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Rate of increase of plasma drug level influences subjective response in humans

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Abstract. This study addressed the commonly held, but seldom tested, notion that faster rates of increase of drug effects are associated with more positive subjective effects. Sodium pentobarbital was administered to normal healthy volunteers in either a single oral dose or in a series of divided, cumulating doses, and subjective responses were monitored. Twelve subjects participated in three weekly sessions, during which they received capsules containing placebo, 150 mg pentobarbital in a single dose (SIN) or 180 mg pentobarbital administered in six divided doses (DIV) of 30 mg every 30 min. Doses of pentobarbital in the SIN and DIV were selected to produce similar peak plasma levels. Blood samples were obtained at regular intervals for plasma drug level determinations, and throughout the session subjects completed self-report mood questionnaires (e.g., Profile of Mood States, visual analog ratings of drug liking and drug "high") and psychomotor performance tests (e.g., Digit Symbol Substitution Test). As expected, the SIN and DIV conditions yielded similar peak levels of pentobarbital, but the peak was attained more rapidly in the SIN condition. Despite the similarity in peak plasma levels, subjects reached greater peaks in ratings of "high" and wanted more of the drug when they were in the SIN condition. On an end-of-session liking questionnaire they also reported significantly greater liking of the drug in the SIN condition. On other measures of drug effects (e.g., sedation and psychomotor impairment) no significant differences were observed between the conditions. Thus, the rate of increase of the drug's effects specifically influenced subjects' ratings on subjective measures (e.g., "high" and liking) that may be associated with risk for abuse. The results have implications for the relative abuse liability of different formulations of psychoactive drugs.

Key words: Pentobarbital – High – Liking – Pharmacokinetics – Rate of increase – Humans

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The euphorigenic, or positive subjective effects of drugs are commonly thought to depend upon the rate at which their effects increase. Drugs that are considered to be highly abusable are usually taken by routes that produce faster rates of increase of effects (e.g., intravenous heroin, crack cocaine). When a single drug is used by different routes, the route with the faster onset is associated with higher abuse liability [e.g., inhaled cocaine ("crack") versus intranasal cocaine, and intravenous versus oral amphetamine]. Medications used in the treatment of drug abuse often have similar pharmacological effects to the abused drug but have a slower onset than the abused drug, reducing the likelihood that the treatment drug itself will be abused [e.g., oral methadone for intravenous heroin use (Dole et al. 1966) and nicotine gum for cigarette smoking (Russell and Feyerabend 1978)]. Surprisingly, the relationship between rate of onset and subjective responses has received relatively little systematic experimental attention.

Several laboratory studies have shown that intravenously administered drugs produce more positive subjective and reinforcing effects when they are injected rapidly than when they are injected more slowly. For example, in human subjects, shorter duration intravenous infusions of cocaine produced greater euphorigenic effects than longer duration infusions (Fischman and Schuster 1984), and in rhesus monkeys, shortening the duration of infusions of cocaine increased the reinforcing effects of the drug (Balster and Schuster 1973). However, faster infusion rates in these studies may have also led to higher peak concentrations of drug reaching the brain, and since higher doses of the drugs produce more positive subjective and/or greater reinforcing effects, these studies confound dose with rate of increase.

Several studies have also examined the subjective and behavioral effects of slowly versus more rapidly absorbed orally administered drugs (Greenblatt et al. 1977; Salonen et al. 1986). In one study, absorption of chlordiazepoxide was slowed by co-administration of an antacid preparation, and in the other study, temazepam was administered in either a semi-liquid soft capsule or a

tablet form. Neither of these studies measured subjective changes that might be directly related to the drugs' potential for abuse.

