than that of the washed portion, and the rate of loss of acid reactivity during aging was also reduced. This behavior confirms the strong stabilizing effect of anions (23). However, the unwashed portion that was precipitated in the presence of a molar ratio of 1.5 *M* mannitol per equivalent aluminum oxide showed the smallest decrease in the rate of acid neutralization during aging. The interaction between polyols and aluminum hydroxide gel apparently is too weak to recommend the incorporation of mannitol or sorbitol in the reaction medium. However, the results suggest the addition of mannitol or sorbitol immediately after washing.

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Effect of Age and Gender on Disposition of Temazepam

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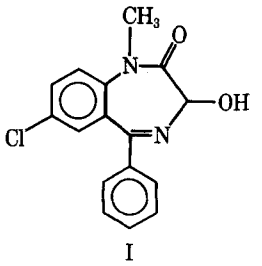
Received December 12, 1980, from the *Division of Clinical Pharmacology, Departments of Psychiatry and Medicine, Tufts University School of Medicine and New England Medical Center Hospital, Boston, MA 02111.* Accepted for publication March 5, 1981.

Abstract □ Thirty-two male and female volunteers, 24–84 years of age, ingested single 30-mg doses of temazepam, a 3-hydroxy-1,4-benzodiazepine derivative used as a hypnotic agent. Kinetics of total and unbound temazepam were determined from multiple plasma temazepam concentrations measured during 48 hr after the dose. The temazepam elimination half-life ranged from 8 to 38 hr and was longer in women than in men (16.8 *versus* 12.3 hr, $p < 0.05$). Likewise, clearance of total temazepam (assuming complete absorption) was higher in men than in women (1.35 *versus* 1.02 ml/min/kg, $p < 0.025$). Neither half-life nor clearance was significantly related to age. The volume of distribution of total temazepam (mean 1.40 liters/kg) was unrelated to age or gender. Temazepam was extensively protein bound, with a mean free fraction of 2.6% (range 1.7–3.4%). The free fraction increased with age ($r = 0.45$, $p = 0.01$), partly due to the inverse relation of the free fraction to plasma albumin concentration ($r = -0.34$, $p = 0.06$) and the age-related decline in plasma albumin ($r = -0.49$, $p < 0.005$). After correction for individual differences in binding, clearance of unbound temazepam in men was higher than in women (50.5 *versus* 39.7 ml/min/kg, $0.05 < p < 0.1$), and it tended to decline with age in both sexes ($r = -0.44$ and -0.43, respectively, $p = 0.1$).

Keyphrases □ Temazepam—effect of age and gender on disposition and elimination □ Tranquilizers—temazepam, effect of age and gender on disposition and elimination □ Hypnotics—temazepam, effect of age and gender on disposition and elimination

Temazepam (I) is a 3-hydroxy-1,4-benzodiazepine derivative used as a hypnotic agent. The major metabolic pathway of temazepam in humans involves conjugation with glucuronic acid at position 3, yielding a water-soluble glucuronide metabolite that is excreted in the urine (1). Since the aging process may alter drug pharmacokinetics, this study was undertaken to assess the disposition and elimination of temazepam in young and elderly volunteers.



I

EXPERIMENTAL

Subjects—Thirty-two healthy male and female volunteers, 24–84 years of age, participated after giving written informed consent. They were divided into four groups of young male, young female, elderly male, and elderly female subjects (Table I). All young subjects were free of any identifiable medical disease and were taking no medications. Elderly individuals were ambulatory, active, and in general good health. Five elderly subjects were taking medications for the treatment of cardiovascular disease that was clinically stable and compensated.

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Table I—Subject Characteristics and Pharmacokinetics of Temazepam

