Post-marketing surveillance of buprenorphine†

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SUMMARY

Purpose This study was undertaken to evaluate the adverse consequences of recently introduced higher strength (0.4 and 2.0 mg per tablet) buprenorphine in Indian market. Buprenorphine, a partial opiate agonist and antagonist, is an emerging alternative to methadone as an agent for long-term treatment of opiate dependence.

Methods The current investigation was conducted through a multi-centric post-marketing surveillance (PMS) study using a structured performa from patients receiving buprenorphine as routine therapy from de-addiction centres. Evaluation included subjective and objective assessments and recording of adverse events.

Results Of the 5551 observations from ten centres, common subjective symptoms were generalised weakness (48.9%), sense of high (euphoria) (44.5%), muscle aches (39.5%) and relief from pain (37.2%). About 5% observations recorded systolic hypertension. Among 55 subjects where laboratory tests were conducted, 12 showed raised levels of AST and 9 had elevated ALT. Twelve adverse events reported included seizure, epistaxis, panic attacks, constipation and dyspnœa. Significant relation was seen between duration of use and time since last dose, and total number of subjective symptoms reported.

Conclusions Majority of the adverse effects could be understood as either effects related to intoxication or withdrawal from agonists. Copyright © 2004 John Wiley & Sons, Ltd.

INTRODUCTION

Among various agents available to treat opiate dependence, buprenorphine has been found to be efficacious for both short-term (detoxification) and long-term (maintenance) therapy. In India, till recently, buprenorphine was available only as 0.2 mg sublingual tablets and generally was prescribed in low doses and mostly for detoxification. In April 1999, the Drugs Controller of India (DCI) permitted introduction of 0.4 and 2 mg sublingual tablets and this in turn enabled the clinicians to prescribe in higher doses. It was perceived that increasing use of enhanced dose might raise the risk of occurrence of adverse effects and the DCI, thus requested to record these side effects if any, through a post-marketing surveillance (PMS) study of higher strength of tablet buprenorphine (0.4 and 2 mg).

The objectives of PMS are to study a drug’s efficacy and toxicity under conditions approaching its actual clinical use in order to identify particular conditions of benefits or hazards as well as to evaluate the drug’s potential and overall impact on the conditions for which it is prescribed. Ideally, both short- and long-term impact should be measured and both beneficial and adverse impact should be identified. The Food and Drug Administration (FDA, U.S.A.) envisages them as the discovery of unknown risks and benefits as well as measurement of known risks and benefits of treatment. Between 1977 and 1982, series of formal studies were carried out to investigate drug toxicity. These studies...
have tended to be referred to by the collective term PMS studies.\textsuperscript{1}

In general, the term PMS connotes observational studies undertaken on a drug following its marketing and lie somewhere between adverse reaction registries and randomised controlled trials. They are mostly uncontrolled cohort studies designed without a specific hypothesis and without predetermined statistical power. Common to all these studies is the idea of identifying a cohort of recipients of a drug, and following up these individuals for various lengths of time, while recording any new diagnosis (events) that occurs for the first time after use of the (new) drug.

**PMS STUDIES INVOLVING BUPRENORPHINE**

The first and the only PMS study was reported by Harcus et al.\textsuperscript{2} on 17,120 administrations of injection buprenorphine as an analgesic, to 9,123 patients. Adverse drug reactions (ADRs) were reported on 8,187 patients. Nausea (8.8%), vomiting (7.4%), drowsiness (4.3%) were the common symptoms. Some other symptoms like sweating, headache, confusion, dry mouth and depression were infrequently reported (below 1%). Although the study confirmed the efficacy of the analgesic, it added little to the knowledge obtained about the drug before marketing, at substantial cost, in time and money. However, it demonstrated the feasibility of such studies to assess drug effects in clinical practice. The current study collected information on ADRs associated with sublingual administration of higher strength (0.4 and 2 mg) tablets of buprenorphine in opiate dependent patients.

**MATERIALS AND METHODS**

It was a multi-centred study with the National Drug Dependence Treatment Centre, (NDDTC), All India Institute of Medical Sciences (AIIMS) being the co-ordinating centre. The participating centres (government and non-government centres) were those who prescribed higher strength buprenorphine (Addnok, 0.4 or 2 mg) to their patients for treatment of opiate dependence syndrome.\textsuperscript{3} Fifteen drug dependence treatment centres were contacted through post/e-mail and requested to participate in the study and ten centres contributed the data between July 2000 and 2001. The information was collected from the subjects during face-to-face interviews through a structured performa. The data items, both subjective and objective items were derived from the list as suggested by Harcus et al.\textsuperscript{2} and those available in a standard text book of pharmacology.\textsuperscript{4} Interviews and physical examinations were carried out on these patients for adverse effects. Additionally haemoglobin (Hb), total leucocytes count (TLC), differential count (DLC), erythrocyte sedimentation rate (ESR) and biochemical tests (serum bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea and creatinine) were done at the co-ordinating centre.