The correspondence between abuse liability and rate of increase among different drugs within the same pharmacological class has been cited frequently. Again, drugs with more rapid onset of effects produce more positive subjective effects than drugs with slower onset, and are also considered to have relatively higher abuse liabilities (Greenblatt et al. 1981). For example, among the barbiturates, pentobarbital is considered to produce more positive subjective effects and have a higher liability for abuse than phenobarbital (Jasinski et al. 1978), and among the benzodiazepines, diazepam is considered to have higher liability for abuse than oxazepam (Griffiths et al. 1984a, b). In both cases, the drugs with the faster onset have greater abuse liability. However, different drugs within the same class may also differ in other respects (e.g., receptor actions or pharmacological properties) which may contribute to their differential subjective and reinforcing effects, independently of their rate of onset.

"Rate of onset" as used here refers to the rate of increase in drug effects, rather than "latency of onset" or the delay before any effects are experienced. Although rate of increase and latency of onset may covary in non-experimental pharmacological situations and both may affect the reinforcing effects of drug stimuli, the two factors are distinct and can be studied separately. The present experiment was designed to study the former.

This study was based in part on previous findings (de Wit et al. 1984, 1989) which suggested that the subjective effects of sodium pentobarbital are more positive when the drug is administered in a single bolus dose compared to a series of divided doses. These and other studies (e.g., de Wit et al. 1989) have also demonstrated the feasibility of using non-drug abusing volunteers to study the subjective effects of abused drugs. The present study utilized a within-subject design in which pentobarbital was administered either in a single dose (rapid onset) or in a series of divided doses (slow onset). The dependent measures included subjective ratings of "high", liking and other drug effects as well as objective measures of psychomotor performance. The results provide the first systematic experimental demonstration that a faster rate of increase of a drug's effects produces greater ratings of "high" and drug liking.

Materials and methods

Subjects

Twelve normal healthy males, aged 21–35, participated in the study. They were recruited from the university and surrounding community through local newspaper advertisements, posters, and word-of-mouth referrals. Subjects 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). Physical health was determined with a health questionnaire, physical exam and an electrocardiogram. Candidates were excluded if they had any history of an Axis I psychiatric disorder (APA 1987) or significant medical problems. Also excluded were cigarette smokers and individuals who deviated by more than 10% from normal body weight (Metropolitan life tables). Candidates reported their current and lifetime recreational drug use on a questionnaire and this information was then confirmed in detail by the social worker. Subjects who had any history of drug or alcohol related problems (e.g., any legal, family or health problems possibly related to alcohol or other drugs) were excluded, as were any individuals who consumed less than one alcoholic drink per week.

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

Procedure

Each subject participated in three sessions, conducted once a week. On these sessions, they received either placebo, sodium pentobarbital in a single oral dose (SIN condition; 150 mg) or pentobarbital in six divided doses (DIV condition; each capsule containing 30 mg pentobarbital), administered at 30 min intervals. In all three conditions subjects received a total of six capsules containing drug or placebo, administered at 30 min intervals. The order of presentation of the three conditions was counterbalanced across subjects. The doses for the SIN and DIV conditions were selected to produce the same peak blood levels of drug but to attain these peaks at different rates. To determine appropriate doses, plasma levels were simulated using a two compartment open kinetic model with first-order absorption and kinetic parameters reported by Smith et al. (1973).

The weekly sessions were conducted in the Clinical Research Center (CRC) from noon to 11 p.m. Subjects consumed a normal-sized lunch before 1 p.m. and were not permitted to eat again until after the session at 11 p.m. (The first six subjects consumed their lunch outside the hospital and reported for their sessions at 3 p.m, while the remaining subjects reported for sessions at noon, and consumed a standard hospital lunch in the CRC.) Subjects had private rooms but were usually tested in pairs and encouraged to interact socially with one another. During the sessions, subjects were free to engage in leisure activities of their choice (e.g., TV, reading, talking), but they were not permitted to work or study.

