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Subjective and behavioral effects of diazepam depend on its rate of onset

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Abstract. This study addressed the assumption that rate of onset affects the euphorigenic effects of drugs. Drugs with rapid onset are commonly thought to be more euphorigenic than drugs with slower onset, but this idea has rarely been studied directly. Nine healthy male social drinkers, with no history of drug- or alcohol-related problems, participated in three sessions. On each session they received oral doses of placebo (PLAC), diazepam in a rapid onset condition (FAST), or diazepam in a slow onset condition (SLOW). In the FAST condition, they received a single 20 mg dose, whereas in the SLOW condition they received six 4 mg doses administered at 30-min intervals. Plasma levels of diazepam and desmethyldiazepam, subjective effects (including measures of euphoria), psychomotor performance and vital signs were monitored throughout each session. Although the FAST and SLOW conditions led to similar peak plasma levels of drug, the peak was attained earlier in the FAST condition (61 min versus 220 min). Subjects' scores on a measure of euphoria (MBG scale of the ARCI) were significantly higher in the FAST condition compared to the SLOW and PLAC conditions. Subjects exhibited significantly more behavioral signs of intoxication and greater psychomotor impairment in the FAST condition. Sedative effects of the drug were similar in magnitude, but the effects lasted slightly longer in the FAST condition. On several measures diazepam produced similar effects in the two conditions (e.g., ratings of strength of drug effect). These data provide limited support for the notion that a faster rate of onset of drug effects is associated with greater euphoria.

Key words: Oral diazepam – Pharmacokinetics – Subjective effects – Euphoria – Humans – Abuse potential – Normal volunteers – Rate of onset

Rate of onset is often cited as an important determinant of the abuse potential of drugs (Busto and Sellers 1986; Jaffe 1990; Farré and Cami 1991). Rapidly-increasing subjective drug effects (e.g., a "rush") are reportedly more euphorigenic, and are hence associated with greater likelihood of abuse, than drug effects which increase more gradually. This principle has been cited as a factor accounting for differences in abuse liabilities among drugs within the same class (e.g., pentobarbital versus phenobarbital), and also in the relative risks of abuse associated with different routes of drug administration (e.g., intravenous versus oral). Surprisingly, however, few studies have specifically examined how the rate of onset affects the subjective, in particular the euphorigenic, effects of a drug using the same drug and the same route of administration. One such study was recently completed in this laboratory examining effects of pentobarbital in normal volunteers: pentobarbital was administered to young male social drinkers, in either a single oral dose ("rapid" onset condition) or a series of divided doses ("slow" onset condition). Similar peak plasma levels of pentobarbital were attained in the two conditions, but the peak was reached sooner in the rapid onset condition (50 versus 200 min in the rapid and slow onset conditions). Subjects reported experiencing more positive subjective responses (i.e., greater liking) when the drug was administered in the rapid onset condition.

The present study was designed to extend this finding to another drug, diazepam. Compared to other benzodiazepines, diazepam is considered to have a relatively high liability for abuse (APA 1990; Griffiths and Wolf 1990), and it also possesses one of the most rapid onset of effects of compounds in this class. Subjective effects of an oral dose of diazepam peak within 0.5–1 h, compared to several hours for other compounds with lower abuse liability, such as oxazepam and prazepam (Greenblatt et al. 1984). Differences among benzodiazepines have also been observed in laboratory studies designed to assess abuse liability. Subjects with histories of sedative abuse show greater preference for, and higher ratings of liking, for diazepam than they do for other benzodiazepines with slower onsets of effects (e.g., oxazepam). Despite the general correspondence between onset rate and abuse liability across different compounds, however, it is not known if

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the observed differences can be attributed solely to their differential rates of onset.

