DIAZEPAM KINETICS IN PATIENTS WITH RENAL INSUFFICIENCY OR HYPERTHYROIDISM

HERMANN R. OCHS¹, DAVID J. GREENBLATT², H.J. KASCHELL¹, U. KLEHR¹, MARCIA DIVOLL² & DARRELL R. ABERNETHY²

¹Medizinische Universitätsklinik, Bonn-Venusberg, West Germany and

²Division of Clinical Pharmacology, Tufts-New England Medical Center, Boston, MA.

1 Eight patients with end-stage renal insufficiency on maintenance haemodialysis, and seven patients with newly diagnosed hyperthyroidism, received a single intravenous dose of diazepam, followed by blood sampling over the next 7 days. Fifteen healthy volunteer controls, matched with patients for age and sex, were similarly studied.

2 Diazepam half-life in renal failure patients (mean 37 h) was greatly reduced compared to controls (mean 92 h, $P < 0.05$) and clearance of total (free plus bound) diazepam correspondingly increased ($0.94 \pm 0.34 \text{ ml min}^{-1} \text{ kg}^{-1}$, $P < 0.01$).

2 However, differences were largely related to disease-related changes in drug binding and distribution. Mean unbound fraction of diazepam in plasma of renal patients (7.0%) was greatly increased over controls (1.4%, $P < 0.01$) and V_d of unbound diazepam greatly reduced ($57 \pm 157 \text{ l/kg}$, $P < 0.01$).

4 Clearance of pharmacologically active unbound diazepam (intrinsic clearance) was not significantly different between renal patients and controls ($23 \pm 30 \text{ ml min}^{-1} \text{ kg}^{-1}$).

5 None of the kinetic variables for total or unbound diazepam in thyrotoxic patients differed significantly from those in controls matched for age and sex.

6 End-stage renal failure (or its associated drug therapy) alters diazepam protein binding and distribution, but does not significantly change clearance of unbound drug. Thyrotoxicosis does not influence diazepam kinetics.

Introduction

Diazepam often is used clinically to treat anxiety and insomnia in patients with renal insufficiency or thyroid disease. Changes in diazepam disposition associated with these diseases may lead to alterations in clinical effects unless doses are appropriately adjusted. The present study assessed the kinetics of intravenous diazepam in a series of patients with end-stage renal insufficiency or with newly diagnosed hyperthyroidism.

Methods

Subjects and procedure

Eight patients with advanced renal insufficiency (Table 1) and seven patients with newly diagnosed hyperthyroidism (Table 2) participated after giving informed consent. The mean plasma creatinine of the patients with renal failure was 9.5 mg/100 ml , and all

were receiving twice weekly maintenance haemodialysis. Patients were taking concurrent medications for the treatment of medical complications of renal insufficiency (hypertension, hyperphosphataemia). Hyperthyroid patients had newly diagnosed disease. Their mean serum thyroxine concentration (by radioimmunoassay) was $15.4 \mu\text{g/100 ml}$, and the mean free T3 concentration was 356 ng/100 ml .

All patients received a single 5–10 mg dose of diazepam intravenously. Multiple venous blood samples were drawn during the first 24 h after dosage, then every 24 to 48 h for up to 7 days after the dose. Samples were not drawn from renal patients concurrent with haemodialysis. Hyperthyroid patients participated in the diazepam study early in the course of diagnostic evaluation. Since antithyroid medication was not begun until at least 5 days after diazepam dosage, patients were clinically hyperthyroid throughout the study.

A study of intravenous diazepam was performed

Table 1 Diazepam kinetics in patients with renal insufficiency (mean $\pm$ s.e. mean)

