Alprazolam in Young and Elderly Men: Sensitivity and Tolerance to Psychomotor, Sedative and Memory Effects

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ABSTRACT

This study was designed to determine whether age influences sensitivity to alprazolam and/or rate of acute tolerance development to the effects of alprazolam. Three treatments were each separated by 4 weeks. Twenty-five young (ages 22–35) and 13 elderly (ages 65–75) men received 2 mg of alprazolam/2 min i.v. Blood samples were obtained over 48 hr, and sedative, psychomotor and memory effects were assessed serially for 12 hr. Clearance was lower (P < .005) in the elderly, but area under the concentration curve to 12 hr and maximum concentration did not differ by age group. Maximum impairment was greater in the elderly for all assessments. Mean EC50 values differed between the elderly (25.3 and 25.0 ng/ml) and the young (39.8 and 36.5 ng/ml) on card sorting and digit symbol substitution, respectively (P < .001). Bolus treatment data were used to individualize doses for the crossover of placebo and alprazolam; infusions were designed to maintain a plateau alprazolam concentration between 1 and 9 hr. Alprazolam concentrations through 12 hr did not differ between the young and elderly. Median t1/2 for offset of effect for digit symbol substitution was 2.8 hr in the young and 4.9 hr in the elderly (P = .05). Therefore, aging decreases alprazolam clearance and increases sensitivity to effects of alprazolam through a mechanism other than pharmacokinetics; aging also decreases the rate of offset of effect of alprazolam. In addition, the data provide insight into the intensity of initial effect as a determinant of rate of tolerance development.

ABBREVIATIONS: AUC, area under the plasma concentration curve; AUEC, area under the effect curve; CS, card sorting task; CPT, continuous performance test; DSST, digit symbol substitution test; EC50, concentration that elicits half-maximal response; E0, baseline; kO, tolerance rate constant or effect offset rate constant; MaxOE, maximum observed effect; Mn1–9hr, mean alprazolam concentration from 1 to 9 hr; MnE1–9hr, mean alprazolam concentration from 1 to 9 hr; NRSS, nurse-rated sedation score; RMT, Randt Memory Test; tMaxOE, time to maximum effect; t1/2EO, half-life for elimination of drug; t1/2EO, half-life for offset of effect.

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significantly higher concentrations of diazepam and desmethyl-diazepam in the elderly than the young. Using logistic regression of the presence or absence of response to a verbal command, it was recently demonstrated that the elderly were more sensitive to the hypnotic effects of an intravenous dose of midazolam (Jacobs et al., 1995). Nikaido et al. (1990) assessed the effect of single oral doses of alprazolam and triazolam and found a more prolonged duration of psychomotor effects in the elderly than in the young. Triazolam was recently evaluated in young and elderly subjects using psychomotor performance and sedation measures after a single doses of 0.125 and 0.25 mg; results indicated that the greater impairment in the elderly than young subjects could be attributed to higher plasma concentrations rather than to sensitivity differences (Greenblatt et al., 1991).

From published data it is not possible to determine whether a receptor-based or other pharmacodynamic change occurs with age separate from the observed change in pharmacokinetics. Some studies did not include a young population for comparison (Pomara et al., 1984). Others did not control for potential confounding factors such as chronic diseases or drug interactions (Castleden et al., 1977; Cook et al., 1984; Reidenberg et al., 1978). In some cases, no concentration data (Bell et al., 1987; Nikaido et al., 1990) or very minimal concentration and assessment data were obtained (Castleden et al., 1977; Reidenberg et al., 1978; Cook et al., 1984). Controlling for variability due to gender (Ellinwood et al., 1984; Kroboth et al., 1985; McAuley et al., 1995) and race (Kalow et al., 1986) may also be important when determining the effects of age on drug sensitivity to limit variability due to factors other than age. None of the previous comparative studies assessed response relative to concentrations of drug to quantify sensitivity in the young and elderly.

Acute tolerance to the psychomotor effects of benzodiazepines such as diazepam (Ellinwood et al., 1985), triazolam (Kroboth et al., 1993), midazolam (Fleishaker et al., 1996) and alprazolam (Ellinwood et al., 1985; Kroboth et al., 1988) is known to occur in humans. Acute or rapid tolerance is defined as a shortened duration and decreased intensity of drug effects that occurs within hours after administration (Crabbe et al., 1979; Frey et al., 1986). The rate of development of acute tolerance to the psychomotor effects of triazolam (Kroboth et al., 1993) and alprazolam (Kroboth et al., 1988) has been quantified in young adult men. Tolerance is important to the assessment of sensitivity because acute tolerance shifts the effect-concentration curve to the right, causing an apparent decrease in sensitivity. Thus, a difference in rate of development of tolerance between young and elderly could account for a difference in apparent sensitivity.

This study was designed with two major objectives. The first was to determine whether age influences sensitivity to alprazolam (i.e., to determine whether response is greater in the elderly after taking into account concentration differences). The second objective was to determine whether age influences the effect offset rate (rate of acute tolerance development) of a benzodiazepine. Alprazolam was chosen because it is a widely prescribed intermediate-acting triazolobenzodiazepine, ranking ninth among all drugs in total prescriptions dispensed for 1993 (Simonsen, 1994). In addition, its availability in an intravenous formulation for experimental use and metabolic profile made it appropriate for use in this design. Alprazolam is oxidized to less active metabolites that are rapidly conjugated and appear to have an insignificant role in the pharmacological activity (Greenblatt and Wright, 1993; Smith et al., 1984).

