hand into the CPT) of the NOP group was 7.9 ± 1.7 (Table 4). The score dropped to 5.5 ± 2.2 after 15 s of immersion in the cold water (test 1). Fifteen and 30 s after removal of the hand from the CPT, heat pain scores were 5.8 ± 1.9 (test 2) and 5.7 ± 2.1 (test 3), indicating that maximal DNIC was demonstrated *during* the conditioning stimulation (test 1). Thus, the calculated maximal magnitude of DNIC was 2.4 ± 1.6. For this reason, all DNIC-related analyses were based on results obtained from baseline and test 1. Mean ± SD baseline test of the OP group was 7.1 ± 2.7. The other pain ratings were 5.7 ± 2.6, 5.6 ± 2.6 and 5.6 ± 2.6 (test 1, test 2 and test 3, respectively). The magnitude of DNIC (baseline versus test1) in this group was 1.4 ± 1.5. The magnitude of DNIC of the NOP treated group was significantly larger than that of the OP treated group ($t = 3.116$, $p = 0.003$; Fig. 2).

Due to the well-known difference in DNIC between men and women [17,22,31,37], we added a further analysis in which gender was also taken into account. How-

Table 2
Analgesic medications consumed by the two treatment groups

OP treated group		NOP treated group	
Drug (*n*)	Daily dose range (mg)	Drug (*n*)	Daily dose range (mg)
Oxycodone (*17*)	20–80	Diclofenac (*3*)	50–100
Morphine (*3*)	10–360	Etodalac (*18*)	400–1800
Tramadol (*21*)	50–400	Celecoxib (*2*)	200–600
Propoxyphene (*18*)	40–200	Ibuprofen (*4*)	400–800
Fentanyl (*13*)	25–375 μg/h	Paracetamol (*3*)	500–2000
Codein (*4*)	15–45	Dipyrone (*4*)	500–1500
		Indometacine (*1*)	200–600
		Etoricoxib (*7*)	60–240
Adjuvant drugs	Number of patients	Adjuvant drugs	Number of patients
Anti-depressants	18	Anti-depressants	12
Anti-convulsants	22	Anti-convulsants	4
Other	7	Other	8

Table 3
Cold pain perception (Mean ± SD) by groups

Group	Threshold (s)	Tolerance (s)	Intensity to 1 °C
Between group analysis: opioids vs. non-opioids			
OP ($n = 73$)	9.9 ± 7.0	22.8 ± 22.7	83.4 ± 19.8
NOP ($n = 37$)	10.1 ± 11.2	24.1 ± 30.6	86.0 ± 13.6
p value	0.957	0.822	0.414
Within (opioids) group analysis: low dose opioids vs. high dose opioids			
LDO ($n = 37$)	8. 8 ± 5.1	23.4 ± 27.6	80.7 ± 23.8
HDO ($n = 36$)	10.5 ± 8.2	22.3 ± 17.3	86.3 ± 14.7
p value	0.717	0.969	0.314
Within (opioids) group analysis: short vs. long opioids treatment duration			
STD ($n = 36$)	10.1 ± 5.5	21.7 ± 13.8	83.3 ± 16.7
LTD ($n = 38$)	9.7 ± 8.2	23.8 ± 28.8	83.4 ± 22.5
p value	0.82	0.68	0.99

OP, opioid treated group; NOP, non-opioid treated group; LDO, low dose opioids (less than the equivalent to 45 mg of oral morphine); HDO, high dose opioids (45 mg of morphine or more); STD, short-duration treatment (<12 months); LTD, long-duration treatment (12 months or more).

ever, in this study no significant differences were found between men and women in both the NOP (2.6 ± 1.5 versus 2.0 ± 1.7, respectively. $p = 0.233$) and the OP (1.2 ± 1.3 versus 1.6 ± 1.7, respectively. $p = 0.271$) groups in the magnitude of DNIC (ΔNPS) (Fig. 2). From a different perspective, men in the NOP group showed a significantly larger magnitude of DNIC as compared to men in the OP group ($t = 3.74$, $p = 0.001$). No significant differences between the OP and NOP groups were found among women (Fig. 2).These results show that DNIC is influenced by opioid treatment. However, since the age differed significantly between the two groups (see table 1) and the magnitude of DNIC was significantly larger within the NOP's men, we further analyzed the data using mixed model ANOVA. By this we attempted to determine the effect of the group (OP vs. NOP) and the gender on heat pain ratings (baseline vs. test 1) while controlling for the age as a covariate. The overall model showed a trend of significance ($F = 2.824$, $p = 0.096$). Specifically, the treatment group had a significant effect ($F = 5.928$, $p = 0.017$), gender failed to contribute to this effect ($F = 0.006$, $p = 0.937$) and age – although significant – was controlled ($F = 4.212$, $p = 0.043$).

