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Diazepam Dose Preference in Humans

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HEALEY, M L AND R W PICKENS *Diazepam dose preference in humans* PHARMACOL BIOCHEM BEHAV 18(3) 449–456, 1983 —Diazepam dose preference was studied in 10 human subjects in a hospital setting Subjects were allowed to select between a standard compound (diazepam or pentobarbital) and one of several doses of diazepam (2–40 mg/capsule) on an ad lib basis When 5 or 10 mg/capsule diazepam was the standard, no clear cut diazepam dose preference was found When 30 or 50 mg/capsule pentobarbital was the standard, clear cut diazepam dose preference in some subjects was found The shape of the dose preference function differed among subjects Within subjects, diazepam dose preference differed within the self-administration day, with some subjects preferring one dose in the morning and a different dose later in the day

Diazepam Pentobarbital Drug self-administration Human subjects Dose preference

DRUG self-administration techniques have provided a means for studying the many variables influencing drug-taking behavior More recently, self-administration methods originating in the animal laboratory have been adapted for research with human subjects in clinical residential settings This approach to date has been used most extensively to examine factors that influence human oral sedative self-administration Whereas alcohol has been the sedative most frequently studied (e g , [3, 4, 9, 10, 11, 12]), pentobarbital, diazepam and chlorpromazine self-administration has also been studied with human subjects (e g , [5,13])

One of the factors examined in human sedative self-administration has been drug or dose preference Selection of a compound for self-administration has been used as a measure of the compound's relative abuse liability For example, Pickens *et al* [13] examined dose preference during free access to different doses of pentobarbital (30–200 mg/capsule) Similarly, Griffiths *et al* [5] compared rates of pentobarbital, diazepam and chlorpromazine self-administration to determine drug preference under limited-access conditions Drug preference has also been used as an indication of relative abuse liability under conditions of acute drug administration [6,8]

In the present study, adults with established histories of sedative abuse were allowed to select among different doses of diazepam to determine dose preference Drug preference was studied under conditions of relatively free access, in which no upper limit was placed on drug intake and drugs were available for self-administration 24 hours per day Under free-access conditions, the influence of duration of drug action on drug preference is minimized Under conditions of limited drug access (i e , fixed number of capsules per day), duration of drug action may become an important factor in drug choice, particularly in the physiologically dependent subject

METHOD

Subjects

Subjects were 5 adult females (F16, F17, F18, F28 and F40) and 5 adult males (M22, M23, M35, M36 and M39) selected from patients entering University of Minnesota Hospitals for treatment of drug dependence All subjects were given a complete medical and psychiatric screening by the ward psychiatrist prior to being accepted into the study The screening, which was conducted within the first several hours of hospitalization, included past medical and drug history, blood and urine screens for recent drug use, physical and mental status examination, and blood chemistry Only subjects with at least a four year history of sedative abuse, in sound physical health and actively self-administering sedatives on hospital admission were selected for the study One subject (M22) showed positive response for hepatitis B antigen during initial screening, and, as a health precaution, no further blood samples were obtained from the subject during the study Table 1 shows the age, weight and self-reported drug history for each subject

Subjects were housed on the Clinical Investigations Unit of the University of Minnesota Hospitals This unit is a 13-bed adult psychiatric ward within a teaching/research hospital Informed consent was obtained from all subjects prior to their admission to the study Participation in the research was voluntary and subjects were assured that they could terminate their participation at any time At the conclusion of the research, subjects were gradually withdrawn from sedative drugs (10% per day of the maximum daily dose of diazepam during self-administration) and given appropriate treatment At any given time, only one subject participated in the research

Apparatus

All drugs for oral self-administration were available from an automatic vending machine [13] The machine was a 10-channel commercial vendor modified by removal of the coin slot and installation of a stimulus light and a keylock above the pushbutton of each channel At the start of testing, subjects were issued keys to unlock assigned channels for drug dispensing Drug availability was signalled by illumination of the stimulus light of a channel When a stimulus light was