At 3 p.m., an intravenous catheter was inserted in the subject's forearm for blood sampling. Blood samples (20 ml) were drawn into a heparinized tube at each of 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. These sampling times were selected to characterize the rise and peak of the plasma levels of drug. Blood samples were centrifuged and frozen, and sent for analysis (BioAnalytical, Chicago; see below). 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. At 5 p.m. and again every 30 min until 7:30 p.m., subjects ingested an opaque gelatin capsule (size 00; total six capsules), containing either pentobarbital or placebo. Each capsule was taken with 100 ml water. In the placebo condition, all six capsules contained only dextrose. In the SIN condition, the first five capsules contained dextrose, and the sixth contained 150 mg pentobarbital. In the DIV condition, each capsule contained 30 mg pentobarbital with dextrose filler. Vital signs (heart rate, blood pressure, temperature) were recorded by nurses hourly between 5:00 and 11:00 p.m. and again 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 overall drug liking questionnaire, on which they indicated what type of drug they thought they had received (stimulant/anorectic, sedative/tranquilizer, alco-

hol or placebo) and how much they liked its effects overall. Liking was rated on a 100 mm visual analog scale labelled "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.

Plasma pentobarbital determinations

Extraction. A 1.0 ml aliquot of each standard, specimen and control was extracted with 5 ml n-butyl chloride after addition of 100 µl glacial acetic acid. Alphenal (5 µg/ml) was used as the internal standard. After centrifugation, the top organic phase was transferred to concentration cups and dried at 75° C under air and vacuum. The extract was reconstituted with 25 µl methanol, and 1 µl was used for gas chromatographic (GC) analysis.

Instrumentation. A Hewlett Packard 5890 GC equipped with a nitrogen phosphorus detector and an OV–17 capillary column (Foxboro; 25 M × 0.25 mm i.d., 0.25 µ film thickness) was used for analysis. GC conditions were as follows: injection port temperature = 250° C, detector temperature = 300° C, injection mode = split (20:1), oven program = 130–280° C at 8°/min. GC/Runtime = 21 min.

Calibration and controls. A standard curve (0–10 000 ng/ml pentobarbital) was extracted with each batch of specimens analyzed. Quantitative values were determined with respect to the standard curve. The assay was internally standardized and peak area ratios (area pentobarbital/internal standard area) were used for calculation. Positive and negative controls were also analyzed with each batch of specimens processed.

Linearity and sensitivity. The linear range of the assay is 100–10 000 ng/ml, r = 0.950. The assay is sensitive to at least 100 ng/ml pentobarbital. Values for specimens ≥ 250 ng/ml were reported quantitatively.

Measuring instruments

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. These tests have been found to be sensitive to the effects of psychoactive drugs (e.g., McLeod et al 1988; Ghoneim and Mewaldt 1990). Five versions of each of these tests were used in mixed order to minimize learning of the symbol or digit orders.

Two instruments were used to measure subjective drug effects, an experimental version of the Profile of Mood States (POMS; McNair et al. 1971; Johanson and Uhlenhuth 1980), and a visual analog liking questionnaire. This version of 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 have been derived through factor analysis. These clusters form the eight scales of the questionnaire and are labelled Anxiety, Depression, Anger, Fatigue, Vigor, Confusion, Friendliness, and Elation. Two additional, derived scales were used: Arousal = (Anxiety + Vigor) – (Fatigue + Confusion), and Positive Mood = Elation – Depression. The liking questionnaire consists of five 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 make a vertical line along a 100 mm line labelled "none/not at all" at one end and "a lot/very much" at the other, according to how they feel at that moment. Because of possible confusion in interpretation of the liking 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). An additional scale, the 49-item Addiction Research Center Inventory (Martin et al. 1971), was administered to the last six subjects, but because of the incomplete data, these results will not be reported.

The Leeds Sleep Questionnaire (Parrott and Hindmarch 1980) was used to assess the quality of sleep following the sessions. It consists of 10 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).