Parameter	Mean Values (Range) Young Male (n = 7)	Young Female (n = 7)	Elderly Male (n = 8)	Elderly Female (n = 10)
Subject characteristics				
Age, years	29.0 (24–39)	29.7 (28–33)	69.1 (60.0–76.0)	69.8 (62.0–84.0)
Weight, kg	71.4 (63.6–79.5)	61.4 (52.7–70.5)	77.2 (64.5–90.9)	61.8 (52.7–75.0)
Smoking, cigarettes/day	8.2 (0–20)	8.4 (0–28)	0	5.0 (0–20)
Albumin, g/100 ml	4.7[a] (4.5–4.9)	4.5 (3.8–5.3)	4.1[a] (3.6–4.7)	4.3 (3.7–4.8)
Kinetics of total (free plus bound) temazepam				
Peak plasma temazepam concentration, ng/ml	430.0 (293–585)	483.0 (359–754)	371.0 (222–687)	409.0 (251–610)
Weight-normalized peak concentration, $\mu g/ml \times kg$	30.3 (21.4–38.6)	29.4 (22.8–45.3)	28.5 (15.9–56.2)	25.0 (13.2–32.5)
Time of peak concentration, hours after dose	2.18 (0.75–4.0)	2.75 (0.75–4.0)	1.84 (0.75–4.0)	4.65 (1.0–12.0)
Elimination half-life, hr	12.8 (9.4–23.3)	16.2 (10.1–25.3)	11.9 (8.3–14.2)	17.2 (8.9–37.9)
Volume of distribution, liters/kg	1.53 (0.67–2.8)	1.40 (1.20–1.76)	1.32 (0.89–2.08)	1.39 (0.68–2.30)
Clearance, ml/min/kg	1.36 (0.82–1.72)	1.10 (0.59–1.54)	1.35 (0.73–2.45)	0.97 (0.70–1.48)
Kinetics of unbound temazepam				
Free fraction, %	2.54 (1.66–4.18)	2.30 (1.74–2.93)	3.12 (2.25–3.89)	2.75 (2.21–3.40)
Unbound V_d, liters/kg	68.0 (32.2–168.7)	61.5 (46.7–81.6)	43.2 (23.7–65.4)	50.8 (30.8–91.3)
Unbound clearance, ml/min/kg	57.2 (37.2–83.7)	46.8 (27.4–70.1)	44.7 (19.8–81.7)	35.4 (24.0–45.1)

[a] $p < 0.005$ for young *versus* elderly of the same sex.

Procedure—After an overnight fast, subjects ingested a single 30-mg capsule of temazepam[1] with 100–200 ml of tap water. They remained fasting until 3 hr after drug ingestion. Venous blood samples were drawn into heparinized tubes from an indwelling butterfly cannula (kept patent by flushing with dilute heparin solution) or by venipuncture prior to the dose and at the following postdosage times: 0.25, 0.5, 0.75, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hr. Plasma was separated and stored at −20° until the time of assay.

Sample Analysis—Temazepam concentrations in all plasma samples were determined by electron-capture GLC after addition of a benzodiazepine analog (3-hydroxyprazepam) as the internal standard (2).

The free fraction (percent unbound) was determined by equilibrium dialysis at 37° (3) of a single sample drawn in the nonfasting state. Since heparin may influence the free fraction of benzodiazepines, no subject received heparin systemically for at least 24 hr prior to sampling. Duplicate 2-ml plasma samples were spiked to contain 500 ng/ml of unlabeled temazepam and 20 nCi/ml of tritiated temazepam (62.5 μCi/mg). The radioactivity was determined in a liquid scintillation counter[2]. The mean coefficient of variation between duplicate samples was <6%. Binding was independent of the total plasma temazepam concentration over a range of 160–4160 ng/ml.

Pharmacokinetic and Statistical Analysis—Each set of data points was analyzed by iterative nonlinear least-squares regression techniques (4). Data points were fitted to the following two functions:

$$C = B(e^{-\beta t} - e^{-k_a t}) \quad \text{(Eq. 1)}$$

$$C = -(A + B)e^{-k_a t} + Ae^{-\alpha t} + Be^{-\beta t} \quad \text{(Eq. 2)}$$

where C is the plasma temazepam concentration at time t after dosage; A and B are hybrid intercept terms; and k_a, α, and β are hybrid exponents representing phases of drug absorption, distribution, and elimination, respectively. When necessary, both equations were modified by addition of a lag time prior to the start of first-order absorption. The choice between Eqs. 1 and 2 as functions of best fit was determined by scatter of actual data points about the fitted function and by comparison of weighted residual errors (5).

The hybrid exponent β was used to calculate the apparent elimination half-life ($t_{1/2\beta}$). The area under the 48-hr plasma concentration curve was calculated using the trapezoidal rule; to this value was added the extrapolated residual area from the final concentration point to infinity, yielding the total area under the plasma concentration curve (AUC). The extrapolated area accounted for an average of 9.8% (range 2.6–36.8%) of the total AUC.

