Significant pain reduction in chronic pain patients after detoxification from high-dose opioids

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ABSTRACT

Opioid tolerance is a well-established phenomenon that often occurs in patients taking opioids for the treatment of chronic pain. Typically, doctors need to periodically elevate patients' opioid doses in an attempt to manage their underlying pain conditions, resulting in escalating opioid levels with only moderate to negligible improvement in pain relief. Recently, opioid-induced hyperalgesia has been recognized as a potential form of central sensitization in which a patient's pain level increases in parallel with elevation of his or her opioid dose. Here, we report a retrospective study of patients undergoing detoxification from high-dose opioids prescribed to treat an underlying chronic pain condition which had not resolved in the year prior. All patients were converted to ibuprofen to manage pain, with a subgroup treated with buprenorphine during detoxification. Self-reports for pain scores were taken at first evaluation, follow-up visits, and termination. Twenty-one of 23 patients reported a significant decrease in pain after detoxification, suggesting that high-dose opioids may contribute to pain sensitization via opioid-induced hyperalgesia, decreasing patient pain threshold and potentially masking resolution of the preexisting pain condition.

Key words: opioid, tolerance, hyperalgesia, sensitization, detoxification, buprenorphine

INTRODUCTION

Opioid treatment is typically implemented in patients suffering from chronic pain who have not responded well to non-narcotic options, and it may also be used to supplement non-narcotic therapies. One concern with opioid treatment is the development of tolerance, which is often reported in patients maintained on opioids over a prolonged period. This results in the need for increased doses of opioids in order to achieve a level of pain alleviation comparable to that initially achieved.[1-4] As drug doses increase, opioid-induced side effects become problematic, as does the potential for physical dependence and opioid abuse.[5] Opioid use can also lead to hyperalgesia, or increased pain sensitivity, leading to the abnormal perception of pain (allodynia).[6] Recently, reports have been made on mechanisms that contribute to both tolerance and hyperalgesia.

Binding of endogenous opiates such as [D-Ala(2),N-MePhe(4),Gly-ol(5)]-enkephalin (DAMGO) to the μ opioid receptor activates G-protein-coupled signaling and receptor internalization. Signaling is terminated upon receptor phosphorylation and β-arrestin binding. Once β-arrestins bind, the receptor internalizes and β-arrestin is removed, allowing the receptor to be returned to the plasma membrane for another round of signaling.[7,8] Tolerance results from excessive stimulation of these pathways leading to receptor desensitization and an uncoupling from G protein signaling cascades.[9-14] Different agonists have been reported to have differential effects on this pathway. For example, morphine disrupts internalization of the receptor entirely.[8,15-17] Other clinically used opioids (oxycodone, fentanyl, and methadone) alter signaling by uncoupling the receptor from downstream effectors such as cyclic adenosine monophosphate.[18,19] Clinically, these molecular mechanisms contribute to the development of tolerance, requiring increased opioid concentrations to maintain signaling.[15,20] While tolerance is one unfortunate side effect of chronic opioid treatment, hyperalgesia is another and may contribute to pain elevation during prolonged opioid use.

Hyperalgesia is a result of biological adaptations that change pain threshold and increase perceived pain and which may contribute clinically to tolerance.[21,22] Hyperalgesia was initially demonstrated in rats when the μ receptor antagonist naloxone was administered after tolerance had been established. This administration led to a decrease in latency to tail flick compared to baseline, revealing an opioid-induced hyperalgesia that could be blocked using the NMDA antagonist MK801, implicating NMDA receptor activation in sensitization.[23]

Recently, a descending pathway from the rostral ventromedial medulla (RVM), an example of a "top-down" pain facilitation pathway, was discovered. Studies have revealed neuroplasticity in the RVM pathway as a result of prolonged opioid use, resulting in an increase in pain facilitation.[24,25] Lidocaine injections into the RVM reversed opioid-induced hyperalgesia, even after sensitivity had been established, revealing the importance of RVM signaling in maintenance of pain facilitation.[22] Mechanisms of opioid-induced tolerance and hyperalgesia are clearly systematic, involving not only cellular but also circuit-level adaptations and resulting in clinical manifestations of allodynia and opioid dependence. While hyperalgesia typically manifests itself as an abnormal increase in pain not usually associated with the pre-existing condition, it is likely that the same mechanisms that cause hyperalgesia decrease pain thresholds globally, resulting in increased pain.

