ORIGINAL ARTICLE

A randomized trial of one-day vs. three-day buprenorphine inpatient detoxification protocols for heroin dependence

John A. Hopper, MD
Joanna Wu, BS
Wesley Martus, BS
James D. Pierre, MD

ABSTRACT

Detoxification from opioids remains an important first step in the treatment of many patients with opioid dependence. Several pharmacologic regimens have been used for opioid detoxification. In the United States, the partial μ-opioid agonist, buprenorphine (BUP) is the most recently approved pharmacotherapy for opioid detoxification and replacement. The literature in recent years has described detoxification protocols using a single high dose of BUP and a three-day BUP regimen. In many settings, such as drug-free programs, a single-dose detoxification protocol would be of significant benefit. There have been no prior studies comparing one-day and three-day BUP-assisted opioid withdrawal.

In this pilot study, we conducted an open-label, randomized trial of one-day vs. three-day BUP/naloxone sublingual tablet-assisted opioid withdrawal. Twenty patients from a therapeutic community treatment program were randomly assigned to receive either 32 mg sublingual BUP over one hour (one-day group), or 32 mg sublingual BUP over three days (three-day group). Nine of 10 subjects (90 percent) in each group completed seven days in the detoxification protocol. There was no statistically significant difference between the two groups in all other outcome variables, including retention in the treatment program, intensity of withdrawal signs and symptoms, amounts of adjunct medications used, and ability to produce opiate-free urine. This study further validates the feasibility of the single high dose of BUP as a rapid detoxification method.

Key words: buprenorphine, detoxification, withdrawal, opioid, heroin

INTRODUCTION

Heroin addiction continues to be a serious problem in the United States. The 2002 National Survey on Drug Use and Health (NSDUH) reports that since the mid-1990s, the prevalence of lifetime heroin use has increased in both youths and young adults.[1] Furthermore, in the past year, 3.7 million Americans reported using heroin at least once in their lives.[1] Detoxification, or "medically supervised withdrawal," is one component of a comprehensive program to treat opioid addiction. Several pharmacological modalities have been used for such a purpose, with buprenorphine (BUP) being the latest agent approved in the United States. BUP is a partial μ-opioid agonist and κ-antagonist. Its unique properties offer several advantages over other detoxification agents, including milder withdrawal symptoms at cessation, lower risk of overdose, and a longer duration of action.[2]

Several studies have reported the effectiveness of a three-day detoxification schedule using a liquid formulation of BUP given sublingually. One study compared the efficacy of a three-day regimen of sublingual (SL) BUP to a five-day course of clonidine for acute detoxification from opioids. BUP was found to be more effective in early relief of withdrawal symptoms.[3] O'Connor[4] compared three methods of opioid detoxification: clonidine, combined clonidine and naltrexone, and BUP given for three days followed by naltrexone. This study demonstrated that the BUP group reported significantly lower mean overall withdrawal symptom scores than the other two groups. Although the detoxification completion and program retention rates among the three groups did not achieve statistical significance, there was a trend toward better retention in the BUP-treated group.[4] Another study conducted by DiPaula[5] using a three-day BUP detoxification regimen again showed high retention in treatment, decreases in withdrawal score, lack of reported adverse events, and a high degree of patient satisfaction. A three-day ambulatory detoxification regimen using intramuscular or tablet BUP formulations with six-month follow-up was described by Gandhi, et al.[6] Almost all patients completed the three-day detoxification regimen, but there was no follow-up between day three and one month after detoxification.[6]

As an alternative to the three-day regimen, a single, high-dose BUP detoxification protocol has also been described in the literature. In Israel, Kutz and Reznik[7,8] tested this regimen in two studies with a total of 30 heroin addicts who were given one dose of a liquid formulation of 32 mg SL BUP. All but one subject completed the seven-day trials with negligible withdrawal symptoms and a smooth transition to naltrexone.[7,8] Recently, Assadi[9] in Iran designed a study comparing patients who received 12 mg BUP intramuscularly over 24 hours to those who received 10.5 mg BUP intramuscularly over five days. The two groups did not significantly differ on treatment retention, successful detoxification, overall symptoms of opioid withdrawal, craving, or drug-induced side effects.[9]

