ABUSE LIABILITY OF NITRAZEPAM: A STUDY AMONG EXPERIENCED DRUG USERS

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ABSTRACT

Objective: To study the abuse liability of nitrazepam among human volunteers.

Methods: Fourteen male post-detoxified experienced drug users received single administration of placebo tablets, 40 mg of nitrazepam and 20 mg of diazepam orally in a single blind cross-over fashion. Subjective states, drug liking, drug discrimination, euphoria, sedation and side effects of benzodiazepines were measured using various scales at baseline and 1, 2 and 8-hour post-administration.

Results: The data suggest that nitrazepam caused significant euphoria as against placebo and was identified as an active drug by the subjects. Nitrazepam resembled diazepam, however, on certain parameters the effects produced by nitrazepam were more pronounced.

Conclusion: Nitrazepam is an abusable drug and has similar abuse liability like diazepam, if not slightly higher.

KEYWORDS Nitrazepam diazepam abuse liability human subjects

INTRODUCTION

Benzodiazepines are prescribed as anticonvulsant, muscle relaxant, anxiolytic and sedative. These are very useful medicines, but form one of the largest class of abused pharmaceuticals. Greenblatt et al in 1987 commented that they are not as safe as once thought to be and indications for their use are more narrow than previously defined. Abuse and dependence occur quite commonly and often within 4-6 weeks of use. Further, it is believed that benzodiazepines are a group of compounds and have differences among them as regards their abuse liability.

WHO in 1991 recommended that most of the benzodiazepines should be in Schedule IV of the United Nations Convention on Psychotropic Substances, 1971, i.e. they constitute a small but significant risk to public health though have therapeutic usefulness. Between 1970 to late 1980s several countries reported their abuse. Following reports of large-scale abuse of flunitrazepam and several others, like triazolam, alprazolam and diazepam, it was recommended by WHO that these should be under critical review.

In India, nine benzodiazepines and several other non-benzodiazepine hypnotics are commercially available. Among these, diazepam, alprazolam and nitrazepam are frequently prescribed and abused as well.

In our Centre, about 50-60% of heroin dependent subjects abuse oral diazepam and nitrazepam and about 20% of intravenous drug users (IDUs) use injection diazepam along with other drugs. Upon enquiry it was reported to us that they use these compounds (self-medication) mainly as a hypnotic. Some however, reported that diazepam provided relief to some of the withdrawal symptoms. This was evident in situations where for some reasons or other they were unable to consume their usual daily dose or were making an effort to reduce consumption of heroin (Clinical Statistics, De-Addiction Centre, AIIMS, 1999- unpublished report). In a subsequent
study we have investigated these observations formally (Saha et al., 2000-unpublished report). Several unconfirmed reports also suggest large-scale abuse of nitrazepam. Thus it appears some benzodiazepines may have a greater abuse potential over others. Greater lipid solubility and bioavailability, smaller volume of distribution and shorter half-life enhance the likelihood of abuse. Amongst benzodiazepines, abuse potential of diazepam has been studied most extensively. However, the data on others including that of nitrazepam is limited.

Considering the expanding prescription of nitrazepam as a hypnotic agent, and its abuse and self-report by addict population, it was proposed to carry out a study to assess the abuse potential of nitrazepam as against diazepam by comparing their acute effects after oral administration. The present study was carried out among experienced drug users in a controlled experimental situation.

**MATERIALS AND METHODS**

Male subjects between 16 and 40 years with heroin dependence were requested to participate in the study. A total of 14 subjects agreed to take part in the study. The department research forum approved the study and informed consent was obtained from the subjects. Subjects having associated psychiatric illness and medical illness, having contraindications for use of benzodiazepines, e.g. acute or chronic pulmonary disease, sleep apnea, renal disease, hepatic disease, organic brain disorder etc. were excluded. Further, subjects having the need to continue any psychoactive drugs including benzodiazepines were also excluded.

The mean age of subjects was 32.2 years, most literate (85.7%) and 15% were graduates (15 years of education). Mean duration of dependence on heroin was 9.4 years (SD ± 4.5). Besides heroin, 25-50% had used several other drugs, like alcohol, cannabis, buprenorphine in previous one month. About 50% had abused (non-prescription) benzodiazepines in the last month.

