

## Chapter 5

### *Ethnicity and Differential Responses to Benzodiazepines*

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[Au: Pls. provide academic degree(s) for last author.]

#### INTRODUCTION

Since the introduction of chlordiazepoxide into medical practice in 1960, benzodiazepines (BZPs) have become among the most frequently prescribed medications (Smith and Wesson 1985). Surveys in the U.S. indicated that approximately 15% of the general population have used BZPs within a 1-year period. The use of BZPs accounts for two-thirds of all psychotropic drug use (Greenblatt et al. 1975). Similar studies conducted in various countries indicated that the prevalence of BZP use in the community ranged between 10% and 20% (Parry et al. 1973). This popularity not only reflects the large safety margin of BZPs (especially as compared to their predecessors, the barbiturates) but also their efficacy in treating anxiety and related symptoms (Ballenger 1984; Greenblatt et al. 1983; Lesser 1989; Smith and Wesson 1985). At the same time, because of their potential for abuse and misuse (Noyes et al. 1988; Woods et al. 1987, 1988), their effect on motor and perceptual functioning (Ellinwood and Nikaido 1987), and occasionally their propensity to cause severe withdrawal syn-

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## PHARMACOKINETIC AND PHARMACODYNAMIC STUDIES

### Intravenous Diazepam Study Conducted in St. Louis

Ghoneim and colleagues (1981) studied the kinetics and behavioral effects of diazepam in 12 Caucasian and 13 Asian healthy control subjects. Each subject received 0.2 mg/kg of diazepam intravenously, along with a placebo-control administered in a double-blind fashion. Nine blood samples for the measurement of diazepam and desmethyldiazepam concentrations were obtained over a 72-hour period after treatment. Serum protein binding of diazepam was also determined. Tests of the behavioral and psychological effects of diazepam including serial learning, subjective ratings, tapping speed, arithmetic test, and delayed recall were administered three times during the first 4 hours posttreatment.

The results showed that the two ethnic groups diverged substantially in their pharmacokinetic but not their pharmacodynamic responses to diazepam. Significantly slower total body clearance, smaller volume of distribution, and higher levels of desmethyldiazepam concentrations were found in the Asian subjects compared to their Caucasian counterparts. These differences could not be explained by factors such as body weight, nativity (immigration) status, or dietary habits, and were most likely secondary to a less active hepatic metabolism of diazepam in Asians. When extrapolated to the steady state, this difference in the rate of metabolism could lead to Asians having (on the average) 40%–50% higher drug concentrations in serum and in tissue.

There was no difference in the proportion of protein binding between the two ethnic groups (98%), which was comparable to previous reports in Caucasians. The psychological and behavioral effects of diazepam also were similar in intensity and duration in both groups, which were most prominent at 0.5 hour posttreatment and no longer apparent 4 hours after drug administration. Potential problems in the study design might have prevented the detection of ethnic differences in drug effects. The relatively high dosage of intravenous diazepam used in this study (about 13 mg in Asians and 14 mg in Caucasians) may be

sion analysis, it became evident that the ethnic differences could be largely explained by the differences in SFT and TBW/IBW between the two groups. This suggests that ethnic differences in the percentage of body fat may be the main reason for the higher serum concentrations of diazepam and its metabolite(s) in Asians as compared to Caucasians. Because the serum concentrations of both parent drug (diazepam) and its metabolite (desmethyldiazepam) were lower in Caucasians, Kumana and colleagues (1987) suggested that there was no evidence of differences between the two groups in the activities of liver enzymes responsible for the metabolism of diazepam. Further, because Chinese subjects had longer  $T_{max}$  yet higher drug concentrations, the efficiency of gastrointestinal absorption also was not likely to be a relevant factor in this regard.

