Published in final edited form as:
Int J Drug Policy. 2012 March ; 23(2): 162–165. doi:10.1016/j.drugpo.2011.06.005.

Short-term safety of buprenorphine/naloxone in HIV-seronegative opioid-dependent Chinese and Thai drug injectors enrolled in HIV Prevention Trials Network 058

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Abstract

Background—Buprenorphine/naloxone (BUP/NX) is not licensed for use in China or Thailand and there was little clinical experience with this drug combination in these countries at the inception of HIV Prevention Trial Network (HPTN) 058, a randomized trial comparing risk reduction counseling combined with either short-term or long-term medication assisted treatment with BUP/NX to prevent HIV infection and death among opioid-dependent injectors.

Methods—We conducted a safety phase that included the first 50 subjects enrolled at each of the three initial study sites (N=150). Clinical and laboratory assessments were conducted at baseline and weekly for the first 4 weeks. Changes in laboratory parameters were estimated with random effects models.

Results—BUP/NX was well tolerated by study subjects and opioid withdrawal scores decreased substantially during the 3-day induction. Two participants experienced grade 3 clinical adverse

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ClinicalTrials.gov identifier: NCT00270257

events, which were categorized as probably not related to the study drug. Grade 2 or 3 increases in alanine aminotransferase (ALT) occurred in 25 (17%) subjects. The magnitude of ALT increase over 4-week follow-up was strongly associated with baseline ALT elevation.

Conclusions—In Chinese and Thai opioid-dependent injectors, we found BUP/NX to be effective in reducing opioid withdrawal symptoms and safe during short-term use. ALT increases were observed over 4-week-follow-up, which are consistent with reports from Western populations. Long-term safety and efficacy evaluations are indicated.

Keywords

buprenorphine/naloxone; injection drug use; opioid dependence; HIV prevention; risk reduction counseling; safety; hepatic toxicity

Introduction

HIV Prevention Trial Network (HPTN) 058 is a phase-3 randomized controlled trial comparing behavioral drug and risk-reduction counseling combined with either short-term or long-term medication assisted therapy (ST-MAT and LT-MAT, respectively) with buprenorphine/naloxone (BUP/NX) to prevent HIV infection and death among HIV-seronegative, opioid-dependent injectors in China and Thailand. Sublingual BUP/NX is an effective treatment for opioid dependence (Fudala et al. 2003; Mattick et al. 2008) and has a lower risk of respiratory depression or overdose than methadone because of partial agonist activity at the opioid mu-receptor (Centers for Substance Abuse Treatment 2004). Naloxone is co-formulated with buprenorphine to reduce the likelihood of misuse by injection (Stoller et al. 2001).

BUP/NX has been widely used in Western Europe, North America, and Australia. However, BUP/NX is not licensed for use in China or Thailand and there was no clinical experience with this drug combination in these countries at the inception of HPTN 058. The HPTN 058 protocol stipulates thrice-weekly observed dosing for participants assigned to the LT-MAT arm. While thrice-weekly BUP/NX dosing has been studied (Schottenfeld et al. 2000), there is substantially less clinical experience with thrice-weekly dosing than with daily dosing. Because of these issues, we conducted a 4-week safety phase to demonstrate the feasibility of our treatment protocol and to provide detailed safety data to regulatory authorities in China and Thailand and to the drug manufacturer.

Methods

Study design and participants

A total of 1500 subjects will be enrolled in HPTN 058. This report describes the first 4 weeks of treatment in the initial 50 subjects enrolled at each of 3 original study sites: Guangxi, China, Xinjiang, China, and Chiang Mai, Thailand. This study was approved by review committees at all participating sites (acknowledgments).

We provided drug and risk-reduction counseling for all subjects weekly for 12 weeks, and monthly thereafter through week 52. All subjects began a 3-day induction to BUP/NX on the day of randomization (day 1). The BUP/NX dose was titrated upward during induction to relieve opioid withdrawal symptoms, as measured by the Clinical Opioid Withdrawal Scale (COWS) (Wesson & Ling 2003). Subjects assigned to ST-MAT began dose tapering at day 4 and discontinued BUP/NX by day 18. Subjects assigned to LT-MAT received daily observed BUP/NX for 3 weeks, and then were converted to thrice-weekly observed BUP/NX through week 52.

