Lofexidine for Rapid Opioid Tapering in Adults

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A. BACKGROUND

Lofexidine has recently been approved by the U.S. Food and Drug Administration (FDA) for mitigation of opioid withdrawal symptoms in order to facilitate abrupt or tapered opioid discontinuation in adults. One potential use of the compound is in situations where rapid detoxification (partial or complete) is desired, such as impending surgery. Lofexidine (racemic mixture of *R*-/+ and *S*-/-enantiomers, dexlofexidine and levlofexidine, respectively) is a full alpha-2 receptor agonist.(1-5) However, lofexidine is pharmacologically distinct from other alpha-2 agonists, such as clonidine whose use has previously been described for the treatment of opioid withdrawal syndrome (OWS). (6-8)

Concerns about OWS are major deterrent for patients on opioid therapy, often hampering success and compliance with opioid tapering regimens.(9-11) Fortunately, amelioration of such negatively experienced signs and symptoms may be accompanied by improved patient outcomes. Lofexidine was originally approved as a pharmacologic agent for opioid detoxification in the United Kingdom and other countries, including much of the European Union, starting in the 1980s. Studies have demonstrated efficacy in the amelioration of OWS with fewer adverse effects and a better safety profile than clonidine.(12, 13) Specifically, lofexidine has a lower incidence of hypotension than clonidine, making it more suitable for the management of OWS in outpatient settings.(12) Additionally, unique from clonidine, lofexidine also binds to 5-HT_{1A} (i.e. serotonin) receptors. As serotonin levels decrease during periods of withdrawal from opioids,(14) compounds with 5-HT_{1A} agonism could potentially be beneficial in combatting OWS. As an example, a compound with 5-HT_{1A} agonist properties was recently shown to decrease withdrawal symptoms in opioid-dependent mice. (15, 16) Hence, activity mediated through 5-HT_{1A} receptors may help explain additional benefit of lofexidine for OWS treatment beyond that of simple alpha-2 agonism.

In a recently published multicenter phase III randomized controlled trial of more than 600 patients dependent on opioid therapy, lofexidine at doses of 2.16 and 2.88 mg/day significantly reduced OWS versus placebo.(17) Additionally, lofexidine increased the rate of completing the 7-day period of 'abrupt discontinuation' by 14% and 12% for the 2.16 and 2.88 mg/day dosing groups, respectively. Hence, lofexidine has the potential to serve as a withdrawal treatment option when non-opioid agents are preferred or required or when opioid agonist-assisted withdrawal is unavailable. Additionally, lofexidine may potentially be used to manage withdrawal symptoms that occur during induction or maintenance treatment with mixed opioid agonists and antagonists.

With increased attention on a widespread national problem of opioid misuse and abuse, recently declared a national Public Health Emergency by the U.S. Department of Health and Human Services, medical practices in the U.S. are trying to shift towards more conservative approaches to pain management with less reliance on opioids as first-line therapy. Consistent with this, recent guidelines released by the Centers for Disease Control and Prevention (CDS) endorse avoidance of opioid therapy to the greatest extent possible for chronic pain states.(18) However, chronic opioid use remains a significant national problem. Data from acute pain and postoperative states suggests that patients taking opioids preoperatively, especially at high doses, have poorer outcomes than those not taking opioids.(19-29) This includes heightened risk for immediate postoperative outcomes such as infection, ileus, and respiratory depression and longer-term complications such as poor wound healing and decreased success rates following spinal fusion.(30) Moreover, patients on opioids preoperative typically require higher doses and durations of opioid therapy postoperatively and generally consume more health care

resources than their opioid-naïve counterparts.(19, 21, 31-35) Given these findings, a drug that facilitates reliable, safe, and rapid detoxification or partial detoxification may be particularly beneficial for patients on chronic opioid therapy preparing to undergo a planned surgical procedure. Patients presenting for elective spine surgery are at particularly high risk for chronic preoperative opioid use,(34) and hence, this group may particularly benefit from targeted approaches to wean opioids preoperatively.

Specific aims

Specific Aim 1: The primary objective is to investigate the effects of lofexidine in adults (N=25) undergoing opioid tapering. In this phase 4 clinical trial, an open label, variable dose design will be used to facilitate opioid tapering during a 15-day period. The primary outcome measure of this study is the number of patients who discontinue opioid use at day 15.

Specific Aim 2: Secondary aims include investigating the effects of lofexidine on the severity of OWS, pain intensity, negative affect, and opioid craving following completion of the 15-day study period. Secondary outcome measures will include the Clinical Opiate Withdrawal Scale, the Short Opiate Withdrawal Scale-Gossop, the numerical pain rating scale, Center for Epidemiologic Studies-Depression scale, the Pain Catastrophizing scale, and a composite scale of opioid craving.