TABLE 1

DRUG HISTORY OF SUBJECTS

Subject	Age	Weight (kg)	Pentobarbital Half-life (hrs)	Behavioral* Tolerance	Drug History	Duration of Problem Drug Use (yrs)	Drug Use on Admission
F16	48	65 8	6 4	0	Alcohol Barbiturates Benzodiazepines Opioids	13	Alcohol Flurazepam (Dalmane) Chlorpromazine (Thorazine)
F17	31	58 7	7 1	0	Barbiturates Meprobamate Benzodiazepines Antidepressants	12	Diazepam (Valium) Clorazepate (Tranxene) Codeine (Percodan, Tylenol #3) Fluphenazine (Prolixin) Propoxyphene (Darvon Darvocet)
F18	32	51 4	8 3	++	Barbiturates Benzodiazepines Stimulants Opioids Hallucinogens Nonbarbiturate Sedatives Antihistamines Antipsychotics	8	Marijuana Methaqualone (Quaalude) Secobarbital (Seconal) Prochlorperazine (Compazine) Antihistamines (Ornade)
M22	28	75 5	Not Available	Not Available	Benzodiazepines Opioids Nonbarbiturate Sedatives Antidepressants Non-narcotic Analgesics	8	Diazepam (Valium)
M23	29	77 1	15 6	+	Alcohol Barbiturates Benzodiazepines Stimulants	19	Phenobarbital (Sodium Phenobarbital) Diazepam (Valium) Secobarbital (Seconal)
F28	63	52 6	22 4	0	Alcohol Benzodiazepines Antipsychotics Antidepressants	19	Oxazepam (Serax) Alcohol Thioridazine (Mellaril) Imipramine (Tofranil)
M35	34	95 3	8 4	0	Alcohol Benzodiazpines Barbiturates Opioids Stimulants Hallucinogens Non-narcotic Analgesics Nonbarbiturate Sedatives Marijuana Antipsychotics	13	Alcohol Diazepam (Valium)
M36	47	76 0	4 2	++	Benzodiazepines Non-narcotic analgesics Alcohol	13	Alcohol Diazepam (Valium)

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TABLE 1
DRUG HISTORY OF SUBJECTS
(Continued)

Subject	Age	Weight (kg)	Pentobarbital Half-life (hrs)	Behavioral* Tolerance	Drug History	Duration of Problem Drug Use (yrs)	Drug Use on Admission
M39	47	95 5	14 4	0	Barbiturates Benzodiazepines Nonbarbiturate Sedatives Alcohol Opioids Stimulants Marijuana Antipsychotics Antidepressants	18	Alcohol Chlorpromazine (Thorazine) Amitriptyline (Elavil)
F40	51	40 8	5 2	++	Benzodiazepines Barbiturates	4	Phenobarbital (Sodium Phenobarbital, Donnatal) Codeine (Tylenol #3) Flurazepam (Dalmane)

*0=Minimal or absent, +=moderate, ++=marked

illuminated, unlocking the switch and pressing the channel button delivered a drug capsule in a small paper envelope All doses of each drug were packaged in identically appearing red capsules (size 00) with lactose filler Upon each machine operation, a chime sounded to alert members of the nursing staff to verify that the delivered capsule was swallowed by the subject After each drug delivery, the stimulus light was extinguished and the channel was inoperable (i e , no drug was available) for 30 minutes This minimum interingestion interval was employed to assure that subjects would not take multiple capsules at or near the same time All machine events were controlled by solid state programming equipment locked in an adjacent cabinet An event recorder was employed to obtain a temporal record of subjects' capsule selections

Procedure

Tolerance assessment Immediately after hospital admission, subjects were randomly assigned to either ad lib diazepam or pentobarbital self-administration for at least four days prior to start of preference testing (range 4–11 days, median 8 5 days) Assays for the determination of both metabolic and behavioral tolerance to pentobarbital were typically given midway during this stabilization period On the day of the assay, all drugs were withheld at midnight A single dose of 200 mg pentobarbital was administered orally at 8 a m Blood samples were obtained at 1, 2, 4, 6 and 8 hour intervals post-drug for quantitative pentobarbital analysis, a checklist of behavioral sedative signs (slurred speech, ataxia and sleep) was completed at 1, 2, and 3 hours post-drug Behavioral tolerance was considered absent or minimal (0) if subject slept and showed slurred speech and/or ataxia during this time, moderate (+) if subject showed only slurred speech and/or ataxia, and marked (++) if none of the above signs were observed Metabolic tolerance was measured by pentobarbital half-life values calculated from the rate of decline of drug serum levels post-drug administration