The Observer Rating Form (ORF) is a behavioral and symptom checklist developed in this laboratory to assess behavioral effects of drugs. An observer records, at every hour, whether or not subjects are engaged in the following activities: solitary, social (interacting with others), reading, games, sleeping, TV/radio, talking, or eating. The observer also 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 sleepiness agitation or restlessness, sluggish, dull or listless. The number of signs noted at each hour is recorded.

Data analysis

Although several of the dependent measures involved repeated determinations over time (and therefore might be analyzed using ANOVAs), the features of greatest experimental interest were the slope of the onset of drug effects and the peak effects attained in the SIN versus the DIV conditions. Therefore, in most cases the results are presented graphically to illustrate the slopes and time course of effects under each condition. Statistical analyses consist of two-tailed, paired *t*-tests comparing the peak values attained in the placebo and two drug conditions. Scores on placebo sessions are included on most measures to illustrate the magnitude of the drug's effects. Although repeated measures ANOVAs could have been conducted with these data, their interpretation would have been complicated by differences in dosing regimens and testing intervals used in the SIN and DIV conditions.

Kinetic analysis was conducted using the CONSAM 30 program on a 80386 microcomputer. Mean pentobarbital plasma concentration data were fitted to a two compartment open kinetic model with elimination from the central compartment. Parameter estimates of the kinetic model were fixed and then used in the fit of a dynamic model to each set of mean effect data by least-squares regression. A linear model was used to describe the plasma concentration-effect relationship, but declining effect in the face of relatively constant pentobarbital levels produced a systematic deviation of the data from the best fit curve, suggesting that the concentration-effect relationship was changing, i.e. the development of acute tolerance. Introduction of a tolerance factor, an approach previously described in modelling the effect of cocaine (Ambre et al. 1988), allowed a fit of the data to the model.

Results

Subject characteristics

The subjects' mean age was 25.7 (range 22–31). Most subjects were white (three oriental, one black), and most were full-time graduate students. Their average weight was 76.6 kg. Their mean alcohol consumption was 8.3

drinks per week (range 1–20), none were cigarette smokers, two reported smoking marijuana at least once within the last month, and only two subjects had ever tried either sedative/tranquilizers or opiates for recreational purposes.

Pentobarbital plasma levels

Mean plasma levels of pentobarbital attained in the two dosing conditions are presented in Fig. 1. After drug administration, plasma levels rose rapidly in the SIN condition (mean time to peak 50.1 min) and slowly in the DIV condition (mean time to peak 200.4 min). Despite the 3-fold difference in the slopes of the ascending portions of the SIN and DIV curves, the two dosing conditions produced almost identical peak levels of drug (peak plasma level in SIN condition 2660 ng/ml and peak level in DIV condition 2758 ng/ml). Although there was variability among subjects in their peak plasma pentobarbital levels (range 1198–4823 ng/ml), the time curves of the plasma levels shown for the group were similar to those observed for individual subjects. The correlation between subjects' peak plasma levels in the SIN and DIV conditions was $r=0.48$ (one-tailed, $P<0.05$). When three single, aberrantly high values (possible assay errors) were deleted from this analysis, this correlation rose to $r=0.85$, while the slopes and peaks of the blood curves remained essentially the same.

In the plasma sample obtained before drug administration, trace amounts of pentobarbital (less than 200 ng/ml) were obtained in three samples (one in SIN condition, two in DIV condition). Plasma drug levels on the morning following drug sessions (12.5 hours following the last active dose) were slightly, but not significantly ($t=1.06$, ns), higher in the DIV condition. No other dependent measures were significantly different the morning after the sessions.

