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Oral opioid administration and hyperalgesia in patients with cancer or chronic nonmalignant pain

Igor Reznikov,[1,2] Dorit Pud[3,4] & Elon Eisenberg[1,4,5]

[1]*Pain Relief Unit, Rambam Medical Center, Haifa,* [2]*Department of Anaesthesiology, Hillel Yafe Hospital, Hadera,* [3]*Faculty of Social Welfare and Health Studies, University of Haifa,* [4]*Haifa Pain Research Group,* [5]*The Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Israel*

Correspondence
Elon Eisenberg MD, Pain Relief Unit, Rambam Medical Center, P.O.B. 9602, Haifa, 31096, Israel.
Tel: +972 4854 2578
Fax: +972 4854 2880
E-mail: e_eisenberg@rambam.health.gov.il

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Aims
Previous research has reported on reduced paw withdrawal latencies to heat and mechanical stimuli after parenteral administration of opioids in animals and on increased pain sensitivity in humans subsequent to postoperative infusions of short-acting opioids or in drug addicts. The aim of the present study was to explore the possibility that oral opioid treated patients with cancer-related or chronic non-malignant pain differ in their pain sensitivity from patients treated with non-opioid analgesics.

Methods
The study population consisted of 224 patients, including 142 in the opioid-treated group and 82 in the non-opioid-treated group. Pain thresholds for punctuate measured by von Frey filaments (g), mechanical pressure measured by pressure algometer (mmHg), heat stimuli measured by quantitative sensory testing (°C), as well as suprathreshold tonic heat pain intensity (46.5 °C for 1 min) measured by 0–10 numerical pain scale (NPS) were obtained at a nonpainful site (thenar eminence) in all patients.

Results
No differences between the groups were found for gender, age, duration of pain, or duration of treatment (independent variables). No significant differences between the groups were found in punctuate (difference = 17.0 g (95% CI –8.8, 42.8), $P = 0.19$), pressure (2.2 mmHg (–28.7, 33.2), $P = 0.89$) and heat (–0.3 °C (–1.5, 0.9), $P = 0.70$) pain thresholds, or in suprathreshold heat pain intensity (difference between maximal pain intensities –0.4 NPS units (95% CI –1.2, 0.4), $P = 0.31$). Pearson correlations within the opioid-treated group failed to show significant relationships between any of the independent variables and the outcome measures. A further comparison of the outcomes between the 'weak' opioid-treated subgroup and the 'strong' opioid-treated subgroup again revealed insignificant results.

Conclusions
These results suggest that the administration of 'commonly used' dosages of oral opioids does not result in abnormal pain sensitivity beyond that of patients receiving non-opioid analgesia.

Introduction

It is well accepted that opioids are the most efficacious analgesics available for the treatment of moderate to severe pain. They have become the cornerstone of cancer pain treatment, are commonly administered for the management of acute pain, and are increasingly used for the management of chronic nonmalignant pain. However, the use of opioids is associated with adverse effects, which are well recognized. Moreover, a growing number of animal and human studies show that under certain circumstances, opioids can elicit unexpected changes in pain sensitivity, resulting in hyperalgesia (abnormally intense pain in response to painful stimulation) and allodynia (abnormally intense pain in response to nonpainful stimulation).

Animal studies have shown brief enhancement of the nociceptive flexion reflex [1, 2] as well as reduced paw withdrawal latencies to heat and mechanical stimuli in rats receiving intrathecal morphine treatment [3, 4]. A reduction of baseline nociceptive thresholds to mechanical pressure has been observed after repeated subcutaneous fentanyl [5, 6] and heroin administration [7].

Opioid-induced pain sensitivity has also been reported in humans subsequent to experimental and intra-operative infusions of short-acting opioids, such as fentanyl or remifentanil, or in drug addicts. Acute remifentanil-induced hyperalgesia and tolerance were detected by models of experimental pressure pain [8] and transcutaneous electrical stimulation at a high current density [9] in healthy volunteers. Chia *et al.* [10] found that a high dose of intra-operative fentanyl induced higher pain intensity, greater incidence of emesis, and increased fentanyl consumption postoperatively as compared with lower doses. In addition, Guignard *et al.* [11] showed that a relatively large dose of intra-operative remifentanil increased postoperative pain and morphine consumption. Similar results were reported by Copper *et al.* [12] subsequent to intrathecal fentanyl administration to 60 women undergoing Caesarean section. These three studies suggest that both fentanyl and remifentanil can cause acute opioid tolerance and hyperalgesia. Notably, Cortinez *et al.* [13] reported contradictory results under similar conditions.