Drug preference To determine dose or drug preference, an ad lib drug self-administration choice procedure was used Two adjacent channels of the vending machine were keyed the same, allowing subjects access to both channels for self-administration To assure initial exposure to both capsules each experimental day, alternate channels only were available for the first two capsule selections Thereafter, both channels were available concurrently for self-administration Drug delivery from one channel was programmed to extinguish the stimulus lights above both channels for 30 minutes, making neither channel available for drug self-administration during that time Throughout testing the same compound (standard) was always available in one channel, whereas the other channel contained a different compound (test) each day At least two replications were obtained with each comparison, and assignments of standard and test compounds was counterbalanced A double-blind procedure was employed in all drug testing

Subjects were instructed to take capsules as they felt they needed them No upper limit was placed on daily drug intake and (except for the 30 minute minimum inter-drug interval) no restriction was placed on drug access Subjects were told to alternate between channels until a preference developed, and then to take whichever capsule they preferred for the remainder of the day Subjects were informed that whereas drug and/or dose available in each channel might change from day to day (all changes were effective at midnight), within a given day the medication in each channel would remain the same

Subjects were told only that the drugs available to them for self-administration were of the sedative class, similar to drugs they had experience with in the past It was stressed to subjects that as doses available would change on a daily basis, they would require varying numbers of capsules each

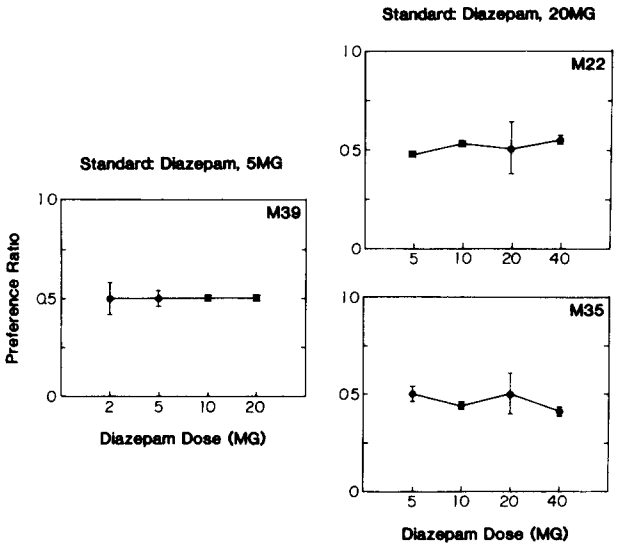

FIG 1 Diazepam dose preference in 3 male subjects with diazepam (5 or 20 mg/capsule) as the standard compound Abscissa dose of diazepam Ordinate preference ratios Each point is the mean of two determinations the vertical bars at each point indicate range

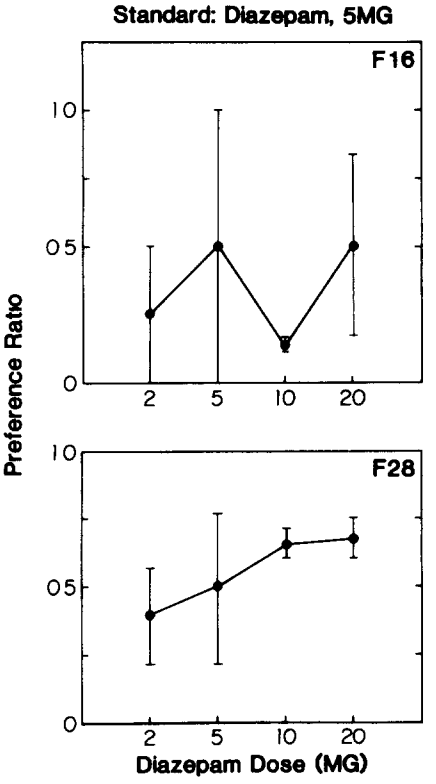

FIG 2 Diazepam dose preference in 2 female subjects with diazepam (5 or 20 mg/capsule) as the standard compound Abscissa dose of diazepam Ordinate preference ratios Each point is the mean of two determinations the vertical bars at each point indicate range

day They were cautioned to avoid counting capsules, or taking them at specific predetermined times Subjects were asked to take enough capsules to remain comfortable and avoid withdrawal symptoms, but not to become overly intoxicated They were informed that if they should become overly intoxicated (with slurred speech and/or ataxia) the nursing or research staff would temporarily confiscate their key to the vending machine until the intoxication cleared

