

ABUSE LIABILITY OF DIAZEPAM THROUGH DIFFERENT ROUTES

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Abstract : Abuse liability of diazepam was examined among experienced drug users. The subjects, randomly divided into two groups, each having eight subjects, received diazepam, 15mg intravenously (gr.1) and 30 mg orally (gr.2). Subjective states, drug liking, sedation and euphoria were assessed at pre-drug, 15 min, 120 min and 240 min post-drug administration. In addition, brief assessment to evaluate euphoria and sedation was carried out at 5 min and 45 min for subjects in gr.1, and at 45 min and 150 min for those in gr.2. Plasma diazepam level was also estimated. Results indicate those subjects in gr. 1 reported quicker and higher euphoria, drug liking, subjective effects and higher plasma level. The study suggests that route of administration of a compound which has faster onset of action is associated with more liability of abuse.

Key words : diazepam routes of administration abuse liability

INTRODUCTION

Reports from different treatment centres as well as surveys on drug abuse indicate that alcohol, cannabis, heroin and other opiates are commonly abused in India (1, 2). Recently, rising incidence of intravenous multi-drug use consisting of buprenorphine, diazepam, promethazine and chlorpheniramine has been observed (3, 4). Among all new patients in our centre, 24% are intravenous drug users (IDU, ever) and out of them 62% of them are current (use in last month) IDUs (unpublished data, Drug Dependence Treatment Centre, All India Institute Medical Sciences, New Delhi, 1998). In another study in our centre, it

was found that most shifted from heroin inhalation to i.v. drug use due to peer pressure, easy availability and comparatively cheaper cost of these drugs (5).

Other than these, choice of a compound may also depend upon subjective effects which in turn are influenced by pharmacokinetic and pharmacodynamic factors like lipid solubility, degree of ionisation, active transport, blood flow at the target tissue etc. of a compound (6). Additionally, absorption, distribution, biotransformation, excretion, dosage form, route of administration, is also important factors, which affect the abuse liability of a

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compound (7). Rapidly increasing subjective drug effects (e.g. rush) cause more euphoria and hence are associated with greater likelihood of abuse. Drugs inhaled or injected intravenously are associated with an almost instantaneous blood level and a fast onset of effects. Drugs which are considered to be highly abusable are usually taken by routes that produce faster rates of increase of effects e.g. heroin, cocaine and amphetamine. In general, the oral route is associated with the lowest abuse liability (7). Thus the same compound may have differential abuse liability because of different routes of administration. Literature on such studies is scanty.

This study was designed to a) assess the perceived subjective effects of a compound (in this case diazepam) when administered through different routes and b) test the hypothesis that the subjects who receive the drug by intravenous route should experience higher degree of euphoria as well as faster than those receiving through oral route, and these should be reflected through plasma concentration of the drug.

Diazepam having both parenteral and oral preparation was used as a prototype compound to test the hypothesis.

METHODS

Study population

Male individuals with substance use disorder (8) in the age group of 20–50 years from our treatment centre were recruited

for the study. They were opiate dependent individuals and besides opiates, had used benzodiazepines, barbiturates, cannabis and alcohol over several years. However, they were free of these drugs for at least 48 hr prior to the study. Additionally, adequate wash out period (i.e. five half-lives) was given for those subjects who were on prescription psychotropics. They were all smokers (10 cigarettes/20 beads per day for 5 years or longer). None of them had any medical contra-indication to use diazepam. Subjects having the need to continue medicines, which have significant interaction with diazepam (e.g. antihistamine except astemizole, chloramphenicol, carbamazepine, disulfiram, isoniazide, phenytoin, antacids) (9) including psychoactive drugs, were excluded. All the subjects were included with informed consent. Further, the departmental committee approved the study.

Study design

Subjects following their inclusion, were assigned to two groups (Group 1 and Group 2) by matching body mass index (BMI). Subjects in Group 1 received 3 ml of injection diazepam (15 mg) i.v. slowly (over 3 minutes) and 3 tablets of placebo orally and the subjects in Group 2 received 3 ml of injection distilled water (placebo) i.e. and 3 tablets of diazepam, each 10 mg (30 mg) orally in a single blind fashion. The subjects were unaware about the route of the active compound. The subjects were admitted to our ward for the study and received the drugs following their acclimatization in the ward.