Abstinence-oriented treatment programs, such as those in the therapeutic community, provide an ideal setting for the use of short opiate detoxification programs. Successful withdrawal treatments will allow rapid engagement in counseling and therapy. Although both one-day and three-day BUP-assisted opiate withdrawal protocols have been developed, prior studies have not compared the two methods. In addition, previous studies have used liquid formulations of BUP, rather than the newer, commercially available tablet formulation. Our pilot study compared subjects who received 32 mg SL BUP on the first day of treatment to those who received 32 mg BUP over three days. We speculated that the two groups would exhibit similar treatment retention rates and comparable severity of withdrawal symptoms.

METHODS

Site of study

The study took place at a residential substance abuse treatment program in Detroit, Michigan. Self-Help Addiction Recovery Inc. (SHAR) is a therapeutic community for men and women seeking substance abuse treatment.

Participants

Subjects were eligible for the study if they were enrolled in the SHAR residential treatment program, met the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria for opiate dependence, were able to provide informed consent, and were 18 years of age or older. Exclusion criteria included pregnant or lactating women, known allergy to BUP, and use of BUP in the last 30 days. Participants had been determined to be medically and psychiatrically stable by the program physician at SHAR.

Detoxification protocols

The BUP formulation used was the combined BUP HCl (8 mg)/naloxone HCl (2mg) SL tablet (Suboxone®, Reckitt Benckiser Healthcare, Berkshire, UK). A total of 20 patients were randomly assigned in an open-label fashion to one of the treatment protocols, with 10 patients in each group. On day one, the one-day group received a total of 32 mg of BUP (8 mg initially, and 24 mg 30 minutes later, if patient tolerated 8 mg); patients did not receive any more BUP thereafter. The three-day group received a total of 32 mg of BUP over three days: 8 mg on day one, 16 mg on day two, and 8 mg on day three. The following adjunct medications were available to all participants on an as-needed basis: clonidine for sympathetically mediated withdrawal symptoms; ibuprofen and/or acetaminophen for bone pain, arthralgia, and headache; trimethobenzamide for nausea; loperamide for diarrhea; and diphenhydramine HCl or trazadone HCl for insomnia. Adjunct medications were given at the discretion of the medical staff of SHAR; SHAR staff members were not aware of the subject's group assignment. Total duration of the study was 17 days. Screening and baseline assessments were performed on day one, detoxification and monitoring took place over the next seven days, and follow-up evaluations were conducted on days 14 through 17.

Assessments

At baseline, all subjects were assessed for drug dependence using DSM-IV criteria. During the detoxification and monitoring period, all participants were assessed each morning for withdrawal symptoms using the Clinical Opiate Withdrawal Scale (COWS). SHAR medical staff also documented vital signs, ancillary medications, and adverse events. Urine drug screens (UDSs) were collected on day one, day three or four, day six or seven, and one last time during follow-up evaluation (days 14 through 17).

Method of study conduct

The Human Investigation Committee of Wayne State University approved the study. Written informed consent was obtained from all patients who participated in the study. A test of individual understanding of the procedures was also given prior to enrollment. Participation in the study was voluntary, confidential, and anonymous.

Outcomes

The primary outcome of this study was the number of treatment responders in each group. A treatment responder was defined as a participant who completed the detoxification protocol and remained in the treatment program at the end of seven days. The secondary outcomes were treatment retention at the end of 14 days,

Table 1. Demographics			
	One-Day Group (n = 10)	**Three-Day Group (n = 10)**	**p**
Age (years)	46.5 ± 7.38	47.6 ± 6.08	0.720*
Male (%)	80	50	0.160**
African-American (%)	90	80	0.589**
Married (%)	20	10	0.408**
Employed in the past 30 days (%)	20	20	0.494**
Education (%) (1 to 12 years/some college)	80/20	60/40	0.427**
Route of heroin use (%) (nasal/injection)	60/40	70/30	0.639**
Average amount of heroin used per day (in dollars)	48.25 ± 29.58	60.5 ± 28.42	0.358*
* p value by t-test; ** p value by χ-square.			

intensity of withdrawal signs and symptoms, amounts of ancillary medications necessary to control them, and ability to produce opiate-free urine on day six or seven.