Methods

Twenty-five young and 13 elderly nonsmoking, healthy white men gave written informed consent to participate in this study, which was approved by the University of Pittsburgh Biomedical Institutional Review Board. Women were excluded because the effects of progesterone on response to benzodiazepines (McAuley et al., 1995) may have confounded the effects of aging with changes in hormone concentrations. All men were screened by history, physical examination, laboratory, urine drug screen and blood alcohol concentration before participation. Subjects were excluded if they were taking any chronic medications (other than a multiple vitamin), had laboratory values that were abnormal (>10% out of normal range), had physical examination findings indicating the presence of a chronic disease, had a positive urine drug screen or blood alcohol level or had a history of psychiatric illness, drug or alcohol abuse or dependency. Subjects were also excluded if they had participated in a clinical drug study using central nervous system drugs within the previous 6 months.

Study design. This three-way crossover study was conducted in two parts. In part 1, all subjects received alprazolam as a rapid (2-min) intravenous infusion in an open-label, single-dose design. Four weeks later, subjects began part 2, which was a randomized two-way double-blind crossover of placebo or an individualized infusion of alprazolam. All treatment days were separated by 28 days. For part 2, the infusion regimen was individualized for each subject to target either a concentration that would produce a 50% psychomotor performance decrement (EC50) predicted from the sigmoid Emax model in the bolus treatment or the maximum maintainable concentration with a dosage limit of 2 mg of alprazolam, whichever was lower.

Subjects were instructed to avoid all medications for 1 week and alcohol and caffeine 48 hr before and throughout the placebo and alprazolam treatment days. Subjects were admitted to the General Clinical Research Center at Montefiore University Hospital (Pittsburgh, PA) on the evening before the study day to allow acclimation to the study environment and for practice of the psychomotor tests. Each was permitted an evening snack and fasted from 10:00 p.m. until a light breakfast was provided at 7:00 a.m. Indwelling catheters were inserted into veins in both forearms before baseline psychomotor testing. At ~8:30 a.m. (0 hr), the administration of alprazolam or placebo was initiated. In part 1 (alprazolam bolus), 2 mg of alprazolam (1 mg/ml concentration of 50% propylene glycol/water) was administered through a catheter over 2 min followed by a normal saline flush. For the alprazolam treatment in part 2 (continuous-infusion treatments), alprazolam 1 mg/ml in 50% propylene glycol (lot #25,704; The Upjohn Co., Kalamazoo, MI) was diluted to a concentration of 10 μg/ml with normal saline solution. A 30-min loading infusion was administered with an IMED pump (ALARIS Medical Systems, Inc. San Diego, CA); this was followed by an infusion designed to maintain the targeted plateau alprazolam concentration throughout the 9-hr study day. For the placebo treatment, an identical-appearing solution containing propylene glycol (lot #26,583; The Upjohn Co.) was diluted and infused in the same manner. Neither the order nor the identification of treatments in part 2 was known by the investigator or subject.

For all treatments, subjects were restricted to bed after drug administration for the first 9 hr of the study day with minimal environmental stimulation, including no conversation or radio, television or telephone use. Dietary intake was controlled on the study day and was the same for each subject. Subjects received juice at 11:00 a.m. (2.5 hr) and a light lunch at 12:30 p.m. (4 hr). A standardized dinner was served at ~6:00 p.m. (9.5 hr). In the bolus...
treatment, subjects were allowed to ambulate after dinner until 1 hr before the 12-hr session in which they again were restricted to bed with environmental limitations until the completion of psychomotor tests. Subjects were discharged the next morning.

Subjects were allowed to participate in part 2 if in part 1 (bolus treatment), their MaxOE was >40% from base line (Eo) and if their impairment at 1 hr was >25% on at least one of the psychomotor performance tests. These criteria were designed to ensure that in the continuous-infusion treatment, the rate of offset of effect was slow enough to be assessed. All 13 elderly but only 13 of 25 young subjects participated in the continuous-infusion treatments. Ten of the young did not meet the performance decrement criteria, and 2 withdrew from the study for personal reasons.

Pharmacokinetic evaluation. Blood samples of 7 ml each were obtained in heparinized collection tubes from the opposite forearm catheter. In the bolus treatment, samples were obtained at time 0 (just before drug administration) and 5, 10, 20 and 40 min and 1, 1.5, 2, 3.5, 5, 7, 9, 12, 16 and 24 hr after the dose. Subjects returned to provide two additional samples at −36 hr (range, 29.5–38.2 hr) and 48 hr (range, 45.6–55.6 hr); actual times were used in the pharmacokinetic analysis. An additional 5-ml sample was collected before alprazolam administration for serum protein binding determination.

In part 2, blood samples were obtained at time 0 (just before initiation of the infusion), at 0.5 hr (end of the loading infusion) and at 1, 2.5, 4, 5.5, 7 and 9 hr. Samples were centrifuged, and plasma was harvested and frozen at −20°C until analysis.

Psychomotor performance, sedation and memory. Subjects practiced the battery of psychomotor tests on four occasions, including the evening before each of the three treatment days, to a plateau of performance defined as no improvement in score on two consecutive trials. Base-line performance was assessed after one practice session on the morning of each treatment. After the alprazolam bolus dose, testing sessions were administered nine times from 20 min to 12 hr. The RMT was administered six times: at 0 and 40 min and 2, 3.5, 5 and 9 hr. Sedation scores were obtained before each blood sample through 12 hr. In the continuous-infusion treatments, the battery of tests was administered at base line plus six times from 1 to 9 hr after initiation of the infusion.

The battery of psychomotor tests used to assess responses consisted of CS, DSST and CPT, which is a computerized Neurobehavioral Evaluation System II test (Baker et al., 1985). The entire battery of tests takes ~10 min to complete. CS requires subjects to sort a deck of playing cards by suits as quickly as possible with a maximum of 90 sec allotted to complete the task. DSST is a 90-sec pen-and-paper test in which subjects are required to draw symbols corresponding to numbers in a key at the top of the page. Different forms of the DSST were used for the repeated testing. For CPT, subjects are instructed to press a control button as quickly as possible to identify the letter “S” among distractor letters flashed on a computer screen; letters appear at a rate of 1/1500 msec for 5 min.

