Desipramine pharmacokinetics in Chinese and Caucasian volunteers

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1 In order to better define the role of pharmacokinetic variation in reported cross-ethnic differences in dosing patterns of some psychoactive drugs, single dose kinetics of the tricyclic antidepressant desipramine (DMI) were studied in 14 Chinese and 16 Caucasian healthy volunteers. DMI and 2-OH-DMI concentrations were assayed with h.p.l.c. in serial plasma and 24 h urine samples over 5 days following an oral 100 mg dose of DMI.

2 Mean total clearance of DMI (CL_{DMI}) from plasma was significantly ($P < 0.05$) higher in the Caucasians (123 ± 57 l/h) than in the Chinese (73.5 ± 38.8 l/h). There was no significant difference in the apparent clearance of DMI by hydroxylation, fraction of dose metabolized to the hydroxy metabolite, DMI $t_{1/2}$ or plasma protein binding between the two groups.

3 Trimodal distribution of CL_{DMI} was found, with 4/14 (29%) Chinese demonstrating slow CL (< 33 l/h) and 4/16 (25%) Caucasians rapid CL (> 195 l/h). Correcting CL values for the greater mean weight of the Caucasians did not alter the pattern of distribution. CL_{DMI} did not correlate with body weight.

4 Although environmental factors cannot be ruled out, these results are consistent with genetically based differences in hepatic metabolism, probably affecting pathways in addition to hydroxylation, and suggest that 30% of Orientals would be at risk for toxicity from routine doses of tricyclics or similarly metabolized drugs.

Keywords desipramine pharmacokinetics ethnic differences metabolism

Introduction

Despite recent advances in the development of new antidepressant drugs, tricyclic antidepressants (TCAs) still constitute the mainstay of pharmacotherapy of depressive illness throughout the world. With the availability of reliable assays for these compounds in the late 1960s, advances in understanding of their pharmacokinetics were possible. A wide range of interindividual plasma concentrations during treatment for any given TCA dose accounted for the common clinical observation of highly variable therapeutic dose requirements (Hammer &

Sjöqvist, 1967). Twin and family studies, primarily in the Scandinavian countries (Alexanderson *et al.*, 1969; Åsberg *et al.*, 1971), documented a genetic basis for much of the variability in TCA metabolism. The metabolic pathway is depicted in Figure 1 for desipramine (DMI), a standard secondary amine TCA.

There are only limited cross-ethnic studies of interindividual differences in psychotropic drug metabolism. Average daily dose requirements of the antipsychotic butyrylperazine were five times higher in New York than in a matched patient

Figure 1 Major pathways of desipramine (DMI) metabolism in man. Abbreviations: DDMI didesmethylimipramine; DBI, iminodibenzyl. Prefix OH represents 2-hydroxylated metabolites.

sample in Germany (Denber *et al.*, 1962). Similarly, when therapeutic neuroleptic doses of a variety of drugs were expressed in chlorpromazine-equivalent units for a mixed Asian psychotic patient group in the United States, the doses were half those needed by matched white Americans (Lin & Finder, 1983). In contrast, in another American study mean therapeutic doses of haloperidol were the same in Asians and other racial groups (Binder & Levy, 1982). Although no comparable multinational therapeutic data exist for the antidepressants, anecdotal reports describe the need for lower routine doses of TCAs in Asian as opposed to Western countries (Yamamoto *et al.*, 1979). Kleinman (1981), an American psychiatrist, reported that in his treatment of scores of depressed patients while working in the People's Republic of China (PRC) minimum effective TCA doses were generally about half those required in Caucasian depressives. We found only one publication in the English language reporting TCA plasma concentrations in Asian patients; Yamashita & Asano (1979) did not find elevated plasma levels in their uncontrolled sample and proposed that pharmacodynamic or psychosocial factors might explain the efficacy of low doses. However, healthy Asian volunteers had higher plasma drug concentrations for 24 h after a single dose of clomipramine than their native British counterparts (Allen *et al.*, 1977; Lewis *et al.*, 1980).