Instruments

- I) A proforma was used to obtain socio-demographic profile, height (meters), weight (kg) and drug use history (lifetime and current).
- II) Modified Single Dose Opiate Questionnaire (SDQ) (10) was used to measure the subjective effects like feeling the drug, drug identification, subjective symptoms and drug liking. Subjects' rating of drug liking from the SDQ have been employed by many workers at NIDA/ Addiction Research Centre, U.S.A. in their studies evaluating sedatives (non-benzodiazepine) and demonstrated dose related increase in ratings of drug liking (11).
- III) Observer's rating scale developed by WHO, 1988 (12) was used to assess the acute effects of diazepam like physical tiredness, dizziness, dryness of mouth etc. on a 4 point scale (none to severe).
- VI) Short forms of Morphine Benzodrine Group (MBG) scale and Pentobarbital Chlorpromazine Alcohol Group (PCAG) scale from Addiction Research Center inventory (ARCI), developed by Haertzen et al, 1963 (13) was used to assess euphoria and sedation respectively. The questionnaire contained 18 questions.
- V) A bipolar 200 mm visual analog scale (VAS) was used to assess the degree of liking of the drug (+100 to -100); 0 representing no effects, +100 representing maximal possible pleasure experience and -100 representing maximal dysphoria. A similar scale was used to assess the sedation, -100 being the maximum sedation, and +100 representing maximum alertness.

Procedure Subjective Effects

Subject effects, in Group 1 (those who received i.v. diazepam), were assessed at 30 minutes before the administration of the drug and at 5, 15, 45, 120 and 240 minutes after administration of the drug. In Group 2 (oral diazepam), assessment was done at pre drug and 15, 45, 120, 150 and 240 minutes post drug administration. Simultaneously, for each subject, physiological parameters- pulses, respiratory rate and blood pressure were measured. Blood samples were collected at 5, 15, 45, 120, and 240 min (gr.1) and at 45, 120, 150, 240 min (gr.2) for analysis of plasma diazepam levels.

A complete assessment comprising of Modified SDQ, observer's rating scale, MBG and PCAG scales, and VAS (for euphoria sedation) was carried out at baseline, 15, 120, and 240 minutes post-administration for all the subjects. Brief assessment by VAS only (euphoria and sedation) was carried out at 5 min and 45 min for subjects in group 1 and at 45 min and 150 min for those in group 2. (Table I).

Table I: Timing for blood sample collection and assessment of drug effects.

Timing for blood sample collection and assessment	Group 1		Group 2	
	Sample No.	Type of scale admn.	Sample No.	Type of scale adman.
-30 Min. (09.30 hrs)	1	F.B.	1	F.B.
0 hr (10.00 hrs)		Administration of drugs		
5 Min (10.05 hrs)	2	VAS	-	-
15 Min (10.05 hrs)	3	F.B.	2	F.B.
45 Min (10.45 hrs)	4	VAS	3	VAS
120 Min (12.00 hrs)	5	F.B.	4	F.B.
150 Min (12.00 hrs)	-	-	5	VAS
240 Min (14.00 hrs)	6	F.B.	6	F.B.

F.B: Full battery of Scales (modified SDQ, MBG, PCAG, VAS)

VAS: Visual analog Scale

Physiological parameters (pulse, respiratory rate and blood pressure) were also measured in the above mentioned timings

Blood sample collection

An intravenous catheter (venflon) was inserted and fixed into a suitable vein in the forearm of the subject, which was heparinized after every sampling of blood. Six blood samples (2 ml each) were collected in EDTA vials from each subject at the specified timings mentioned above. Plasma was separated and stored at -20°C till analysis.

Laboratory Investigation

Blood for AST, ALT was done to rule out any gross liver pathology. Urine analysis was done 48 hours prior to the study and again on the study day by TLC (14) to detect the presence of drugs of abuse (benzodiazepines, opioids, barbiturates and cannabis). It ensured the drug free status of the subjects. Breath alcohol analyser was used to detect alcohol use. Extraction of free diazepam from plasma samples was carried

out by a modified liquid - liquid extraction method (15). Recovery \pm S.D of the method was 90.0 ± 4.7 ($n = 20$), reproducibility on different days 6.3 % (c.v.x 100) ($n = 20$) and the lower limit about 10 ng/ml. Quantitative estimation (15) of diazepam concentration from the serial plasma samples were done by Hewlett Packard 5890 series II gas liquid chromatograph equipped with nitrogen phosphorous detector (NPD) and HP 3396 series II integrator. Flunitrazepam was used as internal standard as it has molecular and physical characteristics similar to diazepam.

Data analysis

Data was entered in 'dbase' and analysed using Biomedical data processing (BMDP) statistical packages. Fisher's Exact test, Pearsons Chi-square test, Wilcoxon's Rank Sum test were applied at various points of time. Analysis of variance (ANOVA) with

repeated measures was applied to compare the inter-group scores. Bonferroni's multiple comparison test was applied to compare changes between all possible pairs e.g. elevation of MBG score at 15 min. from baseline and $P < 0.05$ has been considered statistical significant for the each pair. When the scores vary widely median test was applied.