#### **Oral and Intravenous Alprazolam Study Conducted in Los Angeles**

Another study examined plasma alprazolam concentrations and acute behavioral effects in healthy male volunteer subjects, 14 of whom were American-born Asian, 14 foreign-born Asian, and 14 Caucasian (Lin and colleagues 1988). All subjects were nonsmokers and not regular alcohol drinkers. Subjects were admitted to an inpatient research ward on 2 separate days at least 2 weeks apart. After a 12-hour overnight fast, 0.5 mg alprazolam was administered to the subjects either orally in tablet form with 180 ml of water or as a slow intravenous injection. Prior to drug administration, three baseline blood samples were obtained; over the next 36 hours, 14 posttreatment blood samples were obtained. Plasma derived from these samples were stored at  $-70^{\circ}\text{C}$  and assayed for alprazolam concentrations by high-performance liquid chromatography (HPLC). These plasma samples also were used for the determination of growth hormone concentrations by radioimmunoassay (Koulu et al. 1979; Syvalahti and Kanto 1975). Sedation was rated by nurses at the time of each blood sampling. The digital symbol substitute test (DSST; Ellinwood and Nikaido 1987; Greenblatt et al. 1989; Hindmarch 1980; Johnson and Chernik 1982), a psychomotor test previously proven sensitive to the effect of benzodiazepines, was also administered at baseline

intravenous administration of alprazolam was substantially longer in both Asian groups as compared to the Caucasians, these differences failed to reach statistical significance.

In contrast to the differences between the Asian and Caucasian subjects, the pharmacokinetic parameters of the two Asian groups were remarkably similar. There was no significant statistical difference between the two groups in any of the parameters examined.

Although the results derived from pharmacodynamic measurements consistently revealed greater pharmacological effects of alprazolam on Asians as compared to Caucasians, only the differences in the mean sedation scores reached statistical significance, with foreign-born Asians experiencing significantly more sedation compared to both Caucasian and American-born Asian subjects (Table 5-2). Substantial variances characteristic of studies of this nature have been the main reason for these results.

However, methodological problems may have also contributed to this observation. The relatively low doses of alprazolam

Table 5-2. Comparison of mean sedation scores, growth hormone concentrations (ng/ml), and DSST change scores after oral and intravenous alprazolam administration

	Caucasians (n = 14)	American- born Asians (n = 14)	Foreign- born Asians (n = 14)	ANOVA F	P
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD		
Oral					
Mean sedation	1.39 $\pm$ 0.33	1.54 $\pm$ 0.35	1.59 $\pm$ 0.37	1.31	NS
Max sedation	2.36 $\pm$ 0.74	2.50 $\pm$ 0.65	2.57 $\pm$ 0.76	.32	NS
Mean GH	0.64 $\pm$ 0.88	0.99 $\pm$ 1.42	0.81 $\pm$ 1.80	.21	NS
Max GH	5.08 $\pm$ 5.57	6.86 $\pm$ 8.61	7.55 $\pm$ 8.93	.40	NS
Mean DSST	3.29 $\pm$ 7.10	1.30 $\pm$ 8.62	0.18 $\pm$ 5.74	.66	NS
Max DSST	-2.00 $\pm$ 7.89	-3.79 $\pm$ 10.24	6.14 $\pm$ 6.63	.86	NS
IV					
Mean sedation	1.48 $\pm$ 0.24	1.37 $\pm$ 0.23	1.67 $\pm$ 0.33	4.45	.018
Max sedation	2.50 $\pm$ 0.65	2.36 $\pm$ 0.74	2.71 $\pm$ 0.47	1.13	NS
Mean GH	1.54 $\pm$ 3.02	1.63 $\pm$ 1.79	1.81 $\pm$ 2.65	.04	NS
Max GH	8.83 $\pm$ 13.6	9.84 $\pm$ 10.7	12.32 $\pm$ 15.89	.25	NS
Mean DSST	4.32 $\pm$ 7.21	1.66 $\pm$ 7.15	1.93 $\pm$ 3.60	.78	NS
Max DSST	-0.64 $\pm$ 8.0	-3.43 $\pm$ 8.3	-2.86 $\pm$ 3.74	.61	NS

GH = growth hormone; DSST = digital symbol substitute test.

nese volunteers in Beijing. Among these volunteers, eight were extensive metabolizers (EMs) of S-mephenytoin, the other eight PMs. Other than demethyldiazepam concentrations, which were significantly higher in Chinese EM subjects than in Chinese PM subjects for the whole duration of the study, the two phenotype groups showed no significant difference in most of the pharmacokinetic parameters, including the plasma half-life and clearance of diazepam, which were comparable to Caucasian PMs and drastically different from Caucasian EMs (twice as long for the half-life and only half as fast for the clearance).

[Au: Pls. confirm that edit of 2nd sentence in next para. is acceptable; meaning was unclear.]