Working within the framework of the 1980 Cooperative Health Agreement between the United States and the PRC we had the opportunity to explore these putative cross-cultural TCA pharmacokinetic differences after single dose DMI administration. In addition to total clearance of the drug, we wished to focus specifically on the hydroxylation clearance, using the rationale that differences in a single metabolic

pathway would be more likely to show a genetically based disparity than would a composite measure of drug elimination.

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Methods

The 30 subjects consisted of 14 Chinese and 16 Caucasians, with each racial group evenly divided between males and females. All subjects gave written informed consent for the procedure. For the Chinese, age ranged from 20 to 52 years in the women and 19 to 55 in the men, with an overall mean $\pm$ s.d. of 38.4 ± 12.6 years. Mean age of the Caucasian subjects was 38.4 ± 11.2 years, ranging from 22 to 58 in the women and 28 to 53 in the men. All but two of the women were premenopausal. All Oriental subjects were of pure Chinese lineage. Only one of the Chinese subjects was born in the United States; 10 were natives of the PRC, three of Taiwan and one of Hong Kong. Related Chinese subjects included a mother and her son as well as a pair of Taiwanese sisters. For all Chinese volunteers, mean time in the U.S. at time of study was 4.2 ± 6.1 years; all ate a primarily Western diet. Except for two women (born in Norway and Australia) all Caucasian subjects were natives of the United States. Every subject was free of medical or psychiatric illness and taking no routine medications. No subjects used alcohol more than moderately. Only two Caucasian men used tobacco (one a pipe smoker, and one a cigar smoker).

Experimental procedure

Each volunteer spent the first day of the study on a psychiatric research unit at the National Institutes of Health Clinical Center. At 09.00 h after an overnight fast each subject took a 100 mg oral dose of DMI HCl in the form of two 50 mg tablets (Norpramin). All were encouraged to rest during the morning and to resume normal activity after lunch was served to them.

Venous blood samples were drawn with separate venepunctures through a butterfly needle and cannula into disposable plastic syringes. These samples were obtained just before and at the following times after dosing: 2, 3, 8, 24, 32, 48, 72 and 96 h. Blood samples were immediately transferred to heparinized polypropylene tubes and centrifuged; plasma was frozen at -20°C until assayed. Each subject also

collected serial 24 h urine samples for 5 days beginning with time of dosing; after the volume of each collection was measured, 30 ml aliquots were frozen for later assay.

Analytical methods

Plasma and urinary concentrations of DMI and 2-OH-DMI were determined by the high-performance liquid chromatographic assay of Sutfin & Jusko (1979), with the modifications described by Kitanaka *et al.* (1982). Briefly, to 0.5 ml of plasma standard or test sample, internal standard solution (imipramine) and 0.2 ml carbonate buffer (pH 10.5) were added in polypropylene test tubes. The mixture was extracted with 2.0 ml hexane: ether (1:1) with 5% isobutanol for 15 min on a horizontally reciprocating shaker. After centrifugation, organic layers were transferred to polypropylene tubes and evaporated to dryness at ambient temperature under nitrogen. Extract was reconstituted just before chromatography with 50 μ l methanol and 45 μ l was injected. Samples (1.0 ml) of unhydrolyzed urine were processed in the same manner as the plasma samples. Duplicate 0.2 ml urine samples were also subjected to overnight incubation with 50 μ l β -glucuronidase and 150 μ l acetate buffer (pH 5.2) at 37°C, after which the same procedure as above was repeated.

All chromatography was done at ambient temperature. The mobile phase, pumped at a flow rate of 1.5 ml/min, consisted of methanol: acetonitrile (3:17) and butylamine (0.2%). A fluorescence detector was used with an excitation wavelength of 254-nm and a 370-nm emission filter.

Unbound (free) fraction of DMI was determined by equilibrium dialysis performed at 37°C for 6 h against a phosphate buffer (pH 7.4, 66 mM).

