REDUCED CLEARANCE OF TRIAZOLAM IN OLD AGE: RELATION TO ANTIPYRINE OXIDIZING CAPACITY

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- 1 Thirty-three healthy male and female volunteers aged 21 to 87 years received a single 0.5 mg oral dose of triazolam. Plasma triazolam concentrations were measured in multiple samples drawn during 24 h after the dose.
- 2 Mean triazolam elimination half-life was not significantly different between young and elderly men (3.0 vs 4.6 h), nor between young and elderly women (2.7 vs 3.2 h).
- 3 However, apparent oral clearance of triazolam was significantly reduced in elderly as compared to young groups of both sexes, leading to higher peak plasma concentrations and increased total area under the curve.
- 4 Values of half-life and clearance of antipyrine, a low-extraction hepatically oxidized compound, were poorly correlated with those of triazolam ($r = 0.34$ and 0.44 , respectively), suggesting different mechanisms controlling age-related changes in clearance of these two hepatically oxidized drugs.

Introduction

Triazolam (Figure 1) is a triazolo benzodiazepine derivative used as a hypnotic agent (Pakes *et al.*, 1981). Its major metabolic pathway involves hepatic oxidation yielding at least two hydroxylated meta-

Figure 1 Structural formula of triazolam.

bolites that are rapidly conjugated and excreted (Eberts *et al.*, 1981). Unlike other benzodiazepines currently marketed as hypnotics, the elimination half-life of triazolam is very short, such that minimal accumulation occurs during multiple-dose therapy.

Elderly individuals commonly experience sleep disorders, and hypnotic agents are often prescribed for this purpose. Previous studies of benzodiazepines biotransformed by oxidative metabolic pathways, including diazepam (Greenblatt *et al.*, 1980a; Ochs *et al.*, 1981), desmethyldiazepam (Allen *et al.*, 1980; Shader *et al.*, 1981) desalkylflurazepam (Greenblatt *et al.*, 1981a), clobazam (Greenblatt *et al.*, 1981b), and alprazolam (Greenblatt *et al.*, 1983b) indicate significantly reduced metabolic clearance and prolonged elimination half-life in elderly as opposed to young male subjects. Age-related changes in metabolizing capacity among women, on the other hand, are small. The present study evaluated possible age-related alterations in the absorption and disposition of triazolam in healthy individuals. Also evaluated was the relation of the kinetic profile of triazolam to that of antipyrine, a marker compound commonly used for evaluation of hepatic drug oxidizing capacity (Stevenson, 1977; Vesell, 1979).

Methods

Subjects

Thirty-three healthy male and female volunteers participated after giving informed consent (Table 1).

Table 1 Effect of age and sex on triazolam kinetics.

	Mean (with range) values for			
	Young male (n = 8)	Young female (n = 8)	Elderly male (n = 9)	Elderly female (n = 8)
<i>Subject characteristics</i>				
Age (years)	26 ^c (23–33)	25 ^c (21–31)	70 ^c (61–78)	72 ^c (65–87)
Weight (kg)	70 ^a (57–80)	57 (48–64)	80 ^a (65–96)	63 (56–82)
<i>Triazolam kinetics</i>				
Peak plasma level (ng/ml)	4.6 (2.4–9.7)	4.1 ^b (2.6–10.4)	6.1 (4.4–8.2)	8.2 ^b (3.8–11.8)
Time of peak level (hours after dose)	1.8 (0.5–4.0)	2.1 ^b (0.5–4.0)	2.5 (0.5–6.0)	0.8 ^b (0.5–1.5)
Elimination half-life (h)	3.0 (1.8–4.4)	2.7 (1.8–3.7)	4.6 (2.1–11.4)	3.2 (2.4–5.2)
Apparent total oral clearance (ml min ⁻¹ kg ⁻¹)	6.2 ^b (3.0–9.7)	8.8 ^c (5.5–11.4)	3.2 ^b (0.9–6.1)	4.1 ^c (1.4–8.6)
Free fraction (% unbound)	21.3 ^a (19.3–26.4)	22.9 (20.4–25.9)	24.7 ^a (20.1–31.0)	22.8 (17.8–27.0)
Student's <i>t</i> -test for young vs elderly of the same sex:				
^a <i>P</i> < 0.05				
^b <i>P</i> < 0.025				
^c <i>P</i> < 0.01				

They were divided into four similarly sized groups of young male, young female, elderly male, and elderly female. Three elderly female and one young male subject were cigarette smokers; all others were non-smokers. Young participants were active, ambulatory, and receiving no other medications. Elderly volunteers also were healthy, active adults in good general health. Two men and two women had cardiovascular disease (ischaemic heart disease or essential hypertension) that was full compensated and stable with the use of oral medications (diuretics in three cases, digoxin and diuretic in one).

