Buprenorphine dosing every 1, 2, or 3 days in opioid-dependent patients

Abstract  Rationale: Administration of double the maintenance dose of buprenorphine has been shown to permit every-other-day dosing. Whether longer periods between dosing can be achieved is unknown. Objectives: To examine whether triple the maintenance dose can be administered every 72 h without opioid withdrawal or intoxication. Methods: Sixteen opioid-dependent outpatients each received three conditions (1) the maintenance dose of buprenorphine every 24 h, (2) double the maintenance dose every 48 h, and (3) triple the maintenance dose every 72 h under double-blind placebo-controlled conditions. Each condition was imposed in a random sequence for 21–22 days. Self report and observer measures were taken at 24-h intervals. Results: No significant differences were observed on measures of opioid agonist and withdrawal effects between the dosing conditions. However, averaging effects across conditions may obscure important within-condition effects. When conditions were analyzed by individual days within a condition, several significant effects were observed. For example, 24 h after administration of triple the maintenance dose, significant effects were observed in eight opioid agonist measures. Also, 72 h after administration of triple the maintenance dose, significant effects were observed on four measures of withdrawal. Neither adverse medical reactions nor excessive opioid intoxication were observed. Conclusions: These results suggest that buprenorphine may be administered safely every 72 h by tripling the maintenance dose, with only minimal withdrawal complaints. Importantly, this 72-h dosing may permit patients to attend clinic thrice weekly without the use of take-home doses.

Key words  Buprenorphine · Heroin dependence · Opioid dependence · Human · Opioid withdrawal · Treatment

Introduction

Buprenorphine is a low efficacy, partial mu-opioid agonist under investigation as a medication for the treatment of opioid dependence (see Bickel and Amass 1995, for review). Buprenorphine’s utility as a medication stems from its unique profile of effects. This profile includes a ceiling on agonist activity that decreases toxicity and the possibility of overdose (Lange et al. 1990), and may limit its abuse liability (Walsh et al. 1995). Buprenorphine also exhibits opioid antagonist activity in that it blocks the effects of exogenously administered opioids in a dose-related manner (Bickel et al. 1988a; Rosen et al. 1994) and can precipitate withdrawal (Aceto 1984; Jacobs and Bickel 1999). Moreover, buprenorphine’s slow dissociation from µ-opioid receptors (Rance and Dickens 1978) results in a long duration of action (Jasinski et al. 1978). Clinical trials suggest buprenorphine has efficacy comparable to methadone (Bickel et al. 1988b; Kosten et al. 1993; Ling et al. 1996; Schottenfeld et al. 1997).

Buprenorphine’s ceiling on agonist activity, along with its long duration of action, has led to the examination of alternate-day dosing schedules, where the medication is administered every other day (Fudala et al. 1990; Johnson et al. 1995; Amass et al. 1994, 1998). These less than daily dosing procedures, if clinically efficacious, may result in at least three benefits. First, less than daily attendance may remove the barrier to treat-
moment imposed by a long commute to the treatment facility. Second, because these alternative dosing approaches do not entail the use of take-home medication, they may prevent illegal medication diversion. Third, by reducing the number of clinic visits for each patient, these dosing procedures may permit more patients to be served by treatment facilities.

Alternative dosing schedules were initially examined in a study where the standard daily buprenorphine maintenance dose was administered every 48 h (Fudala et al. 1994). Specifically, two groups of opioid-dependent inpatients received 8 mg buprenorphine sublingual (SL): one group received that dose every day, while the other group received that dose every other day with placebo administered on the intervening days. Although group differences were not observed on measures of self-reported drug and withdrawal effects, increased reports of urges for opioids and dysphoria followed administration of placebo within the alternative-day group. These findings were systematically replicated in a larger, placebo-controlled, outpatient study that compared the effects of administering 8 mg buprenorphine SL every day with the effects of administering that same buprenorphine dose every other day in two groups of patients (Johnson et al. 1995). Again, no significant group differences were observed. However, the group receiving buprenorphine every other day exhibited worse outcomes on measures of retention, medication compliance, illicit opioid use, and self-reported withdrawal relative to the daily dosing group. These two studies suggest that providing the maintenance dose every 2 days results in withdrawal during the second day.