Calculations

Area under the plasma DMI concentration vs time curve (AUC) was computed by the trapezoidal rule, with the area beyond the final sampling time estimated by the last measured concentration/elimination rate constant of DMI. Total clearance of DMI is then equal to dose/AUC, assuming complete absorption. Hydroxylation clearance of DMI was calculated as total amount of OH-DMI (conjugated plus unconjugated) excreted in urine (over the 5 days of collection)/AUC of DMI in plasma, with both terms expressed in molar units; when the denominator equals dose of DMI, this quotient then expresses the fraction of the dose metabolized (f_m) to OH-DMI. The conversion factor

for changing plasma DMI levels from ng/ml to nmol/l is 3.76 and for OH-DMI 3.68.

Results are analyzed with χ^2 , Fisher's exact test, Spearman's correlation coefficient, and, where indicated, Student's *t*-test.

Results

Plasma DMI and OH-DMI concentrations peaked in all subjects between 3 and 8 h after dosing, then declined exponentially (Figures 2

Figure 2 Log plasma DMI concentrations (mean $\pm$ s.e. mean) in Chinese (O) and Caucasians (●) following single 100 mg oral dose.

and 3). Mean peak DMI concentrations were 45.4 and 29.8 ng/ml for Chinese and Caucasians, respectively (both at 8 h). Highest mean OH-DMI levels were measured in the Chinese at 3 h (28.0 ng/ml) and in Caucasians at 8 h (20.6 ng/ml). Mean levels of both substances were higher in the Chinese than in the Caucasians at all times measured; this difference was significant at the $P = 0.05$ level for all DMI values through 48 h and for OH-DMI concentrations at 32 and 48 h. There was no significant group difference for DMI elimination half-life ($t_{1/2}$) or in DMI fraction bound to plasma protein (Table 1).

There was a more than ten-fold range of total DMI clearance, from 18–221 l/h. Mean CL_{DMI} was considerably higher in the Caucasian group (Table 1).

A frequency histogram of CL_{DMI} reveals a clustering of Chinese at the slow end of the spectrum, with Caucasians skewed toward higher values. A probit plot of total CL for all subjects (Figure 4) clearly demonstrates three separate

Figure 3 Log plasma OH-DMI concentrations (mean $\pm$ s.e. mean) in Chinese (O) and Caucasians (●) following single 100 mg oral dose of DMI.

groups: low (< 33 l/h), intermediate (50–150 l/h), and high CL (> 195 l/h). The ethnic composition of the low and high CL groups are opposite: the slow CL group consists of four Chinese individuals and the rapid CL group, four Caucasians (Table 2).

Clearance of DMI to 2-OH-DMI ranged from 6.7 to 77.1 l/h, with no significant difference between Chinese and Caucasians (Table 1). One Caucasian subject was dropped from urinary analysis due to incomplete collection on day of drug administration. For the entire group, hydroxylation CL and total CL were strongly correlated ($r = 0.78$, $P < 0.001$). However, for hydroxylation CL three separate groups are not discernible on

Figure 4 Probit plot of DMI clearance in 30 volunteers (O Chinese, ● Caucasian). Median value is represented by probit score of 5. Breaks in distribution below 50 l/h and above 150 l/h divide the sample into slow, intermediate, and rapid clearance subgroups.

Table 1 Pharmacokinetic variables following DMI 100 mg p.o.