Specific Aim 3: This exploratory aim will investigate the change in heat pain perception attributed to changes in opioid induced hyperalgesia. Prior to the opioid taper and on day 15, quantitative sensory testing will be conducted using the Computer Aided Sensory Evaluator IV (WR Electronics, Stillwater, MN).

B. PROCEDURES AND METHODS

B.1. Study Site

The study will be conducted at the medical (e.g., pain clinic, pain rehabilitation center) and surgical (e.g., orthopedic and spine surgery clinics) clinics at Mayo Clinic Rochester, MN. All patients will be recruited from the medical and surgical clinics at Mayo, and all assessments and follow-up will be conducted in the pain clinic and pain rehabilitation center.

B.2. Study Design

B.2.1. Study methodology

A prospective, open label, single center, variable dose design will be used to investigate the effects of lofexidine in adults undergoing a 15-day taper. The primary outcome will be the number of subjects who discontinue opioid use at day 15.

B.2.2. Opioid tapering

Following informed consent, the baseline opioid dose will be reduced 5% to 50% based on the physician investigators clinical discretion and patient acceptability of the dose reduction. The physician investigators will reassess each patient for further opioid dose reductions (5% to 50% allowed) in the pain clinic or pain rehabilitation center on study days 3, 6, and 9. On all other study days, patients will be contacted by telephone by study personnel to assess for OWS and adverse effects related to lofexidine use.

Prior to initiating the opioid taper, the physician investigators will contact the physician or provider responsible for prescribing long-term opioid therapy. During the 15-day study period, the physician investigators will assume full prescribing authority, and patients and their established prescribers will be asked to halt the provision of all opioid prescriptions during the study period. Upon completion of the study, the physician investigators will contact the

established long-term prescriber to ensure continuity of care with the provision of ongoing prescriptions.

B.2.3. Variable lofexidine dosing

Upon initiation of the opioid taper, patients will receive oral lofexidine 0.54 mg 4 times daily (3 tablets of 0.18 mg 4 times daily) for a total daily dose of 2.16 mg. The variable dose design will allow the lofexidine dose to be increased up to 0.72 mg 4 times daily (4 tablets of 0.18 mg 4 times daily) by the physician investigators if OWS are elevated. The lofexidine dose may also be reduced by the physician investigators to 0.18 mg 4 times daily (1 tablet of 0.18 mg 4 times daily) to relieve adverse effects attributed to lofexidine.

On study days 10 through 15, equal quantities of the baseline lofexidine dose will be reduced, and lofexidine will be discontinued on day 15. All patients will be contacted within 24 hours of study completion to assess for any residual or late emerging adverse effects.

B.2.4. Heat pain perception

Prior to opioid tapering and on day 15, quantitative sensory testing will be conducted using the automated Computer Aided Sensory Evaluator IV (CASE IV; WR Medical Electronics, Stillwater, MN) system based on the method of levels. The CASE IV system delivers a series of short duration heat stimuli of variable magnitude interspersed with null stimuli in random order through a thermode with surface area of 10 cm^2. The validated HP test algorithm takes less than 5 minutes to complete. This protocol includes the standardized test procedures, stimulus waveform, null stimulus, and non-repeating stepping algorithm between the different levels of heat stimuli. The subject is masked to each level of stimulus delivered, including the null stimulus. Immediately after the stimulus is given, the subject then rates the stimulus intensity on an 11-point rating scale (0 denotes no pain, 10 denotes the most intense possible pain). The test is completed when either the maximum stimulus has been delivered, or when the subject grades the stimulus intensity ≥ 5.

In total, there are 25 different magnitudes of heat stimuli, expressed in units termed “just noticeable difference” (JND). The heat stimuli magnitude of each level is comprised of 2 elements: (1) temperature, and (2) duration of exposure. The baseline temperature is 34°C and the thermal rise rate is 4°C/second. There is an exponential increase in the temperature and the thermode reaches 48°C at level 21 for a duration of 1 second. For levels 22, 23, and 24, the temperature remains at 48°C for a duration of 1.5, 5, and 10 seconds, respectively. The maximum heat stimulus is level 25, which is comprised of a temperature of 49°C for a duration of 10 seconds. Higher temperatures are not used in order to avoid thermal tissue injury.