Once these mechanisms are in place, cessation of opioids or inhibition of receptor signaling results in withdrawal symptoms.[9] It is this withdrawal that signifies physical dependence upon the opioids and typically requires another opioid, such as buprenorphine, for treatment during rehabilitation.[26] It is possible that the same mechanisms that create these conditions might reset after opioid abstinence or rehabilitation, reducing overall pain. Here, we present a cohort of patients being rehabilitated from high-dose opioids who reported lower overall pain scores after detoxification, suggesting that central sensitization, hyperalgesia, and tolerance may contribute to long-term chronic pain, and that cessation of opioids may alleviate pain after rehabilitation.

MATERIALS AND METHODS

Patient cohort

Twenty-three patients were evaluated, and 16 were then admitted to the Psychiatric Hospital at Vanderbilt upon referral from their primary pain physician specifically for opioid detoxification. Admission to the hospital for detoxification was based on patient preference, coexisting disease, the proximity of the patient's house to the medical center, resources at home, and social support. This was a voluntary elective procedure and was done because the patient and/or the referring pain doctor felt that the patient was not getting any benefit from his or her current high dose of opioids. No patient presented here was referred for diversion, overuse, abuse, or addiction to opioid medications. The patients were on a variety of opioids, including extended-release (ER) oxycodone (n = 5), fentanyl (n = 6), hydrocodone (n = 2), methadone (n = 2), and morphine (n = 8), for a preexisting pain condition that had not resolved within the previous year. Due to the retrospective nature of this study,

approval from the institutional review board was not required, but informed consent was given by all patients documented in this study. This cohort represents 23 sequential patients specifically treated for opioid detoxification following decreased analgesic efficacy between March 2004 and May 2006.

Procedures and measures

Upon evaluation and prior to detoxification, patients were asked to evaluate their existing pain using an 11-point pain scale (0 to 10) known as the Numerical Rating Scale (NRS). The value recorded was used as the predetoxification value. At the proper time the buprenorphine group received sublingual buprenorphine, with a loading dose of 4 mg every half hour for the first three doses followed by 4 mg TID. All patients were allowed to take ibuprofen 200 mg as needed (up to six doses per day) during detoxification to manage pain and withdrawal symptoms. Patients were weaned off of buprenorphine over a maximal period of 180 days (Table 1). All patients were then reevaluated for pain using the NRS. There was no mean difference in age between the ibuprofen-only and ibuprofen-buprenorphine groups (data not shown), nor was there a difference in age between sexes. There was, however, a significant difference between the number of men versus women in the study (16 men, seven women).

Statistical analysis

Data are presented as the mean ± SEM with 95 percent confidence interval. Comparisons were made using either a Student's t-test (paired, two-way) or a one-way ANOVA. All data were analyzed using Prism 4.0 for Mac (GraphPad Software Inc., San Diego).

RESULTS

Upon admission to the detoxification program, patients were asked to quantify their pain using an 11-point NRS ranging from 0 to 10. They were then reassessed after detoxification and reevaluated using the NRS. Individual pain reports were graphed and displayed a general decrease in individual pain reports for each patient (Figure 1). All but two patients (Patients 5 and 22, Table 1) showed a marked decrease in reported pain following opioid rehabilitation, with 21 of the 23 patients showing significant pain reduction using paired, two-tailed Student's t-test (p < 0.001). Regardless of detoxification regimen, when grouped all patients displayed an overall reduction in reported pain (8.0 predetoxification versus 3.3 post, Student's two-tailed, paired t-test, p < 0.001) after opioid detoxification (Figure 2).

To assess whether buprenorphine made a greater contribution to the reduction of patients' pain scores, patients