Memory was assessed using an adaptation of the RMT (Rundt and Brown, 1983) in which subjects are shown seven black-and-white drawings at the rate of 1/sec; immediately thereafter, subjects are tested on their ability to recognize those seven drawings in a series of 15 pictures that includes eight distractors. Different forms of the RMT were used. Delayed memory recall was tested by presenting five colored pictures of objects at 2 hr after alprazolam administration; 7 hr later, subjects are given a questionnaire that asks whether they have seen any colored pictures of objects. If they have, they are to name the objects. Sedation was rated by an observer using the NRSS, which ranges from 0 (wide awake and alert) to 4 (soundly sleeping, unable to perform tasks) (Kroboth et al., 1990).

Assays. Alprazolam plasma concentrations were determined by a validated capillary gas chromatographic method using electron capture detection with triazolam as the internal standard. This is a modification of a previously reported assay (Derry et al., 1995; Greenblatt et al., 1981). Intra-assay and interassay variability was ±10% for concentrations of 0.25 to 16 ng/ml. Samples from 5 min to 12 hr were diluted with blank plasma to attain concentrations within the detectable range.

The extent of alprazolam protein binding for each subject was determined in triplicate using an established equilibrium dialysis method (Schmith et al., 1991). Briefly, [14C]alprazolam (specific activity, 29.74 mCi/mM; purity, >95%) was diluted in phosphate buffer (pH 7.4) to a concentration of ~25 ng/ml and dialyzed for 8 hr at 37°C against an equal volume of subject serum obtained before alprazolam administration. The free fraction was calculated by dividing disintegrations/min in the buffer by those in serum at the end of dialysis.

Pharmacokinetic analysis. Alprazolam plasma concentration-time data from the bolus treatment was analyzed by compartmental and noncompartmental methods using PCNONLIN Version 4.2. (1992). For the noncompartmental analysis, β (linear regression of terminal points), t_1/2 β (0.693/β), AUC_0–t β (trapezoidal rule + last concentration/β) and clearance (dose/AUC_0–t β) were determined for each subject. Vdβ was calculated as dose/β*AUC_0–t β. AUMC_0–t β was determined by calculating the area of the concentration-time vs. time plot (linear trapezoidal rule + last concentration/β), and mean residence time was determined by [AUMC_0–t β/AUC_0–t β − (infusion time/2)]. Vd_100 was calculated by clearance=mean residence time. AUC_0–0.5 hr, AUC_0–0.5 hr and AUC_0–2 hr were also determined using the linear trapezoidal rule (Yeh and Kwan, 1978). The 5-min concentration point for each subject was excluded from all analyses because it often was lower than the 10-min sample or was so high that it was physiologically unexplainable. A two-compartment model with micro-rate constants was also used to describe this data; results were used to individualize the continuous-infusion treatment.

For the continuous-infusion treatment, alprazolam concentration-time data from 1 to 9 hr were plotted and evaluated for variations over time. Mean concentrations from 1 to 9 hr (Mn_1–9 hr) were determined in each individual subject by calculating the AUC_1–9 hr, and dividing by the 8-hr time interval. Mn_1–9 hr values were compared with mean concentrations predicted from pharmacokinetic model parameters from the bolus. Concentrations at the end of the loading infusions (0.5 hr) were also compared in the young and elderly.

Pharmacodynamic analysis. The CS score is the number of cards sorted per second; DSST score is the number of symbols correctly drawn in 90 sec. CPT score is the average of 50 trials. CPT latency to press a control button (5% CPT Latency) was calculated for each subject using percent decrement (baseline latency) % CPT Latency = (actual latency − baseline latency) / (1500 − baseline latency) * 100

In this equation, 1500 represents the maximum latency and 100% is the maximum attainable decrement. The RMT score is the correctly recognized items (maximum, 7); delayed recall score represents the pictures correctly recalled (maximum, 5).

Bolus treatment. Plots of effect-time and effect-concentration data were made for each subject. The MaxOE and t_{MaxOE} were determined for each test for each subject. AUEC values were calculated for each subject using percent decrement vs. time data from 0 to 9 hr for psychomotor tests and scores from 0 to 12 hr for NRSS. For RMT data, AUEC (from 0 to 5 hr) was calculated by using the difference between a perfect score area and the actual score area, which provides a measure of recognition decrement (Kroboth et al., 1995). The intervals for AUEC evaluation were chosen to include all subjects in the analysis. Effect ratios (AUEC/AUC) for each subject were also calculated to correct for interindividual variation in concentration during the time of pharmacodynamic evaluation.
Effect-concentration data for individual subjects were inspected for the potential of pharmacodynamic modeling. The linear model (Holford and Sheiner, 1981) was fit to data from DSST, CS, and CPT. The inhibitory sigmoid $E_{\text{max}}$ model (Holford and Sheiner, 1981) was also fit to scores from individual subjects for DSST and CS. The equation for the latter model is:

$$\text{Effect} = E_o - \left( \frac{E_o - C_{50}}{1 + \left( \frac{C}{C_{50}} \right)^S} \right)$$

where $\text{effect}$ is observed score at time $t$, $E_o$ is the base-line score and was fixed in this model in which $E_o = E_{\text{max}}$, $C_i$ is alprazolam concentration at time $t$, $s$ is the sigmoidicity or slope factor and $EC_{50}$ is the concentration that produces 50% of the maximum effect.

