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Reduced Cold Pain Tolerance in Chronic Pain Patients Following Opioid Detoxification

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Abstract

Objective—One potential consequence of chronic opioid analgesic administration is a paradoxical increase of pain sensitivity over time. Little scientific attention has been given to how cessation of opioid medication affects the hyperalgesic state. In this study, we examined the effects of opioid tapering on pain sensitivity in chronic pain patients.

Design—Twelve chronic pain patients on long-term opioid analgesic treatment were observed in a 7- to 14-day inpatient pain rehabilitation program, with cold pain tolerance assessed at admission and discharge. The majority of participants were completely withdrawn from their opioids during their stay.

Outcome Measures—We hypothesized that those patients with the greatest reduction in daily opioid use would show the greatest increases in pain tolerance, as assessed by a cold pressor task.

Results—A linear regression revealed that the amount of opioid medication withdrawn was a significant predictor of pain tolerance changes, but not in the direction hypothesized. Greater opioid reduction was associated with decreased pain tolerance. This reduction of pain tolerance was not associated with opioid withdrawal symptoms or changes in general pain.

Conclusions—These findings suggest that the withdrawal of opioids in a chronic pain sample leads to an acute increase in pain sensitivity.

Keywords

Opioids; Hyperalgesia; Taper; Cold Pressor Task; Chronic Pain

Introduction

Opioid analgesics make up one of the most commonly prescribed classes of medications in the United States. While opioids are a mainstay in pain management, they are also associated with a number of undesirable effects [1]. One adverse effect that is gaining increasing clinical attention is opioid-induced hyperalgesia ([OIH] [2,3]). OIH is a state of pain sensitization caused by exposure to opioids [4,5]. The existence of this phenomenon is supported by animal [6–8] and human [9,10] research. OIH has been demonstrated in opioid-dependent human subjects who were maintained on methadone [11], buprenorphine [12], and slow-release oral morphine [13]. Acute hyperalgesia has also been observed in a clinical environment, where surgical patients who were administered large-dose remifentanil showed greater pain

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sensitivity at follow-up than those who received small-dose remifentanil [14]. OIH has not been clearly demonstrated in chronic pain patients taking analgesic doses of opioids; however, preliminary evidence suggests that hyperalgesia is observed following 1 month of sustained opioid therapy [15]. It is possible, then, that the use of opioids for chronic pain management may increase patients' sensitivity to pain [16].

If long-term opioid use does lead to heightened pain sensitivity, it is important to know whether or not simple tapering of these drugs can reverse the condition [17]. To our knowledge, this study is the first attempt to assess changes in pain sensitivity, as measured by the cold pressor task (CPT), in chronic pain patients before and after an opioid taper. The CPT yields an experimental marker of opioid-related hyperalgesia that is independent from the primary pain complaint [10,11]. Previous research has shown the CPT to be more sensitive than other stimulus modalities in assessing hyperalgesia [12,15]. Twelve chronic pain patients entering an inpatient pain rehabilitation program were administered the CPT at admission and discharge. The majority of patients were completely withdrawn from their opioid pain medication over the course of the program. We typically observe a significant improvement in the patients' quality of life and function following this program. Consequently, we hypothesized that individuals with the highest reductions in daily opioid use would experience the greatest increases of pain tolerance.

Methods

Participants

Participants were chronic pain patients (N = 12) who were admitted to the Stanford Comprehensive Interdisciplinary Pain Program (SCIPP). This inpatient program involves a team of specialists from a variety of fields who employ an individualized biopsychosocial approach toward pain management. As part of their treatment, patients may be voluntarily titrated downward or off their opioids. The sample was comprised of a heterogeneous group of patients and pain complaints. Participant demographics and primary pain diagnoses are presented in Table 1. Patients entered the program with a range of opioid dosages (5–1,250 mg morphine equivalency).