Variable	Chinese (n = 14)	Caucasians (n = 16)	P
CL _{DMI} (l/h) (l h ⁻¹ kg ⁻¹)	73.5 $\pm$ 38.8*	123.0 $\pm$ 57.0	$< 0.05^{***}$
	1.27 $\pm$ 0.59	1.78 $\pm$ 0.96	0.05***
CL _{hydroxylation} (l/h) (l h ⁻¹ kg ⁻¹)	29.6 $\pm$ 15.0	39.7 $\pm$ 17.9**	NS
	0.51 $\pm$ 0.23	0.61 $\pm$ 0.30**	NS
AUC _{OH-DMI} (ng ml ⁻¹ h)	946 $\pm$ 350	654 $\pm$ 200	< 0.05
f _m to OH-DMI	0.41 $\pm$ 0.07	0.35 $\pm$ 0.09**	NS
f _{excr} unchanged	0.034 $\pm$ 0.027	0.026 $\pm$ 0.037**	NS
t _{1/2} (h)	23.2 $\pm$ 7.9	18.2 $\pm$ 6.6	NS
% unbound	9.37 $\pm$ 0.87	9.61 $\pm$ 1.22	NS

* all values mean $\pm$ s.d., ** n = 15, *** one-tailed

Table 2 Trimodal distribution of desipramine clearance

	Desipramine clearance		
	Low (<33 l/h)	Intermediate (50–150 l/h)	High (>195 l/h)
Caucasian	0	12	4
Chinese	4 ^{a,b}	10	0

^a $P < 0.1$ (Fisher's exact test), Low vs intermediate^b $P < 0.05$ (Fisher's exact test), Low vs intermediate + high

probit analysis. Since less than 3% of administered DMI was excreted unchanged and the fraction metabolized to OH-DMI was 0.38 ± 0.09 , the clearance of DMI by other pathways was estimated. The sum of metabolic routes other than hydroxylation is taken as the difference between total CL and hydroxylation CL.

The distribution of subjects according to this remainder clearance is similar to that for total clearance: none of the Caucasians show low clearance, with 11 and five subjects displaying intermediate and high clearances, respectively. On the other hand this clearance was low in five Chinese and intermediate in the rest.

It should be noted that although Chinese and Caucasian subjects were matched by sex and age, there were major differences in body weight, with a mean ($\pm$ s.d.) of 57.7 ± 10.0 kg for the Chinese vs 71.8 ± 17.6 kg for Caucasians ($P < 0.02$). However, there is no significant correlation between body weight and CL_{DMI} ($r = 0.40$). Weight corrected CL values, using ideal body weight for two markedly obese Caucasians (Devine, 1974), were distributed in a similar manner to the uncorrected values and the mean values remained significantly different ($P = 0.05$, Table 1), while the frequency distribution of total CL_{DMI} is unchanged. Inter-ethnic hydroxylation CL differences remain insignificant following weight correction (Table 1).

Discussion

This study shows that healthy Chinese volunteers metabolize DMI more slowly than their Caucasian counterparts, thereby suggesting a pharmacokinetic mechanism for the lower dose requirements in Chinese patients. Our Caucasian subjects' mean CL_{DMI} of 123 l/h was similar to the previous reports in the literature (corrected for 70 kg body weight) of 130 l/h (Alexanderson, 1972; DeVane *et al.*, 1981).

Many of the interethnic differences noted above were amplified when the data were grouped according to the trimodal distribution of

CL_{DMI} (Table 2). The disparity between the two extreme outlier groups is illustrated in the plasma concentration/time curves for DMI and OH-DMI (Figures 5 and 6). The separation between rapid and slow metabolizers was more pronounced than in the average data (Figures 2 and 3), with neither parent drug nor metabolite measurable in the high CL group at 72 or 96 h. Peak (8 h) DMI concentrations averaged 66.8 ng/ml in the slow CL group and 19.4 ng/ml in the rapid group. In the case of OH-DMI, plasma levels were initially higher in the rapid clearance group (during the absorptive phase) with a 24.5 ng/ml peak concentration at 3 h, versus 18.0 ng/ml at 8 h in the slow clearance group. There

Figure 5 Log plasma DMI concentrations (mean $\pm$ s.e. mean) in 30 volunteers separated into slow ($\circ$, $n = 4$), intermediate (Δ , $n = 22$) and rapid clearance ($\bullet$, $n = 4$) subgroups following single 100 mg oral dose.