Several previous studies have examined the role of onset rate in subjective and behavioral effects of benzodiazepines. Bliding (1974) compared subjective and psychomotor effects of two benzodiazepines differing in rapidity of onset, diazepam and oxazepam. Diazepam produced more marked effects (e.g., sedation and impairment), and the differences were attributed to the more rapid increase in concentration with this drug. Greenblatt et al. (1977) examined subjective responses to chlordiazepoxide administered with or without an antacid preparation which slowed the rate of absorption. Even though similar peak concentrations were reached with and without the antacid, subjects reported feeling more "spacey" and their thinking was more slowed in the rapid absorption condition. In contrast, however, Tuomainen (1989) administered temazepam in a rapid-onset soft gelatin capsule formulation and in a slower-onset tablet form, and found that this drug produced less drowsiness and mental slowness in the capsule formulation, even though this formulation led to higher concentrations of drug. The reason for the differences across studies is not evident. The present study was designed to further explore the role of onset rate in the effects of a benzodiazepine, specifically with respect to effects associated with abuse liability (i.e., "euphoria", liking ratings and "high"). The study was conducted using moderate (non-problem) social drinkers. In a previous study, diazepam produced modest increases in drug liking and euphoria in social drinkers (de Wit et al. 1989).

Materials and methods

Subjects. Participants were nine normal, male social drinkers, aged 21–35. Social drinkers were defined as individuals who consumed on average six or more drinks per week (a "drink" was defined as 1 oz hard liquor, 8 oz wine, or 12 oz beer), but who had no history of problem drinking. Volunteers were recruited from the university and surrounding community through local newspaper advertisements, posters, and word-of-mouth referrals. They were initially screened by telephone, and then interviewed by a psychiatric social worker and examined by a physician. Psychiatric symptomatology was assessed in a semistructured interview and using the SCL-90 (Derogatis 1983). Candidates were excluded if they: i) had any history of an Axis I psychiatric disorder (APA 1987), ii) had significant medical problems, iii) deviated by more than 10% from normal body weight (Metropolitan Life tables) or iv) had any history of drug- or alcohol-related problems (e.g., any legal, family or health problems possibly related to alcohol or drugs). Current and lifetime histories of recreational and therapeutic drug use were obtained on a questionnaire and verified by the social worker.

Prior to participation subjects read and signed a consent form which explained the nature and procedure of the study and listed possible effects of the drugs they might receive (alcohol, sedative/tranquilizer, stimulant/appetite suppressant, and/or placebo). The protocol was approved by the Institutional Review Board.

Procedure. The study used a double-blind, placebo-controlled, within-subjects design (de Wit et al, 1992). Each subject participated in three sessions, conducted once a week. On these sessions they received, in counterbalanced order, placebo (PLAC condition), diazepam (20 mg) in a single oral dose (FAST condition), or diazepam (total 24 mg) in six divided doses administered over 2.5 h (SLOW condition). Using parameters of a kinetic model described by Kaplan et al. (1973), the doses of diazepam were selected to produce the same peak blood levels in the FAST and SLOW conditions, but to attain these peaks at different rates.

Sessions were conducted in the Clinical Research Center (CRC) from noon to 8:30 a.m. Subjects agreed not to take any medications or drugs (including alcohol) for 12 h before the session, and their breath alcohol was measured before each session to verify compliance. They consumed a standard hospital lunch before 1 p.m., and did not eat again until after the session at 11 p.m. Subjects were tested in pairs to simulate a social, recreational setting. During the sessions when no procedures were scheduled, they were free to engage in leisure activities (e.g., talking, playing board games, watching television or movies, reading). They were not permitted to work or study at any time after the first drug administration (5 p.m.).

