Effects of end stage renal disease and aluminium hydroxide on triazolam pharmacokinetics

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Triazolam 0.5 mg was administered to 11 dialysis patients and 11 age, weight and sex matched controls. Peak plasma concentrations ($C_{\max}$) were higher in control subjects, but there were no other differences between the groups. When dialysis patients took triazolam with 3600 mg aluminium hydroxide suspension, $C_{\max}$ and AUC were increased into the range observed in control subjects. It appears that triazolam can be used at normal doses in patients with renal dysfunction, without regard to interaction with aluminium hydroxide gel, or to alterations in elimination.

Keywords triazolam aluminium hydroxide renal disease pharmacokinetics

Introduction

Triazolam is a relatively new benzodiazepine which is approved for short term treatment of insomnia. Like other benzodiazepines, triazolam is metabolized in the liver (Eberts *et al.*, 1981). It is generally proposed that drugs which are metabolized to inactive forms can be administered in normal doses to patients with chronic renal failure. However, the pharmacokinetics of triazolam in renal failure have not been determined.

Most dialysis patients must take aluminium hydroxide preparations to reduce absorption of dietary phosphate. Previously, antacids have been shown to delay or decrease the absorption of chlordiazepoxide (Greenblatt *et al.*, 1976) and diazepam (Greenblatt *et al.*, 1978). Since delayed absorption of a hypnotic may result in a decreased therapeutic effect, we evaluated the effect of aluminium hydroxide on triazolam pharmacokinetics in a group of dialysis patients. We also evaluated triazolam pharmacokinetics in a group of age and weight matched control subjects so that the effect of end stage renal disease on single dose triazolam kinetics could be determined.

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Methods

Eleven dialysis patients between 18 and 73 years of age gave written informed consent to participate in this two phase study. The protocol and consent form were approved by the Institutional Review Board of the University of Pittsburgh. Seven of the subjects were maintained on haemodialysis (HD) and four on continuous ambulatory peritoneal dialysis (CAPD). Eleven volunteers who were age, weight and sex matched to the dialysis subjects were also selected.

At approximately 08.00 h, after a 12 h fast, a single dose of triazolam 0.5 mg was administered with either 120 ml water or 120 ml water plus 3600 mg aluminium hydroxide gel (AHG). The dose was followed by a 4 h fast. With the exception of AHG administered as part of the study, antacid preparations were withheld during the 12 h before and after study drug administration. Other chronic medications were administered

4 h after the study dose. Blood samples of 5 ml each were obtained at 0 h (just prior to the dose), 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3, 4, 6, 8, 12, 16 and 24 h after drug administration.

Dialysis subjects participated in both the triazolam and triazolam plus aluminium hydroxide (TR + AHG) treatments which were separated by 1 week. Control subjects participated only in the triazolam treatment. Haemodialysis subjects were evaluated on an off-dialysis day, at least 10 h following the last dialysis. In order to determine the effect of routine peritoneal dialysis on drug elimination, aliquots of dialysis fluid outflow were obtained from all CAPD patients.

Triazolam concentrations were determined by a modification of the electron-capture gas chromatographic method of Greenblatt *et al.* (1981). Because plasma samples from the dialysis patients contained unidentified compounds which interfered with the assay, two cleanup steps were added. After mixing and centrifuging 2 ml of sample with 6 ml of 1.5% iso-amyl alcohol in toluene, the organic layer was transferred to a tube containing 1 ml of 0.1 N sulphuric acid. This was mixed for 15 s and centrifuged for 2 min at 2000 rev/min. The aqueous layer was removed and discarded. Sodium carbonate (1 ml, 0.5 M) was added to the organic portion, the mixture was vortexed, centrifuged, and the organic layer