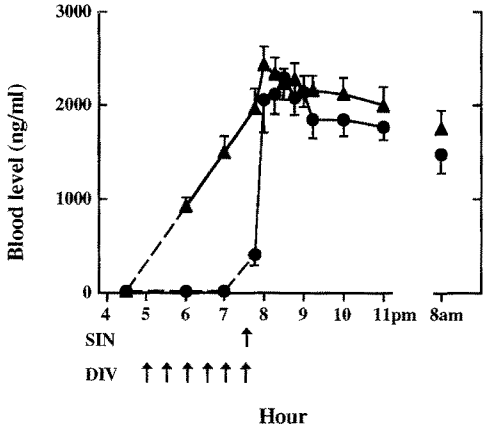

Fig. 1. Mean (and SEM) plasma levels of pentobarbital ($n=12$) after administration of 150 mg in a single dose *(SIN; circle symbols)* and after administration of 180 mg in divided doses *(DIV; triangle symbols)*. *Arrows* indicate times at which active drug doses were administered: divided doses (30 mg each) were administered every 30 min between 5 p.m. and 7:30 p.m., and the single dose was administered at 7:30 p.m. *Dashed lines* refer to time points before drug had been administered

Drug liking questionnaire

On all four scales, pentobarbital (both SIN and DIV conditions) produced significantly higher peak scores, compared to the placebo condition (*t*-tests, all $P<0.01$ except *high* placebo versus DIV, which was $P<0.05$). The SIN and DIV conditions produced significantly different scores on the *high* and *more* scales: subjects scored higher on the *high* and *more* scales after the single dose than after the divided doses (mean peak scores for *high:* placebo 17.1, SIN 57.8 and DIV 42; $t_{SIN\ vs\ DIV}=2.5$ $P<0.05$; mean peak scores for *more* placebo 19.4, SIN 73.9, DIV 55.9, $t_{SIN\ vs\ DIV}=2.34$, $P<0.05$). In addition, peak scores on the *like* scale were also marginally higher in the SIN compared to the DIV condition (mean peak scores placebo 27.2, SIN 70.6, DIV 60.3; $t_{SIN\ vs\ DIV}=1.48$, $P<0.10$). In contrast to these measures on which the SIN and DIV conditions differed, ratings of *feel* drug were not different in the SIN and DIV conditions (mean peak scores placebo 29.5, SIN 69.0 and DIV 63.5; $t_{SIN\ vs\ DIV}=0.87$, ns). The onset and duration of effects on the *high, like* and *more* scales is illustrated in Fig. 2: It can be seen that the increases in effects in the SIN and DIV conditions paralleled the rise in plasma pentobarbital (Fig. 1), but after the peaks had been achieved, subjective ratings of drug effects declined while pentobarbital levels remained high.

Overall liking ratings

On the end of session questionnaire, subjects rated their overall liking of the drug effects significantly higher in the SIN condition than in both the DIV or placebo conditions (mean liking scores: placebo 46.3; SIN 69.4; DIV 49.1; $t_{PL\ vs\ SIN}=4.34$; $t_{SIN\ vs\ DIV}=2.74$, both $P<0.05$; $t_{PL\ vs\ DIV}<1.0$, ns).

Drug identification

In most instances, subjects correctly identified the class of drugs they received. Ten of the 12 subjects correctly identified the placebo, nine subjects labelled the single dose of pentobarbital as a "tranquillizer/sedative", and 11 subjects labelled the divided dose as a "tranquillizer/sedative". Incorrect labels in the placebo condition included "alcohol" and "tranquillizer" and in the pentobarbital conditions included "alcohol" and "placebo".

POMS

Scores on the Arousal scale of the POMS were generally lower after pentobarbital compared to placebo, regardless of dosing condition (mean peak low scores placebo −1.2, SIN −2.3 and DIV −2.6; $t_{PL\ vs\ SIN}=1.8$, $P<0.10$; $t_{PL\ vs\ DIV}=2.8$, $P<0.01$), and scores on Confusion and Fatigue were increased by the drug (mean peak scores Confusion: placebo 1.2, SIN 1.79, DIV 1.7; $t_{PL\ vs\ SIN}=2.9$, $t_{PL\ vs\ DIV}=1.4$, ns; Fatigue: placebo 1.3,

SIN 1.8, DIV 2.3; $t_{PL\ vs\ SIN} = 1.68$, ns; $t_{PL\ vs\ DIV} = 5.0$ $P < 0.001$). Mean peak scores for the SIN and DIV conditions were not different on any of these POMS scales (*all t* values < 1.0). Although the time course of onset and peak of drug effects on the POMS closely paralleled the time course of the change in plasma levels of pentobarbital, the mood effects dissipated rapidly while pentobarbital plasma levels remained high (Figs. 1 and 3).