Opioid Taper Procedure

Opioid detoxification was achieved using a blinded pain cocktail [18]. Upon admission to the program, the patients' medications were converted to a blinded methadone dose that was mixed in cherry-flavored syrup and gradually tapered over the course of the program. Baclofen (approximately 5 mg) was used as a blinding agent. Clonidine (typically 0.1 mg) was also added to reduce any hyperautonomic symptoms due to withdrawing the opioids. All agents were mixed and administered twice daily. For analysis, all narcotic analgesics, including methadone, were converted into daily morphine equivalents using a standard equianalgesic chart (Delaware Pain Initiative, 2002). Three patients, all on low admission levels of opioids, were not tapered from their medication, and otherwise went through the same clinical and experimental protocols.

CPT

The CPT followed a commonly used procedure [19]. The tests were performed by an experimenter who was blinded to the participants' medication usage. A plastic container (11 × 16.5 × 8.5 in.) was filled with 4 in. of shaved ice, followed by 5 in. of cold tap water. The bath was allowed to sit for 10 minutes for temperature equalization. Water temperature was checked with an analog thermometer to be 0.7°C (±0.5°C). Continuous circulation of the water was performed with an MC-450 Micro-Jet (Aquarium Systems, Mentor, OH) pump that circulates at 440 L/h. This task is ideal for a patient environment because it is inexpensive, easily

constructed and calibrated, and safe. The CPT, therefore, provides a useful alternative to experimental heat, electrical, and mechanical pain tasks.

The patients were instructed to sink their hand to the bottom of the water and remark at the first sensation of pain (threshold), and then keep their hand in the water until they could no longer tolerate the cold (tolerance). The instructions were followed by a rehearsal before performing the actual task. Two CPTs were administered on admission to the program. A 10-minute period separated the two trials. If greater than a 20% discrepancy was observed in tolerance scores (seconds of hand in the water), then a third test was conducted. Tolerance times were averaged for analysis. The same process was repeated before discharge from the program. Pain threshold values were not analyzed, because four participants did not provide adequate data for that test.

Measures

In order to determine if changes in pain tolerance were associated with more general indicators of progress, both self-report and behavioral outcomes were assessed. Underlying pain was assessed at admission and discharge with an 11-point visual analog scale (VAS) scale. The scale ranged from 0 (no pain) to 10 (worst pain imaginable).

Because pain sensitivity may be associated with classic opioid withdrawal symptoms (e.g., tremors, nausea, and anxiety), general withdrawal was measured with the objective opioid withdrawal scale (OOWS) and companion subjective opioid withdrawal scale (SOWS [20]). The OOWS is a 13-item experimenter-rated scale that scores behavioral signs of acute opioid withdrawal. The SOWS is a 15-item self-reported scale that measures both physical and psychologic aspects of withdrawal.

Statistical Methods

All tests were performed with SPSS v15 (SPSS, Chicago, IL). All variables were normally distributed, except for the calculated “opioid reduction” variable, which had slight skew and kurtosis. Using the standard criteria of two times the standard error, neither skew (1.5, SE = 0.8) nor kurtosis (1.4, SE = 1.3) were determined to be significant enough to warrant the use of nonparametric tests.

The primary dependent variable (DV) of interest was change in pain tolerance. The change score variable was computed by subtracting the discharge test results from the admission test results. Secondary DVs included changes in VAS pain, OOWS, and SOWS. The primary independent variable (IV) was the reduction of opioid medication (in mg morphine equivalents).

Preliminary tests of significant within-person changes over the course of the program were conducted with paired *t*-tests. Main hypothesis testing was performed using a linear regression, with change in pain tolerance as the DV and opioid reduction as the IV. In order to control for baseline differences, admission CPT scores were also entered as a predictor. Post hoc tests were performed with Pearson's correlations (*r*) and partial correlations.

Results

In general, patients experienced a drop in cold pain tolerance from admission to discharge testing (t [11] = 2.6, P = 0.03). There were no significant changes in spontaneous pain severity or withdrawal symptoms (all P's > 0.1, see Table 2). We determined the significant predictors of changed pain tolerance using linear regression. Admission pain tolerance was first entered to control for baseline differences, followed by the amount of opioids withdrawn. The two-factor model predicted a significant amount of variance in changed pain tolerance (adjusted

$r^2 = 0.94$). Reduction of opioid medication was a significant predictor of changes in pain tolerance (t [11] = −4.1, $P = 0.004$). Contrary to our hypothesis, those individuals who were tapered from the most opioids also experienced the greatest reductions of in pain tolerance. A post hoc correlation (controlling for pain tolerance on admission) found that opioid tapering (mg) was strongly correlated with change in pain tolerance ($r = 0.82$, $P = 0.004$).