transferred to a siliconized 10 ml conical centrifuge tube. Samples were placed in a 55°C water bath and evaporated to dryness under nitrogen. To each tube, 50 µl of 1.5% iso-amyl alcohol in toluene and 5 µl of purified soy phosphatides (Asolectin) in benzene were added. The triazolam standard, controls, blanks, and patient samples were all prepared by this same procedure. The prepared samples were assayed with a Hewlett-Packard 5713 gas chromatograph with a linearized electron capture detector. Because of the range of concentrations over which triazolam was measured, two sets of standard curves (0 to 2.0 ng/ml and 2.0 to 20.0 ng/ml) were constructed each time the assay was performed. The coefficient of variation of the triazolam assay for the low and high curves combined was 8.7%. The lower limit of the assay was 0.2 ng/ml using a 2 ml sample. A triazolobenzodiazepine analogue, U-31485, was used as the internal standard.

Data analysis

Pharmacokinetic parameters were determined by standard methods (Gibaldi & Perrier, 1982). The effect of renal disease on the pharmacokinetics of triazolam was determined by one way analysis of variance of control and dialysis subject data. The effect of AHG on triazolam kinetics in dialysis patients was determined by two-way analysis of variance, since subjects served as their own controls.

Results

Peritoneal dialysis had a limited effect on the removal of triazolam from plasma, removing 0 to 3.4 µg in the 24 h following the dose. This represents a mean of only 0.23% of the administered dose. Furthermore, there were no differences between HD and CAPD patients in triazolam pharmacokinetic parameter estimates. Thus, data from the two dialysis groups were pooled for the comparison with control subjects.

Plots of mean plasma concentrations are presented in Figure 1. Mean triazolam pharmacokinetic parameter estimates for control and dialysis subjects are presented in Table 1. There were no differences between control and dialysis subjects in time to peak concentration (t_{max}) or elimination rate constant (k_e). However, peak concentration (C_{max}) was significantly higher in the control population. Although AUC_{0-8} and $AUC_{0-\infty}$ tended to be higher in the control group, the differences were not statistically significant ($P = 0.0549$, $P = 0.2014$, respectively).

Pharmacokinetic parameter estimates for the triazolam + AHG treatment in dialysis subjects

Figure 1 Mean triazolam plasma concentrations ($\pm$ s.e. mean) observed in control ($\square$) and dialysis ($\bullet$) subjects after a single triazolam 0.5 mg oral dose and in dialysis patients after triazolam 0.5 mg plus aluminium hydroxide gel 3600 mg ($\circ$).

are also presented in Table 1. There were no differences between the triazolam and triazolam + AHG treatments in $t_{\max}$ or $t_{1/2,z}$. However, after triazolam + AHG, $C_{\max}$ was approximately 1.5 times that observed following triazolam alone; AUC_{0-8} and $AUC_{0-\infty}$ were also higher following triazolam + AHG.

Discussion

Had we simply compared the triazolam treatments in control and dialysis subjects (without AHG administration), we might have suggested that the relatively low peak concentrations in dialysis subjects were explained by either an increased apparent volume of distribution or by impaired absorption due to food or concurrent medications. However, none offers adequate explanation. We evaluated protein binding and found that the mean percent free triazolam in dialysis patient plasma was 9.9%, the same as in control subjects (Kroboth *et al.*, 1984). Therefore, altered volume of distribution due to decreased protein binding does not seem to explain the low peak concentrations. Furthermore, since the same protocol was followed for both the triazolam and triazolam + AHG treatments, food or concurrent medications are also not likely explanations.

However, higher serum gastrin concentrations and basal gastric acid secretion have been

observed in azotemic patients compared to control subjects (Gedde-Dahl & Flatmark, 1975). Therefore gastrointestinal changes due to renal disease may be a plausible explanation for the $C_{\max}$ difference between control and dialysis subjects. This is especially true in view of the chemical characteristics of triazolam.