**Continuous-infusion treatment.** The target psychomotor decrement for each subject was 30% decrease from baseline based on data from the bolus treatment. To determine the accuracy of prediction and quantify the rate of tolerance development to each psychomotor performance test, percent decrement was calculated for each time. The data for each subject for DSST, CS and CPT in the alprazolam treatment were plotted on a semilogarithmic scale. A tolerance rate constant or effect offset rate constant ($k_t$) was determined for individual subjects using natural log-linear regression of the data from 1 through 9 hr or through the time that the score returned to base line, whichever occurred first (Kroboth et al., 1993). The $k_t$ is the slope of the resulting regression analysis; the corresponding half-life for offset of effect ($t_{1/2}^o$) is 0.693/$k_t$. Scores were considered to be at base line when they were within 10% of base line; these decrements are a conservative estimate of the observed variability in these tests. For any score ≤0% decrement from base line, a natural log value of 0 (equivalent to a 1% change from base line) was assigned to allow inclusion of that point in the regression. Regression analysis was performed on subject data that included a performance decrement of ≥25%, provided visual evidence of a decline in performance decrement over time and included at least three data points for the regression. A quadratic term was added to the regression to assess whether there was an improvement in model fit.

The MaxOE was also determined from the continuous-infusion treatment data for each subject. MaxOE was the average observed effect during pseudo-steady-state concentrations, was the AUEC divided by the 8-hr time interval. Percent recovery at each psychomotor performance assessment time was calculated for each subject. Percent recovery is defined as the percentage of improvement in psychomotor function from the MaxOE and is calculated by the formula:

$$\text{Percent recovery} = \frac{\text{maximum observed %decrement} - \text{%decrement at time,}}{\text{maximum observed %decrement}} \times 100\%$$

where $t$ is the assessment time during the alprazolam infusion.

RMT and NRSS data were evaluated using logistic regression of the effect-time data pooled by group; the probability of significant memory impairment and sedation at times during the infusion was determined. For memory, RMT scores of ≤4 of a possible 7 were categorized as significant impairment; for sedation, NRSS ratings of ≥3 were considered significant sedation. The proportion of patients with significant impairment was calculated at each assessment time, and a logistic transformation was performed. A slope and intercept were calculated using linear regression of the logistic transformation of the proportion of patients with significant impairment vs. time. A predicted probability curve of significant impairment at a given time was then generated for the young and elderly.

**Statistical analysis.** Pharmacokinetic parameter estimates were assessed for differences between groups using one-way analysis of variance. Repeated measures analysis of variance was used to assess differences in repeated assessments. Duncan’s post hoc test was used to assess specific differences when indicated. Parameter estimates from the inhibitory sigmoid $E_{\text{max}}$ model were compared using the nonparametric Mann-Whitney $U$ test with the two-group $t$ test approximation because of unequal variances. All analyses were performed using SAS Version 6.03 (1985). Differences were considered significant if $P \leq .05$.

**Results**

Twenty-five young and 13 elderly healthy men completed the alprazolam bolus treatment. Unless otherwise specified, results are based on these 38 subjects. The mean age was 27.5 years (range, 22–35 years) in the young and 68.2 years (range, 65–75 years) in the elderly; mean weight was 77.9 kg (range, 61.2–98.6 kg) for young and 80.2 kg (range, 62.2–106.3 kg) for elderly subjects. In the continuous-infusion treatments, there were 13 young and 13 elderly men. All had participated in the bolus treatment 28 days earlier.

Adverse effects were minor and required no intervention; effects included burning on injection (two), dizziness (one), nausea (one) and hiccups (seven). Drowsiness and sleep also occurred and is reported in the NRSS data. Pulse, respirations and blood pressure were monitored throughout the study day and remained stable in all subjects, with little deviation from prealprazolam values.

**Pharmacokinetics.** Figure 1 demonstrates mean concentration-time plots for the alprazolam bolus (fig. 1A) and infusion (fig. 1B) treatments for each age group. Table 1 summarizes mean pharmacokinetic parameter estimates for the young and elderly in the bolus treatment. AUC$_{0–12}$ and C$_{max}$ values illustrate that mean concentrations did not differ between groups over the 12 hr of effect assessments. However, data from the entire 48 hr of sampling (fig. 1A, insert) indicate that the elderly have a slower clearance and longer $t_{1/2}^{\alpha}$, which would result in increased steady-state concentrations and longer time to steady state during chronic treatment.

The design for the continuous-infusion treatment was to target the EC$_{50}$ for each subject. However, due to the 2 mg dosage limitation, this goal was achieved in only 4 of 13 young and 9 of 13 elderly men. In this treatment, the mean alprazolam dose administered during the 9 hr was 1.954 mg (range, 1.780–2.000 mg) in the elderly and 1.998 mg (range, 1.980–2.000 mg) in the young (P = .04). Pharmacokinetic parameter estimates from the bolus treatment relatively accurately predicted concentrations during the continuous-infusion treatment. Mean observed concentrations deviated from predicted values by <10% in 22 of 26 subjects; one deviated by 24.7%, whereas the other three deviated by <15% from predicted. Mean observed alprazolam concentrations from 1 to 9 hr for the young and elderly were 17.8 ± 1.67 and 17.7 ± 1.32 ng/ml, respectively (P = .89); mean concentrations predicted from the bolus treatment were 18.4 ± 2.25 and 17.8 ± 1.18 ng/ml in the young and elderly, respectively (P = .40).

Results of alprazolam binding to serum proteins indicated no difference between the young and elderly (P = .40). Mean free fractions were 0.196 ± 0.012 in the young subjects and 0.192 ± 0.017 in the elderly. Because of the similarity between groups and to allow comparison with previously published reports, concentration data are expressed as total concentrations.

**Pharmacodynamics in the bolus treatment.** Figure 2A is a plot of DSST score vs. time in the bolus treatment. CS,
Young and 13.2% in the elderly (P = 0.27). For CS, mean decrements at 12 hr were 9.6% in the 5 young and 22 elderly returned to base line in the 22 young (pictures recognized); a higher score on CPT (latency in msec) and a lower score on CS (cards/sec), DSST (symbols) and RMT (median, 2; range, 0–4) in the 10 elderly. Impairment is indicated by baseline (Eo) and MaxOE values for all psychomotor performance tests are presented in table 2. Predose base-line (Eo) and MaxOE values for the young (7/2 of 22 men) and elderly (7/2 of 13 men) were 13.5% and 140.5% of Eo, respectively (P = 0.0001); intercept values were 282.0 ± 69.9 for the young and 140.5 ± 110.1 for the elderly (P < .0001).