Individuals were eligible for HPTN 058 if they were at least 18 years old, HIV-seronegative, met Diagnostic and Statistical Manual of Mental Disorder, fourth edition (DSM-IV) (American Psychiatric Association 1994) criteria for opioid dependence, had a positive urine drug test for opiates, and reported opioid injection 12 or more times in the prior 28 days. Exclusion criteria included current or recent use of MAT in a clinician-guided program, allergy to BUP/NX, alcohol or benzodiazepine dependence by DSM-IV criteria, pregnancy, breastfeeding, or unwillingness to use birth control if female, alanine aminotransferase (ALT) > 3 times upper limit of normal (ULN), hemoglobin < 8g/dL (if male) or 7g/dL (if female), bilirubin > 2.5 times ULN, or platelet count < 50, 000/mm^3.

Safety phase

The first 50 participants at each of three initial study sites were enrolled in the safety phase and had clinical and laboratory assessments at baseline and weeks 1, 2, 3, and 4. Subjects completed an interviewer-administered acceptability questionnaire at week 4. Adverse events were categorized and graded according to the Division of AIDS Adverse Event Tables (available at http://rsc.tech-res.com/safetyandpharmacovigilance). Grade 2, 3, and 4 clinical events were defined as moderate, severe, and life threatening, respectively. Grade 2, 3, and 4 changes in laboratory parameters were defined as 9.0 –9.9 g/dL, 7.0 – 8.9 g/dL, and < 7.0 g/dL for hemoglobin; 50, 000 – 99, 999/mm^3, 25, 000 – 49, 999/mm^3, and < 25, 000/mm^3 for platelets; 1, 500 – 1, 999/mm^3, 1, 000 – 1, 499/mm^3, and < 1, 000/mm^3 for white blood cell count; 1.4 – 1.8 times ULN, 1.9 – 3.4 times ULN, and > 3.5 times ULN for creatinine; 2.6 – 5.0 times ULN, 5.1 – 10.0 times ULN , and >10 times ULN for ALT; and 1.6 – 2.5 times ULN, 2.6 – 5.0 times ULN, and > 5.0 times ULN for total bilirubin. Laboratory values for the above parameters were measured locally with laboratory equipment and assays that were subject to routine proficiency testing according to HPTN protocol.

Changes in laboratory parameters over weeks 0 to 4 were estimated with random effects models with random intercepts, adjusting for study site and gender. Changes were considered statistically significant if the 95% confidence intervals (CIs) for 4-week slope did not include 0. We assessed associations of participant characteristics with 4-week changes in ALT by including terms in the models for interactions between factors of interest and time. We assessed age, gender, study site, baseline ALT level, baseline bilirubin level, reactive hepatitis B surface antigen, reactive hepatitis C antibody, self-reported alcohol use, and benzodiazepine-positive drug screen at baseline.

Results

Baseline characteristics

Baseline characteristics of the 150 participants enrolled during the safety phase of HPTN 058 are shown in Table 1. Participants were predominantly male, positive for hepatitis C antibody, and daily injectors. Opium injection was reported only in Chiang Mai, Thailand.

BUP/NX induction, counseling visit adherence, and participant satisfaction

The median BUP/NX dose (expressed as mg of buprenorphine) was 8 mg (interquartile range [IQR] 8–8 mg) on day 1, 16 mg (IQR 12–16 mg) on day 2, and 20 mg (IQR 16–24 mg) on day 3. Correspondingly, pre-dosing COWS scores declined from 10 (IQR 9–12) to 5 (IQR 3–7) to 3 (IQR 2–6) on days 1, 2, and 3, respectively. We observed no episodes of precipitated opioid withdrawal with BUP/NX induction. Adherence to the protocol was high, with 145 (97%) subjects completing the 3-day induction and 134 (89%) completing the first 4 counseling visits. At the week-4 acceptability assessment 114 (77%) subjects

agreed with the statement, “BUP/NX is helpful, ” and only 2 (1%) participants agreed with the statement, “I do not like the way BUP/NX makes me feel.”