RESULTS

All the Subjects were free from psychoactive substances during the study. Thirty-four fulfilled the inclusion and exclusion criteria, fourteen (41.2%) of them left before the study was completed and four declined to participate in the study. Thus sixteen subjects, eight in each group completed the study. The subjects in the two groups were comparable as regards their age, educational status, marital status, occupational status and drug use history.

Subjective effects drugs (SDQ)

Feeling the drug

The responses were categorised as "Yes" or "No". At 15 min, seven subjects who received the drug through i.v. route as against none in the oral route groups perceived the drug as psychoactive substance. However, this improved over time and most could recognise the active compounds except one subject in gr. 2 who did not perceive the drug at all. There was significant difference in "feeling the drug" between the two groups at 15 min. ($P = 0.001$), but not at 120 min. ($P = 0.47$) and 240 min. ($P = 1.0$).

Drug recognition

Sixty two percent in the group 1 (i.v.) as against none in group 2 (oral) identified the drug correctly i.e. as minor tranquilizer (diazepam/nitrazepam) at 15 min. The inter-group difference was significant at 15 min. ($P = 0.006$) but no at 120 min. and 240 min (75% vs. 50%)

Subjective effects of the drug

Commonly reported subjective symptoms were: talkativeness, sleepy, relaxed and drunkenness. Observed symptom included disinhibition, overtalkativeness, and drowsiness. Three subjects in group 1 were observed sleeping during the study but denied marked sleepiness. There were no physical discomfort or any untoward reactions in any of the subjects.

Physiological parameters: There was insignificant increase in pulse rate and decrease in blood pressure after administration of diazepam and the doses used in the study were found to be safe. There was no change in respiratory rate.

MBG Scale Score

Fig. 1 shows the comparative MBG score, which measured euphoria, between the two groups. There was significant rise in MBG score as against baseline at all points of time in group 1 and among group 2 at 120 min. and 240 min. (Bonferroni multiple comparison tests). Euphoria induced by diazepam was obvious i.e. change from baseline MBG scores, when administered through intravenous route but not through oral route. The euphoria once experienced

was maintained for long time in both the groups and, there was no significant inter-group difference as shown by analysis of variance with repeated measures.

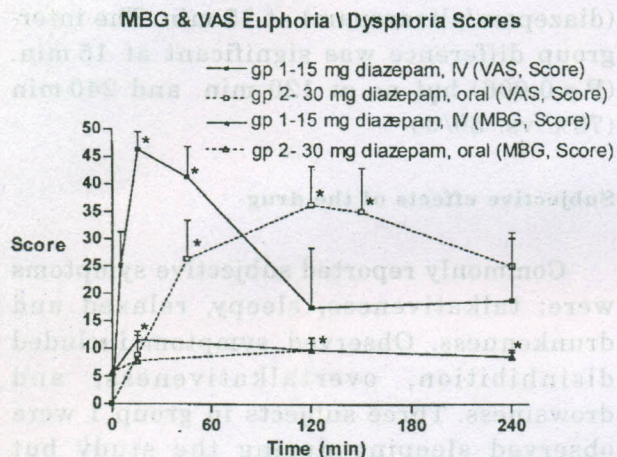


Fig. 1: Comparison of MBG (euphoria) and VAS (euphoria/dysphoria) scores in group 1 (n=8) and in group 2 (n=8). MBG scores were significantly raised from baseline in both the groups but much earlier (15 mins.) in group 1. No. significant inter-group difference was seen. VAS (euphoria) score was significantly higher and reported earliest at 15 mins in group 1 whereas in group 2 significantly higher euphoria was reported at 45 mins., though highest value at 120 mins (P<0.05).

PCAG Scale Score

Baseline values were comparable in both the groups. Analysis of variance with repeated measures of PCAG scores shows no significant changes in sedation between the two (P = 0.29, Fig. 2). Bonferroni multiple comparison test was significant at 120 min. in both the groups but not at other points of observation. It was observed that sedation was reported much later (120 min.) in both the groups whereas euphoria was reported as early as 15 min. in group 1 and at 45 min. in group 2.

Euphoria was more significant than sedation.

