INTERNATIONAL PERSPECTIVE

Buprenorphine in Opiate Withdrawal: A Comparison with Clonidine

A. K. Nigam, MD, R. Ray, MD, and B. M. Tripathi, MD
De-addiction Center, Department of Psychiatry, All India Institute of Medical Sciences, New Delhi - 110029, India

Abstract—Clinical efficacy of buprenorphine in controlling withdrawal symptoms was compared against clonidine among 44 opiate dependent males. Subjective and objective withdrawal symptoms were assessed by withdrawal rating scales daily for 10 days. The subjects were randomly assigned to fixed dose schedule of either buprenorphine (0.6-1.2 mg per day, sublingually) or clonidine (0.3-0.9 mg per day, oral) for 10 days. Buprenorphine was found superior to clonidine in alleviating most of the subjective and objective opiate withdrawal symptoms. Subjective symptoms declined earlier among the subjects receiving buprenorphine. No untoward side-effects of buprenorphine were noticed.

Keywords—opiate withdrawal; buprenorphine; clonidine; treatment-efficacy.

INTRODUCTION

Opiate withdrawal symptoms are very unpleasant and often chronic use continues solely to obtain relief from these symptoms. Hence, management of the withdrawal state is the crucial first step in treatment of opiate dependence. Of the many pharmacological agents tried, methadone has possibly been used most extensively (Jaffe, 1989). However, methadone is not available in many countries including India. Other drugs used are levo-acetyl-methadol (Blaine, 1978), d-propoxyphene (Miller, Fiengold, & Poxinor, 1968), and clonidine (Camí et al., 1985). Agren (1986) in a review article concluded that clonidine produced marked reduction of opiate withdrawal symptoms. However, certain symptoms like sleeplessness and body-aches did not respond well to clonidine (Gossop, 1988). Hypotension as a side effect was a major limitation.

Recently, buprenorphine has been found to be useful in treating opiate withdrawal. Buprenorphine, being a partial opiate agonist, suppresses withdrawal symptoms effectively. It binds strongly to the receptor sites and blocks euphoria caused by further opiate use (Heel, Brogden, Speight, & Avery, 1979; Harcus, Ward, & Smith, 1979; Fudala, Jaffe, & Dax, 1990). Its adverse effects and withdrawal symptoms following abrupt cessation are minimal (Harcus et al., 1979). As a matter of fact Jasinski, Johnson, and Kocher (1985) felt that buprenorphine could be an ideal agent for opiate detoxification. Bickel et al. (1988) found buprenorphine as effective as methadone.

The present study was undertaken to evaluate therapeutic efficacy of buprenorphine for opiate detoxification as against clonidine.

MATERIALS AND METHODS

Male subjects between 15-50 years satisfying DSM-III-R (APA, 1987) criteria for opioid dependence were included. The subjects were hospitalised voluntary patients and given informed consent for inclusion in the study. Subjects reporting after 48 hours of use of opiates, having multiple drug dependence and having contraindications of either clonidine or buprenorphine use were excluded.

The subjects received clonidine (Group A) or buprenorphine (Group B) randomly. Clonidine was
given orally for 10 days in three divided doses as mentioned below: day 1 - 0.3 mg, day 2 - 0.6 mg, day 3 to 8 - 0.9 mg, day 9 - 0.6 mg and day 10 - 0.3 mg. The other group received buprenorphine sublingually also in three divided doses: day 1 - 0.6 mg, day 2 - 0.8 mg, day 3 to 8 - 1.2 mg, day 9 - 0.8 mg and day 10 - 0.6 mg. On day 11 all drugs were stopped.

Clinical assessment and history of drug use were recorded. Withdrawal symptoms were assessed each day at 9:00 a.m. using Subjective Opiate Withdrawal Scale (SOWS) and Objective Opiate Withdrawal Scale (OOWS) (Handelsman et al., 1987). SOWS has 16 items and these were assessed as per subject’s self report on a 4 point scale (0 - absent, 1 - mild, 2 - moderate and 3 - severe). Each item was scored and highest possible score was 48. OOWS has 13 items and was assessed by the first author and rated as present/absent. Highest possible score was 13.

Urinary screening of opiate by thin layer chromatography (TLC) was done among the subjects.

RESULTS

Sample Characteristics

Mean age of the entire sample was 28.7 ± 7.2 years, 63.6% were married, 91.7% were employed and 86.1% had education below 10 years. None were illiterate. Most of the subjects (90.0%) were using heroin (Brown Sugar; street sample purity in India is about 25%). Heroin was chased and opium was consumed orally. None were intravenous users. The subjects were using heroin for 4-5 years and an average of 1.5 gms/day in the previous month. The two groups (Group-A and Group-B) were comparable as regards their demographic features and drug use history. Subjective and objective scores were also similar in both the groups on the first day.