Psychomotor performance tests

Although pentobarbital did not change performance on digit memory tasks (forward or reverse) in either the SIN or DIV condition, the drug significantly decreased DSST scores in both dosing conditions. The mean peak (lowest) scores under the three conditions were placebo 50.7, SIN 43.5 and DIV 44.1; $t_{SIN\ vs\ PL} = 5.32$, $t_{DIV\ vs\ PL} = 4.07$, both $P < 0.05$ but $t_{SIN\ vs\ DIV} < 1.0$, ns). The onset of DSST impairment paralleled the increase in plasma pentobarbital, but, as with other measures, DSST performance began to improve after it peaked while pentobarbital levels remained high (Figs. 1 and 4).

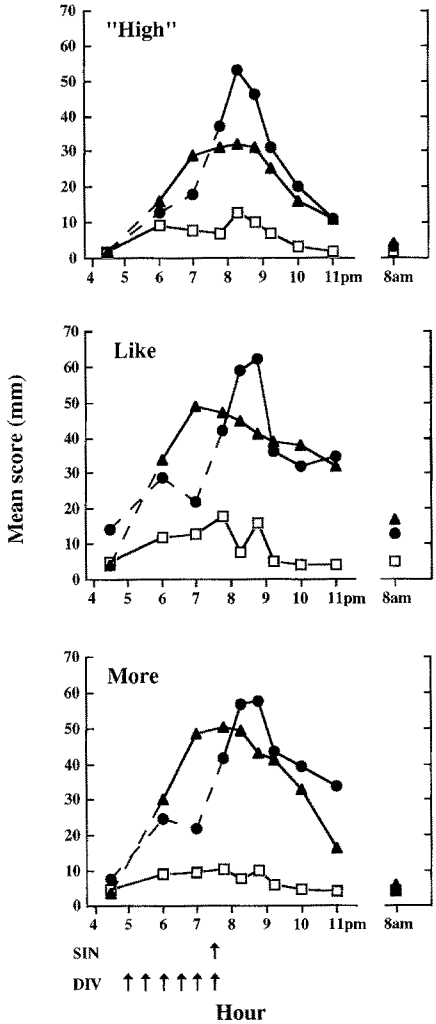

Fig. 2. Mean scores on liking questionnaire ($n = 12$) after placebo (—□—) and pentobarbital in single *(SIN)* (—●—) and divided *(DIV)* (—▲—) dose conditions. Peak scores attained on the *high* and *more* scales were significantly higher in the SIN condition than in the DIV condition, and peak scores on the *like* scale were marginally higher. See Fig. 1 legend for details

Physiological measures

Blood pressure and pulse were not changed by the drug. Temperature decreased significantly after both doses of pentobarbital, compared to placebo (peak low values