The CASE IV software program (WR TestWorks, version 2.0) adjusts the raw sensory data, recorded in units of JND, to account for age, sex, height, weight, body surface area, body mass index, and body region of testing.(36-38) Then, a quadratic regression equation is fitted to the pain ratings, and the CASE IV software calculates HP 0.5, HP 5, and HP 5-0.5. The midpoint between a nonpainful stimulus and the least stimulus magnitude necessary to elicit a threshold sensation of pain is termed HP 0.5. The stimulus magnitude necessary to elicit a pain rating of 5, indicating intermediately intense pain, is labeled HP 5. HP 5-0.5 is named the pain-stimulus response slope and signifies the difference between HP 5 and HP 0.5.

The testing conditions will be consistent between patients. The anatomical site selected for testing (due to ease of accessibility) will be the dorsal surface of the non-dominant hand. If the non-dominant hand is an anatomical site of pain, then the dominant hand will be used.

B.2.5. Postoperative opioid use

For surgical patients, immediate preoperative opioid dose and pain scores will be assessed upon admission to the preoperative area. Opioid dose and pain scores will be reassessed upon hospital dismissal and at day 30 (+/- 5 days) following lumbar spine. The preoperative and hospital dismissal assessments will be performed by members of the study team, and the day 30 assessments will performed via telephone.

B.3. Study Participants

B.3.1. Inclusion criteria

1. Age 18 to 70 years.
2. Chronic pain for ≥ 3 months duration.
3. Daily morphine equivalent dose between ≥ 20 mg.

B.3.2. Exclusion criteria

1. Cancer-related pain.
2. Medical or surgical conditions that could be adversely impacted by opioid tapering or use of lofexidine including, but not exclusively limited to, cardiac disease, inflammatory bowel disease, renal or hepatic impairment, vascular disease, and history of anaphylaxis. Patients may be excluded for other comorbid medical or surgical conditions based on the physician investigator's discretion.
3. History of schizophrenia or other chronic psychiatric disorder that could be adversely impacted by opioid tapering or use of lofexidine. Patients may be excluded for other comorbid mental health conditions based on the physician investigator's discretion.
4. Neurological condition that impair functioning in an ambulatory setting or could be adversely impacted by opioid tapering or use of lofexidine including, but not exclusively limited to, Parkinson's disease, amyotrophic lateral sclerosis, or a dementing illness. Patients may be excluded for other neurological conditions based on the physician investigator's discretion.
5. Active substance abuse disorder.
6. Inability to function in an ambulatory care setting due to severe deconditioning requiring use of supportive gait aids including a cane or walker. Patients may be excluded for other functional problems based on the physician investigator's discretion.
7. History of adverse effects attributed to opioid tapering or lofexidine use.
8. Use of medications from drug classes known to have adverse interactions with lofexidine including, but not exclusively limited to, beta-blockers, calcium channel blockers, alpha 1 and 2 receptor antagonists, tricyclic antidepressants, benzodiazepines, and selective serotonin reuptake inhibitors. Patients may be excluded for use of other medications based on the physician investigator's and research pharmacy's discretion.

B.4. Sample Size

The primary aim of this study is to assess the effects of lofexidine on opioid tapering in adults. The purpose of this open label study is to decide whether additional studies using an experimental design are warranted, and to provide preliminary data for designing a larger efficacy trial. The primary outcome will be the number of subjects who discontinue opioids at day 15. We anticipate opioid discontinuation will be observed in 50% to 70% of patients. Thus, a sample-size of N=25 will be sufficient to assess whether additional studies of lofexidine in this patient population are warranted.

B.5. Data Collection and Assessments

B.5.1. Demographics and clinical characteristics

Baseline demographic and clinical characteristics will be collected including age, sex, race and ethnicity, marital status, work status, educational status, pain diagnosis, pain duration, smoking status, use of non-opioid medications, previous spine surgery history or other non-spine surgery, and indication for current surgery.

B.5.2. Determination of morphine equivalent dose

The daily opioid dose of each patient will be determined by self-report and review of pharmacy and medical records. Using a software program available at our institution, the daily opioid dose will be converted to an oral morphine equivalent dose expressed in milligrams (mg) per day.

B.5.3. Opioid tapering

The primary outcome measure of this study is the number of patients who discontinue opioids at day 15.

B.5.4. Pain intensity

Pain intensity will be assessed using the 11-point numerical pain rating scale (NRS). The validity of the NRS has been well established.

B.5.5. Negative affect

Depressive symptoms and pain catastrophizing are key components of negative affect. The Center for Epidemiologic Studies-Depression scale provides a validated measure of depressive symptoms in patients with chronic pain. The Pain Catastrophizing Scale provides a measure of negative cognitions and emotions associated with actual or anticipated pain experiences.