	Controls (n = 8)	Patients (n = 8)	Value of Student's t
<i>Characteristics</i>			
Age (years)	50.4 ($\pm$ 6.9)	48.8 ($\pm$ 6.7)	0.17 (NS)
Males/Females	4/4	4/4	—
Weight (kg)	69.9 ($\pm$ 3.0)	62.8 ($\pm$ 4.2)	1.10 (NS)
Plasma albumin (g/100 ml)	4.3 ($\pm$ 0.3)	4.0 ($\pm$ 0.3)	0.82 (NS)
Plasma creatinine (mg/100 ml)	1.0 ($\pm$ 0.1)	9.5 ($\pm$ 1.1)	8.0 ($P < 0.001$)
<i>Kinetics of total (free plus bound) diazepam</i>			
V_d (l/kg)	2.1 ($\pm$ 0.3)	2.8 ($\pm$ 0.4)	1.21 (NS)
$T_{1/2}$ (h)	92.4 ($\pm$ 22.5)	36.6 ($\pm$ 6.7)	2.38 ($P < 0.05$)
Clearance (ml min ⁻¹ kg ⁻¹)	0.34 ($\pm$ 0.06)	0.94 ($\pm$ 0.15)	3.84 ($P < 0.005$)
<i>Kinetics of unbound diazepam</i>			
Unbound fraction (%)	1.44 ($\pm$ 0.14)	6.97 ($\pm$ 1.52)	3.63 ($P < 0.005$)
Unbound V_d (l/kg)	157 ($\pm$ 22)	57 ($\pm$ 14)	3.85 ($P < 0.005$)
Unbound clearance (ml min ⁻¹ kg ⁻¹)	29.5 ($\pm$ 9.5)	23.0 ($\pm$ 8.4)	0.52 (NS)

identically in a series of 15 healthy volunteer controls recruited from the general population of healthy ambulatory adults and matched with patients for age and sex. Control subjects had normal renal function and were clinically euthyroid.

Data analysis

Concentrations of diazepam and its major metabolite, desmethyldiazepam, in all plasma samples were determined by electron-capture gas-liquid chromatography (Greenblatt, 1978). A linear sum of exponential terms was fitted by computer to the plasma drug concentrations using iterative nonlinear least-squares regression techniques (Ochs *et al.*, 1978). Coefficients and exponents from the fitted function were used to calculate diazepam volume of distribution using the area method (V_d), half-life of

elimination during the terminal or beta phase ($T_{1/2}$), and total clearance. The extent of diazepam binding to plasma protein for each subject was determined by equilibrium dialysis (Greenblatt *et al.*, 1980; Woo & Greenblatt, 1979). Values of V_d and clearance were corrected for individual differences in binding, yielding corresponding values of unbound V_d and unbound clearance.

Difference between patients and controls were analysed using Student's *t*-test.

Results

Diazepam disposition in all subjects was adequately described by a linear sum of 2 or 3 exponential terms (Figure 1). Disappearance of diazepam was always mirrored by formation of its metabolic product,

Table 2 Diazepam kinetics in patients with hyperthyroidism (mean $\pm$ s.e. mean)

	Controls (n = 7)	Patients (n = 7)	Value of Student's t
<i>Characteristics</i>			
Age (years)	57.7 ($\pm$ 6.8)	55.6 ($\pm$ 6.8)	0.22 (NS)
Male/Female	1/6	1/6	—
Weight (kg)	64.3 ($\pm$ 5.8)	66.0 ($\pm$ 4.8)	0.22 (NS)
Plasma albumin (g/100 ml)	4.1 ($\pm$ 0.2)	4.1 ($\pm$ 0.2)	0.17 (NS)
<i>Kinetics of total (free plus bound) diazepam</i>			
V_d (l/kg)	2.0 ($\pm$ 0.2)	2.6 ($\pm$ 0.5)	1.16 (NS)
$T_{1/2}$ (h)	63.3 ($\pm$ 14.1)	77.1 ($\pm$ 12.0)	0.74 (NS)
Clearance (ml min ⁻¹ kg ⁻¹)	0.47 ($\pm$ 0.08)	0.43 ($\pm$ 0.07)	0.32 (NS)
<i>Kinetics of unbound diazepam</i>			
Unbound fraction (%)	1.35 ($\pm$ 0.16)	1.59 ($\pm$ 0.15)	1.07 (NS)
Unbound V_d (l/kg)	163 ($\pm$ 19)	165 ($\pm$ 24)	0.07 (NS)
Unbound clearance (ml min ⁻¹ kg ⁻¹)	39.5 ($\pm$ 8.8)	27.3 ($\pm$ 4.3)	1.24 (NS)

Figure 1 Plasma concentrations of diazepam (■) and its major metabolite, desmethyldiazepam (○), in a patient with renal insufficiency and in a healthy volunteer control subject matched for age and sex. Solid line represents the pharmacokinetic functions for diazepam determined by nonlinear least-squares regression analysis.

desmethyldiazepam. However, the duration of sampling was not sufficient for formal kinetic analysis of the metabolic product.