Several other observations have suggested that opioid-addicted subjects differ in their sensitivity to pain compared with normal subjects [14, 15]. In a recent small study, Compton *et al.* [16] found shorter withdrawal latencies for cold-pressor pain in opioid addicts maintained on methadone and buprenorphine, as compared with a non-opioid treated control group, indicating that prolonged opioid use in that population may enhance abnormal pain sensitivity.

In his recent review on 'Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy', Mao [17] stated that: 'To date, little information is known concerning cancer or noncancer pain patients with chronic opioid therapy with respect to changes in their pain sensitivity. Clinical studies are urgently needed to address this issue in this large population of pain patients.' The present study was aimed to explore the possibility that patients with cancer and chronic nonmalignant pain who are treated with 'commonly used' dosages of oral opioids in an outpatient setting differ in their sensitivity to experimentally evoked pain from patients treated with non-opioid drugs.

Methods

Patients

The study population consisted of 224 patients who were referred to the Pain Relief Unit at Rambam Medical Center in Haifa, Israel between November 2003 and April 2004. Consecutive patients aged 18–70 years were enrolled in the study upon meeting the following criteria: 1) presence of either chronic nonmalignant or cancer-related pain for at least 3 months, 2) use of analgesic medications, either opioids (study group) or nonsteroidal anti-inflammatory drugs (NSAIDs; control group) and 3) administration of a constant dose of analgesic medications for at least 1 week. Exclusion criteria were pregnancy; evidence of peripheral neuropathy per history or clinical examination, diabetes, pain involving the upper extremities, or treatment with repeated injections, infusions, or spinal opioids. The study was approved by the hospital's Ethics Committee, and written informed consent was obtained from all patients.

Evaluation 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 and (b) measurement of the intensity of pain (for which the patients were referred) on a 10 cm blank visual analogue scale (VAS).

Assessment of hyperalgesia

It is important to note that we chose to apply mechanical and thermal stimuli to our subjects due to the fact that both opioid-induced thermal hyperalgesia and tactile allodynia have been observed in animals during active opioid administration [17, 18].

The presence of hyperalgesia was tested in the thenar eminence of the nondominant hand (a nonpainful site)

and included the following measures: (a) Mechanical punctuate pain thresholds were determined by applying graded punctuate stimuli to the skin, using a set of 15 nylon filaments of varying bending pressure (von Frey filaments). The series of filaments represents stimuli ranging from 10 mg to 300 g. The weakest stimulus for which the patient identified two out of three stimulus applications as painful was recorded as the punctuate pain threshold, (b) mechanical pressure pain threshold was detected by using a manual pressure algometer with a 3 mm diameter paddle (algometer; Medical-Hako, Hamburg, Germany), which was pressed perpendicularly to the skin above the thenar eminence. Pressure was increased by 20 mmHg per second. Participants were asked to say 'now' when they first perceived a painful sensation. The measurement shown on the algometer scale (measured in mmHg) was recorded as the threshold of mechanical pain, (c) quantitative heat pain thresholds were determined with the method of limits [19] on a Medoc TSA-2001 device (Medoc, Israel). A Peltier thermode, size 30 × 30 mm, was attached to the skin above the thenar eminence. Stimulator temperature range was 32–50°C, and skin adaptation temperature was a constant 32°C, increasing at a rate of 1°C s^{-1}. Subjects were asked to depress a switch at the instant that they perceived a specific sensation. Three readings were obtained, three readings were obtained for each mechanical or thermal sensation, and their average was determined as the threshold score and (d) a suprathreshold heat pain stimulation at 46.5°C was applied for 1 min, and patients were requested to report their pain level (0–10 numerical pain scale) every 15 s.

Prior to assessment of the mechanical and thermal thresholds, a training run was performed. All tests were carried out by one trained investigator (IR), who was blind to which group was being tested. The tests were conducted under controlled room temperature at intervals of at least 5 min, between 09.00 h and 13.00 h, subsequent to self-administration of the morning dose of analgesic medications.

