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DIAZEPAM PHARMACOKINETICS AFTER INTRAVENOUS ADMINISTRATION IN ALCOHOL WITHDRAWAL

Diazepam in a 'loading' dose could be a simple pharmacotherapeutic approach for treating alcohol withdrawal. The half-lives of diazepam and its active metabolite (desmethyldiazepam) are 33 ± 11 and 50–90 h, respectively (Kaplan *et al.*, 1973; Klotz *et al.*, 1976). Hence following an adequate loading with diazepam, therapeutic levels of diazepam and desmethyl-diazepam will be present considerably longer than the 72 h usually required for alcohol withdrawal symptoms to subside without pharmacological intervention. In the course of testing this hypothesis (Sellers *et al.*, 1981; Shaw *et al.*, 1982), we had an opportunity to study the pharmacokinetics of intravenous diazepam in eight patients (six men and two women, age 29–61 years) in moderate—severe withdrawal. None had clinically apparent liver disease nor medical complications requiring treatment. We report on eight patients who received a single intravenous loading dose of diazepam. Normal saline was infused intravenously for 1 h at the rate of 4 ml/h using Sage pump model 351. Subsequently, diazepam was infused at the rate of 0.34 mg/min (20 mg/h) until the patient was clinically asymptomatic. Initial blood samples were collected from the contralateral arm via a saline lock into an all glass non-heparinized system. Tubes were covered with Teflon®. After 8 h, further samples were drawn intermittently up to 300 h. Samples were allowed to coagulate for 30 min, then serum was separated by centrifugation at 500 rev/min for 10 min and stored at −20°C. Diazepam free fraction was determined in duplicate by equilibrium dialysis using [^{14}C]-

Table 1 Intravenous diazepam pharmacokinetics in alcohol withdrawal

	Diazepam								*Desmethyldiazepam*	
	Total					*Free*				
Subject	*Peak (ng/ml)*	*Mean free fraction (%)*	$t_{½}$ (β) (*h*)	CL_T (*ml/min*)	V_d (*l*)	$t_{½}$ (β) (*h*)	CL_F (*ml/min*)	V_{dF} (*l*)	*Peak (ng/ml)*	$t_{½}$ (β)b (*h*)
03	87	1.34	32.1	27.1	56	21.2	2,022	4,187	403	34.1
19	659	1.46	67.5	25.7	150	68.3	1,760	10,274	656	94.6
23	308	2.16	14.7	57.7	73	15.1	2,759	3,598	4,217	26.7
24	210	1.79	39.0	70.5	238	37.2	4,340	13,977	210	104.6
26	494	1.62	36.5	36.9	116	30.7	2,274	7,160	494	60.1
Median	656	1.62	36.5	36.9	116	30.7	2,274	7,160	494	60.1
06a	707	--a	20	--a				715		
12	1,425	--	36.0	--				504		
28	1,415	--	24.1	--				1,415		

a Subjects 06, 12 and 28 had diazepam detectable in blood prior to initiation of the infusion (7, 20 and 300 ng/ml, respectively) and hence calculations on AUC determinations are not reliable. Data for subjects 03, 19 and 26 derived from fitting to $Ae^{-\alpha t} + Be^{-\beta t}$. For these subjects V_d area is given.
b Estimates only.

diazepam (Amersham Corporation; 87% radiochemically pure specific activity 200 μCi/mg) as a tracer added to 0.5 ml aliquots of serum mixed with cold drug to achieve a concentration of 600 ng/ml and dialysed against a saline phosphate buffer (pH 7.4), at 37°C for 6 h (Abel *et al.*, 1979). The coefficient of variation of duplicate determinations was less than 2%. Diazepam and desmethyldiazepam concentrations were determined by gas chromatographic method (MacLeod *et al.*, 1977).

Pharmacokinetic analyses were conducted in two ways. Post-infusion plasma diazepam concentrations were analysed by weighting iterative non-linear least squares regression analysis (Greenblatt *et al.*, 1979). Using this procedure, subjects' 03, 19 and 26 data could be fitted to the linear sum of two exponential terms. The coefficients were corrected for the infusion time (Loo & Riegelman, 1970). The volume of distribution (V_d), half-life ($t_{½}$) and clearance (CL), etc. were calculated by the usual method (Table 1). Subjects 23 and 24 could not be fitted because of extreme fluctuations in total diazepam concentrations associated with meals. In these patients the following pharmacokinetic parameters were calculated: CL apparent V_d and apparent elimination $t_{½}\beta$. The latter was determined after a long–linear regression analysis on the points on the log–linear terminal phase (usually 24 h onwards of a log concentration *vs* time profile). The area under the curve (AUC) to infinity was determined using the trapezoidal rule for the area out to the last point and concentrations/β for the area from the last point out to infinity. Clearance was determined from the dose/AUC and V_d was determined from dose/AUC $\times$ β. Free diazepam plasma concentration for each sample was calculated from the product of free fraction and plasma concentration. The mean fraction for each subject was calculated from the AUC free concentration/AUC total concentration.

Results are the mean ± s.d. Statistical significance was tested Student's *t*-test (two-tailed).

The median duration of the infusion was 1.9 h (range 0.75–4.7 h) and the median diazepam dose was 0.66 mg/kg (range 15–94 mg). The median terminal phase elimination half-life ($t_{½}\beta$) for total diazepam was 36.5 h (range 14.7–67.5 h) (Table 1). Desmethyldiazepam apparent $t_{½}$ was 60 h (range 27–10 h), but cannot be accurately determined because of continued conversion of diazepam. Clearance and volume of distribution could be reliably determined for total and free diazepam and desmethyldiazepam in five subjects (Table 1). The three other subjects had detectable levels of diazepam or desmethyldiazepam before the start of infusion precluding further pharmacokinetic analysis. Figure 1 shows the concentration time profiles of total drug for each patient.