Neither the linear nor the sigmoid $E_{\text{max}}$ model adequately described all of the data. Because data from most subjects demonstrated obvious sigmoidicity, the linear regression line deviated systematically from the observed data at extreme observations. Evidence of this is the lower mean intercepts for DSST and CS (table 5; scores decrease with impairment) than observed Eo values (table 4), particularly for the elderly. Likewise, mean intercepts for CPT (latency increases with impairment), are lower than observed Eo values. The sigmoid $E_{\text{max}}$ model described the data well from both groups; however, a maximum response was not observed in most young subjects, limiting the reliability of the resulting estimates for EC50 and slope factor. As indicated in table 5, DSST data from two young men were not described by the sigmoid $E_{\text{max}}$ model because of low MaxOE values, indicating that they were even less sensitive than the other young men.

**Pharmacodynamics in the continuous-infusion treatments.** Figure 2, B and C, shows DSST score vs. time data for the continuous-infusion treatments of alprazolam and placebo, respectively. Tables 6 and 7 summarize response data from the young and elderly men after the continuous-infusion and placebo treatments, respectively. Figure 2C demonstrates the stability of DSST scores during the placebo treatment day in young and elderly subjects; placebo CPT and CS data show similar stability (table 7). Repeated-measures analysis of variance revealed that there was no effect due to time or to a group-by-time interaction for any psychomotor test (P = .26); thus, time did not influence performance scores in either group during the placebo treatment. On the RMT, no subject had a score ≥4 of 7 in either age group at any time on the placebo day.

Table 8 summarizes MaxOE and MnE1–9hr values for DSST and CS data. For CPT, MaxOE values for the young and elderly were 13.5 ± 10.9% and 18.5 ± 11.3%, respectively (P = .25); MnE1–9hr values were 5.3 ± 4.8% in the young and 7.3 ± 3.6% in the elderly (P = .17). For all three tests, MaxOE > MnE1–9hr (P < .05).

**Fig. 1.** A, Mean alprazolam concentration-time data for young (△) and elderly (○) men after a 2 mg/2 min i.v. dose through the time of last pharmacodynamic assessment at 12 hr and through 48 hr (insert). Error bars represent S.D. B, Concentrations at the end of the loading infusion (0.5 hr) and during the time of performance testing from 1 to 9 hr in the alprazolam continuous-infusion treatment in young (△) and elderly (○) subjects.

CPT, NRSS and RMT data from the bolus treatment are summarized in table 2. Predose base-line (Eo) and MaxOE values for all psychomotor performance tests are presented in table 3 for young and elderly. Impairment is indicated by a lower score on CS (cards/sec), DSST (symbols) and RMT (pictures recognized); a higher score on CPT (latency in msec) indicates impairment. Nearly all (12/13) elderly but only 5 of 25 young had a performance decrement of ≥75% on at least one psychomotor test.

Mean values for the ratio of AUEC0–9hr to AUC0–9hr during the bolus treatment are presented in figure 3. Results were similar for AUEC0–9hr/AUEC0–9hr values were 1.5–1.8- and 2.1-fold higher in the elderly than in the young for CS, DSST and CPT, respectively. By 12 hr, the mean DSST decrement was −0.3% (range, −25.0% to 16.7%) in the young and 13.2% (range, −9.3% to 32.0%, P = .004) in the elderly (see fig. 2A). Despite similar concentrations, only 3 of 10 elderly had decrements of <10% at 12 hr vs. 20 of 22 young. CPT latency returned to base line in the 22 young (−1.05%) and 10 elderly (0.35%) in whom performance was assessed at 12 hr (P = .27). For CS, mean decrements at 12 hr were 9.6% in the young and 13.2% in the elderly (P = .51).

Memory and sedation data are presented in tables 2 and 4. At the 10-min NRSS assessment, 10 of 13 elderly subjects were scored as 4 (sleeping soundly; median, 4; range, 1–4); this contrasts with only 1 of 25 young who were scored as a 4 (median, 2; range, 0–4). During at least one assessment after alprazolam administration, 12 of 13 elderly and 6 of 25 young subjects were scored as 4.

In the delayed recall test, 6 of 25 young and 0 of 13 elderly remembered seeing any of the five pictures shown 2 hr after alprazolam bolus administration. There was no difference in the number of pictures recalled by the young (0.4) and the elderly (0.0; P = .07); the median number recalled was 0 in both groups.

Mean parameter estimates from fitting the inhibitory sigmoid $E_{\text{max}}$ and linear models to CS and DSST data from each subject after the bolus are presented in table 5. CPT data were not described well by the sigmoid $E_{\text{max}}$ model for many subjects and is therefore not proposed as an acceptable model for CPT data. For CPT, the linear model resulted in a slope of 9.24 ± 6.43 and 25.5 ± 6.7 for the young and elderly, respectively (P = <.0001); intercept values were 282.0 ± 69.9 for the young and 140.5 ± 110.1 for the elderly (P = .17).
develop tolerance to DSST impairment, and another did not develop tolerance to CS impairment. Repeated-measures analysis of variance showed significant group-by-time interaction for DSST ($P = .02$) but not CS ($P = .17$). Trend analysis of the DSST interaction term showed that the linear component was significant ($P = .05$), whereas the higher-order quadratic component was not ($P = .95$). Thus, adding a quadratic term to the offset rate regression model did not significantly improve the model fit. Because the MaxOE value for CPT during continuous infusion was low and subjects returned rapidly to baseline ($<5\%$ decrement in 20 of 26 subjects by 4 hr), mathematical determination of effect offset rate constant was precluded for CPT data.