Statistical analysis and equianalgesic dosage calculation

Comparisons of demographic data, pain levels and thresholds between the opioid and the non-opioid treated groups were calculated using the Student's *t*-test. Pearson correlations and ANOVA were used to study the relationships between age, pain duration, treatment duration, and opioid dose (independent variables) and the outcome measures (dependent variables). Correlation studies were conducted for each type of opioid separately as well as for the entire patient population. In order for us to be able to conduct correlation studies of the entire patient population, all used opioids were converted to their equi-analgesic dosages of oral morphine according to previously published tables. Accordingly, oral oxycodone preparations were multiplied by 2 [20] (e.g. 10 mg of oxycodone were converted to 20 mg of oral morphine); methadone was multiplied by 5–10, dose dependently [21]; and codeine, propoxyphene, and tramadol were multiplied by 10 [22]. Notably, although not regarded as a 'classical' opioid, tramadol was included in some of the analyses because its analgesic effect is mediated in part by opioid mechanisms [23].

Most previous reports on opioid-induced hyperalgesia have been related to the use of 'strong' opioids. In an attempt to evaluate the possible effect of the 'strength' of the opioids used on the presence of hyperalgesia, the opioid-treated group in the present study was divided into two subgroups according to the opioid 'strength': 'strong' opioid users (e.g. morphine, oxycodone, methadone) *vs.* 'weak' opioid users (e.g. propoxyphene, tramadol). Additional analyses of the 'strong' opioid subgroup were conducted. First, Pearson correlations and ANOVA were used to study the relationships between the independent and the dependent variables in this subgroup. Second, the 'strong' opioid subgroup was further divided into additional subgroups according to the duration of treatment (short-term *vs.* long-term) and the equianalgesic dosage (high *vs.* low). Student's *t*-test was used to compare the pain measures of the short-term and the long-term treatment opioid subgroups (below and above median duration, respectively). Similar comparisons were conducted between the low dosage and the high dosage subgroups (below and above median equi-analgesic dose, respectively).

Excel (Microsoft Corp, WA, USA), JMP, and SAS (SAS Institute, NC, USA) was employed. Results were considered significant at the 0.05 level. Data are presented as means ± SEM and confidence intervals for differences when appropriate.

Results

Patients

Of the 224 study participants, 115 were males and 109 were females, and their mean ± SEM age was 51.5 ± 3.9 years.

Evaluation of pain history and treatment

Mean pain duration of the entire group was 51.5 ± 17 months, ranging from 3 to 57.8 months (median 11.6 months). Of the 142 patients in the opioid-treated group, 72 had chronic nonmalignant pain and 70 had cancer-related pain. Of the 82 patients in the non-opioid group, 77 patients suffered from nonmalignant

Table 1
Characteristics of the patients in each of the treatment groups

	Opioids	Non-opioids	Statistical analysis difference (95% CI)	*P*
n	142	82		
Gender (M/F)	72/70	41/41		
Age[$] (years)	52.6 ± 1.3	49.3 ± 1.9	3.3 (–1.0, 7.7)	0.10
Range	18–80	19–75		
Median	53	51		
Pain duration[$] (months)	48.2 ± 16.8	57.5 ± 11.3	–9.3 (–56.3, 37.5)	0.44
Range	0.5–520	0.5–578		
Median	12	23		
Treatment duration[$] (weeks)	31.7 ± 4.3	43.5 ± 6.5	–11.8 (–26.7, 3.1]	0.08
Range	1–364	2–364		
Median	12	24		
VAS[$] (0–100)	70 ± 0.2	71 ± 0.2	–1 (–6–4)	0.49
Range	20–100	20–100		
Median	70	70		
Equi-analgesic opioid dose[$]*	69.8 ± 7.0			
Range	4–464			
Median	40			

[$]*Mean ± SEM; *mg of oral morphine.*

pain and the other five from cancer pain. No differences between the groups were found according to gender. The opioid group was slightly older (difference = 3.3 years; 95% CI –1.0, 7.7, $P = 0.10$), reported slightly lower pain intensities (difference = –1 VAS point (95% CI –6, 4), $P = 0.49$), and had shorter pain duration (–9.3 months (95% CI –56.3, 37.5), $P = 0.44$) and shorter treatment duration (–11.8 weeks (95% CI 26.7, 3.1), $P = 0.08$) as compared with the non-opioid group. However, these differences were not statistically significant. The characteristics of the two study groups are presented in Table 1, and the medications consumed by the patients in each group are listed in Table 2.