At 2:30 p.m., an intravenous catheter was inserted in the subject's non-dominant forearm for blood sampling. Blood samples (7 ml) were drawn into a heparinized tube at the following times: 4:30 p.m. (baseline), 6:00, 7:00, 7:45, 8:00, 8:15, 8:30, 8:45, 9:00, 9:15, 10:00, 11:00, and 8:00 a.m. the next morning. Blood samples were centrifuged, frozen, and later sent for analysis (Dr. D. Greenblatt, Tufts University, Boston). Subjects completed psychomotor tasks and subjective effects questionnaires (see below) at the following times: 4:30 p.m. (baseline), 6:05, 7:05, 7:50, 8:20, 8:50, 9:20, 10:05, 11:05, and 8:05 a.m. the next morning. The tasks and questionnaires took about 5 min to complete. Subjects ingested six powdered doses containing diazepam or placebo at 30-min intervals between 5 p.m. and 7:30 p.m. Powders contained taste masks (varied flavors of unsweetened Kool-Aid, quinine sulfate and dextrose; Griffiths et al. 1980) and, when appropriate, diazepam (Valium; Hoffman La Roche, Inc.). In the PLAC condition, all six powders contained only the base mixture. In the FAST condition, the first five powders contained base mixture, and the sixth contained the base plus 20 mg diazepam. In the SLOW condition, each powder contained the base plus 4 mg diazepam. The powders were placed directly on the subject's tongue, and followed by 100 ml of water or juice. Nurses recorded vital signs (heart rate, blood pressure, temperature; Critikon Dinamap and Ivac Temp-plus II) every hour between 5:00 and 11:00 p.m., and at 8:00 a.m. Subjects' behavior was rated (see below) at regular intervals during the sessions by an observer who was blind to the experimental conditions.

At 11:05 p.m. subjects completed an end-of-session questionnaire, on which they indicated what type of drug they thought they had received (stimulant/anorectic, sedative/tranquilizer or placebo) and how much they liked its effects overall. Liking was rated on a 100 mm visual analog scale labeled "dislike" (0), "neutral" (50) and "like a lot" (100). Subjects also completed a sleep questionnaire (see below) on the morning following each session.

Subjects were fully debriefed following completion of the study and they were paid for their participation.

Plasma diazepam determinations. Plasma levels of diazepam and desmethyl-diazepam were determined using the method of Greenblatt et al. (1980).

Measuring instruments. Three instruments were used to measure subjective drug effects, an experimental version of the Profile of Mood States (POMS; McNair et al. 1971), a 49-item version of the Addiction Research Center Inventory (ARCI; Martin et al. 1971) and a visual analog liking questionnaire (LQ). The POMS consists of 72 adjectives commonly used to describe momentary mood states. Subjects indicate how they feel at that moment in relation to each of the adjectives on a 5-point scale ranging from "not at all" (0) to "extremely" (4). Eight clusters of items, derived through factor analysis, form the eight scales of the questionnaire: Anxiety, Depression, Anger, Fatigue, Vigor, Confusion, Friendliness, and Elation. Two additional scales derived by Johanson and Uhlenhuth (1980) were also used: Arousal = (Anxiety + Vigor) − (Fatigue + Confusion), and Positive Mood = Elation − Depression. The 49-item ARCI is a widely used questionnaire developed to measure reactions to drugs. It consists of five scales: The Benzedrine Group scale (BG) and Amphetamine scale (A) measure effects typical of stimulants, the

Pentobarbital, Chlorpromazine and Alcohol Group scale (PCAG) measures sedative responses, the Lysergic Acid (LSD) scale measures dysphoric or psychotomimetic effects, and the Morphine-Benzedrine Group (MBG) scale measures euphoric effects. The LQ consists of four visual analog scales associated with the following questions: Do you *feel* any drug effects? Do you *like* the effects you are feeling now? Are you *high*? How much would you like *more* of what you consumed, right now? Subjects indicate their response on a 100 mm line labeled "none/not at all" to "a lot/very much". Because of possible confusion in interpretation of the *like* and *high* questions, data for the *like*, *high*, and *more* questions were analyzed only if subjects reported feeling some effect (i.e., scored higher than 5 mm on the *feel* drug scale).