We further analyzed the data using the same mixed model ANOVA as was used above in an attempt to determine the effect of the diagnosis (cancer vs. non-cancer patients) on heat pain ratings within the opioid treated group. Results showed that the diagnosis had no significant effect on the magnitude of DNIC ($p = 0.361$).

3.3.2. Effect of opioid dose and duration of treatment

As previously described, the OP treated group was further divided into two subgroups according to the opioid equianalgesic dose. No significant difference in the magnitude of DNIC was found between the LDO and the HDO. In contrast, when analyzed according to the duration of opioid treatment, a trend of significance in the difference in magnitude of DNIC was found between the STD and LTD (1.71 ± 1.34 vs.1.09 ± 1.61, respectively; $p = 0.07$).

Since a significant difference in the magnitude of DNIC between OP and NOP treated patients was found in men but not in women, an attempt was made to look for possible role of opioid dosage and treatment duration on the magnitude of DNIC in the OP men only. A within group regression analysis of OP men ($n = 38$) was significant ($F = 4.515$, $p = 0.018$). Specifically, opioid dosage and treatment duration, each negatively

Table 4
Intensity of pain in response to the heat stimuli in the OP and NOP treated groups (Mean ± SD)

	OP	NOP
Baseline	7.1 ± 2.7	7.9 ± 1.7
Test 1	5.7 ± 2.6	5.5 ± 2.2
Test 2	5.6 ± 2.6	5.8 ± 1.9
Test 3	5.6 ± 2.6	5.7 ± 2.1

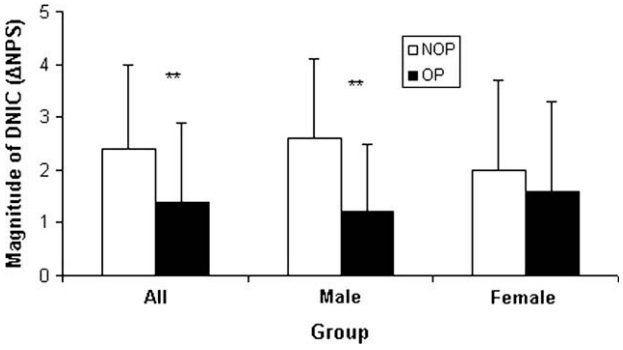

Fig. 2. Maximal magnitude of DNIC exhibited as deltas from baseline to test 1 in the conditioned heat-evoked pain (see text). NOP: non-opioid treated group – white bars; OP: opioid treated group – black bars. $^{**}p \leqslant 0.01$; Data are means ± SD.

contributed to the magnitude of DNIC ($\beta = -2.175$, $p = 0.036$ and $\beta = -2.061$, $p = 0.047$, respectively).

4. Discussion

In this study, we further explored the hypothesis according to which the use of opioids in patients with chronic pain would result in OIH. The main findings of this study were: (1) Using 'standard' psychophysics tests of measuring pain threshold, tolerance and intensity in response to the CPT, we found no evidence for OIH in patients receiving opioids as compared to those receiving non-opioid analgesic drugs. (2) Utilizing more 'advanced' methods of measuring DNIC, we found that the magnitude of DNIC was significantly smaller in opioid treated than in non-opioid treated patients. The difference was significant between OP and NOP men but not between OP and NOP women.

The first finding, which showed that the opioid and the non-opioid treated groups did not differ in their sensitivity to cold pain suggests that 'common use' of oral opioids by patients with chronic pain of either malignant or non-malignant origin does not result in abnormal sensitivity to evoked cold pain. Comparisons between subgroups of patients who consumed high versus low equianalgesic morphine dosages as well as those who received opioids for long versus short periods yielded similar results.