When neither Eq. 1 nor 2 provided an adequate fit of the data, $t_{1/2\beta}$ was calculated using the terminal log-linear portion of the plasma concentration curve. The total AUC was calculated as described.

Although absolute bioavailability of temazepam is not known, previous studies of lorazepam, a structurally similar 3-hydroxy-1,4-benzodiazepine derivative, indicated that absolute systemic availability of orally administered drug is close to 100% (6, 7). Accordingly, it was assumed that the entire 30-mg temazepam dose reached the systemic circulation (100% bioavailability). Total clearance was calculated as the administered dose divided by the AUC, and the apparent volume of distribution (V_d) using the area method was calculated as total clearance divided by β. The volume of distribution and clearance of unbound temazepam were calculated as the quotient of total V_d or clearance divided by the unbound fraction.

RESULTS

Peak plasma temazepam concentrations ranged from 222 to 754 ng/ml. Peak concentrations were not significantly influenced by age, although they tended to be higher in women then in men and lower in elderly than in young of both sexes (Table I). After normalization for weight, peak plasma concentrations were similar among groups. Temazepam was slowly absorbed, with the time of peak concentrations ranging from 0.75 to 12.0 hr after dosage. The mean time of peak concentration among the four groups ranged from 1.8 to 4.7 hr after dosage and was not significantly influenced by age or gender. Iterative analysis provided satisfactory solutions in only 11 of the 32 subjects (Fig. 1).

The V_d value for temazepam ranged from 0.7 to 2.3 liters/kg. Mean values for the four groups (1.32–1.53 liters/kg) were very close regardless of age or sex.

Within sexes, age was not significantly related to temazepam half-life or clearance (Figs. 2 and 3). However, $t_{1/2\beta}$ was significantly longer in women (mean 16.8 hr) than in men (12.3 hr) regardless of age ($p < 0.05$). Likewise, clearance of total temazepam was lower in women than in men regardless of age (1.02 *versus* 1.35 ml/min/kg, $p < 0.025$).

The free fraction of temazepam ranged from 1.67 to 4.18% and increased significantly with age ($r = 0.45$, $p < 0.02$) (Fig. 4). Elderly of both

[1] Restoril, Sandoz, East Hanover, N.J.
[2] Beckman Instruments.

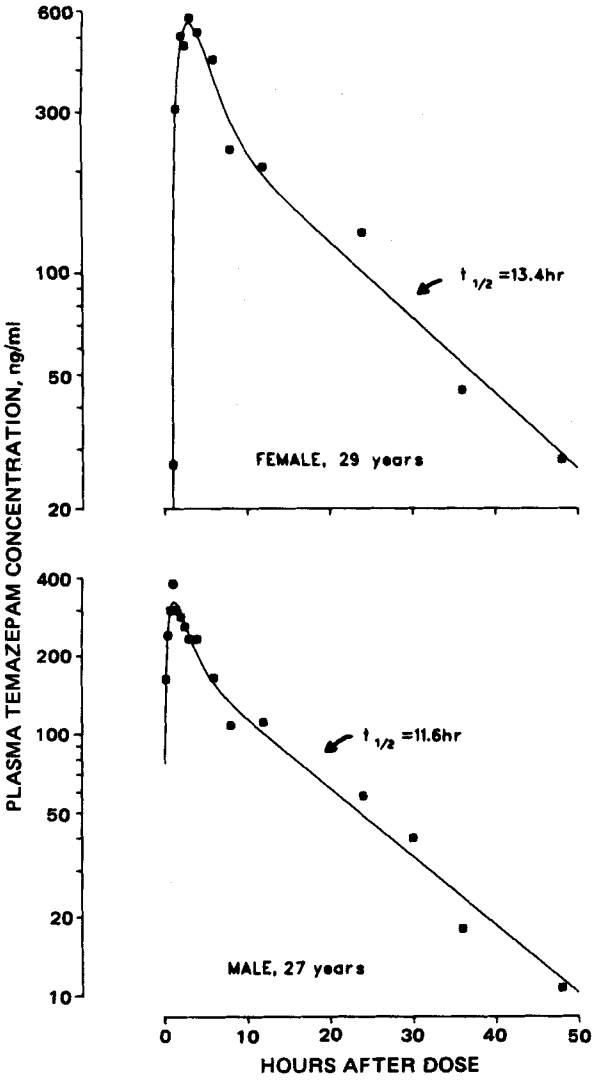

Figure 1—*Plasma temazepam concentrations in two representative subjects who displayed first-order absorption. Solid lines are pharmacokinetic functions determined by nonlinear least-squares regression analysis.*