Two instruments were used to assess cognitive or motor impairment, the Digit Symbol Substitution Test (DSST) and the forward and reverse digit memory tasks (Wechsler 1958). The DSST was scored using the number of items completed in 60 s, and the memory tasks were scored using the maximum number of digits correctly recalled before making two consecutive errors. Five versions of each of the tests were used to minimize learning of the symbol or digit orders. The DSST has been found to be sensitive to the effects of psychoactive drugs, and the memory tasks were used because benzodiazepines are known to impair memory (e.g., McLeod et al. 1988; Ghoneim and Mewaldt 1990).

The Observer Rating Form (ORF) is a behavioral checklist developed in this laboratory to assess behavioral effects of drugs. The observer records the presence or absence of 11 signs of intoxication and sedation, including slurred speech, glazed or bloodshot eyes, trouble walking or incoordination, loquacity, problems filling out forms, flushed face, drowsiness or sleeping, and agitation or restlessness, sluggishness, dullness or listlessness. The number of signs were noted just prior to each time subjects completed questionnaires.

The Leeds Sleep Questionnaire (Parrott and Hindmarch 1980) was used to assess the quality of sleep following the sessions. It consists of ten questions concerning Getting to Sleep (GTS; higher score = faster, easier), Quality of Sleep (QOS; higher score = more restful), Awakening from Sleep (AFS; higher score = easier awakening), and Behavior Following Wakefulness (BFW; higher score = more alert).

Data analysis. Subjective effects questionnaires (e.g., POMS, ARCI, LQ) were analyzed using repeated measures ANOVAs (drug condition × time). Analyses of POMS and ARCI conducted using absolute scores revealed that there were no significant pre-drug differences across conditions. Therefore, to reduce variability due to non-experimental factors, scores were analyzed as change from pre-drug score. Other subjective, behavioral and physiological measures were analyzed using one- or two-way ANOVAs. Tukey post-hoc tests were used to compare means when appropriate. Peak plasma levels of diazepam and time to peak levels were compared in the two diazepam conditions using *t*-tests.

Results

Subject characteristics

The subjects' mean age was 22.4 (range 21–24). Most subjects were white (one black), most were full-time graduate students (6/9), and their average weight was 156 lb (range 140–180 lb). The subjects consumed a mean of 12.3 alcohol drinks (range 8–18), and the maximum number of drinks they reported consuming per occasion in an average week was 7.0 (range 5–8). These subjects reported very little use of illicit drugs: none reported ever having used benzodiazepines recreationally, and only two had used opiates recreationally. Most of the subjects had tried marijuana but were not regular users, and most had never tried stimulants or hallucinogens.

Diazepam plasma levels

Figure 1 shows the mean plasma levels of diazepam and desmethyldiazepam at each of the sampled times. The mean peak levels attained in the FAST and SLOW conditions were not different (mean of individual subjects' peak levels FAST 601.2 and SLOW 544.9 ng/ml; $t = 0.15$, ns). However, as planned, plasma levels rose more rapidly in the FAST condition (mean time to peak in the FAST and SLOW conditions 61 min and 220 min respectively; $t = 7.33$, $P < 0.001$). Peak diazepam levels attained varied across subjects (range in FAST condition 349–862 ng/ml; range in SLOW condition 302–794 ng/ml). The correlation between subjects' peak levels in the FAST and SLOW conditions was $r = 0.49$ ($P < 0.10$), and the correlation in their time to peak levels was $r = 0.46$ ($P < 0.10$). Levels of desmethyldiazepam were negligible and not different across the two diazepam dosing conditions.