All the subjects following their detoxification were admitted to the ward at least 4 days prior to the study for acclimatisation and stayed there during the study period. They were there free of all psychoactive drugs for the previous 96 hours. Absence of morphine (heroin), benzodiazepines and barbiturates in the urine as determined by thin layer chromatography (TLC) confirmed their drug free status.

All the subjects were smokers, and smoking an equivalent of 10 cigarettes per day for last 5 years. These subjects refrained from smoking following admission to the ward and did not smoke for the entire duration of the study.

**Drug administration**

Each subject received single administration of oral tablets of each of the drug in a single blind (subjects were unaware), cross-over fashion and in the following order:

- Day 1: Placebo 4 tablets
- Day 2: Nitrazepam 40 mg (4 tablets, of 10 mg each)
- Day 6: Diazepam 20 mg (4 tablets, of 5 mg each)

As is evident, equi-potent dosage of tablets diazepam and nitrazepam was used.

**Assessment and tools**

The subjects were informed that they were likely to receive either a drug(s), which could cause intoxication, or a chemically inert substance. They were expected to report their post-treatment subjective states as accurately as possible. Further, they were instructed to remember the effect of various drugs identified by the number code.

Following intake of each of these tablets, acute drug effects such as drug liking, drug discrimination, drug identification, euphoria and sedation were assessed using the following instruments at baseline, then at 1 hour, 2 hour and 8 hour post-administration. Physiological parameters like pulse, blood pressure (BP) and respiratory rates were also measured.

In addition to the formal assessment of “drug liking” through the instruments listed below, the subjects were also asked to report and compare these compounds as regards their liking and ability to recognise if these were to be administered in future. This was possible by asking the subjects to remember these effects through a number code e.g., 1, 2 & 3 in the order of their administration as discussed earlier. Serum levels of nitrazepam and diazepam were assessed for both the drugs at 1 hour and 2 hour by gas liquid chromatography (GLC).
**Table 1.** Drug recognition as per Single Dose Opiate questionnaire (SDQ) at 1 and 2 hours of drugs administration (n=14)

<table>
<thead>
<tr>
<th>Administered compound</th>
<th>Blank (n)</th>
<th>Opiate (n)</th>
<th>Minor tranquiliser (n)</th>
<th>Other drug (n)</th>
<th>Correct Identification %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>9 (9)</td>
<td>3 (2)</td>
<td>0 (2)</td>
<td>2 (1)</td>
<td>64.3 (64.3)</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>2 (2)</td>
<td>4 (1)</td>
<td>4 (1)</td>
<td>4 (1)</td>
<td>28.6 (71.4)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>6 (1)</td>
<td>1 (1)</td>
<td>4 (10)</td>
<td>3 (2)</td>
<td>28.6 (71.4)</td>
</tr>
</tbody>
</table>

* Respective values at 2 hours (n or %) are given in parenthesis

**Instruments**

1. **Single Dose Opiate Questionnaire (SDQ)**: SDQ measures subjective effects and provides observer’s rating for quality of drug effect, like morphine. In this study it measured subjective awareness of any drug, drug identification from a list of commonly used addictive substances, acute effects of benzodiazepines and degree of drug liking on a four-point scale. Appropriate modifications were made to study acute effects of benzodiazepines.

2. **Rating Scale for side effects of benzodiazepines**: as proposed by WHO (1988) was used. The rater enquired about 7 symptoms on 4 point scale, where '0' meant absent and '3' meant severe.

3. **Addiction Research Centre Inventory (ARCI)**: Short forms of ARCI to measure euphoria through Morphine- Benzedrine- Group (MBG) Scale and sedation through Pentobarbital-Chlorpromazine - Alcohol Group (PCAG) Scale were used. Both these scales (MBG-16 items, PCAG-15 items) were translated to Hindi (local language) and back translated to English and opinion of bilingual experts was obtained.

4. **Visual Analog Scale (VAS)**: A bipolar 200 mm VAS was used to assess degree of drug liking, where, (-) 100 represented maximum dysphoria and (+) 100 represented maximum possible euphoria.

All the above rating instruments have been used by us in an earlier study and were found easy to administer and generally reliable.

**Statistical analysis**: Frequency distribution of dichotomous responses following administration of the three compounds at various points of time was compared. Median values obtained on various parameters (scales) at various points of time were used for both within and inter-group comparison using non-parametric tests viz. Fisher’s Exact Probability Test, Friedman Test, Kruskal-Wallis Test. The data on plasma levels of diazepam/nitrazepam are expressed as means ± SD. P values less than 0.05 were considered significant.