Adverse events and changes in laboratory parameters

During the first 4 weeks of treatment, 2 clinical adverse events were reported: gastroenteritis (grade 3, probably not related) and osteomyelitis (grade 3, probably not related). The events resolved in 2 days and 5 weeks, respectively.

Baseline laboratory values and estimated 4-week changes in values are shown in Table 2. A statistically significant decrease from baseline was observed for platelet count, and statistically significant increases were observed for creatinine, total bilirubin, and ALT. However, the toxicity grade distributions for platelet count, creatinine, and total bilirubin in the first 4 weeks of treatment were similar to baseline (Table 2). In contrast, 19 (12.9%) and 6 (4.1%) subjects had grade 2 and grade 3 ALT levels during follow-up, respectively, compared to just 4 (2.7%) subjects with grade 2 ALT levels at baseline, . The average estimated 4-week increase in ALT was 18 U/L (95% CI 12 to 24 U/L). No grade 4 severity changes were observed for the laboratory parameters assessed.

In unadjusted models, study site and ALT elevation at baseline were significantly associated with ALT increases during follow-up. The estimated 4-week increase in ALT was 27 U/L (95% CI 18 to 35) in subjects with grade 1 or 2 ALT at baseline compared to just 2 U/L (95% CI −4 to 8) in subjects with normal baseline ALT. The estimated 4-week ALT increase was 9 U/L (95% CI −2 to 19) in Chiang Mai, Thailand, 22 U/L (95% CI 11 to 32) in Guangxi, China, and 25 U/L (95% CI 14 to 36) in Xinjiang, China. Gender, reactive hepatitis B surface antigen, reactive hepatitis C antibody, alcohol use, and positive benzodiazepine drug screen at baseline were not statistically significantly associated with 4-week ALT change.

Discussion

HPTN 058 is enrolling participants in China and Thailand, where BUP/NX has not previously been used, and includes thrice-weekly observed dosing in the LT-MAT arm, with which clinical experience is limited. Because of these issues, we conducted a 4-week safety phase comprising the first 50 subjects enrolled at each of the three initial sites. We found that BUP/NX was safe, well tolerated, and effective in reducing opioid withdrawal signs and symptoms in opioid-addicted Chinese and Thai injectors. The two observed clinical adverse events during the safety phase were categorized as probably not related to BUP/NX. We observed a statistically significant decrease in platelet count and statistically significant increases in creatinine and total bilirubin. However changes in these parameters were unlikely to be of clinical significance as only a single participant experienced a grade 3 or higher abnormality in these parameters (platelet count).

In contrast, the average 4-week ALT increase was 18 U/L and 25 subjects (17%) experienced grade 2 or 3 ALT increases. Elevations in hepatic transaminases with BUP treatment have been reported previously (Lange et al. 1990) and clinical guidelines recommend monitoring transaminase levels in patients treated with BUP or BUP/NX (Centers for Substance Abuse Treatment 2004; Johnson et al. 2003). Additionally, case reports have linked BUP use with acute symptomatic hepatitis with or without concurrent renal failure (Berson et al. 2001b; Herve et al. 2004; Houdret et al. 1999; Zuin et al. 2009). Most of these cases resolved spontaneously with decreased BUP dose or drug discontinuation, and rechallenges with BUP were sometimes tolerated. On the basis of an *in vitro* rat model, one group suggested that BUP hepatitic toxicity is mediated by mitochondrial toxicity and is correlated with drug concentration (Berson et al. 2001a)

In a cohort of 120 BUP-treated subjects with laboratory data from baseline and 6 to 12 weeks after starting BUP, Petry and colleagues reported that the median ALT concentration increased by 8.5 U/L (P=0.04) in subjects with hepatitis B or hepatitis C infection, but did not change significantly in subjects without viral hepatitis (Petry et al. 2000). In contrast, Bruce and Altice identified 4 patients who initiated BUP/NX during acute hepatitis C infection and found that transaminase concentrations decreased in all patients following initiation of BUP/NX (Bruce & Altice 2007). In our study, elevated baseline ALT levels were strongly associated with larger increases in ALT during 4-week follow-up. However, neither hepatitis C nor hepatitis B was statistically significantly associated with 4-week ALT change.