Statistical analysis methods

All analyses were performed using SPSS for Macintosh (Version 11.0) computer statistical package (SPSS, Inc., Chicago, IL). Univariate comparisons between groups were made using independent *t* test for continuous measures and χ-square analysis for categorical variables. Two-tailed probabilities were used for all *t* tests.

RESULTS

Subject characteristics

Twenty eligible SHAR residential treatment program participants enrolled in the study, 10 of which were assigned to each detoxification protocol. The features of the two groups were comparable with no statistically significant differences in demographic or heroin use characteristics (Table 1). At baseline, six subjects in each group met DSM-IV criteria for cocaine dependence. There were no individuals who met criteria for BUP dependence. One subject in the one-day group was alcohol-dependent by DSM-IV criteria, without physiologic dependence.

Treatment responders and treatment retention

All 20 participants received all of the scheduled doses of BUP during the first three days of the protocol. Eighteen of 20 subjects completed seven days in the detoxification protocol. One subject in the one-day group left the program on day five, and one subject in the three-day group left the program on day three. Fourteen-day retention was 70 percent (n = 7) for subjects in the One-Day Group and 50 percent (n = 5) for those in the Three-Day Group, without statistically significant difference (χ-square; p = 0.361).

Severity of withdrawal symptoms

Both groups reported moderate withdrawal symptoms on day one and mild symptoms on days two through seven. Throughout the study, there was no statistically significant difference between groups on the total daily COWS score. The mean total COWS score at baseline for the one-day group was 13.20 ± 3.615, and the mean score for the three-day group was 14.20 ± 2.658 (p = 0.533). The day after the first administration of BUP, the mean total COWS scores for the one-day and three-day groups were 2.50 ± 2.224 and 3.00 ± 2.160, respectively (p = 0.616). COWS scores remained at or below this level for the remainder of the study.

Ancillary medications usage

The two groups required similar amounts of adjunct medications to control their withdrawal symptoms (Table 2). No correlation was detected between the amounts of ancillary medications and daily mean COWS scores.

Table 2. Adjunct medication usage on days 1 through 7				
	Clonidine or clonidine plus other adjunct medications Number of subjects (%)	**No clonidine Number of subjects (%)**	**No adjunct medications given Number of subjects (%)**	**p**
Day 1				
One-Day Group (n = 10)	0	0	10 (100)	0.329*
Three-Day Group (n =10)	1 (10)	1 (10)	8 (80)	
Day 2				
One-Day Group (n = 9)**	7 (77.8)	1 (11.1)	1 (11.1)	0.445*
Three-Day Group (n = 10)	5 (50)	3 (30)	2 (20)	
Day 3				
One-Day Group (n = 9)**	7 (77.8)	0	2 (22.2)	0.319*
Three-Day Group (n = 10)	7 (70)	2 (20)	1 (10)	
Day 4				
One-Day Group (n = 9)**	7 (77.8)	0	2 (22.2)	0.300*
Three-Day Group (n = 9)	6 (66.7)	2 (22.2)	1 (11.1)	
Day 5				
One-Day Group (n = 9)**	6 (66.7)	2 (22.2)	1 (11.1)	0.319*
Three-Day Group (n = 9)	8 (88.9)	0	1 (11.1)	
Day 6				
One-Day Group (n = 8)**	4 (50)	3 (37.5)	1 (12.5)	0.755*
Three-Day Group (n = 9)	3 (33.3)	4 (44.4)	2 (22.2)	
Day 7				
One-Day Group (n = 8)**	3 (37.5)	5 (62.5)	0	0.138*
Three-Day Group (n = 9)	1 (11.1)	5 (55.6)	3 (33.3)	
* p value by χ-square; ** missing data for one subject.				

