Prolongation of Drug Half-Life due to Obesity: Studies of Desmethyldiazepam (Clorazepate)

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Abstract □ Desmethyldiazepam pharmacokinetics were determined after oral administration of its precursor, clorazepate, to 12 obese subjects (mean weight: 105.4 kg; mean percent ideal body weight: 170%) who were matched for age, sex, and smoking habits with 12 normal controls (66.5 kg; percent ideal body weight: 103.3%). After an overnight fast, a single 15-mg clorazepate capsule, equivalent to 10.3 mg of desmethyldiazepam, was administered. Multiple plasma samples drawn 10–42 days postdose were analyzed for desmethyldiazepam by electron-capture GLC. Obese subjects compared to controls had a prolonged desmethyldiazepam elimination half-life ($t_{1/2}$) (154.1 hr *versus* 57.1 hr; $p < 0.005$). Assuming quantitative conversion of clorazepate to desmethyldiazepam and 100% systemic availability, volume of distribution (V_d) was greatly increased in the obese (158.8 liters *versus* 63.3 liters; $p < 0.001$). The value of V_d remained greater even after correction for body weight (1.52 liter/kg *versus* 0.94 liter/kg; $p < 0.005$). However, clearance of desmethyldiazepam was not different between groups (13.2 ml/min in obese *versus* 13.4 ml/min in controls). The percent ideal body weight was highly correlated with V_d ($r = 0.82$), as was total body weight ($r = 0.86$). The value of $t_{1/2}$ was correlated highly with V_d ($r = 0.89$) but only weakly with clearance ($r = -0.38$). Therefore, the large increase in the desmethyldiazepam $t_{1/2}$ value seen in obese subjects is predominantly due to the disproportionate distribution of this lipid-soluble drug into body fat as opposed to lean tissue. The contribution of clearance to desmethyldiazepam $t_{1/2}$ was of much less importance than was V_d in this obese study population.

Keyphrases □ Desmethyldiazepam—prolongation of drug half-life due to obesity □ Pharmacokinetics—prolongation of drug half-life due to obesity, desmethyldiazepam □ Obesity—prolongation of drug half-life, desmethyldiazepam

The elimination half-life ($t_{1/2}$) of drugs has often been equated with the rate of biotransformation and clearance (1). However, principles of pharmacokinetics indicate that half-life is a hybrid variable, depending upon both drug distribution and clearance (2):

$$t_{1/2} = \frac{0.693 \times \text{Volume of Distribution } (V_d)}{\text{Clearance}} \quad \text{(Eq. 1)}$$

To date only a few experimental circumstances have been described in which a high inverse correlation between clearance and elimination half-life did not exist, with a significant contribution to variability in elimination half-life being attributable instead to changes in the volume of distribution (3, 4). Clorazepate, a prodrug which is converted to desmethyldiazepam after oral administration (5), has been used in this laboratory and by others as a means of evaluating desmethyldiazepam pharmacokinetics (6, 7). The present study demonstrates that in obese individuals, comprising perhaps 20% of the population of the United States (8), a potentially serious misinterpretation of drug metabolizing capacity may occur with some lipid-soluble drugs when elimination half-life is used as a measure of drug metabolism.

EXPERIMENTAL

Subjects—Twelve obese (>133% ideal body weight) and 12 control (<125% ideal body weight) subjects participated in the study (Table I).

Table I—Subject Characteristics and Kinetic Variables for Diazepam

	Mean (with range) Values[a]	
	Obese ($n = 12$)	Control ($n = 12$)
Subject Characteristics		
Age, years	33(23–61)	33(24–74)
Sex, F/M	8/4	7/5
Total body weight, kg	105(77–197)	67(51–91)[b]
Ideal body weight, kg	62(41–77)	65(50–82)
Percent ideal body weight	170(134–257)	103(86–125)[c]
Smoking, no/yes	9/3	9/3
Kinetic Variables of Absorption		
Absorption lag time, hr	0.20(0.06–0.25)	0.40(0.18–0.73)[c]
Half-Time for absorption, hr	0.94(0.25–2.03)	0.48(0.02–1.85)
Time to peak plasma concentration, hr	1.3(0.5–2.5)	1.5(0.5–3.0)
Peak plasma concentration, ng/ml	149(90–239)	249(89–590)[d]
Kinetic Variables of Elimination		
Elimination half-life, hr	154(64–369)	57(30–77)[b]
V_d, liter	159(91–340)	63(38–119)[c]
V_d/kg total body weight, liter/kg	1.52(1.00–2.51)	0.94(0.63–1.30)[b]
V_d/kg ideal body weight, liter/kg	2.58(1.49–4.43)	0.98(0.60–1.45)[c]
Clearance, ml/min	13.2(7.4–18.2)	13.4(5.7–21.8)
Clearance/kg total body weight, ml/min/kg	0.14(0.05–0.23)	0.20(0.10–0.31)
Free fraction, percent	2.4(1.5–3.1)	2.5(1.8–3.7)

[a] Student t test for difference between control and obese groups; [b] $p < 0.005$. [c] $p < 0.001$. [d] $p < 0.02$.