At a pH less than 4, triazolam undergoes rapid reversible acid hydrolysis and cleavage of the azo-methine bond resulting in an open ring inactive structure (Konishi *et al.*, 1982). Solution pH determines the relative amounts of triazolam and the open ring moiety at equilibrium. At a pH above 5, little hydrolysis occurs and the mixture contains more than 99% closed ring triazolam. The lower the pH, the more rapid the hydrolysis reaction, and the higher the concentration of the open ring benzophenone. Although the reaction is reversible, the half-time of cyclization which results in reformation of the closed ring triazolam is about 80 min (Konishi *et al.*, 1982). If absorbed in the open ring form, metabolism can occur directly, without cyclization to triazolam. This effectively reduces systemic availability of triazolam.

We postulate that a relatively high basal gastric acid secretion in our dialysis patient population resulted in formation of the open ring structure, decreasing the bioavailability of triazolam when taken alone. The 3600 mg dose of aluminium hydroxide (AlternaGel) administered in this study is approximately equivalent in acid neutralizing capacity to 27 ml Mylanta® or 56 ml

Table 1 Triazolam pharmacokinetic parameter estimates* observed in control and in dialysis subjects

	Control subjects	Dialysis subjects	
	Triazolam	Triazolam	Triazolam plus aluminium hydroxide gel
$C_{\max}$ (ng/ml)	6.53 ± 1.70 (3.50–9.30)	4.04 ± 1.83 ¹ (1.55–8.42)	6.44 ± 4.08 (2.14–17.0)
$t_{\max}$ (h)	1.34 ± 1.04 (0.5–4.0)	1.25 ± 0.95 (0.5–3.0)	1.16 ± 1.04 (0.5–4.0)
$t_{1/2,z}$ (h)**	2.60 (1.68–5.17)	2.29 (1.41–5.73)	2.27 (1.55–4.81)
AUC_{0-8} (ng ml ⁻¹ h)	27.2 ± 9.6 (15.9–44.2)	17.4 ± 12.7 ² (3.6–77.8)	23.5 ± 15.9 (8.5–67.4)
$AUC_{0-\infty}$ (ng ml ⁻¹ h)	33.9 ± 16.2 (16.7–72.0)	23.2 ± 21.6 ² (3.8–77.8)	29.6 ± 24.7 (8.9–98.5)
Apparent oral clearance (ml min ⁻¹ kg ⁻¹)**	3.50 (1.41–8.58)	5.50 (1.45–31.2)	4.07 (1.16–13.3)

*Mean ± s.d. and range of values are presented.

**Mean values for half-life and apparent oral clearance are harmonic means.

¹Statistically different from control subjects ($P = 0.0036$) and from triazolam + AHG treatment in dialysis patients ($P = 0.0079$).

²Statistically different from triazolam + AHG treatment in dialysis patients ($P = 0.006$).

Amphojel® (Anon., 1982), and could be expected to raise gastric pH, limiting the extent of triazolam hydrolysis.

Our observations and hypothesis parallel those of Elwood *et al.* (1983), who reported that ranitidine increased the bioavailability of midazolam, a benzodiazepine also subject to benzophenone formation. When Abernethy *et al.* (1983) evaluated the effect of cimetidine on triazolam kinetics, they found that cimetidine did not alter half-life, but tended to increase the peak concentration, while significantly increasing area under the curve. Although they attributed this to decreased first pass effect, their findings are consistent with our hypothesis of increased pH and decreased triazolam hydrolysis.

In conclusion, renal disease does not affect triazolam elimination. When triazolam is administered either with water or with AHG, it is rapidly absorbed, with no difference in $t_{\max}$. Aluminium hydroxide gel enhances the absorption of triazolam in dialysis patients. Since concentrations were increased with coadministration

of AHG into the range observed in control subjects but not beyond, dosage adjustment in renal disease does not seem warranted. Based on the $t_{\max}$ and $t_{1/2,z}$ observed in dialysis patients, approximately eight to nine half-lives would elapse before administration of a subsequent dose, and accumulation would not be expected. The results of the present single dose study suggest that triazolam may be used at normal doses in patients with renal dysfunction, without regard to interaction with the phosphate binding antacid, aluminium hydroxide, or to alterations in elimination.

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