Almost all subjects received some ancillary medications each day, but the types of medication used in each group were similar. The majority of subjects received clonidine on study days two through five. By day seven, only four of 17 remaining subjects received clonidine.

Abstinence from opiates measured by UDS

All participants had opiate-positive urine specimens at the beginning of the study. Only one subject who was in the one-day group remained opiate-positive during a repeat UDS at day six/seven. At baseline, 80 percent (n = 8) of the one-day group and 70 percent (n = 7) of the three-day group subjects were cocaine-positive on UDS. At day six/seven, one subject remained cocaine-positive on UDS.

DISCUSSION

This is the first study to compare one- and three-day sublingual BUP-assisted opioid withdrawal protocols. Our results confirmed the original hypothesis that high-dose BUP given only on the first day of detoxification would not differ significantly from the three-day regimen on all outcome variables. It is also consistent with study results by Kutz and Reznik[7,8] and Assadi,[9] who demonstrated that a single high-dose BUP was an effective detoxification method. This study conducted urine drug testing during the protocol, which has not been done in many prior detoxification studies.

This study uses commercially available BUP tablets for both detoxification regimens. Previous studies of one- and three-day detoxification regimens have used liquid

formulations for either injection or SL administration. Liquid formulations of BUP have been shown to result in higher plasma levels of drug when compared to equivalent tablet doses, particularly at the 8 mg dose.[10] This study is the first to demonstrate the effectiveness of the tablet formulations of BUP in both three- and one-day detoxification protocols.

The results of this study may be largely dependent on subject characteristics and the supportive environment of the therapeutic community. The inpatient treatment setting may be critical in helping subjects remain engaged in treatment. Although both studies by Kutz and Reznick[7,8] took place with outpatients, this population in Israel seems to have been a highly selected subject group. All of our subjects were heroin-dependent and using similar amounts of drug. Persons with a high level of physiologic dependence and those using long-acting opiates may not respond as well to the single-dose detoxification. Similarly, patients with chronic pain who are maintained on opioids and need detoxification treatment might not respond well to single-dose therapy.

The limitations of this study include the small sample size, lack of control group, and the open-label design. A much larger group of participants may be necessary to detect a significant difference between the two protocols. A control group would be difficult to implement in a study of treatment-seeking individuals. Although a double-blinded study is more desirable, we do not anticipate results from such a design would differ greatly from ours.

The high treatment retention rate at seven days and high dropout rate at 14 days were expected. BUP-assisted opioid detoxification led to much greater initial program retention in the therapeutic community than did historical controls. The overall 14-day retention rate of 60 percent was viewed as a positive improvement at the therapeutic community. At least four patients who left before 14 days had enrolled near the end of the protocol recruitment period and admitted that they sought treatment with the intent of leaving after detoxification.

This study shows similar levels of ancillary medication use by both groups of subjects over the duration of the study. Both groups showed reductions in the use of clonidine, as well as other supportive medications, over the course of the detoxification period. In contrast with some other detoxification regimens,[4,9] benzodiazepines were not needed for this population. In the setting of the therapeutic community, many patients will request supplementary medications during the open dispensary hours. It is not clear whether subjects "required" supplementary medications or if it was simply requested due to availability. The very low COWS scores for all subjects suggest that medication was taken due to availability. Further work in controlled settings is warranted.

In conclusion, one- and three-day BUP detoxification protocols can be equally effective in managing opioid withdrawal in an inpatient setting. The effectiveness and simplicity of the one-day regimen demonstrates that this is a feasible method for opioid detoxification. Further study with a larger number of subjects is warranted.

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John A. Hopper, MD, Departments of Internal Medicine, Pediatrics, and Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, Michigan.
Joanna Wu, BS, Wayne State University School of Medicine, Detroit, Michigan.
Wesley Martus, BS, Wayne State University School of Medicine, Detroit Michigan.
James D. Pierre, MD, Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, Michigan.

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