End-of-session questionnaire

Subjects' overall ratings of drug liking, obtained at the end of each session, did not differ across the three conditions (means: PLAC 53.0, SD 12.6; FAST 59.9, SD 15.3; SLOW 61.0, SD 18.7; $F = 1.5$ ns) Drug liking ratings under the FAST and SLOW conditions were significantly correlated

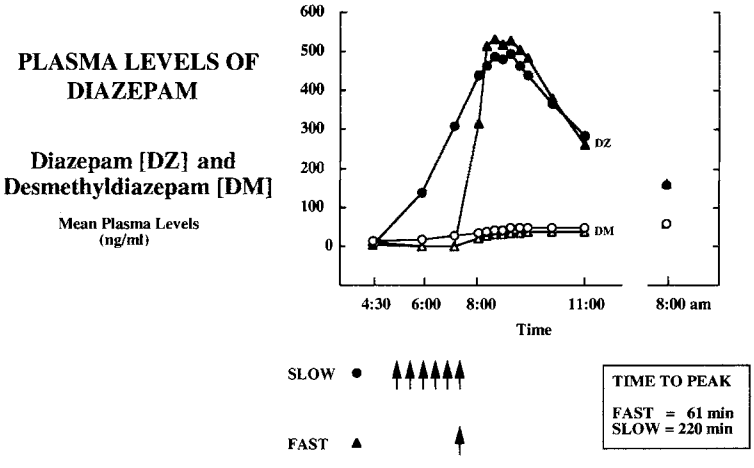

Fig. 1. Mean plasma levels (ng/ml) of diazepam (*DZ*; *filled symbols*) and desmethyldiazepam (*DM*; *open symbols*) after administration of oral diazepam in divided doses (total 24 mg; *SLOW*) or a single dose (20 mg; *FAST*). In the SLOW condition (*circle symbols*) subjects received 4 mg every 30 min between 5 p.m. and 7:30 p.m., and in the FAST condition (*triangles*) subjects received a single 20 mg dose at 7:30 p.m. *Arrows* below the abscissa indicate the times of drug administration

($r = 0.85$; $P < 0.001$), indicating that there were consistent individual differences in subjects' liking of diazepam. Most subjects correctly identified the drugs they received: 6/9 identified PLAC as "placebo"; 6/9 identified FAST as "tranquilizer/sedative"; 7/9 identified SLOW as "tranquilizer/sedative".

POMS

F and *P* values for POMS scales are shown in Table 1. The only scale which differentiated the SLOW and FAST conditions was the Fatigue scale: scores on this scale were significantly higher in both the FAST and SLOW conditions, relative to PLAC. FAST and SLOW condition scores were higher than PLAC at 20, 50 and 80 min. At 80 min, scores in the SLOW condition began to return to baseline, while scores in the FAST condition remained elevated. Significant main effects of hour were obtained on Fatigue, Vigor, Confusion and Friendliness scales. Marginally significant ($P < 0.10$) drug effects or drug-by-hour interactions were obtained on Vigor, Confusion and Friendliness.

ARCI

Table 1 shows the *F* and *P* values for the ARCI scales. Only the PCAG and MBG scales were differentially affected by the FAST and SLOW conditions: mean scores on these scales are shown in Fig. 2. Subjects scored significantly higher on the MBG scale after receiving diazepam in the FAST condition, compared to *both* the SLOW and the PLAC condition. This increase in MBG scores occurred at 20 and 50 min following drug administration. On the PCAG scale, scores in both the FAST and SLOW conditions were higher than PLAC at 20, 50, 80 and 110 min. At 155 and 215 min PCAG scores remained high in the FAST condition but began to decrease in the SLOW condition, and were no longer greater than PLAC at these points. BG and LSD scores also changed across time points.