Figure 4, A and B, shows mean percent recovery during the alprazolam continuous infusion. The figures demonstrate apparent biphasic recovery, with a similar rate of recovery in the young and the elderly through 4 hr and slowing at 5.5 and 7 hr in the elderly. There were no differences in percent recovery at any time point between the young and elderly for CS ($P > .05$). Recovery differences were evident at the 5.5- and 7-hr time points for DSST with average recoveries of 42.0% and 37.3%, respectively, in the elderly and 64.5% and 61.7% in the young ($P < .04$ for both times). The group-by-time interaction term approached significance for DSST ($P = .115$) but not for CS ($P = .209$). Trend analysis showed the linear ($P = .067$) but not the quadratic ($P = .485$) component of the DSST interaction was significant.

The percent of subjects with significant memory impairment and sedation in the continuous-infusion treatment is presented in figure 5, A and B, respectively. Results of logistic regression analysis for these data are also shown. Significant memory impairment occurred in a similar proportion of young and elderly subjects at 1 and 4 hr but more frequently in the elderly at 5.5 hr. A similar pattern was seen for sedation data, with the probability of significant sedation higher in the elderly than in the young from 5.5 through 9 hr.

On delayed recall during the alprazolam continuous infusion, the elderly recalled an average of 0.2 pictures (range, 0–2), whereas the young recalled 1.9 (range, 0–5; $P = .003$). Specifically, 2 of 13 elderly and 9 of 13 young recalled at least one of the 5 pictures they had been shown. Conversely, 8 of 13 elderly and 2 of 13 young did not remember being shown any pictures. During the placebo treatment, the young and elderly recalled 3.6 (1–5) and 3.9 (0–5) pictures, respectively ($P = .64$).

**Discussion**

The data from this study demonstrate that age influences both the pharmacokinetics and pharmacodynamics of alprazolam. In addition to decreasing alprazolam clearance, age increases sensitivity to the psychomotor, sedative and memory effects of alprazolam through a mechanism other than increased concentrations. Age also decreases the rate of offset of the psychomotor, memory and sedative effects of alprazolam. Additionally, the data provide insight about the intensity of initial effect as a determinant of rate of tolerance development.

An important but unsurprising observation is the lower performance scores in the elderly in the absence of drug (baseline and placebo). Hinrichs and Ghoneim (1987) reported that lower performance scores are evidence for homeostatic changes with aging present in the absence of drug. In the presence of alprazolam, our data show that the elderly experience greater impairment than young men: the elderly have lower absolute performance scores, greater absolute decrements in scores and greater percentage decrements than do young subjects at equivalent concentrations.
Pharmacokinetics and sensitivity. Although there is a lower clearance and a longer $t_{1/2}$ in the elderly men, these differences do not explain the increased psychomotor effects observed after bolus alprazolam administration. Mean plasma alprazolam concentrations are similar in the young and elderly during the first 12 hr; in contrast, memory and psychomotor performance impairment as well as sedation are greater in the elderly. Furthermore, when response is corrected for individual variability in alprazolam concentration and for differences in base-line scores between young and elderly using AUEC/AUC, the elderly have higher ratios than the young; effect-concentration modeling with either the linear or the sigmoid Emax model shows a greater response through the range of alprazolam concentrations. Collectively, these results demonstrate that the elderly are more sensitive than the young to the effects of alprazolam through a mechanism apart from pharmacokinetics. Possible reasons include a slower rate of tolerance development, higher brain concentrations due to alterations in blood-brain barrier permeability, an increase in benzodiazepine receptor binding, an increase in receptor functionality or a decrease in homeostatic reserve. This study was designed to evaluate the potential contribution of tolerance to differences in sensitivity; the evaluation of other mechanisms was beyond the scope of this investigation. Differences in sensitivity between young and elderly have been examined for a number of classes of drugs, as reviewed by Feely and Coakley (1990).
The elderly are more sensitive to the effects of scopolamine (although concentrations were not obtained) (Molchan et al., 1992) and diazepam (Reidenberg et al., 1978) but less sensitive to the effects of propranolol (Feely and Stevenson, 1979). The elderly also showed less suppression of endogenous cortisol despite higher concentrations of prednisolone (Stuck et al., 1988). Thus, generalizations about the influence of aging on sensitivity to drugs cannot be made.

**TABLE 4**

<table>
<thead>
<tr>
<th></th>
<th>RMT</th>
<th>NRSS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eo</td>
<td>MaxOEa</td>
</tr>
<tr>
<td>Young (n = 25)</td>
<td>6.82</td>
<td>2.32</td>
</tr>
<tr>
<td>Elderly (n = 13)</td>
<td>6.92</td>
<td>0.85</td>
</tr>
<tr>
<td>P</td>
<td>.42</td>
<td>.01</td>
</tr>
</tbody>
</table>

Values are presented as mean (S.D.).

a The lower the score, the worse is the performance.

b The larger value indicates a greater decrement or decrement per unit of concentration. The AUEC and effect ratios are for data from 0 to 5 hr for RMT and 0 to 12 hr for NRSS.

**TABLE 5**

<table>
<thead>
<tr>
<th></th>
<th>CS</th>
<th>DSST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>ECso</td>
</tr>
<tr>
<td>Sigmoid Emaxb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>25</td>
<td>39.8 (14.2)</td>
</tr>
<tr>
<td>Elderly</td>
<td>13</td>
<td>25.3 (5.5)</td>
</tr>
<tr>
<td>P</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Linear model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>25</td>
<td>1.48 (0.30)</td>
</tr>
<tr>
<td>Elderly</td>
<td>13</td>
<td>1.41 (0.16)</td>
</tr>
<tr>
<td>P</td>
<td>.44</td>
<td></td>
</tr>
</tbody>
</table>

a Eo values used for this model are presented in table 3.
b Parameter estimates are presented as mean and (S.D.) with range of observations.

d The lower the score, the greater is the decrement.
e The higher the score, the greater is the decrement or sedation.
f Data are presented as median (range of values).
g RMT was not assessed at this interval.