The study of Bertilsson and colleagues (1989) thus suggested that the S-mephenytoin hydroxylase present in the Chinese EMs were not able to metabolize diazepam; consequently, unlike the Caucasian subjects, the metabolism of diazepam among the Chinese subjects was independent of the S-mephenytoin hydroxylation phenotype. It also suggests that the higher incidence of EM of S-mephenytoin in Chinese subjects is not the only factor responsible for the interethnic difference in response to diazepam. Other factors could include differences in substrate specificity of the S-mephenytoin hydroxylase, or the activities of other enzyme systems that are also responsible for the metabolism of diazepam.

Related to this puzzling finding is yet another study (Horai et al. 1989) comparing the metabolic rates of metoprolol (used for testing debrisoquine phenotype) and S-mephenytoin between 200 Japanese subjects living in Japan and 98 Chinese subjects living in the People's Republic of China. Confirming earlier reports, both ethnic groups showed extremely low rates for PM phenotype of debrisoquine-type hydroxylation and a greater incidence of PM phenotype of mephenytoin oxidation. However, Chinese EMs metabolized both drugs significantly slower than did Japanese EMs. It is still unclear whether these differences represent differential environmental influences (differential exposures to various enzyme inducing agents) or are the results of subtler cross-ethnic differences in the distribution of different variants of the enzymes responsible for the metabolism of these

ministration (Fleishaker et al. 1990, 1992). This may be responsible for the larger drug effects on blacks despite their higher metabolic capacity for adinazolam.

[Au: In next para., pls. clarify if blacks in the study cited were exclusively African-Americans, or if other blacks were included in the study.]

## CONCLUSION AND FUTURE DIRECTIONS

Five studies have compared the pharmacokinetics and pharmacodynamics of benzodiazepines in different ethnic groups. Among these, four studies involved comparisons between Asians and Caucasians and one study compared blacks with Caucasians. At present, to our knowledge, no study has been conducted with other major ethnic groups in this country, such as Hispanics and American Indians. The lack of information in this regard is particularly problematic for several major reasons:

1. These populations, along with Asians and blacks, are rapidly growing in this country;
2. Benzodiazepines are widely used in practically all ethnic groups in this country as well as worldwide; and
3. Many factors, genetic as well as environmental, could lead to significant ethnic differences in response to benzodiazepines.

[Au: In next 2 paras., pls. clarify use of "North American" to describe two studies: American and Canadian?]

All four studies involving Asians and Caucasians demonstrated significant kinetic differences between the two ethnic groups. Because they were conducted at different geographic sites (two in North America, one in Hong Kong, and one in the People's Republic of China) and possibly included different Asian subcultural groups (i.e., not all subjects included in the North American studies were of Chinese origin), questions could be raised regarding the generalizability of the findings. At the same time, however, the consistency in these reports of a slower metabolism of benzodiazepines in Asians is quite remarkable, suggesting that perhaps genetic factors are more important than environmental considerations in causing such a phenomenon.



despite the existence of significant ethnic pharmacokinetic differences. This is not surprising, because results of studies conducted by other investigators attempting to correlate dynamic with kinetic parameters of benzodiazepines are not always successful (Ellinwood and Nikaido 1987). More precise and sensitive measurements of drug pharmacodynamics will, one hopes, become available in the near future to help quantify the effects of ethnicity on benzodiazepine responses.

Lastly, the absence of studies involving measurement of steady-state plasma drug concentrations in patient populations represents another important issue that needs to be addressed in future research. Although single-dose pharmacokinetic and pharmacodynamic parameters do provide useful information and in general are highly predictive of the steady-state drug levels and effects, such inferences ultimately need to be substantiated with studies that directly and systematically assess the kinetics and effects of the benzodiazepines in the clinical settings.

In summary, newer developments in pharmacokinetics, pharmacogenetics, and pharmacodynamics have made it possible for several research groups to demonstrate significant differences in the metabolism of some of the benzodiazepines between Asians and Caucasians. The mechanisms responsible for such differences remain to be determined, and the findings need to be tested in patient populations receiving benzodiazepines on an ongoing basis. Similar research strategies should be applied to studies involving other ethnic populations. Progress in this area of research should prove significant in the clinical care of the rapidly increasing ethnic minority populations, as well as for the majority of the world's population who are of non-Western backgrounds.

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dromes (Dupont 1986; Noyes et al. 1988; Woods et al. 1987; 1988), the dosing and prescription patterns of these medications have often been the focus of much scrutiny (Dupont 1986; Greenblatt et al. 1975; Lesser 1989).