Renal insufficiency

Patients and normal controls were comparable with respect to age, sex, and body weight (Table 1). Plasma albumin concentrations tended to be lower in renal patients, but the difference was not significant.

Diazepam disposition based on total (free plus bound) plasma concentrations differed between patients and controls (Table 1). Mean V_d was larger in patients (2.8 ± 2.1 l/kg), but the difference was not significant. However, $T_{1/2}$ was considerably shorter in patients (37 ± 92 h, $P < 0.05$), and total clearance higher (0.94 ± 0.34 ml min⁻¹ kg⁻¹, $P < 0.005$). These differences were explained largely by the greatly reduced extent of diazepam protein binding in renal insufficiency patients. The unbound fraction averaged 7% in patients, as opposed to 1.4% in controls ($P < 0.005$). After correction for individual

differences in binding, unbound V_d was smaller in patients than in controls ($P < 0.005$), whereas unbound clearance did not differ significantly between the two groups.

Hyperthyroidism

Patients and controls were comparable with respect to age, sex, body weight and albumin concentration (Table 2). There were no significant differences between patients and controls in any of the kinetic variables for total (free plus bound) diazepam. The unbound fraction for diazepam was similar between groups ($1.4 \pm 1.6\%$). After correction for individual differences in binding, there still were no significant differences between patients and controls in unbound V_d or unbound clearance (Table 2).

Discussion

The major metabolic pathway of diazepam in humans involves hepatic *N*-demethylation, yielding desmethyldiazepam (Greenblatt *et al.*, 1980). Since the kidney does not play a role in diazepam biotransformation, hepatic clearance of diazepam should not be altered by renal insufficiency unless renal disease as such influences hepatic function. Comparison of diazepam kinetics in patients with end-stage renal insufficiency versus healthy controls matched for age and sex indicated that clearance of unbound diazepam in fact did not differ significantly between groups. Thus steady-state concentrations of unbound diazepam at any given daily dose on the average should be similar between patients with renal insufficiency and healthy individuals of similar age, sex, and body weight. The similarity in clearance of unbound diazepam between the two groups, however, was obscured by the large difference in diazepam protein binding. The kinetics of total (free plus bound) diazepam indicated higher values of total clearance in patients as opposed to controls, incorrectly suggesting that larger doses may be required by renal insufficiency patients to produce equivalent plasma concentrations. As in the case of many drugs (Reidenberg, 1976; Reidenberg *et al.*, 1971; Gugler *et al.*, 1975), renal insufficiency is associated with greatly reduced binding of diazepam to plasma protein (Sjoholm *et al.*, 1976; Kangas *et al.*, 1976; Kober *et al.*, 1979; Abel *et al.*, 1979). Thus meaningful comparison of diazepam kinetics between these two groups requires correction for individual differences in binding (Reidenberg *et al.*, 1971; Gugler *et al.*, 1975; Koch-Weser & Sellers, 1976). Unbound V_d in patients was significantly smaller than in controls, probably reflecting a reduction in adipose tissue and therefore reduced peripheral distribution of diazepam (Abernethy *et al.*, 1981) in the renal patients.

Since $T_{1/2}$ depends both on V_d and clearance ($T_{1/2} = 0.693 \times V_d/\text{clearance}$), the shorter value of $T_{1/2}$ in renal patients reflects the reduction in unbound V_d . We should emphasize that since the renal failure patients were taking multiple medications, we cannot rule out that the pharmacokinetic findings were attributable to the concurrently ingested drugs.

Previous studies have suggested that hyperthyroidism may be associated with altered drug disposition (Eichelbaum, 1976). In the case of diazepam, however, no significant differences were observed between hyperthyroid patients and matched controls in any of the kinetic variables for diazepam.

The findings indicate that no alterations in dosage of intravenous diazepam are required for patients with renal insufficiency or thyrotoxicosis based on pharmacokinetic considerations alone. This conclusion would also apply to orally-administered dia-

zepam provided diazepam absorption is not altered by the disease processes. Since desmethyldiazepam, the major pharmacologically active metabolite of diazepam, contributes importantly to clinical effects during long-term diazepam therapy, it remains to be verified whether desmethyldiazepam kinetics are altered by renal or thyroid disease.

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Address for reprints: Hermann R. Ochs, M.D. Medizinische Universitätsklinik, D-5300 Bonn-Venusberg, West Germany.

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