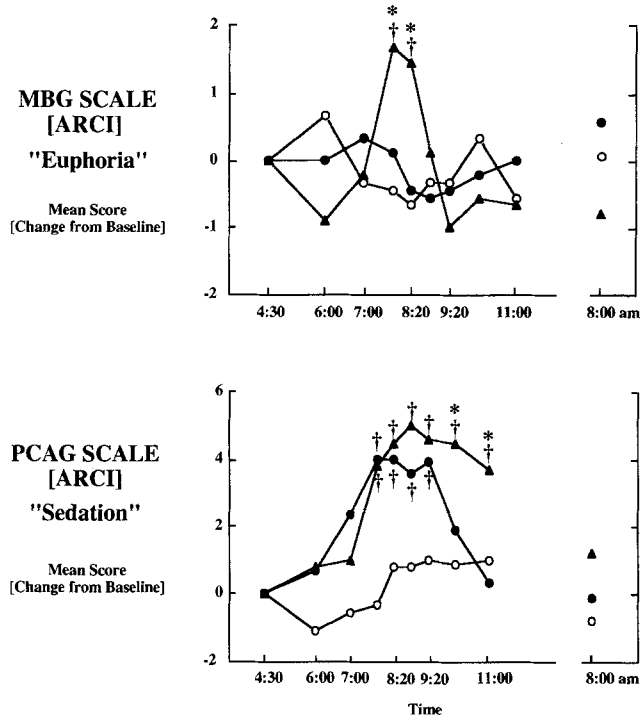

Fig. 2. Mean scores on "euphoria" (*MBG*) and "sedative" (*PCAG*) scales of the ARCI on sessions following administration of placebo (*open circles*), diazepam in divided doses (*SLOW; filled circles*) and diazepam in a single dose (*FAST; triangles*). *Asterisks* indicate time points when means in the FAST condition were significantly higher than both the SLOW and PLAC conditions. *Daggers* indicate means which differed significantly from PLAC

Table 1. Summary of significant *F* values for dependent measures analyzed using ANOVA. *F* values with no asterisk are $P < 0.05$, one asterisk signifies $P < 0.01$ and two asterisks signify $P < 0.001$

	Drug	Hour	Drug × Hour
POMS			
Fatigue	–	5.1**	1.9
Vigor	–	2.4	–
Confusion	–	2.8*	–
Friendliness	–	4.8**	–
ARCI			
BG scale	–	3.1*	–
PCAG scale	6.8**	5.1**	1.9
LSD scale	–	2.1	–
MBG scale	–	–	2.2**
Liking questionnaire			
Feel drug	14.8**	13.5**	5.0**
High	4.4	8.1**	3.0**
DSST	6.1*	3.6**	3.0**
Temperature	4.7	9.9**	2.0
Signs of intoxication	7.3**	6.7**	2.7**

Liking questionnaire

Table 1 shows the *F* and *P* values for the two LQ scales which showed significant drug or hour effects. Diazepam significantly increased scores on the *feel* and *high* scales of the Liking Questionnaire. Post-hoc tests showed that scores in both the FAST and SLOW conditions exceeded PLAC scores on these scales at all time points after drug administration, but scores in the two drug conditions did not differ from one another.

Psychomotor/memory tests

Relative to PLAC, diazepam significantly decreased DSST scores (Table 1). Post-hoc tests showed that scores were lower at all time points after drug administration in the FAST condition, and at 20 and 50 min in the SLOW condition. Diazepam had no effect on the forward or reverse digit memory tests.

Physiological measures

Body temperature decreased in both the FAST and SLOW conditions, relative to PLAC (Table 1). The effects were not different in the FAST and SLOW conditions. The decreases peaked at 90 min (mean temperatures: PLAC 98.5 °C, FAST 97.8 °C, SLOW 97.9 °C). Blood pressure was unaffected.

Signs of intoxication

Diazepam significantly increased signs of intoxication (Table 1). Subjects showed significantly more signs of intoxication in both the SLOW and FAST condition, compared to PLAC, at 20, 50, 80 and 110 min. In addition, subjects showed more signs of intoxication in the FAST condition than either the PLAC and SLOW conditions at 50 and 80 min following drug administration (Fig. 3).