Procedure

After an overnight fast, subjects ingested a single 0.5 mg tablet of triazolam with 100–200 ml of tap water. They remained fasting until 3 h after the dose. Venous blood samples were drawn prior to triazolam dosage and at the following post-dosage times: 5, 10, 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 15, 18, and 24 h. Samples were drawn through an indwelling Butterfly cannula (kept patent by slow infusion of physiological saline), or by separate venepuncture, into heparinized (green-top) tubes. Samples were centrifuged, and the plasma separated and frozen until the time of assay.

Twenty-six of the 33 volunteers participated in a study of antipyrine kinetics separated in time from the triazolam study by at least 1 month (Greenblatt *et*

al., 1982b). A single 0.8–1.2 g intravenous dose of antipyrine was administered as a sterile aqueous solution for a period of 5 min into an antecubital vein. Venous blood samples were collected at multiple points in time over the next 24 h. Plasma was separated and frozen until assay.

Analysis of samples

Concentrations of triazolam in all plasma samples were determined by electron-capture gas-liquid chromatography (Greenblatt *et al.*, 1981c). For each subject, the extent of triazolam binding to plasma protein was determined in a single sample drawn in the nonfasting state. Two ml samples were spiked to contain 14 ng/ml of ¹⁴C-triazolam (specific activity: 108 μ Ci/mg). Binding was determined following equilibrium dialysis at 37°C. Each sample was dialyzed in duplicate, with an overall mean deviation between duplicate samples of 3.1%. Binding was concentration independent up to total plasma triazolam concentrations of 10,000 ng/ml (Moschitto & Greenblatt, 1983).

Plasma concentrations of antipyrine in each sample were determined by spectrophotometric assay (Greenblatt & Locniskar, 1979), of which the specificity for intact antipyrine was validated by gas chromatography (Abernethy *et al.*, 1981) and high-pressure liquid chromatography (Greenblatt *et al.*, 1983a).

Kinetic and statistical analysis

Plasma triazolam concentrations were analyzed by iterative nonlinear least-squares regression techniques previously described in detail (Greenblatt *et al.*, 1980b). The exponent (beta) corresponding to the terminal elimination phase of the plasma concentration curve was used to calculate the apparent elimination half-life. Area under the plasma concentration curve up to the final detectable plasma concentration was determined by the trapezoidal method; to this was added the residual area extrapolated to infinity, calculated as the final detectable concentration divided by beta, yielding the total area under the plasma concentration curve (AUC). Apparent total oral clearance of triazolam was calculated as administered dose divided by AUC, assuming 100% absorption.

Post-infusion plasma antipyrine concentrations

were fitted by computer to a linear sum of exponential terms. Exponents and infusion-corrected coefficients were used to calculate antipyrine elimination half-life and total clearance.

Statistical methods included Student's *t*-test and linear regression analysis.

Results

Peak plasma triazolam concentrations were higher in elderly than in young individuals. Among women, the difference reached significance (8.2 vs 4.1 ng/ml, $P < 0.025$). The overall time of peak concentration was 1.8 h after dosage. There were no significant differences in peak time between young and elderly males; however, peak times were significantly earlier in elderly as opposed to young female subjects (Table 1).

Figure 2 Plasma triazolam concentrations, and pharmacokinetic functions, following single 0.5 mg oral doses administered to four representative volunteers.

Triazolam elimination half-life did not differ significantly between young and elderly groups of either sex (Table 1, Figures 2, 3 and 4). With the exception of one elderly male subject, triazolam elimination half-life was less than 5.2 h. The long half-life value in a single elderly male volunteer (Figure 3) was not explained by any apparent unusual demographic characteristics of this subject.