<table>
<tr><td colspan="12" align="center">Table 1: Patient data</td></tr>
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Patient	Age	Sex	Diagnosis	Pain meds (pre)	Pre-detox pain	Post-detox pain	Inpatient?	Buprenorphine adjunct therapy?*	Buprenorphine taper
1	48	F	Fibromyalgia	480 mg/d oxycodone (ER)	6	1	No	No	0
2	34	M	Degenerative disk disease	1200 mg/d oxycodone (ER)	10	6	No	No	0
3	38	M	Herniated cervical disk	160 mg/d morphine	8	3	Yes	No	0
4	46	M	Lumbar disk disease	400 mg/d morphine	8	3	Yes	No	0
5	45	M	Degenerative disk disease	125 µg/hr fentanyl	7	6	Yes	No	0
6	44	M	Burst lumbar vertebrae	720 mg/d oxycodone (ER)	10	3	Yes	Yes	60 days
7	66	M	Fibromyalgia	60 mg/d methadone	8	3	Yes	Yes	50 days
8	36	M	Degenerative disk disease	200 mg/d morphine	6	3	No	Yes	30 days
9	55	M	Degenerative disk disease	200 µg/hr fentanyl	8	4	Yes	Yes	180 days
10	62	F	Spinal stenosis	150 mg/d hydrocodone	10	4	No	Yes	45 days
11	35	F	Degenerative disk disease	120 mg/d morphine	10	4	Yes	Yes	14 days
12	50	M	Rotator cuff	320 mg/d oxycodone (ER)	9	2	No	Yes	90 days
13	56	M	Post-laminectomy syndrome	240 mg/d oxycodone (ER)	5	1	Yes	Yes	90 days
14	66	F	Vertebral fracture	45 mg/d hydrocodone	7	3	Yes	Yes	120 days
15	44	M	Degenerative disk disease	260 mg/d methadone	7	3	Yes	Yes	150 days
16	42	M	Ruptured disk	120 mg/d morphine	7	4	Yes	Yes	45 days
17	54	F	Degenerative disk disease	75 µg/hr fentanyl	8	4	Yes	No	0
18	56	F	Degenerative disk disease	400 µg/hr fentanyl	8	2	Yes	Yes	90 days
19	53	M	Degenerative disk disease	50 µg/hr fentanyl	8	4	No	Yes	30 days
20	69	M	Degenerative disk disease	400 mg/d morphine	8	4	Yes	Yes	120 days
21	61	M	Peripheral neuropathy	160 mg/d morphine	9	3	No	Yes	120 days
22	56	F	Failed Back Syndrome	100 µg/hr fentanyl and 150 mg/d meperidine	10	7	Yes	No	0
23	51	M	Neuropathy induced by chemotherapy	580 mg/d morphine	7	0	Yes	Yes	120 days

*IB group was allowed 200 mg PRN; Bup group was given buprenorphine 12 mg/d and ibuprofen 200 mg PRN.

were sorted according to their detoxification medication (ibuprofen alone [IB] and ibuprofen with buprenorphine [Bup]). Both groups reported a significant decrease in pain after rehabilitation (one-way ANOVA, $p < 0.001$), with the IB group reporting a 47.44 percent decrease in pain and the Bup group reporting a 62.99 percent decrease. This translated on average to a final pain report of 4.2 for the IB group and of 2.9 for the Bup group (Figure 3). There was no significant difference between the two groups' pain reports at time of admission (7.2 for IB versus 8.25 for Bup). Despite the apparent difference between the Bup and IB groups' final pain score reports, the final levels of pain relief achieved were not significantly different (one-way ANOVA).
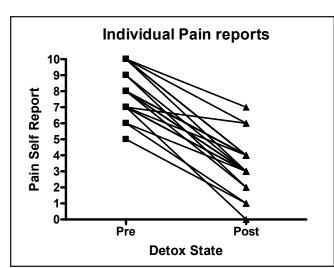
Figure 1: Changes in pain scores reported by individuals. NRS scores for all 23 patients represented in this study (patients having the same score are represented by a single symbol). Individual patients are charted using their pre- and post-detoxification NRS scores; lines connect individual scores to show overall pain-change trends. Only two patients reported insignificant pain relief after detoxification (changing from scores of 7 to 6 and 10 to 7, respectively).

DISCUSSION

We have reported a retrospective study of patients taking high-dose opioids who experienced a significant decrease in their overall pain condition after opioid detoxification. All patients in this study were referred by their primary pain physicians for opioid detoxification. All patients had been receiving a substantial dose of opioids before referral and complained of significant chronic pain. Each patient reported a desire to stop opioid treatment, ruling out psychological dependence as a reason for referral. No patient was included in this retrospective cohort if he or she displayed addiction pathology such as overuse, multiple providers, running out of medications early, "dirty" urine drug screens, or a history of addiction. Physical dependence was noted in all patients in terms of withdrawal symptoms during detoxification, with some rebound pain reported in the Bup group that calls for further examination. Opioid detoxification was completed when the patient no longer displayed acute and/or chronic withdrawal symptoms or had been weaned off of buprenorphine, with all but two patients reporting a significant decrease in pain upon discharge.

We are not the first to report reduction in pain after discontinuation of opiates. Sjogren et al.[27] reported four individual cases of cancer patients who developed hyperalgesia while on morphine. In each of the four cases presented, hyperalgesia resolved after either morphine withdrawal or opioid substitution. While classical hyperalgesia was not examined or reported by any of the patients in our
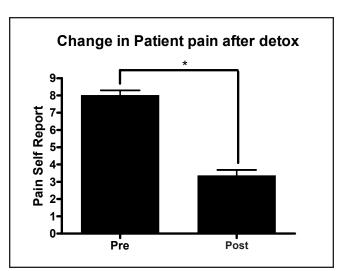

Figure 2. Patient pain reduction after opioid detoxification. *All patients were grouped and their pre- and post-pain reports were compared using the NRS. Patients' mean pain scores prerehabilitation were 8.00 ± 0.30 (N = 23) compared to a post-treatment report of 3.35 ± 0.33 (N = 23). Significance was calculated using a paired Student's two-tailed t-test ($p < 0.001$).

cohort, our data are consistent with reversal of pain upon opioid substitution or cessation.