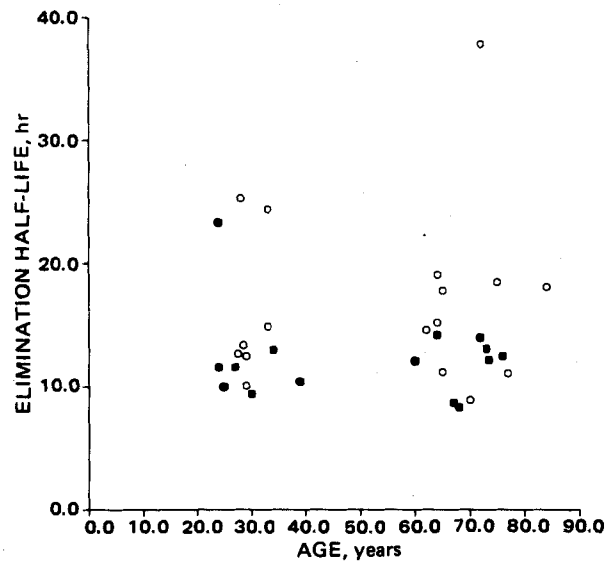

Figure 2—*Relation of age to temazepam elimination half-life in males and females. Key:* ■, *male* (r = −0.17); *and* O, *female* (r = 0.11).

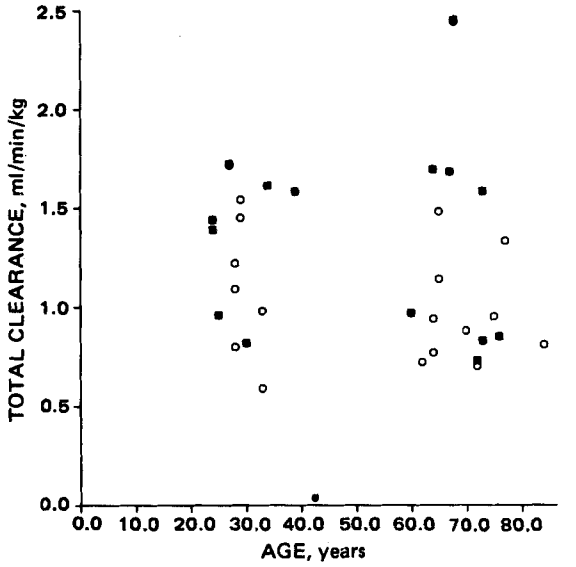

Figure 3—*Relation of age to clearance of total temazepam in males and females. Key:* ■, *male* (r = −0.04); *and* O, *female* (r = −0.23).

sexes had a higher free fraction than did the young subjects. The increased free fraction of temazepam in the elderly was partly explained by plasma albumin concentrations, which declined significantly with age ($r = -0.49$, $p < 0.01$).

Values of unbound V_d were lower in the elderly than in the young subjects of both sexes, but the differences were not significant (Table I). Clearance of unbound temazepam declined with age in both sexes (Table I and Fig. 5), although differences did not reach statistical significance. As in the case of clearance of total temazepam, unbound clearance was higher in men than in women (50.5 *versus* 39.7 ml/min/kg, $0.05 < p < 0.1$).

DISCUSSION

Previous studies with benzodiazepines that undergo oxidative biotransformation (such as chlordiazepoxide, diazepam, and desmethyldiazepam) suggest that metabolic clearance may be impaired among the elderly, particularly in elderly males (8–13). However, for benzodiazepines that undergo glucuronide conjugation (such as oxazepam and lorazepam), the aging process has minimal, if any, effect on metabolic disposition (6, 14–16).

In the present study, the absorption of temazepam from the GI tract was relatively slow. The time of peak concentration averaged 3 hr after dosage and was not significantly influenced by age or sex.