Data from the safety phase of HPTN 058 demonstrate that BUP/NX is safe and effectively reduces opioid withdrawal symptoms in Chinese and Thai injectors – populations with little or no clinical experience with BUP/NX. Completion rates for medication visits and counseling sessions during the safety phase were high and a substantial majority reported satisfaction with treatment at the week-4 survey. We observed increases in ALT concentrations during the first 4 weeks of therapy that are consistent with prior reports from Western populations. The long-term persistence and clinical significance of early ALT increases are not known and warrant assessment.

Acknowledgments

This study was approved by Chiang Mai University Research Institute for Health Sciences, Thailand; Ministry of Public Health Ethical Review Committee for Research in Human Subjects, Nonthaburi, Thailand; Guangxi Center for Disease Prevention and Control Institutional Review Board (IRB), China; Xinxiang Uighur Autonomous Region Bureau of Health Disease Control and Treatment IRB, China; The Chinese National Center for AIDS/STD Control and Prevention IRB; and Johns Hopkins Medicine IRB, United States. We want to acknowledge Marek Chawarski, David Burns, Deborah Donnell, and Scott Rose for their valuable input on the manuscript.

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Table 1

Baseline characteristics of 150 opioid-dependent, HIV-seronegative participants enrolled in the safety phase of HPTN 058.

Characteristics	Guangxi, China (n=50)	Xinjiang, China (n=50)	Chiang Mai, Thailand (n=50)	Overall (N=150)
Treatment assignment, n (%)				
LT-MAT	26 (52)	25 (50)	26 (52)	77 (51)
ST-MAT	24 (48)	25 (50)	24 (48)	73 (49)
Age (years), median (IQR)	32 (28–38)	36 (30–40)	36 (31–42)	35 (29–40)
Male, n (%)	47 (94)	42 (84)	42 (84)	131 (87)
Hepatitis B surface antigen positive, n (%)	11 (22)	11 (22)	6 (12)	28 (19)
Hepatitis C antibody positive, n (%)	48 (96)	42 (84)	35 (70)	125 (83)
Opioid injected, n (%)				
Heroin	50 (100)	50 (100)	6 (12)	106 (71)
Opium	0	0	45 (90)	45 (30)
Days injected in prior month, median (IQR)	28 (28–30)	30 (30–30)	30 (29–30)	30 (28–30)
Urine drug test positive, n (%)				
Opiate	50 (100)	50 (100)	50 (100)	150 (100)
Benzodiazepine	24 (48)	0	10 (20)	34 (23)
Methadone	0	0	4 (8)	4 (3)
Amphetamine	0	0	0	0
Drank alcohol in prior 6 months, n (%)	32 (64)	5 (10)	26 (52)	63 (42)

LT-MAT, long-term medication assisted therapy; ST-MAT, short-term medication assisted therapy

Table 2

Baseline and 4-week changes in laboratory parameters in 150 opioid-dependent, HIV-seronegative subjects enrolled in the safety phase of HPTN 058.

Laboratory parameter	Baseline			Week 4			
	Value, median (IQR)	Severity [a], n (%)		Change from baseline[b] (95% CI)	P value	Severity [a], n (%)	
		Grade 2	Grade 3			Grade 2	Grade 3
Hemoglobin (g/dL)	14.5 (13.1, 15.5)	0	1 (0.6)	0.01 (−0.12 to 0.15)	0.85	0	1 (0.7)
Platelets (K/mm^3)	243 (193, 283)	5 (3.3)	0	−23 (−31 to −16)	<0.001	4 (2.7)	1 (0.7)
WBC (K/mm^3)	7.6 (6.4, 9.3)	0	0	−0.2 (−0.5 to 0.2)	0.30	0	0
Creatinine (mg/dL)	0.8 (0.7, 0.9)	0	0	0.03 (0.01, 0.04)	<0.001	0	0
ALT (U/L)	36.5 (23, 62)	4 (2.7)	0	18 (12, 24)	< 0.001	19 (12.9)	6 (4.1)
Total bilirubin (mg/dL)	0.6 (0.5, 0.8)	3 (2.0)	0	0.07 (0.03, 0.11)	<0.001	6 (4.1)	0

[a] See text for definitions.

[b] Adjusted for gender and study site.