Assessment of hyperalgesia

Comparison between opioid and nonopioid treatments Thresholds for mechanical punctuate pain, mechanical pressure pain and heat pain, as well as the intensity of pain in response to tonic suprathreshold heat stimuli failed to demonstrate statistically significant differences between the opioid-treated and the non-opioid-treated groups (Table 3). This indicates that as a whole, the opioid treatment did not result in mechanical or thermal hyperalgesia. Importantly, these results also do not significantly differ from previous findings obtained from healthy volunteers in our laboratory (unpublished data).

Comparison between 'weak' opioid, 'strong' opioid and non-opioid treatment As previously described, the opioid-treated patients were divided into two subgroups: a group of 79 patients who used opioids for moderate to severe pain ('strong' opioid users) and another group of 63 patients who used opioids for mild to moderate pain ('weak' opioid users). ANOVA failed to show any differences in the dependent variables between these two opioid subgroups (Table 4) or between each of these two subgroups and the non-opioid group.

Assessment of the 'strong' opioid subgroup Pearson correlations did not show significant relationships between the dependent and the independent variables within the 'strong' opioid subgroup. The median duration of pain treatment among these patients was 6 weeks. Student's *t*-tests failed to demonstrate significant differences in any of the pain measurements between the long-term treatment ($n = 39$; mean = 40 ± 11 weeks) and the short-term treatment ($n = 40$; mean = 5 ± 1 weeks) subgroups (Figure 1). The median equianalgesic dose consumed by the 'strong' opioid users was 80 mg of oral morphine. Notably, nine patients who have used this dose were included in the-high dose group.

Comparisons of the pain measurements between the high-dose ($n = 41$; mean = 147.9 ± 13.6 mg of oral morphine) and the low-dose subgroups ($n = 38$;

Table 2
Analgesic medications consumed by the two treatment groups

Opioid treated group		Non-opioids treated group	
Drug (*n*)	Daily dose range (mg)	Drug (*n*)	Daily dose range (mg)
Oxycodone (93)	5–200	Rofecoxib (33)	25–50
Morphine (19)	30–200	Celecoxib (2)	200–400
Tramadol (52)	50–500	Etodolac (18)	400–800
Propoxyphene (14)	40–250	Diclofenac (4)	100–100
Methadone (1)	16	Ibuprofen (1)	1000
		Indomethacin (1)	25
		Paracetamol (4)	500–1000
		Dypirone (15)	500–4000
		Ketorolac (1)	10
Adjuvant drugs			
Clonazepam (1)	0.25	Clonazepam (2)	0.5–1.5
Amitriptyline (2)	25	Amitriptyline (2)	10–20
		Chlomipramine(1)	10

n = *number of subjects using that drug; Note that since some patients received more than one opioid (e.g. morphine tablets together with percocet) or more than one NSAID simultaneously, therefore the total number of subjects in the table exceeds total number of patients in each group).*

Table 3
Results of quantitative sensory testing and suprathreshold pain intensities of the opioid *vs.* non-opioid groups (mean ± SEM)

Pain threshold/intensity	Opioids	Non-opioids	Statistical analysis difference (95% CI)	*P*
Punctate (g)	191.7 ± 7.9	174.7 ± 10.5	17.0 (–8.8, 42.8)	0.19
Pressure (mmHg)	369.2 ± 9.2	367.0 ± 11.8	2.2 (–28.7, 33.2)	0.89
Heat (°C)	45.4 ± 0.3	45.7 ± 0.7	–0.3 (–1.5, 0.9)	0.70
Pain intensity (NPS) at 46.5°C				
15 s	5.9 ± 0.2	5.7 ± 0.2	20.2 (–0.4, 0.9)	0.45
30 s	6.1 ± 0.2	5.6 ± 0.	0.5 (–0.2, 1.1)	0.12
45 s	6.1 ± 0.2	5.7 ± 0.3	0.4 (–0.2, 1.1)	0.19
60 s	5.9 ± 0.2	5.6 ± 0.3	0.3 (–0.3, 1.0)	0.31

NPS 0–10 numerical pain scale.

mean = 44.1 ± 2.4 mg of oral morphine) also failed to show significant differences (Figure 2).

