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Population study of triazolam pharmacokinetics

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1 The kinetics of a single 0.5 mg oral dose of the triazolobenzodiazepine hypnotic triazolam, were studied in 54 healthy young men aged 20–44 years, with a mean body weight of 77 kg. Triazolam kinetics were determined from multiple plasma concentrations measured during 14 h post-dose.

2 The overall mean ± s.e. mean (with range) kinetic variables were: peak plasma concentration, 4.4 ± 0.3 (1.7–9.4) ng ml^{-1}; time of peak, 1.3 ± 0.1 (0.5–4.0) h after dose; elimination half-life, 2.6 ± 0.1 (1.1–4.4) h; total AUC: 19.1 ± 1.1 (4.4–47.7) ng ml^{-1} h; oral clearance, 526 ± 38 (175–1892) ml min^{-1}.

3 All kinetic variables were consistent with Poisson distributions, based on the Kolmogorov-Smirnov Goodness of Fit test. None of the variables fit normal distributions. Four of five were consistent with a log normal distribution.

4 Peak plasma level was highly correlated with clearance ($r = -0.85$, $P < 0.0001$), and AUC ($r = 0.85$, $P < 0.0001$) but not with body weight ($r = 0.21$, NS). Clearance and body weight were not correlated ($r = -0.01$).

5 Triazolam clearance may vary widely even within a homogeneous group of healthy young men.

Keywords triazolam pharmacokinetics hypnotic benzodiazepines

Introduction

Inferences regarding the distribution of pharmacokinetic properties of drugs among large populations are usually based on detailed kinetic studies of small numbers of subjects, or on statistical analysis of a limited number of plasma concentrations measured in a larger group of patients (Beal & Sheiner, 1982, 1985; Sheiner *et al.*, 1979). However it is seldom possible to directly validate these inferences because of the need to undertake actual pharmacokinetic studies in large numbers of subjects or patients. The present study evaluated the pharmacokinetic profile of triazolam, a triazolobenzodiazepine in clinical use as a hypnotic (Roth *et al.*, 1983), in a group of 54 healthy young males. This sample size was sufficient to characterize the non-Gaussian nature of each kinetic parameter.

Methods

Subjects

Fifty-four healthy male volunteers participated after giving written informed consent. All were healthy active ambulatory adults with no evidence of medical disease and taking no other medications. Mean ± s.e. mean (with range) values of their demographic characteristics were: age: 28.6 ± 0.9 (20–44) years; body weight: 76.7 ±

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1.2 (58.1–100.7) kg; height: 176 ± 1 (165–193) cm. Prior to participation in the study, each subject had a pre-dosage sample analyzed by electron-capture gas liquid chromatography to exclude the presence of benzodiazepines.

Design and procedure

Each subject received a single 0.5 mg oral dose of triazolam with 100–200 ml of tap water after an overnight fast. They resumed a normal diet at 3 h after dosage. Venous blood samples were drawn into heparinized tubes prior to the dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, and 14 h after dosage. Blood samples were centrifuged and the plasma separated and frozen at −20° C until the time of assay.

Analysis of samples

Two ml of plasma, containing 10 ng of the triazolobenzodiazepine analogue U-31485 as internal standard, were extracted at neutral pH into 2 ml benzene:isoamyl alcohol (98.5:1.5). Following vortexing and centrifuging, the organic layer was evaporated to dryness in a 2 ml Wheaton automatic sampling vial and reconstituted with 0.2 ml toluene:isoamyl alcohol (85:15). Six microliters were autoinjected and analyzed by electron-capture gas chromatography (Hewlett-Packard Model 5840A) on a 1.22 meter × 44 mm 10% OV-101 80/100 mesh Chromosorb WHP column (Greenblatt *et al.*, 1981; Scavone *et al.*, 1986). Carrier gas was argon:methane (95:5) at a flow rate of 50 ml min^{-1}. Operating temperatures were: injection port, 310° C; column, 275° C; and detector, 310° C. The column was initially primed with asolectin. Standard curves were prepared by similar extraction from drug-free plasma, to which known concentrations of triazolam (0.5 to 10 ng ml^{-1}) were added.