Figure 3 Plasma triazolam concentrations following oral administration of a 0.5 mg dose to an elderly volunteer having an 'outlying' value of half-life ($t_{1/2,z} = 11.4$ h).

Although elimination half-life did not differ among groups, total AUC for triazolam was significantly increased in elderly as opposed to young subjects for both sexes, yielding significantly reduced values of apparent total oral clearance in elderly volunteers (Table 1, Figure 5). This was also true after correction for body weight, which increased with age.

Triazolam free fraction averaged 23% of the total plasma concentration. Free fraction increased slightly although significantly with age in men, and was unrelated to age in women (Table 1).

The effects of age on the disposition of antipyrine are described elsewhere (Greenblatt *et al.*, 1982b). Elimination half-life of antipyrine was not significantly correlated with that of triazolam (Figure 6). Clearance of antipyrine and triazolam likewise were poorly correlated ($r = 0.44$), although the correlation was statistically significant ($P < 0.05$).

Figure 4 Elimination half-life of triazolam in relation to age and sex. Individual and mean ($\pm$ s.e. mean) values are shown. See Table 1 for statistical analysis.

Discussion

The pharmacokinetic profile of triazolam in humans indicates that its elimination half-life is considerably more rapid than other currently marketed benzo-

Figure 5 Apparent oral clearance of triazolam in relation to age and sex. Individual and mean ($\pm$ s.e. mean) values are shown. See Table 1 for statistical analysis.

Figure 6 Relation of antipyrine elimination half-life (left) and total clearance (right) to corresponding values of triazolam half-life and clearance in the same individuals. The half-life correlation was not significant; the correlation of clearance values reached significance ($P < 0.05$). (■) = young male; (○) = young female; (▲) = elderly male; (◇) = elderly female.

diazepines. Since intravenous dosage pharmacokinetic studies are not yet available, the total metabolic clearance of triazolam is not established. However, previous studies of other benzodiazepines including chlordiazepoxide (Greenblatt *et al.*, 1978), diazepam (Divoll *et al.*, 1983), and lorazepam (Greenblatt *et al.*, 1979a, 1979b, 1982c) indicate that absorption after oral administration is consistently 100% complete, even in the elderly. Under the assumption that triazolam behaves similarly, we calculated values of apparent oral clearance for triazolam. The findings of the present study indicated that triazolam half-life was not influenced by age, but total AUC was significantly increased in elderly as opposed to young volunteers of both sexes. Accordingly, peak plasma concentrations were higher in the elderly group, and calculated total oral clearance significantly reduced. These age-related differences are probably explained by reduced hepatic oxidizing capacity in the elderly, and possibly by an age-related reduction in hepatic blood flow (Greenblatt *et al.*, 1982a; Wood *et al.*,

1979; Vestal, 1982; Wilkinson & Shand, 1975). On the average, AUC in the elderly group was approximately twice that in the young controls despite administration of the same dose. The findings provide a kinetic rationale for the recommendation that the initial hypnotic dose of triazolam in elderly individuals with insomnia should be approximately half that anticipated for a young person of similar weight.

Previous studies of intravenous antipyrine have demonstrated a reduction in hepatic oxidizing capacity with age (O'Malley *et al.*, 1971; Liddel *et al.*, 1975; Vestal *et al.*, 1975; Wood *et al.*, 1979; Bach *et al.*, 1981). In the study from our laboratory (Greenblatt *et al.*, 1982b), the impairment of antipyrine clearance with age was relatively gender-specific, with greater age-related clearance reductions observed in men than in women. Furthermore, a given individual's ability to oxidize antipyrine, based on pharmacokinetically-determined elimination half-life or total clearance, was correlated with the same person's capacity to biotransform a number

of other oxidatively metabolized benzodiazepines (Greenblatt *et al.*, 1982b, 1983a). In the present study, however, age-related reductions in triazolam clearance were similar in men and in women, and there was poor correlation of triazolam half-life and clearance with those of antipyrine. Thus the antipyrine test has very limited value for identification of persons with high or low values of triazolam clearance, possibly because triazolam disposition may depend in part on hepatic blood flow as well as microsomal oxidizing capacity.

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