Sleep questionnaire

The only scale on the sleep questionnaire to show a significant drug effect was the GTS scale, and it was affected only in the SLOW condition: relative to placebo, subjects found it easier to get to sleep after diazepam in the SLOW condition (mean GTS scores PLAC 43.2, FAST 52.2, SLOW 68.7; one-way ANOVA; $F_{2,14} = 9.58$, $P < 0.002$).

AM measures

In separate one-way ANOVAs subjects' scores on measures obtained the next morning were compared across the three conditions. Plasma levels of diazepam and its metabolite remained elevated the next morning but did not differ in the FAST and SLOW conditions (mean levels 160.6 and 160.2 ng/ml, respectively). On the POMS, subjects scored significantly lower on the Anxiety scale in the SLOW condition compared to PLAC (mean scores on Anxiety for PLAC, SLOW and FAST conditions were 0.51, 0.37 and 0.43, respectively; $F_{2,14} = 4.59$, $P < 0.03$). No differences among the conditions were observed on the mornings following the sessions on other POMS scales or on the ARCI, Liking Questionnaire, psychomotor tests or physiological measures.

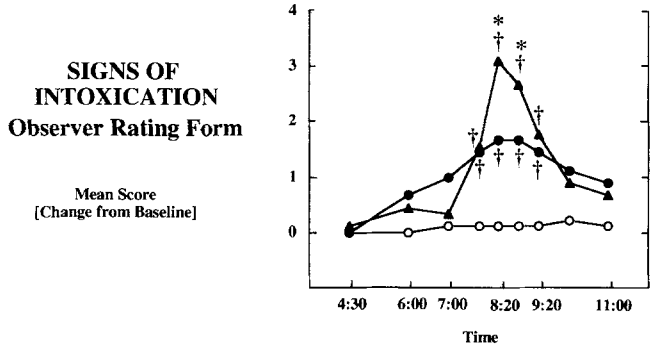

Fig. 3. Mean number of signs of intoxication on the Observer Rating Form after receiving placebo (*open symbols*), divided doses of diazepam (*SLOW; filled circles*) and single dose of diazepam (*FAST; triangles*). *Asterisks* indicate time points when FAST means differed significantly from both SLOW and PLAC conditions, and *daggers* indicate points when means differed significantly from PLAC. Subjects exhibited significantly more signs of intoxication when diazepam was administered in a single dose

Discussion

The present study provided limited empirical support for the assumption that the rate of increase of a drug's effects is an important determinant of its euphorigenic effects. Diazepam was administered in two conditions, a single dose, rapid onset condition and a divided dose, slow onset condition. Although the two conditions differed in the time to reach peak plasma level, the peak levels attained were the same in the two conditions. Subjects reported more "euphoria" (i.e., higher scores on the MBG scale of the ARCI) and more observable signs of intoxication in the rapid, compared to the slow onset condition. The rapid onset condition was also associated with greater psychomotor impairment and longer-lasting sedative effects. On other measures, the two dosing conditions produced similar effects (e.g., ratings of strength of drug effects, liking of effects, feeling "high"). The data provided partial support for the idea that the euphorigenic effects of drugs are positively associated with their rate of onset.

Although the differences in subjective effects observed in the slow and rapid onset conditions were modest in magnitude, the fact that they occurred at all, in this subject population and by this route of administration, is noteworthy. Diazepam is not reliably euphorigenic nor is it a highly reinforcing drug in normal healthy volunteers (Johanson and Uhlenhuth 1980; de Wit and Griffiths 1991). The subjects in this study were moderate social drinkers, without histories of excessive drug or alcohol use. In such subjects diazepam may be expected to produce at most a modest increase in subjective reports of liking and euphoria. Further, the rapidity of onset of any drug administered by the oral route is necessarily limited by the process of absorption. Thus, in the present study the rate of onset even under the rapid (single dose) condition was slow, relative to onset times by other routes of administration commonly associated with abuse, such as the inhaled or intravenous routes. Nevertheless, the difference between a rise to peak of 61 min and 220 min in the two conditions was sufficient to demonstrate the phenomenon under investigation: even under these relatively limited conditions the faster onset time was associated with differential drug effects, including greater euphoria.