Pharmacokinetic analysis

The slope of the terminal log-linear phase of the plasma concentration curve was determined by linear regression analysis (Greenblatt & Koch-Weser, 1975). This was used to calculate the apparent elimination half-life. Area under the plasma concentration curve up to the last detectable plasma concentration was determined by the linear trapezoidal method. To this was added the residual area extrapolated to 'infinity', calculated as the last detectable concentration divided by the terminal slope, yielding the total area under the plasma concentration curve. Oral clearance was calculated as the administered dose of triazolam (0.5 mg) divided by total area under the curve.

Statistical analysis

The data for each kinetic variable were stratified into frequency distributions for a series of 7 to 12 discrete intervals. Based on the Gaussian, log-Gaussian, and Poisson statistical distributions, the expected frequency within each interval was calculated. The Komolgorov–Smirnov Goodness of Fit test was used to evaluate the significance of the divergence between the observed and theoretical distributions (Siegel, 1956). Also calculated was the sample estimate of the coefficient of skewness (Snedecor & Cochran, 1980).

Results

Figure 1 shows the overall mean plasma triazolam concentrations at each point in time.

Each pharmacokinetic variable distribution pattern departed significantly from a Gaussian distribution ($P < 0.05$ in every case). The coefficient of skewness was highly significant for all variables except elimination half-life (Table 1). Peak plasma concentration, elimination half-life, area under the curve and clearance were also consistent with a log-Gaussian distribution,

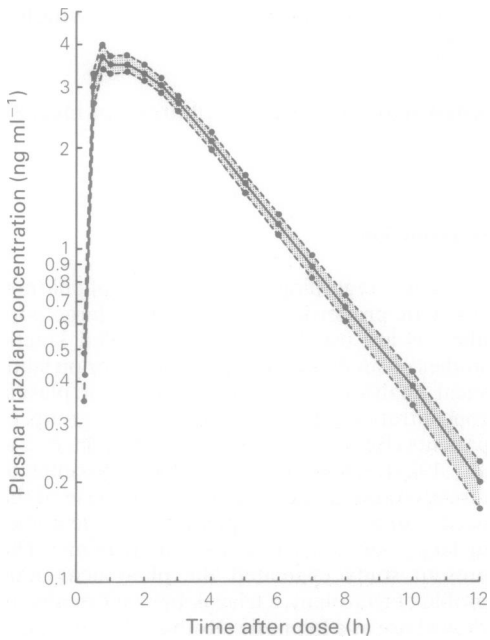

Figure 1 Mean plasma triazolam concentrations following the 0.5 mg oral dose. Each point is the mean value for all 54 subjects at each corresponding time. Shaded area indicates ± 1 s.e. mean at each point.

Table 1 Kinetic variables for triazolam

	Mean	*Median*	*s.d.*	*Range*	*Coefficient of skewness*
Peak plasma concentration (ng ml^{-1})	4.41	4.34	1.84	1.67–9.39	0.76[a]
Time of peak concentration (h after dose)	1.30	1.00	0.81	0.5–4.0	1.50[a]
Elimination half-life (h)	2.56	2.40	0.81	1.13–4.44	0.45[b]
Total area under plasma concentration curve (ng ml^{-1} h)	19.1	18.1	8.1	4.4–47.7	1.11[a]
Oral clearance (ml min^{-1})	526	462	279	175–1892	2.56[a]