Assessment of each type of opioid separately Given the heterogeneity of the opioid treated group in terms of the type of opioids used, their dosages and the duration of treatment, a series of correlation analyses was conducted for each type of opioid separately. Pearson correlations did not show significant relationships between any of the evoked pain parameters (dependent variables) and the age, pain duration, treatment duration, or dosage (independent variables) of any of the opioids consumed by these patients.

Discussion

Over the last several years, compelling evidence has emerged to indicate that paradoxical abnormal pain sensitivity, including hyperalgesia and allodynia, may occur in animals and in humans receiving opioids [1–12]. It should be emphasized that this phenomenon is not just a loss of opioid analgesic efficacy (tolerance), but refers to an increase in pain sensitivity in the opi-

Table 4
Results of quantitative sensory testing and suprathreshold pain intensities of the 'weak' *vs.* 'strong' opioids groups (mean ± SEM)

Pain threshold/intensity	'Weak' opioids (*n* = 63)	'Strong' opioids (*n* = 79)	Statistical analysis difference (95% CI)	*P*
Punctate (g)	183.4 ± 11.5	198.4 ± 10.8	15.0 (16.4, 46.4)	0.34
Pressure (mm Hg)	360.6 ± 13.0	376.2 ± 13.0	15.6 (–212, 52.5]	0.40
Heat (°C)	45.0 ± 0.4	45.7 ± 0.4	0.7 (–0.5, 1.8)	0.24
Pain intensity (NPS) at 46.5°C				
15 s	6.3 ± 0.3	5.5 ± 0.2	–0.8 (–1.5, 0.3)	0.06
30 s	6.4 ± 0.3	5.8 ± 0.3	–0.6 (–1.4, 0.2)	0.17
45 s	6.4 ± 0.3	6.0 ± 0.3	–0.4 (–1.2, 0.4)	0.31
60 s	6.3 ± 0.3	5.7 ± 0.3	–0.6 (–1.5, 0.2)	0.15

NPS = 0–10 numerical pain scale.

oid treated subjects. Two types of increased pain sensitivity associated with opioid treatment have been observed. The first is associated with cessation of opioid treatment [5–7]. In contrast, in the second type, mechanical allodynia and thermal hyperalgesia occur while the opioid therapy is being actively administered [17, 18]. Our study was aimed to explore the possibility that patients with cancer and chronic nonmalignant pain, who are treated with 'commonly used' dosages of oral opioids, exert abnormal pain sensitivity of the second type during the course of their treatment regimen.

The results of the present study show no differences between the opioid treated and the non-opioid treated groups in the thresholds for mechanical punctuate pain, mechanical pressure pain, and heat pain or in the intensity of pain in response to tonic suprathreshold heat stimuli. The non-opioid treated patients were selected as the control group because this was the only patient population that resembled the study group in many ways. Patients in both groups had pain (cancer or chronic) and consumed medications on a regular basis. Therefore, the selection of this control group seemed to reduce any potential bias that might have been associated, for example, with a control group of healthy subjects.

Since the relationships between opioid type, dosage, and duration of treatment and the occurrence of increased pain sensitivity in patients with chronic or cancer pain are currently unknown, we conducted a series of correlation studies of the entire patient population, for the 'strong' and 'weak' opioids separately, and for each administered opioid discretely. We also compared subgroups of patients who consumed high *vs.* low opioid dosages, as well as long *vs.* short treatment periods. However, the statistical analyses consistently failed to show any significant correlation between these parameters and the outcome measurements. Similarly, no significant differences between the subgroups could be found. Furthermore, since only a small number of patients in each group consumed adjuvant drugs (anticonvulsants or antidepressants), which have the potential to alter the pain sensitivity tests, it is unlikely that those drugs changed the results of the study. Taken together, these results suggest that the administration of 'regular' dosages of oral opioids to patients with chronic or cancer pain does not result in abnormal pain sensitivity, as compared with patients receiving non-opioid analgesia.