The present results are consistent with those of a previous study which examined the effects of varying rates of onset of another drug, pentobarbital (de Wit et al. 1992). In that study, peak plasma levels of pentobarbital were reached in 50 and 200 min after oral dosing in a fast and a slow onset condition, respectively. Subjects' ratings of drug liking and "high" were higher in the fast onset condition (the ARCI was not administered). However, the

fast and slow conditions did not produce differential effects on measures of sedation, psychomotor impairment or observer ratings. It is not obvious why drug liking and "high" were affected by the dosing manipulation in the pentobarbital study and not in the present study with diazepam. Presumably, differences between the drugs or the doses or the subject samples accounted for this. Nevertheless, in both studies it was found that measures of apparently "pleasant" or euphorigenic drug effects were sensitive to the dosing manipulation.

In the present study, the peak blood levels of diazepam attained under the two conditions were similar, even though the time taken to reach the peak differed across the two conditions. Because plasma concentrations of diazepam are likely to be good indicators of brain concentrations at the times sampled (Jones et al. 1988; Greenblatt and Sethy 1990), the differential subjective effects under the two dosing conditions cannot be accounted for by differences in drug concentrations at the central site of action. Rather, the brain mechanisms which mediate the euphorigenic effects of drugs may be sensitive to the rate of change during the onset of a drug effect. Another interpretation of the differential subjective effects under the two dosing conditions is that the subjects' responses in the gradual onset condition were dampened because of the development of acute tolerance (Greenblatt and Shader 1987). It is possible that, in the SLOW condition, acute tolerance developed over the 220 min that elapsed from the initial onset of drug effects to the time of the peak plasma levels. Although this is a plausible explanation, it should be noted that the different measures of drug effects were affected differentially by the dosing manipulation.

Peak plasma levels of diazepam varied widely across subjects, even though the sample was homogeneous with respect to age, gender, body weight, drug and alcohol use history, medical status and time since their last meal. Variability in the pharmacokinetics of diazepam has been previously reported (Greenblatt et al. 1989) in a similar but larger sample of subjects, and using more frequent sampling of plasma levels. The reasons for the individual differences are not known, although it has been suggested (Bertilsson et al. 1989) that genetic factors may influence diazepam pharmacokinetics.

Several factors limit the conclusions that can be drawn from this study. First, the subjective drug effects reported by these subjects were mild, relative to the effects observed with this dose in previous studies (de Wit et al. 1989; de Wit 1991). Although most of the subjects correctly identified the diazepam as a tranquilizer under both dosing conditions, the magnitude of sedative effect was modest: several POMS scales that usually reveal robust diazepam effects (e.g., Arousal and Confusion) were unaffected. A possible explanation for the attenuated subjective effects is the fact that in this study sessions were conducted in a hospital setting (Clinical Research Center) whereas previous studies were conducted in a more naturalistic, recreational setting. The effect of varying the rate of onset may be more evident in individuals who are more likely to experience euphorigenic drug effects (e.g., individuals with histories of alcohol or drug abuse), or with drugs that are more likely to produce these effects (e.g., cocaine). The effect also may be more apparent if testing includes a wider range of onset rates (i.e., including more rapid and more gradual). Finally, the small number of subjects in this study may have limited the strength of the observed effect. The rate of onset phenomenon should be investigated using more subjects, and a more heterogeneous sample of subjects, and using other routes of administration.

In sum, the results of this study provide empirical support for the commonly-held belief that the degree of euphoria experienced from a drug is related to its onset rate. Because the euphorigenic effects of drugs are often predictive of their likelihood of abuse, the findings suggest that drugs or drug formulations with slower onset rates would be less likely to be abused. The neuropharmacologic mechanisms underlying these differential subjective effects will be an interesting subject for future study.

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