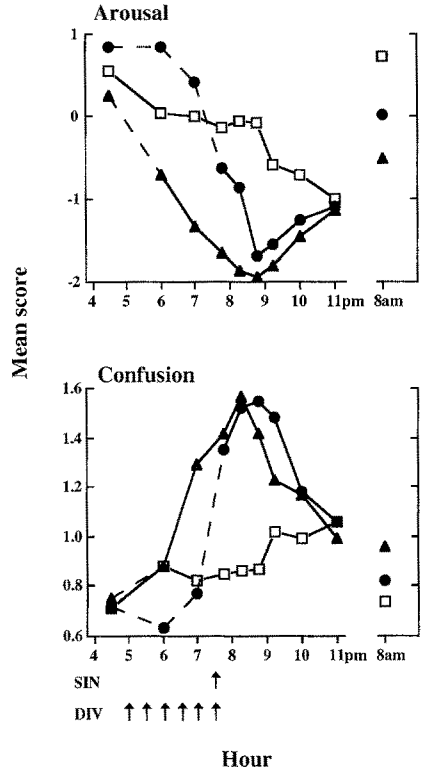

Fig. 3. Mean scores on the Arousal and Confusion scales ($n = 12$) of the POMS after administration of placebo *(open squares)*, pentobarbital in the SIN condition (150 mg at 7:30 p.m; *filled circles*) and pentobarbital in the DIV condition (30 mg every 30 min from 5 to 7:30 p.m; *filled triangles*)

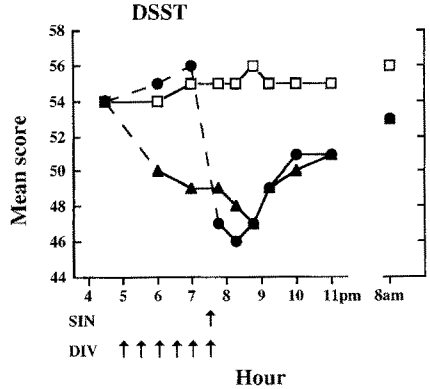

Fig. 4. Mean scores on DSST ($n = 12$) after placebo and after pentobarbital administered in a single dose *(SIN)* or divided doses *(DIV)*. See Fig. 1 legend for details

placebo 36.44° C, SIN 36.17° C, DIV 36.18° C; *t*-tests $P < 0.05$). However, the magnitude of the decrease was negligible (about 0.3° C).

Observer ratings

Under the placebo condition, the maximum number of subjects out of 12 who showed any signs of intoxication at any time point was four (7:50 p.m.). Under the SIN condition, nine subjects showed signs (at 7:50 p.m.), and under the DIV condition, seven subjects showed signs (at 8:50 p.m.).

Sleep questionnaire

Relative to placebo, pentobarbital (both dosing conditions) increased scores on the GTS scale (i.e., made it easier to get to sleep) and the QOS scale (i.e., improved sleep; mean scores GTS: placebo 49.0, SIN 76.0, DIV 72.6; QOS: placebo 41.8, SIN 63.8, DIV 59.6; placebo differed significantly from drug in each case, *t*-tests). The effects on these scales were not different for the two dosing conditions (SIN versus DIV *t*-tests non-significant in each case). The other two scales, awakening from sleep (AFS scale) and behavior following wakefulness (BFW scale), were unaffected by the drug.

Discussion

Certain pharmacokinetic properties of drugs are believed, with some empirical basis, to explain differences among drugs in liability for abuse. One of these properties is the rapidity with which the drug is delivered to the central nervous system. Different drugs within the same class are thought to differ in abuse liability because of this characteristic, and different routes of administration are thought to be associated with differential likelihood of abuse for similar reasons. There is, however, little direct experimental evidence that rate of increase *per se* alters subjective and/or behavioral effects of drugs in ways that might affect their abuse liability. In this study we studied the same drug under two conditions, a relatively slow and a faster rate of onset, to determine the relationship between rate of rise of plasma levels and the quality and magnitude of the drug's subjective and behavioral effects.

The main finding of this study was that on several subjective indicators of abuse liability, ratings of "high", wanting more of the drug, and overall drug liking, pentobarbital produced significantly greater effects when it was administered rapidly than when it was administered slowly. Despite the fact that similar peak plasma levels of drug were attained under both conditions, subjects rated themselves as feeling more "high" and wanting more drug, and reported liking the overall effects of the drug significantly more under the SIN condition compared to the DIV condition. Momentary liking ratings during the sessions were also marginally higher in the SIN compared to the DIV condition.