[Au: In next para., re: Rosenblat and Tang 1987 study: pls. clarify if "North American" means American *and* Canadian. The use of North American to mean American is now considered nonstandard.]

Given the enormity of the issues involved, factors that may affect the response to and dose requirement of BZPs evidently should be carefully examined. Ethnicity has been identified by several clinical and survey reports (Kumana et al. 1987; Murphy 1969, 1972; Rosenblat and Tang 1987) as an important factor in determining benzodiazepine responses. Based on his extensive cross-cultural experiences, as well as international surveys, Murphy (1969, 1972) first suggested that, compared to Caucasians, Asians may be more sensitive to the effects of various psychotropics, including anxiolytics. This was supported by a survey of the prescription patterns of 21 North American psychiatrists who regularly treat both Asian and non-Asian patients (Rosenblat and Tang 1987). The results of this study showed that the mean dosages of benzodiazepines received by Asians were about one-half to two-thirds of those prescribed for their Caucasian counterparts (i.e., diazepam: 12 versus 21 mg/day,  $P < 0.001$ ; chlordiazepoxide: 32 versus 46 mg/day,  $P < 0.01$ ). Concurrently, Kumana and colleagues (1987) also indicated that Chinese patients living in Hong Kong generally were treated with substantially small amount of benzodiazepines as compared to Caucasian patients.

In the past decade, a small number of studies have utilized pharmacokinetic, pharmacogenetic, and pharmacodynamic research designs to examine ethnic differences in responses to benzodiazepines. In this chapter, we review these findings and their implications. We then discuss their clinical implications and make suggestions for future research.

too sedating to optimally discern ethnic differences in behavioral or psychological responses; also, the assessment points may not have been frequent enough to catch the maximal response time point. In addition, Choneim and colleagues (1981) suggested that although ethnic dynamic difference may be negligible after a single dose of diazepam, it may become substantial after chronic dosing because of the accumulation of the metabolites as well as the parent drug.

#### Oral Diazepam Study Conducted in Hong Kong

Kumana and colleagues (1987) compared diazepam pharmacokinetics in 16 Chinese and 18 Caucasian healthy male volunteer subjects in Hong Kong. Compared to their Caucasian counterparts, the Chinese subjects were younger, lighter in weight, shorter, and leaner, as judged by skin fold thickness (SFT) (1.14 versus 1.44 cm subscapular,  $P = .03$ ) and total body weight to "ideal" body weight ratio (TBW/IBW) (0.93 versus 1.07,  $P = .02$ ). The Chinese subjects also had lower albumin concentrations (46 versus 50 g/L,  $P = .0001$ ). After screening and collection of the pretreatment blood sample, a 10-mg diazepam (Valium) tablet was administered. This was followed by the collection of a total of 10 blood samples in the next 72 hours at predetermined intervals. Serum concentrations of diazepam and desmethyldiazepam were measured by an enzyme-linked immunoassay for the first 6 samples (0–3 hours) and HPLC for the last 4 samples (3–72 hours).

The researchers found that  $T_{max}$  (time needed to achieve maximal drug concentration) was significantly more prolonged in the Chinese subjects. As reflected by similar  $C_{max}$  (actual data not reported) between the two groups, there were no apparent differences in predistribution diazepam concentrations between the two groups. In contrast, the Chinese subjects had 14%–61% higher diazepam and desmethyldiazepam concentrations during the postdistribution period (6–72 hours). They also had a significantly larger first order elimination rate constant ( $k_e$ ), longer elimination half-life ( $t_{1/2}$ ), and smaller apparent volume of distribution ( $V_{area}$ ). However, when two of these variables,  $k_e$  and  $V_{area}$ , were treated as dependent variables in a multiple regres-

and again at 2, 4, 6, and 24 hours after the administration of the test drug.

Plasma concentration curves for each individual subject were constructed. The area under the plasma concentration curve (AUC) was then calculated. Also calculated were the peak plasma concentration ( $C_{max}$ ) and time required to reach the peak concentration ( $T_{max}$ ), as well as the total plasma clearance (CL) and the volume of distribution.