The average pharmacokinetic parameters of diazepam disposition in our population of chronic

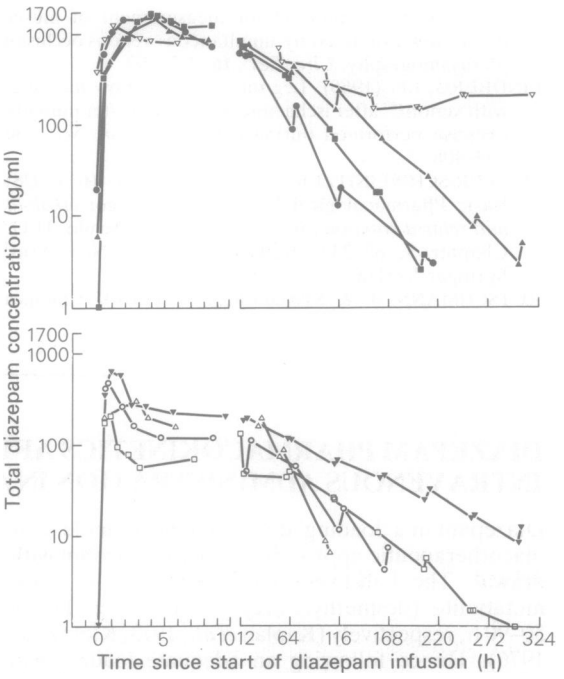

Figure 1 Total diazepam concentrations in eight chronic alcoholics in moderate-severe withdrawal. Upper panel includes three patients with diazepam detectable prior to infusion and patients with highest peak levels. Lower panel shows four remaining subjects with lower diazepam concentrations.

alcoholics did not differ significantly from the values reported in normal age matched controls. However, two chronic alcoholics had free drug clearances in excess of 2,500 ml/min suggesting enzyme induction or extra-hepatic biotransformation. The marked variations in peak diazepam levels associated with a similar clinical end-point indicates considerable inter-patient variation in sensitivity possibly due to differing extents of alcohol or prior diazepam-induced tolerance. Both subjects who required the highest doses of diazepam were prior users of diazepam.

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EFFECT OF INDORAMIN ON HUMAN SPERM MOTILITY

Indoramin, a selective α_1-adrenoceptor antagonist, is an effective anti-hypertensive drug in man. Animal studies have also demonstrated anti-histamine, anti-5-hydroxytryptamine and myocardial membrane stabilising properties (Alps *et al.*, 1970, 1972; Archibald, 1981). Electrophysiological studies of the effects of indoramin on canine isolated myocardial strips, indicated a statistically significant ($P = < 0.001$) decrease in V_{max} of depolarization with concentrations achieved in man after therapeutic doses (Coltart *et al.*, 1971).

Human sperm motility is a potential model to study pharmacological and toxicological effects of drugs (Hong *et al.*, 1981b, 1981c). Propranolol, lignocaine and other membrane stabilizing drugs have been shown to inhibit sperm motility (Hong, 1982; Hong & Turner, 1982). The effect of indoramin on this experimental model was therefore studied.

Fresh samples of human semen were collected from either healthy volunteers or patients attending the seminology laboratory at our hospital. The method of Hong *et al.* (1981a) was followed to study human sperm motility. Only samples with sperm counts higher than 15×10^6 ml^{-1} and more than 20% of progressive forward moving sperms were used. Indoramin maleate was freshly dissolved in a mixture of 5% ethanol and phosphate buffered saline at a pH of 6.0. The maleate was used because of the relative insolubility of the hydrochloride salt. Sperm motility was measured using the ability of forward moving sperms to cross a 5 μm pore nucleopore membrane during 2 h incubation time at 37 °C. The transmembrane migration ratio (TMMR) was compared with a semen buffer mixture which was used as control at the same pH. The use of 5% ethanol as a solvent has already been demonstrated not to interfere in the basal motility values (Hong *et al.*, 1981c). Six samples were tested for each concentration of drug.

Figure 1 shows the log concentration response curve for indoramin and its inhibition of human sperm motility. A concentration of 4 mM decreased sperm motility to 50% of the control value. This compares

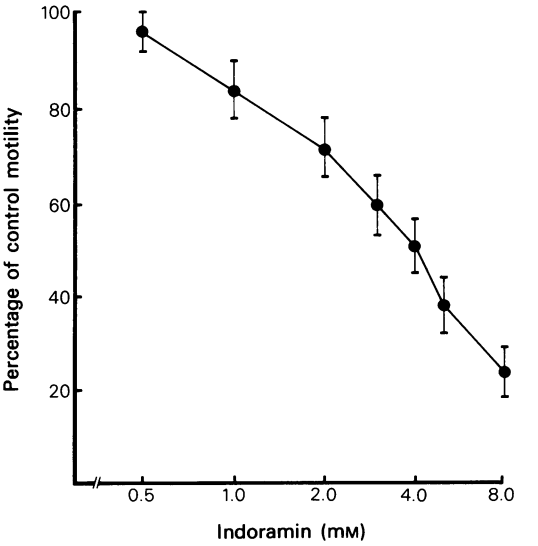

Figure 1 Log concentration-response curve for the inhibition of human sperm motility by indoramin. The motility of sperms in semen-buffer mixture was used as control. All points are mean ± s.e. mean of six samples.