In the first study, dose preference for diazepam was determined for 5 subjects These subjects were allowed to choose between a standard dose of diazepam (5 mg/capsule for F16, F28, and M39, and 20 mg/capsule for M35 and M22) and a range of diazepam doses (2, 5, 10, 20 and 40 mg/capsule) Selection of standard dose as well as the range of diazepam doses tested reflect individual differences in total drug intake and both behavioral and metabolic tolerance among subjects determined during the stabilization period In a second study, eight subjects were allowed to choose between a standard dose of pentobarbital (30 mg/capsule for F16, F17, M22, M23, M35 and M36, and 50 mg/capsule for F18 and F40) and a range of diazepam doses (2, 5, 10, 20 and 40 mg/capsule)

In addition, event records of drug self-administration were examined to determine if dose and/or drug preference were consistent throughout the self-administration day Patterns of drug responding were examined to determine their relation to individual differences in drug and dose preference

Date analysis To quantify drug and dose preference, data were expressed as a preference ratio, the ratio of test drug selections to total drug selections (test + standard) for a given day The first two capsule selections on any day were not included when calculating preference ratios as these were essentially forced choice selections Ratio values of 0 5 indicate no preference between standard and test compound, whereas ratio values greater than 0 5 indicate preference for test over standard compound and ratio values less than 0 5 indicate preference for the standard compound

RESULTS

Throughout testing, subjects maintained daily drug intake at levels sufficient to avoid the appearance of withdrawal symptoms Only rarely did subjects show slurred speech or ataxia Subject F28 had her key confiscated once during Study 1 In Study 2, Subject M22 also had his key confiscated on one occasion while Subject M23 had his key confiscated 3 times The results of the assay for determination of both metabolic and behavioral tolerance to pentobarbital are shown for each subject in Table 1 Pentobarbital half-lives ranged from 4 2 to 22 4 hours (mean = 10 2 hours) No data is available for Subject M22 who, due to a previous hepatitus infection, did not have blood samples drawn as a safety precaution

Diazepam as Standard Compound

When diazepam dose preference ratios were determined using diazepam as the standard compound, consistent dose preferences were not observed in any subject Figure 1 illustrates preference data for three male subjects (M22, M35, M39) Subject M39 was allowed to select between 5 mg/capsule diazepam (the standard compound) and 2, 5, 10 and 20 mg/capsule diazepam and Subjects M22 and M35 were allowed to select between 20 mg/capsule diazepam and 5, 10, 20 and 40 mg/capsule diazepam Preference ratios for test/standard comparisons are plotted as a mean and range for two replications for each test condition On days when the same dose of diazepam appeared in both channels, pref-

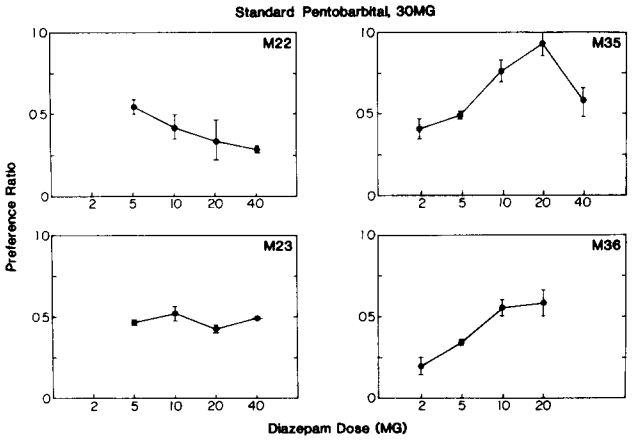

FIG 3 Diazepam dose preference in 4 male subjects with pentobarbital (30 mg/capsule) as the standard compound Abscissa dose of diazepam Ordinate preference ratios Each point is the mean of two determinations, the vertical bars at each point indicate range