As shown in Table 5-1, when compared to the Caucasian subjects, both Asian groups had higher AUC and  $C_{max}$  and smaller CL after both oral and intravenous administration of alprazolam. These differences either reached statistical significance (AUC and CL after oral administration;  $C_{max}$  after intravenous administration) or approached significance ( $C_{max}$  after oral administration, AUC after intravenous administration). These statistical differences either remained significant or became significant (for the oral- $C_{max}$  and intravenous-AUC) after body surface area was covaried. Although the  $t_{1/2}$  after both oral and

Table 5-1. Comparison of mean pharmacokinetic parameters after oral and intravenous alprazolam administration

	Caucasians (n = 14)	American- born Asians (n = 14)	Foreign- born Asians (n = 14)	ANOVA F	P
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD		
Oral					
AUC	138 $\pm$ 42.0	183 $\pm$ 43.8	173 $\pm$ 45.0	5.42	.01
$C_{max}$	9.79 $\pm$ 1.49	11.1 $\pm$ 2.62	11.7 $\pm$ 1.89	3.0	.1
CL	3.91 $\pm$ 1.04	2.88 $\pm$ 0.68	3.05 $\pm$ 0.69	5.4	.01
$t_{1/2}$	12.6 $\pm$ 4.05	15.9 $\pm$ 4.59	15.8 $\pm$ 5.24	2.60	.1
$T_{max}$	44.4 $\pm$ 11.6	69.4 $\pm$ 6.05	44.4 $\pm$ 11.6	1.37	NS
$V_{area}$	66.2 $\pm$ 10.4	62.5 $\pm$ 9.24	65.1 $\pm$ 8.15	0.47	NS
IV					
AUC	165 $\pm$ 39.2	213 $\pm$ 63.7	210 $\pm$ 68.7	2.97	.1
$C_{max}$	12.6 $\pm$ 2.04	15.2 $\pm$ 2.78	14.4 $\pm$ 2.8	3.79	.05
CL	3.17 $\pm$ 0.66	2.52 $\pm$ 0.69	2.65 $\pm$ 1.00	2.58	.1
$t_{1/2}$	13.4 $\pm$ 3.42	16.0 $\pm$ 5.36	17.8 $\pm$ 6.80	2.34	NS
$T_{max}$	10.9 $\pm$ 2.6	12.2 $\pm$ 4.1	16.6 $\pm$ 2.1	0.55	NS
$V_{area}$	59.2 $\pm$ 10.5	54.2 $\pm$ 8.9	60.0 $\pm$ 10.4	1.64	NS

Units of measurements: AUC = ng  $\times$  hour/ml;  $C_{max}$  = ng/ml; CL = liter/hour;  $t_{1/2}$  = hour;  $T_{max}$  = minutes;  $V_{area}$  = liter.

(0.5 mg) given to the subjects may not have been sufficient for producing dynamic changes conducive to cross-ethnic comparisons. Further, the DSST performance has been demonstrated to be strongly influenced by educational levels and levels of anxiety. The Caucasian subjects in this study had significantly lower baseline DSST scores than their Asian counterparts, raising the possibility of uneven distribution or discrepancy in education or baseline anxiety levels that could, in turn, complicate the post-treatment findings. To deal with these issues, it may be important to explore the use of other possibly more sensitive dynamic measures and to also attempt to ensure that the comparison groups are more comparable.

#### A Pharmacokinetic and Pharmacogenetic Study Conducted in Beijing, China

The cytochrome P<sub>450</sub> isozymes are involved in the metabolism of most benzodiazepines as well as other psychotropics (Bertilsson et al. 1989; Dahl-Punsten et al. 1989; Mellstrom et al. 1983; Shen and Lin 1990; Skjelbo et al. 1991). Two of these isozymes, whose activities can be determined with probe drugs such as debrisoquine (Steiner et al. 1988) and S-mephenytoin (Wilkinson et al. 1989), have been found to be polymorphic. Poor metabolizers (PMs) of debrisoquine are extremely rare among Asians (less than 1%; Nakamura et al. 1985) but are relatively common among Caucasian populations (6%–10%). In contrast, the rate of PMs of S-mephenytoin is quite high among Chinese and Japanese (15%–23%) as compared to Caucasians (3%–5%; Horai et al. 1989; Kupper and Preisig 1984; Wedlund et al. 1984).

