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ABUSE LIABILITY OF BUPRENORPHINE - A STUDY AMONG EXPERIENCED DRUG USERS

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Abstract : Six male post-detoxified opiate dependent subjects were evaluated for abuse liability of buprenorphine (0.6 mg), morphine (16 mg), pentazocine (30 mg) and distilled water (placebo) intramuscular injection in a single blind cross-over random order. Subjective states, drug discrimination, drug linking, sedation and euphoria were assessed at pre-injection, 30 min and 4 hrs post-injection.

Buprenorphine caused significant euphoria and was identified as heroin. On all parameters, buprenorphine resembled morphine rather than pentazocine and placebo. The data suggest that abuse liability of buprenorphine is similar to morphine i.e. moderate rather than low.

Key words : buprenorphine abuse liability human volunteers

INTRODUCTION

The agonist-antagonist opioids compounds viz buprenorphine, butorphanol, nalbuphine and pentazocine were developed with the claim that their abuse potential is low (1). Buprenorphine at low dose, produces morphine like effects, however, at higher doses it has antagonist properties with minimal dsyphoria (2).

Besides its analgesic effects, buprenorphine has been found to be useful for opioid detoxification (3). Further, it blocks opioid induced euphoria and suppresses opiate self administration (4, 5). Thus several authors have proposed it as a suitable compound for long term treatment of heroin dependence and alternative to methadone maintenance (6, 7).

Therapeutic efficacy of such a drug must also be assessed against its possible abuse potential. Case reports of abuse of buprenorphine have been reported from Australia, New Zealand, Germany, U. K. and recently India (8–11). Between 12–14% of patients registered in our OPD (De-addiction Centre, AIIMS) abuse buprenorphine intravenously either along or in combination with diazepam and promethazine (unpublished data), though, abuse of buprenorphine tablet is rare.

Case reports of buprenorphine abuse need to be supplemented with human drug

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abuse liability test. In a typical experimental situation, a small number of subjects in a residential unit, are given single or multiple dose of reference drugs (positive control) and placebo. A within-subject design is preferred and various subjective and objective parameters are measured at multiple intervals following drug administration.

The present study was undertaken to test abuse liability of buprenorphine among post-detoxified heroin dependent subjects using the above paradigm.

METHODS

Male subjects between 16–50 years with heorin dependence, participated in the study following their detoxification after obtaining informed consent. The study was approved by the Institute's Ethics Committee. They did not receive any opiates viz. codeine, buprenorphine, pentazocine or propoxyphene for at least two weeks prior to the study. Further, they were free of all psychoactive drugs including benzodiazepines for at least 48 hours prior to the study and stayed in the de–addiction ward during the entire study period. This ensured their drug free status.

Subjects having multidrug dependence, contraindications for use of opiates (e.g. bronchial asthma, corpulmonale, chronic lung disease, benign prostatic hypertropy) and associated syndromal psychiatric diagnosis were excluded. All the subjects were negative for urinary opiates during the experiments, as evidenced by Thin Layer Chromatography (TLC) (15).

Drug administration

Each subject received single intramuscular administration of the following drugs in equianalgesic dose (16) : morphine 16 mg, pentazocine 30 mg, buprenorphine 0.6 mg and placebo (2 ml of distilled water).

Each injection was given a number code and administered in a random single blind cross-over fashion. A gap of 48 hours between administrations of any two drugs was kept.

Assessment and tools

The subjects were informed that they were likely to receive either drug(s) which might produce intoxication or a chemically inert substance. They were expected to report the current subjective states as accurately as possible. Further, they were instructed to remember the effects of various drugs identified by the number code.

Following these injections, acute drug effects, drug liking, drug discrimination, drug identification, euphoria and sedation were assessed. Physiological parameters like pulse rate, blood pressure and respiration rates were also noted. Three assessments on each day of experiment were carried out. These were: pre-injection, 30 mins and 4 hours post-injection. The above procedures were repeated following administration of all the four compounds.

Instruments

1. Single Dose Opiate Questionnaire (SDQ) (17) : SDQ measures subjective and objective

effects of drugs like morphine. It has 4 questions namely subjective awareness of any drug, drug identification from a list of commonly used addictive substances, acute effects of morphine and degree of liking on a 4 point scale.

2. *Addiction Research Centre Inventory (ARCI) (18)* : Short forms of Morphine-Benzedrine Group (MBG) scale having 16 questions to measure euphoria and Pentobarbital Chlorpromazine-Alcohol Group (PCAG) scale having 15 questions to measure sedation were used. The above questionnaires were translated to Hindi and back translated to English and opinion of bilingual experts were obtained.

3. *Visual Analog Scale (VAS) (19)* : The degree of "liking" of a drug administered, was assessed through VAS on scale of '0' – '100', where '0' representing no effect and '100' representing maximum possible pleasure experienced.

After completion of the study i.e. following administration of all the four compounds, each subject was asked about a) their comparative drug liking between these four compounds and b) their ability to recognise these compounds if administered in the future (yes/no).

RESULTS

Nineteen patients met inclusion and exclusion criteria. Out of these, three refused consent, six left before the study was complete and four patients were dropped as they required benzodiazepines for persistent insomnia. Thus 6 out of 19 subjects completed the study.

Mean age of the included subjects was 32.5 years, (range 21–42 years), they were dependent on heroin for an average of 4.3 ± 2.4 years, and had varying years of education (8 yrs – 18 yrs). All had consumed heroin through inhalation (chasing).