**TABLE 6**

<table>
<thead>
<tr>
<th></th>
<th>CS</th>
<th>Sedation and memory data for young and elderly men in the alprazolam continuous infusion treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (hr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Young</td>
<td>Elderly</td>
</tr>
<tr>
<td>Young</td>
<td>1.45 (0.35)</td>
<td>0.94 (0.30)</td>
</tr>
<tr>
<td>Elderly</td>
<td>1.29 (0.17)</td>
<td>0.67 (0.20)</td>
</tr>
<tr>
<td>Continuous testb</td>
<td>Young</td>
<td>Elderly</td>
</tr>
<tr>
<td>Young</td>
<td>365 (31)</td>
<td>505 (136)</td>
</tr>
<tr>
<td>Elderly</td>
<td>422 (45)</td>
<td>619 (122)</td>
</tr>
<tr>
<td>NSRTc</td>
<td>Young</td>
<td>Elderly</td>
</tr>
<tr>
<td>Young</td>
<td>0 (0–1)</td>
<td>3 (1–3)</td>
</tr>
<tr>
<td>Elderly</td>
<td>0 (0–0)</td>
<td>3 (3–4)</td>
</tr>
<tr>
<td>RMTtc</td>
<td>Young</td>
<td>Elderly</td>
</tr>
<tr>
<td>Young</td>
<td>7 (6–7)</td>
<td>3 (1–7)</td>
</tr>
<tr>
<td>Elderly</td>
<td>7 (5–7)</td>
<td>2 (0–6)</td>
</tr>
</tbody>
</table>
lam during the continuous infusion, subjects demonstrated a gradual improvement in psychomotor performance and memory and an offset of sedation after 1 hr. This pattern of response can be explained by the development of acute functional tolerance.

Before accepting tolerance as the explanation for declining effect in the presence of plateau alprazolam concentrations, a pharmacokinetic explanation for improvement in scores over time was considered. To achieve relatively stable plasma concentrations within 1 hr, a 30-min loading infusion followed by a continuous infusion (for 8.5 hr) was administered. This regimen resulted in plasma concentrations at 30 min that were higher than the target. To project the potential impact of these concentrations on brain concentrations, simulations were done using mean two compartment pharmacokinetic parameter estimates from the bolus treatment for young and elderly subjects. The results indicate that equilibrium between the central (plasma) and peripheral (brain) compartments is achieved before 2.5 hr and that the concentration peak evident in the plasma compartment is not observed in the peripheral (brain) compartment; concentrations would theoretically increase slowly in the peripheral compartment to reach the plateau by 2.5 hr. In contrast, the observed decline in psychomotor response continues through 9 hr. Therefore, improvement in performance over time and differences between the young and elderly do not appear to be explained by pharmacokinetics and are consistent with development of tolerance.

Development of acute tolerance causes the effect-concentration curve to shift to the right and results in a higher apparent EC₅₀ value (Kroboth et al., 1993; Porchet et al., 1988). Thus, slower development of tolerance in the elderly could explain some of the increased sensitivity to benzodiazepines with age. In this study, there was no way to assess the hypothesis that acute tolerance can be explained by redistribution of benzodiazepines from the central nervous system to peripheral tissues (Greenblatt et al., 1990).

**Tolerance and aging.** The data from this study suggest that the elderly develop acute tolerance to alprazolam effects more slowly than the young. Again, alprazolam concentra-
tions do not explain the observations because there were no significant differences in concentrations between the young and elderly at any time point during the continuous infusion. This study was designed so that the young and elderly would achieve the same level of initial psychomotor decrement (MaxOE) during the alprazolam continuous-infusion treatment. This was achieved with DSST and CPT. Despite the fact that MaxOE for DSST was similar in young and in elderly men, the MnE	extsubscript{1–9 hr} was greater in the elderly (table 8). In addition, the elderly have a shallower slope of the regression line for offset of effect ($k_t$) and a longer $t_{1/2}$ (table 8), and they recovered function more slowly than the young (fig. 4A). Furthermore, the only two subjects who did not show any evidence of offset of effect during the alprazolam continuous infusion were elderly. As stated earlier, the offset of CPT effect occurred too rapidly to allow mathematical evaluation (MnE	extsubscript{1–9 hr} $<$8% for both young and elderly men). CS results are discussed in the section on intensity of effect. The elderly also had a slower offset of effect of sedation and memory impairment (fig. 5).

The stability of DSST, CS and CPT scores during the placebo treatment in young or elderly men (fig. 2C and table 7) indicates that the age groups were equivalent in achieving a true base line during training. Practice effects were minimized. However, two factors can contribute to the observed apparent tolerance: age-related receptor-mediated changes and age-related differences in learning to adapt to drug-induced impairment during repeated testing.

Published reports support the observation that tolerance develops more slowly with aging. In a study in rats, Stijnen et al. (1992) assessed the effect of age on the time course of anticonvulsant response after a single intravenous bolus of oxazepam and found a biphasic response of anticonvulsant effect followed by a proconvulsant effect in young, but not in aged (35-month-old), BN/BiRij rats. The investigators attributed the results to the absence of a tolerance/withdrawal phenomena with aging. Other investigators have suggested that the elderly may have an altered homeostatic reserve (Feely and Coakley, 1990; Swift, 1990), to which differences in sensitivity and tolerance development may both be attributed. The elderly may not be able to compensate as readily for the effects of benzodiazepines on cognitive function, coordination and motor skills, an adaptation that may involve the many steps after receptor binding and activation. Nikaido et al. (1990) reported longer drug effect half-lives in the elderly than in the young after the administration of triazolam and alprazolam and indicated consistency of their data with an age-related decline in adaptive capacity to inhibit adverse drug effects. We have observed that psychomotor performance of healthy elderly men did not return to base line during four days of multiple-dose alprazolam (Kroboth et al., 1990); this contrasts with results in the young in a similar 4-day study (Smith and Kroboth, 1987). Together, the results
of the latter two studies in humans suggest that chronic tolerance to alprazolam also develops more slowly in the elderly than in the young. The present study is the first to attempt to quantify and compare rates of offset (tolerance) of acute benzodiazepine effects in the young and elderly while drug concentrations were maintained constant.