The ideal body weight was defined from life insurance tables as follows (9):

Ideal body weight (males) = 50 kg ± 0.9 kg/cm above or below 150-cm height.

Ideal body weight (females) = 45 kg ± 0.9 kg/cm above or below 150-cm height.

The percent ideal body weight was calculated as the ratio of actual or total body weight to ideal body weight. Other measures of adiposity such as weight/height and weight/height^2 (10) have been evaluated in such populations, but it was found that none of these other indexes provides more information than dose comparison of total body weight and ideal body weight.

Obese and control subjects were matched for age, sex, and cigarette smoking habits. No subjects were on a special diet designed for weight loss and all remained at the same weight during the study.

Procedure—After an overnight fast, all subjects received a capsule containing 15 mg of clorazepate dipotassium[1] with 75 ml of water. Subjects remained fasting for 3 hr after drug ingestion. Venous blood samples were drawn into heparinized tubes before the dose, at 5, 15, 30, and 45 min, and 1, 1.5, 2.0, 2.5, 3, 4, 6, 8, 12, and 24 hr, and every 1 to 2 days for 10–42 days. An indwelling butterfly cannula, kept patent by a slow infusion (20 ml/hr) of physiologic saline, was used to obtain blood samples during the first 8 hr postdosing. All other samples were drawn by separate venipuncture. Samples on subsequent days were drawn in the nonfasting state. Blood specimens were centrifuged, and the plasma was separated and stored at −20° until assayed.

Analysis of Samples—Plasma desmethyldiazepam concentrations were determined by electron-capture GLC (6). The extent of diazepam binding to plasma protein for each subject was determined from pooled samples drawn in the nonfasting state at least 72 hr postdose. Binding

[1] Tranxene, Abbott Laboratories, North Chicago, Ill.

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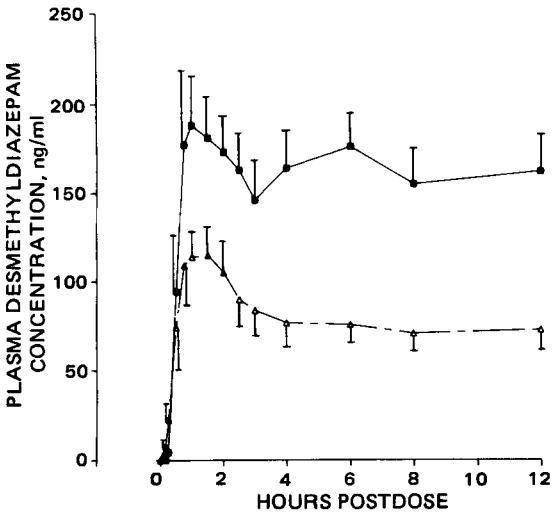

Figure 1—*Mean plasma desmethyldiazepam concentrations over the initial 12 hr after drug administration. Each value is the mean (±SE) for the 12 subjects in obese and control groups at the corresponding time. Pharmacokinetic variables of absorption are listed in Table I. Key: (■) control; (△) obese.*

was determined by equilibrium dialysis using duplicate 2-ml samples spiked to contain 500 ng of desmethyldiazepam/ml. Recovery of desmethyldiazepam from the dialysis system was 100% and the variation for replicate samples was <10%. Binding was independent of the total desmethyldiazepam plasma concentration up to levels of 5000 ng/ml (11, 12).

Data Analysis—Plasma desmethyldiazepam concentrations were analyzed by weighted iterative nonlinear least-squares regression techniques as described previously (13–15). Since desmethyldiazepam derived from orally ingested clorazepate is 100% bioavailable[2], coefficients and exponents from the function of best fit were used to calculate the following kinetic variables: lag time prior to the start of absorption, absorption half-life, total volume of distribution (V_d) using the area method, elimination half-life, and total clearance (16, 17). The data were further analyzed by determination of kinetic parameters for the fraction not bound to plasma protein (18, 19). Assuming that protein binding of desmethyldiazepam for a given subject was constant over time and independent of total concentration, values for V_d and clearance were divided by the subject's unbound fraction yielding values of unbound V_d and unbound (intrinsic) clearance.