Our current report directly contradicts an earlier report by Cowan et al.[28] in which patient pain reports were significantly elevated after opioid cessation. In the Cowan study, patients were initially sustained on a lower dose of opiates, with the majority using a 30 mg equivalent dose of morphine before cessation. In addition, none of the patients in the study displayed symptoms of tolerance or withdrawal upon cessation of treatment. Our sample represents a potentially different subset of patients, all of whom exhibited symptoms of both tolerance and physical dependence. This implies that patients who display tolerance to opioid treatment may be more susceptible to underlying pain facilitation pathways. A genetic difference has been noted in various strains of rats during laboratory testing. In a study performed by Hoffman et al.,[29] inbred rats were assayed for morphine-induced tolerance and hyperalgesia, and it was noted that the strain that initially displayed the least amount of antinociceptive effect displayed the highest rate of tolerance acquisition, indicating that tolerance may be linked to rapid requirements for dose increase. While all strains displayed withdrawal symptoms upon naloxone administration, the animals were not assayed for opioid-induced hyperalgesia.

In the current study, patients treated with the partial μ agonist buprenorphine reported both rebound pain and withdrawal symptoms during initial rehabilitation. This is consistent with reports of hyperalgesia revealed by naloxone treatment seen in the literature, and it reveals that these patients had developed physical tolerance to opioids.[23] While buprenorphine is not an
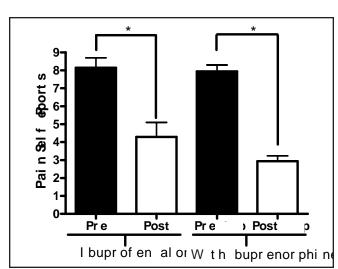
Figure 3: Effect of buprenorphine or ibuprofen during detoxification. *To examine whether buprenorphine or ibuprofen might be responsible for the amount of pain relief reported, patient data were binned according to detoxification regimen. Both the buprenorphine and ibuprofen groups showed significant reduction in pain reports after rehabilitation (two-way ANOVA, p < 0.001). The levels of predetoxification pain and pain relief reported between the two groups were not significantly different.

antagonist per se, the effect of a partial agonist is to reduce signaling (both basal and stimulated) to a submaximal level.[30] The use of buprenorphine in these patients would mean a severe blunting of the established opioid pathways, resulting in partial antagonism. The fact that buprenorphine treatment resulted in transient rebound pain in these patients leads us to believe that pain facilitation pathways were potentiated in this population.

To investigate the effect of buprenorphine coadministration during detoxification, we binned the patient data so that those detoxified using buprenorphine were compared to those detoxified on ibuprofen alone. Buprenorphine treatment for opioid therapy is used to decrease withdrawal effects seen with opioid cessation. Because buprenorphine acts as a partial agonist at the μ opioid receptor, we were interested to see if there would be a difference in reported pain in the group that used buprenorphine during rehabilitation. Interestingly, while there was a trend toward decreased final pain levels in the Bup group, this difference did not reach a significant level.

A similar phenomenon is reported elsewhere in the pain literature. Patients who take daily over-the-counter pain medications for headaches can become "dependent" and develop "rebound" headaches once the medication has been metabolized or excreted.[31] The typical treatment for analgesic-induced rebound headache is withdrawal of the offending medication. Our data are

consistent with a similar mechanism of medication-induced pain facilitation, which may or may not involve similar molecular pathways or neurocircuitry.

This report represents an initial finding of pain reduction in a small cohort of patients following opioid rehabilitation and warrants further examination in a larger-scale study. This cohort may also represent an interesting subpopulation of patients who are more susceptible to both opioid tolerance and sensitization than other populations previously reported, as several other studies investigating long-term use of opioids for chronic pain have seen no significant tolerance or development of hyperalgesia in their subjects.[28,32]

There is little information in the literature regarding reversal of pain reports following long-term opioid rehabilitation in human subjects. Here, we propose that the mechanisms of both tolerance and sensitization may combine to increase underlying pain conditions, leading to an increase in subjective pain which can be alleviated by opioid detoxification.

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