A better profile of results was produced by alternate-day dosing procedures that administered twice the daily dose every other day (Amass et al. 1994, 1998). For example, in a double-blind, placebo-controlled, crossover trial, opioid-dependent outpatients were exposed to 8 mg/70 kg of buprenorphine SL every day and 16 mg/70 kg SL every other day (Amass et al. 1994). Significant differences were not found between alternate-day and daily dosing in terms of opioid intoxication, opioid withdrawal, the ability to discriminate placebo from active doses, or treatment retention. Subject-rated opioid agonist ratings, however, distinguished the two treatments, with alternate-day treatment producing lower agonist ratings. A systematic replication of this study demonstrated that administering double the maintenance dose every 48 h produced results comparable to daily dosing when examined under open-label conditions. Importantly, that study also demonstrated that patients preferred double the maintenance dose when given a choice between double the maintenance dose every other day or every day dosing with the maintenance dose (Amass et al. 1998). Collectively, these studies suggest that double the maintenance dose does not increase withdrawal symptomatology.

The results obtained with alternate-day dosing, where double the maintenance dose was administered every other day, raise the possibility that even less frequent dosing may be possible and effective with buprenorphine. To investigate this possibility, the current study used a double-blind, placebo-controlled, crossover design to examine (1) whether tripling the buprenorphine maintenance dose would permit dosing once every 72 h and (2) replicate our prior findings of doubling the maintenance dose every 48 h. These two conditions were compared to a condition where the maintenance dose was administered every 24 h. Central to this study is to determine whether sufficient withdrawal or agonist effects would be observed that would preclude clinical application. To observe these effects required that results not be confounded by illicit opioids, thus evidence of continued illicit opioid use was grounds for discontinuation from the study.

### Materials and methods

#### Subjects

Sixteen opioid-dependent outpatients (13 male, three female) completed the study. Individuals had to be ≥18 years old, in good health, meet DSM-III-R criteria for opioid dependence and FDA qualification criteria for methadone treatment (i.e., a history of opioid dependence and either significant current opioid use, e.g., opioid-positive urine samples, or signs of opioid withdrawal, e.g., gooseflesh, sweating, lacrimation, excessive yawning, etc.) for inclusion. Health status was determined by history, physical exam, and laboratory evaluation (including electrocardiogram, complete blood cell count, clinical chemistry profiles, and urinalyses). Evidence of active psychosis, manic-depressive illness, organic psychiatric disorders or serious medical illness (e.g., cardiovascular disease) were exclusion criteria. Co-dependence for cocaine, ethanol or sedative-hypnotics did not exclude individuals from participation. The study was approved by the appropriate Institutional Review Board for human research. Subjects provided written informed consent after receiving a full explanation of the procedures. Five additional subjects were enrolled but failed to complete the study: Three subjects withdrew from the study for personal reasons, one subject was discharged for repeated opioid use during the double the maintenance dose every 48 h condition, and one subject was discharged for violating urinalysis testing procedures in the maintenance dose every 24 h condition.

Subjects completing the protocol had a mean age of 36.9 years (range 21–44), and mean weight of 82.8 kg (range 61–114). Subjects reported using opioids regularly for an average of 8.9 years (range 1–23) and spending $468.8 (range $10–2000) per week on opioids; all subjects reported using opioids intravenously. Nine subjects received one previous treatment episode with buprenorphine, and an additional subject received four previous treatment episodes with buprenorphine via participation in prior research protocols. Weekly pregnancy tests conducted with the three female subjects were negative throughout the study.

#### General procedures

Continuation in the study and weekly monetary compensation ($50 per week) for participation were contingent on daily clinic attendance and opioid abstinence. In order to facilitate collection of dependent measures every 24 h, subjects were required to attend the clinic at the same time each day. Participation was discontinued immediately if a subject missed a clinic visit, and participants were offered either a referral to another treatment facility or a detoxification treatment in our clinic. Opioid abstinence was confirmed via urinalysis. Urine samples were collected thrice weekly (Mondays, Wednesdays and Fridays) under observation and analyzed immediately onsite for the presence of opioids using the En