Differences in kinetic variables between obese and control groups were

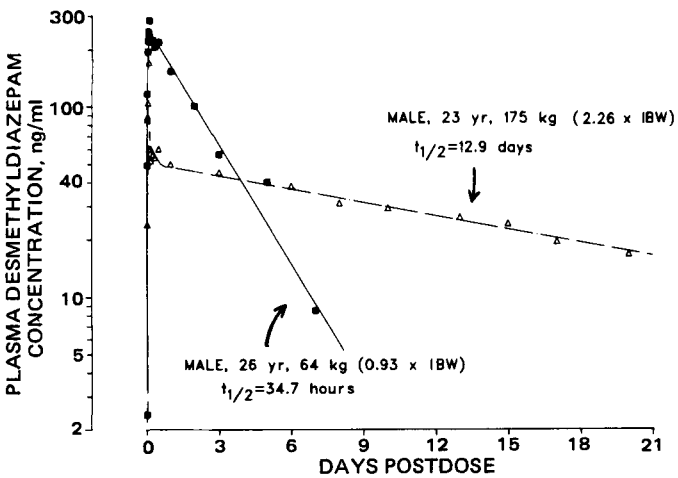

Figure 2—*Plasma desmethyldiazepam concentrations and pharmacokinetic functions following oral chlorazepate administration to a representative obese male [(△); 23 years; 175 kg (2.26 × IBW); $t_{1/2}$ = 12.9 days] and to a matched control male of normal weight [(■); 26 years; 64 kg (0.93 × IBW); $t_{1/2}$ = 34.7 hr].*

[2] Unpublished observation.

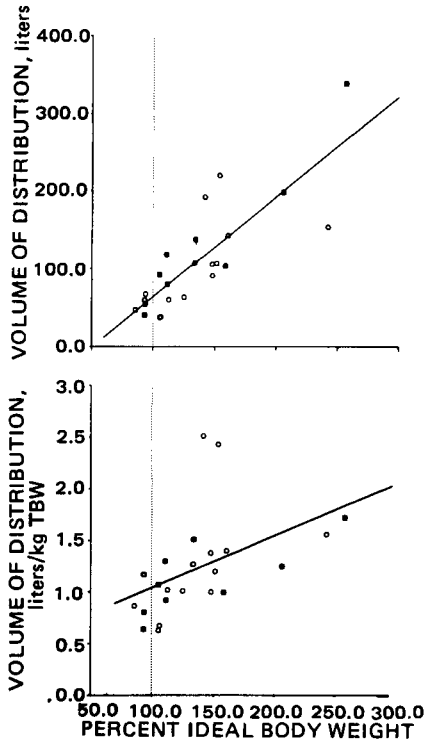

Figure 3—*Relation of percent ideal body weight (abscissa) to desmethyldiazepam absolute volume of distribution (top) and corrected for total body weight (r = 0.82) (bottom). Solid lines were determined by least-squares regression analysis. Key: (■) male; (○) female.*

assessed by Student t test. Relationships among kinetic variables and subject characteristics were evaluated by linear regression analysis.

RESULTS

Lag time elapsing prior to the appearance of desmethyldiazepam in plasma after clorazepate was significantly shorter in the obese than in the control subjects ($p < 0.001$). However, absorption half-life and the time to peak plasma concentration did not differ significantly between groups (Table I). Peak plasma concentrations were much lower in the obese subjects ($p < 0.02$), presumably reflecting the much more extensive distribution of desmethyldiazepam in obesity (Fig. 1, Table I).

Elimination of desmethyldiazepam from plasma after ingestion of clorazepate was adequately described in all subjects by a linear sum of exponential terms (Fig. 2). Pharmacokinetic variables (Table I) reveal a significantly prolonged elimination half-life ($p < 0.001$) in obese as compared to control subjects. This is not explained by a change in clearance, as total metabolic clearance was nearly identical in the two groups (Table I). Since the extent of protein binding was similar in obese and control groups (Table I), intrinsic (unbound) clearance was also similar in the two groups.