These results seem to contradict findings of three other human reports. Each of two such reports includes four patients with chronic non-malignant pain, in whom pain was exacerbated by the administration of opioids [1,36]. This disappeared when the drug was discontinued. The third report is a prospective, pilot study, which showed that 6 patients with chronic pain became hyperalgesic to cold but not to heat pain after 4 weeks of oral morphine treatment [9]. However, no firm conclusions could be drawn from these reports due to their small sample size, and a lack of control groups [6]. Yet, the results of this study are in agreement with our previous report in which we found no differences between opioid and non-opioid treated groups of patients with chronic pain in response to heat and mechanical evoked pain [34]. Thus, the findings of our two studies may indicate that if OIH indeed exists in patients with chronic pain who consume oral opioids, this phenomenon is neither dose nor temporal-dependent, and is unlikely to be detected by 'standard' psychophysical tests.

The second interesting and innovate finding that emerges from our study is the smaller magnitude of DNIC exhibited by opioid treated patients as compared to non-opioid treated controls. Studies from the early 90's showed that morphine blocks the descending pain inhibitory effects, in a naloxone reversible fashion in rats [2,3,24] and in healthy humans [25,42]. It should be emphasized though, that all these human studies were conducted in healthy subjects who received only single intravenous injections of morphine and therefore their clinical relevance is questionable. In this study, we show for the first time that opioid treatment has an effect on DNIC in patients with chronic pain.

The fact that a difference in the magnitude of DNIC between opioid and non-opioid treated patients was found in men but not in women is novel and suggests that there is a clear gender difference in the effect of opioids on descending inhibition. Furthermore, the effect of opioid treatment on DNIC in men seems to be dose- and time-related, since both high opioid dose and long treatment duration result in reduced magnitude of DNIC.

Several mechanisms have been suggested to explain OIH. First, sensitization of spinal neurons that accompany opioid-induced enhanced nociception. This mechanism is known to be mediated by central glutamatergic system via the *N*-methyl-D-aspartate (NMDA) and reversed by NMDA receptor antagonists such as MK801 [20,30]. Second, repeated morphine administration has also been shown to elicit increased levels of the pro-nociceptive peptides CGRP and SP within the dorsal root ganglion [30]. Third and most interestingly with respect to this study, OIH has been suggested to result from the activation of descending pain facilitation mechanisms that arise from the rostral ventromedial medulla (RVM). Increased activity of the excitatory peptide neurotransmitter cholecystokinin (CCK) in the RVM activates spinal pathways that up-regulate spinal dynorphin and consequently enhance nociceptive inputs at the spinal level [14,16,38,39,45]. DNIC on the other hand, represents the key mechanism of central pain modulation known as endogenous analgesia [23,26]. It is well established that the neuroanatomical basis of DNIC consists of portions of the brainstem as well as ascending spino-bulbar and descending bulbo-spinal tracts [12]. There is compelling evidence that DNIC is mediated via descending serotonergic pathways [8] and is likely to contain opioidergic links [12,25,42]. These mechanisms taken together suggest it is not unlikely that OIH and DNIC are two phenomena that are related to each other. Hence, we suggest that DNIC rather than standard psychophysical tests (i.e., pain thresholds) may contribute to a better understanding of OIH.

The implications of the attenuating effect of opioids on DNIC are not entirely clear, and whether or not the magnitude of DNIC is directly related to patients' pain perception is yet to be found. Interestingly, a recent study showed that when tested pre-operatively, DNIC magnitude can predict the intensity of chronic post-thoracotomy pain [46]. However, the fact that no correlations were found between the magnitude of DNIC and any of the CPT parameters or the patients' intensity of spontaneous pain in our patients brings about more questions than answers with respect to the clinical implications of our findings.

This has a few limitations. First, a control test for repeated heat pain stimulation has not been conducted. Second, this is not a prospective study and therefore it does not allow the repeated psychophysical testing of individual patients under different temporal conditions (i.e., before and after treatment). Third, we have enrolled heterogeneous patients in terms of their underlying pain states and the opioids administered. While this made the interpretation of the results more difficult, it allowed us to test the effects of opioids on CPT and on DNIC in the 'real' clinical world. We believe that future prospective, large clinical studies using advanced psychophysics tests such as DNIC have the potential to improve the understanding of OIH.

Acknowledgement

The authors state that there are no conflicts of interest regarding this work.