On other measures of the drug's effects, responses under the SIN and DIV conditions did not differ. Ratings of overall drug effect ("feel drug" on the liking questionnaire), sedation (decreases in POMS Arousal scale and increased Fatigue scale) and Confusion (POMS scale) were similar across the two conditions. Psychomotor performance was impaired to a similar degree in the SIN compared to the DIV condition. Thus, the differential effects of the two dosing regimens were most evident with measures that were most likely to be associated with likelihood of abuse.

Because a greater amount of time necessarily passes during the administration of the drug in the DIV condition compared to the SIN condition, some of the differences between the two conditions may be attributable to acute tolerance. Acute tolerance to the psychomotor impairing effects of pentobarbital have previously been reported by Ellinwood et al. (1983). They reported lesser effects on a psychomotor tracking task when subjects were on the descending, compared to the ascending limb of the plasma pentobarbital curve. The development of acute tolerance in the present study is evident in Fig. 4, where DSST performance recovered toward baseline levels while the plasma levels of pentobarbital remained relatively high. The differential peak effects on the liking and "high" scales could also be accounted for by similar mechanisms of acute tolerance. Alternatively, however, certain subjective drug effects (e.g., ratings of "high" and liking) may depend exquisitely on the rate of change from the non-drugged to drugged state (i.e., the so-called "rush"). Although this possibility is at present purely speculative, it is notable that the differential effects of pentobarbital delivered in the SIN and DIV were not apparent on all dependent measures (e.g., sedation or psychomotor performance) but were significant for two subjective measures closely associated with drug abuse (i.e., high and liking).

An important feature of the present study was that dosing regimens were selected to produce the same peak drug concentrations. Because a slower input rate (such as might occur with slowed absorption from the gastrointestinal tract) necessarily lowers peak concentration from the same dose, we used a slightly larger total drug dose to achieve similar peaks. Furthermore, we chose, under the slow onset condition, to administer the drug in repeated equal increments at regular intervals. These repeated doses do not exactly simulate the blood curves observed after differential absorption rates that would occur under naturalistic conditions (e.g., after different stomach loads). However, the dosing intervals were designed to maximize the differences in rate of increase of plasma levels under the two conditions. In a recent report, Busto et al. (1990) administered midazolam intravenously under conditions designed to simulate the plasma levels achieved under differential absorption rates and found greater euphoria, liking and psychomotor impairment following the faster onset condition.

The question can be raised whether the plasma concentrations of drug paralleled the brain concentrations. At least two factors suggest that they did. First, pentobarbital is known to cross the blood/brain barrier very

rapidly (i.e., within 2 min, compared to 10–20 min delays for less lipid soluble barbiturates such as phenobarbital; Goldstein and Aronow 1960; Paulson et al. 1982; Pratt and Taylor 1990). Second, the fact that the peak drug effects observed in the present study coincided with peak plasma levels is evidence that there was not a significant dissociation between plasma and brain levels.

In summary, these data provide one of the first demonstrations that the rate at which blood levels of a drug increase determine subjective drug effects that might be associated with abuse. Although it has been widely assumed that faster onset (e.g., more rapidly absorbed) drugs produce more positive (i.e., euphoriant) subjective effects because of their pharmacokinetic characteristics, this idea has not been tested systematically. In the present study comparing subjective and behavioral responses to pentobarbital in a faster and a slower onset condition, we found that the faster onset condition was associated with reports of greater liking and "high". The fact that these differences were observed even with a drug administered orally (i.e., onset even in the "faster" onset condition is relatively slow because of absorption) and that they were observed in normal, non-drug-abusing volunteers suggest that the effect is robust and general. Future studies may explore this phenomenon using other drugs (e.g., benzodiazepines), administered by other routes (e.g., intravenously). The data provide empirical support for a commonly held notion regarding the effects of rate of onset, and they have implications for the development of drugs that may have some liability for abuse: for example, pharmacological agents and drug formulations with relatively slower onset would clearly have lower potential for abuse than those with faster onset.

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