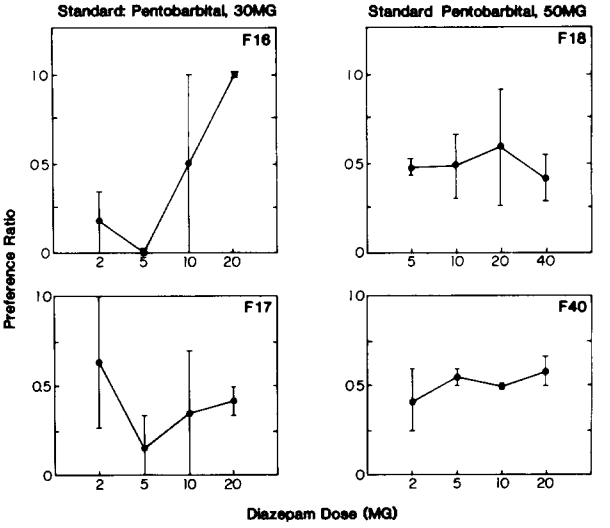

FIG 4 Diazepam dose preference in 4 female subjects with pentobarbital (30 or 50 mg/capsule) as the standard compound Abscissa dose of diazepam Ordinate preference ratios Each point is the mean of two determinations, the vertical bars at each point indicate range

erence ratios were computed twice by treating first the left and then the right channel as the test dose The range plotted was the larger of the two replications with the midpoint of this range (always 0 5) used for graphing purposes For all three male subjects, the dose effect curve was essentially flat, there was little variability within or between subjects with respect to dose preference as reflected in choice behavior

Figure 2 illustrates dose preference data for 2 female subjects (F16 and F28) allowed to select between 5 mg/capsule diazepam (the standard compound) and 2, 5, 10 and 20 mg/capsule diazepam As with male subjects, no consistent dose preference for diazepam was seen Unlike the data obtained for the three male subjects, the female subjects showed considerable within and between subject variability Whereas Subject F28 showed a tendency to prefer the two higher doses of diazepam (10 and 20 mg/capsule), Subject F16 did not

Pentobarbital as Standard Compound

Contrary to the results obtained with diazepam as the standard compound, clear cut patterns of diazepam dose preference were found when pentobarbital was employed as the standard compound Figure 3 illustrates preference data for four male subjects (M22, M23, M35 and M36) allowed to choose between 30 mg/capsule pentobarbital and 2, 5, 10, 20 and 40 mg/capsule diazepam Consistent preference for different doses of diazepam are clearly apparent in three of the four subjects Two subjects preferred pentobarbital to some diazepam doses Subject M22 preferred 30 mg pentobarbital to the higher diazepam doses (20 and 40 mg per capsule) whereas Subject M36 preferred 30 mg pentobarbital to the lower diazepam doses (2 and 5 mg per capsule) At no doses was diazepam clearly preferred Subject M35, on the other hand, preferred medium diazepam doses (10 and 20 mg per capsule) to 30 mg pentobarbital and did not indicate preference for pentobarbital at any diazepam dose The one subject (M23) who had an essentially flat dose effect curve similar to those illustrated in Fig 1 was not a subject in the first study As when diazepam was employed as the standard compound, the within-subject variability in these subjects was quite low, however, there were marked differences between subjects which were not apparent in male subjects in the first study

Figure 4 illustrates diazepam preference data for two female subjects (F16 and F17) with 30 mg/capsule pentobarbital as the standard compound, and two additional female subjects (F18 and F40) with 50 mg/capsule pentobarbital as the standard compound In contrast to male subjects allowed a similar choice, consistent preference trends were not apparent and within subject variability was high Whereas F16 appeared to prefer pentobarbital to low doses of diazepam and to prefer high doses of diazepam to pentobarbital, the variability in responding was high This same subject responded in a highly variable manner in the first study as well (see Fig 2)

The length of the drug self-administration day (time from the first drug administration in the morning to the last capsule administration at night) was consistent within-subjects, as was the distribution of responses across a self-administration day In four of the subjects (F17, M22, M23, M39), drug self-administration took place irregularly throughout the night, however, the other six subjects (F16, F18, F28, M35, M36, F40) had long intervals of sleep without drug administration These subjects had mean drug self-administration days ranging from 13 02 to 17 86 hours

Whereas rates of responding varied widely among subjects, rates of responding within subjects were very consistent from day to day In general, response rates remained relatively constant, resulting in increased daily drug intake when capsule dose available increased Many subjects self-administered approximately the same number of capsules per day despite instructions that dose and/or drug would vary For example, when diazepam alone was available in the first study and the dose available was varied by 10-fold (2 mg per capsule to 20 mg/capsule) for three subjects and by 8-fold (5 mg per capsule to 40 mg/capsule) for the remaining two subjects, the number of capsules selected per day varied