**DATA ANALYSIS**

The data were expressed as descriptive statistics using measures of central tendency for demographic, drug use (prescription and non-prescription), adverse reactions (subjective and objective), laboratory parameters, and dose and duration of buprenorphine. Significant adverse events occurring during the therapy were recorded. The relationship between dose, duration, time since last administration and adverse reactions was assessed using Pearson’s ‘rho’.

**RESULTS**

*Background information*

The mean age of these patients was 35.6 years (SD 7.6) and was similar across the centres except in one centre where the subjects were younger (mean 29.4 years). The dose administered in different centres varied ($p < 0.000$) and the mean dose was 2.9 mg (SD 3.5) (range 0.4–36 mg) per day and the median dose being 2.8 mg. The duration of treatment with buprenorphine was also variable, the mean being 177.5 days (SD 167.7) (range 1–1080 days) and the median being 138 days.

*Adverse effects*

Table 1 shows the common subjective symptoms reported from all the centres. Subjective symptoms most often reported by the subjects, in order of decreasing frequency were: generalised weakness (48.9%), sense of high (44.5%), muscle aches (39.5%), yawning (38.5%), relief from pain (37.2%) and constipation (33.1%). Symptoms like flatulence, cramps, headache, pain abdomen, giddiness, light-headedness, drowsiness, blurred vision, vomiting, pre-mature ejaculation, low libido and poor appetite were reported less frequently and was less than 10%. Some had however, reported better sexual performance and increased appetite. Patients from three agencies namely, Calcutta Samaritans ($n = 2543$), NDDTC, AIIMS ($n = 1267$) and SHARAN ($n = 879$) reported most of these symptoms.
Among the objective signs recorded it was seen that pupil size was normal in 61.9% of occasions, however among 24.5% it was dilated. The mean systolic blood pressure was 114.4 and diastolic blood pressure was 74 mm Hg, respiratory rate was 18.8/minute and pulse rate was 75.8/minute. Systolic hypertension (BP > 140 mm Hg), diastolic hypertension (BP > 95 mm Hg) and tachypnoea (respiratory rate > 30/minute) were seen among 5.2, 0.8 and 2.2% of the observations respectively.

Some (22%) had received additional prescription medication and about 36% were using illicit drugs along with the prescribed buprenorphine. The subjects in both these groups reported higher subjective symptoms, and the subjects using non-prescription (illicit drugs) many more symptoms.

**Significant adverse events**

Significant adverse event was defined as any effect that was not in keeping with available literature on pharmacological effects of buprenorphine (Type B ADR). Altogether, 12 such events were reported. These include seizure, epistaxis, dyspnoea, fever with chills, constipation, premature ejaculation and anger outbursts. One patient had panic attacks after initiation of the drug and finally, one patient reported improvement in pre-mature ejaculation after starting of bupernorphine. No major events like cardiovascular ailments, jaundice or death were reported.

Correlation analysis revealed significant correlations between duration, time since administration and the total subjective symptoms reported. There was however, no relationship between dose and subjective symptoms (Table 2).

Laboratory parameters available among 55 subjects following 1–12 months of consumption of buprenorphine revealed that the mean values of haemoglobin, TLC, DLC, ESR and bilirubin were within normal range. In total, 12 and 9 subjects had elevated AST and ALT values respectively. Creatinine was elevated in six patients and urea in one.

**DISCUSSION**

Buprenorphine, a partial μ-agonist, is a semi-synthetic highly lipophilic opiate derived from thebaine is 25–50 times more potent than morphine as an analgesic. The dose recommended for maintenance using buprenorphine is between 4 and 8 mg a day. In India, till recently only 0.2 mg tablet was available. Higher strength of buprenorphine has now been introduced in India in two preparations namely 0.4 and 2.0 mg per tablet. This study looked into the adverse effects on patients receiving these higher strengths of buprenorphine (Addnok).

The data consisted of 5551 observations from ten de-addiction centres across the country. The subjects in this study were mostly young adults. The prescribed dose of bupernorphine was variable and the median was about 3 mg. The median dose prescribed among these subjects was less than those reported in the world literature, i.e. around 4–8 mg a day for maintenance.