Figure 6 Log plasma OH-DMI concentrations (mean $\pm$ s.e. mean) in 30 volunteers grouped into slow (O, $n = 4$), intermediate (Δ , $n = 22$) and rapid ($\bullet$, $n = 4$) clearance distribution following single 100 mg oral dose of DMI.

was no significant difference at 8 h, after which the slow CL subjects had higher concentrations.

In the low CL subgroup, $7.4 \pm 0.6\%$ of the administered dose of DMI was excreted unchanged in the urine compared to $1.0 \pm 0.3\%$ in the high CL Caucasians ($P < 0.001$). Within the large intermediate CL subgroup there were no interethnic differences in any parameter. There were no demographic differences between the slow CL group and the rest of the Chinese subjects, nor between rapid and intermediate CL Caucasians. It appears likely that genetic differences account for these findings since the predominant role of hereditary factors in TCA metabolism has been well documented (Alexanderson *et al.*, 1969; Asberg *et al.*, 1971). Much of the recent work in the pharmacogenetics of oxidative metabolism has focused on the antihypertensive, debrisoquine, for which large samples of varying populations have been phenotyped as poor or extensive metabolizers based on urinary ratios of parent drug to 4-hydroxy metabolite after a single dose (Idle & Smith, 1979). Debrisoquine hydroxylation, in turn, has been found to be closely correlated with metabolism of several agents which are also metabolized primarily via hepatic oxidation, such as sparteine (Eichelbaum *et al.*, 1982; Inaba *et al.*, 1983), propranolol (Alvan *et al.*, 1982),

and in a stereospecific manner (E-hydroxylation), nortriptyline (Mellström *et al.*, 1981). Very recently the debrisoquine phenotype was demonstrated to show strong correlation with steady-state DMI concentrations earlier obtained in the same individuals (Bertilsson & Aberg-Wistedt, 1983).

Nine percent of the British white population (Price Evans *et al.*, 1980), 8% of Canadian Caucasians (Inaba *et al.*, 1983), and 3% of a Swedish sample (Alvan *et al.*, 1982) have been identified as poor metabolizers of debrisoquine. Of particular pertinence to the current work, about 30% of Oriental volunteers have been found to be poor metabolizers of debrisoquine (Kalow *et al.*, 1980; Inaba *et al.*, 1981), with only 20% (vs 50% of British Caucasians) homozygous for rapid hydroxylation (Kalow, 1982). Earlier work suggested a similar, 5% rate of deficient DMI hydroxylators in an American mixed patient population (Potter *et al.*, 1982). Gram *et al.* (1983) recently found a 21% rate of slow hydroxylation (affecting DMI more than the parent compound) in a mixed group of Danish patients during steady-state imipramine (IMI) dosing. While the number of subjects in the present study was relatively small, the difference in distribution of CL_{DMI} in Chinese and Caucasian subjects, respectively, is generally consistent with these earlier reports. As discussed below, however, the cross-ethnic CL results in the present investigation cannot be explained purely on the basis of hydroxylation deficiencies in one population.

As many of our Chinese volunteers were newly arrived in the United States at time of testing, we cannot rule out environmental factors such as diet or exposure to chemical inducers or retardants of relevant enzyme systems as having played a part in the observed pharmacokinetic differences. Ghoneim *et al.* (1981), however, did not find an effect of length of time in this country and mild dietary differences sufficient to explain pharmacokinetic variation in diazepam metabolism between Orientals and Caucasians. In addition, our Chinese subjects had significantly lower body weight than did the Caucasians, but as there was no correlation between CL_{DMI} and body weight, differences observed were unchanged by a weight correction of clearance.