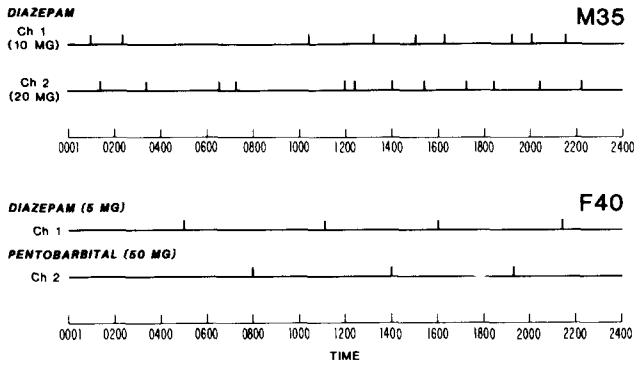

FIG 5 Representative patterns of drug responding during one 24-hour drug self-administration day for 2 subjects Upper panel Subject M35 allowed a choice between 10 mg/capsule diazepam and the standard, 20 mg/capsule diazepam Lower panel Subject F40 allowed a choice between 5 mg/capsule diazepam and the standard, 50 mg/capsule pentobarbital Each pen deflection represents a single drug self-administration

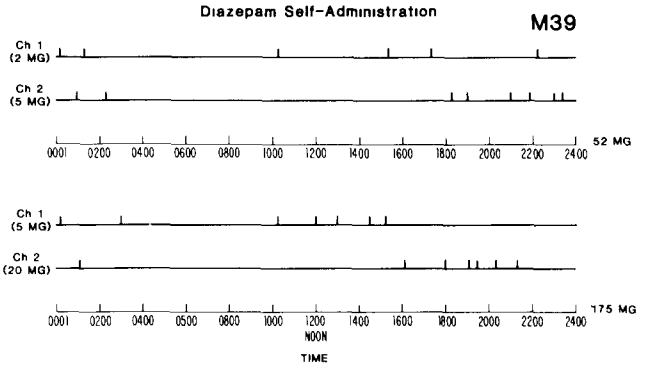

FIG 6 Representative patterns of drug responding during two drug self-administration days for Subject M39 Upper panel Subject M39 allowed a choice between 2 mg/capsule diazepam and the standard 5 mg/capsule diazepam Lower panel Subject M39 allowed a choice between 20 mg/capsule diazepam and the standard 5 mg/capsule diazepam Each pen deflection represents a single drug self-administration

by less than 2-fold Subject M39 selected the identical number of capsules [14] on six of eight self-administration days

The pattern of drug responding was also analyzed to determine if dose preference was related to time of day In subjects whose daily drug intake was relatively low, drug responding tended to occur only during the day and, when no dose or drug preference was observed, responding was generally evenly distributed across available machine channels In subjects whose daily drug intake was relatively high, drug responding tended to occur late into the night and early morning hours and to be more randomly distributed across machine channels

Figure 5 illustrates representative patterns of drug responding for two subjects during self-administration (midnight to midnight) The upper panel represents one day of responding by Subject M35 with diazepam as the standard compound, the doses available were 10 and 20 mg/capsule diazepam This subject did not demonstrate dose preference for diazepam in this study, mean preference ratios for all doses were close to 0 5 (see Fig 1) Whereas alternation of responding between available channels was not consistent, by the end of each self-administration day an even distribution of responses across the two channels was approximated In the lower panel, a clearer pattern of channel alteration is illustrated by the data from Subject F40 with 50 mg/capsule pentobarbital as the standard compound This subject had a preference function similar to that of Subject M35, with less variability in preference ratios from day to day than any other female subject in either study (see Figs 2 and 4)

The pattern of responding illustrated for Subject M35 is representative of the pattern of responding produced by subjects in which no preference for drug or dose was apparent and in which drug intake (capsules/day) was relatively high (Subjects F18, M22, and M23) The more regular pattern of responding seen in Subject F40 is representative of that found in subjects when preference ratios approached 0 5, but when daily drug intake was relatively low (Subjects F16 and F28)