**RESULTS**

**Drug recognition**: After 1 hour of administration, only 28.6% recognised diazepam/nitrazepam correctly as "minor tranquillisers". It improved with time, as at 2 hour and at 8 hour, 71.4% and 85.7% of the subjects, respectively identified the quality of drug effect correctly (Table 1). Between 14 and 36% misidentified placebo as an active compound at various points of time. Two subjects even though clearly intoxicated after receiving nitrazepam (40 mg), did not report feeling the drug.

**Subjective drug effects**: Twelve out of 14 subjects (85.7%) reported ‘yes’ for nitrazepam (active compound) both at 1 hour and 2 hour of post administration. Upon administration of diazepam, 8 subjects (57.1%) and 13 subjects (92.8%) reported ‘yes’ at 1 hour and 2 hour respectively. All the subjects identified diazepam and nitrazepam correctly as active agents at 8 hour.

Most frequently reported symptoms following administration of diazepam and nitrazepam were: feeling energetic, relaxed, drunken and talkative. Subjects
after receiving nitrazepam reported slightly higher frequency of these symptoms at all points of time. Peak subjective effects (symptoms) were seen at 2 hour both for nitrazepam and diazepam.

Drug liking (SDQ) was assessed on a subjective two-point scale where '0' implied no liking and '1' signified liking. Drug liking scores using Fisher’s Exact test showed that following administration of nitrazepam and diazepam, the values were significantly elevated. The values at 2 hour were: a) placebo vs. nitrazepam (lower tail 0.001 and upper tail 0.999), b) placebo vs. diazepam (lower tail 0.032 and upper tail 0.999) and c) nitrazepam vs. diazepam (lower tail 0.500 and upper tail 0.837). Liking for nitrazepam in comparison to placebo was significantly higher both at 2 hour and 8 hour (lower tail 0.023 and upper tail 0.998) and this was not so between placebo and diazepam(lower tail 0.107 and upper tail 0.979). Thus, it was seen that liking for nitrazepam and diazepam was significantly higher (p <0.05) as against placebo; however, there were no differences between the two benzodiazepines (Fisher’s Exact Probability Test).

Assessment of side effects of benzodiazepines (viz. physical tiredness, drowsiness, dizziness, dryness of mouth etc.) showed that scores were higher for nitrazepam at all points of time. Physiological parameters, i.e. BP, pulse and respiration were essentially unchanged following drug administration.

Euphoria: MBG scores were very variable and thus median values were used for this non-parametric test. The values for each compound were compared against the baseline score. As seen in Table 2, baseline scores were comparable for all the three compounds. Within group comparison showed that nitrazepam caused significant (p <0.001) euphoria at all points of time, wherein diazepam caused significant (p <0.01) elevation only at 2 hour, placebo did not cause any change (Friedman’s, multiple range test). Inter group comparison, i.e. MBG scores at various time points following administration of diazepam and nitrazepam, did not reveal any significant difference (Kruskal-Wallis Test). Euphoria as seen through VAS scores, i.e. (changes from the baseline score) it was reported by 12-13 subjects and 10-11 subjects following administration of nitrazepam and diazepam, respectively at various points of time. The range of scores was not different for these two active compounds. Thus the degree of euphoria caused by the use of diazepam and nitrazepam was similar.

One subject following administration of nitrazepam and three subjects following intake of diazepam reported dysphoria. Five subjects reported positive VAS scores (i.e. euphoria) following administration of placebo though, the elevation was minimal.

Sedation: PCAG scores were comparable for all the three compounds and no significant elevation was seen as against baseline. Baseline values varied between 4.0 and 5.5, and the corresponding values for the test drugs at various points of time varied between 3.0 and 6.5.

Plasma level: Approximately fifty percent of the subjects had higher plasma value at 1 hour following intake of nitrazepam and higher plasma value of diazepam was achieved invariably at 2 hour. Plasma concentration of nitrazepam (40 mg, p.o) at 1 hour was 830 ± 249.8 ng/ml (range 300 - 1180) and for that of diazepam (20 mg, p.o.) at 2 hour was 677.7 ± 297.7 ng/ml (range 150 - 1004).