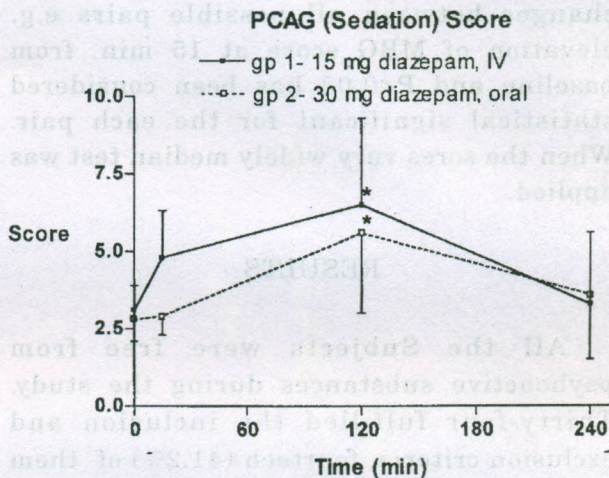


Fig. 2: Comparison of PCAG Scores in group 1 (n=8). Sedation was significantly higher at 120 mins in both the groups (P<0.05). No significant inter-group difference was seen.

Visual Analog Scale (VAS)

Laboratory Data

Mean scores in VAS (euphoria) are shown in Fig. 1. ANOVA showed significant variations in VAS (euphoria/dysphoria) score amongst subjects in group 1 & group 2 (P = 0.007 and P = 0.0019 respectively). Higher euphoria was observed at 15 and 45 min. in group 1 and at 45, 120 and 240 min. in group 2, which was in agreement with the score of euphoria in MBG scale. There was no inter-group difference between the two groups. The same scale (VAS) was applied to rate the sedation (-100 representing maximal sedation and +100 representing maximal alertness). None of the subjects showed more alertness after administration. Sedation was reported earlier (15 min.) in group 1 (-35), in

comparison with group 2 (0) who reported sedation at 120 min. Highest score (sedation) was observed at 120 min. amongst subjects in gr. 1 (-80) and at 150 min in gr. 2 (-80). Sedation was maintained for about 2 hour in both the groups. There was no statistically significant difference in sedation in both the groups.

There were no serious adverse effects like hypersensitivity, respiratory distress, cardio-vascular-complications observed during the study. The patients were comfortable.

Laboratory Data

Altogether ninety six blood samples, six each from sixteen subjects were collected. One set of plasma diazepam concentration readings in each group was discarded because of technical errors. The remaining data (eighty four readings) were analysed.

There was wide variation in the plasma diazepam concentration amongst the subjects at different point of time, more so in group 2. Highest plasma concentration of 2423 ± 736 ng/ml was achieved at 5 min. in group 1, and 1027 ± 799 ng/ml in group 2, which was achieved at 45 min. Plasma level was achieved earlier and was higher when diazepam was administered through intravenous route (Wilcoxon's Rank Sum test, $P = 0.01$) and declined after 45 min in subjects who received diazepam orally. Further, plasma concentration achieved in group 1 was significantly higher than in group 2 (Wilcoxon's Rank Sum test). These are seen in Fig. 3.

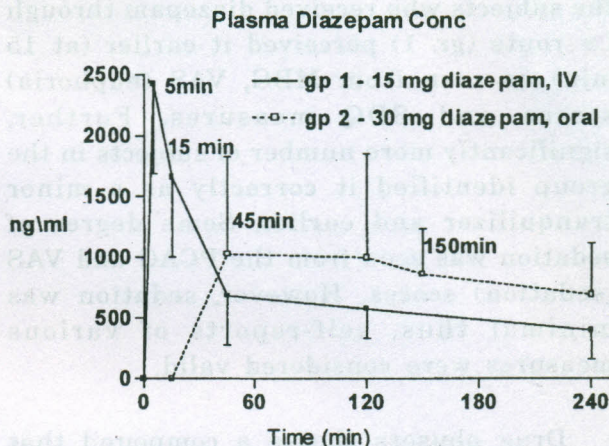


Fig. 3 : Comparison of Plasma diazepam concentration in group 1 (n=7) and group 2 (n=7). Significantly higher peak value of plasma diazepam concentration was seen in group 1 ($P < 0.05$) and the peak was achieved earlier in the same group.

DISCUSSION

Studies evaluating abuse liability of a compound can be carried out among both experienced drug users and drug naive subjects. However, most have preferred experienced drug users as they can reliably discriminate between different compounds and tolerate higher dose without showing impairment (16). Further, it may not be ethically appropriate to administer high dose to non-tolerant subjects. In accordance with the above view, the subjects recruited for this study were dependent users. The two groups were comparable as regards their demographic parameters, history of drug use and anthropomorphic parameters.