Generally, when a dose preference was indicated by a high preference ratio, similar evidence of a dose preference was seen in the subject's pattern of responding In some cases, however, a dose preference was evident in the subject's pattern of responding that was not reflected by the preference ratio Figure 6 shows representative patterns of responding on two drug self-administration days when diazepam was the standard compound for Subject M39 This subject had a dose preference function similar to that of M35 (see Fig 1) In the upper panel, 2 mg/capsule diazepam was available in Channel 1 and 5 mg/capsule diazepam was available in Channel 2 Following the initial forced channel alteration there was a tendency for Subject M39 to self-administer the lower dose of diazepam (2 mg/capsule) throughout the day and to select the higher dose of diazepam (5 mg/capsule) during the evening hours When the magnitude between the available doses of diazepam was greater (5 mg/capsule in Channel 1 and 20 mg/capsule in Channel 2 shown in the lower panel of Fig 6), this tendency to prefer larger doses in the evening (or, conversely, smaller doses during the day) was clearer Despite this apparent change in preference according to time of day, the number of capsules per channel selected over the course of the self-administration day was generally evenly distributed, therefore, no preference was indicated by preference ratio determination

DISCUSSION

When diazepam was employed as the standard compound, no consistent within-subject diazepam dose preference was observed In general, subjects alternated between the two doses available on a given drug self-administration day This finding is surprising considering the extensive histories of sedative use in all subjects (see Table 1) and the broad range of diazepam doses tested (2 to 40 mg/capsule) When pentobarbital was used as the standard compound, consistent within-subject diazepam dose preference was evidenced in three of four male subjects In female subjects, however, where within-subject variability in day-to-day responding was generally high, no consistent diazepam dose preference was observed

In those subjects in which consistent dose preference for diazepam was observed, there were considerable individual differences in the shape of the preference function This var-

iability was probably a function of many factors In animal studies of sedative drug self-administration, between-subject variability is much less apparent (e g , see [2]) In such studies, the past drug history of the subjects is under the control of the experimenter In addition, animals bred for laboratory research may be genetically quite similar

Although all subjects shared extensive histories of sedative drug abuse, there were considerable differences among subjects in terms of abuse of non-sedative drugs, alcohol abuse, and even the extent and nature of their sedative abuse Table 1 gives an indication of some of the differences in both the extent (number of years of drug abuse) and nature of individual subjects' past drug histories Table 1 also shows metabolic and behavioral tolerance for pentobarbital for each subject measured by drug half-life and observable behavioral signs of sedation With the exception of Subject F28, who did not have a history of barbiturate abuse, the pentobarbital half-life values for all subjects are well below that typically reported for the general population (21–42 hours, [7]) Whereas differences in metabolic and behavioral tolerance can be partially accounted for by past drug history, genetic factors may also play a role

Thus, between-subject differences in past drug history, as well as differences in metabolic and behavioral tolerance, might account for some of the between-subject variability observed in dose and drug preference

It is unclear why pentobarbital as the comparison standard should influence diazepam dose preference and why this influence should only be apparent in male subjects It is possible that different doses of diazepam were more easily discriminable by the subjects when pentobarbital separated consecutive diazepam doses It is also possible that the effect was related to the generally lower total daily diazepam intake that occurred on such days There is no evidence, however, that preference for particular diazepam doses was more likely to occur on days when total diazepam intake was relatively low than on days when total diazepam intake was relatively high There is some evidence to suggest that preference for diazepam dose is enhanced by the concurrent availability of non-sedative drugs such as methadone [15]

Rates of responding during diazepam self-administration have been compared to rates of responding during pentobarbital self-administration in separate groups of monkeys [16] On the basis of lower rates of responding during diazepam self-administration, as well as on lower daily diazepam intake and less severe withdrawal symptoms upon abrupt withdrawal of diazepam availability, the authors concluded that pentobarbital was more reinforcing than diazepam

Both diazepam and pentobarbital self-administration by humans have previously been studied under limited-availability conditions Griffiths *et al* [5] compared pentobarbital, diazepam, chlorpromazine and placebo self-administration under double-blind conditions in an inpatient clinical setting During a 7½ hour experimental day, up to 10 capsules of pentobarbital (30 or 90 mg/capsule), diazepam (10 or 20 mg/capsule), chlorpromazine (25 or 50 mg/capsule) or placebo were available for self-administration When the higher dose of pentobarbital was available, subjects self-administered more of the 10 available capsules than when the higher dose of diazepam was available Lower doses of both pentobarbital and diazepam were self-administered at lower rates than those same compounds at higher doses, and neither placebo nor chlorpromazine were systematically self-administered Griffiths *et al* [5] concluded that their results were in agreement with animal data on sedative self-administration as well as data pertaining to the reported relative incidence of sedative drug abuse In the present study where drug access was unlimited, drug preference ratios rather than rates of drug self-administration were used, thereby minimizing the effects of duration of drug action on the measure of abuse liability