Bertilsson and colleagues (1989) demonstrated a high correlation between the metabolism of diazepam and the phenotype status of S-mephenytoin in Caucasian subjects. This finding led to the hypothesis that the higher percentage of S-mephenytoin-type enzyme deficiency among Chinese may be mainly responsible for the slower metabolism of diazepam in this ethnic group. This theory, however, was not supported by a recent report by Zhang and colleagues (1990). In this study, diazepam and demethyldiazepam concentrations were measured over 21 days after the administration of 5 mg of diazepam in 16 healthy Chi-

drugs.

In contrast to the Hong Kong study (Kumana et al. 1987), Zhang and colleagues (1990) also reported a larger mean  $V_{area}$  in Chinese subjects than in Caucasian subjects. This difference reached statistical significance when Chinese EMs were compared with their Caucasian EM counterparts.

[Au: In next section, pls. clarify if black subjects were African-Americans or if subjects included other blacks.]

#### Comparison of the Pharmacokinetics of Adinazolam Between Blacks and Caucasians

Two of us (Fleishaker and Phillips 1989) conducted a study of the pharmacokinetics and pharmacodynamics of adinazolam, a triazolo-benzodiazepine currently being investigated as an anxiolytic and antidepressant, with eight black and eight Caucasian control subjects. The analysis of the pharmacokinetic dose-proportionality and pharmacodynamics in the total population has been published and the results have been reanalyzed to assess ethnic differences in kinetics and dynamics. The results showed that blacks had increased clearance of adinazolam, which resulted in a lower AUC, lower  $C_{max}$ , and longer half-life in blacks compared to Caucasians. Concurrently, however, the  $C_{max}$  and AUC of N-demethyladinazolam, a metabolite of adinazolam, were significantly higher in blacks. Along with these pharmacokinetic findings, blacks also manifested a significantly greater drug effect on psychomotor performance. Adinazolam is almost exclusively eliminated by hepatic oxidation to N-demethyladinazolam. Thus, these findings suggest that blacks may have a higher metabolic capacity for adinazolam. Because N-demethyladinazolam is cleared directly by renal excretion in addition to hepatic metabolism (approximately 50% of a dose of adinazolam is recovered in the urine as N-demethyladinazolam), increases in oxidative capacity are expected to have a lesser effect on N-demethyladinazolam AUC values. The increased  $C_{max}$  and AUC of N-demethyladinazolam in blacks may be due to increased first-pass conversion of adinazolam to N-demethyladinazolam. N-demethyladinazolam has been shown to primarily mediate the benzodiazepine-like side effects, including effects on psychomotor performance, after adinazolam ad-

Findings from the two North American studies also indirectly point to the importance of genetic influences. Although the results of Zhang and colleagues (1990) were compatible with the hypothesis linking ethnic differences in S-mephenytoin phenotype with benzodiazepine metabolism, they also indicated additional mechanisms, either genetic or environmental, that are responsible for the slower elimination rate of diazepam in Chinese EMs of mephenytoin phenotype.

In contrast to the other three studies, Kumana and colleagues (1987) suggested that volume of distribution, secondary to ethnic differences in the percentage of fat in the body, was the major factor for differential ethnic responses to diazepam. However, results from the other studies have not consistently supported such an assertion. Perhaps this inconsistency resulted at least partially from sampling biases. Although the Caucasian subjects included in the study of Kumana and colleagues were older and heavier, the other studies have recruited Caucasians whose degree of "fatness" was more comparable to their Asian subjects. However, in clinical situations, this factor may be an additional reason that the majority of Caucasian patients require higher doses of benzodiazepines.

Ghoneim and colleagues (1981) reported no difference in protein binding between their Asian and Caucasian subjects. This was confirmed by a study (Zhou et al. 1990) comparing the protein binding of various drugs, including diazepam, between Asians and Caucasians. Zhou and colleagues further reported that, although there were clear-cut differences between Asians and Caucasians in the concentrations of  $\alpha_1$  acid glycoprotein, as well as in the degree of protein binding of drugs primarily bound to this plasma protein, the two groups did not differ in their plasma albumin concentrations nor in the proportion of protein binding with drugs primarily bound to albumin. Because most benzodiazepines are bound to albumin, it appears reasonable to believe that protein binding does not represent an important factor in causing ethnic differences in benzodiazepine responses.

Although two of the studies (Ghoneim et al. 1981; Lin et al. 1988) included pharmacodynamic measurements, the researchers were not able to detect substantial differences in drug effects,



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