[a] $P < 0.01$, [b] $P > 0.05$

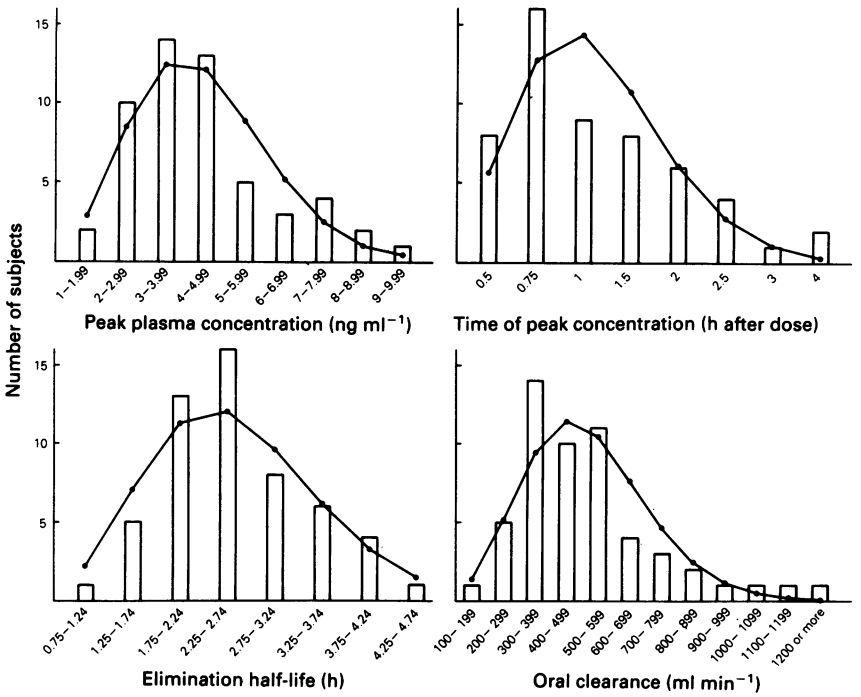

Figure 2 Frequency distributions of four of the pharmacokinetic variable. The bars indicate actual frequencies in the indicated intervals. Points connected by solid lines are the expected values for that interval based on the Poisson distribution. In no case was there a significant difference between observed and expected frequency (see text).

but peak time departed significantly ($P < 0.05$) from a log-Gaussian distribution. However, all pharmacokinetic variables were consistent with a Poisson distribution (Figure 2).

Body weight was not correlated with area under the curve ($r = 0.05$, NS), clearance ($r = 0.01$, NS), or peak plasma concentration ($r = 0.21$, NS). However the log of peak plasma concentration was highly correlated with the log of area under the curve ($r = 0.85$, $P < 0.0001$) and log of clearance ($r = -0.85$, $P < 0.001$).

Discussion

The present study evaluated the kinetic profile of triazolam, a triazolobenzodiazepine biotrans-

formed mainly by hepatic microsomal oxidation (Eberts *et al.*, 1981) following a single 0.5 mg oral dose administered to a group of 54 healthy young males. Consistent with earlier reports (Greenblatt *et al.*, 1983; Abernethy *et al.*, 1984; Scavone *et al.*, 1986; Smith *et al.*, 1983), triazolam had a relatively short half-life (mean: 2.6 h), and a mean oral clearance of 526 ml min^{-1}. Clearance varied widely among individuals, with a range of more than tenfold.

The distribution of each kinetic parameter, with the exception of elimination half-life, was significantly skewed, and all departed significantly from a Gaussian distribution. However all variables were consistent with the Poisson distribution, and four were consistent with log-Gaussian distributions. Other investigators using statistical procedures have estimated population characteristics of pharmacokinetic parameters (Beal & Sheiner, 1982, 1985; Sheiner *et al.*, 1979). Many of these simulations have assumed that the population parameters were consistent with log-Gaussian distributions. If triazolam is representative of other drugs, the validity of this approach may be justified. It might also be useful if simulations using alternative distributions such as Poisson were examined.

The high negative correlation observed between peak plasma concentration and clearance of triazolam suggests that oral clearance may be predicted from peak level following a single oral dose. Likewise, maximum pharmacodynamic effects, coincident with peak drug levels, may be inversely proportional to clearance. Such relationships may hold for oral administration of other high clearance drugs with short half-lives (Friedman *et al.*, 1986).

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