Finally, through the self report based on number codes of administered compounds as mentioned earlier, eleven out of fourteen subjects (78.6%) indicated that nitrazepam, the drug they liked most and expressed their confidence in their ability to recognise it, if administered in the future.

| Table 2. MBG scores at various points of time (Median values are shown, n=14) |
|------------------|------------------|------------------|------------------|------------------|
| Administered compound | Baseline | 1 hr | 2 hr | 8 hr |
| Placebo | 5 | 7 | 7 | 7 |
| Nitrazepam | 5 | 12.5** | 12.0* | 12.5** |
| Diazepam | 7 | 11.5 | 13.0* | 8.5 |

** p <0.001  * p <0.01

Values compared against baseline score for each of the compound (Friedman test)
DISCUSSION

The results indicated that among experienced drug users, nitrazepam consistently produced effects which could be described as pleasure, drug-liking and euphoria akin to diazepam. However, on a few parameters, effects produced by nitrazepam were more pronounced than those due to diazepam. Nitrazepam was identified earlier, caused significantly higher euphoria (MBG scores) at all points of time. Most reported increased liking for nitrazepam. Further, high plasma protein binding of diazepam over nitrazepam, and rapidity of onset of action and shorter half-life of nitrazepam may contribute to higher abuse liability of the drug. Thus, it can be inferred that nitrazepam has similar abuse liability like diazepam, if not slightly higher.

Measurements of subjective effects following drug administration have been the hallmark to test abuse liability. Parameters, like euphoria, drug liking and positive discrimination predict a substance’s abuse liability. As a matter of fact, induction of euphoria is very crucial and there is a striking concordance between euphoria and future abuse. Pre-clinical testing in animals are useful, however, human testing provides additional information, like subjective well being and euphoria which are determinants for drug seeking and drug self administration behaviours. Such testing are ethical and justified.

Literature review suggests that in few individuals, benzodiazepines may have differential (greater) abuse potential than in the others of the same class. Previous studies suggest that lorazepam and diazepam have similar abuse liability, while oxazepam and chlor diazepoxide have lesser abuse potential. Nitrazepam is not an approved drug in USA but is widely prescribed in Asia and Africa as hypnotic. However, data on its abuse liability are scanty and this drug has not been as widely investigated as diazepam. As early as 1972, some authors suggested that nitrazepam to be close to barbiturate in producing dependence. Experimental studies confirm withdrawal symptoms following cessation of chronic use of nitrazepam, similar to those produced by flunitrazepam and are even more pronounced as against lorazepam and diazepam withdrawal.

Nitrazepam has a half-life of 24-36 hours against 100 hours for diazepam. Peak plasma level of nitrazepam is expected around 81 minutes after oral administration as against 30-90 minutes after oral diazepam. Peak plasma level of nitrazepam following administration of 10 mg of nitrazepam has been reported to be around 82 ng/ml and that of diazepam following intake of 20 mg was between 300-800 ng/ml. The time to achieve peak concentration varied and so was the level. The values obtained for diazepam in this study are similar to those quoted earlier, however, there are no studies reporting plasma level after intake of 40 mg of nitrazepam. We could not carry out serial analysis and determine the area under curve (AUC) to determine the peak plasma level due to logistic and ethical reasons. However, in this study more often higher plasma level for nitrazepam was achieved after 1 hour as against at 2 hour for diazepam. Early onset of higher plasma value along with clinical evidence of euphoria and drug-liking behaviour clearly suggest abuse potential of nitrazepam. Some have felt that despite its relatively long half life, nitrazepam is similar to short acting benzodiazepines producing significant withdrawal symptoms following chronic use.

We selected post-detoxified heroin addicts who were also using other drugs of addiction as these subjects were experienced drug users and could report reliable results and posed less ethical problems. The subjects were clearly free of all psychoactive substances including nicotine before their exposure to diazepam/ nitrazepam and adequate washout period (96 hours) was given between administration of the active compounds.

There are a few limitations of this study. Because of logistic difficulties, the study was single blind and the drugs were presented in a fixed order. A double-blind random order of each administration would have been ideal. Secondly, serial collection of blood sample would have allowed estimation of peak plasma level of diazepam/nitrazepam and adequate washout period (96 hours) was given between administration of the active compounds.

To conclude, both nitrazepam and diazepam are clearly abusable as the two compounds were reported by subjects to be distinct as against placebo. However, their abuse liability should be judged against their therapeutic usefulness. The zeal to control abuse should not limit their availability for genuine medical reasons.
REFERENCES