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Table 1. Common subjective symptoms reported

<table>
<thead>
<tr>
<th>Symptom</th>
<th>n (5551)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalised weakness</td>
<td>2711</td>
<td>48.9</td>
</tr>
<tr>
<td>Sense of high</td>
<td>2469</td>
<td>44.5</td>
</tr>
<tr>
<td>Muscle ache</td>
<td>2192</td>
<td>39.5</td>
</tr>
<tr>
<td>Yawning</td>
<td>2137</td>
<td>38.5</td>
</tr>
<tr>
<td>Relief from pain</td>
<td>2063</td>
<td>37.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>1833</td>
<td>33.1</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>1476</td>
<td>26.6</td>
</tr>
<tr>
<td>Craving</td>
<td>1442</td>
<td>26.1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1053</td>
<td>18.9</td>
</tr>
<tr>
<td>Sleeplessness</td>
<td>1052</td>
<td>18.9</td>
</tr>
<tr>
<td>Sadness</td>
<td>1039</td>
<td>18.7</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>1010</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Table 2. Relationship of dose of buprenorphine, duration of treatment, time since last dose of buprenorphine and adverse effects (subjective symptoms)

<table>
<thead>
<tr>
<th>Duration</th>
<th>Dose</th>
<th>Time since last administration</th>
<th>Subjective symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>1.000</td>
<td>Dose 0.040 (0.008)*</td>
<td>1.000</td>
</tr>
<tr>
<td>Time</td>
<td>-0.171 (0.000)*</td>
<td>-0.0190 (0.168)*</td>
<td>1.000</td>
</tr>
<tr>
<td>Subjective symptoms</td>
<td>0.291 (0.000)*</td>
<td>-0.0071 (0.589)*</td>
<td>-0.131 (0.000)*</td>
</tr>
</tbody>
</table>

Time: Time since last administration.
*Correlation coefficient.
*Significant at p < 0.05.
Concurrent use of additional prescribed medication and illicit drugs used influenced the subjective symptoms reported.

Generalised weakness, reported by about half of the sample is non-specific and can be related to drug use, recovery or the medication consumed. Some of the symptoms like muscle ache and yawning (around 40%) and lacrimation (26%) could be interpreted as opiate (buprenorphine as well) withdrawal symptoms. The others like sense of high and relief from pain are akin to those resembling agonist actions of opiates (buprenorphine) along with use of benzodiazepines and heroin. It would be very difficult to attribute these effects solely to the administration of buprenorphine.

Among the objective parameters, majority of the subjects showed normal pupils (61.9%) and some (24.5%) showed dilated pupils. This could be due to the fact that the observations were recorded after a long time interval (mean, 6 hours) since last dose of buprenorphine. This was unlike what had been found in other studies,6,7 which showed miosis following buprenorphine administration. Between 16 and 21% had elevated serum levels of two (AST and ALT) of the parameters of liver functions following intake of buprenorphine. Ling et al.8 had reported deranged liver functions in some subjects on higher doses of buprenorphine in a multi-centred randomised clinical trial.

The adverse effects noted in the study are well known side effects of opiates4 and have been documented in other studies as well.3,6,7,9,10 However, the frequency of occurrence of symptoms in one of the studies2 was less compared to the present study. Between 1 and 9% of patients reported these symptoms following single administration of injection of 0.3 mg buprenorphine.2

The occurrence of 12 significant adverse events (Type B events) like seizure, fever, constipation, abdominal pain etc. not hitherto associated with buprenorphine would cause some concern. It would seem that there is a definite increase in such events although these results are best replicated in case-control studies.

To conclude, administration of higher strength preparation of buprenorphine (S/L) is associated with certain side effects. Most of these effects are mild and do not necessitate discontinuation of medication. Some of the effects, which are of concern, are liver function abnormalities, which may need to be monitored in the course of therapy. Additionally some of the adverse events (Type B events) may need to be monitored in future studies.

KEY POINTS

- Higher strength sub-lingual formulations were recently introduced in the Indian market and the Drugs Controller of India (DCI) required study on the post-marketing survey on adverse reactions with this new preparation.
- The study was conducted through 11 participating centers across the country on 5551 observations using a structured Performa for collecting the information relating to the overdose effects, withdrawal effects, any other significant effects and death reported during use of the new preparation.
- The results indicated subjective symptoms noted were generalised weakness (48.9%), sense of high (44.5%), muscle aches (39.5%) and relief from pain (37.2%). The objective signs noted viz. pupil size, blood pressure, respiratory rate and pulse were mostly normal. Twelve significant adverse events reported included seizure, epistaxis, panic attacks, constipation and dyspnoea.
- Significant relation was seen between duration of use and time since last dose, and total number of subjective symptoms reported.
- The adverse reactions seen upon administration of higher strength buprenorphine were related mostly either to the toxic effects or withdrawal effects and that no mortality was reported in the study during the observation period.

REFERENCES