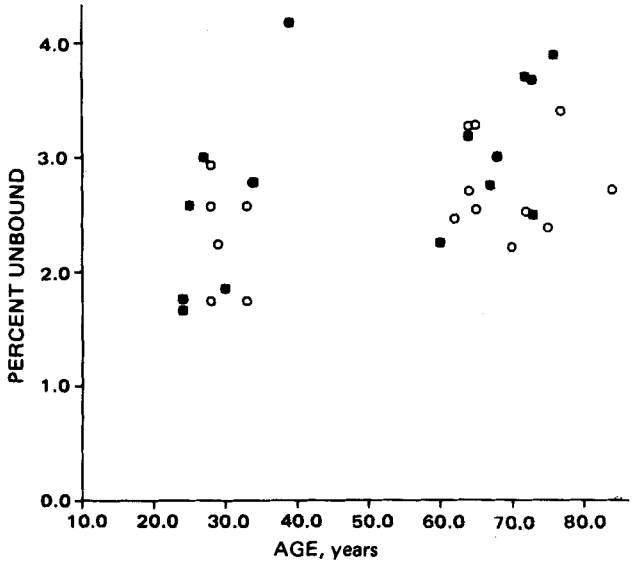

Figure 4—*Relation of age to temazepam protein binding in males and females. Key:* ■, *male* (r = 0.53); *and* O, *female* (r = 0.43).

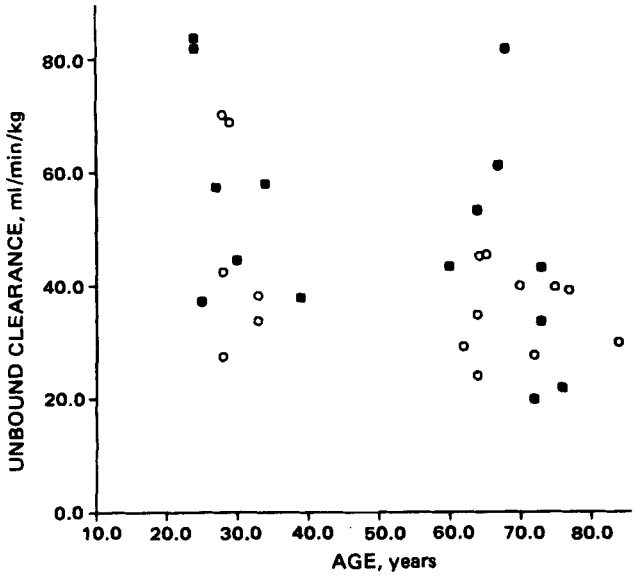

Figure 5—*Relation of age to clearance of unbound temazepam in males and females. Key: ■, male (r = −0.43); and ○, female (r = −0.44).*

The apparent elimination half-life of temazepam was somewhat longer than suggested by previous reports (17, 18). The mean value of $t_{1/2\beta}$ was 14.7 hr (range of 8–38 hr). Women had longer $t_{1/2\beta}$ times than men regardless of age. An essentially identical relation of gender to $t_{1/2\beta}$ was observed in a previous study of oxazepam (16).

The relation of clearance of total temazepam to age and sex also was very similar to that observed with oxazepam. Temazepam clearance was higher in men than in women and was essentially uninfluenced by age. However, the effect of age on clearance of unbound temazepam was partly obscured by an age-related increase in the free fraction. After correction for individual differences in temazepam protein binding, unbound clearance was reduced, but not significantly, in the elderly of both sexes, although it was still higher in men than in women of corresponding age. Neither age nor sex significantly influenced the volume of distribution of total or unbound temazepam, but unbound V_d values tended to be smaller in the elderly than in the young of both sexes.

The effect of age and sex on temazepam distribution and clearance closely resembles the findings of previous studies of oxazepam and lorazepam, two other 3-hydroxy-1,4-benzodiazepines biotransformed by glucuronide conjugation (6, 16). The results contrast strikingly with studies of benzodiazepines transformed by oxidative pathways such as chlordiazepoxide, diazepam, and desmethyldiazepam. Clearance of these compounds declines with increasing age, and the extent of distribution increases with age. For diazepam and desmethyldiazepam, the age-related decline in clearance is more striking in men than in women (8, 13). Distribution of these two compounds is related to sex as well as age, with larger V_d values associated both with increasing age and female sex.

Thus, the relation of age to benzodiazepine disposition is not easily generalized since it may be dependent on the metabolic pathway of the drug in question as well as the gender composition of the study population.

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