The mechanism of tolerance development to benzodiazepines is poorly understood. Although acute functional tolerance occurs within hours and maximally within 1 day (Crabbe et al., 1979; Frey et al., 1986; Haefley, 1986; Jaffe, 1990), chronic tolerance develops over days or weeks of continuous drug use (Jaffe, 1990); the latter has been studied more extensively. Investigators have reported benzodiazepine receptor down-regulation and a decrease in chloride ion flux (Miller et al., 1989), a change in the setpoint of the benzodiazepine receptor with chronic agonist exposure (Nutt et al., 1992) and an uncoupling of benzodiazepine binding to GABA\(_A\) receptor (Nutt et al., 1992). Studies supporting the setpoint theory have shown an attenuation of chronic tolerance development when the antagonist flumazenil is administered (Gonsalves and Gallager, 1988) or a partial, rather than a full agonist, is administered (Hernandez et al., 1989). All of these effects take several days or weeks to develop. Changes that occur in acute tolerance have not been apparent in receptor binding and functional studies in animals. Despite probable mechanistic differences, acute tolerance has been used to predict chronic tolerance and cross-tolerance between ethanol and pentobarbital in rats, suggesting that these forms of tolerance may be related (Khanna et al., 1991).

**Tolerance and intensity of effect.** Two separate observations from the bolus and continuous-infusion treatments lead to the generation of a hypothesis that the greater the intensity of initial effect, the more rapidly is tolerance developed. First, in the bolus treatment, the elderly had a greater psychomotor decrement and a significantly steeper slope of the effect vs. concentration curve (slope and \(s\), depending on model).

The second observation is from the continuous-infusion treatment. When MaxOE was the same in the two groups (DSST), the elderly had a slower offset of effect than the young. When MaxOE was higher in the elderly (CS), the offset of effect occurred at a similar rate in the two groups. Thus, the higher CS MaxOE in the elderly may have masked a difference between the young and elderly in offset of effect. To rigorously evaluate this hypothesis, a study that is designed to assess the offset of effect with different initial intensities of effect is needed.

The literature also suggests that initial effect intensity influences the rate of tolerance development. When triazolam was given by continuous rectal infusion to healthy subjects, concentrations rose slowly until steady state was achieved at \(\approx 8\) to 10 hr; tolerance was not noted until the second day of administration (Breimer et al., 1985). Kroboth et al. (1993) have shown in a crossover study of young men that relative to a bolus dose, infusion of intravenous triazolam over 9 hr increases apparent sensitivity to psychomotor effects; the higher intensity of initial effect after the bolus dose appears to result in more rapid development of tolerance to benzodiazepine effects than does slow administration. These benzodiazepine data are also consistent with morphine data in rabbits. Hovac and Weinstock (1987) demonstrated that increasing the dosage of morphine, and thus the degree of initial intensity of effect, results in an accelerated rate of acute tolerance development to cardiovascular and respiratory effects of morphine.

Although a difference in effect intensity is a plausible and likely explanation for the disparate results of DSST and CS in the young and elderly, an alternative exists. Nine hours may not have been long enough to realize potential differences in CS between the young and elderly. For reasons that are not clear, the estimated \(t_{1/2}\) for CS in the young (5.5 hr) was nearly twice that of DSST (2.8 hr). For CS, \(<60\%\) recovery in psychomotor function was evident for both the young and the elderly at 9 hr; differences between the young and elderly on DSST were not apparent until recovery reached \(~50\%\).

**Conclusions and implications.** Based on the data from this study, the elderly would be more impaired than the young during treatment with alprazolam for two reasons: (1) higher alprazolam concentrations during chronic treatment and (2) greater sensitivity coupled with slower offset of effect. To estimate the clinical impact of these differences during a treatment regimen of 0.5 mg of alprazolam orally every 6 hr, steady-state concentrations and corresponding psychomotor impairment were calculated for young and elderly. Predicted average steady-state concentrations (using mean clearance data and assuming 90\% bioavailability) are 16.7 and 20.3 ng/ml in the young and elderly, respectively. The corresponding decrements at these concentrations (from the sigmoid \(E_{\text{max}}\) model and mean CS data) are 11.8\% in the young and 28.7\% in the elderly. In other words, although mean steady-state concentrations for the elderly would be \(~1.2\)-fold higher than in the young, psychomotor performance decrement would be 2.4-fold higher. The estimate of psychomotor decrement does not take into account the tolerance development and therefore is more accurate for potential age-related differences at the initiation of therapy. The effect of aging on the therapeutic effect is uncertain, as is the presence of anxiety on psychomotor impairment. However, low doses and caution should be used while titrating response in the elderly.

This study also shows that aging is associated with a slower rate of acute tolerance development, which in turn could explain some of the differences in sensitivity between the young and elderly. Furthermore, the data also indicate that in addition to aging, initial effect intensity may also influence the rate of tolerance development.

To define more clearly the impact of MaxOE on tolerance development rate, future studies should be done that target specific different intensities of performance decrement during a pseudo-steady state infusion. To accomplish those objectives, doses larger than those used in this study would be needed, however, because 2 mg/9 hr achieved a mean impairment of only \(~30\%\) during the 9 hr. Other, theoretically more specific measures of central nervous system function such as electroencephalography and saccadic eye movement should be included. In addition, first-order rather than zero-order infusion pumps should be used to avoid peak concentrations higher than the targeted concentration.

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References


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