The V_d value, in liters, as well as V_d corrected for total body weight (V_d/kg of total body weight) and V_d corrected for ideal body weight (V_d/kg of ideal body weight), were significantly larger in obese subjects than controls (Table I). Represented as a continuous function among all subjects, there was a highly significant ($r = 0.82$; $p < 0.001$) positive correlation between percent ideal body weight and absolute V_d, as well as V_d/kg total body weight ($r = 0.49$, $p < 0.05$) (Fig. 3). This indicates disproportionate distribution of desmethyldiazepam into excess body weight over ideal body weight that is greater than distribution into ideal body weight. Using mean values for total body weight and V_d, distribution of desmethyldiazepam into excess body weight over ideal body weight is approximately twice as extensive as distribution into ideal body weight.

The difference in elimination half-life between groups is the result of the marked increase in V_d in the obese group. This is demonstrated by the highly significant correlation between elimination half-life and V_d ($r = 0.89$; $p < 0.001$) and the nonsignificant correlation between elimination half-life and clearance ($r = -0.38$; *NS*) (Fig. 4).

DISCUSSION

Many drugs are administered on the basis of dose per unit body weight. This assumes that drug clearance is proportional to weight, and that drug

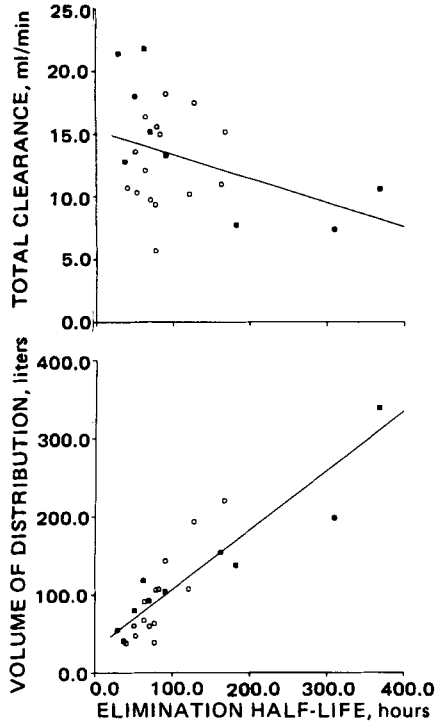

Figure 4—*Relation of desmethyldiazepam volume of distribution (top) and total clearance (bottom) to desmethyldiazepam elimination half-life (abscissa). Volume of distribution was highly correlated with half-life (r = 0.89), but clearance is not significantly related to half-life (r = −0.38). Key: (■) male; (○) female.*

distribution per unit weight is unchanged with large variations in body weight. However, such assumptions may not be warranted since obese individuals may have a significant incidence of hepatocellular disease (20), changes in renal blood flow (21), and marked deviation in body composition from normal (8). A recent report demonstrates a marked increase in tissue enflurane uptake and an increase in the rate and amount of metabolite appearing in peripheral blood in the obese state in the absence of other pathological processes (22). In addition, drug distribution may be quite different in the obese individual as compared to one of normal body weight. Evaluation of the kinetics of digoxin (23), gentamicin (24), tobramycin (24, 25), and amikacin (26) in obesity suggest that distribution of these drugs is mainly into lean body mass, such that an incorrect drug dosage may result from calculation based on total body weight. Similar results are reported for theophylline (27). In contrast, fat-soluble drugs such as diazepam may be much more extensively distributed into body weight in excess of ideal body weight than into ideal body weight (3). Again, this may result in incorrect drug dosage and/or prolongation of time to steady-state plasma concentration if loading and maintenance doses do not take the degree of obesity into consideration.

The present study assessed the effect of obesity on the absorption, distribution, and clearance of desmethyldiazepam, a lipid-soluble benzodiazepine antianxiety agent. Subjects in both obese and control groups varied in age, sex, and cigarette smoking habits, all of which can influence drug disposition. However, these factors are unlikely to have influenced the results, since control and obese subjects were matched for these characteristics. The findings indicate that distributional changes in obesity can remarkably alter the apparent half-life of elimination despite no change in metabolic clearance. Furthermore, the extent of distribution into excess body weight over ideal body weight is even more extensive than into ideal body weight. This is presumably due to the lipophilic character of desmethyldiazepam.

Thus, elimination half-life of lipid-soluble drugs changes greatly in obese patients in the absence of change in total metabolic clearance. Total clearance is the appropriate pharmacokinetic parameter to use for evaluation of the rate of biologic drug removal, as drug dose required to achieve a given steady-state plasma level is a function of this independent variable, not the dependent variable elimination half-life.

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