As a post hoc analysis, we attempted to determine if worsening pain tolerance was part of a larger opioid withdrawal symptom cluster. Change in pain tolerance was not correlated with changes in underlying pain or opioid withdrawal symptoms (all P's > 0.1). Furthermore, these outcomes were not predicted by opioid tapering (all P's > 0.1).

Discussion

Approximately 50 million Americans have a chronic pain disorder, and as high as 44% of those prescribed analgesics are given an opioid medication [21]. As OIH may be confused with a worsening of the original pain complaint or interpreted as a natural generalization of pain [3], it is important that OIH be properly described, diagnosed, and treated within the context of the original pain condition.

In this study, we examined the effects of opioid tapering on cold pain tolerance. Chronic pain patients undergoing a taper in a 7- to 14-day inpatient environment showed significant decreases of pain tolerance at the end of the program. This decrease was significantly correlated with the total milligrams (morphine equivalent) of opioids withdrawn. More than 60% of the variance in the change of pain tolerance was explained by the reduction of opioids use. Our results further show that this hyperalgesia was not associated with a change in underlying pain, or part of a general opioids withdrawal syndrome. Despite the opioids tapering, patients reported (nonsignificant) improvements in both opioids-withdrawal symptoms and overall pain. These results suggest that increased pain sensitivity can occur following opioids cessation, even if no objective signs of withdrawal are observed. The findings also raise the possibility that chronic pain and tolerance to experimentally evoked pain may operate via separate mechanisms. Improvements in general outcome have been previously reported in an interdisciplinary opioid detoxification program [22]. We have noted similar improvements in SCIPP, leading to our initial hypothesis that patients would experience an improvement in pain tolerance following opioid tapering.

While the increase of pain sensitivity immediately following the opioid taper was not predicted, our results seem to parallel the phenomenon of opioid-abstinence hyperalgesia [23]. Acute hyperalgesia following opioid cessation in chronic pain patients has been previously reported [24], and a number of animal studies have shown similar increases of hyperalgesia following rapid (e.g., naloxone-precipitated) opioid withdrawal [25–28]. Human studies of abrupt withdrawal in postaddict humans [29] and chronic pain patients [30], have likewise observed increased pain complaints. Short-term administration of ultrafast-acting opioids such as remifentanil similarly show hyperalgesia during withdrawal in healthy human subjects (e.g., [31]).

While converging evidence suggests an immediate increase of hyperalgesia follows opioid tapering, there is less consensus on the longer-term effects of opioid cessation. Some research has found that former opioid addicts have less evidence of hyperalgesia when compared with current abusers, possibly indicating reversal of the hyperalgesic state after prolonged abstinence [9]. However, the most well-controlled, longitudinal trial found that hyperalgesia was not reduced at 7 and 28 days after drug cessation (as confirmed by urine toxicology tests [32]). The results from opioid abuse studies may be relevant to chronic pain patients taking opioid analgesics, as the degree of hyperalgesia is similar between these two groups [33]. We

note the similarity in tolerance between our chronic pain group (18.3 seconds) and previously reported individuals on a methadone maintenance program (15 seconds), both of which are considerably less than healthy controls (56 seconds [11]).

The acute hyperalgesic state following opioid withdrawal may be the result of pronociceptive system sensitization following prolonged opioid exposure [34]. In this model, prolonged opioid exposure leads both to tolerance of its analgesic effects and sensitization of pronociceptive systems. These changes would manifest clinically as a lag time following opioid cessation where drug-opposite effects are experienced before pronociception adaptation responses cease [35]. During this time, exaggerated hyperalgesia is likely to be experienced. Célèrier and colleagues [21] reported that 12, once-daily administrations of heroin to rats (2.5 mg/kg) caused hyperalgesia (-54% of baseline tolerance) that continued to increase temporarily even after cessation of the drug. After a few days of continued hyperalgesia, pain sensitivity gradually decreased until, at 9 days post opioid cessation, there was no difference from baseline. While that study shows a rapid return to baseline after opioid cessation, it is important to note that those animals were not exposed to opioids over an extended duration of time (i.e., months or years).