There was clearer interethnic differentiation in total as opposed to hydroxylation clearance of DMI. The calculation of hydroxylation clearance and fraction metabolized to hydroxy DMI was based upon the assumption that all of the hydroxy DMI formed is excreted in urine as hydroxy DMI or its glucuronide. Therefore the values reported may be underestimates if hydroxy DMI is metabolized to any other product or if hydroxy

DMI glucuronide is eliminated via the faeces. Crammer *et al.* (1969) measured many metabolites of IMI in the urine of patients administered the radioactively labeled drug. OH-DMI and OH-DMI glucuronide accounted for 30% of the label recovered in urine. Another OH-DMI conjugate accounted for 9%; hydroxy didesmethyl IMI and conjugates, 7%; and hydroxyiminodibenzyl and conjugates, 7%. At least to the extent that any unidentified conjugates of OH-DMI were formed in our subjects the hydroxylation CL is underestimated. Whether hydroxy didesmethyl IMI and hydroxyiminodibenzyl are formed directly from DMI or via OH-DMI is unknown. These dealkylations may account for a substantial part of the remainder CL in our subjects. Interethnic differences in metabolic routes other than hydroxylation are implied by studies comparing the clearance of diphenhydramine (demethylation, oxidation) (Spector *et al.*, 1980) and diazepam (demethylation as well as hydroxylation) (Ghoneim *et al.*, 1981) in Orientals and Caucasians. However, the difference reported in the former study may be a result of the lower plasma protein binding of drug found for Orientals.

The trend toward a larger fraction of DMI hydroxylation in the slow (0.44 ± 0.07) vs rapid metabolizers (0.31 ± 0.08) stands in contrast to the demonstration by Mellström *et al.* (1981) of more extensive NT hydroxylation after a single dose in these phenotyped as rapid hydroxylators of debrisoquine, who showed f_m to 10-OH-NT of 0.60 to 0.75 compared to 0.24 to 0.49 for the slow debrisoquine hydroxylators. In light of the reported correlation between CL of NT and DMI (Alexanderson, 1972), this inconsistency is difficult to explain. Nevertheless, consideration of only plasma data supports the observation of higher f_m to hydroxy DMI in the low clearance group. A combination of higher AUC(OH-DMI) and lower ratio AUC(OH-DMI)/AUC(DMI) in the low CL group implies that the partial CL of DMI to hydroxy DMI is lower but f_m to hydroxy DMI is higher in the low clearance Chinese subjects. It is assumed that there is no difference in the clearance of hydroxy DMI

among these subjects. These results imply that the difference between the two groups lies in the clearance of DMI to metabolites other than hydroxy DMI (Levy *et al.*, 1983).

In conclusion, healthy Chinese volunteers were shown to metabolize single doses of DMI more slowly than sex- and age-matched Caucasians. This difference was not exhibited in the hydroxylation pathway of metabolism. All of the interethnic differences can be explained on the basis of a minority of outliers in each group: 29% of Chinese (slow CL) and 25% of Caucasians (fast CL). Nearly three quarters of the entire sample fell in the intermediate cluster in terms of CL and the related parameters, indistinguishable on the basis of ethnicity.

The clinical implications are clear: patients with relatively high or low CL of a tricyclic antidepressant are at risk for developing subtherapeutic or toxic concentrations, respectively, when such medications are prescribed in usual clinical doses. Larger populations, including families, better controlled for environmental variables and monitored for multiple metabolites, must be studied to elucidate definitively that portion of the CL under genetic control. The usefulness of a simple phenotyping technique for tricyclic CL such as the urinary ratio of hydroxy metabolite to parent drug after single dose debrisoquine has been suggested (Mellström *et al.*, 1981; Bertilsson & Aberg-Wistedt, 1983). In the present work a modest correlation ($r = 0.7$) was found between 24 h OH-DMI/DMI ratio in urine and CL_{DMI}.

In any event, prudent clinical practice would indicate a necessity for cautious dosing with such drugs in populations at risk such as Orientals, combined with careful plasma concentration monitoring during treatment. Concern about excessive dosing should be balanced with the realization that about 70% of these vulnerable populations will *not* display slow hepatic CL. Whenever possible, prospective prediction of unusual CL rates, such as through use of an initial dose for pharmacokinetic modeling (Potter *et al.*, 1980), will permit the most appropriate dosing regimen to be instituted at the start of treatment.

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