Unfortunately, the studies of Griffiths *et al* [5] comparing diazepam and pentobarbital self-administration did not take into account the differences between the two compounds in duration of action For example, the relatively longer duration of action of diazepam may have partially accounted for subjects taking less drug when diazepam was available than when pentobarbital was available It is not surprising that a drug with a shorter duration of action (e g , pentobarbital) would be self-administered at a higher rate than a drug with a longer duration of action (e g , diazepam) In the present study, differences in duration of action between diazepam and pentobarbital should not have influenced drug choice as drug availability was unlimited except for 30 minutes minimum interingestion intervals Clear preference for pentobarbital over diazepam was only observed in 2 of 8 subjects (M22 and M36, Fig 3) In addition, preference for pentobarbital in these subjects was limited to certain diazepam doses It is possible, however, that if a wider range of pentobarbital doses had been examined, stronger and more consistent preference for pentobarbital relative to diazepam would have been demonstrated

Preference between different doses of diazepam and between single doses of diazepam and pentobarbital has also been studied under conditions of acute drug access Griffiths *et al* [6] allowed subjects to choose between low and medium diazepam doses (50 and 100 mg) medium and high diazepam doses (100 and 200, 300, or 400 mg) and various doses of diazepam and placebo under double blind conditions Drug access was limited to one capsule per day with alternate days when drugs were not available Whereas all subjects preferred diazepam to placebo, consistent diazepam dose preferences were not observed When subjects were allowed to choose between 200 mg diazepam and 400 mg pentobarbital under similar conditions, subjects preferred pentobarbital on 67–100% of all trials In the present study, consistent dose preference for diazepam was also not observed when diazepam alone was available When both diazepam and pentobarbital were available, however, only two of eight subjects preferred pentobarbital, and only at certain diazepam doses

These studies differ in several important respects The doses used in the present study were chosen as they are those commercially available or simple multiples of these doses The doses used by Griffiths *et al* [5] were quite high the authors note that 200 mg diazepam was in excess of doses their subjects reported as daily drug intake in the past As these doses are not those commonly abused it is possible that they produce adverse effects Indeed, the subjects in the diazepam dose preference phase of the Griffiths *et al* [5] study were reported as exhibiting more negative mood and behavior (e g , frequent complaining) than those receiving pentobarbital in the same study Furthermore, only one of the subjects who preferred pentobarbital to diazepam reported preferring pentobarbital to diazepam when asked about their past drug history In the present study, when diazepam alone was available, the mean daily diazepam intake was 183 4 mg, however, this dosage was achieved over a 24 hour drug self-administration day In addition, dose preference was not constant across the self-administration

day for some subjects It is conceivable that had drug self-administration been restricted to a certain hour or hours of the day in the present study that drug and dose preference may have been more consistent Finally, whereas subjects in both studies had similar past drug histories, the subjects in the present study were physiologically dependent on sedatives at the time of testing, the subjects in the Griffith *et al* [5] study were not

In an acute drug self-administration preference study in subjects without histories of extensive sedative use, Johnson and Uhlenhuth [8] found no preference for diazepam over placebo The authors point out, however, that their subjects were given a choice between single blinded diazepam or placebo capsules in the morning when most were expected at work or school It is conceivable, therefore, that drug preference was influenced by behavioral contingencies of school or work Scores on a mood checklist one or three hours post-diazepam administration did indicate decreased vigor and arousal and increased fatigue and confusion compared to placebo In addition, it is conceivable that preference for diazepam over placebo is facilitated by a past history of sedative abuse

In the present study, wide individual differences in dose preference were obtained In some subjects, drug and dose preference were related to time of day Subjects may have preferred a low dose of diazepam during the first half of the experimental day and a higher dose during the later half of the experimental day Personality factors may have contributed in part to the preference patterns seen since persons with certain personality characteristics have been found to be more likely to self-administer pentobarbital during particular times of the day [14]

Rates of responding within subjects were relatively constant This resulted in many subjects increasing their daily drug intake when doses available were increased This finding is in general agreement with both animal and human studies in which increasing the dose of a sedative drug available during self-administration does not result in a decrease in response rates sufficient to maintain constant levels of drug intake over time [1 3, 13]

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