B.5.6. Opioid craving

Opioid craving will be assessed using responses (0 to 100 VAS) to 3 questions: (1) How much do you crave opioids? (2) How often do you think about the next dose? (3) How strong is your urge to take more medication than prescribed? This approach has been used to assess craving in patients with chronic pain.

B.5.7. Heat pain perception

Heat pain perception will be quantified using the Computer Aided Sensory Evaluator IV (WR Electronics, Stillwater, MN). This QST device has been validated, and we have used it to quantify opioid-induced hyperalgesia and to study other pain-related states associated with altered heat pain perception.

B.5.8. Signs and symptoms of opioid withdrawal

The severity of opioid withdrawal symptoms will be assessed using two measures. First, the Clinical Opiate Withdrawal Scale (COWS) is an observer-rated instrumaent. Total score range from 0 to 47. Scores ranging from 5-12 denote mild withdrawal symptoms, scores from 13-24 signify moderate withdrawal, scores from 25-36 indicate moderately severe symptoms, and scores greater than 36 indicate severe withdrawal symptoms. Second, the Short Opiate Withdrawal Scale-Gossop (SOWS-Gossop) is a subjective score provided by the subject. It includes 10 items assessed by the patient as none/not present (0 points), mild (1 point), moderate (2 points), or severe (3 points).

B.5.9. Lofexidine adverse effects

According to previous reports, common adverse effects associated with lofexidine include orthostatic hypotension, hypotension, bradycardia, insomnia, somnolence, sedation, dry mouth, syncope, and tinnitus. Management of adverse effects is described in the Human Subjects section.

B.5.10. Urine toxicology screening

The opioid status of all patients will be biochemically verified with a confirmed urine toxicology screen prior to the opioid taper and at day 15.

B.5.11. Timeline of patient assessments

Screening visit (at least (7) days before baseline assessment)
Screen for inclusion and exclusion criteria.
Obtain informed consent.
Obtain urine toxicology screen and ECG.

Day 1 (baseline)
Informed consent reviewed and documented.
Physical examination performed, vital signs documented.
Determine opioid dose reduction.
Start lofexidine.
Obtain baseline assessments.

Day 3+3 days (pain clinic follow-up with physician investigator)
Physical examination performed, vital signs documented.
Determine opioid dose reduction.
Assess for opioid withdrawal and lofexidine adverse effects.
Lofexidine dose adjustment if indicated.

Day 6 +3 days(pain clinic follow-up with physician investigator)
Physical examination performed, vital signs documented.
Determine opioid dose reduction.
Assess for opioid withdrawal and lofexidine adverse effects.
Lofexidine dose adjustment if indicated.

Day 9 + 3 days (pain clinic follow-up with physician investigator)
Physical examination performed, vital signs documented.
Determine opioid dose reduction.
Assess for opioid withdrawal and lofexidine adverse effects.
Lofexidine dose reduction initiated.

Day 12 to 15 (pain clinic follow-up with physician investigator)
Physical examination performed, vital signs documented.
Assess for opioid withdrawal and lofexidine adverse effects.
Determine opioid new baseline dose.
Lofexidine discontinued.
Obtain day 15 assessments.

Days 1-15 (telephone assessment)
Daily telephone call to assess for opioid withdrawal, pain, and lofexidine adverse effects.

B.6. Data Handling

The working database will be maintained on a secure institutional server. All computer files and systems will be password protected and accessible by authorized study personnel only. Data entry will be performed by the research coordinator.

B.7. Data Analysis

Demographics (e.g., age, sex, marital status, educational status, employment status), and clinical characteristics (e.g., pain duration, depression, pain intensity) will be summarized. Mean and standard deviation will be calculated for continuous variables, and count and proportion will be calculated for categorical variables. The primary outcome measure will be the number of patients who discontinue opioid use at day 15. In the analysis of secondary aims, nonparametric paired tests will be used to assess for differences in pre- and post-taper scores of opioid withdrawal, pain intensity, negative affect, and heat pain perception. The frequency of all lofexidine adverse effects will be documented. Perioperative opioid use and pain scores will be summarized.

B.8. Strengths and Limitations

At the conclusion of this project, we will have investigated the effects of lofexidine in adults undergoing opioid tapering. These data will be critical to the design of a future efficacy trial of lofexidine in this patient population.

All study participants will be recruited from the medical and surgical clinics at a tertiary referral medical center. As a result, the study findings may not be applicable to all adults undergoing elective lumbar spine surgery.

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