The results of the present study seem to disagree with those of at least some animal and human studies that provide evidence of opioid-induced hyperalgesia. However, several aspects of those studies were different from ours. First, in the other studies, the animals were pain-free and the human subjects were either pain-free or had only brief lasting pain prior to opioid administration [3–12], whereas in the present study the patients were taking opioids for already existing pain. Second, in the other studies, both the human and animal subjects received fixed doses of opioids, either as single doses or at constant intervals in strictly controlled conditions [3–12]. In contrast, in the clinical setting, opioids were administered in a much less controlled fashion. Even though many of the patients in our study used controlled released opioid preparations, it cannot be assumed that their plasma opioid concentrations were controlled as well as those of the animal or human subjects in the other studies. Third, while opioids were administered via intrathecal [3, 4] or subcutaneous [5–7] routes in the animal studies, and intravenously [10, 11] or intrathecally [12] in the intra-operative human trials, the oral

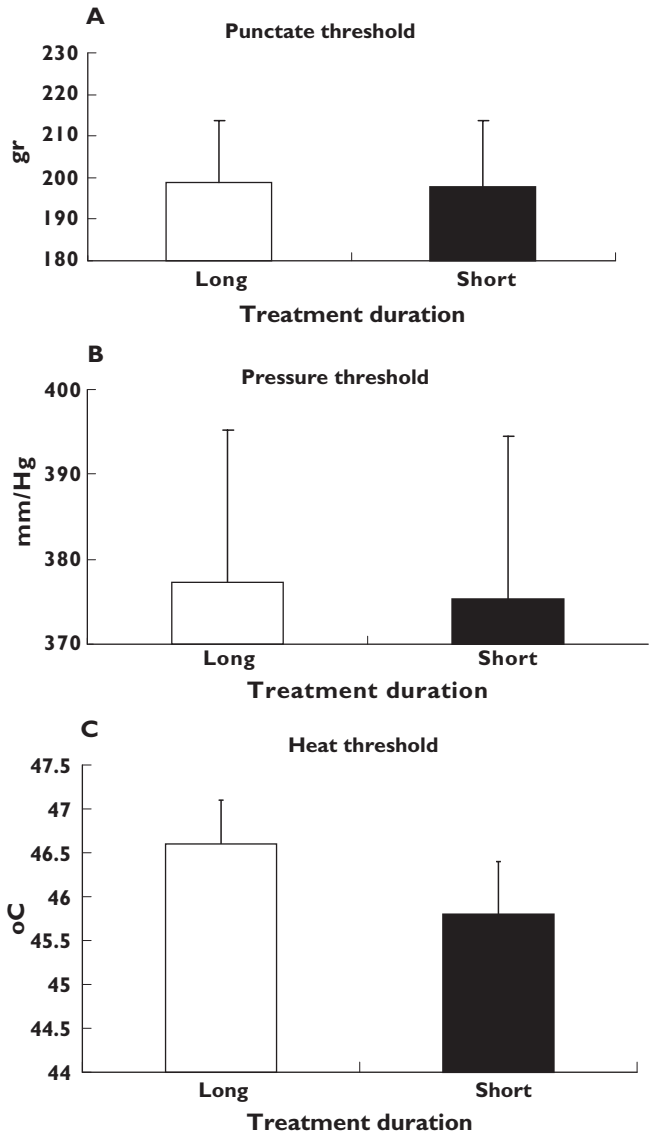

Figure 1
Pain thresholds of the 'strong' opioid subgroup: effect of treatment duration. Comparisons of punctuate (A), pressure (B) and heat (C) pain thresholds between the long-term treatment (open bars) and the short-term treatment subgroups (dark bars)