The most important finding of this study is that these subjects experienced significant euphoria following administration of diazepam (15mg i.v. or 30 mg oral). However,

the subjects who received diazepam through i.v. route (gr. 1) perceived it earlier (at 15 min) as seen from MBG, VAS (euphoria) scores and SDQ measures. Further, significantly more number of subjects in the group identified it correctly as a minor tranquilizer and earlier. Some degree of sedation was seen from the PCAG and VAS (sedation) scores. However, sedation was minimal thus, self-reports of various measures were considered valid.

Drug abusers choose a compound that cause euphoria and they prefer to experience the pharmacological effects as fast as possible and as long as possible (17). Euphoria is very crucial as it leads to drug seeking behaviour and self-administration. It can be seen that the dose of diazepam used in this study was sufficient for producing euphoria even among experienced drug user. Though the euphoria was achieved much earlier when diazepam was administered intravenously, the magnitude was equal in the two groups. This is probably due to equipotent dose of diazepam (15 mg i.v., 30 mg oral) used in the two groups. Subjective symptoms noted in the study are in keeping with the expected acute effects of diazepam (18, 19).

Dose related increase in subjective ratings of drug liking and euphoria (MBG) for pentobarbital, diazepam and oxazepam among sedative- hypnotic abusers have been reported (11, 19). Though sedatives are abused, overall the abuse potential of diazepam is considered low as against heroin and cocaine. Generally, benzodiazepines are abused orally (7), however, in our treatment centre it has been seen that about 20% of patients abuse

diazepam and mostly through i.v. route (4, 5). Some even crush these tablets and inject after dissolving in water. When the same drug is used by different routes, the route with the faster onset is associated with higher abuse liability e.g. oral vs. i. v. amphetamine. Intravenously administered drug produce more positive and reinforcing effects. Attempts to improve the sensitivity of assessment of abuse potential of sedative hypnotic in experimental situation through various scales has not been very successful (20).

In this study scores on euphoria measured though different instruments were similar as regards onset and duration. The failure to recognize the drug and delay to perceive its effects among those in group 2 could be explained by the fact that among these subjects the highest level of diazepam concentration was delayed due to slow absorption of the drug from gastrointestinal tract (16). Plasma level would be the most rational explanation such observations.

The plasma concentration varied between 396 ± 237 (at 240 min) to 2423 ± 736 ng/ml (at 5 min) in gr.1, and in gr.2 varied from 693 ± 422 (at 240 min) to 1027 ± 799 ng/ml (at 45min). Plasma level of diazepam has been found be variable and was between 630 to 1670 ng/ml after 10mg of iv diazepam, achieved in a few minutes (18) The plasma level following oral diazepam (30 mg) have been reported to vary between 600-900 ng/ml (21), and the peak level being achieved around 1 hour. The peak plasma concentration achieved was significantly lower in group 2 (oral) as against those receiving intravenously (1027 vs. 2423 ng/ml). Similar findings have been observed

earlier (18). Plasma levels of diazepam varied widely within the group as well as between the groups, even though the sample was homogeneous with respect to age, BMI, drug use history and medical status. The reasons for individual variations though not known precisely, may be due to genetic factors in diazepam pharmacokinetics (22).

Generalization of self-report measures for the evaluation of drug abuse liability among different cultures and across languages is an important issue. In this study the instruments were translated and back translated to *Hindi*. Some of the expressions like 'pleasant sick' or "I am coasting" were difficult to be expressed in Hindi and the subjects has difficulty to understand as seen by us earlier (27). ARCI was originally developed in USA using substance abusers incarcerated in a Federal penitentiary during the late 1940s and 1950s. Some of the inconsistencies currently being obtained with these scales might well be related to the condition under which it was developed and validated.

Summarizing, it would appear that a drug might have differential abuse liability depending upon its route of administration. As seen here, even a compound like diazepam (with low abuse potential) has higher abuse potential, if administered through intravenous route as euphoria is achieved earlier. This could be due to rapid

attainment of highest plasma level. The findings have important implications in clinical practice and public health policy. Stricter control is required for the parenteral and other dosage forms of a compound, which can be dissolved in water to be used as injections.

There are certain limitations of the study. Firstly, the time of assessment and collection of blood samples in the two groups were not uniform. However, this was done keeping in mind the ethical aspects of human volunteer study. The subjects in group 2 (oral diazepam) could not have had the drug in the plasma within 5 minutes. The sample could not be collected at 150 min among subjects in gr. 2 due to logistic problems. Secondly, due to small sample size non-parametric tests was applied which are less robust. Finally, the subjects in this study were drug dependent individuals, such a study could be carried out among non-abusers and along with plasma values of diazepam and its active metabolite. These shortcomings may effect the generalisability of the results to other sections of population.

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