Two additional findings are worthy of note. First, we observed an interesting divergence between psychophysical measures of cold pain tolerance and underlying chronic pain. The lack of relationship between the two suggests that experimental measures of pain may not always serve a useful proxy of clinical pain. It is possible that experimental cold pain tolerance and underlying clinical pain operate via distinct mechanisms, or that changes in one precede changes in the other.

Second, we found that underlying pain was not significantly affected by a 2-week opioid taper. This finding suggests that the long-term use of opioids may not be effective in managing chronic pain. Given the increasing evidence for OIH, we are confronted with a question of whether to increase or decrease opioid dosage in response to worsening pain. More research must be conducted on this issue, as patients in the present study underwent inpatient programs that may have countered any negative effects of the opioid taper.

A few aspects of the study limit the interpretability of results. First, while the patients admitted to this study are representative of those commonly seen at inpatient pain clinics, the sample size is low (N = 12). This study should be replicated in a larger sample of chronic pain patients. Second, patient heterogeneity was very high, and it is possible that the effect of opioid tapering could differ based on the chronic pain condition. Third, potential psychologic and other mediators were not measured. Fourth, our analyses covered a wide range of admission opioid dosages (from 5 to 1,250 mg). Again, a larger sample size would allow us to better define the relationship between the amount of opioids withdrawn and the degree of cold pain tolerance change. Last, inpatients chose whether or not to participate in the study; therefore, some systemic bias due to participant self-selection could be present.

These initial results suggest that a relatively quick (1–2 week) withdrawal of long-term opioid treatment may decrease pain tolerance. This decrease of tolerance seems to occur independent of other withdrawal effects and may contribute to the difficulty of tapering opioid medications, even when classic withdrawal symptoms appear to be well-managed. Further research should determine the long-term time course of pain sensitivity, by testing individuals longitudinally.

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Table 1

Demographics, opioid medication tapering (in morphine mg equivalent units), and cold pressor task (CPT) scores

Sex	Age	Primary Diagnosis	Admission Opioids (mg)	Discharge Opioids (mg)	Change Opioids (mg)	Admission CPT (Second)	Discharge CPT (Second)	Change CPT (%)
M	47	Low back pain	5	5	0	5.4	7.8	+30.8
M	47	Low back pain	9	9	0	93.3	120.0	+22.2
M	42	CRPS	37	37	0	35.5	35.0	−1.4
F	57	CRPS	50	0	50	9.3	10.1	+7.9
F	42	Low back pain	120	0	120	14.4	13.6	−5.6
F	39	CRPS	150	0	150	7.5	9.5	+21.1
M	30	Failed back syndrome	285	0	285	28.2	15.0	−46.8
M	54	Migraine	400	30	370	11.3	10.5	−7.1
F	47	Cervicalgia	420	0	420	9.0	6.6	−73.3
F	59	Low back pain	238	0	238	24.3	14.4	−40.7
M	56	Low back pain	1,010	6	1,004	14.0	5.6	−60.0
M	55	Cervicalgia	1,250	15	1,235	37.9	18.9	−50.1

CRPS = complex regional pain syndrome.

Table 2

Means and standard deviations for all test variables at admission and discharge observation points

	Admission	Discharge	Paired Samples *t* (11)
Tolerance	18.3 (12.3)	12.7 (6.3)	2.8, $P = 0.03$
VAS pain	6.9 (2.3)	6.4 (2.2)	0.6, $P = 0.57$
OOWS	1.1 (1.4)	0.7 (1.3)	1.5, $P = 0.17$
SOWS	22.8 (13.9)	15.8 (8.8)	1.2, $P = 0.26$

VAS = visual analog scale; OOWS = objective opioid withdrawal scale; SOWS = subjective opioid withdrawal scale.