Therapeutic Effects

Subjective withdrawal scores were significantly lower among patients receiving buprenorphine (Table 1). Mean cumulative score for each symptom during the 10 day period was also calculated. Muscle ache, restlessness, and yawning were most prominent in descending order in both the groups. These were significantly less among patients receiving buprenorphine. Objective withdrawal scores during these 10 days were also less among patients receiving buprenorphine. The difference was statistically significant (Wilcoxon’s rank sum test) on third (5.2 ± 2.2 vs 3.0 ± 2.3, p < 0.002) and fourth (3.7 ± 1.8 vs 2.3 ± 2.2, p < 0.002) days. Subjects receiving buprenorphine had a lower score. This is clearly shown in Figure 1. Mydriasis and tremor were the two most prominent signs. Only tremor was significantly less among group-B. Overall, both subjective and objective symptoms were less intense and less sustained among subjects receiving buprenorphine. Subjective withdrawal symptoms declined significantly on seventh (Zst value -3.28, p = 0.0005) and fifth (Zst value -2.82, p = 0.002) day in group-A and group-B, respectively, as compared to the first day. Highest SOWS score was obtained on the second day for the groups. Significant reduction (Wilcoxon’s rank test) from the highest score was seen on the fourth and third days for group-A and group-B, respectively. Objectively, scores lessened significantly for both the groups on the fourth day as against the highest score obtained on the second day (Figure 1).

Side Effects

Three patients receiving clonidine were dropped from the study because of hypotension (B.P. < 90/60 mmHg). Most of these patients (80%) complained of giddiness. Dry mouth (48%) and constipation (33%) were other significant side effects. Nausea (17%) and vomiting (17%) and constipation (13%) were the most common side effects reported by the patients receiving buprenorphine.

Additional Medicines

Most of the patients (75%) in either of the groups needed nitrazepam 15 mg p.o. at bed time as a hypnotic agent. Immodium and aspirin were prescribed to a few subjects.

Thin Layer Chromatography Findings

It was possible among 27 subjects. Urinary opiate was positive among 3 patients on the second day and 1 on third day. None were positive from fourth day onward.
Safe detoxification under medical supervision is essential to initiate treatment of drug dependence. Both clonidine (Cami et al., 1985; Agren, 1986; Gossop, 1988; Jasinski et al., 1985; Gangadhar, Subramanya, Venkatesh, & Channabasavana, 1982; Gupta & Jha, 1988) and buprenorphine (Bickel et al., 1988; Johnson, Pharn, Cone, Henningfield, & Fudala, 1989; Fudala et al., 1990) have been found effective in treatment of opiate withdrawal state. To the best of our knowledge, as yet, there is no published report comparing buprenorphine and clonidine for opiate detoxification. In this study it was observed that withdrawal symptoms, both subjective and objective, were better controlled with buprenorphine in comparison to clonidine. Subjective symptoms like muscle ache, restlessness, yawning, cold flashes, and tearfulness were also relieved earlier during treatment with buprenorphine. The overall symptom profile resembled classical opiate withdrawal. However, the withdrawal symptoms were less severe among our patients. This may be related to lower potency of street heroin, lower average daily consumption, chasing rather than intravenous use and shorter duration of dependence.

Dosage of clonidine used in this study was in keeping with the published literature. Dosage of buprenorphine for opiate detoxification has not been established. In earlier studies (Bickel et al., 1988; Fudala et al., 1990) buprenorphine in dose range of 2–16 mg per day sublingually was used. The dose of buprenorphine (up to 1.2 mg per day) used in this study was lower as compared to earlier reports. It is likely that the subjects in our study had less severe withdrawal and, hence, obtained relief even on a lower dose.

Insomnia was not controlled with either clonidine or buprenorphine alone. Most of the patients needed nitrazepam 15 mg p.o. at bed time. Bickel et al. (1988) reported that one third of their patients required temazepam along with buprenorphine.

Clonidine, being a non-narcotic drug, has been favoured by some workers (Cami et al., 1985; Agren, 1986; Gossop, 1988; Gupta & Jha, 1988) but has a limited role in out-patient programmes because of hypotensive effect. Buprenorphine, on the other hand, has very few side effects. However, its efficacy has to be judged against its dependence liability (W.H.O., 1989). Recently, case reports on buprenorphine abuse and dependence have been published (Connor, Moloney, Travers, & Campbel, 1988; Lal, 1991).

In summary, buprenorphine even in analgesic dose was superior to clonidine for opiate detoxification. No significant side effects of buprenorphine were noticed. It is our suggestion that variable dose regimen should be studied on larger sample size to establish the optimal dose of buprenorphine for detoxification. The risk of dependence on buprenorphine should be kept in mind.
REFERENCES