Subjective drug effects (SDQ)

Drug recognition at 30 mins following administration, (coinciding with peak drug levels) is shown in Table I. The responses were categorized as opiates (heroin like), other drugs and no drug. All the subjects identified morphine and buprenorphine as psychoactive substances (drug) both at 30 mins and 4 hours post-injection. Buprenorphine was identified as an opiate by all the subjects. Fifty percent misidentified placebo as an active compound at 30 mins but none at 4 hours. At 4 hours, the profile remained unchanged.

TABLE I : Drug recognition (SDQ) at 30 mins (n=6).

Compound administered	*Identified as*		
	Opiate	*Other drugs*	*No drug*
Morphine	2	4	0
Buprenorphine	6	0	0
Pentazocine	2	2	2
Placebo	0	3	3

Most frequently reported following administration of all the three active compounds were : feeling relaxed, pleasant, sick, drunken and talkative. Effects of buprenorphine and morphine were most pronounced. Placebo did not cause any appreciable effects.

No significant changes in pulse, B.P. and respiration were noted following administration of drugs.

TABLE II : MBG scores at various points of time (Mean & SD).

Compound administered	*Pre-injection*	*At 30 mins*	*At 4 hrs*
Morphine	7.3 ± 1.8	11.2 ± 1.6	10.3±1.6
Buprenorphine	6.0 ± 0.9	12.0 ± 1.5	11.6±2.1
Pentazocine	7.3 ± 1.8	11.3 ± 1.6	10.6±1.5
Placebo	6.5 ± 1.4	5.3 ± 1.0	5.6±1.1

Euphoria

MBG scores were analysed using non-parametric test (Kruskal-Wallis Test). The pre-injection MBG scores were comparable for all four compounds (P=0.72, df3). At 30 mins and 4 hours, scores obtained for the three active compounds as against placebo assumed a significant value (P=0.06, P=0.05 respectively df3). All the three drugs resembled each other as regards production of euphoria and were distinct from placebo (Table II).

Sedation

The mean pre-injection PCAG scores of all four compounds were similar (between 2.3–3.3). Further, following administration of these compounds the scores did not show elevation either at 30 mins (between 3.3–5.3) or at 4 hours (between 3.5–6.1) across drug categories. In other words, the subjects experienced euphoria, but little sedation.

VAS scores

The data is shown as mean change of value from base line (pre-injection) scores. Here too, buprenorphine produced maximum increase in scores (pleasurable effects) and resembled morphine. This difference was distinct from placebo and statistically significant (Kruskal-Wallis Test, P<.001) both at 30 mins and 4 hours (Table III).

TABLE III : Visual analog scale, mean changes against base line values.

Compound administered	*At 30 mins*	*At 4 hrs*
Morphine	22.8	22.3
Buprenorphine	30.6	33.1
Pentazocine	19.1	14.3
Placebo	1.0	1.2

Finally, five out of six subjects indicated (number code) that buprenorphine was liked most. It produced highest mean liking score on a 4 point scale (SDQ), where 'O' meant 'no liking' and '3' 'like a lot'. Further, they expressed their confidence in their ability to recognize it if administered in future.

DISCUSSION

Our results indicate that among post-detoxified heroin dependent individuals, buprenorphine caused pleasurable effects, was identified as heroin (an opiate) and caused euphoria, but little sedation. On all these parameters, buprenorphine resembled morphine more closely than pentazocine. Placebo was identified as an inert substance as no effects were seen following its administration.

Thus buprenorphine is akin to morphine in abuse potential. Abuse liability of morphine has been categorised as moderate and that of pentazocine as low (20). WHO stated therapeutic usefulness of buprenorphine as moderate to high and abuse liability as low to moderate (21).

Measurement of subjective effects following drug administration has been the corner stone for abuse liability testing. Euphoria and discriminative properties predict abuse. As a matter of fact, induction of euphoria is most crucial and there is striking concordance between euphoria and likelihood of being abused. Physical dependence i.e. withdrawal symptoms alone is not sufficient to maintain drug seeking behavior (22, 23).

As is seen here, buprenorphine is discriminated, liked and cause euphoria. These facts should be kept in mind by physicians. Liberal prescriptions should be avoided.

Buprenorphine has several therapeutic indications including a maintenance drug for heroin dependent subjects. The study though, do not suggest to stop the use of buprenorphine, however, caution is warranted.

Alternatively, combination of buprenorphine with naloxone/naltrexone, should be considered. This will attenuate abuse liability without minimising effectivity (24).

We selected post-detoxified addicts as subjects, as experienced users produce reliable results and pose less ethical problems (12). Though the study sample was small, recruitment of large sample in such a study is extremely difficult as also experienced in studies from USA which were conducted on 4–9 subjects (4, 13, 22). The current study, yielded 72 sets of observations across subjects. The data was examined as changes from base line observations (pre-injection) and averaged across subjects. These provided sufficient meaningful insight to the problem.

Certain cross-cultural difficulties involving administration of various questions were noted. For example, statements like "I have a feeling of just dragging along rather than coasting" and "A thrill has gone through me" were difficult to translate and answered by our subjects. These issues are yet to be resolved.

To conclude, buprenorphine is clearly abusable. But the zeal to control should not lead to very restricted availability of this very useful compound.

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