References

[1] Bronder RA, Taub A. Chronic pain exacerbated by long term narcotic use in patients with nonmalignant disease: clinical syndrome and treatment. Mt. Sinai J Med 1978;45:233–7.
[2] Bouhassira D, Villanueva L, Le Bars D. Effects of systemic morphine on diffuse noxious inhibitory controls: role of the periaqueductal grey. Eur J Pharmacol 1992;216:149–56.
[3] Bouhassira D, Chitour D, Villanueva L, Le Bars D. Morphine and diffuse noxious inhibitory controls in the rat: effects of lesions of the rostral ventromedial medulla. Eur J Pharmacol 1993;232:207–15.
[4] Celerier E, Laulin JP, Corcuff JB, Le Moal M, Simonnet G. Progressive enhancement of delayed hyperalgesia induced by repeated heroin administration: a sensitization process. J Neurosci 2001;21:4074–80.
[5] Celerier E, Rivat C, Jun Y, Laulin JP, Larcher A, Reynier P, et al. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. Anesthesiology 2000;92:465–72.
[6] Chang G, Chen L, Mao J. Opioid tolerance and hyperalgesia. Med Clin North Am 2007;91:199–211.
[7] Chia YY, Liu K, Wang JJ, Kuo MC, Ho ST. Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. Can J Anaesth 1999;46:872–7.
[8] Chitour D, Dickenson AH, LeBars D. Pharmacological evidence for the involvement of serotonergic mechanisms in diffuse noxious inhibitory controls (DNIC). Brain Res 1982;236:329–37.
[9] Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. J Pain 2006;7:43–8.
[10] Compton P, Charuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. Drug Alcohol Depend 2001:39–146.
[11] Cooper DW, Lindsay SL, Ryall DM, Kokri MS, Eldabe SS, Lear GA. Does intrathecal fentanyl produce acute cross-tolerance to iv. morphine? Br J Anaesth 1997;78:311–3.
[12] De Broucker TH, Cesaro P, Willer JC, Le Bars D. Diffuse noxious inhibitory controls in man. Brain 1990;113:1223–34.
[13] Doverty M, White JM, Somogyi AA, Bochner F, Ali R, Ling W. Hyperalgesic responses in methadone maintenance patients. Pain 2001;90:91–6.
[14] Dourish CT, Hawley D, Iversen SD. Enhancement of morphine analgesia and prevention of morphine morphine tolerance in the rat by the cholecystokinin antagonist L-364,718. Eur J Pharmacol 1988;147:469–72.
[15] Fillingim RB, Doleys DM, Edwards RR, Lowery D. Clinical characteristics of chronic back pain as a function of gender and oral opioid use. Spine 2003;15;28:143–50.
[16] Gardell LR, Wang R, Burgess SE, Ossipov MH, Vanderah TW, Malan Jr TP. Sustained morphine exposure induces a spinal dynorphin-dependent enhancement of excitatory transmitter release from primary afferent fibers. J Neurosci 2002;22:6747–55.
[17] Ge HY, Madeleine P, Arendt-Nielsen L. Sex differences in temporal characteristics of descending inhibitory control: an evaluation using repeated bilateral experimental induction of muscle pain. Pain 2004;110:72–8.
[18] Guignard B, Bossard AE, Coste C, Sessler DI, Lebrault C, Alfonsi P. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology 2000;93:409–17.
[19] Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler DI. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. Anesthesiology 2005;103:147–55.
[20] King T, Gardell LR, Wang R, Vardanyan A, Ossipov MH, Malan Jr TP. Role of NK-1 neurotransmission in opioid-induced hyperalgesia. Pain 2005;116:276–88.
[21] Laulin JP, Maurette P, Corcuff JB, Rivat C, Chauvin M, Simonnet G. The role of ketamine in preventing fentanyl-induced hyperalgesia and subsequent acute morphine tolerance. Anesth Analg 2002;94:1263–9.
[22] Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. Clin J Pain 1997;13:189–96.
[23] Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. Pain 1979;6:283–304.
[24] LeBars D, Chitour D, Kraus E, Clot AM, Dickenson AH, Besson JM. The effect of systemic morphine upon diffuse noxious inhibitory controls (DNIC) in the rat: evidence for a lifting of certain descending inhibitory controls of dorsal horn convergent neurones. Brain Res 1981;215:257–74.
[25] LeBars D, Willer JC, De Broucker T. Morphine blocks descending pain inhibitory controls in humans. Pain 1992;48:13–20.
[26] Le Bars D. The whole body receptive field of multireceptive neurones. Prog Brain Res 2002;40:29–44.
[27] Mao J, Price DD, Mayer DJ. Thermal hyperalgesia in association with the development of morphine tolerance in rats: roles of excitatory amino acid receptors and protein kinase C. J Neurosci 1994;14:2301–12.
[28] Mao J, Sung B, Ji RR, Lim G. Chronic morphine induces down regulation of spinal glutamate transporters: implications in morphine tolerance and abnormal pain sensitivity. J Neurosci 2002;22:8312–23.
[29] Mao J. Opioid-induced abnormal pain sensitivity. Curr Pain Headache Rep 2006;10:67–70.
[30] Ossipov MH, Lai J, King T, Vanderah TW, Porreca F. Underlying mechanisms of pronociceptive consequences of prolonged morphine exposure. Biopolymers 2005;80:319–24.
[31] Pielsticker A, Haag G, Zaudig M, Lautenbacher S. Impairment of pain inhibition in chronic tension-type headache. Pain 2005;118:215–23.
[32] Pud D, Cohen D, Lawental E, Eisenberg E. Opioids and abnormal pain perception: new evidence from a study of chronic opioid addicts and healthy subjects. Drug Alcohol Depend 2006;82:218–23.
[33] Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and non-opioid components independently

contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. J Pharmacol Exp Ther 1992;260:275–85.
[34] Reznikov I, Pud D, Eisenberg E. Oral opioid administration and hyperalgesia in patients with cancer or chronic non-malignant pain. Br J Clin Pharmacol 2005;60:311–8.
[35] Schug S, Gandham N. Opioids: clinical use. In: Wall PD, Melzack R, editors. Textbook of pain. Edinburgh: Churchill Livingstone; 2006. p. 443–57.
[36] Sjorgen P, Jensen NH, Jensen TS. Disappearance of morphine-induced hyperalgesia after discontinuing or substituting morphine with other opioid agonists. Pain 1994;59:313–6.
[37] Staud R, Robinson ME, Vierck Jr CJ, Price DD. Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. Pain 2003;101:167–74.
[38] Vanderah TW, Gardell LR, Burgess SE, Ibrahim M, Dogrul A, Zhong CM. Dynorphin promotes abnormal pain and spinal opioid antinociceptive tolerance. J Neurosci 2000;15;20: 7074–9.
[39] Vanderah TW, Suenaga NM, Ossipov MH, Malan Jr TP, Lai J, Porreca F. Tonic descending facilitation from the rostral ventro-medial medulla mediates opioid-induced abnormal pain and antinociceptive tolerance. J Neurosci 2001;21:279–86.
[40] Wiesenfeld-Hallin Z, Duranti R. Intrathecal cholecystokinin interacts with morphine but not substance P in modulating the nociceptive flexion reflex in the rat. Peptides 1987;8:153–8.
[41] Wiesenfeld-Hallin Z, Xu XJ, Hakanson R, Feng DM, Folkers K. Low-dose intrathecal morphine facilitates the spinal flexor reflex by releasing different neuropeptides in rats with intact and sectioned peripheral nerves. Brain Res 1991;551:157–62.
[42] Willer JC, Le Bars D, De Broucker T. Diffuse noxious inhibitory controls in man: involvement of an opioidergic link. Eur J Pharmacol 1990;182:347–55.
[43] Wolff BB. Methods of testing pain mechanisms in normal man. In: Wall PD, Melzack R, editors. Textbook of pain. Edinburgh: Churchill Livingstone; 1984. p. 186–94.
[44] Woolf CJ. Intrathecal high dose morphine produces hyperalgesia in the rat. Brain Res 1981;209:491–5.
[45] Xu XJ, Wiesenfeld-Hallin Z, Hughes J, Horwell DC, Hokfelt T. CI988, a selective antagonist of cholecystokinin B receptors, prevents morphine tolerance in the rat. British J Pharmacol 1992;105:591–6.
[46] Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, Best LA, Granot M. Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. Pain 2008;138:22–8.