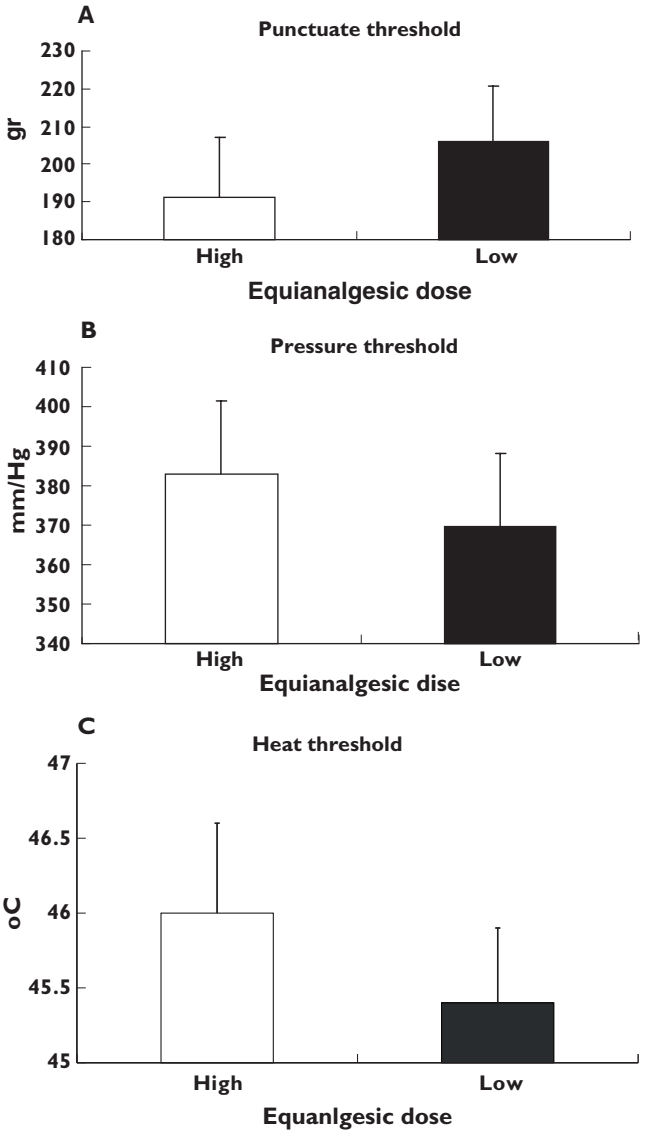

Figure 2
Pain thresholds of the 'strong' opioid subgroup: effect of equianalgesic dosage. Comparisons of punctuate (A), pressure (B) and heat (C) pain thresholds between the high-dose (open bars) and the low-dose (dark bars) subgroups

route of administration was the only one used by our patients. All of these factors may influence the development of opioid-induced pain sensitivity [17].

A recent study conducted with drug addicts [16] showed that former opioid addicts enrolled in a methadone maintenance programme reported increased sensitivity to experimental pain induced by cold pressor, as compared with the matched former opioid addicts not enrolled in a methadone maintenance program. Seemingly, this study bears more resemblance to ours insofar as the oral administration of opioids in both studies was carried out in a less controlled fashion than that of the previously discussed studies. However, there are also considerable differences between the two studies. Unlike the drug-addict study, in which methadone (or buprenorphine in another subgroup of patients) was administered, only one patient in our study used methadone. Furthermore, the drug addicts were exposed to cold-induced pain, whereas the patients in our study received mechanical and heat stimuli. Lastly, as mentioned by Compton *et al.* [16], the high rates of continued use of illicit and presumably short-acting opioids

(heroin) made the results of the drug-addict study difficult to interpret.

About 10%-30% of the patients with cancer pain and possibly a much larger percentage of the patients with chronic nonmalignant pain fail to achieve sufficient analgesia in response to oral opioid therapy [24]. In other patients, unexplained pain exacerbation is reported following a period of successful opioid treatment. It is well known that increasing the opioid dose may not improve the outcome, at least in some of these patients. In an attempt to explain these observations, the development of opioid-induced pain hypersensitivity has been suggested as a possible mechanism. Although the exact neural mechanisms underlying the development of opioid-induced pain sensitivity are not entirely clear, a growing body of evidence suggests that this phenomenon is mediated through neural mechanisms similar to those underlying the development of pathological pain. These mechanisms likely include activation of the central glutamatergic system via the *N*-methyl-D-aspartate (NMDA) receptors, increased spinal dynorphin content, which allows evoked-release of spinal excitatory neuropeptides, such as calcitonin gene-related peptide (CGRP) from primary afferents and modulation of the opioid-induced descending facilitation system [17, 25 for a review]. Nonetheless, the results of the present study do not show evidence of opioid-induced hyperalgesia, in comparison with a group of patients receiving non-opioid analgesia, for the scope of medications, dose-range, and duration of treatment tested.

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